

RESEARCH ARTICLE

Editorial Process: Submission:11/11/2025 Acceptance:10/10/2026 Published:24/10/2026

Design and Validation of Evidence-Based Peripheral Chemotherapy-Induced Neuropathy Guideline Among the Children with Cancer

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Abstract

Objective: Chemotherapy induced peripheral neuropathy (CIPN) is a frequent and debilitating complication among children receiving chemotherapy, yet evidence based clinical guidance specific to pediatrics remains limited. This study aimed to develop and validate a clinical guideline for managing CIPN in children using the Stetler model. **Methods:** This methodological study applied the five phase Stetler model (Preparation, Validation, Decision Making, Application, and Evaluation) to develop the guideline. A systematic search was performed in multiple databases, including PubMed, Cochrane Library, and Scopus, without time restrictions, and 89 studies met the inclusion criteria. Content validity was assessed using the Content Validity Ratio (CVR) and Content Validity Index (CVI). A panel of experts (physicians and nurses) evaluated the guideline using the AGREE II tool. The final guideline included three components: protocol, diagnosis/treatment, and patient education. **Results:** The guideline achieved high scores in Purpose and Scope (92%), Stakeholder Involvement (84%), and Rigor of Development (81%). Evidence supported the use of Pyridoxine and Pyridostigmine for pediatric CIPN management. The TNS-PV and ped-mTNS tools were identified as appropriate for neuropathy assessment in children aged 5–18 years. Identified implementation challenges included workforce shortages and the need for specialized training. **Conclusion:** This evidence-based guideline provides structured recommendations for the assessment and management of pediatric CIPN. While both pharmacological and non-pharmacological strategies show promise, further research across diverse pediatric populations is recommended.

Keywords: Neoplasms, Child, Practice Guideline, Peripheral Nervous System Diseases

Asian Pac J Cancer Prev, 27 (10), 3669-3677

Introduction

Cancer is among the chronic diseases that affect the pediatric age group [1]. According to available statistics, the incidence of cancer among children from birth to 19 years of age is about 400,000 cases annually worldwide; among these, the incidence in developing and low- and middle-income countries is about 200,000 children each year [2]. The prevalence of cancer in children is higher in low- and middle-income countries, but the survival rate for these children is lower compared to high-income countries due to limited access to advanced treatments. In developed countries, the five years survival rate for childhood cancer can reach approximately 80% or higher, whereas in low-income countries, this figure decreases to

20-30% [3]. Nowadays, advanced treatments have led to increased survival in children with cancer [4]. However, the diagnostic and therapeutic methods used for children with cancer, such as chemotherapy are associated with multiple complications and problems [5]. One of the most common side effects of chemotherapy drugs in children with cancer is peripheral neuropathy. Acute neuropathy has been reported in 20 to 60% of children with acute lymphoblastic leukemia [6, 7] and up to 85% in children with lymphoma and non-CNS solid tumors [8]. Chemotherapy induced peripheral neuropathy (CIPN) is defined as a dose dependent neurotoxic complication resulting from damage to peripheral sensory, motor, or autonomic nerves during chemotherapy. CIPN can significantly impair motor function, sensory performance,

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daily activities, and overall quality of life, and may even affect treatment adherence in children [9]. Guidelines developed for adults cannot be directly applied to children because pediatric patients differ substantially in neurodevelopmental stage, chemotherapy metabolism, symptom expression, and vulnerability to long term neurotoxicity [10].

Given that, for effective care and treatment of patients, the World Health Organization (WHO) has emphasized that health services should be based on the best scientific evidence [11], the use of evidence-based guidelines is recommended. One such evidence-based guideline for the prevention and treatment of neuropathy in adult cancer patients was designed and published by the American Society of Clinical Oncology (ASCO) in 2014 [12], with the latest updated version available in 2020. This guideline presents the latest evidence regarding the management and treatment of patients with neuropathy [13]. Another guideline in this field was published in 2020 in collaboration with the European Society for Medical Oncology, the European Association of Neuro-Oncology, and the European Oncology Nursing Society (ESMO–EONS–EANO) [14]. In Iran, the latest guideline was published in 2021 by a team of researchers under the supervision of the Ministry of Health and Medical Education and has been communicated to medical universities for use [15]. All of these guidelines have been developed for adults, and so far, no guideline has been specifically designed for the pediatric age group. The development of a global guideline for managing chemotherapy-induced peripheral neuropathy in children has not been achieved due to several major challenges. These include ethical concerns, research limitations, complexities in diagnosis and treatment in children, insufficient clinical data specific to pediatric populations, and the variability in chemotherapy types and individual responses [16].

