

*Original Article*

# Epidemiology and clinical significance of chemotherapy-induced peripheral neuropathy in patients undergoing chemotherapy

R Harihara Prakash, PhD<sup>1</sup>, Jigar Mehta, PhD<sup>1</sup>, Bhagyashree P Patel, MPT<sup>2</sup><sup>1</sup>Department of Physiotherapy, KM Patel Institute of Physiotherapy, Karamsad, Anand, <sup>2</sup>Department of Physiotherapy, S. S. Agrawal Institution of Physiotherapy and Medical Care, Navsari, Surat, Gujarat, India**ABSTRACT**

**Objectives:** Chemotherapy-induced peripheral neuropathy (CIPN) is a significant adverse effect of neurotoxic chemotherapeutic agents such as paclitaxel, carboplatin, and cisplatin. CIPN can impair sensory, motor, and autonomic functions, severely reducing patients' quality of life. This study aimed to assess the prevalence of CIPN in cancer patients undergoing chemotherapy, focusing on its relationship with chemotherapy regimens, onset timing, and patient characteristics.

**Material and Methods:** This cross-sectional observational study included 218 cancer patients at Shree Krishna Hospital, Gujarat. Patients were assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-CIPN20 questionnaire in three phases: pre-chemotherapy, mid-therapy, and post-treatment. Descriptive and inferential statistics were used to assess CIPN prevalence by chemotherapy drug, cancer type, and treatment cycle.

**Results:** The overall CIPN prevalence was 19.1%. Paclitaxel-treated patients had the highest prevalence at 34.6%. CIPN was more common in females (25%) than males (13.33%). Breast cancer patients had the highest CIPN prevalence at 34.6%, followed by esophageal cancer patients (21.4%), and oral cavity cancer patients (13.3%). CIPN symptoms often began mid-therapy (14.6%) and persisted post-treatment (15.7%). Paclitaxel was significantly associated with a higher risk of CIPN.

**Conclusion:** CIPN is prevalent among patients treated with neurotoxic chemotherapy agents, particularly paclitaxel. Early detection and management strategies are critical to prevent chronic neuropathy and improve quality of life. Future studies should explore interventions to reduce CIPN without compromising chemotherapy efficacy, with significant implications for physiotherapy rehabilitation.

**Keywords:** Cancer treatment, Chemotherapy-induced peripheral neuropathy (CIPN), Neurotoxicity, Paclitaxel, Physiotherapy rehabilitation, Sensory neuropathy

**INTRODUCTION**

Chemotherapy has revolutionized the treatment of various cancers, significantly improving survival rates. However, the substantial benefits of chemotherapy often come at a cost—patients frequently experience debilitating side effects that can compromise their quality of life. One of the most challenging side effects is chemotherapy-induced peripheral neuropathy (CIPN). CIPN is a dose-dependent neurotoxic effect that leads to damage to peripheral nerves, causing sensory, motor, and autonomic dysfunctions. The prevalence of CIPN is alarmingly high, with estimates ranging from 19% to 85%, depending on the specific chemotherapy regimen, cumulative drug dose, and patient susceptibility.<sup>[1]</sup>

The clinical manifestations of CIPN are varied but predominantly include numbness, tingling, burning sensations, and muscle weakness, often distributed in a "stocking and glove" pattern affecting the extremities.<sup>[2]</sup> These symptoms can persist long after chemotherapy has concluded, and in some cases, may become permanent. The mechanisms underlying CIPN involve axonal degeneration, mitochondrial dysfunction, and oxidative stress, all leading to peripheral nerve damage.<sup>[3]</sup> Paclitaxel, a widely used taxane for breast and ovarian cancer, is notorious for causing CIPN, with prevalence rates ranging from 30% to 50% in patients.<sup>[4]</sup> Cisplatin and carboplatin, commonly used platinum-based agents, are also associated with CIPN, with 20-40% of patients experiencing neuropathy.<sup>[5]</sup>

