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Circulating Neurofilament Light Chain as a Biomarker of Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review, Dependency-Robust Meta-Analysis, and Multi-Omics Evidence Integration

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Abstract

Purpose

Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting toxicity. We evaluated associations of circulating neurofilament light chain (NfL) with clinical CIPN severity and objective peripheral nerve injury and integrated multi-omics evidence for biological context.

Methods

PubMed/MEDLINE, Embase, Web of Science Core Collection, and Cochrane CENTRAL were searched through August 25, 2026. Direction-harmonized correlations were pooled with restricted maximum-likelihood random-effects models and Hartung-Knapp inference. Within-study dependence was addressed using multilevel meta-analysis with CR2 robust variance estimation. Risk of bias was assessed with QUIPS, certainty with GRADE, and public paclitaxel transcriptomic and proteomic data were explored.

Results

Twenty-three reports were included. Seven independent effects yielded r = 0.456 for clinical CIPN severity (95% CI 0.341–0.558; I^2 = 0.01%), and five yielded r = 0.420 for objective nerve injury (95% CI 0.299–0.528; I^2 = 0%). The dependency-robust analysis of nine effects from six clusters yielded r = 0.451 (95% CI 0.351–0.540). GRADE certainty was low for both outcomes. Of 19,605 shared genes, 3,289 met FDR < 0.05 and 3,115 were directionally concordant; sterol biosynthesis was the only batch-robust pathway. Across 93 RNA-protein pairs, Spearman rho was 0.601 and directional concordance was 79.6%.

Conclusion

Circulating NfL shows a stable moderate association with CIPN severity and objective nerve injury. It may serve as an objective adjunct for longitudinal supportive-care monitoring, but current evidence does not support a universal stand-alone predictive threshold. The multi-omics findings are exploratory and do not establish an NfL-specific causal mediator.

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is an important clinical complication of several widely used antineoplastic agents, including taxanes, platinum compounds, vinca alkaloids, proteasome inhibitors, and antibody–drug conjugates. A representative systematic review estimated that CIPN occurs in approximately 68% of patients within 1 month after chemotherapy, 60% at 3 months, and 30% at 6 months or later [1]. In addition to sensory symptoms such as numbness, tingling, paresthesia, and neuropathic pain, CIPN can cause motor and functional impairment, reduce quality of life, and necessitate chemotherapy dose reduction, delay, or discontinuation. Current American Society of Clinical Oncology guidance recommends intensified clinical monitoring and consideration of treatment modification when neuropathy becomes intolerable or functionally limiting, while noting the lack of proven pharmacologic prevention strategies [2].

Objective quantification of CIPN remains difficult in routine oncology practice. Clinician-graded toxicity scales may be insufficiently sensitive to change, whereas patient-reported measures and composite neurologic scores capture partly different dimensions of neurotoxicity. Electrophysiologic testing objectively reflects axonal dysfunction but is resource intensive and usually impractical for repeated routine assessments during treatment. An accessible blood biomarker that reflects ongoing axonal injury could therefore complement clinical examination, improve longitudinal monitoring, and potentially identify patients at risk of clinically important toxicity before irreversible damage occurs.

Neurofilament light chain (NfL) is a cytoskeletal protein that is highly expressed in large myelinated axons. After axonal injury, NfL is released into cerebrospinal fluid and subsequently enters the circulation; ultrasensitive immunoassays now permit repeated quantification in blood. Circulating NfL has been extensively validated as a marker of neuroaxonal injury in inflammatory, degenerative, traumatic, and vascular neurologic disorders [3, 4, 28, 29]. Importantly, NfL reflects axonal damage rather than a disease-specific pathologic process, and its interpretation may be influenced by age, coexisting neurologic disease, treatment context, and the anatomic source of injury.

Clinical research on NfL in CIPN has expanded rapidly since 2020. Independent cohorts have linked elevated NfL concentrations to neurotoxicity caused by paclitaxel, oxaliplatin, bortezomib, vincristine, and mixed regimens; however, the literature is heterogeneous with respect to cancer type, treatment regimen, sampling schedule, assay platform, neuropathy scale, and the definition of clinically significant CIPN. A 2026 Multinational Association of Supportive Care in Cancer narrative review highlighted the promise of serum NfL but also identified variation in absolute concentrations, treatment exposure, sampling time, and outcome measures as major barriers to clinical implementation [5]. Quantitative synthesis is therefore needed to estimate the magnitude and consistency of the association between circulating NfL and clinical neurotoxicity.

This study aimed to: (1) quantify the association between circulating NfL and clinical CIPN severity; (2) assess the association between NfL and objective peripheral nerve injury; (3) account for within-study effect dependence using multilevel models and robust variance estimation; (4) systematically characterize temporal, diagnostic, and prognostic evidence; and (5) integrate publicly available transcriptomic and proteomic results to provide an independent molecular context for clinical biomarker discovery.