These gaps highlight an urgent need for structured, evidence based recommendations tailored specifically to pediatric oncology settings. Without pediatric focused instructions, children are at risk of delayed diagnosis and inconsistent management of CIPN [17]. Despite the high prevalence of CIPN among children with cancer and its considerable impact during treatment and survivorship, comprehensive clinical guidelines specifically addressing the management of CIPN in pediatric populations remain limited. Therefore, this study aimed to develop and validate an evidence based clinical guideline for the management of CIPN in children with cancer using the Stetler model.

Materials and Methods

The present study is a guideline development study that designed and validated an evidence based guideline for chemotherapy induced peripheral neuropathy (CIPN) in children with cancer using the Stetler model. The Stetler Model is one of the evidence based frameworks developed to facilitate the translation of research evidence into clinical practice. This model was selected because it provides a systematic and practical approach

for integrating research findings into clinical decision making and is particularly suitable for developing practice guidelines based on existing evidence.

The model guides the process of translating research evidence into clinical practice through five main stages: Preparation, which involves identifying the problem, determining objectives, and specifying the need for evidence translation; Validation, which includes assessing the quality and validity of existing evidence through a systematic review of relevant studies; Comparative Review/Decision Making, where evidence is synthesized and analyzed to determine its applicability in the intended context; Translation/Application, which refers to applying the synthesized evidence to design guidelines and practical interventions; and Evaluation, which focuses on assessing the impact and effectiveness of the developed guideline in practice [18].

Phase 1 (Preparation)

An extensive literature search was conducted to identify articles or reference books addressing clinical symptoms, diagnosis, assessment methods, treatment, and education regarding neuropathy in children with cancer.

The search strategy included combinations of Medical Subject Headings (MeSH) and keywords related to chemotherapy induced peripheral neuropathy and pediatric cancer. The main keywords included: chemotherapy induced peripheral neuropathy, CIPN, peripheral neuropathy, child, children, pediatric, childhood cancer, neoplasm, chemotherapy, assessment, nursing care, management, treatment, and guideline. Boolean operators (AND/OR) were used to combine the search terms.

Inclusion criteria

(1) studies addressing chemotherapy induced peripheral neuropathy in children with cancer, (2) articles related to assessment, prevention, management, or education regarding CIPN, (3) clinical guidelines, systematic reviews, randomized controlled trials, and observational studies, and (4) articles published in English or Persian.

Exclusion criteria

(1) studies focusing exclusively on adult populations, (2) studies unrelated to CIPN or chemotherapy complications, (3) conference abstracts, editorials, and letters without sufficient methodological details, and (4) duplicate publications.

Eligible articles meeting inclusion/exclusion criteria were retrieved from reputable databases and graded using an evidence hierarchy pyramid. Reference books were also utilized. The comprehensive search covered medical databases without time restrictions (inception to December 2024), including: Cochrane Library, Clinical Key (Guidelines), Trip Database, PubMed, CINAHL, Scopus, Web of Science, Embase, Google Scholar, SID, and Magiran. Prior guideline repositories were searched:

- National Guideline Clearinghouse (NGC)
- National Institute for Health and Care Excellence
- Canadian Medical Association Info base: Clinical

Practice Guidelines (CPG)

- Scottish Intercollegiate Guidelines Network (SIGN)
- National Health and Medical Research Council (NHMRC): Clinical Practice Guidelines
- e-Guidelines
- Guidelines International Network (G-I-N)
- Canadian Pediatric Society
- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- Oncology Nursing Society (ONS)
- National Cancer Institute (NCI)
- National Comprehensive Cancer Network (NCCN)