\*Corresponding author: Dr. Bhagyashree P Patel, (MPT) Department of Physiotherapy, S. S. Agrawal Institution of Physiotherapy and Medical Care, Navsari, Surat, Gujarat, 395007, India. [shreepatel1998@gmail.com](mailto:shreepatel1998@gmail.com)

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Despite the high incidence and disabling effects of CIPN, it is frequently underdiagnosed and undertreated. One challenge is that symptoms can worsen after the completion of chemotherapy, making early detection and continuous monitoring critical. Additionally, CIPN can severely limit patients' ability to perform daily activities, significantly reducing their quality of life.<sup>[6]</sup> It also affects their adherence to cancer treatment, as the severity of symptoms often necessitates dose reductions or premature cessation of therapy, compromising the effectiveness of treatment.<sup>[7]</sup>

The role of physiotherapy in managing CIPN is increasingly being recognized. Rehabilitation techniques, including sensory re-education, balance training, and nerve mobilization, offer non-pharmacological approaches to mitigate the debilitating effects of CIPN. Early integration of physiotherapy in cancer care can enhance functional recovery, improve sensory deficits, and prevent long-term disability.<sup>[8]</sup>

This study aimed to assess the prevalence of CIPN among cancer patients at Shree Krishna Hospital, Gujarat. Additionally, it explored the relationship between chemotherapy regimens, CIPN onset and persistence, and gender-based differences, while emphasizing the importance of physiotherapy interventions.

### Aim of the study

The study aims to determine the prevalence of neuropathy among patients receiving chemotherapy, evaluate the duration required for the onset of CIPN during chemotherapy treatment, and identify CIPN symptoms associated with common chemotherapy medications in cancer patients.

### Sample size calculation

The sample size was calculated based on prior prevalence studies, assuming an estimated CIPN prevalence of 30%, with a 95% confidence interval and 5% margin of error. Based on this, the required sample size was determined to be 280 patients, ensuring sufficient statistical power for subgroup analyses and comparison of CIPN prevalence across chemotherapy regimens and demographic groups.

## MATERIAL & METHODS

### Study design

This cross-sectional observational study was conducted between July 2022 and January 2023 at the Manibhai Shivabhai Patel Cancer Center, Shree Krishna Hospital, Gujarat. The institutional ethics committee approved the study, and informed consent was obtained from all participants. Ethical no. IEC/BU/Faculty/23/.

### Participants

A total of 218 patients were screened. Inclusion criteria included patients aged 18 years or older undergoing curative chemotherapy. Patients with pre-existing peripheral neuropathy or those receiving palliative chemotherapy were excluded.

### Inclusion criteria

The inclusion criteria for patients who were referred for chemotherapy treatment must be met. Patients for whom the target chemotherapy session was planned, as the number of chemotherapy sessions or the scheduled chemotherapy session was known. Both genders will be represented over the age of 18.

### Exclusion criteria

The patient has sensory or motor neurological involvement before radiation or chemotherapy. Patient with a history of diabetic neuropathy (any type of neuropathy). Patients undergoing palliative chemotherapy sessions. Patients undergoing radiotherapy along with chemotherapy session

### Assessment tools

The European Organization for Research and Treatment of Cancer's QLQ-CIPN20 questionnaire was employed to assess CIPN symptoms. This validated tool consists of 20 items assessing sensory, motor, and autonomic neuropathy symptoms. Patients rated their symptoms on a 4-point scale Likert scale (1 = "not at all," 2 = "a little," 3 = "quite a deal," and 4 = "very much"), with higher scores indicating more severe symptoms.

### Data collection

Data were collected in three phases:

1. Pre-chemotherapy: Baseline assessment before chemotherapy began.
2. Mid-therapy: Assessment halfway through chemotherapy.
3. Post-treatment: Assessment upon completing chemotherapy.