2. Materials and methods

2.1 Reporting framework and research question

This systematic review was reported in accordance with the PRISMA 2020 statement and methodological guidance from the Cochrane Handbook [6, 7]. The clinical research question was whether circulating serum or plasma NfL is associated with CIPN occurrence, severity, objective neuroaxonal injury, or subsequent progression among patients receiving potentially neurotoxic antineoplastic therapy. A structured database prospectively specified eligibility criteria, effect-size selection, management of overlapping cohorts, stopping rules, and sensitivity analyses. Protocol registration status must be confirmed by the authors before submission. Multi-omics analyses were prespecified as exploratory evidence integration and did not alter eligibility decisions or effect estimates in the clinical meta-analysis.

2.2 Eligibility criteria

We included original human studies of patients receiving systemic antineoplastic therapy with neurotoxic potential that measured serum or plasma NfL and reported clinical CIPN, patient-reported outcomes, nerve-conduction or small-fiber measures, or diagnostic/prognostic performance. Eligible designs included prospective or retrospective cohorts, biomarker studies nested within trials, and translational studies containing an analyzable human cohort. Reviews, editorials, protocols, abstracts without a full peer-reviewed report, exclusively animal or in vitro studies, studies measuring only cerebrospinal-fluid NfL, and studies without a peripheral neurotoxicity outcome were excluded. Overlapping reports were retained in the systematic review but were not counted more than once within the same model.

2.3 Information sources and search strategy

PubMed/MEDLINE, Embase, Web of Science Core Collection, and Cochrane CENTRAL were searched from inception through August 25, 2026. Search concepts covered NfL, neurotoxic antineoplastic therapy, and peripheral neuropathy/neurotoxicity without language restrictions. Reference lists of included studies and relevant reviews were also screened. Complete search strategies are provided in Online Resource 1 (Supplementary Table S1).

2.4 Study selection and data extraction

Deduplication was verified using DOI, PMID, normalized titles, and approximate matching. Study design, sample size, treatment, NfL assay, CIPN instrument, time point, correlation coefficient, group comparison, receiver operating characteristic curve/area under the curve, sensitivity, specificity, and evidence of participant overlap were extracted into structured tables. The 385 original database records were rededuplicated before screening.

2.5 Risk of bias and certainty of evidence

Risk of bias in observational biomarker studies was assessed with the Quality In Prognosis Studies (QUIPS) tool across six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting [34]. The workbook risk_of_bias.xlsx served as the final controlled master file, and all 35 initially conflicting ratings were resolved by full-text reassessment. Certainty of evidence for clinical severity, objective nerve injury, temporal change, and diagnostic/prognostic performance was evaluated with GRADE across risk of bias, inconsistency, indirectness, imprecision, and publication bias [37]. Formal funnel-plot or regression assessment of small-study effects was not planned because each quantitative synthesis contained fewer than 10 independent effects.

2.6 Conventional correlation meta-analysis

The primary outcome was the correlation between NfL and clinical CIPN severity; the secondary outcome was the correlation between NfL and objective peripheral nerve injury. Effect directions were harmonized so that $r > 0$ consistently indicated that higher NfL corresponded to more severe injury. Pearson, Spearman, and partial correlation coefficients were transformed using Fisher's z, with sampling variance approximated as $1/(n - 3)$. Random-effects models were fitted by restricted maximum likelihood, with Hartung–Knapp small-sample inference [8], and estimates were back-transformed to r. Tau-squared, Q, and I-squared were reported. Each independent cohort contributed only one compatible effect to each conventional model. The $R = 0.33$ statistic in S16 originated from a Kruskal–Wallis comparison across ordinal groups rather than an ordinary correlation and was therefore excluded from the conventional correlation meta-analysis.

2.7 Dependency-robust extension and stopping rules

To retain multiple compatible clinical effects from the same study without treating them as independent, we fitted a multilevel random-effects model with dependency clusters defined by study/cohort. Inference used CR2 robust variance estimation with Satterthwaite degrees-of-freedom correction [35, 36]. Prespecified stopping rules required at least three independent compatible study clusters for temporal synthesis and independent, reconstructable true-positive, false-positive, false-negative, and true-negative counts for diagnostic-accuracy synthesis. Outcomes that did not meet these criteria were summarized descriptively.

2.8 Multi-omics data sources and analysis

The primary transcriptomic analysis used complete and comparable 48-h paclitaxel (PTX) versus dimethyl sulfoxide (DMSO) contrasts from GSE305998 and GSE312881; effect directions were integrated across shared genes with false discovery rate (FDR) control. Because the public differential-expression report for GSE173610 contained only significance-filtered records, it was used for directional verification rather than complete ranked analysis. Pathway analyses were restricted to 12 prespecified Gene Ontology Biological Process sets from MSigDB 2025.1, and robustness was evaluated using an alternative control batch from GSE305998. For the proteomic analysis, RNA and protein effects were mapped by gene using the author-supplied table for PXD070094, followed by calculation of Spearman correlation and directional concordance. Multi-omics findings were interpreted as orthogonal consistency and mechanistic context, not as evidence of an NfL-specific causal mediator.

2.9 Software and reproducibility

Statistical analyses were performed in R version 4.6.1, primarily using metafor and cluster-robust inference tools. All clinical and omics tables and figures were generated by scripts. Random seeds were fixed, and input files, analysis scripts, session information, stage logs, and file-level SHA-256 manifests were retained in the project archive.

