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Analysis Of Risk Factors For Peripheral Neuropathy In Patients With Gynecological Chemotherapy Treatment

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Abstract:

Aim & Objective:

To evaluate the risk factors for chemotherapy-induced peripheral neuropathy (CIPN) among patients with gynecological cancer receiving chemotherapy.

Methodology:

In a retrospective case-control study conducted between June 2020 to June 2021 across 15 Cancer Hospitals of India, women with gynecological cancer received taxane and platinum-complex combination therapy.

The European Organization for Research and Treatment of Cancer Quality of Life, gynecological cancer module questionnaire, was used to assess the severity of neuropathy by tele-interview/Face to face interview.

Sample:

A convenience sample of 120 patients with gynecologic cancer.

Results:

The present study comprised 120 (100) patients included in the study. The age-wise distribution of patients was found to be 45.±14.5 years which was found to be statistically significant. The average number of chemotherapy cycles was 7.1 (range 2–14). A total of 100 (83.3%) patients reported some level of CIPN.

Among these, 68 (68%) patients reported CIPN after the first cycle of chemotherapy, and 20 (20%) patients reported CIPN after the last cycle of chemotherapy. Out of 120 participants, 60 (50%) patients received liposomal paclitaxel, 40 (33.3%) patients received docetaxel and 20 (16.26%) patients received paclitaxel.

Fisher exact test indicated that patients receiving liposomal paclitaxel were less likely to develop CIPN. Patients receiving docetaxel or paclitaxel were more likely to suffer from SPN, which was statistically significant (p - 0.01).

Conclusion:

The present study showed that a significant proportion of patients with gynecological cancer receiving taxanes suffered from long-term residual neuropathy. The use of docetaxel and paclitaxel was associated with Sensory Peripheral Neuropathy.

Chemotherapy-induced peripheral neuropathy can significantly impact a large portion of the gynecologic oncology population. The clinician needs to have a fundamental understanding of clinical manifestations and treatment modalities available.

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KEYWORDS: Cancer, Chemotherapy-Induced Peripheral Neuropathy, Platinum Chemotherapy, Risk Factors, Taxanes

LIST OF ABBREVIATIONS
CIPN – Chemotherapy-Induced Peripheral Neuropathy
SPN – Sensory Peripheral Neuropathy
MPN – Motor Peripheral Neuropathy
FIGO - International Federation of Gynecology and Obstetrics.
QOL – Quality Of Life

1. INTRODUCTION

Peripheral neuropathy refers to symptoms arising from damage to peripheral nerves. These nerves carry sensation, control movements of the arms and legs, and control the bladder and bowel. Chemotherapy and other drugs used to treat cancer can cause peripheral neuropathy. This is termed chemotherapy-induced peripheral neuropathy (or CIPN)[1].
Certain chemotherapy drugs are more likely to cause neuropathy. These include platinum drugs, such as oxaliplatin; taxanes, such as docetaxel; vinca alkaloids, such as vincristine; and myeloma treatments, such as bortezomib. Other chemotherapy drugs can also cause neuropathy[1].
The risk of developing CIPN is higher with higher doses, multiple courses, and combination chemotherapy. Patients are more likely to develop CIPN if they are older or have diabetes, vitamin deficiencies, or pre-existing peripheral neuropathy[1]
No medication or supplement has been shown to prevent CIPN definitively. Regular exercise, reducing alcohol use, and treating pre-existing medical conditions (vitamin B12 deficiency) may reduce the risk of CIPN[1].
Depending on the nerves affected, symptoms include:

- Tingling ("pins and needles")
- Pain, which may be severe and constant, may come and go or may feel like burning • Decreased sensation ("legs feel like jelly")
- Increased sensitivity to touch, temperature, pressure, pain
- Muscle weakness Symptoms can appear hours to days after chemotherapy and may reduce in intensity with time.

