Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 10 May 2026
Revised 23 June 2026
Accepted 06 July 2026

Natural Resources for Human Health 2026, Vol. 6 (11s): 1038–1050

KEYWORDS:
Acute lymphoblastic leukemia; vincristine; chemotherapy-induced peripheral neuropathy; peripheral neurotoxicity; fine motor function; manual dexterity

Vincristine-Related Peripheral Neurotoxicity and Fine Motor Function in Pediatric Acute Lymphoblastic Leukemia: A Systematic Review

Lestari BM[1]*, Nilla Mayasari[1], Sylvia Evelyn Aritonang[1], Rumaisah Hasan[1]

[1]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

ABSTRACT: Vincristine-induced peripheral neuropathy (VIPN) is a frequent treatment-related complication of pediatric acute lymphoblastic leukemia (ALL), but its relationship with fine motor function across treatment phases remains unclear. This systematic review synthesized evidence on the association between vincristine-related peripheral neurotoxicity and fine motor function in pediatric ALL, with particular attention to maintenance chemotherapy. MEDLINE via PubMed, Scopus, and Dimensions were searched from inception through August 22, 2026, supplemented by backward reference screening and forward citation tracking. Eligible studies reported either directly measured chemotherapy-induced peripheral neuropathy/VIPN or vincristine exposure together with an extractable fine motor outcome. Evidence was classified as direct neurotoxicity assessment (Tier 1) or vincristine dose, schedule, frequency, or timing (Tier 2), appraised using design-specific Joanna Briggs Institute tools, and synthesized narratively. Of 168 records identified, seven reports representing six unique cohorts were included. Fine motor abnormalities were reported during active treatment, maintenance, post-treatment follow-up, and long-term survivorship. Associations between directly measured neuropathy and fine motor function were inconsistent, while cumulative vincristine exposure generally showed no clear dose–response relationship with fine motor performance. Manual dexterity and coordination deficits could persist despite relatively preserved broader fine motor composite scores. Directly measured neurotoxicity and vincristine exposure should therefore be regarded as related but distinct constructs. Paired assessment of peripheral neurotoxicity and domain-specific fine motor function may improve characterization of treatment-related functional impairment across the ALL treatment continuum.

1. INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most frequently diagnosed childhood malignancy, and contemporary treatment has raised survival to approximately 90% in many high-resource settings, increasing the importance of treatment-related morbidity during and after therapy [1,2]. Vincristine remains a mainstay of multiagent ALL chemotherapy but can produce vincristine-induced peripheral neuropathy (VIPN), a form of chemotherapy-induced peripheral neuropathy (CIPN) involving both motor and sensory nerve dysfunction [3].

VIPN can emerge early during treatment and may persist despite subsequent reduction in vincristine exposure. In a multicenter longitudinal study of children with B-ALL, CIPN was already prevalent at the end of consolidation and remained detectable during maintenance and 12 months after therapy, with little evidence that reducing vincristine frequency eliminated most neuropathic abnormalities [4]. Prospective clinical and neurophysiological studies similarly indicate that vincristine produces an early, predominantly motor sensorimotor neuropathy, with abnormalities detectable during treatment and persisting in some

children at follow-up [3,5]. Across pediatric cancers, CIPN has also been associated with functional limitations including impaired manual dexterity and motor proficiency [6].

Fine motor performance is particularly relevant in childhood because manual dexterity, precision, and coordination contribute to object manipulation, self-care, handwriting, and school-related activities [7]. Among children with ALL receiving maintenance chemotherapy, upper-limb coordination and the manual coordination composite have been reported below age- and sex-referenced norms [8]. A broader scoping review likewise found fine motor limitations during treatment and after treatment completion, although assessment methods and findings varied substantially across studies [7]. More recent off-therapy data reinforce this heterogeneity: overall fine motor performance was comparable with normative values, whereas manual dexterity and manual coordination remained significantly impaired [9].

Previous reviews have examined fine motor difficulties in pediatric ALL, the relationship between CIPN and broader physical function across pediatric cancers, and the clinical manifestations, risk factors, and management of vincristine-induced neurotoxicity in ALL [6,7,10]. These reviews address overlapping but distinct questions. A focused synthesis of whether the presence or severity of vincristine-related peripheral neurotoxicity is associated specifically with fine motor performance in pediatric ALL, and how this relationship varies across treatment phases, remains limited. This systematic review therefore aimed to synthesize evidence on the association between vincristine-related peripheral neurotoxicity and fine motor function in children and adolescents with ALL across treatment phases, with particular attention to maintenance chemotherapy.

2. MATERIALS AND METHODS

2.1 Protocol and reporting

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [11]. Because substantial clinical and methodological heterogeneity was anticipated, reporting of the narrative synthesis was additionally informed by the Synthesis Without Meta-analysis (SWiM) guideline [12]. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420261490843).

2.2 Review question and eligibility criteria

The review examined the association between vincristine-related peripheral neurotoxicity and fine motor function in children and adolescents with acute lymphoblastic leukemia (ALL) across treatment phases. Eligibility criteria were defined using a modified Population–Exposure–Comparator–Outcome (PECO) framework (Table 1).