2.10 Use of generative artificial intelligence in manuscript preparation

OpenAI ChatGPT (OpenAI; accessed August 31, 2026) was used solely to translate the manuscript from Chinese into English..

3. Results

3.1 Study selection

The four databases yielded 385 original records. After removal of 166 duplicates, 219 records underwent title/abstract screening and full-text eligibility assessment. Twenty-one reports were included from database searching and two additional reports were identified through other methods, resulting in 23 reports in the systematic review (Fig. 1).

3.2 Characteristics of included studies

The 23 included reports were published between 2020 and 2026 and were predominantly prospective longitudinal biomarker studies. Populations included adults and children/adolescents with cancer; neurotoxic exposures included taxanes, platinum compounds, bortezomib, vincristine, brentuximab vedotin, and mixed regimens. Simoa was the most frequently used NfL assay platform. CIPN outcomes included CTCAE, CIPN20, TNSc/TNSr, CIPN-RODS, nerve-conduction studies, and intraepidermal nerve fiber density. Reports S20–S23 added evidence on intervention-related temporal patterns, sarcopenia, genetic associations, and longitudinal findings in children and adolescents [30–33].

Most studies collected serum, whereas a smaller number used plasma or described specimen type inconsistently. In addition to Simoa, assays included Ella, ELISA, and other high-sensitivity immunoassays. Cohorts were recruited in Asia, Europe, and North America and included breast, gynecologic, gastrointestinal, hematologic, and mixed solid malignancies. Study sizes varied widely, and the effective sample sizes for some clinical correlation analyses were substantially smaller than total enrollment; attrition and complete-case selection therefore contributed importantly to QUIPS ratings.

Evidence roles were not identical across reports: seven independent effects informed the conventional meta-analysis of clinical severity, five informed the objective nerve-injury meta-analysis, and nine compatible clinical effects from six dependency clusters informed the robust variance estimation extension. The remaining reports contributed primarily to evidence on longitudinal change, between-group differences, treatment modification, diagnostic/prognostic performance, genetic context, or proteomics. Multiple reports from the same study program or participant cohort remained in the systematic review, while overlap groups and model-selection rules prevented duplicate weighting. Characteristics and evidence roles are summarized in Table 1.

Table 1
Characteristics of the 23 included reports

Reference	Study	Design/population	Neurotoxic treatment	N	Specimen/assay	CIPN or neurologic outcome	
[9]	Kim 2020	Prospective longitudinal cohort; colorectal/gastrointestinal cancers	Oxaliplatin-based	43	Serum; Simoa	NCI-CTC; EORTC QLQ-CIPN20; NCS	
[10]	Kim 2022	Prospective longitudinal cohort; gynecologic cancers	Paclitaxel + carboplatin	48	Serum; Simoa	CTCAE; EORTC QLQ-CIPN20; NCS	
[11]	Burgess 2022	Prospective biomarker analysis nested in a randomized trial; NSCLC	Paclitaxel + carboplatin ± bevacizumab/pertuzumab	103	Serum; high-sensitivity immunoassay	CTC adverse-event grade	
[12]	Huehnchen 2022	Prospective controlled longitudinal cohort + in vitro experiments; mixed solid tumors	Neurotoxic chemotherapy; mainly paclitaxel-based	31 treated patients	Serum; Simoa	TNSr; patient-reported CIPN; CTCAE; NCS	
[13]	Karteri 2022	Prospective longitudinal cohort; breast cancer	Weekly paclitaxel-based	59	Serum; Simoa	TNSc; CTCAE	
[14]	Mortensen 2023	Prospective observational cohort + in vitro experiments; ovarian cancer	Paclitaxel + carboplatin	200 enrolled	Serum; Simoa	CTCAE PIPN; discontinuation/dose reduction	
[15]	Cebulla 2023	Cross-sectional/observational cohort; multiple myeloma	Bortezomib	70	Serum; Ella	Clinical neuropathy grade; NCS	
[16]	Velasco 2023	Secondary analysis of a prospective cohort; breast cancer	Weekly paclitaxel	27	Serum; Simoa	TNSc; NCS	
[17]	Cavaletti 2023	Two independent prospective noninterventional longitudinal studies; breast cancer	Paclitaxel	49 total	Serum; Simoa	TNSc; CIPN20	
[18]	Adra 2024	Prospective exploratory longitudinal cohort; breast cancer	Weekly paclitaxel after EC	10	Blood (serum/plasma described); Simoa	EORTC QLQ-CIPN20; CTCAE	
[19]	Velasco 2024	Prospective longitudinal multicohort study; mixed cancers	Taxanes/bortezomib/platinum	82	Plasma; Simoa HD-1	TNSc; NCS; CTCAE	
[20]	Gehr 2025	Prospective clinical cohort + in vitro experiments; colorectal cancer	Oxaliplatin vs non-oxaliplatin chemotherapy	30	Serum; Simoa	Probable OIPN score/clinical symptoms	
[21]	Makówka 2025	Prospective longitudinal cohort; breast cancer	Taxane-based neoadjuvant chemotherapy	94	Serum; Ella	EORTC QLQ-CIPN20; clinical grade	
[22]	Stephan 2025	Prospective longitudinal cohort; lymphoma, leukemia, and gastrointestinal malignancies	Mixed chemotherapy; short and prolonged regimens	108	Serum; serum NfL assay	TNSr; neurologic examination; electroneurography	
[23]	Kittaka 2026	Exploratory prospective/validation dual cohort + plasma proteomics; breast cancer	Paclitaxel/taxane-based	22 total	Plasma; Simoa NfL V2 Advantage	CTCAE PSN/PMN; NCS	
[24]	Pontoppidan 2026	Prospective self-controlled pediatric study + in vitro experiments; acute lymphoblastic leukemia	Vincristine	21	Serum; Simoa	CTCAE VIPN; TNS-PV	
[25]	Smyth 2026	Prospective longitudinal cohort; mixed solid tumors	Platinum or taxane	42	Serum; Simoa	CIPN-RODS; TNSc; CTCAE	