Commonly, symptoms occur weeks to months after chemotherapy. They can get worse with additional cycles of chemotherapy[1].
Gynecological cancers comprise about 15% of all cancers in women, with 6% ovarian, 6% endometrial, 3% uterine, and less than 1% cervical (National Cancer Institute [NCI], 2007).
Chemotherapy regimens for gynecologic cancers typically combine platinum and taxanes after surgical debulking or radiation therapy[2].
The combination of platinum and taxane is considered the standard first-line chemotherapy for women with gynecological cancer[3]. However, chemotherapy-induced peripheral neuropathy (CIPN) is one of the most life-affecting adverse effects of chemotherapy associated with the use of taxanes[4]. It causes chemotherapy dose reduction or cessation and is inversely associated with quality of life (QOL) in cancer patients [5].
The symptoms of CIPN can be divided into peripheral sensory neuropathy (SPN), including paresthesia, numbness, or neuropathic pain in hands or feet, and motor peripheral neuropathy (MPN), including weakness or muscle wasting[6].

Depending on the onset and duration of CIPN, it can be classified as acute CIPN, which has a rapid onset ranging from hours to days after treatment and may regress between treatment cycles but often recurs with further treatment, and persistent or chronic CIPN where onset is gradually progressive and is related to the cumulative dose[7].

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of taxane and platinum-based chemotherapy, with prevalence ranging from 12%–to 96%.[8] Although these drug combinations have increased survival significantly, a high incidence of peripheral neuropathy is associated with this chemotherapy regimens[9].

Research around risk factors for CIPN has increased over recent years, although findings are often inconsistent or a limited pool of potential factors is assessed. In a large study (n = 3,106), worse neurotoxicity was observed in ovarian cancer patients, those with longer duration of cancer, on current therapy, older patients, and African Americans.

However, many of the potential predictors of CIPN have not been thoroughly investigated to date.

Chemotherapy-induced peripheral neuropathy significantly impacts patients' quality of life and often results in chemotherapy dose reductions or discontinuation. Multiple treatment modalities have been investigated, with few showing measurable clinical improvement.

Hence, this study aimed to assess the risk factors for chemotherapy-induced peripheral neuropathy (CIPN) among patients with gynecological cancer receiving chemotherapy, thus providing a more robust explanatory model and further exploring the potential link between CIPN and other symptoms[10]. We narrowed the focus of the research only to include chemotherapy regimens used in gynecologic oncology.

2. REVIEW OF LITERATURE

Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is hypothesized to occur when neuronal fibers are damaged by toxic agents and cannot meet their metabolic needs of axonal regeneration. This causes a disruption of myelinization, which results in the interruption of axonal transport of nervous impulses[11].

Peripheral neuropathy can be classified as causing motor deficits, sensory deficits, or mixed deficits. Motor neuropathy ranges from transient asymptomatic muscle weakness to weakness that interferes with functioning to total paralysis. Paresthesia, decreased deep tendon reflexes characterize sensory neuropathy and, in extreme cases, may result in a total loss of sensation[11].

Most chemotherapy-induced neuropathy is sensory, although rare cases of motor neuropathy leading to complete paralysis have been reported[12,13].

Incidence of Neuropathy

Reports of the incidence of peripheral neuropathy vary widely in the literature, likely because of the use of varied chemotherapy regimens and different measurement tools.

Although, in theory, the rate of residual neuropathy decreases after treatment, only one long-term study with a median follow-up of 28 months was found[14]. In it, 11% of patients experienced residual neuropathy.

In all of the reviewed studies, sensory neuropathy was the most common type, with rare motor neuropathy occurrences.

In the Multicenter Italian Trial in Ovarian Cancer by ***Pignata et al.***, 56% of patients experienced neurologic toxicity during chemotherapy. The rate of any grade of residual neuropathy was 23% at a median follow-up of 48 months[14].

Intraperitoneal (IP) is another method of delivering chemotherapy that has been used more frequently after studies showed significant survival benefits. However, little data exist on the relationship between IP chemotherapy and the rate of neuropathy.

Fujiwara et al. (2005) reported on a retrospective study analyzing the toxicities of IV paclitaxel (dose = 175 mg/m²) followed by IP carboplatin (dose = area under the curve [AUC] 5–7.5).

