Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

The heterogeneous chemotherapy-induced peripheral neuropathy trajectories and its predictors in patients with gastrointestinal tumors : a cohort study

Hongyu Zhu
Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital
Yun zhen Peng
Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital
Jing Qiu
Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital
Yi Zhou
Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital
Wenting Huang
Fujian Medical University
Liqin Jiang
Fujian Medical University
Xingyu Ren
Fujian Medical University
Lei Ren
Fujian Medical University
Qingyue Chen
15959063004@163.com

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Article

Keywords: Chemotherapy-induced peripheral neuropathy, Gastrointestinal tumors, Trajectory patterns, latent class growth analysis, Predictors

Posted Date: August 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9968527/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and important nerve-related side effect of chemotherapy. However, researchers still know little about how CIPN changes over time in patients with gastrointestinal tumors. This prospective cohort study aimed to identify different CIPN patterns during chemotherapy and to examine factors related to these patterns. We recruited 233 patients with gastrointestinal tumors from a tertiary cancer center. All patients had a pathological diagnosis and received first-line chemotherapy with drugs known to cause peripheral nerve damage. At baseline, we collected demographic and clinical data. We also measured cancer-related fatigue with the Revised Piper Fatigue Scale, physical performance with the Short Physical Performance Battery, and self-management efficacy with the Strategies Used by People to Promote Health scale. We assessed CIPN symptoms with the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool after the 1st, 3rd, 5th, and 7th chemotherapy cycles. We used latent class growth modeling to identify CIPN trajectory patterns. We used chi-square tests, analysis of variance, and logistic regression analyses to examine factors related to these patterns. We identified four CIPN trajectories: worsening CIPN symptoms (71 patients, 30.5%), mild stable CIPN symptoms (81 patients, 34.8%), improving CIPN symptoms (42 patients, 18.0%), and severe stable CIPN symptoms (39 patients, 16.7%). Age, smoking history, number of chronic diseases, chemotherapy regimen, standardized cumulative dose of neurotoxic agents, cancer-related fatigue, physical performance, and self-management efficacy were related to CIPN trajectory membership. These findings show that CIPN does not follow the same course in all patients with gastrointestinal tumors during chemotherapy. Early identification of high-risk patients and individualized symptom management may help reduce nerve damage, maintain physical function, and improve tolerance to chemotherapy.

Introduction

As cancer survival continues to improve, the potential impact of treatment on patients' quality of life has become increasingly evident, highlighting the need for greater attention to long-term toxicities associated with cancer therapy[1]. Chemotherapy-induced peripheral neurotoxicity (CIPN) is recognized as a prominent form of long-term toxicity among oncology patients[2]. Clinically, CIPN primarily affects the hands and feet, where sensory loss, numbness, tingling, pain, heat sensitivity, and motor disturbances may impair coordination[3], cause balance problems, and elevate the risk of falls[4]. These symptoms result from exposure to several widely used chemotherapeutic agents. CIPN is a common adverse effect of platinum compounds (cisplatin, carboplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), vincristine, and eribulin. These agents are routinely administered for the treatment of various malignancies[5], especially gastrointestinal (GI) cancers[6–8].

The incidence of chemotherapy-induced peripheral neurotoxicity (CIPN) has been reported to range from 19% to more than 85%[9,10], with substantial variability in severity among patients[11]. During treatment, severe CIPN often necessitates dose reduction or discontinuation of chemotherapeutic agents by oncologists[12]. Such dose modifications may negatively affect disease control and progression-free survival[13]. Long-term follow-up studies have further shown that CIPN symptoms may persist for years, or even a lifetime, after cessation of chemotherapy, exerting a considerable impact on patients' quality of life[13–15]. A recent meta-analysis involving patients with gastrointestinal malignancies reported CIPN prevalence rates of 58% at 6 months post-treatment and 45% at 12 months. The prevalence decreased to 32% at 24 months and 24% at 36 months[4]However, The underlying mechanisms of CIPN remain incompletely understood. hemotherapy treatments result in numerous changes to cellular structure and function, including loss of sensory terminals in the skin, and alterations of membrane receptors, intracellular signaling, neurotransmission, excitability and metabolism all of which can negatively influence neuronal and glial cell phenotypes, thereby contributing to CIPN[5,11]. Despite its clinical relevance, the temporal evolution and heterogeneity of CIPN symptoms during chemotherapy have not been adequately characterized, particularly among patients with gastrointestinal malignancies who frequently receive combination regimens containing multiple neurotoxic agents[16,17].

Existing research has largely focused on the cross-sectional prevalence or cumulative severity of CIPN rather than the longitudinal evolution of its symptoms[2,18]. However, increasing evidence indicates that CIPN does not follow a single trajectory; substantial heterogeneity may exist across patient subgroups [11,19]. These heterogeneous patterns likely reflect complex interactions among demographic, clinical, behavioral, and psychosocial factors. This underscores the need for longitudinal analyses to identify high-risk subgroups and potential protective mechanisms, such as genetic or behavioral factors. In this study, latent class growth analysis (LCGA),a person-centered statistical approach, which was applied to identify unobserved heterogeneous subgroups based on longitudinal symptom trajectories[20]. By dynamically tracking changes in CIPN symptoms during chemotherapy, we can reveal variations in symptom progression across individuals. This enables a more comprehensive understanding of CIPN's temporal patterns and the identification of patient subgroups with differing neurotoxicity risk profiles. This approach provides a basis for individualized symptom surveillance and targeted interventions, ultimately supporting improvements in treatment tolerance and quality of life.

Multiple predictors of CIPN have been identified to date. Risk factors include the specific chemotherapeutic agents used[7,21];cumulative dose[22]; number of chemotherapy cycles; duration of treatment; combination regimens; genetic susceptibility[5]; age[22,23]; pre-existing neuropathy and the severity of acute neurotoxic symptoms[24]. Beyond biomedical contributors, recent research has emphasized the role of behavioral and psychosocial factors[25], such as anxiety and depression [26], fatigue[27], physical function[25], and self-management efficacy[28], all of which have been shown to influence CIPN symptoms. The findings suggest that the onset and progression of CIPN result from complex interactions between physiological vulnerability and behavioral adaptation. This highlights the need for a more comprehensive examination of its heterogeneity within a longitudinal research framework. Building on these predictors, this study aimed to address two primary questions: (1) What types of chemotherapy-induced peripheral neurotoxicity (CIPN) trajectories emerge among patients with gastrointestinal malignancies during chemotherapy? (2) What predictors—spanning demographic, clinical, symptomatic (e.g., cancer-related fatigue, emotional distress), and lifestyle factors—are associated with subgroup membership, defined as distinct patterns of CIPN progression? By characterizing the dynamic evolution and heterogeneity of CIPN during treatment, the study seeks to provide evidence to support more precise clinical assessment of neurotoxicity risk. The findings may also contribute to the development of individualized symptom monitoring and intervention strategies, ultimately improving chemotherapy tolerance and quality of life for patients.

Methods

Study design

This longitudinal follow-up study was conducted at a large tertiary cancer hospital in mainland China from December 2019 to December 2023. Participants were patients with gastrointestinal malignancies who were scheduled to receive their first chemotherapy regimen containing neurotoxic agents, such as platinum- or taxane-based drugs. Baseline assessments were completed at enrollment and included demographic characteristics, disease-related information, chemotherapy regimen, psychological condition, and lifestyle factors.

Chemotherapy-induced peripheral neurotoxicity (CIPN) was evaluated using the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT). Repeated CIPN measurements were obtained at the end of the first, third, fifth, and seventh chemotherapy cycles to capture the dynamic progression of neurotoxicity. Throughout treatment, specific clinical indicators and medication dosages were continuously monitored by the research team. To complement this monitoring, the follow-up schedule was designed to account for the progressive nature of CIPN and interindividual variability. This approach ensured that heterogeneous neurotoxicity trajectories could be accurately identified during chemotherapy. All participants provided written informed consent. The study protocol was approved by the Ethics Review Committee of Fujian Cancer Hospital (Approval No. K2024-117-01), according to Swedish regulations (https://etikprovning.se/for-forskare/ansvar/).

Participants and sampling

The inclusion criteria were as follows: (1) a pathological diagnosis of gastrointestinal malignancy [29,30], including cancers of the stomach, esophagus, colon, rectum, small intestine, and biliary tract; (2) the planned initiation of a chemotherapy regimen containing neurotoxic agents; (3) a first-line chemotherapy with an expected duration of ≥ 4 cycles; (4) age ≥ 18 years; (5) an estimated survival time of ≥ 6 months; (6) the ability to complete the survey independently or with assistance; and (7) provision of written informed consent and voluntary participation. The exclusion criteria were as follows: (1) coma or severe communication impairment; (2) severe cardiac or pulmonary diseases; and (3) the presence of another malignancy. Sample size was determined based on the 10-events-per-variable (EPV) rule in logistic regression, ensuring at least 10 outcome events for each predictor in the regression Eq. 2^9 A maximum of six predictors were expected to be included in the model. Previous studies have reported CIPN incidence rates ranging from approximately 19% to 90% in this population and similar cancer groups[6]. For this study, a conservative incidence estimate of 30% was assumed. Based on this assumption, the required sample size was calculated as 60 divided by 0.30, resulting in 200 participants. Allowing for a 10% attrition rate, the final target sample size was set at approximately 220 participants.