Reference	Study	Design/population	Neurotoxic treatment	N	Specimen/assay	CIPN or neurologic outcome	I s
[26]	Tikhonova 2026	Prospective cohort; solid tumors	Platinum and/or taxane	66	Serum; ELISA	NCI-CTCAE; NDS; SRAR; sural SNAP; IENFD	C a I
[27]	Beales 2026	Prospective cohort; breast cancer	Taxane-containing chemotherapy	NR	Plasma; plasma NfL assay	PRO-CTCAE sensory symptoms; pain outcomes	S n I a
[30]	Tantawy 2025	Randomized double-blind parallel trial; gastric cancer	FOLFOX-4; duloxetine/gabapentin/lacosamide	93	Serum; NfL and inflammatory markers	CTCAE; NTX-12; pain and quality of life	I f
[31]	Velasco 2026	Prospective observational cohort; mixed cancers	Paclitaxel/oxaliplatin/brentuximab vedotin	105	Plasma; Simoa	TNSc; CTCAE; NCS; sarcopenia	T c
[32]	Kassem 2025	Prospective cohort; breast cancer	Taxane	100	Serum; ELISA; EPHA5/SOD2 genotyping	CTCAE v5.0	T g c
[33]	Belsky 2026	Prospective longitudinal pilot; pediatric/adolescent-young-adult leukemia or lymphoma	Vincristine/microtubule-toxic regimens	26	Plasma; Simoa HD-X	FACT-GOG/NTx; 240 observations	I c

3.3 Primary meta-analysis: NfL and clinical CIPN severity

Seven independent effects were included in the primary synthesis. Higher circulating NfL showed a moderate positive correlation with more severe clinical CIPN (pooled r = 0.4564, 95% CI 0.3408–0.5584; p = 0.000123). Between-study variance was minimal (tau-squared = 0.000004; I-squared = 0.01%; Q = 4.05, p = 0.670), although a low I-squared value does not imply clinical homogeneity. S16 was excluded because the reported statistic was an ordinal between-group comparison rather than a correlation coefficient (Fig. 2).

3.4 Secondary meta-analysis: NfL and objective peripheral nerve injury

Five independent effects provided objective outcomes based on nerve conduction or intraepidermal nerve fiber density. After harmonization of direction, NfL correlated with more severe objective peripheral nerve injury (pooled r = 0.4205, 95% CI 0.2991–0.5285; p = 0.000879; I-squared = 0%; tau-squared = 0; Q = 1.75, p = 0.781) (Fig. 3).

3.5 Dependency-robust extension

The multilevel/robust variance estimation extension included nine compatible effects from six dependency clusters. The pooled estimate was r = 0.4506 (95% CI 0.3509–0.5401; CR2 p = 0.000685; Satterthwaite degrees of freedom = 3.334), closely matching the conventional model with one effect per cohort (Fig. 4). This agreement indicates that the primary conclusion was not driven by the choice among multiple within-study effect estimates.

3.6 Temporal, diagnostic, and prognostic performance

Only two independent compatible study clusters contributed temporal evidence, below the prespecified threshold of at least three clusters for pooling. No diagnostic-accuracy study provided a complete, independent, reconstructable 2 × 2 table; odds ratios adjusted for repeated observations could not uniquely recover true-positive, false-positive, false-negative, and true-negative counts. Diagnostic meta-analysis was therefore not performed. Reported areas under the curve ranged from approximately 0.526 to 0.982, but thresholds, sampling times, and target outcomes differed substantially; these results were summarized descriptively (Online Resource 1, Supplementary Table S3).

3.7 Risk of bias

All 23 reports underwent QUIPS assessment. The final master table contained 53 domain cells rated above low risk. Higher risk was concentrated in study attrition, outcome measurement, confounding, and statistical analysis/reporting. S12, S21, and S22 were rated as high risk overall; most other reports were rated as moderate risk. Study-level judgments and the overall domain distribution are provided in Online Resource 1 (Supplementary Figs. S1 and S5).