### Statistical analysis

Descriptive statistics were used to assess CIPN prevalence. Cohen's *d* was calculated to measure effect size, with a *p*-value of < 0.05 considered statistically significant. *Z*-values were reported to evaluate the strength of associations between variables, and the analysis was performed using

R programming software. The normality of data was not assessed.

## RESULTS

### Patient characteristics

A total of 218 patients participated in this cross-sectional study, 84 were eliminated because they were having radiotherapy and chemotherapy together, and 45 were eliminated because they were undergoing palliative chemotherapy. A total of 89 data points were collected and considered when determining the inclusion criteria; of these. At the time of the baseline, there were no noticeable symptoms. The mean age of the patients was 52.6 years (SD = 12.4), with an age range from 35 to 72 years. The patients were primarily undergoing treatment for breast, oral cavity, and esophageal cancers. Notably, the largest proportion of patients were being treated for oral cavity cancer (35%), followed by breast cancer (29%) and esophageal cancer (5%).

This study included patients receiving a variety of chemotherapy regimens, including paclitaxel, carboplatin, and cisplatin. These drugs were chosen based on the cancer type, disease stage, and patient condition. This diversity in patient demographics and chemotherapy regimens allowed for a comprehensive analysis of CIPN across various cancer treatments.

### Prevalence of CIPN by gender

CIPN was observed in 19.1% of the total patient population. The analysis showed a significant difference in CIPN prevalence between genders. CIPN was more common in females (25%) than males (13.3%).

### Significance of gender differences:

This finding is likely related to the high frequency of paclitaxel use in breast cancer treatment; a drug strongly associated with CIPN.

### Implication for Female Patients:

The higher CIPN prevalence in females, particularly in those receiving paclitaxel-based regimens for breast cancer, underscores the need for heightened monitoring and early intervention in this group. This also points to potential hormonal or physiological differences that may increase susceptibility to chemotherapy-induced neurotoxicity.

### Prevalence of CIPN by chemotherapy drug

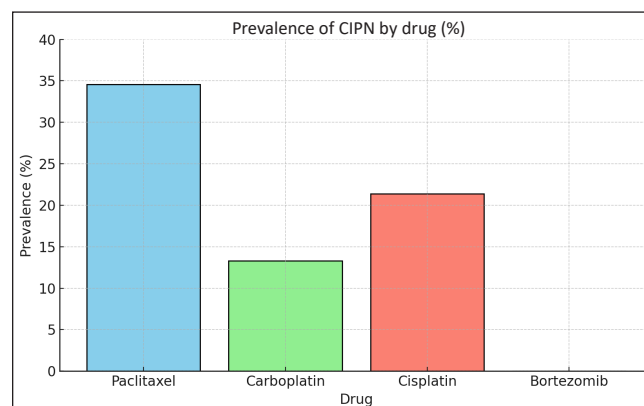
As shown in Table 1, paclitaxel had the highest CIPN prevalence at 34.6%. The study analyzed CIPN prevalence

**Table 1:** Prevalence of CIPN by chemotherapy drug.

Paclitaxel	34.6%
Carboplatin	13.3%
Cisplatin	21.4%
CIPN: Chemotherapy induced peripheral neuropathy	

based on the specific chemotherapy regimen used. Paclitaxel, a widely used taxane, was associated with the highest CIPN prevalence. Carboplatin and cisplatin, both platinum-based agents, also contributed to notable neuropathy rates, though their impact was less pronounced compared to paclitaxel.