Instruments

General demographic questionnaire

The questionnaire was developed through group discussions and a review of relevant literature. It comprised the following components: (1) sociodemographic information, including age, gender, educational level, and other basic characteristics; (2) disease-related information, such as cancer type and tumor stage. Additionally, it included the history of surgery or radiotherapy concurrent with or prior to

chemotherapy; and (3) treatment related information, including the chemotherapy regimen and standardized cumulative dose of neurotoxic agents. More specifically, the standardized cumulative dose was calculated as the actual cumulative dose (mg/m²) divided by the established neurotoxicity threshold dose (mg/m²) for each agent. A value ≤ 1 indicated that the actual dose did not exceed the recognized neurotoxic threshold, whereas a value > 1 indicated that the threshold had been surpassed. Common threshold doses for neurotoxic agents known to induce CIPN were as follows: cisplatin, 400–450 mg/m²[16]; paclitaxel, 1,000 mg/m²[7]; oxaliplatin, 850 mg/m²[8]; and docetaxel, 400 mg/m²[7].

Chemotherapy-Induced Peripheral Neuropathy Assessment Tool(CIPNAT)

The Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT) was developed by Tofthagen et al.[30]as a patient-reported questionnaire designed to assess the severity of chemotherapy-induced peripheral neuropathy. The instrument consists of two sections. The first section evaluates the symptom experience of CIPN, comprising nine symptoms and 36 subitems distributed across two dimensions—the sensory and motor impairment dimensions. It assesses symptom occurrence, severity, distress, and frequency. Except for the occurrence items, which are scored on a 0–1 scale, all other items are rated on a 0–10 scale. The total score for each symptom ranges from 0 to 31 points. Total scores range from 0 to 279, with higher scores indicating more severe symptoms. The second section assesses the impact of CIPN on daily activities, including 14 items that measure fine motor tasks (such as buttoning clothes and writing) and general activity performance. These items are rated on a 0–10 scale, yielding a total score of 0–140, where higher scores indicate greater interference with daily functioning. The Chinese version of the CIPNAT has demonstrated strong reliability and validity, with a Cronbach's α of 0.94 for the total scale; 0.92 for the sensory subscale and 0.89 for the motor subscale. As the present study focused specifically on the longitudinal changes in CIPN severity, only data from the first section of the CIPNAT questionnaire were used for analysis.

The Revised Piper Fatigue Scale, RPFS

The Revised Piper Fatigue Scale (RPFS), adapted from the original Piper Fatigue Scale (PFS)[31], was used to assess fatigue experienced by patients with gastrointestinal malignancies during chemotherapy. The scale comprises 22 items across four dimensions of fatigue—sensory, affective, cognitive, and behavioral—each rated on a 0–10 scale. The overall score is calculated as the mean of all 22 items. Fatigue levels are categorized as mild (0.0–3.3), moderate (3.4–6.7), or severe (6.8–10.0). In the present study, the RPFS demonstrated high internal consistency, with a Cronbach's α coefficient of 0.91[31].

Short Physical Performance Battery, SPPB

The Short Physical Performance Battery (SPPB) was developed by the National Institute on Aging (NIA) [32]and is primarily used to assess patients' physical function. The instrument includes three components: a balance test (side-by-side, semi-tandem, and tandem positions), a 4-meter gait speed test (time required to walk 4 meters), and a repeated chair-stand test (five consecutive sit-to-stand repetitions). Each component is scored using a five-level Likert scale ranging from 0 (unable to perform) to 4 (best performance), yielding a total score of 0–12. Higher scores indicate better physical function[32]. SPPB scores ≤ 6 indicate poor physical performance, scores of 7–9 reflect moderate performance, and scores of 10–12 indicate good performance[33]. The Cronbach's α coefficient for the scale in this study was 0.76. The operational procedures for the SPPB were summarized and illustrated based on the original publication and are provided in Supplementary Fig. 1. Additionally, the original tool and detailed instructions are available at:https://geriatrictoolkit.missouri.edu/SPPB-Score-Tool.pdf?utm_source=chatgpt.com

Strategies Used by People to Promote Health, SUPPH

The Strategies Used by People to Promote Health (SUPPH) scale was developed by Lev et al.[34]and subsequently translated and culturally adapted for Chinese patients with cancer [35]to assess self-efficacy in self-management. The SUPPH consists of 28 items across three dimensions: positive attitude, stress reduction, and decision-making. Each item is scored on a 5-point Likert scale (1–5), yielding a total score ranging from 28 to 140. Higher scores indicate stronger self-efficacy. Scores ≥ 103 reflect high self-efficacy; scores between 66 and 102 indicate moderate self-efficacy; and scores ≤ 65 indicate low self-efficacy. The Cronbach's α coefficient for the total scale in the Chinese version was 0.978[35]

Follow-up information questionnaire

Data collection was conducted through face-to-face interviews. Eligible participants were approached in outpatient clinics or inpatient wards, where the study purpose and procedures were explained. The survey formally began after written informed consent was obtained. At the time of enrollment, sociodemographic information and questionnaire data, including the Revised Piper Fatigue Scale (RPFS), Short Physical Performance Battery (SPPB), and Self-Efficacy for Managing Chronic Disease Scale (SUPPH), were collected. Relevant clinical information was extracted from the patients' medical records using a standardized data collection form. Participants who met the inclusion criteria completed the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT) at the end of the 1st and 3rd chemotherapy cycles (time points T1 and T2). They also completed it at the end of the 5th and 7th cycles (time points T3 and T4), respectively, allowing for dynamic assessment of peripheral neurotoxicity throughout treatment. To protect participant confidentiality, a unique identification code was assigned to each individual for data entry and management. A small gift card was provided after each completed assessment to enhance follow-up adherence.

Data analysis

Data were analyzed using SPSS 23.0 and Mplus version 7.4. For descriptive statistics, continuous variables were expressed as medians and interquartile ranges for non-normally distributed data, or as means ± standard deviations for normally distributed data. Categorical variables were summarized as frequencies and percentages. Latent class growth analysis (LCGA) was first conducted in Mplus 7.4 to identify heterogeneous CIPN trajectories among patients with gastrointestinal malignancies. Model evaluation followed established criteria. First, information indices were considered, including the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample size–adjusted BIC (aBIC), and entropy. An entropy value > 0.80 was considered indicative of high classification precision, whereas lower AIC, BIC, and aBIC values suggested better model fit[36]. Second, statistical tests were used, including the Lo–Mendell–Rubin likelihood ratio test (LMR) and the bootstrapped likelihood ratio test (BLRT). A p-value < 0.05 for LMR or BLRT indicated that a model with k classes provided a better fit than a model with k–1 classes. After identifying the latent trajectory classes via LCGA, univariate and multivariate logistic regression analyses were conducted in SPSS 23.0 to identify predictors of CIPN trajectory membership. Variables entered into the analyses included sociodemographic characteristics, fatigue, physical performance, and self-management self-efficacy, selected based on prior literature and data availability.

Results

General demographic characteristics of participants

A total of 250 patients met the eligibility criteria, and details of the criteria for inclusion and exclusion for the longitudinal analysis are presented in the flowchart (Fig. 1). No significant differences in age, sex, or specific clinical characteristics such as disease stage and treatment type were observed between excluded and included patients. Ultimately, longitudinal data from 233 patients were analyzed. Among these patients, 62.23% were male and 37.77% were female; 36.91% were aged 40–60 years, while 41.20% were older than 60 years. Primary education was reported by 45.49% of patients. Seventy-eight participants had never smoked, and 98 had a history of smoking. Furthermore, 45.49% had two to three comorbid chronic conditions. Regarding cancer type, 52.79% of cases involved upper gastrointestinal malignancies such as gastric or esophageal cancer. Standardized cumulative doses of neurotoxic agents exceeded the neurotoxicity threshold (greater than 1) in 177 patients, while 56 patients received doses less than or equal to 1. Detailed characteristics are summarized in Table 1.

Table 1
Participants' demographic characteristics (n = 233)

Variables	Category	n	%	Variables	Category	n	%
Age (year)	< 40	51	21.89	Tumor Types	Upper gastrointestinal cancer	123	52.79
	40–60	86	36.91		Lower gastrointestinal cancer	76	32.62
	> 60	96	41.20		Other gastrointestinal malignancies	34	14.59
Gender	Male	145	62.23	Stage	Stage I- II	77	33.05
	Female	88	37.77		Stage III- IV	156	66.10
BMI(kg/m2)	< 18.5	105	45.06	Concurrent or Previous Surgery / Radiotherapy	No	56	24.03
	18.5–23.9	84	36.05		Yes	177	75.97
	> 24	44	18.88	Metastasis	No	65	27.90
Educational Levels	Primary education	106	45.49		Yes	168	72.10
	Secondary education	88	37.77	Chemotherapy Regimen	Platinum-based	93	39.91
	Higher education	39	16.74		Taxane-based	70	30.04
Marital Status	Divorced/widowed	28	12.02		Others	26	11.16
	Married	205	87.98		Platinum + taxane	44	18.88
Smoking History	Never smoked	78	33.48	Standardized Cumulative Dose of Neurotoxic Agents	≤ 1	56	24.03
	Former smoker	98	42.06		> 1	177	75.97
	Current smoker	57	24.46	RPFS,mean (SD)	4.23 ± 1.85		
Chronic Diseases	0–1 type	68	29.18	SPPB,mean (SD)	6.55 ± 3.113		
	2–3 types	106	45.49	SUPPH,mean (SD)	75.04 ± 31.425		
	≥ 4 types	59	25.32				

CIPNAT, RPFS, SPPB, and SUPPH scores among patients with gastrointestinal cancers

The mean RPFS score of participants was 4.23 ± 1.85, the mean SPPB score was 6.55 ± 3.11, and the mean SUPPH score was 75.04 ± 31.42. The CIPNAT scores at time points T1, T2, T3, and T4 were 65.85 ± 45.48, 77.43 ± 44.45, 91.10 ± 50.28, and 101.18 ± 57.91, respectively. A significant difference in CIPNAT scores was observed across these four time points ($F = 61.955$, $P < 0.001$). Scores for the sensory and motor impairment subscales are presented in Table 2.