3.8 Certainty of evidence

Certainty of evidence was low for both the association of NfL with clinical CIPN severity and its association with objective peripheral nerve injury, primarily because of risk of bias in observational studies and indirectness across outcomes and time points. Temporal evidence was very low because few independent study clusters were available and estimates were imprecise. Diagnostic/prognostic evidence was very low because reconstructable 2 × 2 tables were unavailable, targets were heterogeneous, and risk of bias was substantial (Online Resource 1, Supplementary Fig. S6). Formal small-study-effect analyses were not performed because the quantitative syntheses contained fewer than 10 independent effects. The final clinical evidence synthesis is summarized in Table 2.

Table 2
Final synthesis of clinical evidence

Analysis	Evidence base	Pooled r	95% CI	I-squared	Inference/conclusion
Clinical CIPN severity	7 independent effects	0.4564	0.3408–0.5584	0.01%	HK p = 0.000123; GRADE low
Objective nerve injury	5 independent effects	0.4205	0.2991–0.5285	0%	HK p = 0.000879; GRADE low
Multilevel/RVE extension	9 effects/6 dependency clusters	0.4506	0.3509–0.5401	0%	CR2 p = 0.000685
Temporal NfL change	2 independent compatible clusters	—	—	—	Did not meet prespecified ≥ 3-cluster rule
Diagnostic/prognostic performance	0 reconstructable independent 2 × 2 tables	—	—	—	No diagnostic meta-analysis; GRADE very low

3.9 Multi-omics evidence integration

The primary transcriptomic analysis used two complete and comparable 48-h PTX–DMSO contrasts. Among 19,605 shared genes, 3,289 met FDR < 0.05, and 3,115 showed concordant directions in both datasets. Among significance-filtered genes reported for GSE173610, 363 of 364 comparable genes agreed in direction with the primary analysis. A three-dataset sensitivity analysis identified 412 genes with FDR < 0.05 among 585 jointly covered genes, although this analysis was affected by prefiltering of the reported result table.

Seven of the 12 prespecified pathways met FDR < 0.05 in the primary matched-control analysis. After substitution of the GSE305998 control batch, only sterol biosynthesis retained FDR < 0.05, within-dataset directional agreement, and a consistent pooled sign, indicating substantial batch sensitivity for the remaining pathways. Ninety-three RNA–protein pairs were mapped in the proteomic analysis; Spearman rho was 0.6015 ($p = 1.82 \times 10^{-19}$), and directional concordance was 79.6% (Online Resource 1, Supplementary Figs. S2-S4 and S7-S8; Supplementary Table S4).

4. Discussion

4.1 Principal findings and clinical relevance

The most important finding is not a single pooled estimate but the strong agreement across evidence domains and statistical frameworks. Conventional meta-analysis showed moderate positive correlations of circulating NfL with clinical CIPN severity (r = 0.456) and objective peripheral nerve injury (r = 0.420). After multiple compatible effects from the same study were included in a multilevel model with CR2 robust variance estimation, the pooled effect remained r = 0.451. The nearly overlapping estimates indicate that the association between NfL and the extent of CIPN-related injury is statistically robust and does not depend on a particular scale, study, or effect-selection rule.

This consistency gives NfL a clear potential clinical role. Clinical severity scales capture symptoms and functional effects, whereas nerve-conduction measures, sensory nerve action potentials, and intraepidermal nerve fiber density more directly assess peripheral nerve structure or function. Similar correlations with both outcome classes suggest that NfL reflects a shared dimension of axonal injury burden. Circulating NfL may therefore serve as an objective adjunct to symptom assessment and neurologic examination in patients receiving neurotoxic chemotherapy, particularly for longitudinal evaluation of worsening or recovery.

Although statistical heterogeneity was low, the included studies spanned different drugs, sampling times, assay platforms, and CIPN instruments. At present, the stability of direction and effect magnitude should therefore be emphasized over a universal absolute reference value across clinical settings.

4.2 The most practical role for NfL is longitudinal monitoring

The existing evidence structure suggests that the near-term value of NfL lies in dynamic monitoring rather than one-time screening. Obtaining an individual pretreatment baseline and repeating measurements at prespecified chemotherapy time points would allow NfL to serve as an objective signal that changes with treatment exposure. Within-person change may reduce the influence of age, preexisting neurologic status, assay platform, and baseline variation compared with a single absolute concentration, and it is also more consistent with the biology of NfL release after axonal injury.

In clinical research and future practice, NfL is best interpreted together with validated instruments such as TNSc/TNSr and CIPN20 and, when required, nerve-conduction studies or intraepidermal nerve fiber density. A pronounced longitudinal NfL increase accompanied by worsening symptoms or objective nerve-function measures could support intensified neurologic assessment, shorter follow-up intervals, or further evaluation of neurotoxicity. Its present value is to add a quantifiable objective reference rather than replace clinical judgment.

4.3 NfL metrics that warrant priority validation

Future studies should move beyond simple comparisons of high versus low NfL and prioritize dynamic measures that characterize the longitudinal course of nerve injury. Candidate metrics include: (1) early change from baseline (absolute or percentage/fold change) as an index of the early axonal response after treatment initiation; (2) the rate of NfL increase or the slope across serial measurements as a measure of injury progression; (3) the on-treatment peak and time to peak to characterize neurotoxicity kinetics across regimens; and (4) post-treatment decline or persistent elevation to distinguish reversible injury from persistent CIPN. These measures require prospective validation as research endpoints and should not be treated as established clinical thresholds.