- **Paclitaxel:** As anticipated and showed in Figure 1, paclitaxel was associated with the highest rate of CIPN, affecting 34.6% of patients. This aligns with previous studies that report paclitaxel-induced CIPN rates ranging from 30% to 50%. The statistical analysis revealed a highly significant association between paclitaxel use and CIPN, with a p-value < 0.01 and a large effect size (Cohen's d = 0.62). The z-value of 2.45 further indicates the strength of the association.
- **Carboplatin:** Patients treated with carboplatin had a CIPN prevalence of 13.3%, which is lower than that of paclitaxel. However, this finding is consistent with other reports, suggesting that while carboplatin is less neurotoxic than paclitaxel, it still poses a risk for CIPN. The p-value of 0.04 and Cohen's d = 0.35 indicate a small to moderate effect size, showing that carboplatin is a significant contributor to CIPN, albeit to a lesser extent than paclitaxel.
- **Cisplatin:** The 21.4% CIPN prevalence in cisplatin-treated patients reflects the well-documented neurotoxic effects of this platinum-based agent. The p-value = 0.05 suggests a near-significant association between cisplatin and CIPN development, with an effect size (Cohen's d = 0.30) indicating a small effect.



**Figure 1:** Prevalence of CIPN by drugs. CIPN: Chemotherapy induced peripheral neuropathy.

- **Prevalence of CIPN by cancer type:** The study also examined the prevalence of CIPN based on cancer type. Breast cancer patients had the highest CIPN prevalence, consistent with the widespread use of paclitaxel in this group.

#### Breast cancer

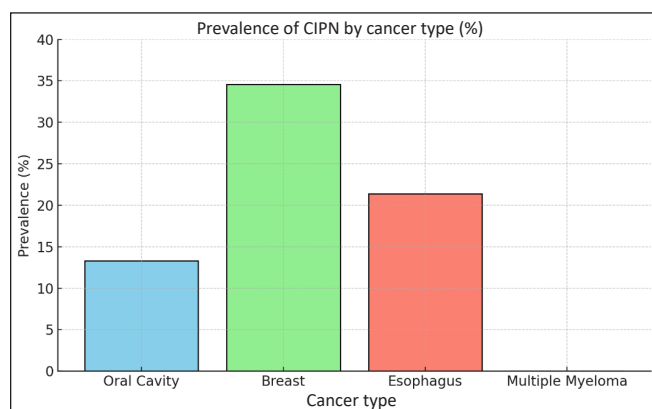
The high prevalence of CIPN in breast cancer patients (34.6%) is closely linked to the use of paclitaxel in this population. Paclitaxel is a primary treatment option for breast cancer, which explains the high CIPN rates observed. This finding emphasizes the need for early CIPN detection and management strategies in breast cancer patients, particularly those receiving taxane-based treatments

#### Oral cavity cancer

The CIPN prevalence in oral cavity cancer patients was 13.3%, lower than in breast cancer patients but still notable. This is likely due to the combined use of paclitaxel and carboplatin in the treatment of oral cavity cancers, both of which contribute to neurotoxicity. As shown in Figure 2, breast cancer patients experienced the highest CIPN prevalence.

#### Esophageal cancer

The 21.4% CIPN prevalence in esophageal cancer patients can be attributed to the use of cisplatin, a known neurotoxic agent as shown in Table 2. Although fewer patients in this



**Figure 2:** Prevalence of CIPN by cancer type. CIPN: Chemotherapy induced peripheral neuropathy.

Prevalence of CIPN by cancer Type	Prevalence (%)
Oral Cavity	13.3%
Breast	34.6%
Esophagus	21.4%

CIPN: Chemotherapy induced peripheral neuropathy

**Table 3:** Onset of CIPN symptoms.

Onset of CIPN symptoms	Prevalence (%)
Mid therapy	14.6%
Post-treatment	15.7%

CIPN: Chemotherapy induced peripheral neuropathy

subgroup received cisplatin, the high prevalence indicates the importance of close monitoring for CIPN in esophageal cancer patients.