Table 1. PECO framework and eligibility criteria

Component	Eligibility criterion
Population	Children and adolescents diagnosed with ALL; adult survivors were eligible when ALL had been diagnosed and treated during childhood
Primary exposure	Directly measured CIPN/VIPN using a validated neuropathy scale, clinical/neurological examination, quantitative neurological assessment, or electrophysiology
Secondary exposure	Cumulative vincristine dose, administration frequency, treatment schedule, or timing relative to vincristine administration
Comparator	Lower/no neuropathy; lower vincristine exposure; alternative vincristine schedule; healthy/normative controls; or within-participant longitudinal comparison. A separate comparator was not mandatory
Primary outcome	Fine motor function/manual dexterity
Other eligible fine motor domains	Fine motor precision, fine motor integration, manual coordination, upper-limb coordination, handwriting, drawing performance, and objectively measured hand function

Treatment phase	Any phase of treatment or follow-up, including induction, consolidation, delayed intensification/reinduction, maintenance, end of therapy, and survivorship
Principal subgroup	Maintenance chemotherapy
Eligible study designs	Randomized or non-randomized clinical studies, prospective or retrospective cohort studies, analytical cross-sectional studies, case-control studies, and case series with extractable exposure–outcome data
Main exclusions	No eligible neurotoxicity/vincristine exposure; no extractable fine motor outcome; mixed cancer population without separately extractable ALL data; case reports; reviews; editorials; insufficient conference reports; animal studies
Publication date	No restriction
Language at search stage	No language filter applied

Abbreviations: ALL, acute lymphoblastic leukemia; CIPN, chemotherapy-induced peripheral neuropathy; PECO, Population–Exposure–Comparator–Outcome; VIPN, vincristine-induced peripheral neuropathy.

Eligible populations included children and adolescents with ALL and adult survivors who had been treated for ALL during childhood. The primary exposure was directly measured chemotherapy-induced peripheral neuropathy (CIPN) or vincristine-induced peripheral neuropathy (VIPN), assessed using clinical, neurological, quantitative, or electrophysiological methods. Vincristine cumulative dose, administration frequency, treatment schedule, and timing relative to vincristine administration were considered secondary exposure measures.

The primary outcome was fine motor function or manual dexterity, including fine motor precision, fine motor integration, manual coordination, handwriting, drawing, and objectively assessed hand function. Studies conducted during any treatment or follow-up phase were eligible, with maintenance chemotherapy prespecified as the principal subgroup of interest.

Eligible study designs included clinical studies, cohort studies, analytical cross-sectional studies, case-control studies, and case series with extractable exposure–outcome data. Studies involving mixed pediatric cancer populations were eligible only when ALL-specific data could be extracted separately. Studies were excluded if they lacked an eligible neurotoxicity or vincristine exposure measure, did not assess fine motor outcomes, reported only gross motor or general physical function, or were case reports, reviews, editorials, insufficient conference reports, or animal studies. No publication-date restriction was applied.

2.3 Information sources and search strategy

MEDLINE via PubMed, Scopus, and Dimensions were searched from inception through August 22, 2026. Database searching was supplemented by backward reference screening and forward citation tracking (Table 2). Search strategies combined controlled vocabulary and free-text terms related to ALL, pediatric populations, vincristine-related peripheral neurotoxicity, and fine motor function. Fine motor search terms included *manual dexterity*, *manual coordination*, *handwriting*, *pegboard*, *BOT-2*, and *Movement Assessment Battery for Children*. Broader combinations of ALL and fine motor terms were used in Scopus and Dimensions to maximize sensitivity, with exposure eligibility confirmed during full-text review. "Maintenance" was not required as a search term because studies from all treatment phases were eligible. No publication-year, language, study-design, document-type, or open-access filters were applied. Complete database-specific search strategies are provided in Supplementary Table S1.

Table 2. Information sources and search yield

Database/source	Search field	Coverage	Search date	Records identified
MEDLINE via PubMed	MeSH and title/abstract	Inception–August 22, 2026	August 22, 2026	32

Scopus	Title, abstract, and keywords	Inception–August 22, 2026	August 22, 2026	48
Dimensions	Title and abstract	Inception–August 22, 2026	August 22, 2026	88
Total database records	—	—	—	**168**
Backward reference screening	Reference lists of included studies and relevant reviews	—	August 2026	0
Forward citation tracking	Citations to eligible reports	—	August 2026	0

2.4 Study selection and data extraction

After duplicate removal, two reviewers independently screened titles and abstracts and subsequently assessed potentially eligible full-text reports. Disagreements were resolved through consensus or, when necessary, adjudication by a third reviewer. Reasons for exclusion at the full-text stage were documented for the PRISMA flow diagram.

Two reviewers independently extracted study and participant characteristics, treatment phase, vincristine exposure, neurotoxicity assessment, fine motor measures, comparator characteristics, statistical methods, effect estimates, measures of precision, and relevant findings. Discrepancies were resolved by consensus. Reports arising from overlapping cohorts were linked for cohort-level interpretation while retaining report-specific outcomes and avoiding participant double-counting.

2.5 Exposure classification

To distinguish clinically measured peripheral neurotoxicity from vincristine treatment exposure, evidence was classified into two prespecified categories (Table 3).

Tier 1 included studies directly assessing CIPN or VIPN using neuropathy-specific clinical, neurological, quantitative, or electrophysiological methods.

Tier 2 included studies evaluating vincristine cumulative dose, administration frequency, treatment schedule, or timing relative to vincristine administration.

Studies reporting both constructs could contribute to both categories. However, vincristine exposure was not assumed to represent the presence or severity of peripheral neuropathy.