Another important direction is to test the incremental information provided by NfL. Future studies could compare models containing clinical variables such as age, cumulative dose, diabetes, and preexisting neuropathy with models that additionally include early NfL change, slope, or peak concentration, and then evaluate discrimination, calibration, and clinical net benefit. Demonstrating consistent information beyond existing clinical risk factors would provide stronger evidence of clinical utility than reporting a study-specific optimal cutoff alone.

Prognostic studies should also report true-positive, false-positive, false-negative, and true-negative counts, or sufficient data to reconstruct a 2 × 2 table, and should specify sampling time, specimen matrix, assay platform, and the target CIPN definition. Such reporting will help determine which dynamic NfL metrics are most informative, when measurement is optimal, and whether different treatment regimens require different reference ranges.

4.4 Multi-omics findings reinforce an axonal-injury biological context

The multi-omics analyses provided an independent biological context for the clinical associations. Across two complete 48-h PTX–DMSO transcriptomic datasets, 3,289 of 19,605 shared genes met FDR < 0.05 and 3,115 were directionally concordant. Among the comparable significant genes in GSE173610, 363 of 364 agreed in direction. Furthermore, 93 RNA–protein pairs had a Spearman rho of 0.6015 and directional concordance of 79.6%. These findings show that paclitaxel-induced neuronal molecular responses are consistent across datasets and omics layers and complement the stable clinical meta-analytic association with axonal injury.

Sterol biosynthesis was the only pathway that retained all prespecified robustness criteria after substitution of the control batch and is therefore a priority candidate for mechanistic follow-up. Cytoskeletal organization, axonal transport, mitochondrial processes, and stress-related signaling remain secondary leads. At this stage, the principal value of the omics findings is to identify molecular processes for joint evaluation with NfL dynamics, not to establish any pathway as the direct cause of elevated circulating NfL.

4.5 Strengths, evidence boundaries, and next steps

This study integrated 23 clinical reports published through 2026, objective nerve-injury outcomes, dependency-robust meta-analysis, QUIPS/GRADE assessments, and public multi-omics evidence within one analytical framework. Overlapping cohorts and within-study effect dependence were handled explicitly. The close agreement among the conventional clinical model, objective-outcome model, and robust variance estimation extension makes a reproducible moderate association between circulating NfL and the extent of CIPN-related injury the most stable conclusion.

More standardized longitudinal studies are required to define optimal sampling windows, dynamic change metrics, and generalizable reference thresholds. The primary meta-analysis still contained relatively few independent effects; temporal and diagnostic data were insufficient for formal pooling; and multi-omics datasets were not derived from the same participants as the clinical studies. These limitations constrain clinical implementation and threshold definition more than they undermine the observed direction of association. The next priority is not a single universal cutoff but prospective validation of baseline-adjusted NfL change, rate of change, peak/recovery trajectories, and their joint relationship with TNSc/TNSr, CIPN20, nerve-conduction studies, and intraepidermal nerve fiber density.

5. Conclusion

Circulating NfL showed stable, moderate correlations with both clinical CIPN severity and objective peripheral nerve injury, with concordant results in dependency-robust analyses. Current evidence supports NfL as an adjunctive monitoring biomarker, whereas diagnostic thresholds, optimal sampling times, and regimen-specific performance require prospective validation. Transcriptome–proteome integration identified a reproducible but exploratory molecular context for CIPN, with sterol biosynthesis showing comparatively greater robustness to control-batch substitution. Direct links between the clinical biomarker and these molecular pathways require validation in independent cohorts with joint measurement.

Abbreviations

AUC, area under the receiver operating characteristic curve; CIPN, chemotherapy-induced peripheral neuropathy; CR2, small-sample-corrected cluster-robust inference; CTCAE, Common Terminology Criteria for Adverse Events; FDR, false discovery rate; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IENFD, intraepidermal nerve fiber density; NCS, nerve-conduction studies; NfL, neurofilament light chain; OIPN, oxaliplatin-induced peripheral neuropathy; PIPN, paclitaxel-induced peripheral neuropathy; QUIPS, Quality In Prognosis Studies; REML, restricted maximum likelihood; RVE, robust variance estimation; Simoa, single-molecule array; SNAP, sensory nerve action potential; TNSc/TNSr, Total Neuropathy Score clinical/reduced versions.

Declarations

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

Ethics approval was not required because this systematic review and secondary analysis used previously published reports and publicly available datasets and did not recruit new participants.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

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Author Contribution

Z.L., A.X., and P.L. contributed to the conception and design of the study. Z.L. performed the literature search, data extraction, statistical analysis, multi-omics analysis, data visualization, and drafted the manuscript. A.X. contributed to study selection, data extraction, data curation, and validation. T.H., B.W., K.W., C.W., and S.X. contributed to data verification, risk-of-bias assessment, interpretation of the results, and critical revision of the manuscript. P.L. supervised the study, contributed to methodology and interpretation of the results, and critically revised the manuscript. All authors reviewed and approved the final manuscript.