No existing pediatric CIPN guideline was identified. Selected studies were imported into EndNote, and screened by title/abstract. Two researchers independently assessed quality using rapid critical appraisal checklists [19] based on study design (RCTs, cohort, case-control, systematic reviews, guidelines). Inter rater reliability for the critical appraisal scores was calculated using Cohen's kappa and demonstrated substantial agreement ($\kappa = 0.78$). Checklists used Melnyk et al.'s tool [19] with scoring: "Yes"=1 point, "No"/"Unclear"=0. Extracted evidence was tabulated (author, year, country, study type, findings) and graded using an evidence pyramid. The levels of evidence were categorized based on the evidence hierarchy as follows [19]: Level A: systematic reviews and meta-analyses conducted on clinical trial studies, clinical guidelines based on systematic reviews and meta-analyses; Level B: clinical trial studies; Level C: observational studies (cohort, case-control, and analytical) and qualitative studies; Level D: case studies, laboratory studies, and expert opinions. Subsequently, the extracted evidence was synthesized into diagnostic and nursing care protocols. Given that the evidence supporting pyridoxine and pyridostigmine originates from a single clinical trial, conclusions regarding their effectiveness should be interpreted cautiously. The synthesis process involved grouping evidence by clinical themes, comparing the strength and consistency of findings across studies, and integrating congruent results into step wise diagnostic and care recommendations that aligned with the Stetler model's decision making stage.

Phase 2 (Validation/Review)

In this stage, the face validity of the guideline (including writing, grammar, and the placement of words and sentences) was first assessed by a specialized panel consisting of 15 members, including physicians, nurses, and faculty members in nursing and medicine. The number of reviewers in the second stage was smaller because a subset of the original panel consented to participate in the AGREE II appraisal; however, these individuals were drawn from the same expert pool as Phase 1.

To examine content validity, the panel members evaluated each item of the guideline using forms designed for Content Validity Ratio (CVR) and Content Validity Index (CVI). CVR assesses the "necessity" of the guideline items, while CVI evaluates their "relevance and clarity." Subsequently, for a critical quality assessment of the guideline, the developed content was reviewed by 10 individuals from a panel comprising faculty

members of Guilan University of Medical Sciences, pediatric hematology and oncology specialists from 17 Shahrivar Educational and Medical Center in Rasht, nursing instructors specializing in pediatric oncology, and clinical nursing educators in pediatric wards. The panel members evaluated the designed guideline using the standard checklist "AGREE II" [20], which was emailed to them. This tool includes 23 items across six domains: scope and purpose (3 items), stakeholder involvement (3 items), rigor of development (8 items), clarity of presentation (3 items), applicability (4 items), and editorial independence (2 items). All items of this tool are rated on a seven-point Likert scale (1–7), where a score of 1 indicates "strongly disagree" and 7 represents "strongly agree" [20]. According to the guideline design team, each domain holds special importance, and the tool scores must be reported domain by domain, as calculating an overall score is not possible [20]. The scores of this tool are reported for each domain as follows:

$$\frac{(\text{Obtained score} - \text{Minimum possible score})}{(\text{Maximum possible score} - \text{Minimum possible score})} \times 100$$

The Persian AGREE II version validated by Ghanbari et al. [21] was used. Post-feedback revisions were implemented. Agreement among AGREE II reviewers was also assessed, showing high inter rater reliability (ICC = 0.89).