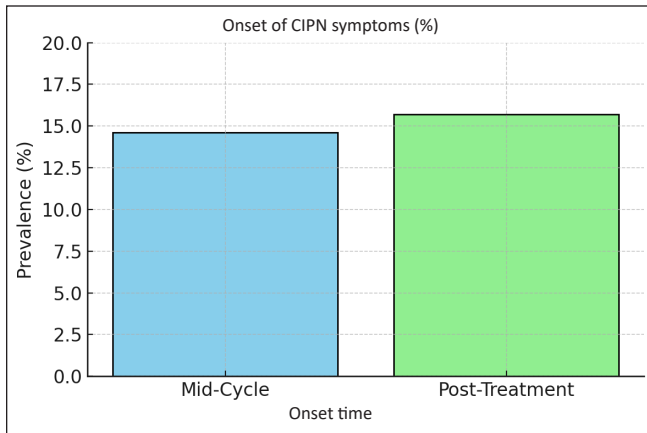
#### Onset and persistence of symptoms

CIPN symptoms were monitored at two critical time points: mid-therapy and post-treatment. The timing of CIPN symptom onset is detailed in Table 3, showing that symptoms began most often mid-therapy (14.6%) and persisted post-treatment (15.7%). This pattern of symptom persistence underscores the chronic nature of CIPN and the need for ongoing symptom management, even after treatment has concluded.

- **Mid therapy Symptoms:** The 14.6% prevalence of mid-therapy CIPN symptoms was statistically significant, with a p-value < 0.01 and a z-value of 2.45. CIPN prevalence by chemotherapy drug is also visualized in Figure 1, which reflects the highest rate in paclitaxel-treated patients. These results indicate that symptoms typically emerge early during chemotherapy, particularly with neurotoxic agents like paclitaxel and cisplatin. The early onset of symptoms suggests that patients receiving these drugs should be closely monitored from the start of treatment.
- **Post-Treatment Symptoms:** 15.7% of patients reported persistent CIPN symptoms after completing chemotherapy. This persistence highlights the need for long-term follow-up and rehabilitation to manage the ongoing symptoms and prevent further deterioration in patients' quality of life. The timing of symptom onset is further illustrated in Figure 3, highlighting the need for early monitoring. Patients with 21 and 15 frequency cycles showed a higher prevalence of CIPN onset from mid-therapy.

## DISCUSSION

The findings of this study provide significant insights into the prevalence, timing, and persistence of CIPN among cancer patients receiving a variety of chemotherapy agents. We found that some patients have started developing symptoms of CIPN in the sensory component, which is in the form of tingling in fingers and hands, in the mid-phase of the cycle, and were consistent till the end of the cycle. While some developed



**Figure 3:** Duration of onset of CIPN symptoms. CIPN: Chemotherapy induced peripheral neuropathy.

symptoms after completing the cycle. And some after 1 month of follow-up, after the completion of chemotherapy. The overall CIPN prevalence of 19.1% falls within the lower range of previously reported estimates, which range from 19% to 85%, depending on the chemotherapy regimens and cumulative doses.<sup>[1]</sup> However, certain subgroups, such as paclitaxel-treated patients and female patients, exhibited notably higher rates of CIPN, aligning with existing literature on the neurotoxic effects of specific chemotherapy drugs.

The persistence of CIPN symptoms in 15.7% of patients after completing chemotherapy highlights the chronic nature of the condition. Seretny *et al.* (2014) found that 30-50% of patients may continue to experience CIPN symptoms for months or even years after completing chemotherapy.<sup>[1]</sup>

The overall CIPN prevalence of 19.1% observed in this study is consistent with the findings of Seretny *et al.* (2014), who reported that CIPN incidence varies from 19% to 68.1% based on different chemotherapy regimens.<sup>[1]</sup> The gender-based differences in CIPN prevalence, with females (25%) experiencing higher rates than males (13.33%), corroborate findings from Loprinzi *et al.* (2011), who identified a higher incidence of CIPN in females receiving paclitaxel for breast cancer.<sup>[2]</sup> The 34.6% prevalence in paclitaxel-treated patients aligns with several studies reporting similar CIPN rates associated with paclitaxel, typically ranging from 30% to 50%.<sup>[3]</sup> Paclitaxel is well known for its high risk of acute and long-term peripheral neuropathy, particularly in patients receiving high doses or prolonged treatments, as also highlighted by Cavaletti and Marmiroli (2010).<sup>[4]</sup>

