Article

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The Diagnostic Value of Multimodal Neurophysiological Assessment in Chemotherapy-Induced Peripheral Neuropathy: A Prospective Diagnostic Accuracy Study

Xiaohe Shi[1], Kaixin Li[2], Yinliang Liu[3,*]

[1]Electromyography Department, Hebei Medical University Third Hospital, 050051 Shijiazhuang, Hebei, China
[2]College of Medical Technology, Hebei Medical University, 050031 Shijiazhuang, Hebei, China
[3]Oncology Department, Hebei Medical University Third Hospital, 050051 Shijiazhuang, Hebei, China
*Correspondence: liuyinliang66@163.com (Yinliang Liu)
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Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common and dose-limiting toxicity associated with platinum and taxane based anticancer agents. However, early detection remains challenging due to the lack of objective assessment tools. This study aims to compare the dynamic changes in multimodal neurophysiological parameters before and after chemotherapy, assess the diagnostic value of conventional nerve conduction studies (NCS), sympathetic skin response (SSR), and the N9 wave tibial nerve somatosensory evoked potential (tSEP) in detecting CIPN, and explore the utility of combined testing in identifying subclinical neuropathy.

Methods: Forty cancer patients undergoing platinum - or taxane-based chemotherapy and 40 healthy controls were prospectively enrolled. NCS, SSR, and tSEP were administered before chemotherapy and after its completion, or three weeks following the onset of neurological symptoms. CIPN positivity was defined using a composite endpoint (NCI-CTCAE grade ≥1 combined with electrophysiological deterioration), and subclinical CIPN was characterized as NCI-CTCAE grade 0 with abnormal electrophysiological findings. Changes in parameters before and after chemotherapy were statistically compared. The sensitivity, specificity, and area under the curve (AUC) of each parameter for diagnosing CIPN were calculated. Additionally, the detection rates of different testing strategies for subclinical CIPN were compared.

Results: After chemotherapy, 28 patients (70.0%) met the composite endpoint criteria for CIPN. In addition, 5 patients (12.5%) were classified as having subclinical CIPN. Post-chemotherapy analysis revealed significant declines in the sensory conduction velocity (SCV) and sensory nerve action potential (SNAP) of the medial and lateral plantar nerves, prolongation of SSR latency and reduction of SSR amplitude, as well as a decrease in tSEP N9 wave amplitude (all $p < 0.001$). Individually, upper limb SSR amplitude exhibited the highest diagnostic efficacy (AUC = 0.844, 95% confidence interval (CI): 0.721–0.967), while the medial plantar nerve SCV showed a specificity of 92% (AUC = 0.798). A logistic regression model incorporating these two parameters improved the AUC to 0.881 (95% CI: 0.772–0.990). In an exploratory analysis of five patients with subclinical CIPN, SSR alone detected all cases, while the combination of NCS and SSR also achieved complete detection (McNemar's exact test, $p = 1.00$). However, due to the extremely small sample size, this finding should be interpreted as preliminary and hypothesis-generating, warranting validation in larger studies.

Conclusion: Multimodal neurophysiological assessment effectively delineates the pattern of nerve fiber damage in CIPN. The combination of SSR amplitude and medial plantar nerve SCV shows promising diagnostic performance in an exploratory analysis, but these findings require validation in independent cohorts using a truly independent reference standard.

Keywords: neurophysiological assessment; CIPN; sympathetic skin response; nerve conduction studies

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent, dose-limiting toxicity associated with commonly used antineoplastic agents, including platinum compounds and taxanes. The incidence rates are as high as 73% for platinum-based drugs and 79.1% for taxanes [1,2]. CIPN typically presents as symmetric distal sensory disturbances in the extremities, manifesting as numbness, tingling, burning sensations, and diminished perception of pain and temperature. In some cases, motor or autonomic nerve function may also be affected [3]. These symptoms not only significantly impair the quality of daily life for patients but also frequently lead to the necessity of dose reduction, delay, or even premature discontinuation of chemotherapy, thus compromising anti-tumor efficacy and long-term survival [4,5]. Consequently, the early identification and objective assessment of CIPN are critical for clinical management.

Currently, no universally accepted gold standard exists for the diagnosis of CIPN. Clinical evaluations primarily depend on patient-reported outcome measures and physician-graded scales, such as the NCI-CTCAE. However, studies have shown that most current tools for assessing CIPN possess limited sensitivity and are susceptible to confounding factors, which undermines their ability to provide substantial guidance for clinical interventions [6]. These tools often depend on physician ratings and are predominantly used to document only severe manifestations of the disease [7]. Thus, transitioning from subjective assessments to objective evaluations represents a pivotal step toward precision medicine in the diagnosis and management of CIPN.

Conventional nerve conduction studies (NCS), which quantitatively assess the function of large myelinated sensory and motor nerve fibers, are the cornerstone of electrodiagnostic tools for evaluating peripheral neuropathy [8]. However, NCS are relatively insensitive to thin, myelinated (Aδ) and unmyelinated (C) fibers, which are frequently the initial targets of chemotherapeutic agents [9].

Sympathetic skin response (SSR), by assessing the function of sympathetic sudomotor fibers (unmyelinated C fibers), can provide insights into the integrity of small fibers and the autonomic nervous system [10]. Moreover, the N9 wave of the tibial somatosensory evoked potential (tSEP) offers valuable information on the conduction function of the lumbosacral plexus and proximal sensory nerves. The integration of SSR and tSEP with NCS offers a comprehensive neurophysiological assessment, encompassing both large and small nerve fibers, as well as both distal and proximal segments. In studies of diabetic peripheral neuropathy, the combined use of NCS (assessing large fibers) and SSR (assessing small fibers) has proven to effectively enhance the diagnostic yield for early detection [11]. Despite this, systematic investigations into their combined application in the CIPN context remain limited. This prospective cohort study aims to systematically analyze changes in a range of neurophysiological parameters, including NCS, SSR, and the tSEP N9 wave, before and after chemotherapy in cancer patients. Our objectives are to delineate the pattern of nerve fiber damage in CIPN, assess the diagnostic performance of individual and combined neurophysiological parameters, and explore their utility in the early detection of subclinical CIPN. The ultimate goal of this research is to equip clinicians with a precise and sensitive electrodiagnostic strategy for evaluating CIPN.

Methods

Study Design and Participants

This was a prospective, observational, exploratory diagnostic accuracy study designed to establish the diagnostic value of multimodal neurophysiological parameters in CIPN. Data collection took place at the Hebei Medical University Third Hospital between October 2024 and October 2025.