Phase 3 (Comparative Review/Decision-making/Feasibility)

Feasibility, benefits, and limitations were evaluated by nursing/medical teams. A total of 27 participants (24 nurses and 3 physicians) completed the feasibility assessment. We used a modified checklist by Ghajarzadeh et al. [22], adjusted by Ghanbari et al. [21]. This checklist consisted of 23 items, of which 15 focused on the content of the guideline and 8 addressed the potential advantages and disadvantages of its future implementation. Additionally, an open-ended question was included at the end, asking physicians and nurses to provide their overall opinion regarding the designed guideline. Responses to the checklist were binary (yes/no), and it was emailed to the participants. Since children with cancer suffering from neuropathy are treated and cared for exclusively at the 17 Shahrivar Educational and Medical Center in Rasht, the participants included all nurses and physicians from the inpatient hematology-oncology ward and the outpatient chemotherapy unit of this center. These individuals evaluated the guideline for its feasibility in their clinical settings using the checklist. Finally, the items in the guideline requiring revisions were reviewed, and the finalized guideline was developed.

However, only three medical specialists participated in the feasibility assessment, which limits the diversity of expert perspectives and reduces the generalizability of these findings. This limitation should be considered when interpreting the feasibility results.

Phase 4 (Application)

The guideline was submitted to Iran's Ministry of Health and Medical Education (Health Technology Assessment, Standard Development, and Tariff Department) for expert review and national implementation approval.

Phase 5 (Implementation and Evaluation)

Post-ministry approval and dissemination to medical centers, implementation and impact evaluation will be conducted in a separate study.

Results

The results of the study are presented in accordance with the steps of the research process

Phase 1

In the initial search, 1280 studies were identified. After reviewing the titles, abstracts, and full texts, 180 studies were selected, and following critical appraisal, 89 articles were chosen for guideline development (Figure 1). The included evidence comprised review articles ($n = 6$), systematic reviews ($n = 10$), systematic reviews and meta analyses ($n = 4$), and other review types including an overview of systematic reviews and meta analyses ($n = 1$) and a comprehensive integrative review ($n = 1$). In addition, analytical studies ($n = 12$), cross sectional studies ($n = 4$), and one analytical cross sectional study were identified. Randomized controlled trials and their variants accounted for nine studies, including randomized controlled trials ($n = 3$), a double blind randomized controlled trial ($n = 1$), a multicenter randomized controlled trial ($n = 1$), randomized placebo controlled trials ($n = 2$), an open label randomized controlled trial ($n = 1$), and a randomized sham controlled trial ($n = 1$). Other study designs included descriptive studies ($n = 3$), a descriptive hypothesis generating study ($n = 1$), case reports ($n = 5$), a case series ($n = 1$), and a case study ($n = 1$). Furthermore, experimental studies ($n = 2$), laboratory experimental studies ($n = 4$), pilot studies ($n = 2$), a pilot randomized clinical trial ($n = 1$), a pilot prospective cohort study ($n = 1$), a prospective study ($n = 1$), a prospective self controlled trial ($n = 1$), a feasibility study ($n = 1$), and a safety/tolerability study ($n = 1$) were included. In addition, one validation study and two clinical guidelines (WHO guideline and ASCO guideline update) were used as sources of evidence for developing the guideline.

Furthermore, these studies addressed various aspects of the topic, including the diagnosis, prevention, management, and treatment of neuropathy. The data obtained from these studies provided a solid scientific foundation and reliable evidence for the development of a comprehensive and practical guideline aimed at addressing the clinical needs related to the care of children with cancer. Examples of these studies include the systematic review by Bjornard et al. (focused on defining, diagnosing, and exploring pharmacological and non-pharmacological treatments for CIPN in children) [17], the clinical trial by Aydin Köker et al., (aimed at evaluating the effect of pyridoxine combined with pyridostigmine on vincristine-induced peripheral neuropathy in pediatric patients with acute lymphoblastic leukemia) [23], and

the review by Tay et al. (focused on CIPN in children and adolescents with cancer) [24]. The details of the 89 articles are provided in Appendix 1.

Phase 2

Certain recommendations in the guideline that had CVI values below 0.79 and CVR values below 0.62 [25] were reviewed and revised, and if deemed unnecessary based on consensus, they were removed. The quality of the guideline was evaluated by the expert panel using the AGREE II instrument, with the following domain scores: scope and purpose (92%), stakeholder involvement (84%), rigor of development (81%), clarity of presentation (78%), applicability (76%), and editorial independence (84%).