Table 2
Patient-Reported Occurrence and Severity of CIPN-Related Sensory and Motor Symptoms in Patients With Gastrointestinal Tumors

Dimensions	Items	T1		T2		T3		T4	
		Occurrence (%)	Median (P25, P75)	Occurrence (%)	Median (P25, P75)	Occurrence (%)	Median (P25, P75)	Occurrence (%)	Median (P25, P75)
Sensory Nerve Impairment	Numbness in fingers/toes	40.4	10(7.16)	65.7	12(7,18)	87.7	19(8,26)	90.3	19(8,25)
	Numbness in hands/feet	54.4	10(5.5, 17)	63.7	13(6,18)	80.6	18(7,25)	91.3	19(7,25)
	Tingling in fingers/toes	32.9	0(0, 11)	51.5	9(0,17)	71.2	9(0,18)	76.0	7(4,15.5)
	Tingling in hands/feet	44.9	4(0, 15)	45.5	0(0,15)	76.8	8(4,13.5)	85.0	8(4.5,20)
	Discomfort in hands/feet or arms/legs	47.7	8(7, 15)	75.8	14(7,19)	82.6	17(9,23)	92.8	19(8,27)
Motor Nerve Impairment	Sensitivity to cold	34.4	1(0, 12.5)	52.8	1(0,15)	74.7	9(0,15)	74.2	9(0,19)
	Joint or muscle pain	27.2	0(0, 13)	55.4	6(0,16)	50.6	4(0,7)	54.5	4(0,7)
	Muscle weakness or loss of strength	28.9	2(0, 11)	59.7	7(0,14)	78.5	7(4,10)	77.7	12(4,18)
	Difficulty maintaining balance	24.5	0(0, 0.5)	25.3	0(0,4)	30.9	0(0,4)	29.6	0(0,4)

Note: Occurrence was defined as any patient-reported presence of the corresponding CIPNAT symptom at each assessment point. Percentages represent symptom-level reporting rates rather than clinically diagnosed CIPN incidence. Each symptom score was calculated as the sum of occurrence, severity, distress, and frequency ratings, with a possible range of 0–31; higher scores indicate more severe symptoms. Symptom scores are presented as median (P25, P75).

Heterogeneous CIPN trajectory in patients with gastrointestinal tumors

Latent class growth analysis (LCGA) was conducted to model CIPN trajectories during chemotherapy in patients with gastrointestinal malignancies. Model evaluation based on AIC, BIC, and aBIC showed that information index values decreased as the number of classes increased, with all entropy values exceeding 0.80. However, both the VLMR and LMR tests were non-significant for the five-class model ($P > 0.05$), which indicates that the four-class model provided a better fit than the five-class solution. Considering model fit, classification accuracy, and clinical interpretability, a four-class model (C1–C4) was selected as the optimal solution. Model fit indices are presented in Table 3.

Interpretation of classes was based on the CIPNAT scores, the intercepts, the slopes, and clinical relevance. In Class 1, CIPNAT scores were low at T1 but increased markedly throughout chemotherapy ($I = 46.451$; $S = 42.495$; $P < 0.001$). This class was labeled the “Worsening CIPN Group” (Group 1, n = 71, 30.5%). In Class 2, baseline scores were low and the rate of increase was minimal ($I = 26.806$; $S = 5.869$; $P < 0.001$), and this class was designated the “Mild Stable CIPN Group” (Group 2, n = 81, 34.8%). In Class 3, CIPNAT scores were high at T1, but showed substantial improvement over time before stabilizing ($I = 112.446$; $S = -16.317$; $P < 0.001$). This class was labeled the “Improving CIPN Group” (Group 3, n = 42, 18.0%). In Class 4, baseline CIPNAT scores were high and remained persistently elevated with minimal change ($I = 132.908$; $S = -0.474$; $P < 0.001$). This class was named the “Severe Stable CIPN Group” (Group 4, n = 39, 16.7%).The four CIPN trajectory patterns are illustrated in Fig. 2.

Table 3
Model selection criteria of the Latent Class Growth Model (LCGM) analysis

Class	AIC	BIC	aBIC	Entropy	VLMR	BLRT	LMR	Class probability
C1	9917.252	9937.959	9918.942	-	-	-		1
C2	9378.297	9409.356	9380.831	0.970	< 0.001	< 0.001	< 0.001	0.51502/ 0.48498
C3	9152.485	9193.898	9155.864	0.992	0.0002	< 0.001	0.0004	0.30472/ 0.34764/0.34764
C4	8960.896	9012.662	8965.119	0.982	< 0.001	< 0.001	< 0.001	0.30472/0.34764/0.18026/0.16738
C5	8933.590	8995.709	8938.657	0.963	0.0927	< 0.001	0.1010	0.34764/0.30472/0.08155/0.12017/0.14592

Predictors of heterogeneous CIPN trajectory

Univariate analysis indicated that eight variables were significantly associated with heterogeneous CIPN trajectories during chemotherapy in patients with gastrointestinal malignancies ($p < 0.05$), including age, smoking history, chronic diseases, chemotherapy regimen, cumulative dose of neurotoxic agents, cancer-related fatigue, physical performance, and self-management efficacy (Table 4).

Multinomial logistic regression was performed using the Mild Stable CIPN Group (C2) as the reference category to identify factors associated with different CIPN trajectory classes (Table 5). Compared with C2, patients in the Worsening CIPN Group (C1) were more likely to report higher levels of fatigue (OR = 3.583, 95% CI: 2.311–5.557, $p < 0.001$) and lower self-management efficacy (OR = 0.969, 95% CI: 0.948–0.991, $p = 0.006$). Younger patients were less likely to be classified into C1 (< 40 years: OR = 0.171, 95% CI: 0.035–0.831, $p = 0.028$; 40–60 years: OR = 0.155, 95% CI: 0.038–0.630, $p = 0.010$). This finding indicates that older individuals have a higher likelihood of symptom worsening. Additionally, compared with current smokers, the likelihood of being classified into C1 was significantly lower among never smokers (OR = 0.091, 95% CI: 0.018–0.453, $p = 0.003$). Patients with fewer chronic conditions (0–1 condition: OR = 0.005, 95% CI: 0.001–0.048, $p = 0.002$; 2–3 conditions: OR = 0.095, 95% CI: 0.021–0.433, $p = 0.002$) and those with lower standardized cumulative neurotoxic doses (≤ 1 mg/m²: OR = 0.176, 95% CI: 0.033–0.940, $p = 0.042$) were also less likely to be classified into C1. Furthermore, compared with patients receiving platinum–taxane combination therapy, those treated with platinum alone were associated with a substantially lower probability of experiencing worsening CIPN symptoms (OR = 0.066, 95% CI: 0.012–0.352, $p = 0.001$).

In the Improving CIPN Group (C3), better physical performance (OR = 1.216, 95% CI: 1.048–1.411, $p = 0.010$) and higher self-efficacy in self-management (OR = 1.013, 95% CI: 1.000-1.025, $p = 0.046$) were positively associated with symptom improvement.

In the Severe Stable CIPN Group (C4), higher levels of cancer-related fatigue (OR = 1.937, 95% CI: 1.322–2.838, $p < 0.001$) were associated with an increased likelihood of remaining in the persistently severe trajectory. Additionally, poorer physical performance (OR = 0.828, 95% CI: 0.703–0.974, $p = 0.023$) and lower self-efficacy in self-management (OR = 0.967, 95% CI: 0.950–0.986, $p < 0.001$) were also linked to this increased likelihood. Compared with patients who had ≥ 4 chronic conditions, those with 0–1 chronic condition (OR = 0.069, 95% CI: 0.013–0.354, $p = 0.001$) or 2–3 chronic conditions (OR = 0.147, 95% CI: 0.034–0.630, $p = 0.010$) were significantly less likely to be classified in the C4 group. Additionally, relative to patients receiving platinum-taxane combination therapy as reference, those treated with platinum alone had a reduced probability of belonging to the Severe Stable trajectory (OR = 0.098, 95% CI: 0.022–0.431, $p = 0.002$).To ensure transparency, the full model results are provided in Supplementary Table 1.