Patient Group: Forty patients with malignant tumors, scheduled to undergo platinum-based (carboplatin, cisplatin, oxaliplatin) or taxane-based (paclitaxel, docetaxel) chemotherapy regimens for 4-6 cycles, were enrolled. Inclusion criteria included: (1) ages 18–80 years; (2) histopathologically confirmed solid tumors; (3) scheduled to receive the specified chemotherapy regimen with a minimum of four cycles completed; and (4) provision of written informed consent. Exclusion criteria encompassed: (1) pre-existing peripheral neuropathy of a definitive etiology prior to chemotherapy (e.g., clinical symptoms and typical electrophysiological alterations caused by diabetes, alcoholism, vitamin B12 deficiency, and uremia); however, isolated asymptomatic electrophysiological variations such as unilateral absence of lateral plantar nerve sensory nerve action potential (SNAP) with otherwise normal nerve conduction were not grounds for exclusion; (2) severe bleeding tendency or presence of infection/skin lesions at the testing sites; (3) severe concurrent cardiac, pulmonary, hepatic, or renal insufficiency, or psychiatric disorders; and (4) anticipated inability to complete follow-up or expected incomplete data collection. All 40 patients successfully completed the study and all necessary assessments.

Healthy Control Group: Concurrently, 40 age- and sex-matched healthy volunteers with no history of malignancy, peripheral nervous system disorders, or severe systemic diseases were recruited. The control group helped establish reference ranges for certain neurophysiological parameters, such as H-reflex and SSR latencies, and provided a baseline for comparison.

Chemotherapy administration details: cisplatin (75–80 mg/m^2, day 1, q3w), oxaliplatin (85–130 mg/m^2, day 1, q2–3w), paclitaxel (175 mg/m^2, day 1, q3w), and docetaxel (75–100 mg/m^2, day 1, q3w). Combination regimens followed similar schedules with both agents on day 1. All chemotherapeutic agents were administered via intravenous infusion (cisplatin over 2–3 hours, oxaliplatin over 2 hours, paclitaxel over 3 hours, and docetaxel over 1 hour). Clinical data, including demographics, cancer type, chemotherapy details, and comorbidities, were extracted from electronic medical records by a trained research coordinator. Data quality was ensured by double-entry verification and regular auditing by the principal investigator.

The study protocol was approved by the Ethics Committee of the Hebei Medical University Third Hospital (Approval No. W2024-087-1). Participation was contingent upon the provision of written informed consent, and the study adhered to the ethical principles outlined in the Declaration of Helsinki.

Neurophysiological Assessments

All participants in the study group underwent standardized neurophysiological examinations at two time points: prior to the initiation of chemotherapy (T0, measured within one week) and following the completion of all chemotherapy cycles or onset of neurotoxicity symptoms (T1, measured three weeks later). The healthy control group was assessed once at baseline.

Equipment and Conditions

Examinations were conducted using a Nicolet VikingQuest 4-channel electromyography/evoked potential system (Nicolet, USA). The ambient temperature was controlled between 24–26 °C, and the skin temperature for the hand and foot being tested was maintained at no less than 32 °C and 30 °C, respectively. All assessments were conducted on the same side of the body, preferably the non-dominant side, which was typically the left to ensure comparability of pre- and post-chemotherapy data. Patients were examined in a supine and relaxed position. A single, experienced neurophysiology technician, who was unaware of the participants' clinical symptoms (NCI-CTCAE grade) and group allocation (CIPN+/−), performed all assessments. An independent neurologist, also blinded to the participants' clinical statuses, performed the data analysis and interpretation using a single-blind design to reduce bias.

Parameters and Procedures

Conventional Nerve Conduction Studies (NCS). Motor Nerve Conduction: The common peroneal, tibial, median, and ulnar nerves were evaluated. Measurements included motor conduction velocity (MCV) and distal compound muscle action potential (CMAP) amplitude.

Sensory Nerve Conduction: Sensory nerve conduction velocity (SCV) and SNAP amplitude were recorded for the median (digit III and I), ulnar (digit V), superficial peroneal, sural, medial plantar, and lateral plantar nerves using surface electrodes.

All NCS recordings were performed using surface electrodes according to standard international guidelines. For motor nerve conduction studies, the active recording electrode was placed over the muscle belly (median: abductor pollicis brevis, APB; ulnar: abductor digiti minimi; tibial: abductor hallucis, AH; common peroneal: extensor digitorum brevis), with the reference electrode placed 3 cm distally. Stimulation sites were standardized with distances of 8 cm (wrist to APB for median nerve), 10 cm (ankle to AH for tibial nerve), and 6–8 cm for other nerves. Sensory nerve conduction studies were performed with ring electrodes (digits) or surface electrodes (lower limb nerves) using antidromic stimulation. Filter settings were 2 Hz – 10 kHz for both motor and sensory studies, with a stimulation frequency of 1 Hz. Stimulus intensity was supramaximal, defined as 20–30% above the level required to elicit a maximal response.

Sympathetic Skin Response (SSR). Surface recording electrodes were placed on the palm and dorsum of the hand (upper limb) and on the sole and dorsum of the foot (lower limb). A single electrical stimulus (intensity 40–60 mA, duration 0.1 ms) was applied to the ipsilateral wrist and ankle. The first reproducible SSR waveform was documented, noting the onset latency and peak-to-peak amplitude. In instances where the waveform was absent, latency was considered unmeasurable, and the amplitude was recorded as zero.

Surface recording electrodes were placed on the palm and dorsum of the hand (upper limb) and on the sole and dorsum of the foot (lower limb), with the active electrode on the palm/sole and the reference on the dorsum. Filter settings were 0.5–100 Hz. A single electrical stimulus (intensity 40–60 mA, duration 0.1 ms) was applied to the ipsilateral wrist (upper limb) or ankle (lower limb). The first reproducible SSR waveform was documented, noting the onset latency and peak-to-peak amplitude.

Tibial Nerve Somatosensory Evoked Potential (tSEP) and H-Reflex. tSEP: The tibial nerve was stimulated at the medial malleolus, with the resultant N9 wave recorded at the popliteal fossa. Both latency and amplitude of the wave were analyzed.

H-Reflex: The response latency for the tibial nerve's H-reflex was measured on the left side using needle electrodes.

For tSEP, the tibial nerve was stimulated at the medial malleolus. The N9 wave was recorded using surface electrodes placed at the popliteal fossa (active) and 5 cm proximal (reference). Filter settings were 5–3000 Hz, with a stimulation frequency of 2.1 Hz. Stimulus intensity was adjusted to produce stable, reproducible waveforms (usually 15–25 mA). For the H-reflex, the tibial nerve was stimulated at the popliteal fossa, and the response was recorded from the soleus muscle using needle electrodes (active on the muscle belly, reference on the Achilles tendon). Filter settings were 2 Hz – 10 kHz, with a stimulus duration of 1 ms and interstimulus interval of 1 s. The latency of the H-wave was measured as the time from stimulus artifact to the onset of the H-response.