Phase 3

To assess the feasibility of implementing the guideline, 22 pediatric oncology nurses and 3 pediatric oncology subspecialists from the 17 Shahrivar Medical Center in Rasht (northern Iran) participated and provided their feedback and revision suggestions. Regarding the content of the guideline, all physicians and nurses agreed that the objectives and target population of the guideline were clearly defined, the recommendations were concise, and the content was clear. In terms of the advantages and disadvantages of the guideline, the participants noted that its implementation would have significant positive impacts on patient outcomes. However, challenges such as the need for interdisciplinary collaboration and the availability of specialized equipment, such as nerve electrophysiology devices in the hospital were highlighted as disadvantages.

In response to the open-ended question seeking their overall opinion on the guideline, all participants emphasized the necessity of using the guideline. However,

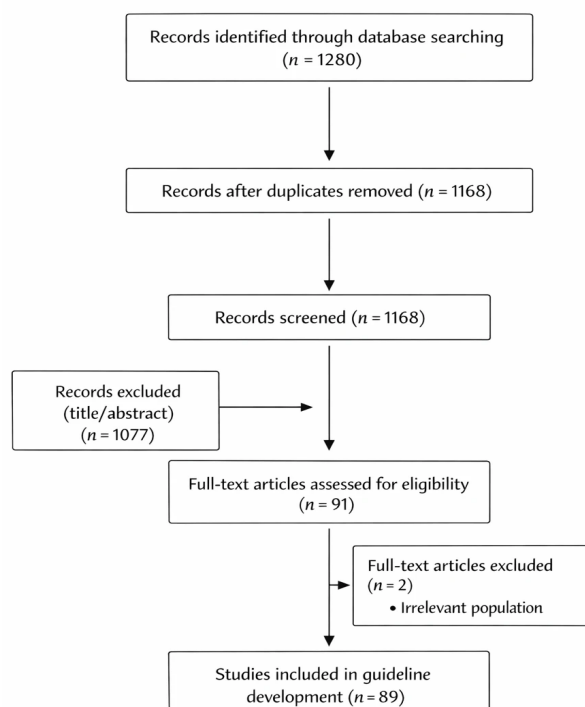


Figure 1. Flow Diagram of the Study Selection Process

many nurses expressed concerns about the lack of sufficient time to implement the guideline due to staff shortages and high workloads, the potential inefficiency of interdisciplinary teamwork, and the need for specialized training courses.

At the end of this phase, the final guideline was developed. The designed guideline consisted of three sections: a) guideline profile, b) clinical manifestations, diagnosis, and treatment, c) patient education.

A) Guideline Profile

Includes authors' names, expert panel members, purpose and rationale for guideline development, definition of CIPN, target population, systematic search methodology, evidence selection criteria, evidence levels, and references.

B) Clinical Manifestations, Diagnosis, and Treatment

The clinical manifestations of CIPN in children often present as a combination of sensory symptoms (e.g., numbness, burning), motor symptoms (e.g., gait disturbances, muscle atrophy, imbalance), and autonomic symptoms (e.g., orthostatic hypotension and gastrointestinal disorders), with varying degrees of severity. CIPN symptoms significantly impair the quality of life of pediatric cancer patients and survivors of childhood cancer. The severity of CIPN is dose-dependent, correlating with the cumulative chemotherapy dosage, and symptoms may persist for weeks or months after the completion of chemotherapy. The clinical presentations of neuropathy vary depending on the type of chemotherapy drug used.

To assess CIPN, it is crucial to ensure that the child does not have a prior history of neuropathy, polymyositis, or other disorders that may lead to neuropathy, and that the neuropathy onset occurs following the initiation of chemotherapy treatment. Given that studies have shown that CIPN can develop both after cumulative doses [26] and following single doses of chemotherapy drugs [27, 26, 24], it is recommended that children be screened for CIPN after each chemotherapy. If CIPN is diagnosed, appropriate interventions should be implemented [17].