Table 3. Operational classification of exposures for synthesis

Evidence category	Definition	Examples of eligible measures	Interpretation
Tier 1: measured CIPN/VIPN	Direct clinical or objective measurement of peripheral neurotoxicity	Ped-mTNS/mTNS, structured sensory or motor examination, clinical CIPN assessment, electrophysiological measures	Represents presence or severity of peripheral neurotoxicity
Tier 2: vincristine exposure	Amount, frequency, schedule, or timing of vincristine treatment	Cumulative dose, dose frequency, reduced versus standard schedule, timing before/after vincristine administration	Represents treatment exposure; not assumed to equal neuropathy severity

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; mTNS, modified Total Neuropathy Score; Ped-mTNS, pediatric-modified Total Neuropathy Score; VIPN, vincristine-induced peripheral neuropathy.

2.6 Risk-of-bias assessment

Two reviewers independently assessed methodological quality using the Joanna Briggs Institute (JBI) critical appraisal tool appropriate to each study design [13], as summarized in Table 4. Applicable items were rated as *Yes*, *No*, *Unclear*, or *Not Applicable*, with attention to participant selection, validity of exposure and outcome measurement, control of confounding, completeness of follow-up where applicable, and appropriateness of statistical analysis.

Disagreements were resolved through consensus or third-reviewer adjudication. Risk-of-bias findings informed interpretation of the evidence but were not used as an automatic basis for study exclusion.

Table 4. JBI appraisal framework applied in the review

Study design/analytic structure	JBI appraisal tool
Randomized treatment comparison	JBI Critical Appraisal Checklist for Randomized Controlled Trials
Prospective or retrospective longitudinal cohort	JBI Critical Appraisal Checklist for Cohort Studies
Analytical cross-sectional association	JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies
Uncontrolled case series with analyzable exposure/outcome data	JBI Critical Appraisal Checklist for Case Series
Quasi-experimental comparison, if applicable	JBI Critical Appraisal Checklist for Quasi-Experimental Studies

Abbreviation: JBI, Joanna Briggs Institute.

2.7 Data synthesis

Because the included studies differed substantially in treatment phase, neurotoxicity assessment, vincristine exposure, fine motor instrument, and effect measure, narrative synthesis was prespecified as the primary synthesis approach, with SWiM principles applied where appropriate [12].

Evidence was synthesized first according to exposure category (Tier 1 vs Tier 2) and subsequently according to treatment timing, including active or intensive treatment, maintenance chemotherapy, post-treatment follow-up, and long-term survivorship. For each report, the direction, magnitude, and precision of the exposure–fine motor association were considered together with study design and risk of bias. Statistical significance was not used as a simple vote-counting criterion.

Comparisons with healthy controls or normative values were distinguished from direct exposure–outcome analyses. Poorer fine motor performance alone was therefore not interpreted as evidence of a vincristine-related association unless neuropathy or vincristine exposure had been separately evaluated.

Meta-analysis was planned only if studies were sufficiently comparable in population, exposure, outcome, and effect measure. Where these conditions were not met, findings were synthesized narratively. Formal GRADE ratings were not undertaken because of substantial heterogeneity in exposure constructs and outcome measures; considerations of risk of bias, consistency, directness, and precision were instead incorporated into the interpretation of findings.

3. RESULTS AND DISCUSSION

3.1 Study selection

The searches identified 168 records (PubMed, n = 32; Scopus, n = 48; Dimensions, n = 88). After removal of 60 duplicates, 108 records were screened and 21 full-text reports were assessed. Fourteen were excluded for absence of an eligible neurotoxicity/vincristine exposure–fine motor analysis (n=7), no extractable fine-motor-specific outcome (n=4), non-extractable ALL data from mixed cancer populations (n=2), or an exposure outside the prespecified PECO (n=1). Seven reports representing six unique cohorts were included (Figure 1).

Natural Resources for Human Health
eISSN: 2583-1194

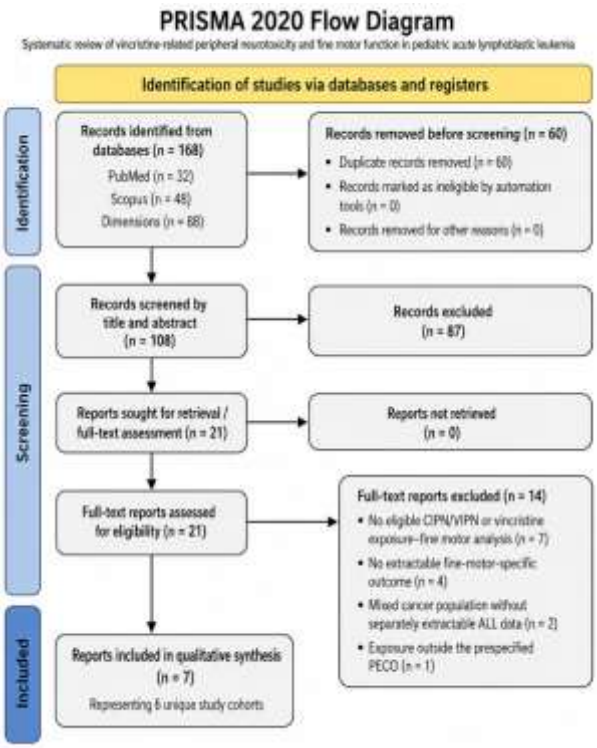

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram of study identification, screening, eligibility assessment, and inclusion. Seven reports representing six unique study cohorts were included in the narrative synthesis.