As the dose of IP carboplatin increased, the incidence of sensory neuropathy also increased. At the recommended dose of AUC 6.5, 44% of patients lost deep tendon reflexes or paresthesia (grade 2 neurotoxicity), and 11% had neuropathy that interfered with function (grade 3 neurotoxicity)[15].

Therefore, more research should be conducted on the effect of IP carboplatin and rates of persistent effects of neuropathy and their effect on patients' ability to function. Although incidence rates vary significantly according to different regimens and dose intensities, what is clear is that neuropathy is a problem for patients with gynecologic cancer receiving chemotherapy.

3. METHODOLOGY

The present study is a retrospective tri-center case-control study. Clinical characteristics and information on received chemotherapy were collected between June 2020, to June 2021, for women with gynecological cancer across 3 Cancer hospitals in India.

Inclusion Criteria

- Those who were older than 18 years
- Those who were newly diagnosed with gynecological cancer,
- Those who were pathologically confirmed in the respective hospitals.
- Those who received combination therapy of Taxane agents and Platinum-complex.

Exclusion Criteria

- Patients who were lost to follow-up or unable to complete the questionnaire were excluded from the study.

Obtaining Ethical Clearance and Permission from The Concerned Authorities:

Ethical Clearance:

- The Institutional Review Board approved the research of the concerned hospitals.

Informed Consent

- All participants provided verbal consent for the use of their records.
- Paclitaxel 135–175 mg/m2 , liposomal paclitaxel 135–175 mg/m2 , or docetaxel 75mg/m2 , was given every 3 weeks.
- Carboplatin , cisplatin 70–80 mg/m2 , lobaplatin 50 mg/m2 , or nedaplatin 80–100 mg/m2 was given every 3 weeks (other category).
- Amifostine 0.4 g was given over 15 minutes as an intravenous infusion diluted in saline solution 100ml during chemotherapy, and Vitamin B1 10 mg was given three times a day as an intervention.

Evaluation of Chemotherapy-Induced Peripheral Neuropathy (FIGO PROFORMA)

Participants were assessed for CIPN using the EORTC[11] (European Organization for Research and Treatment of Cancer CIPN-20), answering three questions:

- ***"Have you had tingling in your hands or feet?",***
- ***"Have you had numbness in your fingers or toes?", and***
- ***"Have you felt weak in your arms or legs?".***
-

In the present study, CIPN was categorized into two types: the SPN scale, as per the first two questions, and the MPN scale, as per the last question[12].
Patients' responses were recorded on a four-point scale:

- ***"Not At All,"***
- ***"A Little,"***
- ***"Quite A Bit," And***
- ***"Very Much."***

Higher scores represented a more significant symptom burden. Patients were followed up, and symptoms' onset and disappearance time were recorded.
The prevalence of symptoms on 1 day (T1), 1 month (T2), 3 months (T3), 6 months (T4,) and 12 months (T5) after the last cycle were calculated.

4. STATISTICAL ANALYSIS

- The data was collected and transferred from pre-coded proforma to the computer. The data were analyzed using SPSS (IBM) version 23.
- Descriptive statistics included mean, standard Deviation, Frequency, and Percentage.
- Fisher exact tests were used to assess group differences.
- The comparison was made between acute and chronic symptoms by nonparametric tests. Predictors of CIPN were analyzed using univariate logistic regression analysis, and ORs
- The level of significance was set at 0.05 at 95% confidence intervals.

5. RESULTS

Patient Clinical characteristics

- The present study comprised 120 (100) patients included in the study.
- The age-wise distribution of patients was found to be 45.±14.5 years which was found to be statistically significant.
- The average number of chemotherapy cycles was ***7.1 (range 2–14).***
- The clinical characteristics of the participants are displayed in ***Table 1.***
- Patients with CIPN were younger and more likely to have a lower FIGO (International Federation of Gynecology and Obstetrics) stage at diagnosis.
- No other clinical characteristics were significantly different between the two groups, including histology, number of chemotherapy cycles, or presence of diabetes or hypertension (Table 1).