The TNS-PV tool is applicable for children aged 6 to 18 years. Scores range from 0 to 4, with higher scores indicating greater neuropathy severity (Grade 0 = no neuropathy, Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = disabling/life-threatening). The validity of this tool has been confirmed in various international studies (25–30). This form is completed by a nurse or treating physician. The ped-mTNS tool is suitable for children aged 5 to 18 years undergoing chemotherapy [28].

Pharmacological Management

Among pharmacological interventions used for prevention or management of CIPN are calcium, Acetyl-L-carnitine, glutamine, omega-3 fatty acids, and drugs such as Amifostine, amitriptyline, venlafaxine, carbamazepine, and oxcarbazepine. However, the efficacy of these drugs in children remains unclear, as most studies have been conducted in adult populations or with small sample sizes,

and the existing evidence is insufficient [17, 29, 24].

According to the clinical trial study conducted by Aydin Köker and et al., only two drugs Pyridoxine (vitamin B6) and Pyridostigmine have been evaluated in clinical trials for vincristine-induced neuropathy in children and have shown favorable effects. It is recommended that these two drugs be prescribed at the early stages of neuropathy diagnosis (mild grade) to achieve optimal efficacy. The combined use of pyridoxine tablets and pyridostigmine tablets for a duration of three months is advised [23]. To maintain methodological focus, specific drug dosages were removed from the main text and are provided separately within the full clinical guideline.

It should be noted that dose reduction or discontinuation of chemotherapy drugs is sometimes used to prevent or treat CIPN; however, no clinical guidelines exist on this matter, and dose adjustments vary under different physicians' supervision. Therefore, further research is needed in this area [17, 29, 24].

Other drugs mentioned for CIPN in studies are mainly derived from case reports or clinical trials in adult populations. Future randomized clinical trials are needed to evaluate the efficacy of these drugs in pediatric populations (see Table 1).

Non-Pharmacological Management

There is limited evidence regarding the effectiveness of non-pharmacological methods for managing CIPN in children, and most existing evidence comes from adult populations. Only a few pilot studies with small sample sizes in children, using interventions such as graded motor imagery (GMI) and orthotic braces, have shown improvements in balance and pain relief following non-pharmacological approaches [30, 31, 24]. In one study conducted on children with cancer [32] who experienced muscle weakness early in treatment after chemotherapy and scored 4 or less on muscle strength tests of the dorsiflexors and extensor muscles of the big toe, the use of ankle orthoses was recommended. In this study, children wore the ankle orthosis during one chemotherapy cycle (approximately one month). It is important to monitor the child's discomfort and skin irritation during orthosis use. Additionally, the level of fatigue at the end of the orthosis use period should be assessed.

C) Patient Education

This section thoroughly explains topics such as the definition of peripheral neuropathy, its causes, and home care instructions.

Discussion

In the present study, an evidence-based guideline for CIPN in children with cancer was designed and validated based on the Stetler model. During the validation phase, the guideline was evaluated by an expert panel using the AGREE II instrument, which is the most comprehensive tool for assessing clinical practice guidelines. Gupta et al. in the United States used this tool to evaluate prostate disease treatment guidelines [33]. Laudie et al. assessed the national evidence-based infection prevention guidelines in