Criteria for Defining Abnormal Neurophysiological Parameters. The thresholds for abnormal neurophysiological findings in this study were established by combining the following two methodologies:

Cross-Sectional Reference Range: Reference ranges for each neurophysiological parameter were established based on data from 40 healthy controls (**Supplementary Table 1**). Specifically, ranges were defined as the mean ± 2 standard deviations for normally distributed variables, and as the 2.5th to 97.5th percentiles for non-normally distributed variables.

Longitudinal Change Threshold: Based on previous electrophysiological studies on CIPN [12], and preliminary findings from our research group, minimal clinically significant changes from baseline after chemotherapy were predefined. These thresholds were employed for electrophysiological verification within the composite CIPN endpoint and for the evaluation of combined testing strategies.

Definition of CIPN Outcome

To enhance diagnostic objectivity, this study utilized a composite endpoint to define the occurrence of CIPN. This definition integrated clinical assessment with objective electrophysiological changes:

Clinical Criteria

The clinical criteria were defined by a minimum grade of 1 for sensory neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0) [13]. Clinical assessments were performed by an independent neurologist who was blinded to all electrophysiological results. The evaluating neurologist had no access to the NCS, SSR, or tSEP data at the time of clinical grading.

Assessments were conducted at two time points: at baseline (T0, within one week prior to the first chemotherapy cycle) and at T1 (following completion of chemotherapy or three weeks after symptom onset). A standardized neurological symptom questionnaire was administered to each patient at both time points, followed by a focused neurological examination (including pinprick, light touch, vibration, and proprioception testing of the distal extremities) to confirm the sensory neuropathy grade. All gradings were performed by the same neurologist throughout the study to ensure consistency.

Electrophysiological Confirmation Criteria

An electrophysiological deterioration was established based on achieving any of the longitudinal change thresholds specified in Table 1 at time point T1 compared to baseline (pre-chemotherapy) measurements at time point T0.

CIPN Positive/Negative Classification

CIPN Positive (CIPN+): Characterized by meeting both the clinical and the electrophysiological confirmation criteria.

CIPN Negative (CIPN–): Characterized by fulfilling either one of the criteria or neither.

Definition of Subclinical CIPN

Subclinical CIPN was identified as having a NCI-CTCAE grade of 0 while still meeting any one of the electrophysiological confirmation criteria.

Statistical Analysis

Statistical analyses were conducted using SPSS software (version 25.0, IBM Corp., Armonk, NY, USA) and the R programming language (version 4.4.3, R Foundation for Statistical Computing, Vienna, Austria).

Descriptive and Comparative Analyses

The normality of the continuous data was assessed using the Shapiro-Wilk test. Data that conformed to a normal distribution were presented as mean ± standard deviation (Mean ± SD). Comparisons between paired groups (pre- and post-chemotherapy) were performed using the paired-sample *t*-test. Data that did not follow a normal distribution were presented as median (interquartile range, IQR); comparisons within these groups before and after chemotherapy were executed using the Wilcoxon signed-rank test. Categorical data were quantified and expressed as frequencies (percentages), and intergroup comparisons were made employing the chi-square test or Fisher's exact test, as applicable. To adjust the significance level for multiple comparisons, the Bonferroni correction was applied.

Evaluation of Diagnostic Performance

Using the composite endpoint as the reference standard, we calculated the sensitivity, specificity, positive predictive value, and negative predictive value of each individual neurophysiological parameter (post-chemotherapy absolute values) as well as combined parameters for diagnosing CIPN. Receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC), along with its 95% confidence interval (CI), was computed. A logistic regression model was developed to generate a combined diagnostic index. The AUC of the combined model was then compared with that of the individual parameters using the DeLong test. The optimal cut-off values for continuous electrophysiological parameters were determined using the Youden index (maximizing sensitivity + specificity − 1) based on the receiver operating characteristic (ROC) analysis.

Definition of Combined Testing Strategies

Isolated NCS Abnormality: Defined as meeting the criteria for "sensory axonal damage" or "sensory conduction slowing" as specified in the "Criteria for Defining Abnormal Neurophysiological Parameters" subsection.

Isolated SSR Abnormality: Defined as meeting the criteria for "small fiber/autonomic dysfunction" as specified in the "Criteria for Defining Abnormal Neurophysiological Parameters" subsection.

Isolated tSEP Abnormality: Defined as meeting the criteria for "proximal sensory nerve dysfunction" as specified in the "Criteria for Defining Abnormal Neurophysiological Parameters" subsection.

Combined Test Positivity: Defined as the detection of an abnormality by any one of the individual tests (NCS, SSR, or tSEP).

Table 1. The specific criteria were as follows (applicable to the subsections on "Electrophysiological Confirmation Criteria" and "Definition of Combined Testing Strategies").

Damage type	Neurophysiological parameter	Longitudinal change threshold (abnormal if any one criterion is met)	Cross-sectional reference range (our laboratory)
Sensory axonal damage	Sensory Nerve Action Potential (SNAP) Amplitude	Decrease of >20% from baseline (in at least 2 different sensory nerves)	Lower limb: Medial plantar nerve >3.0 μV, Sural nerve >10 μV, etc.
Sensory conduction slowing	Sensory Conduction Velocity (SCV)	Decrease of >10% from baseline (in at least 2 different sensory nerves)	Medial plantar nerve >40 m/s, etc.
Small fiber/autonomic dysfunction	SSR Latency / Amplitude	Waveform absence, or latency prolongation of >20% from baseline; or amplitude reduction of >20% from baseline	Upper limb latency <1.51 s, Lower limb latency <2.23 s; Upper limb amplitude <0.50 mV, Lower limb amplitude <0.36 mV
Proximal sensory nerve dysfunction	tSEP N9 Wave Amplitude	Decrease of >50% from baseline	>0.54 uV

Note: The lower limit of the reference range for the tSEP N9 wave amplitude was calculated using data from the 40 healthy controls (mean 1.02 uV, standard deviation 0.24 uV; calculated as mean minus two standard deviations, 0.54 uV). Patients with values below this threshold prior to chemotherapy were considered to have baseline abnormalities and were excluded. The cross-sectional reference ranges for all other neurophysiological parameters are fully detailed in **Supplementary Table 1**. SSR, sympathetic skin response; tSEP, tibial somatosensory evoked potential.