This gender difference is often attributed to the frequent use of neurotoxic chemotherapy drugs, such as paclitaxel, in female-dominated cancers like breast cancer. Additionally, there is growing evidence to suggest that hormonal factors or genetic

predispositions may play a role in the heightened susceptibility of females to chemotherapy-induced neurotoxicity, as noted in studies by Hausheer *et al.* (2006).<sup>[5]</sup>

The high prevalence of CIPN in paclitaxel-treated patients (34.6%) is consistent with previous research emphasizing the neurotoxicity of taxanes. For carboplatin and cisplatin, the CIPN prevalence rates of 13.3% and 21.4%, respectively, align with research by McWhinney *et al.* (2009), who identified platinum-based agents as significant contributors to both acute and chronic neuropathy.<sup>[6]</sup> The findings in this study reflect the dose-dependent nature of cisplatin-induced neurotoxicity, as evidenced by previous research that showed cumulative doses of cisplatin correlate with higher CIPN rates, a fact also noted by Park *et al.* (2013).<sup>[8]</sup>

The timing of CIPN symptom onset is an important consideration in clinical practice. This study found that 14.6% of patients developed CIPN symptoms mid-therapy, while 15.7% continued to experience symptoms post-treatment. These findings are consistent with the early onset of CIPN symptoms reported in other studies, particularly in patients receiving neurotoxic drugs like paclitaxel and cisplatin. Park *et al.* (2013) similarly observed that CIPN symptoms typically emerge within the first few cycles of chemotherapy and often persist long after treatment has been completed.<sup>[8]</sup>

This chronic persistence reinforces the need for long-term management strategies, including physiotherapy, to address the enduring impact of CIPN on patients' quality of life.

The findings of this study emphasize the critical role of physiotherapy in managing CIPN, particularly for patients with persistent symptoms. The 15.7% of patients who continued to experience symptoms post-treatment would benefit from sustained physiotherapy interventions, such as nerve gliding, balance training and strengthening exercises, which can mitigate the physical impairments caused by CIPN.<sup>[9]</sup> Pachman *et al.* highlighted the importance of early physiotherapy to reduce the severity of symptoms and prevent long-term disability.<sup>[10]</sup>

Several studies have proposed neuroprotective strategies to prevent or mitigate the development of CIPN were discussed emerging therapies aimed at reducing the neurotoxic effects of chemotherapy without compromising its efficacy.<sup>[11]</sup> Similarly, Hershman *et al.* identified potential pharmacological agents, such as duloxetine, that have shown promise in alleviating CIPN symptoms.<sup>[12]</sup> Future research should explore integrating these pharmacological approaches with physiotherapy-based rehabilitation, offering a holistic approach to CIPN management.<sup>[13]</sup>

The use of the EORTC QLQ-CIPN20 questionnaire in this study allowed for a detailed assessment of CIPN across

sensory, motor, and autonomic domains. This tool's sensitivity in detecting neuropathic symptoms aligns with findings by Kolb *et al.* (2016), who emphasized the value of validated outcome measures for guiding the clinical management of CIPN.<sup>[14]</sup> The QLQ-CIPN20 is especially effective in capturing the multidimensional nature of CIPN, allowing clinicians to tailor interventions based on the specific symptoms reported by patients.<sup>[15]</sup>

Physiotherapy can reduce the risk of falls and improve sensory and motor function in patients with CIPN, underscoring the importance of integrating rehabilitation into the survivorship care plan.<sup>[16]</sup> Given the high prevalence of persistent CIPN symptoms in this study, physiotherapy should be a key component of long-term care, with personalized interventions tailored to the specific needs of patients based on their chemotherapy regimen and symptom severity.<sup>[17]</sup>