3.2 Characteristics of Included Studies

The seven reports, published between 1999 and 2025, represented six cohorts ranging from 15 to 875 participants with ALL and covered active treatment, maintenance, early post-treatment follow-up, and long-term survivorship. Two reports arose from an overlapping Dutch cohort and were retained because they evaluated different fine motor outcomes but were not treated as independent populations [14, 15]. Study characteristics are summarized in Table 5.

Table 5. Characteristics of included reports

Study	Country and design	ALL sample	Treatment phase/follow-up	Neurotoxicity or VCR exposure	Fine motor assessment
Reinders-Messelink et al., 1999	Netherlands; prospective longitudinal controlled study	17 ALL + 10 controls; age 4–12 y	Active treatment through approximately 6 months after final studied VCR course	VCR timing; cumulative and recovery neurotoxicity models	Movement ABC; manual dexterity
Reinders-Messelink et al., 2001*	Netherlands; prospective longitudinal controlled study	11 ALL + 11 controls	Active treatment; repeated assessments around VCR administration	Timing relative to VCR administration	Computerized handwriting/drawing: velocity, pauses, pressure, accuracy
Sabarre et al., 2014	Canada; prospective case series	15; age 5–16 y	Maintenance	Cumulative VCR exposure	MABC-2 manual dexterity; parent-reported motor function

Hanna et al., 2020	Egypt; analytical cross-sectional controlled study	54 ALL + 54 matched controls; age 4–7 y	Maintenance	Cumulative VCR and other chemotherapy exposure	BOT-2 fine motor domains and composites
Rodwin et al., 2022	USA; multicenter prospective longitudinal study embedded in randomized treatment trial	150 assessed initially; 113 randomized	End consolidation, maintenance, and 12 months post-therapy	Clinical CIPN assessment; randomized VCR/DEX pulse frequency	Purdue Pegboard
Iijima et al., 2024	USA; survivor cohort	875 survivors + 460 controls	Long-term survivorship	mTNS; cumulative VCR dose	Grooved Pegboard and fine motor Physical Performance Test
Jevic et al., 2025	Czech Republic; cross-sectional study	39	Mean 1.5 y after maintenance	Ped-mTNS	BOT-2 Complete Form

Note: *Substantial participant overlap with Reinders-Messelink et al. (1999); both reports were retained because they provided distinct fine motor outcomes but were considered one underlying cohort.

Abbreviations: ALL, acute lymphoblastic leukemia; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency, Second Edition; CIPN, chemotherapy-induced peripheral neuropathy; DEX, dexamethasone; MABC, Movement Assessment Battery for Children; mTNS, modified Total Neuropathy Score; Ped-mTNS, pediatric-modified Total Neuropathy Score; VCR, vincristine.

3.3 Assessment of Peripheral Neurotoxicity

Three reports provided Tier 1 evidence through direct peripheral neurotoxicity assessment: structured sensory/motor examination [4], mTNS [16], and Ped-mTNS [9]. Other reports primarily evaluated vincristine dose, schedule, or treatment timing and were classified as Tier 2 evidence (Table 6).

Table 6. Peripheral neurotoxicity, vincristine exposure, and fine motor findings

Study	Evidence tier	Key findings	Interpretation
Reinders-Messelink et al., 1999	Tier 2	Manual dexterity impairment varied during treatment; approximately 14% were below the 15th percentile before VCR exposure, 25% after induction, and 33% at final follow-up. Prespecified VCR neurotoxicity models were not statistically supported.	Fine motor impairment occurred during treatment, but a clear VCR exposure effect was not demonstrated.
Reinders-Messelink et al., 2001*	Tier 2	Handwriting/drawing measures varied around VCR administration: velocity $P = 0.017$, pen pressure $P = 0.002$, pauses $P = 0.006$.	Temporal variation around VCR administration, without direct measurement of CIPN severity
Sabarre et al., 2014	Tier 2	Nearly half performed below age expectations for manual dexterity; 27% were significantly impaired. Cumulative VCR vs manual dexterity: $r_s=0.03$, $P = 0.91$.	Fine motor impairment was common, without a cumulative VCR dose–response relationship.
Hanna et al., 2020	Tier 2	ALL participants performed worse than controls across BOT-2 fine motor domains ($P < 0.00001$); approximately 67% had fine motor difficulties.	Marked maintenance-phase impairment relative to controls,

		Cumulative VCR was not significantly correlated with BOT-2 outcomes.	without evidence of cumulative VCR dose dependence.
Rodwin et al., 2022	Tier 1 + Tier 2	Any motor or sensory CIPN impairment at the end of consolidation: 81.8%; dexterity impairment: 55.0% at the end of consolidation and 33.3% at 12 months post-therapy. Reduced maintenance VCR/DEX frequency did not materially improve most outcomes	Neurotoxicity and dexterity impairment appeared early and persisted despite reduced maintenance exposure.
Iijima et al., 2024	Tier 1 + Tier 2	Fine motor impairment: 33.6%. CRT-exposed survivors: mTNS OR 1.08, 95% CI 1.01–1.17; P = 0.037; no-CRT group: OR 1.04, 95% CI 0.93–1.16; P = 0.474. Cumulative VCR dose was not significantly associated with impairment.	Direct neuropathy–fine motor association was observed in CRT-exposed survivors but not in those without CRT; cumulative VCR dose showed no clear association.
Jevic et al., 2025	Tier 1	Neuropathy in 7/39. Ped-mTNS vs fine motor composite: r=−0.21, NS. Manual dexterity $P < 0.001$, d=0.59; manual coordination P = 0.018, d=0.45 versus norms.	Direct neuropathy association was not evident for the composite score, although specific fine motor domains were impaired.