All hypothesis tests were two-sided, and a p-value < 0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics of Participants

Table 2 summarizes the baseline characteristics of the participants. This study included 40 patients, comprising 22 females (55.0%). The mean age was 59.1 ± 11.6 years, with no significant age difference noted between the CIPN positive and CIPN negative groups (58.9 ± 12.4 years vs. 59.6 ± 10.2 years, respectively). The primary cancer types were lung (32.5%), breast (25.0%), and gastrointestinal cancers (20.0%). Diabetes mellitus was present in 25.0% of patients, being more prevalent in the CIPN positive group (32.1%) compared to the CIPN negative group (8.3%), although this disparity was not statistically significant. Regarding the chemotherapy regimens, 15.0% of patients received a platinum-based regimen alone, 22.5% received a taxane-based regimen alone, while 62.5% underwent combination therapy. No significant differences were observed in baseline variables between the two groups (all $p > 0.05$).

Incidence and Clinical Characteristics of CIPN Based on the Composite Endpoint

Table 3 illustrates the distribution of NCI-CTCAE grades among all participants, detailing grade 0 in 12 patients, grade I in 24, grade II in four, and grade III in none. Based on the criteria for the composite endpoint, the incidence of CIPN in this cohort post-chemotherapy was recorded at 70.0% (28/40). The most frequently observed abnormalities included decreased SCV or SNAP of the medial/lateral plantar nerves (82.1%, 23/28), and prolonged latency or reduced amplitude of the lower limb SSR (92.9%, 26/28). Abnormalities in the tSEP-N9 wave amplitude were detected in 46.4% (13/28) of patients. The predominant clinical symptoms were numbness and tingling in the distal limbs. In the subclinical CIPN group, consisting of five patients, all exhibited mild reductions in SSR amplitude (100%), and four of these patients (80%) also presented with slowed SCV of the medial plantar nerve. In the true negative group (seven patients), all neurophysiological parameters fell within the normal reference range. Notably, objectively detectable neurophysiological damage was present in 12.5% (5/40) of patients before any clinical symptoms had emerged, underscoring the significant value of neurophysiological assessment in early screening for CIPN.

Comparison of NCS, H-Reflex, tSEP N9 Wave, and SSR in Cancer Patients Before (T0) and After (T1) Chemotherapy

To further elucidate the specific patterns of change in neurophysiological parameters associated with CIPN, we conducted a paired comparative analysis using assessment results from before (T0) and after (T1) chemotherapy within the patient cohort. These results are delineated in **Supplementary Table 2**. All neurophysiological parameters in the 40 age- and sex-matched healthy controls conformed to the laboratory's normal reference ranges. Data derived from the healthy control group were instrumental in establishing the cross-sectional reference thresholds and the cutoff value for abnormal tSEP N9 wave amplitude utilized in this study (refer to the "Criteria for Defining Abnormal Neurophysiological Parameters" subsection). These data are not presented separately in the main text.

Table 2. Baseline characteristics of participants.

Variable	Overall	CIPN_neg	CIPN_pos	Statistic	*p*_value
Gender (%)				$\chi^2 = 0.08$	0.781
Female	22 (55.0%)	7 (58.3%)	15 (53.6%)		
Male	18 (45.0%)	5 (41.7%)	13 (46.4%)		
Age (years), Mean ± SD	59.1 ± 11.6	59.6 ± 10.2	58.9 ± 12.4	t = 0.19	0.848
Cancer-Type (%)				-	0.686
Lung cancer	13 (32.5%)	3 (25.0%)	10 (35.7%)		
Breast cancer	10 (25.0%)	2 (16.7%)	8 (28.6%)		
Gastrointestinal cancer	8 (20.0%)	4 (33.3%)	4 (14.3%)		
Cervical cancer	3 (7.5%)	1 (8.3%)	2 (7.1%)		
Other	6 (15.0%)	2 (16.7%)	4 (14.3%)		
Diabetes (%)				-	0.231
Yes	10 (25%)	1 (8.3%)	9 (32.1%)		
No	30 (75%)	11 (91.7%)	19 (67.9%)		
Chemotherapy-Agent (%)				-	0.545
Platinum-based alone	6 (15%)	3 (25%)	3 (10.7%)		
Taxane-based alone	9 (22.5%)	2 (16.7%)	7 (25%)		
Combination of both	25 (62.5%)	7 (58.3%)	18 (64.3%)		

CIPN, chemotherapy-induced peripheral neuropathy.

Table 3. NCI-CTCAE grade distribution in CIPN+ and CIPN– subgroups.

Variable	CIPN+ (n = 28)	CIPN– (n = 12)
NCI-CTCAE Grade [n (%)]		
Grade 0	0 (0)	12 (100)
Grade I	24 (85.7)	0 (0)
Grade II	4 (14.3)	0 (0)
Grade III	0 (0)	0 (0)

Motor Nerve Conduction

Motor nerve conduction parameters were generally stable post-chemotherapy. No statistically significant differences were identified in MCV or compound muscle action potential (CMAP) amplitude for the median, ulnar, common peroneal, or tibial nerves before and after chemotherapy. Although a mild decrease in tibial nerve CMAP amplitude was observed ($p = 0.017$), it failed to achieve statistical significance following Bonferroni correction, rendering it of limited clinical relevance (**Supplementary Table 2**).

Sensory Nerve Conduction

Following chemotherapy, sensory nerve function showed widespread and varying degrees of impairment **(Supplementary Table 2)**:

Upper Limb Sensory Nerves: The sensory conduction velocity (SCV) of the median (digit III) and ulnar (digit V) nerves exhibited a mild reduction ($p < 0.05$). However, this reduction was not significant following Bonferroni correction. Nonetheless, the SNAP amplitudes for both nerves were significantly reduced ($p < 0.001$), with this finding remaining significant even after correction.

Lower Limb Sensory Nerves: There were no significant changes in the SCV for the superficial peroneal or sural nerves. However, significant reductions were observed in the SNAP amplitudes for these nerves ($p < 0.001$), which remained significant after correction.

Plantar Sensory Nerves: The most substantial damage was noted in the medial and lateral plantar nerves. The median SCV of the medial plantar nerve decreased from 45.0 m/s to 39.5 m/s, and the median SNAP amplitude reduced from 4.85 µV to 3.0 µV. In the case of the lateral plantar nerve, the median SCV became unmeasurable (i.e., absent waveforms) in several patients, and the median SNAP amplitude decreased from 1.0 µV to 0 µV. The declines in these parameters were all highly statistically significant ($p < 0.001$) and remained so after Bonferroni correction.

H-Reflex and Somatosensory Evoked Potentials

H-Reflex: Post-chemotherapy, no significant change in the latency was observed ($p = 0.502$), suggesting that the function of proximal sensory afferent fibers and the spinal reflex arc was relatively preserved (**Supplementary Table 2**).

Somatosensory Evoked Potentials: Following stimulation of the tibial nerve, the amplitude of the N9 wave, representing the lumbosacral plexus potential, decreased sig-

Table 4. Diagnostic performance of individual neurophysiological parameters for CIPN.