Table 4
Univariate analysis of predictive factors for heterogeneous CIPN trajectories (n = 233)

Variables	C1 (n = 71)	C2 (n = 81)	C3 (n = 42)	C4 (n = 39)	X^2/F	P
Age (year)					27.891[1)]	< 0.001
< 40	9(12.68)	22(27.16)	12(28.57)	8(20.51)		
40–60	15(21.13)	34(41.98)	17(40.48)	20(51.28)		
> 60	47(66.20)	25(30.86)	13(30.952)	11(28.21)		
Gender					5.667[1)]	0.132
Male	38(53.52)	49(60.49)	29(69.05)	29(74.36)		
Female	33(46.48)	32(39.501)	13(30.95)	10(25.64)		
BMI(kg/m2)					10.209[1)]	0.116
< 18.5	36(50.70)	35(43.21)	14(33.33)	20(51.28)		
18.5–23.9	26(36.62)	24(29.63)	21(50.00)	13(33.33)		
> 24	9(12.68)	22(27.16)	7(16.67)	6(15.38)		
Educational Levels					3.176[1)]	0.792
Primary education	32(45.07)	38(46.91)	19(45.24)	17(43.59)		
Secondary education	31(43.66)	28(34.57)	14(33.33)	15(38.46)		
Higher education	8(11.27)	15(18.52)	9(21.43)	7(17.95)		
Marital status					2.540[3)]	0.474
Divorced/widowed	6(8.45)	9(11.11)	6(14.29)	7(17.95)		
Married	65(91.55)	72(88.89)	36(85.71)	32(82.05)		
Smoking History					24.399[1)]	< 0.001
Never smoked	9(12.68)	38(46.91)	18(42.86)	13(33.33)		
Former smoker	35(49.30)	29(35.80)	16(38.10)	18(46.15)		
Current smoker	27(38.03)	14(17.28)	8(19.05)	8(20.51)		
Chronic Diseases					59.674[1)]	< 0.001
0–1 type	7(9.86)	33(40.74)	20(47.62)	8(20.51)		
2–3 types	27(38.03)	43(53.09)	19(45.2)	17(43.59)		
≥ 4 types	37(52.11)	5(6.17)	3(7.14)	14(35.90)		
Tumor Types					4.708[1)]	0.588
Upper gastrointestinal cancer	32(45.07)	46(56.79)	26(61.90)	19(48.72)		
Lower gastrointestinal cancer	25(35.21)	25(30.86)	12(28.57)	14(35.90)		
Other gastrointestinal malignancies	14(19.72)	10(12.35)	4(9.52)	6(15.38)		
Stage					7.112[1)]	0.069
Stage I- II	15(21.12)	30(37.04)	18(42.86)	14(35.90)		

Footnotes: 1) X^2= chi-square test; 2) F = one-way ANOVA; 3) Fisher = Fisher's exact test.

Variables	C1 (n = 71)	C2 (n = 81)	C3 (n = 42)	C4 (n = 39)	X^2/F	P
Stage III- IV	56(78.87)	51(62.96)	24(57.14)	25(64.10)		
Concurrent or Previous Surgery / Radiotherapy					2.139[1)]	0.555
No	15(21.13)	24(29.63)	9(21.43)	8(20.51)		
Yes	56(78.87)	57(70.37)	33(78.57)	31(79.49)		
Metastasis					1.637[1)]	0.657
No	23(32.39)	20(24.69)	10(23.81)	12(30.77)		
Yes	48(67.61)	61(75.31)	32(76.19)	27(69.23)		
Chemotherapy Regimen					28.055[1)]	0.001
Platinum-based	19(26.76)	43(53.09)	21(50.00)	10(25.64)		
Taxane-based	19(26.76)	25(30.86)	14(33.33)	12(30.77)		
Others	14(19.72)	4(4.94)	3(7.14)	5(12.82)		
Platinum + taxane	19(26.76)	9(11.11)	4(9.52)	12(30.77)		
Standardized Cumulative Dose of Neurotoxic Agents					20.594[1)]	< 0.001
≤ 1	7(9.86)	31(38.27)	13(30.95)	5(12.82)		
> 1	64(90.14)	50(61.73)	29(69.05)	34(87.18)		
RPFS,mean (SD)	5.79 ± 2.03	3.35 ± 1.10	3.29 ± 0.97	4.26 ± 1.60	39.747[2)]	< 0.001
SPPB,mean (SD)	5.30 ± 2.302	7.17 ± 3.197	8.76 ± 2.555	5.18 ± 3.119	17.637[2)]	< 0.001
SUPPH,mean (SD)	61.55 ± 20.613	83.16 ± 33.099	95.45 ± 35.069	60.74 ± 21.496	18.009[2)]	< 0.001

Footnotes: 1) X^2= chi-square test; 2) F = one-way ANOVA; 3) Fisher = Fisher's exact test.

Table 5
Multivariate analysis of predictors for heterogeneous CIPN trajectories

	B	S.E.	Wald X^2	p-value	OR	95%CI	
						Lower limit	Upper limit
C1 vs C2							
Constants	3.880	1.650	5.532	0.019			
RPFS	1.276	0.224	32.512	< 0.001	3.583	2.311	5.557
SUPPH	-0.031	0.011	7.669	0.006	0.969	0.948	0.991
Age (year):<40	-1.764	0.805	4.799	0.028	0.171	0.035	0.831
40–60	-1.866	0.716	6.789	0.009	0.155	0.038	0.630
Smoking History:Never smoked	-2.395	0.818	8.579	0.003	0.091	0.018	0.453
Chronic Diseases:0–1 type	-5.231	1.124	21.652	< 0.001	0.005	0.001	0.048
2–3 types	-2.351	0.773	9.253	0.002	0.095	0.021	0.433
Chemotherapy Regimen:Platinum-based	-2.724	0.858	10.088	0.001	0.066	0.012	0.352
Standardized Cumulative Dose of Neurotoxic Agents:≤1	-1.737	0.855	4.128	0.042	0.176	0.033	0.940
C3 vs C2							
Constants	-2.668	1.376	3.761	0.052			
SPPB	0.196	0.076	6.637	0.010	1.216	1.048	1.411
SUPPH	0.012	0.006	3.972	0.046	1.013	1.000	1.025
C4 vs C2							
Constants	3.926	1.463	7.197	0.007			
RPFS	0.661	0.195	11.519	0.001	1.937	1.322	2.838
SPPB	-0.189	0.083	5.188	0.023	0.828	0.703	0.974
SUPPH	-0.034	0.01	10.935	0.001	0.967	0.948	0.986
Chronic Diseases:0–1 type	-2.68	0.837	10.246	0.001	0.069	0.013	0.354
2–3 types	-1.917	0.742	6.667	0.010	0.147	0.034	0.630
Chemotherapy Regimen:Platinum-based	-2.319	0.754	9.455	0.002	0.098	0.022	0.431

C1: Worsening CIPN group; C2: Mild Stable CIPN group; C3: Improving CIPN group; C4: Severe Stable CIPN group. Reference group: C2.

Reference categories: Age > 60 years; Smoking History: Current smoker; Chronic Diseases: ≥4; Chemotherapy Regimen: platinum + taxane; Standardized Cumulative Dose of Neurotoxic Agents: >1.

Discussion

This study demonstrated marked heterogeneity in CIPN symptom trajectories among patients with gastrointestinal malignancies undergoing chemotherapy, identifying four distinct patterns: the Worsening CIPN Group, Mild Stable CIPN Group, Improving CIPN Group, and Severe Stable CIPN Group. Accurate characterization of these trajectories is essential for symptom management and prognosis, as they reflect not only the dynamic progression and individual variability of CIPN, but also the associations of these symptom trajectories with chemotherapy tolerance, decline in quality of life, and risk of treatment interruption.Importantly, the study further identified age, smoking history, chronic conditions, chemotherapy regimen, standardized cumulative neurotoxic dose, cancer-related fatigue, physical performance, and self-management efficacy as independent predictors of CIPN trajectory membership. These findings elucidate the temporal patterns and interindividual differences in CIPN during chemotherapy and highlight the multifactorial determinants underlying its heterogeneity. Moreover, they underscore the importance of early identification and individualized management strategies for CIPN.By delineating distinct CIPN trajectories, this study provides a scientific foundation for developing more targeted clinical interventions.

Effective stratified approaches may help reduce neurotoxic burden during chemotherapy and ultimately enhance treatment tolerance, functional status, and overall quality of life.

This study identified significant heterogeneity in CIPN symptom trajectories among patients with gastrointestinal malignancies undergoing chemotherapy, which could be categorized into four distinct patterns. The number of trajectory classes identified was consistent with the number reported by Wang et al.[18], but exceeded the number found in the CIPN trajectory study of breast cancer patients by Xu et al.[19]. These differences may be attributable to variations in tumor types, chemotherapy regimens, and levels of exposure to neurotoxic agents; as well as differences in sample size, follow-up intervals, and the sensitivity of measurement tools. Collectively, these findings reinforce that CIPN progression is neither linear nor uniform across individuals; instead, patients exhibit divergent pathways of symptom trajectories and recovery, underscoring the need for stratified and dynamic monitoring throughout rehabilitation and follow-up.