Note: *Overlapping cohort with Reinders-Messelink et al. (1999). Tier 1: directly measured CIPN/VIPN. Tier 2: vincristine dose, frequency, schedule, or timing. Tier 2 exposure was not considered equivalent to neuropathy severity.

Abbreviations: ALL, acute lymphoblastic leukemia; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency, Second Edition; CIPN, chemotherapy-induced peripheral neuropathy; CRT, cranial radiation therapy; DEX, dexamethasone; mTNS, modified Total Neuropathy Score; Ped-mTNS, pediatric-modified Total Neuropathy Score; VCR, vincristine; VIPN, vincristine-induced peripheral neuropathy.

3.4 Assessment of Fine Motor Function

Fine motor measures included Movement ABC/MABC-2, computerized handwriting and drawing tasks, BOT-2, Purdue Pegboard, Grooved Pegboard, and fine-motor components of the Physical Performance Test. Outcomes therefore ranged from global fine motor composites to more specific domains such as manual dexterity and manual coordination (Tables 5 and 6).

3.5 Association Between CIPN and Fine Motor Function

Direct evidence relating measured neuropathy to fine motor function was limited and inconsistent. Rodwin et al. (2022) reported motor or sensory CIPN impairment in 81.8% of children at the end of consolidation, with dexterity impairment in 55.0%; dexterity impairment declined but persisted in 33.3% at 12 months post-therapy [4].

Among long-term survivors, Iijima et al. (2024) reported fine motor impairment in 33.6%. In survivors exposed to cranial radiation therapy (CRT), each one-point increase in mTNS was associated with greater odds of fine motor impairment (OR 1.08, 95% CI 1.01–1.17; P = 0.037), whereas this association was not observed in survivors without CRT [16].

Jevic et al. (2025) found no significant association between Ped-mTNS and the fine motor composite (r=−0.21), although manual dexterity ($P < 0.001$; d=0.59) and manual coordination (P = 0.018; d=0.45) were poorer than normative values [9].

3.6 Findings Across Treatment Phases

Fine motor abnormalities were identified throughout the treatment trajectory. During active treatment, Reinders-Messelink et al. (1999, 2001) documented changes in manual dexterity and handwriting-related performance around vincristine administration [14,15]. During maintenance chemotherapy, Sabarre et al. (2014) and Hanna et al. (2020) identified substantial fine motor impairment, although neither demonstrated a cumulative vincristine dose–response relationship [17,18]. Rodwin et al. (2022) showed persistence of CIPN and dexterity impairment from consolidation through maintenance and post-treatment follow-up [4]. In survivorship, Iijima et al. (2024) reported persistent fine motor impairment [16], whereas Jevic et al. (2025) found deficits primarily in specific fine motor domains rather than in the overall composite score [9].

3.7 Vincristine Exposure and Fine Motor Function

Across Tier 2 studies, cumulative vincristine exposure was not consistently associated with fine motor performance. Sabarre et al. (2014) found no association between cumulative vincristine exposure and manual dexterity (r_s=0.03; p=0.91) [18]. Similarly, Hanna et al. (2020) found no significant correlations between cumulative vincristine dose and BOT-2 outcomes despite marked impairment relative to controls [17].

Reinders-Messelink et al. (1999) likewise found no statistically supported cumulative neurotoxicity model [14]. However, the overlapping 2001 report identified temporal changes in movement velocity (p=0.017), pen pressure (p=0.002), and pauses (p=0.006) around vincristine administration [15]. Reduced vincristine/dexamethasone pulse frequency did not materially improve dexterity in Rodwin et al. (2022) [4], and cumulative vincristine dose was not associated with fine motor impairment in Iijima et al. (2024) [16].

3.8 Risk of Bias

JBI appraisal showed generally adequate measurement and analytical methods across the included reports, particularly through the use of standardized fine motor assessments and clearly characterized treatment exposures. The main methodological concerns were small sample sizes in earlier studies, residual confounding related to multiagent chemotherapy, incomplete reporting of some randomization safeguards, potential selection bias in convenience or survivor cohorts, and limited temporal inference in cross-sectional analyses.

These limitations were considered when interpreting the findings, and no report was excluded solely on the basis of critical appraisal. Detailed assessments are presented in Table 7 and Supplementary Table S2.