Parameter	Sensitivity	Specificity	PPV	NPV	AUC	AUC (95% CI)	Cut-off
Upper limb SSR amplitude	0.786	0.917	0.957	0.647	0.844	(0.721–0.967)	0.85 mV
Lower limb SSR amplitude	0.821	0.750	0.885	0.643	0.832	(0.706–0.958)	0.45 mV
Medial plantar nerve SCV	0.643	0.917	0.947	0.524	0.798	(0.661–0.934)	44.0 m/s
Lateral plantar nerve SCV	0.643	0.917	0.947	0.524	0.777	(0.626–0.927)	40.5 m/s
tSEP N9 wave amplitude	0.714	0.833	0.909	0.556	0.760	(0.600–0.921)	0.65 µV
Medial plantar nerve SNAP	0.500	1.000	1.000	0.462	0.737	(0.584–0.889)	2.6 µV
Lower limb SSR latency	0.500	1.000	1.000	0.462	0.720	(0.563–0.877)	2.11 s
Lateral plantar nerve SNAP	0.750	0.667	0.84	0.533	0.693	(0.524–0.863)	0.5 µV
Superficial peroneal nerve SNAP	0.607	0.833	0.895	0.476	0.661	(0.491–0.830)	12.85 µV
Upper limb SSR latency	0.679	0.667	0.826	0.471	0.626	(0.445–0.808)	1.53 s

Cut-offs were determined by the Youden index, and that all metrics are based on the total 40 patients (28 CIPN+ and 12 CIPN−). PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

nificantly from 1.02 uV to 0.52 uV ($p < 0.001$, significant after correction). The latency, however, showed no significant alteration. These results indicate that chemotherapy can impair not only the distal peripheral nerves but also the synchronous discharge capacity of proximal nerve trunks or plexuses (**Supplementary Table 2**).

Sympathetic Skin Response (SSR)

SSR serves as an essential indicator for assessing small fiber function (**Supplementary Table 2**). Post-chemotherapy findings include:

Latency: There was a prolongation of median SSR latency in the left upper limb from 1.43 s to 1.56 s ($p < 0.001$, significant after correction), and in the left lower limb from 2.27 s to 2.39 s ($p < 0.001$, significant after correction).

Amplitude: The median SSR amplitude decreased in the left upper limb from 1.00 mV to 0.80 mV, and in the left lower limb from 0.60 mV to 0.30 mV ($p < 0.001$, significant after correction), with absent waveforms noted in some patients.

These results demonstrate that chemotherapy can lead to autonomic small fiber dysfunction, characterized by prolonged SSR latency and reduced amplitude, with the lower limbs showing more severe impairment.

Diagnostic Performance of Neurophysiological Parameters for CIPN

After chemotherapy, several parameters exhibited significant declines, including plantar nerve SCV/SNAP, SSR latency/amplitude, and superficial peroneal nerve SNAP (all $p < 0.001$). The study aimed to evaluate the clinical utility of these neurophysiological abnormalities in identifying CIPN. We assessed the diagnostic performance of these parameters individually and collectively, using a composite endpoint as the reference standard. The findings are detailed in Table 4 and Fig. 1.

Diagnostic Performance of Individual Parameters

Upper Limb SSR Amplitude: Displayed the highest diagnostic value with an AUC of 0.844 (95% CI: 0.721-0.967). It achieved a sensitivity of 78.6% and a specificity of 91.7%.

Lower Limb SSR Amplitude: Recorded an AUC of 0.832 (95% CI: 0.706–0.958), with a sensitivity of 82.1% and a specificity of 75.0%.

Medial Plantar Nerve SCV: Exhibited an AUC of 0.798 (95% CI: 0.661–0.934), a high specificity of 91.7%, and a sensitivity of 64.3%.

Lateral Plantar Nerve SCV: Showed an AUC of 0.777 (95% CI: 0.626–0.927), with a specificity of 91.7% and a sensitivity of 64.3%.

Other Parameters: Such as superficial peroneal nerve SNAP and SSR latency demonstrated AUCs ranging from 0.626 to 0.737, indicating moderate diagnostic performance.

The findings are detailed in Table 4 and Fig. 1.

Diagnostic Performance of Combined Parameters

To further improve diagnostic accuracy, we constructed a binary logistic regression model incorporating the two parameters with the highest individual AUCs: upper limb SSR amplitude and medial plantar nerve SCV. The model was fitted using the entire cohort (n = 40), with CIPN status (composite endpoint) as the dependent variable. The resulting regression equation was:

$$\begin{aligned}\text{Logit}(P) = -2.314 - 3.562 \times (SSR < \text{sub} \\ > \text{upper} < /\text{sub} >, mV) - 0.098 \times (SCV < \text{sub} \\ > \text{medial plantar} < /\text{sub} >, \text{m/s})\end{aligned}$$

where P denotes the predicted probability of CIPN positivity.

The regression coefficients, Wald statistics, odds ratios (ORs), and their 95% confidence intervals (CIs)