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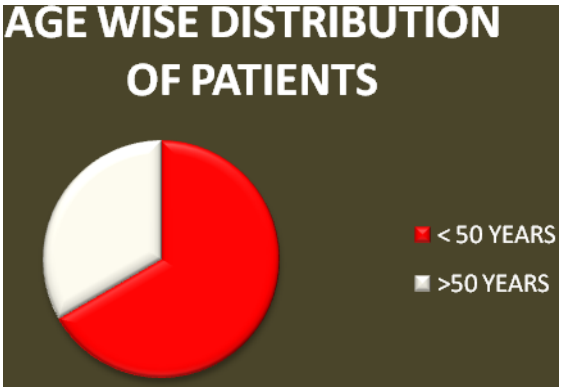
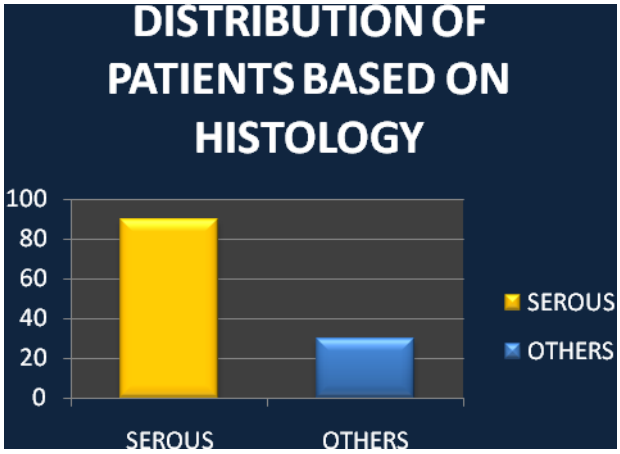
Variable	Total N - 120	CIPN N – 100	No CIPN N – 20	p-Value
Age				
<50 years	80	70	10	**0.01***
>50 years	40	30	10	
Histology				
Serous	90	72	18	0.42
Others	30	28	02	
FIGO Stage				
1 – 2	50	45	05	**0.03***
3 – 4	70	55	15	
Diabetes	10	6	4	0.21
Hypertension	15	7	8	0.33
Chemotherapy cycle				
<6 cycles	80	60	20	0.64
>cycles	40	30	10	

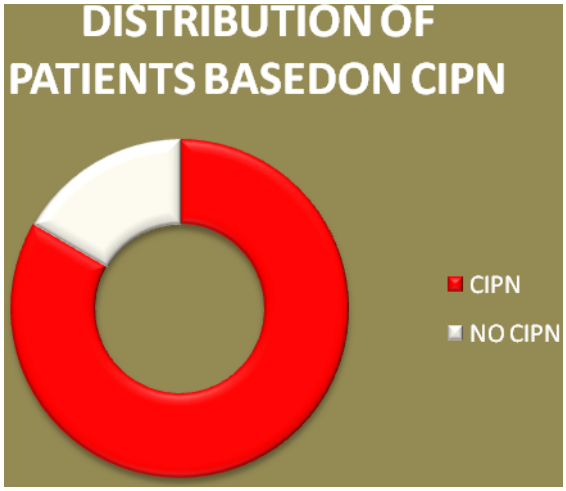
Table 1 - Distribution of patients based on characteristics and treatment plan



GRAPH 1



GRAPH 2



GRAPH 3

<u>Chemotherapy-Induced Peripheral Neuropathy Assessment</u>

A total of 100 (83.3%) patients reported some level of CIPN. Among these, 70 (70%) patients reported CIPN after the first cycle of chemotherapy, and 30 (30%) patients reported CIPN after the last cycle of chemotherapy.