Table 7. Summary of risk-of-bias appraisal

Study	JBI tool	Principal methodological strengths	Main limitations relevant to interpretation
Reinders-Messelink et al., 1999	Cohort	Prospective repeated assessment; control group; standardized motor testing	Small sample; potential multiagent-treatment confounding; indirect VCR neurotoxicity modeling
Reinders-Messelink et al., 2001	Cohort	Prospective repeated measurements; objective computerized motor outcomes	Very small sample; overlapping cohort; residual treatment confounding
Sabarre et al., 2014	Case Series	Defined maintenance population; standardized MABC-2 assessment	Convenience sample; n=15; no concurrent control; low power
Hanna et al., 2020	Analytical Cross-Sectional	Matched controls; validated BOT-2; domain-specific assessment	Cross-sectional design; no direct neuropathy measurement; residual confounding
Rodwin et al., 2022	Randomized Controlled Trial	Multicenter; repeated assessments; randomized maintenance schedule; objective dexterity outcome	Randomization concerned treatment schedule rather than neuropathy status; attrition; concurrent DEX schedule
Iijima et al., 2024	Cohort	Large cohort; objective neuropathy and fine motor measures; multivariable analysis	Survivor selection; heterogeneous historical therapies; residual confounding
Jevic et al., 2025	Analytical Cross-Sectional	Ped-mTNS and full BOT-2; domain-specific assessment	Small sample; cross-sectional design; normative comparison; limited multivariable adjustment

Abbreviations: BOT-2, Bruininks-Oseretsky Test of Motor Proficiency, Second Edition; DEX, dexamethasone; JBI, Joanna Briggs Institute; MABC-2, Movement Assessment Battery for Children, Second Edition; Ped-mTNS, pediatric-modified Total Neuropathy Score; RCT, randomized controlled trial.

3.9 Discussion

Fine motor difficulties were reported across the ALL treatment continuum, but their relationship with vincristine-related peripheral neurotoxicity was not uniform. A central distinction emerging from this review was between clinically measured neurotoxicity and vincristine exposure itself. Direct associations between measured neuropathy and fine motor impairment were observed in some settings but were not consistent, whereas cumulative vincristine exposure generally showed no clear dose–response relationship with fine motor performance. Domain-specific deficits, particularly manual dexterity and coordination, could also remain detectable despite relatively preserved broader fine motor composites. These findings extend an ALL-specific review documenting fine motor limitations during and after treatment and complement broader pediatric cancer evidence linking CIPN with manual dexterity and other functional outcomes [6,7].

The Tier 1 evidence indicates that neuropathy and functional motor impairment overlap but are not interchangeable. Rodwin et al. (2022) showed that CIPN was already prevalent by the end of consolidation and persisted 12 months after therapy; dexterity impairment was also present early and remained detectable after treatment, although the study did not establish a direct neuropathy severity–dexterity relationship [4]. In long-term survivors, higher mTNS was associated with greater odds of fine motor impairment among those exposed to CRT in Iijima et al. (2024) [16], whereas Jevic et al. (2025) found no significant association between Ped-mTNS and the overall fine motor composite despite deficits in manual dexterity and manual coordination [9]. This heterogeneity is biologically and functionally plausible because vincristine produces an early, motor-predominant sensorimotor neuropathy, whereas fine motor performance integrates peripheral sensory-motor function with coordination and visual-motor processing and may also be influenced by broader treatment-related central nervous system effects [3,5,19,20].

Cumulative vincristine dose was a comparatively weak marker of fine motor dysfunction. No significant cumulative dose relationship was demonstrated by Sabarre et al. (2014) [18], Hanna et al. (2020) [17], or Iijima et al. (2024) [16]. Similarly, the randomized reduction in vincristine/dexamethasone pulse frequency during maintenance in Rodwin et al. (2022) did not materially alter dexterity or most other PT/OT outcomes [4]. These findings should not be interpreted as evidence that vincristine is unrelated to neuropathy. Rather, they indicate that cumulative exposure and the clinically expressed neurotoxicity phenotype are distinct constructs. Pediatric evidence likewise suggests that cumulative chemotherapy dose alone does not adequately predict CIPN severity, while VIPN risk appears to reflect interindividual variation in pharmacokinetics, drug interactions, and pharmacogenomic susceptibility; however, reported genetic associations remain heterogeneous and require replication [21–24].

Across the treatment continuum, the evidence was more consistent with heterogeneous persistence and recovery than with a progressive phase-specific gradient, a pattern broadly compatible with ALL motor-function literature showing treatment-related deficits during therapy and persistence of some impairments into survivorship [25]. Reinders-Messelink et al. (1999, 2001) assessed motor and handwriting performance at time points aligned with vincristine administration; the 2001 study identified temporal changes in handwriting-related performance, whereas the earlier study did not statistically confirm a relationship between vincristine and motor impairment [14,15]. During maintenance, substantial fine motor difficulties were observed by Sabarre et al. (2014) [18] and Hanna et al. (2020) [17], despite absent cumulative vincristine dose associations. Rodwin et al. (2022) documented persistent CIPN and dexterity impairment from consolidation through maintenance and post-therapy follow-up [4]. Long-term findings were similarly heterogeneous: Iijima et al. (2024) identified substantial fine motor impairment decades after childhood ALL [16], whereas Jevic et al. (2025) found preserved overall fine motor performance approximately 1.5 years after therapy but persistent deficits in manual dexterity and coordination [9].