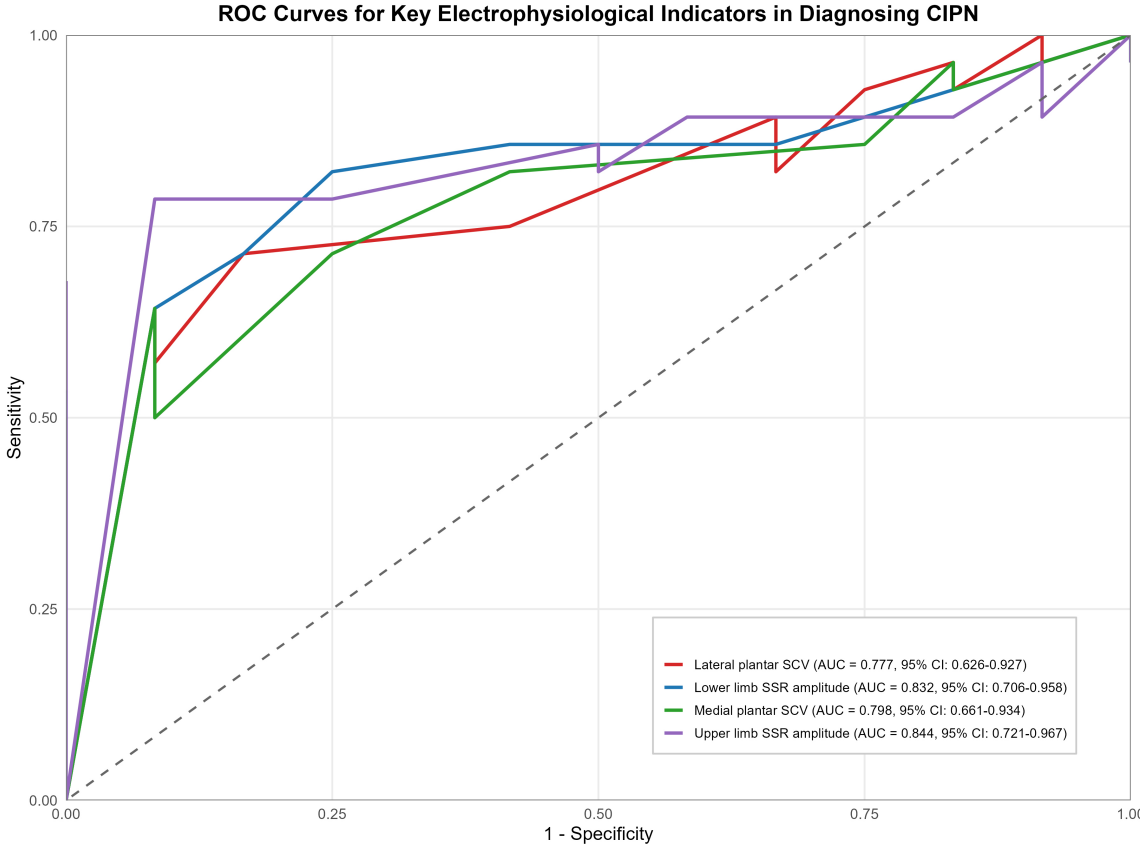

Fig. 1. ROC curves of the top four main diagnostic indicators ranked by AUC values.

Table 5. Multivariable logistic regression model for predicting CIPN using combined neurophysiological parameters.

Variable	β coefficient (SE)	Wald χ^2	*p* value	OR	95% CI for OR
Intercept	−2.314 (0.891)	6.74	0.009	—	—
Upper limb SSR amplitude (mV)	3.562 (1.145)	9.68	0.002	35.21	(4.42–498.67)
Medial plantar nerve SCV (m/s)	0.098 (0.034)	8.31	0.004	1.10	(1.04–1.21)

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; SSR, sympathetic skin response; SCV, sensory conduction velocity.

Model calibration: Hosmer-Lemeshow test, $\chi^2 = 4.21$, df = 8, $p = 0.838$.

are summarized in Table 5. Both variables were statistically significant independent predictors of CIPN (SSR_{upper} amplitude: OR = 35.21, 95% CI: 4.42–498.67, $p = 0.002$; medial plantar nerve SCV: OR = 1.10, 95% CI: 1.04–1.21, $p = 0.004$). The model demonstrated good calibration (Hosmer-Lemeshow test, $\chi^2 = 4.21$, df = 8, $p = 0.838$).

Using the predicted probability from this model, we evaluated the overall diagnostic performance of the combined strategy. The combined model yielded an area under the curve (AUC) of 0.881 (95% CI: 0.772–0.990), which was significantly higher than that of upper limb SSR amplitude alone (DeLong test, $p = 0.041$) and medial plantar nerve SCV alone ($p = 0.038$). The optimal cut-off value for the predicted probability, determined by the Youden index, was 0.52. At this threshold, the combined model achieved a sensitivity of 82.1%, specificity of 91.7%, positive predictive value (PPV) of 95.8%, and negative predictive value (NPV) of 68.8%, with an overall accuracy of 85.0%. These findings indicate that the combination of upper limb SSR amplitude and medial plantar nerve SCV provides a balanced and effective non-invasive diagnostic strategy for CIPN, with excellent specificity and favorable sensitivity.

Preliminary Exploratory Analysis: Detection of Subclinical CIPN by Combined Testing

In an exploratory analysis of the five patients with subclinical CIPN (NCI-CTCAE grade 0 but with electrophysiological abnormalities), we compared the detection rates of different testing strategies (**Supplementary Table 3**):

NCS alone (including plantar nerve conduction): Detected 4 patients (80%).

SSR alone: Detected 5 patients (100%).

tSEP alone: Detected 2 patients (40%).

NCS combined with SSR: Detected 5 patients (100%), equivalent to SSR alone.

NCS + SSR + tSEP combined: Still achieved 100% detection, with no further benefit.

Conclusion: NCS combined with SSR detected 5 patients, equivalent to SSR alone. The difference between NCS alone and NCS combined with SSR was not statistically significant (McNemar's exact test, $p = 1.000$), consistent with the extremely small sample size (n = 5).

Sensitivity Analysis

Diagnostic Performance Under the Purely Clinical Reference Standard

When employing a purely clinical reference standard (NCI-CTCAE grade ≥1) as the reference, the composition of the positive and negative groups resembled that of the original composite endpoint (28 positive, 12 negative). This consistency occurs because all clinically positive patients also met the electrophysiological criteria for deterioration, and there were no instances where patients were clinically positive but electrophysiologically normal. Consequently, the AUC, sensitivity, and specificity of each neurophysiological parameter were consistent with the primary analysis (for example, upper limb SSR amplitude: AUC = 0.844; medial plantar nerve SCV: AUC = 0.798).

Change in AUC After Excluding Subclinical Patients

When defining the negative group strictly as true negatives (by excluding the five subclinical cases), the AUC of each neurophysiological parameter showed a slight increase compared to the primary analysis (**Supplementary Table 4**). For instance, the AUC for the upper limb SSR amplitude rose from 0.844 to 0.872, while the AUC for the lower limbs SSR amplitude increased from 0.832 to 0.895. These results suggest that the electrophysiological measurements of subclinical patients had already shifted towards those seen in the positive group, implying an early sensitivity of electrophysiological testing in detecting these changes, a phenomenon that significantly affected overall diagnostic performance.

Re-Evaluation of Diagnostic Performance After Excluding Diabetic Patients

Subsequent to the exclusion of 10 diabetic patients, the analysis was performed on the remaining cohort of 30 patients (21 CIPN+ and 9 CIPN negative). The AUC for the upper limb SSR amplitude insignificantly decreased from 0.844 to 0.842, while the AUC for the medial plantar nerve SCV negligibly increased from 0.798 to 0.799. These changes were not statistically significant (DeLong test, all $p > 0.05$). A detailed comparison of the AUCs for the main electrophysiological parameters, before and after the exclusion of diabetic patients, is presented in **Supplementary Table 5**.

Sensitivity Analysis Adjusting for Chemotherapy Cycles

The variability in T1 timing prompted a repeat of t he ROC analyses with the number of completed chemotherapy cycles as a covariate. Following this adjustment, the AUC for the upper limb SSR amplitude increased from 0.844 to 0.865, and that for the medial plantar nerve SCV from 0.798 to 0.842 (both changes were statistically insignificant, $p > 0.05$) (detailed in **Supplementary Table 6**). These results suggest that the diagnostic performance estimates were not materially influenced by the variability in T1 timing, supporting the robustness of the primary findings.