In this study, the Worsening CIPN Group (30.5%) and the Mild Stable CIPN Group (34.8%) accounted for the largest proportions among the four identified trajectories. This indicates that nearly one-third of patients undergoing chemotherapy followed a pattern of progressively worsening symptoms, whereas another one-third maintained mild and relatively stable symptom levels. These findings highlight the marked heterogeneity in CIPN progression. Not all patients experience rapid symptom escalation, and some remain at a low or stable level throughout treatment. Teng et al.[14]reported that CIPN prevalence decreased by approximately 28% annually during the first three years after chemotherapy, indicating a gradual decline. Such evidence suggests that with neurological support and functional interventions, symptom stabilization may occur in some patients as treatment progresses. However, in the present study, approximately 30.5% of patients showed a clear trajectory of worsening CIPN. Although some research indicates that CIPN may gradually diminish over time, long-term clinical studies have shown that symptoms can persist beyond 12 months and may be more common and severe than previously expected[8,37]. Several factors may contribute to a worsening trajectory. First, variability in pretreatment status, chemotherapy regimens, pre-existing neuropathy, or metabolic conditions—such as diabetes, nutritional status, vitamin D levels, and physical function—can influence tolerance to neurotoxic exposure[19]. Second, early or subclinical abnormalities in nerve function may predispose patients to greater symptom progression. Lower compound muscle action potential (CMAP) or sensory nerve action potential (SNAP) values before chemotherapy have been shown to predict more severe symptoms during and after treatment[25]. Third, inflammatory profiles, such as elevated IFN-γ and reduced IL-10 levels before chemotherapy, have been linked to CIPN exacerbation[2]These results underscore the clinical importance of CIPN trajectory classification. Rather than focusing solely on the presence of CIPN, greater emphasis should be placed on its developmental pattern. For patients in the Worsening CIPN Group, early identification of high-risk factors and implementation of individualized neuroprotective and functional interventions are warranted. For those in the Mild Stable CIPN Group, although symptoms remain mild and stable, continued monitoring and preventive care are recommended, as stability may shift with time or cumulative neurotoxic exposure.

In this study, the Improving CIPN Group represented patients whose CIPN symptoms gradually alleviated after the onset of symptoms during chemotherapy, accounting for 18.0% of the sample. Therefore, this proportion suggests that symptom improvement during chemotherapy is relatively uncommon among patients with gastrointestinal malignancies. Notably, patients in this group exhibited high CIPN scores at T1, followed by a steady decline during subsequent assessments. The elevated T1 score may reflect acute neurotoxic reactions during the early phase of chemotherapy, and the subsequent improvement could be associated with adjunctive pharmacological interventions, such as anticonvulsants or antidepressants[38], or psychological adaptation mechanisms[39].Prior evidence from Teng[14], and Lemanska[4] have described neurotoxicity as comprising acute and chronic forms. Approximately 90% of patients receiving platinum-based therapy experience acute neuropathy that peaks within the first three days after infusion and typically resolves within one week; this acute phase is characterized primarily by cold-induced distal sensory disturbances such as paresthesia and dysesthesia. In contrast, patients in the Severe Stable CIPN Group demonstrated persistently moderate-to-severe symptoms with little evidence of improvement or recovery. This trajectory suggests that CIPN may evolve into a long-term residual condition in a subset of patients. For example, in a colorectal cancer FOLFOX cohort, 36.5% of patients continued to report severe neuropathic pain five years after treatment, with minimal symptom resolution[13]. Persistent CIPN severity—associated with adverse outcomes such as functional impairment and increased fall risk[15], indicates that these patients may require more intensive, individualized symptom management strategies. Moreover, long-lasting CIPN has been shown to substantially increase annual healthcare costs[40], and negatively affect disease control and treatment adherence[13]. These findings underscore the need for early identification and proactive intervention to mitigate both clinical and economic burdens associated with chronic CIPN.

This study identified age, smoking history, chronic conditions, chemotherapy regimen, standardized cumulative neurotoxic doses, cancer-related fatigue, physical performance, and self-management efficacy as independent predictors of heterogeneous CIPN trajectories among patients with gastrointestinal malignancies undergoing chemotherapy. These findings provide an empirical foundation for developing targeted clinical intervention strategies. First, patients aged ≤ 60 years had a lower likelihood of belonging to the Worsening CIPN Group

(C1) than those older than 60 years, suggesting that CIPN worsens with increasing age. This observation is consistent with prior research indicating that patients over 65 years who receive neurotoxic agents—such as platinum compounds, taxanes, and vinca alkaloids, which

are at higher risk for more severe CIPN[22]Aging is associated with a variety of peripheral-nerve changes, including slower nerve conduction velocity and increased sensory fibres with signs of damage or degeneration; this may put older patients at increased risk for developing CIPN[41].However, the relationship between age and CIPN severity remains inconclusive in the literature. Some studies have reported no significant differences in the incidence or severity of CIPN between patients ≥ 65 years and their younger counterparts, suggesting that age may not serve as an isolated predictor but rather interacts with other factors to influence CIPN progression[23]. Therefore, age should be considered as part of a multidimensional risk framework rather than a single determining factor.

In this study, current smokers were more likely to be classified in the Worsening CIPN Group (C1), suggesting that smoking may be an important risk factor for CIPN progression. Previous research has also reported a positive association between smoking and the development of CIPN[13]. Mechanistically, nicotine and other harmful constituents of tobacco smoke can induce peripheral vasoconstriction, reducing blood flow to nerve tissues. This reduction impairs neuronal repair capacity following chemotherapy-induced injury[42]. In addition, smoking may increase oxidative stress and disrupt neurotrophic support systems, making peripheral nerves more susceptible to neurotoxic damage. These findings underscore the importance of smoking cessation guidance for patients undergoing chemotherapy. Enhanced monitoring of CIPN symptoms, such as more frequent neurological assessments and the implementation of targeted neuroprotective interventions should be considered for individuals who continue to smoke, with the aim of reducing the risk of symptom progression.

In this study, patients with a greater number of chronic conditions were more likely to belong to either the Worsening CIPN Group (C1) or the Severe Stable CIPN Group (C4), suggesting that a higher comorbidity burden may increase the risk of CIPN. Johnson et al.[43]noted that metabolic comorbidities such as diabetes[10] and obesity[44]can trigger chronic low-grade inflammation and oxidative stress, impair mitochondrial function, and exacerbate microvascular neuropathic changes. Hypertension may contribute to inadequate perfusion and ischemia–reperfusion injury, thereby promoting axonal degeneration and demyelination[45]. Moreover, multimorbidity is frequently accompanied by polypharmacy and altered drug metabolism, which may increase effective neurotoxic exposure and cumulative nerve damage. This, in turn, increases patients' likelihood of entering the "worsening" or "severe stable" trajectories (C1 or C4).

This study found that patients receiving a combined platinum–paclitaxel regimen were more likely to follow the worsening CIPN (C1) or the severe stable CIPN (C4) trajectory, suggesting that concurrent exposure to two highly neurotoxic agents within the same treatment course may amplify cumulative peripheral nerve injury. A large-scale study by Argyriou et al.[23], involving 500 cancer patients, similarly reported an increased risk of CIPN with platinum–paclitaxel combination therapy. These findings are consistent with the present study.Platinum-based chemotherapeutic agents are associated with the highest CIPN prevalence, affecting approximately 70% of patients. Their primary anatomical target is the dorsal root ganglia, where these agents disrupt ion channel function, induce mitochondrial damage, and promote neuroinflammation, leading to cold allodynia and distal sensory axonopathy[17,46]. Moreover, Studies have identified an increase in the incidence of abnormal axonal mitochondria in C-fibres when compared to controls after ~ 1 month of paclitaxel treatment[47]. Paclitaxel interacts with the mitochondrial permeability transition pore, leading to mitochondrial dysfunction, decreased mitochondrial respiration and disruption of neuronal ATP generation, with disruption of the axonal microtubule network[17,48]. When administered together, these agents exert synergistic neurotoxic effects, making recovery from axonal degeneration and repair of myelin more difficult.

This study found that patients with a standardized cumulative neurotoxic drug dose > 1 unit were more likely to follow the Worsening CIPN trajectory, indicating that cumulative neurotoxic exposure is an important driver of progressive CIPN phenotypes. Clinically, cumulative oxaliplatin dose has been strongly associated with long-term CIPN; patients receiving ≥ 842 mg/m² of oxaliplatin are more likely to report toe and foot paresthesia[8]. Similarly, the incidence of paclitaxel, induced CIPN has been shown to increase markedly when cumulative doses approach 1,000 mg/m²[7]Therefore, these findings suggest that standardized cumulative dose monitoring should be incorporated into routine practice as an early warning indicator. In such cases, proactive measures, such as dose adjustments, regimen modifications, or treatment delays should be actively implemented to prevent CIPN trajectories from shifting toward worsening patterns.