Measurement heterogeneity is likely to contribute to these apparently inconsistent findings because neuropathy and fine motor instruments assess related but distinct constructs. Ped-mTNS and mTNS quantify clinician-assessed neurological manifestations, while pediatric patient-reported tools such as the P-CIN capture symptom burden; BOT-2, MABC-2, pegboard tests, and handwriting tasks instead assess different dimensions of functional performance [26,27]. An updated systematic review identified Ped-mTNS and TNS-PV as the most appropriate clinician-administered pediatric CIPN tools currently

available [26]. Instrument selection also matters: the BOT-2 Short Form systematically underestimated motor proficiency relative to the Complete Form in ALL survivors [28], while Jevic et al. (2025) demonstrated that an apparently normal overall fine motor composite can coexist with impaired manual dexterity and coordination [9]. Paired assessment of neuropathy and domain-specific hand function may therefore provide more clinically informative surveillance than cumulative vincristine exposure alone. A recent quality-improvement initiative demonstrated the feasibility of adding motor, sensory, and motor-performance assessments to longitudinal physical therapy surveillance in children with ALL, although evidence remains insufficient to establish the efficacy of specific physical therapy interventions in pediatric cancer populations [29,30].

This review specifically examined the relationship between peripheral neurotoxicity and fine motor function in pediatric ALL, distinguished direct neuropathy assessment from vincristine exposure, and evaluated evidence across treatment phases while accounting for overlapping reports. Interpretation remains limited by seven reports representing six unique cohorts, small samples in several studies, heterogeneous outcome measures, differences in treatment era, multiagent-therapy confounding, and predominantly observational exposure–outcome evidence. These sources of clinical and methodological heterogeneity precluded meaningful quantitative synthesis and are consistent with heterogeneity reported in broader reviews of ALL-related fine motor impairment and pediatric CIPN-associated physical dysfunction [6,7]. Future prospective studies should repeatedly pair validated neuropathy measures with domain-specific dexterity assessments while documenting vincristine dose modifications, concomitant therapies, and relevant individual susceptibility factors.

4. CONCLUSION

Fine motor impairment occurs across the ALL treatment continuum, but its association with vincristine-related peripheral neurotoxicity is inconsistent. Directly measured neuropathy may be more informative than cumulative vincristine exposure, which showed no clear dose–response relationship with fine motor performance. Manual dexterity and coordination deficits may persist despite preserved composite scores. Prospective longitudinal studies using standardized neuropathy and fine motor measures are needed to clarify these relationships and guide targeted rehabilitation.

AUTHOR CONTRIBUTIONS

LBM: Conceptualization, Methodology, Investigation, Literature Search, Study Selection, Data Extraction, Data Synthesis, Formal Analysis, and Writing – Original Draft.

NM: Conceptualization, Methodology, Supervision, Validation, Interpretation of Findings, and Writing – Review & Editing.

SEA: Methodology, Supervision, Validation, Interpretation of Findings, and Writing – Review & Editing.

RH: Methodology, Supervision, Validation, Interpretation of Findings, and Writing – Review & Editing.

All authors critically reviewed the manuscript, approved the final version, and agreed to be accountable for the accuracy and integrity of the work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

This research received no external funding.

ETHICS STATEMENT

Ethical approval and informed consent were not required for this systematic review because it synthesized data from previously published studies and did not involve direct recruitment of human participants or collection of identifiable individual-level data. The review protocol was prospectively registered in PROSPERO (CRD420261490843).

DATA AVAILABILITY STATEMENT

All data supporting the findings of this systematic review were derived from the published studies included in the review and are presented within the article and its supplementary materials. Additional review data are available from the corresponding author upon reasonable request.