Table 1. Medications Used for Treating CIPN

Source	Level of Evidence	Study Type	Studied Population	Description	Drug Category	Drug Name
[13, 17, 24, 36]	A	Clinical guidelines/ Systematic review	Adults	The only medication with moderate effects on CIPN in adults, approved by ASCO*, ESMO**, NCI***, and ONS****. No sufficient evidence for children.	Antidepressant (Serotonin Reuptake Inhibitor)	Duloxetine
[17, 24, 29, 37, 38]	B	Clinical trial and cohort studies	Adults	Modulates neuronal ion channel functioning; also used in neuropathic pain. No sufficient evidence for children.	Anticonvulsant	Carbamazepine, Gabapentin, and Pregabalin
[39]	B	Clinical trial	Children aged 3 to 21 years	No sufficient evidence available for children.	Amino Acid	Glutamic Acid
[23, 24, 40]	A	Systematic review/ Clinical trial/Case studies	Children under 18 years	Effective for preventing CIPN.	Anti-Myasthenia	Pyridostigmine
[24, 40-42]	A	Systematic review/ Clinical trial/Case studies	Children under 18 years	Effective for treating CIPN induced by Vincristine.	Water-soluble vitamin	Pyridoxine (Vitamin B6)
[29, 43, 44]	A	Systematic review/ Clinical trial	Adults	Protects cells from oxidative stress, reduces side effects such as numbness, burning, tingling, or pain in limbs. No sufficient evidence for children.	Fat-soluble vitamin	Vitamin E
[24, 45, 46]	A	Systematic review/ Cohort studies	Adults	Vitamin D deficiency exacerbates CIPN symptoms. No sufficient evidence for children.	Vitamin	Vitamin D
[13, 24, 47, 48]	A	Clinical guidelines/ Systematic review	Adults	Reduces muscle cramps, neuropathic pain, and sensory symptoms like tingling, but increases overall body toxicity.	—	Topical gels containing Baclofen (10 mg), Amitriptyline (40 mg), and Ketamine (20 mg)
[24, 49]	A	Systematic review/ Clinical trial	Adults with breast cancer	Enhances inhibition of macrophage activation and reduces release of pro-inflammatory cytokines; alleviates peripheral neuropathy and bone pain but exacerbates gastrointestinal symptoms.	Anti-diabetic	Metformin*
[24, 50, 51]	A	Systematic review/ Clinical trial	Laboratory animals	Improves nerve repair and restores their functionality; partially prevents loss of epidural fibers following Cisplatin and Docetaxel administration. No studies on human subjects available.	Anti-anemia	Erythropoietin

UK hospitals [34], and Sae-Sia et al. [35] in Thailand used it to evaluate nursing performance guidelines for patients with multiple trauma admitted to trauma wards. In Iran, Rahmatpour et al. also used this tool to design a clinical nursing care guideline for diabetic foot ulcers [21]. This finding underscores the rigor of the development process and highlights the need for structured, evidence based tools when creating pediatric clinical guidelines.

In the quality assessment of the designed guideline based on AGREE II, the highest scoring domains were Scope and Purpose, Editorial Independence, and Stakeholder Involvement, while the lowest was Applicability, consistent with the findings of Rahmatpour et al. [21]. Similarly, Gupta et al. reported the highest guideline quality scores in the domains of Clarity of Presentation, Editorial Independence, and Scope and Purpose, with the lowest in Applicability [33]. The lower

score in Applicability may reflect common implementation challenges in pediatric oncology settings, such as limited resources, variability in clinical workflows, and the absence of standardized care pathways for neuropathy. This finding also highlights an important gap between guideline development and real-world implementation. While the methodological rigor of guideline development ensures scientific credibility, successful implementation requires organizational readiness, adequate staffing, and availability of clinical resources. Without addressing these contextual factors, even well-designed guidelines may remain underutilized in clinical practice. Therefore, implementation planning should be considered an integral component of guideline development, particularly in resource-constrained healthcare systems.

Another important barrier identified during guideline validation was nurses' concern regarding lack of time

and limited availability of assessment equipment. These factors can substantially affect the successful implementation of the guideline. Early detection of chemotherapy-induced peripheral neuropathy requires regular neurological assessments and careful monitoring of subtle sensory or motor changes. In busy pediatric oncology wards, high workload and limited staffing may reduce the opportunity for nurses to perform systematic assessments. Similarly, lack of simple neurological assessment tools may limit the accuracy and consistency of neuropathy evaluation, leading to delayed recognition and management of symptoms.

To address these challenges, several managerial and organizational strategies may facilitate the implementation of the guideline. Integrating brief CIPN screening items into routine nursing assessment forms can help reduce the additional time burden. Providing targeted training for nurses on rapid neurological assessment techniques may also improve confidence and efficiency in detecting early symptoms. In addition, hospital managers can support implementation by ensuring the availability of basic, low-cost assessment tools and by incorporating neuropathy monitoring into standard pediatric oncology care protocols. Such strategies may enhance adherence to the guideline and improve the early identification and management of CIPN in clinical practice.