This study found that higher levels of cancer-related fatigue were associated with an increased likelihood of belonging to the Worsening CIPN (C1) and Severe Stable CIPN (C4) trajectories. This suggests that fatigue is not merely a co-occurring symptom during chemotherapy but may also contribute to the progression and persistence of CIPN. Longitudinal evidence has shown that elevated fatigue prior to chemotherapy predicts more severe subsequent CIPN[2,27]. Cancer-related fatigue has been closely linked to chronic low-grade inflammation and oxidative stress. These factors can disrupt hypothalamic–pituitary–adrenal axis function, impair mitochondrial bioenergetics, and alter sensory nerve metabolism. Consequently, this reduces the nervous system's capacity for recovery following

chemotherapy-induced injury and increases the susceptibility of both peripheral and central nerves to neurotoxic insults[27]Furthermore, cancer-related fatigue is often accompanied by reduced physical activity and sleep disturbances[44], both of which may exacerbate neuroinflammatory cascades and pain sensitization. These findings highlight the importance of incorporating repeated fatigue monitoring into clinical management alongside routine assessments of neurotoxicity.

This study further found that patients with higher physical performance and greater self-efficacy in self-management were more likely to belong to the Improving CIPN Group (C3), whereas those with lower physical performance and reduced self-efficacy in self-management tended to fall into the Severe Stable CIPN Group (C4). Taken together, these findings suggest that patients' "functional reserve" and "self-regulatory capacity" may serve as important protective factors against CIPN progression. The Short Physical Performance Battery (SPPB) is a well-established tool for assessing lower-extremity function and physical reserve[32]. In this study, higher SPPB scores likely reflected greater muscle strength. This muscle strength may support peripheral nerve perfusion and improve the local metabolic microenvironment through regular muscle activity, thereby mitigating neurotoxic injury[49]Conversely, lower SPPB scores often indicate muscle weakness, gait instability, and reduced mobility, all of which may contribute to impaired peripheral perfusion and delayed neural repair, increasing the likelihood of persistent CIPN. Prior studies have similarly shown that higher levels of physical activity are significantly associated with reduced CIPN risk, as regular physical activity can activate antioxidant pathways and enhance neurotrophic factor expression, thereby improving neural function[45]. Better baseline physical performance has also been found to predict improvement in CIPN symptoms during chemotherapy[21]. These findings underscore the importance of routinely assessing SPPB scores during chemotherapy and implementing early exercise-based rehabilitation interventions for patients with lower physical performance.

Prior studies have shown that higher levels of self-efficacy in self-management during cancer treatment are closely associated with better quality of life, improved functional maintenance, and fewer complications [28]. This study further demonstrated that greater self-efficacy in self-management was linked to reduced cumulative neurotoxic effects and enhanced functional recovery[50]. From a physiological perspective, patients with higher self-efficacy often engage in more active health behaviors, which may improve endothelial function, enhance mitochondrial antioxidant capacity, and reduce chronic inflammation, thereby mitigating oxidative damage—a major contributor to neurotoxicity—to peripheral nerves caused by chemotherapy[51]. From a psychological standpoint, patients with higher self-efficacy tend to exhibit stronger perceived control and greater initiative in managing adverse effects of chemotherapy. They are more likely to monitor symptoms in a timely manner, seek appropriate support, and maintain treatment adherence[52]. Conversely, individuals with low self-efficacy often lack engagement in health-promoting behaviors and may delay symptom reporting, contributing to the accumulation of neurotoxic injury and limited recovery. These findings highlight the importance of incorporating physical function assessment and self-efficacy in self-management into CIPN risk screening. Moreover, early initiation of exercise-based rehabilitation, self-management education, and supportive interventions should be considered for patients with low physical performance or inadequate self-efficacy during chemotherapy.

Limitations

Despite the valuable insights provided by this study, several limitations should be acknowledged. First, this was a single-center cohort study conducted in mainland China, which may limit the generalizability of the findings. The demographic characteristics and treatment practices of patients in this institution may not fully represent those in other regions or healthcare systems. Future multicenter studies involving diverse populations are warranted to enhance the external validity and applicability of the results. Second, the assessment of chemotherapy-induced peripheral neurotoxicity (CIPN) primarily relied on patient-reported outcome measures, such as symptom questionnaires and self-rated scales. Although these tools are widely used and validated, they are subject to subjective reporting bias, as patients may underreport or overreport their sensory symptoms depending on their perception, tolerance, or psychological status. Combining patient-reported measures with objective clinical or electrophysiological evaluations in future research could provide a more comprehensive assessment of CIPN trajectories. Finally, while several demographic, clinical, and treatment-related variables were included in the model, other important factors, such as genetic susceptibility, nutritional status, and sleep quality were not assessed. These unmeasured confounders may influence the development and progression of peripheral neurotoxicity. Future prospective studies incorporating biological markers and multidimensional data are needed to further clarify the mechanisms and predictors underlying heterogeneous CIPN trajectories in gastrointestinal cancer patients.

Conclusion

This study identified distinct heterogeneous trajectories and predictors of chemotherapy-induced peripheral neurotoxicity (CIPN) among patients with gastrointestinal malignancies during chemotherapy. The findings highlight the importance of continuous monitoring and individualized management of CIPN throughout the treatment course. Specifically, age, smoking history, number of chronic conditions; chemotherapy regimen; cumulative neurotoxic drug dose; cancer-related fatigue; physical performance; and self-management efficacy

were found to play critical roles in shaping CIPN trajectories. Moreover, recognizing and managing these factors early in the treatment process may support the development of more effective intervention strategies. These strategies aim to reduce neurotoxic burden and improve treatment tolerance and quality of life, both in future research and clinical practice.

Declarations

Ethics approval and consent to participate

Our research was guided by the Declaration of Helsinki for ethical standards. This study was reviewed and approved by the centralized ethics committee of Fujian Cancer hospital(K2024-117-01). Informed consent was obtained from all participants included in the study and they could withdraw from the study at any time for any reason. Moreover, they were assured that the questionnaires would only be used for research.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical Trial Number

Not applicable

Funding

This research was supported by the Fujian Provincial Traditional Chinese Medicine Science and Technology Project Foundation (NO. 2025YBB016), the University-Administered Project of Fujian University of Traditional Chinese Medicine (NO. XB2024191), Nursing Sciences Foundation of Fujian Cancer Hospital(NO: 2024YN12).

Author Contribution

HZ contributed to the conceptualization, investigation, formal analysis, and writing – original draft. YP, QC and ML contributed to the investigation, methodology, and formal analysis. YZ, WH and LJ contributed to the investigation and formal analysis. QC contributed to the conceptualization, supervision, and writing – review & editing. All authors gave final approval and agree to be accountable for all aspects of the work to ensure its integrity and accuracy

Acknowledgement

The authors are grateful to the patients with gastrointestinal tumors who participated in this study, and also to the health providers for their strong support in sample collection.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and ethical restrictions, but are available from the corresponding author upon reasonable request.

References

1. Park, S. B. et al. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. *CA Cancer J. Clin.* **63**, 419–437. 10.3322/caac.21204 (2013).
2. Kleckner, I. R. et al. Longitudinal study of inflammatory, behavioral, clinical, and psychosocial risk factors for chemotherapy-induced peripheral neuropathy. *Breast Cancer Res. Treat.* **189**, 521–532. 10.1007/s10549-021-06304-6 (2021).