Out of 100 study participants who reported CPIN, 60 (60%) patients reported no tingling in hands or feet, and 20 (20%) reported high levels of tingling ("Very much"), 10 (10%) reported moderate levels of tingling ("Quite a bit"), and 10 (10%) reported low levels of tingling ("little"),

Out of 100 study participants who reported CPIN, 50 (50%) patients reported no numbness in hands or feet, and 30 (30%) reported high levels of tingling ("Very much"), 10 (10%) reported moderate levels of tingling ("Quite a bit"), and 00 (10%) reported low levels of tingling ("little"),

Out of 100 study participants who reported CPIN, 65 (65%) patients reported no weakness, and 15 (15%) reported high levels of tingling ("Very much"), 05 (5%) reported moderate levels of tingling ("Quite a bit"), and 15 (15%) reported low levels of tingling ("little"),

Score	Tingling	Numbness	Weakness
0 (not at all)	60 (60%)	50 (50%)	65 (65%)
1 (little)	10 (10%)	10 (10%)	15 (15%)
2 (quite a bit)	10 (10%)	10 (10%)	05 (5%)
3 (very much)	20 (20%)	30 (30%)	15 (15%)

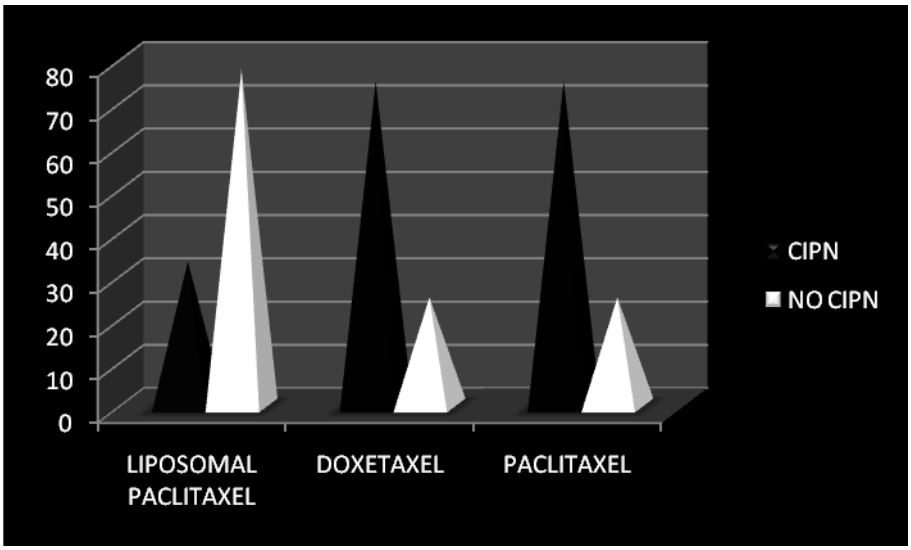
TABLE 2 – Patient responses regarding their CIPN Symptoms

Symptoms of tingling, numbness, and weakness lasted shorter than one week in 20 (16.6%), 20 (16.6%), and 15 (12.5%) patients, respectively.
The average scores for tingling and numbness in acute CIPN were lower than those for chronic CIPN, although the difference was not significant (p-Value – 0.38), which was not statistically significant.
The average score for weakness in acute CIPN was lower than for chronic CIPN (p - 0.01), which was statistically significant.

Interventions for prevention of Chemotherapy-Induced Peripheral Neuropathy
Out of 120 participants, 60 (50%) patients received liposomal paclitaxel, 40 (33.3%) patients received docetaxel and 20 (16.26%) patients received paclitaxel.
Among those receiving docetaxel, 30 (75%) patients developed CIPN
Among those receiving paclitaxel, 15 (75%) patients developed CIPN; and
Among those receiving liposomal paclitaxel, 20 (33.3%) patients developed CIPN.
Fisher exact test indicated that patients receiving liposomal paclitaxel were less likely to develop CIPN. Patients receiving docetaxel or paclitaxel were more likely to suffer from SPN, which was found to be statistically significant (p - 0.01).
In uni-variate modeling, SPN was associated with the type of taxane (docetaxel vs. liposomal paclitaxel with Odds Ratio of 4.39, with 95% Confidence Interval (1.69–11.42),

CHEMOTHERAPY PLAN TAXANE	TOTAL	CIPN		No CIPN	p VALUE
		SPN	MPN		
Liposomal paclitaxel	**60**	**10**	**10**	**40**	
Docetaxel	**40**	**15**	**15**	**10**	**0.01***
Paclitaxel	**20**	**10**	**05**	**05**	
PLATINUM					
Carboplatin	**90**	**40**	**40**	**10**	**0.06**
Others	**30**	**20**	**05**	**05**	

Table 3 – Distribution of patients based on their chemotherapy plan and its relation to CIPN



Graph 4 – Taxane Therapy And CIPN

Vitamin B1 Intervention

Among patients with CIPN, 30 (46.1%) received vitamin B1 during chemotherapy. One month after chemotherapy, the percentage of patients with CIPN dropped to 60.5% and 45.8% in the vitamin B1 and no vitamin B1 groups, respectively.