Data and code availability

Public omics datasets analyzed in this study are available under GSE173610, GSE305998, GSE312881, and PXD070094. Clinical extraction tables, QUIPS and GRADE judgments, and analysis code are retained in the project archive and are available from the corresponding author on reasonable request.

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Figures

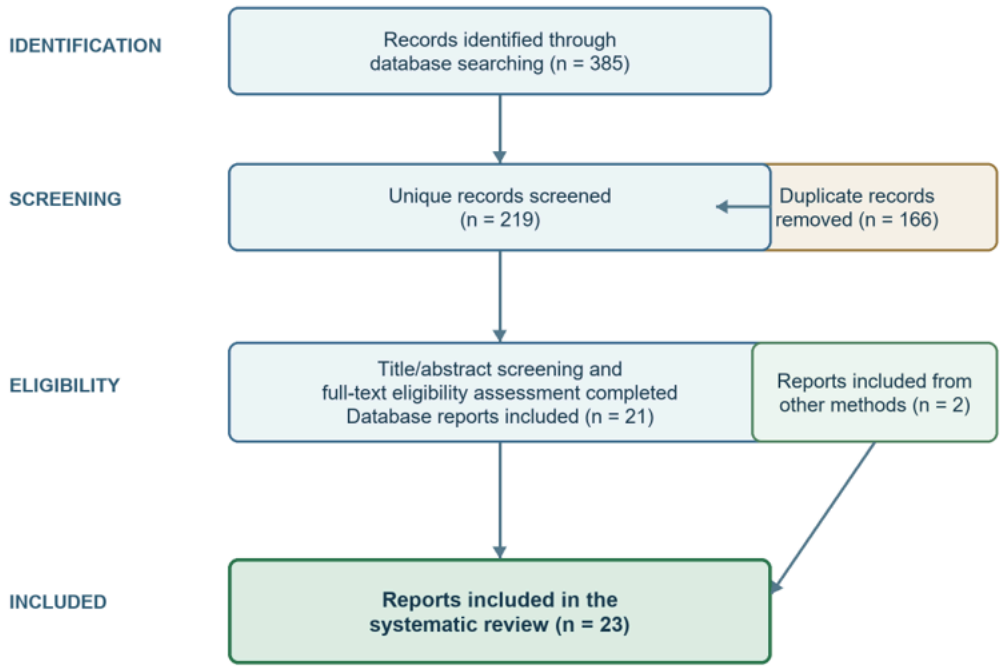


Figure 1

PRISMA 2020 flow diagram of study identification, screening, eligibility assessment, and inclusion

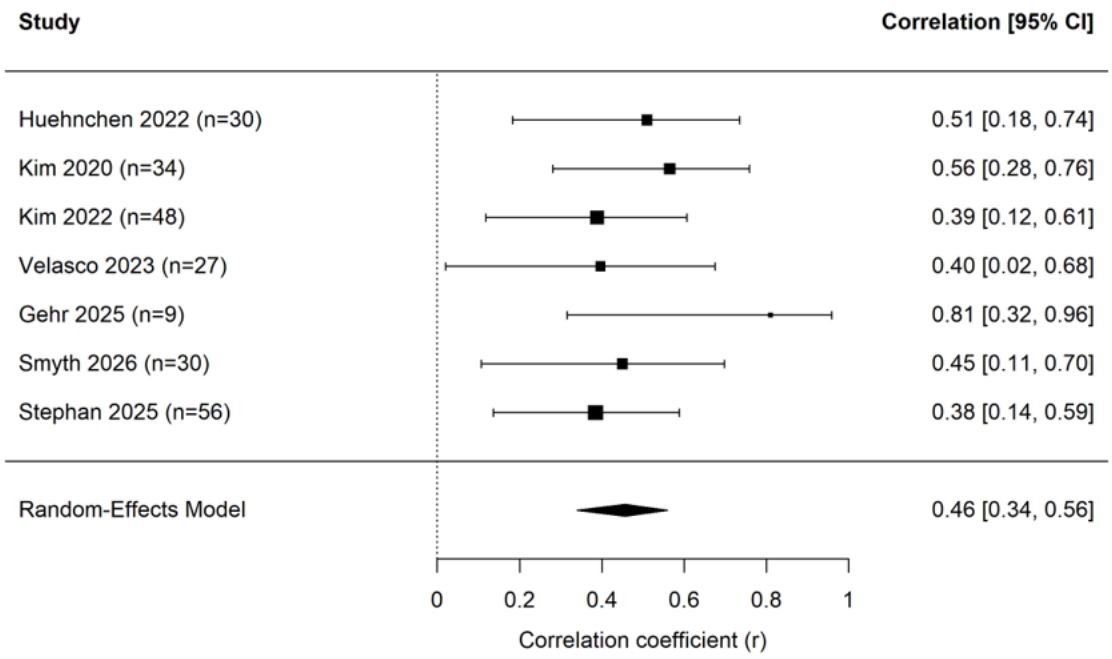


Figure 2

REML-Hartung-Knapp forest plot of correlations between circulating NfL and clinical CIPN severity