REFERENCES

[1] Elgazar S, Constantinou C. Paediatric acute lymphoblastic leukaemia: a narrative review of current knowledge and advancements. Curr Oncol Rep. 2024;26(12):1586–1599.
[2] Rujkijyanont P, Inaba H. Diagnostic and treatment strategies for pediatric acute lymphoblastic leukemia in low- and middle-income countries. Leukemia. 2024;38(8):1649–1662.
[3] Li T, Kandula T, Cohn RJ, Kiernan MC, Park SB, Farrar MA. Prospective assessment of vincristine-induced peripheral neuropathy in paediatric acute lymphoblastic leukemia. Clin Neurophysiol. 2023;154:157–168.
[4] Rodwin RL, Kairalla JA, Hibbitts E, Devidas M, Whitley MK, Mohrmann CE, *et al.* Persistence of chemotherapy-induced peripheral neuropathy despite vincristine reduction in childhood B-acute lymphoblastic leukemia. J Natl Cancer Inst. 2022;114(8):1167–1175.
[5] Viinikainen K, Isohanni P, Kanerva J, Lönnqvist T, Lauronen L. Without ENMG, detecting pediatric vincristine neuropathy is a challenge. Clin Neurophysiol Pract. 2024;9:94–101.
[6] Tanner LR, Demers C, Schorr EN, Rosenberg NS, Hooke MC, Turcotte LM, *et al.* Impact of chemotherapy-induced peripheral neuropathy on physical function in pediatric cancer survivors: a systematic review. J Cancer Surviv. 2026;20(4):1631–1647.
[7] Hanna S, El-Ayadi M, Abdelazeim F. Identifying fine motor difficulties in children with acute lymphoblastic leukemia: a scoping review. Support Care Cancer. 2024;32(7):488.
[8] Tejeda-Castellanos X, Sánchez-Medina CM, Márquez-González H, Alaniz-Arcos JL, Ortiz-Cornejo ME, Brito-Suárez JM, *et al.* Impairments in fine motor skills in children with acute lymphoblastic leukaemia: a cross-sectional study. BMC Pediatr. 2023;23(1):513.
[9] Jevic F, Andel R, Hrdouskova M, Kobesova A. Investigating fine and gross motor deficits in pediatric patients off therapy for acute lymphoblastic leukemia. Ann Med. 2025;57(1):2477292.
[10] Ahmed HS, D'Souza L, Suhas D, Nair SV, Singhvi M, Bhat CSP. Vincristine-induced neurotoxicity in acute lymphoblastic leukemia: a comprehensive systematic review. Indian J Hematol Blood Transfus. 2026;42(1):11–49.
[11] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
[12] Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, *et al.* Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ. 2020;368:l6890.
[13] Aromataris E, Lockwood C, Porritt K, Pilla B, Jordan Z, editors. JBI manual for evidence synthesis. Adelaide: JBI; 2024.
[14] Reinders-Messelink H, Schoemaker M, Snijders T, Göeken L, van den Briel M, Bökkerink J, *et al.* Motor performance of children during treatment for acute lymphoblastic leukemia. Med Pediatr Oncol. 1999;33(6):545–550.
[15] Reinders-Messelink HA, Schoemaker MM, Snijders TAB, Göeken LNH, Bökkerink JPM, Kamps WA. Analysis of handwriting of children during treatment for acute lymphoblastic leukemia. Med Pediatr Oncol. 2001;37(4):393–399.
[16] Iijima M, Hyun G, Brinkman TM, Khan RB, Srivastava DK, Robison LL, *et al.* Fine motor impairment and its impact on social outcomes in survivors of pediatric acute lymphoblastic leukemia: St. Jude Lifetime Cohort Study. Phys Ther. 2024;104(11):pzae142.
[17] Hanna S, Elshennawy S, El-Ayadi M, Abdelazeim F. Investigating fine motor deficits during maintenance therapy in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2020;67(7):e28385.
[18] Sabarre CL, Rassekh SR, Zwicker JG. Vincristine and fine motor function of children with acute lymphoblastic leukemia. Can J Occup Ther. 2014;81(4):256–264.
[19] Tay N, Laakso EL, Schweitzer D, Endersby R, Vetter I, Starobova H. Chemotherapy-induced peripheral neuropathy in children and adolescent cancer patients. Front Mol Biosci. 2022;9:1015746.
[20] Gandy K, Scoggins MA, Jacola LM, Litten M, Reddick WE, Krull KR. Structural and functional brain imaging in long-term survivors of childhood acute lymphoblastic leukemia treated with chemotherapy: a systematic review. JNCI Cancer Spectr. 2021;5(5):pkab069.
[21] Smith EML, Kuisell C, Cho Y, Kanzawa-Lee GA, Gilchrist LS, Park SB, *et al.* Characteristics and patterns of pediatric chemotherapy-induced peripheral neuropathy: a systematic review. Cancer Treat Res Commun. 2021;28:100420.
[22] Yang QY, Hu YH, Guo HL, Xia Y, Zhang Y, Fang WR, *et al.* Vincristine-induced peripheral neuropathy in childhood acute lymphoblastic leukemia: genetic variation as a potential risk factor. Front Pharmacol. 2021;12:771487.

[23] Uittenboogaard A, Neutel CLG, Ket JCF, Njuguna F, Huitema ADR, Kaspers GJL, *et al.* Pharmacogenomics of vincristine-induced peripheral neuropathy in children with cancer: a systematic review and meta-analysis. Cancers (Basel). 2022;14(3):612.

[24] Yuan Y, Hu W, Chen C, Yao R, Zhang S, Zhu X, *et al.* Pharmacokinetic, pharmacodynamic and pharmacogenetic studies related to vincristine-induced peripheral neuropathy in Chinese pediatric ALL patients. Clin Pharmacol Ther. 2025;117(2):454–464.

[25] Brito-Suárez JM, Camacho-Juárez F, Sánchez-Medina CM, Hernández-Pliego G, Gutiérrez-Camacho C. Gross motor disorders in pediatric patients with acute lymphoblastic leukemia and survivors: a systematic review. Pediatr Hematol Oncol. 2022;39(7):658–671.

[26] Mao T, Yorke J, Shi Y, Shen N, Wang H, Wong FKY, *et al.* Assessment measures for chemotherapy-induced peripheral neuropathy among pediatric oncology patients: an updated systematic review. Support Care Cancer. 2025;33(6):514.

[27] Smith EML, Kuisell C, Kanzawa-Lee G, Bridges CM, Cho Y, Swets J, *et al.* Assessment of pediatric chemotherapy-induced peripheral neuropathy using a new patient-reported outcome measure: the P-CIN. J Pediatr Oncol Nurs. 2021;38(2):131–141.

[28] Šnajdrová T, Patrmanová E, Jevič F, Bořilová K, Hrdoušková M, Musálek M. Clinical applicability of short form of Bruininks-Oseretsky Test of Motor Proficiency Second Edition in patients after treatment of acute lymphoblastic leukemia. Front Pediatr. 2023;11:1071572.

[29] Ospina PA, McComb A, Pritchard-Wiart LE, Eisenstat DD, McNeely ML. Physical therapy interventions, other than general physical exercise interventions, in children and adolescents before, during and following treatment for cancer. Cochrane Database Syst Rev. 2021;8(8):CD012924.

[30] Ospina PA, Fisher S, Wilson BA, Pritchard L, Eisenstat DD, Fuengeling C, *et al.* Physical therapy surveillance in children with acute lymphoblastic leukemia: a quality improvement initiative. Pediatr Rep**.** 2026;18(2):36