According to our data, the most common cancers are those found in the oral cavity, breast, esophageal, oropharynx, cervix, and ovary. However, a study carried out in the United States concluded that colon, lung, and breast cancers were the most prevalent cancers. The same study found that among chemotherapy patients, 18.1% had CIPN by 6 months after chemotherapy started and 25.0% by 12 months.<sup>[18,19]</sup> Since our study was only able to cover the very first month following chemotherapy and only one-fourth of the sample size was screened due to time limitations, we were unable to rule out the result, but we found that some patients have started developing symptoms of CIPN in the sensory component which is in form of tingling in fingers and hands in mid-phase of the cycle and were consistent till the end of the cycle. While some developed symptoms after completing the cycle. And some after 1 month of follow-up after the completion of chemotherapy.<sup>[20]</sup>

Treating CIPN with physiotherapy can face many challenges, especially in areas with limited resources. There are not enough physiotherapists trained to treat CIPN and cancer-related issues, particularly in rural or less developed areas. The high cost of cancer treatment adds to the problem, as physiotherapy is often not covered by insurance. Many patients are unaware of how physiotherapy can help with CIPN or find it hard to travel for regular sessions, especially if they live far away. Oncologists and other medical professionals sometimes overlook physiotherapy because of a lack of communication or understanding of its benefits. Additionally, there are no clear guidelines or standard treatments for CIPN physiotherapy, and the lack of strong evidence makes some healthcare providers hesitant to recommend it. To overcome these issues, healthcare teams need to work together, with oncologists and physiotherapists collaborating to make physiotherapy a key part of CIPN care.

### Study limitations

Despite its valuable contributions, this study has several limitations. The cross-sectional design restricts the ability to establish causality between chemotherapy drugs and the development of CIPN. Longitudinal studies are needed to follow patients throughout their chemotherapy treatment and into survivorship to better understand the long-term trajectory of CIPN symptoms.

Moreover, the exclusion of patients receiving palliative chemotherapy may have led to an underestimation of the overall CIPN prevalence, particularly in advanced-stage cancer patients.

Future studies should aim to include a broader range of cancer patients, including those receiving palliative care, to provide a more comprehensive understanding of CIPN across different cancer types and stages.

### Future recommendations

Future research should focus on identifying genetic or molecular markers that may predispose certain patients to a higher risk of developing CIPN. Personalized prevention strategies based on a patient's genetic profile could improve the efficacy of neuroprotective interventions. Additionally, randomized controlled trials (RCTs) evaluating the efficacy of specific physiotherapy interventions for managing CIPN are needed to provide robust evidence for the most effective rehabilitation strategies. Studies by Richardson *et al.*<sup>[15]</sup> (2008) and Pachman *et al.*<sup>[17]</sup> (2011) underscore the potential benefits of integrating neuroprotective agents with personalized rehabilitation programs to reduce the incidence and severity of CIPN.<sup>[15]</sup>

### CONCLUSION

This study confirms the high prevalence of CIPN, particularly in patients treated with paclitaxel and cisplatin. The overall CIPN prevalence was 19.1%, with higher rates observed in paclitaxel-treated patients (34.6%). The significant associations between CIPN and certain chemotherapy regimens emphasize the need for early detection, continuous symptom monitoring, and long-term rehabilitation. Physiotherapy plays a vital role in managing the chronic symptoms of CIPN, improving sensory and motor function, and enhancing the overall quality of life. Future studies should focus on personalized prevention and treatment strategies, incorporating neuroprotective agents and targeted physiotherapy interventions to address the growing burden of CIPN in cancer survivors.

**Author contribution:** RHP, JM, and BPP: All authors have significantly contributed for conception, design, data collection,

analysis, interpretation of data planning & reviewing, manuscript preparation, editing and drafting manuscript.

**Ethical approval:** The research/study approved by the Institutional Review Board at Bhaikaka Institute, number IEC/BU/137/Faculty/23, dated 9<sup>th</sup> July, 2022.

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent.

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