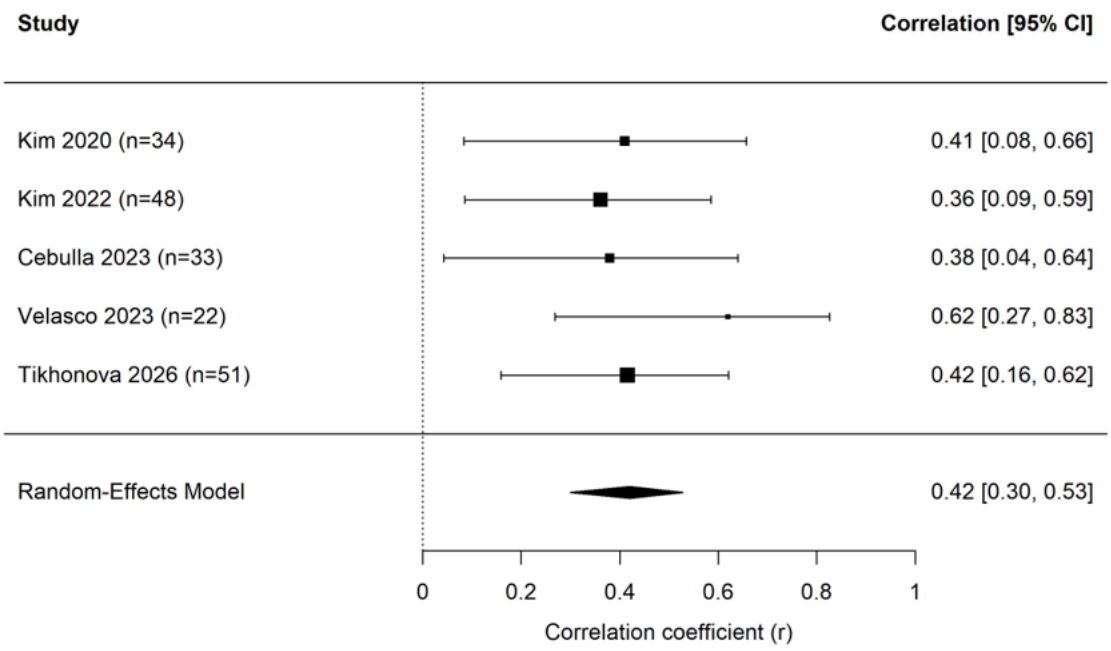


Figure 3

REML-Hartung-Knapp forest plot of correlations between circulating NfL and objective peripheral nerve injury

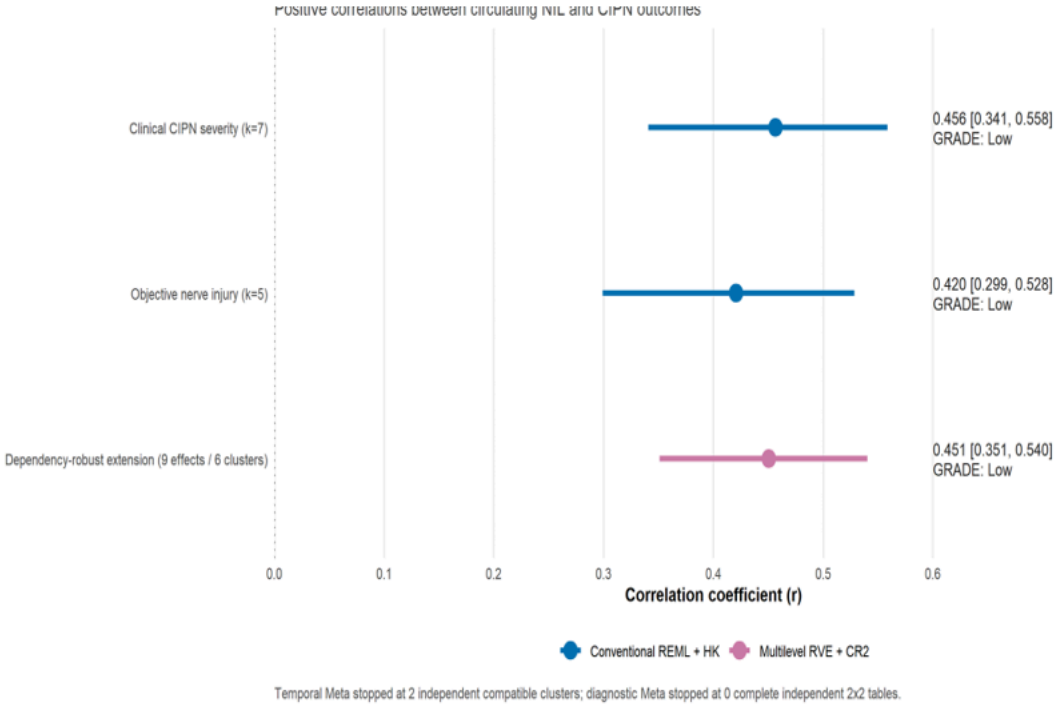


Figure 4

Overview of conventional correlation meta-analyses and the multilevel/robust variance estimation extension

Supplementary Files

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- PRISMA2020Checklist.pdf
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- ESM1.pdf