3. Cavaletti, G. & Marmiroli, P. Management of Oxaliplatin-Induced Peripheral Sensory Neuropathy. *Cancers (Basel)*. **12** 10.3390/cancers12061370 (2020).
4. Lemanska, A. et al. The association of clinical and patient factors with chemotherapy-induced peripheral neuropathy (CIPN) in colorectal cancer: secondary analysis of the SCOT trial. *ESMO Open.* **8**, 102063. 10.1016/j.esmoop.2023.102063 (2023).
5. Boyette-Davis, J. A., Walters, E. T. & Dougherty, P. M. Mechanisms involved in the development of chemotherapy-induced neuropathy. *Pain Manag*. **5**, 285–296. 10.2217/pmt.15.19 (2015).
6. Tao, Z., Chen, Z., Zeng, X., Cui, J. & Quan, M. An emerging aspect of cancer neuroscience: A literature review on chemotherapy-induced peripheral neuropathy. *Cancer Lett.* **611**, 217433. 10.1016/j.canlet.2024.217433 (2024).
7. Wu, S. et al. An up-to-date view of paclitaxel-induced peripheral neuropathy. *J. Cancer Res. Ther.* **19**, 1501–1508. 10.4103/jcrt.jcrt_1982_22 (2023).
8. Beijers, A. J. et al. Peripheral neuropathy in colorectal cancer survivors: the influence of oxaliplatin administration. Results from the population-based PROFILES registry. *Acta Oncol.* **54**, 463–469. 10.3109/0284186x.2014.980912 (2015).
9. Ewertz, M., Qvortrup, C. & Eckhoff, L. Chemotherapy-induced peripheral neuropathy in patients treated with taxanes and platinum derivatives. *Acta Oncol.* **54**, 587–591. 10.3109/0284186x.2014.995775 (2015).
10. Gu, J. et al. Diabetes mellitus as a risk factor for chemotherapy-induced peripheral neuropathy: a meta-analysis. *Support Care Cancer*. **29**, 7461–7469. 10.1007/s00520-021-06321-7 (2021).
11. Staff, N. P., Grisold, A., Grisold, W. & Windebank, A. J. Chemotherapy-induced peripheral neuropathy: A current review. *Ann. Neurol.* **81**, 772–781. 10.1002/ana.24951 (2017).
12. Dault, R. et al. Impact of oxaliplatin-induced neuropathy in patients with colorectal cancer: a prospective evaluation at a single institution. *Curr. Oncol.* **23**, e65–69. 10.3747/co.23.2780 (2016).
13. Selvy, M. et al. Long-Term Prevalence of Sensory Chemotherapy-Induced Peripheral Neuropathy for 5 Years after Adjuvant FOLFOX Chemotherapy to Treat Colorectal Cancer: A Multicenter Cross-Sectional Study. *J. Clin. Med.* **9** 10.3390/jcm9082400 (2020).
14. Teng, C., Cohen, J., Egger, S., Blinman, P. L. & Vardy, J. L. Systematic review of long-term chemotherapy-induced peripheral neuropathy (CIPN) following adjuvant oxaliplatin for colorectal cancer. *Support Care Cancer*. **30**, 33–47. 10.1007/s00520-021-06502-4 (2022).
15. Kolb, N. A. et al. The Association of Chemotherapy-Induced Peripheral Neuropathy Symptoms and the Risk of Falling. *JAMA Neurol.* **73**, 860–866. 10.1001/jamaneurol.2016.0383 (2016).
16. van den Bent, M. J., van Putten, W. L., Hilkens, P. H., de Wit, R. & van der Burg, M. E. Retreatment with dose-dense weekly cisplatin after previous cisplatin chemotherapy is not complicated by significant neuro-toxicity. *Eur. J. Cancer*. **38**, 387–391. 10.1016/s0959-8049(01)00381-1 (2002).
17. Burgess, J. et al. Chemotherapy-Induced Peripheral Neuropathy: Epidemiology, Pathomechanisms and Treatment. *Oncol. Ther.* **9**, 385–450. 10.1007/s40487-021-00168-y (2021).
18. Wang, M. et al. Redefining chemotherapy-induced peripheral neuropathy through symptom cluster analysis and patient-reported outcome data over time. *BMC Cancer*. **19**, 1151. 10.1186/s12885-019-6352-3 (2019).
19. Xu, H. et al. Trajectory of Chemotherapy-Induced Peripheral Neuropathy and Its Predictive Factors in Breast Cancer Patients: A Prospective Longitudinal Study. *Clin. Breast Cancer*. 10.1016/j.clbc.2025.08.002 (2025).
20. Herle, M. et al. Identifying typical trajectories in longitudinal data: modelling strategies and interpretations. *Eur. J. Epidemiol.* **35**, 205–222. 10.1007/s10654-020-00615-6 (2020).
21. Srivastava, S. P., Sinha, A. P., Sharma, K. K., Malik, P. S. & Severity Risk Factors and Quality of Life of Patients associated with Chemotherapy-Induced Peripheral Neuropathy. *Clin. Nurs. Res.* **31**, 1080–1090. 10.1177/10547738221085613 (2022).
22. Raphael, M. J. et al. Neurotoxicity Outcomes in a Population-based Cohort of Elderly Patients Treated With Adjuvant Oxaliplatin for Colorectal Cancer. *Clin. Colorectal Cancer*. **16**, 397–404e391. 10.1016/j.clcc.2017.03.013 (2017).
23. Argyriou, A. A. et al. Is advanced age associated with increased incidence and severity of chemotherapy-induced peripheral neuropathy? *Support Care Cancer*. **14**, 223–229. 10.1007/s00520-005-0868-6 (2006).
24. Molassiotis, A. et al. Are we mis-estimating chemotherapy-induced peripheral neuropathy? Analysis of assessment methodologies from a prospective, multinational, longitudinal cohort study of patients receiving neurotoxic chemotherapy. *BMC Cancer*. **19**, 132. 10.1186/s12885-019-5302-4 (2019).
25. Müller, J. et al. Chemotherapy-induced peripheral neuropathy: longitudinal analysis of predictors for postural control. *Sci. Rep.* **11**, 2398. 10.1038/s41598-021-81902-4 (2021).

26. Hong, J. S., Tian, J. & Wu, L. H. The influence of chemotherapy-induced neurotoxicity on psychological distress and sleep disturbance in cancer patients. *Curr. Oncol.* **21**, 174–180. 10.3747/co.21.1984 (2014).
27. Bonhof, C. S. et al. Anxiety and depression mediate the association between chemotherapy-induced peripheral neuropathy and fatigue: Results from the population-based PROFILES registry. *Psychooncology* **28**, 1926–1933. 10.1002/pon.5176 (2019).
28. Yin, Y. et al. Self-efficacy and positive coping mediate the relationship between social support and resilience in patients undergoing lung cancer treatment: A cross-sectional study. *Front. Psychol.* **13**, 953491. 10.3389/fpsyg.2022.953491 (2022).
29. Peduzzi, P., Concato, J., Kemper, E., Holford, T. R. & Feinstein, A. R. A simulation study of the number of events per variable in logistic regression analysis. *J. Clin. Epidemiol.* **49**, 1373–1379. 10.1016/s0895-4356(96)00236-3 (1996).
30. Tofthagen, C. S., McMillan, S. C. & Kip, K. E. Development and psychometric evaluation of the chemotherapy-induced peripheral neuropathy assessment tool. *Cancer Nurs.* **34**, E10–20. 10.1097/NCC.0b013e31820251de (2011).
31. Piper, J. Case of Partial Paralysis, Cured by Urtication. *Lond. Med. Phys. J.* **46**, 278–280 (1821).
32. Guralnik, J. M. et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J. Gerontol.* **49**, M85–94. 10.1093/geronj/49.2.m85 (1994).
33. Guralnik, J. M., Ferrucci, L., Simonsick, E. M., Salive, M. E. & Wallace, R. B. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl. J. Med.* **332**, 556–561. 10.1056/nejm199503023320902 (1995).
34. Lev, E. L. & Owen, S. V. A measure of self-care self-efficacy. *Res Nurs Health* 19, 421–429, (1996). 10.1002/(sici)1098-240x(199610)19:5<421::Aid-nur6>3.0.Co;2-s
35. HJ, Q. & CR, Y. Reliability and validity of the Chinese version of the Strategies Used by People to Promote Health (SUPPH) scale in patients with cancer. *Chin. J. Nurs.* **46**, 87–89. 10.3761/j.issn.0254-1769.2011.01.032 (2011). (in Chinese).
36. Tein, J. Y., Coxe, S. & Cham, H. Statistical Power to Detect the Correct Number of Classes in Latent Profile Analysis. *Struct. Equ Model.* **20**, 640–657. 10.1080/10705511.2013.824781 (2013).
37. Vatandoust, S. et al. A descriptive study of persistent oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer. *Support Care Cancer*. **22**, 513–518. 10.1007/s00520-013-2004-3 (2014).
38. Meng, J. et al. Duloxetine, a Balanced Serotonin-Norepinephrine Reuptake Inhibitor, Improves Painful Chemotherapy-Induced Peripheral Neuropathy by Inhibiting Activation of p38 MAPK and NF-κB. *Front. Pharmacol.* **10**, 365. 10.3389/fphar.2019.00365 (2019).
39. Tofthagen, C., Donovan, K. A., Morgan, M. A., Shibata, D. & Yeh, Y. Oxaliplatin-induced peripheral neuropathy's effects on health-related quality of life of colorectal cancer survivors. *Support Care Cancer*. **21**, 3307–3313. 10.1007/s00520-013-1905-5 (2013).
40. Pike, C. T., Birnbaum, H. G., Muehlenbein, C. E., Pohl, G. M. & Natale, R. B. Healthcare costs and workloss burden of patients with chemotherapy-associated peripheral neuropathy in breast, ovarian, head and neck, and nonsmall cell lung cancer. *Chemother Res Pract* 913848, (2012). 10.1155/2012/913848 (2012).
41. Lee, K. T. et al. Chemotherapy-Induced Peripheral Neuropathy (CIPN): A Narrative Review and Proposed Theoretical Model. *Cancers (Basel)*. **16** 10.3390/cancers16142571 (2024).
42. Trendowski, M. R. et al. Chemotherapy-induced peripheral neuropathy in African American cancer survivors: Risk factors and quality of life outcomes. *Cancer Med.* **10**, 8151–8161. 10.1002/cam4.4328 (2021).
43. Johnson, C. et al. Candidate pathway-based genetic association study of platinum and platinum-taxane related toxicity in a cohort of primary lung cancer patients. *J. Neurol. Sci.* **349**, 124–128. 10.1016/j.jns.2014.12.041 (2015).
44. Bao, T. et al. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. *Breast Cancer Res. Treat.* **159**, 327–333. 10.1007/s10549-016-3939-0 (2016).
45. Lixian, S. et al. Risk factors of paclitaxel-induced peripheral neuropathy in patients with breast cancer: a prospective cohort study. *Front. Oncol.* **14**, 1327318. 10.3389/fonc.2024.1327318 (2024).
46. Krøigård, T. et al. Characterization and diagnostic evaluation of chronic polyneuropathies induced by oxaliplatin and docetaxel comparing skin biopsy to quantitative sensory testing and nerve conduction studies. *Eur. J. Neurol.* **21**, 623–629. 10.1111/ene.12353 (2014).
47. Kidd, J. F. et al. Paclitaxel affects cytosolic calcium signals by opening the mitochondrial permeability transition pore. *J. Biol. Chem.* **277**, 6504–6510. 10.1074/jbc.M106802200 (2002).
48. Bae, E. H., Greenwald, M. K. & Schwartz, A. G. Chemotherapy-Induced Peripheral Neuropathy: Mechanisms and Therapeutic Avenues. *Neurotherapeutics* **18**, 2384–2396. 10.1007/s13311-021-01142-2 (2021).
49. Chung, K. H. et al. Mechanisms, Mediators, and Moderators of the Effects of Exercise on Chemotherapy-Induced Peripheral Neuropathy. *Cancers (Basel)*. 14. 10.3390/cancers14051224 (2022).