Discussion

CIPN represents a prevalent and burdensome complication associated with the use of widely prescribed antineoplastic agents, such as platinum compounds and taxanes [3]. The incidence of CIPN can reach up to 73% with platinum-based treatments and 79.1% with taxanes [1,2]. In our study, all participants received chemotherapy regimens that included either taxane-based or platinum-based drugs. Patients typically exhibited symptoms like tingling, numbness, paresthesia, neuropathic pain, cold-induced dysesthesia, and muscle cramps, which tended to worsen following chemotherapy but typically improved after the cessation of treatment [14]. Consequently, combining patient-reported sensory symptoms with objective electrophysiological assessments is essential for both diagnosing and managing CIPN. While previous studies have explored the diagnostic utility of NCS or SSR individually, none has systematically examined the dynamic changes in these modalities before and after chemotherapy or developed an integrated diagnostic model that combines large fiber and small fiber metrics. Consequently, the present study aimed to evaluate, within the same CIPN cohort, the prospective diagnostic accuracy of large fiber (NCS), small fiber/autonomic (SSR), and proximal nerve (tSEP N9) parameters concurrently.

Susceptibility to injury in nerve fibers is closely associated with their length, diameter, and the extent of myelination. Axonal terminals and supporting cells of peripheral nerves are susceptible to damage from chemotherapeutic agents due to various pathophysiological mechanisms [15]. Although platinum compounds and taxanes target different molecules, both induce a length-dependent, sensory neuron-selective peripheral neuropathy, predominantly characterized by axonal damage [16]. In this study, the most pronounced decreases following chemotherapy were observed in the SNAP amplitude and SCV of distal sensory nerves, particularly the medial and lateral plantar nerves. However, motor nerve conduction parameters and H-reflex latency remained largely intact. This pattern is a classic manifestation of length-dependent sensory axonopathy, in which longer nerve fibers are more susceptible to damage than shorter ones, typically resulting in symptoms that begin in the distal extremities. This finding is consis-

tent with previous research [17,18]. The relative preservation of motor function aligns with the characteristic pathology of CIPN as primarily a sensory axonal neuropathy. This is consistent with the mechanism by which taxanes and platinum agents cause primary injury to dorsal root ganglion (DRG) neurons and their distal axons. Due to their length, the terminal axons of the plantar nerves are particularly vulnerable to mitochondrial dysfunction, disruption of axoplasmic transport, and oxidative stress [19,20].

Taxanes exert their neurotoxic effects by stabilizing microtubules, which disrupts axonal transport. They also influence the mitochondrial permeability transition pore, leading to the release of calcium and subsequent activation of calpain, which catalyzes the degradation of neurofilaments and microtubule-associated protein networks [21,22]. Conversely, platinum compounds induce retrograde Wallerian-like degeneration (i.e., axonal damage that spreads backwards from the distal end towards the cell body) through mitochondrial DNA damage and oxidative stress within DRG neurons [23,24]. Cell culture studies have shown that, compared to paclitaxel, platinum agents are more likely to induce atrophy and apoptosis of sensory neuron cell bodies rather than pure axonopathy [25]. In this study, the complete absence of SCV and SNAP waveforms in the lateral plantar nerve observed in some patients indicates irreversible axonal damage. Thus, these parameters should be considered essential indicators for monitoring in high-risk patients.

SSR is a reliable, non-invasive electrophysiological measure for assessing sympathetic sudomotor function, which pertains to the unmyelinated C fibers that innervate sweat glands [26,27,28]. This sudomotor function is regulated by postganglionic cholinergic sympathetic fibers, reflecting directly the function or density of sweat gland nerve endings (unmyelinated C fibers) [29]. Characterized by their long axons, high metabolic demands, and absence of a myelin sheath, unmyelinated fibers are particularly vulnerable to distal axonopathy. The oxidative stress and mitochondrial dysfunction induced by platinum agents are especially detrimental to these highly metabolic unmyelinated fibers [30]. Taxanes, on the other hand, affect these fibers by disrupting microtubule-based transport, leading to disturbances in pain and temperature perception [31]. The current study found that SSR latency was significantly prolonged and SSR amplitude was notably reduced following chemotherapy treatment. Moreover, the rate of SSR abnormalities (92.9%) exceeded that observed with conventional NCS (82.1%). Among the five patients with subclinical CIPN (NCI-CTCAE grade 0), SSR alone identified 100% of cases, significantly higher than that detected by NCS alone (80%) or tSEP alone (40%). These results suggest that SSR is the most sensitive method for the ultra-early detection of CIPN. Furthermore, these findings align with the established role of SSR in the early diagnosis of diabetic peripheral neuropathy [11,32]. In our exploratory subclinical cohort (n = 5), SSR showed promising detection capability, suggesting that it may have potential utility in early screening for CIPN. However, given the small sample size and lack of statistical significance in the comparison, these findings should be considered preliminary and hypothesis-generating, warranting validation in larger prospective studies.

Regarding the N9 wave of the tSEP, which primarily reflects the proximal conduction function of Aβ fibers, it originates from the volume conduction of SNAPs in the lumbosacral plexus. Abnormalities in the N9 wave are typically observed in later disease stages or after higher cumulative doses of chemotherapy, illustrating its limited sensitivity in the subclinical phase. In the current study, there was a significant reduction in the amplitude of the N9 wave, whereas its latency remained normal. This suggests that the involvement is more indicative of proximal axonal dysfunction rather than demyelinating changes. Platinum agents, which accumulate in the dorsal root ganglia, cause direct neuronal apoptosis and axonal degeneration [23]. Although taxanes primarily induce distal axonopathy, proximal axons may also exhibit secondary dysfunction due to retrograde Wallerian degeneration or the effects of local inflammatory mediators, including IL-1β, IL-8, and TNF-α [33,34]. Despite its moderate diagnostic performance (AUC 0.760), the clinical importance of the decreased N9 wave amplitude lies in demonstrating that CIPN is not only a distal peripheral neuropathy but can also involve nerve roots or plexus, presenting as a multifocal axonopathy.

In this study, the amplitude of upper limb SSR demonstrated the highest diagnostic performance for CIPN with an AUC of 0.844, whereas the medial plantar nerve SCV exhibited a specificity of 92% (AUC 0.798). By integrating these two parameters through logistic regression modeling, the AUC of the resultant model improved to 0.881, significantly surpassing that of each individual parameter ($p < 0.05$). This integrated approach effectively balances the sensitivity of assessing small fibers with the specificity of evaluating large fibers. More notably, in an exploratory analysis of patients with subclinical CIPN (NCI CTCAE grade 0), the combined use of NCS and SSR achieved complete detection. This suggests that a streamlined combination of NCS, including plantar nerve conduction, and SSR may effectively detect neuropathy in high-risk patients without overt neurological symptoms, thereby offering a potential advantage for early intervention. Furthermore, it could provide a critical window for early dose adjustment or neuroprotective interventions.