Regarding the content of the designed guideline, consistent with the study by Bjornard et al. [17], CIPN is one of the adverse effects of cancer treatments in children, causing sensory, motor, or autonomic complications depending on the affected nerves. Their study referred to both pharmacological and non-pharmacological management methods for neuropathy [17], aligning with the present study's findings. By consolidating these scattered recommendations into a structured clinical pathway, the present guideline enhances the practical usability of existing evidence for frontline clinicians.

It was also found that only two drugs, pyridoxine (vitamin B6) and Pyridostigmine, have been examined in clinical trials for vincristine-induced neuropathy in children, showing favorable effects. It is recommended that these drugs be prescribed at the early stages of neuropathy diagnosis (mild grade) for optimal efficacy [17]. Early pharmacological intervention, as emphasized in this guideline, may help reduce symptom progression and prevent treatment interruptions in children undergoing neurotoxic chemotherapy. However, the current evidence supporting pharmacological management of pediatric CIPN remains limited. Most available studies in this area are small in scale and often conducted in single centers, which restricts the generalizability of their findings. In addition, differences in neurodevelopmental physiology and drug metabolism between children and adults make it difficult to extrapolate evidence from adult oncology populations. Consequently, pharmacological recommendations for pediatric CIPN should be interpreted cautiously and considered provisional until stronger evidence becomes available. Furthermore, the recommendation of pyridoxine and pyridostigmine in this guideline should be interpreted as a cautious, evidence-informed suggestion rather than a definitive therapeutic recommendation. Given that these

medications have been evaluated in only a limited number of pediatric studies, recommending their routine use based on a single clinical trial may not be fully justified. Instead, these agents may be considered as potential options in early stages of neuropathy when clinicians judge that the expected benefits outweigh possible risks, while awaiting further large-scale pediatric trials.

Overall, the recommendations of this guideline are generally consistent with the available evidence on CIPN. Most findings support what has already been emphasized in previous studies and major guidelines, such as the importance of early assessment, regular monitoring, and the use of multimodal non pharmacological approaches. At the same time, this guideline adds value by translating the evidence into more practical, nursing focused actions that are easier to apply in daily care. A few recommendations also reflect newer evidence that is not yet fully included in existing guidelines, helping to close the gap between research and clinical practice. Nevertheless, further pediatric specific trials are needed to strengthen pharmacological recommendations and to evaluate long term outcomes of CIPN into survivorship.

Study Limitations

One limitation of this study was the selection of nurses and physicians exclusively from the single pediatric specialty hospital in Guilan for assessing guideline feasibility. To mitigate this limitation, after guideline development, it was shared with pediatric oncology subspecialists and oncology nursing faculty from various universities, and their corrective feedback was incorporated.

In conclusion, this study successfully developed and validated the first evidence-based clinical guideline for the management of CIPN in children with cancer, utilizing the Stetler model. Future research should focus on evaluating its clinical impact across diverse pediatric populations and refining management strategies to further improve quality of life for affected children. Following endorsement by the Ministry of Health and Medical Education, this guideline is poised for integration into clinical practice within healthcare centers.

Author Contribution Statement

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by SP, NJP, ZTE and BD. The first draft of the manuscript was written by SP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

General

The authors would like to extend their sincere thanks to the Deputy of Research and Technology of Guilan University of Medical Sciences, Social Determinants of Health Research Center, the healthcare workers of 17-Shahrivar Children's hospital and faculty members.

Funding Statement

We would like to express our gratitude to the Research and Technology Deputy of Guilan University of Medical Sciences and Social Determinants of Health Research Center for supporting this project.

Approval

This study was conducted as part of a research project approved by the Research and Technology Deputy of Guilan University of Medical Sciences and Social Determinants of Health Research Center (Research project code=1403090512).

Ethical Declaration

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Guilan University of Medical Sciences (IRB No: IR.GUMS.REC.1404.047). Written informed consent was obtained from the healthcare team. Written informed consents were obtained from the participants.

Conflict of Interest

There is no conflict of interests.

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