50. Crichton, M. et al. Non-Pharmacological Self-Management Strategies for Chemotherapy-Induced Peripheral Neuropathy in People with Advanced Cancer: A Systematic Review and Meta-Analysis. *Nutrients* **14** 10.3390/nu14122403 (2022).
51. Huang, Q. et al. Risk factors for low self-care self-efficacy in cancer survivors: Application of latent profile analysis. *Nurs. Open.* **9**, 1805–1814. 10.1002/nop2.926 (2022).
52. White, L. L., Cohen, M. Z., Berger, A. M., Kupzyk, K. A. & Bierman, P. J. Self-Efficacy for Management of Symptoms and Symptom Distress in Adults With Cancer: An Integrative Review. *Oncol. Nurs. Forum*. **46**, 113–128. 10.1188/19.Onf.113-128 (2019).

Figures

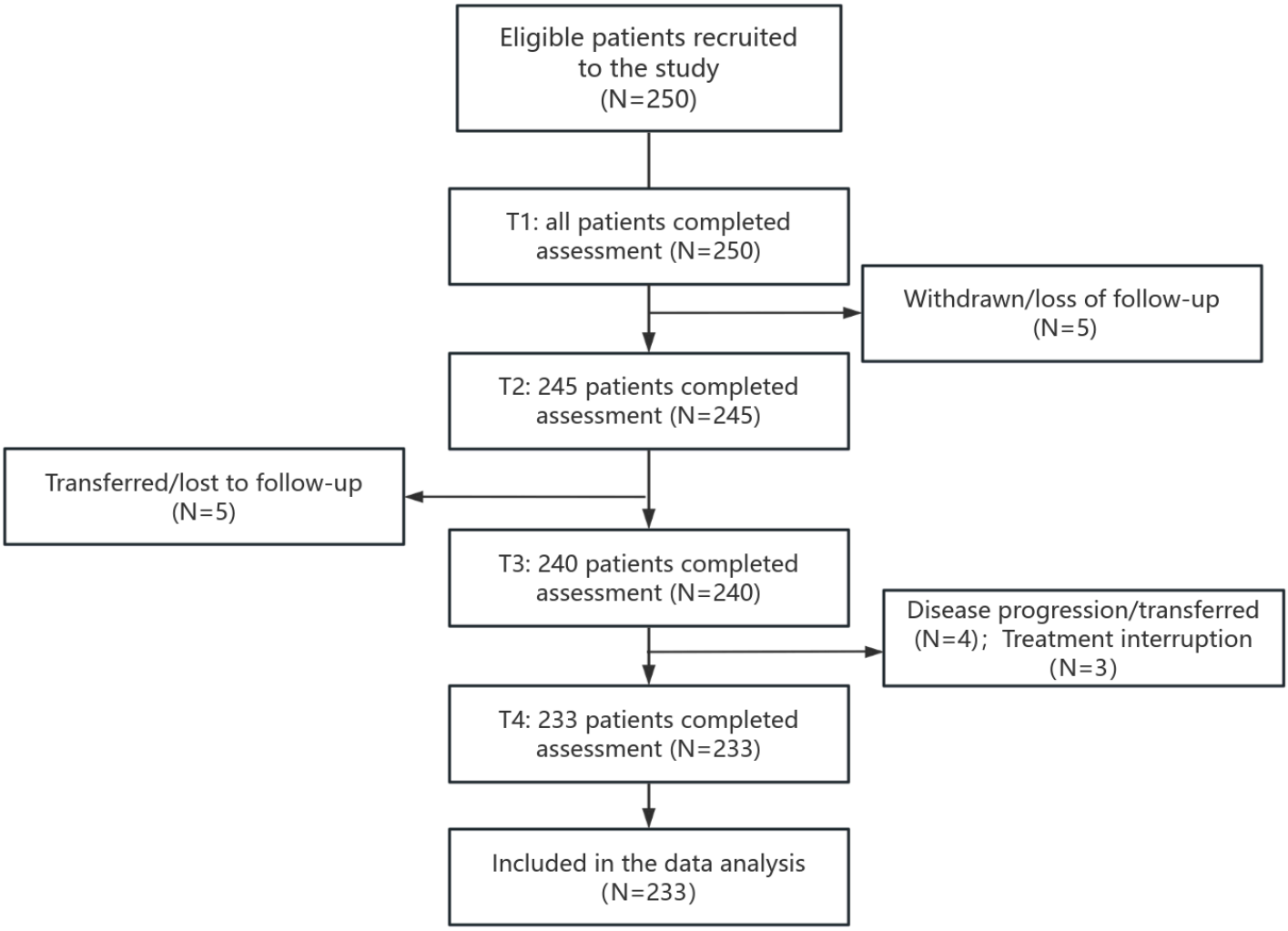


Figure 1

Flow chart summarizing study sample recruitment and inclusion and exclusion for longitudinal data analysis.

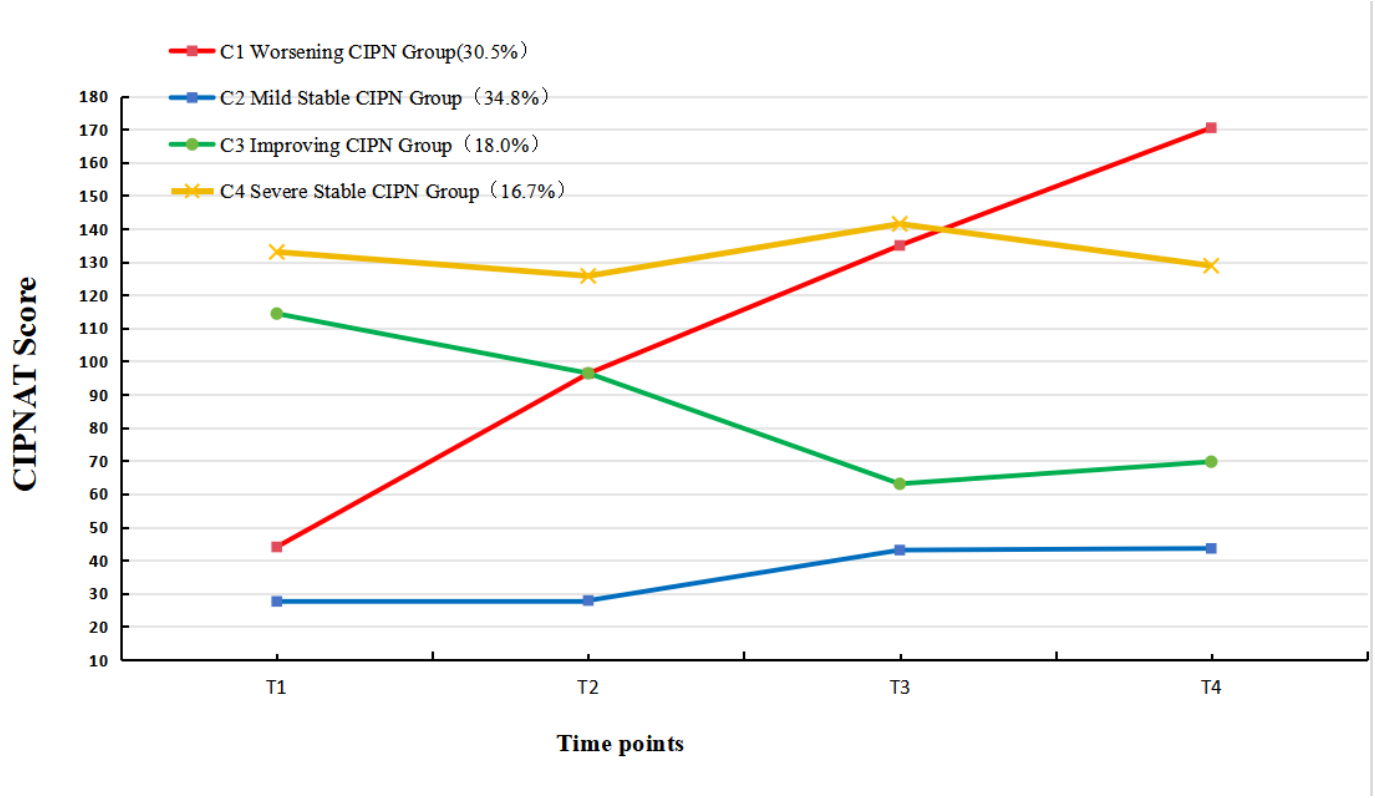


Figure 2

Trajectories of CIPN during chemotherapy in patients with gastrointestinal tumors

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.pdf
- SupplementaryTable1.docx