Based on our findings, we recommend that for patients receiving platinum- or taxane-based regimens, particularly those with pre-existing diabetes or borderline baseline electrophysiological parameters, repeated measurements of SSR and medial plantar nerve SCV every two to three cycles may aid in the early detection of nerve damage, thus enabling timely dose adjustment or neuro-

protective interventions. This combined testing strategy is straightforward and feasible for routine electromyography laboratories. We acknowledge a more fundamental limitation: the use of a composite endpoint that incorporates electrophysiological deterioration to re-evaluate the same electrophysiological indices (NCS, SSR, and tSEP) inevitably creates incorporation bias or circular validation. The nearly identical ROC results obtained when using the purely clinical NCI-CTCAE standard (sensitivity analysis 3.6.1) do not demonstrate elimination of this bias; rather, they merely reflect that the positive/negative outcome labels were largely preserved across the two reference definitions. Therefore, the reported AUC, sensitivity, and specificity values are likely overestimated and should be interpreted as exploratory internal calibrations, not as definitive measures of test accuracy.

This study presents several limitations. First, the single-center design and relatively small sample size (n = 40), particularly the inclusion of only five patients with subclinical CIPN, resulted in wide confidence intervals for some diagnostic performance metrics. Additionally, while we used a composite endpoint as the reference standard, this approach introduces incorporation bias, as the same neurophysiological parameters were used both to define the reference and as index tests. Consequently, the ROC-derived estimates are likely overestimated and should be interpreted as exploratory. This limited the reliability of sensitivity and specificity estimates and precluded robust subgroup analyses based on different chemotherapeutic agents, cancer types, or dose intensities. In particular, the subclinical CIPN analysis was severely underpowered for formal statistical inference; the comparison between testing strategies (NCS alone vs. NCS+SSR) yielded a McNemar's exact test *p*-value of 1.00, confirming that no reliable statistical conclusion can be drawn from this small subgroup. The observed detection rates should therefore be considered descriptive and exploratory only. Moreover, no formal sample size calculation was performed prior to study initiation, as this was an exploratory diagnostic study without prior effect size estimates in this specific multimodal context. Second, the timing of the post-chemotherapy assessment (T1) was not uniformly standardized across all participants. Although we conducted a sensitivity analysis adjusting for the number of completed cycles, which suggested that the primary analysis provided a conservative estimate of diagnostic performance, future prospective studies should adopt a fixed assessment window (e.g., after a predetermined number of cycles) to minimize this confounding. Third, the combined logistic regression model was derived from the same dataset without internal validation (e.g., bootstrapping or cross-validation), external validation, or model calibration assessment. Therefore, the observed improvement in AUC should be regarded as exploratory and hypothesis-generating, and external validation in independent cohorts is urgently needed. Fourth, residual confounding cannot be fully excluded. Although we performed a sensitivity analysis excluding diabetic patients and found no significant change in AUC, diabetes and potential subclinical peripheral neuropathy may still influence SSR and plantar nerve conduction measurements, and the relatively small number of diabetic patients (n = 10) limited the power of this subgroup analysis. Fifth, the normal reference ranges were established using only 40 healthy controls from a single center, which may limit their stability, reproducibility, and external generalizability to other populations or laboratories. Sixth, structural and pathological markers—such as nerve ultrasound, skin biopsy, and corneal confocal microscopy—were not incorporated, limiting our ability to comprehensively correlate electrophysiological abnormalities with structural changes and pathological evidence of nerve fiber loss. Seventh, patient-reported outcome measures (e.g., FACT-GOG-Ntx or EORTC QLQ-CIPN20) were not included. Consequently, the relationship between electrophysiological abnormalities and patients' subjective symptom burden, quality of life, or long-term clinical benefits remains unclear. We also acknowledge that the NCI-CTCAE grading system is an imperfect clinical reference standard rather than a true gold standard. It relies on clinician-reported symptoms and physical examination, which are subject to inter-observer variability and may lack sensitivity for subtle neuropathic changes. The sensitivity analysis using the purely clinical NCI-CTCAE standard yielded nearly identical ROC results, which does not demonstrate elimination of incorporation bias but rather reflects that the same outcome labels were largely preserved.

Despite these limitations, our findings provide valuable preliminary evidence supporting the utility of multimodal neurophysiological assessment in detecting CIPN, particularly at the subclinical stage. Further research should involve multicenter collaborations with larger sample sizes, standardized follow-up protocols, and prospective validation of the combined diagnostic model. Additionally, integrating neurophysiological assessments with serum biomarkers (e.g., neurofilament light chain), structural imaging, and patient-reported outcomes will be essential to develop robust early warning systems and prognostic prediction models for CIPN. Expanding the sample size will also enable a more detailed exploration of the distinct electrophysiological damage patterns induced by different chemotherapeutic agents (platinum-based, taxane-based, and combination regimens), thereby informing the development of individualized monitoring and intervention strategies.

Conclusion

Multimodal neurophysiological assessment can systematically characterize the pattern of nerve fiber damage in CIPN. The combination of SSR amplitude and plantar nerve SCV constitutes an effective and non-invasive diag-

nostic strategy for CIPN. In addition, the combination of NCS and SSR showed promising detection capability in a small exploratory subclinical cohort, suggesting potential utility for early screening that warrants validation in larger prospective studies. These findings provide an objective electrophysiological foundation for early identification and clinical decision-making in CIPN, with meaningful translational implications.

Abbreviations

AUC, Area under the curve; CI, Confidence interval; CIPN, Chemotherapy-induced peripheral neuropathy; CMAP, Compound muscle action potential; IQR, Interquartile range; MCV, Motor conduction velocity; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NCS, Nerve conduction studies; ROC, Receiver operating characteristic; SCV, Sensory conduction velocity; SD, Standard deviation; SNAP, Sensory nerve action potential; SSR, Sympathetic skin response; tSEP, Tibial nerve somatosensory evoked potential.

Availability of Data and Materials

The datasets generated and analysed during the current study are not publicly available due to ethical restrictions, patient privacy and institutional policies but are available from the corresponding author on reasonable request.

Author Contributions

XHS: Methodology, writing-original draft, Data management. KXL: Formal analysis. YLL: Review, and conceptualization. All authors have been involved in revising it critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Hebei Medical University Third Hospital (W2024-087-1) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects involved in the study.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638211.204.

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