Amifostine Intervention

Among patients with CIPN, 35 (54.9%) received amifostine during chemotherapy. One month after chemotherapy, the percentage of patients with CIPN dropped to 71.7% and 40.3% in the amifostine group and the no amifostine group, respectively.

6. DISCUSSION

Women undergoing treatment for gynecologic malignancy may be exposed to one or more of the chemotherapeutic agents known to induce CIPN.

This can limit treatment dose and duration and contribute to significant long-term morbidity and reduced quality of life. Recognition of clinical symptoms and a basic understanding of their underlying pathophysiology is the first step toward helping affected women[16].

Taxanes are a group of microtubule-binding compounds that suppress microtubule depolymerization and dynamic instability. It is widely used as a chemotherapeutic drug in treating gynecological cancer, including ovarian, endometrial, and cervical cancer. However, the administration of taxanes is associated with many adverse effects, with chemotherapy-induced peripheral neuropathy being the most common toxicity[16].

The present study shows the age-wise distribution of patients was 45.±14.5 years which was following to study conducted by ***Lin Jen et al. in China*** wherein they reported 52 .±4.5[16].

In the present study, 83.3% of participants reported CIPN, which was under ***Seretny M et al. and Fallon MT et al.,*** wherein they reported 80% and 85% prevalence of CIPN reported by patients[18,19].

Prevalence of neuropathy was mainly linked with motor CIPN, with patients having such history being more than eight times at a higher risk for developing motor CIPN. In the past, there were not many studies that differentiated the role of this variable in the type of neuropathy; hence this is a novel finding.

In the present study, 83.3% of patients reported the symptoms of CIPN, wherein 40% reported tingling, 50 % numbness, and 35 % reporting weakness. After 12 months, 19.3% of patients were still suffering from CIPN.
The difference in the prevalence of CIPN may be partly due to inherited genetic variation, and further research with larger samples is needed and studies of genetic predictors[13].
According to ***Hou S et al.***, there is no effective management for chemotherapy-induced peripheral neuropathy. The use of duloxetine was considered to have a beneficial effect on CIPN caused by taxanes[20].
Vitamin B1 plays a critical role in cell energy metabolism, and vitamin B1 deficiency is associated with nerve dysfunction and nerve damage that could lead to peripheral neuropathy[18].
In the present study, patients with CIPN who received vitamin B1 or amifostine during chemotherapy had a better outcome. The results are following ***Schloss JM et al.*** and ***Popovic J et al.*** wherein the patients who received vitamin B1 and amifostine had a better outcome[22,21]
According to ***Molassiotis et al.,*** it is essential to identify patients who are potentially susceptible to the development of CIPN before using chemotherapy. Factors such as older age, chemotherapy plan, history of neuropathy, number of chemotherapy cycles received, and alcohol intake also showed a trend in the development of CIPN[23].
The present study showed that the patients with CIPN were younger and more likely to have a lower FIGO (International Federation of Gynecology and Obstetrics) stage at diagnosis, compared to those without CIPN which was found to be statistically significant, and the results are as per ***Lin Jen et al. in China[22,23].***
The present study showed that the docetaxel or paclitaxel was a risk factor of SPN, indicating that liposomal paclitaxel is safer than docetaxel and paclitaxel of neurotoxicity. Additional research will need to focus on CIPN in docetaxel, paclitaxel, and liposomal paclitaxel.

7. LIMITATIONS

- Some variables in the study had small frequency counts, which may affect the interpretation and generalizability of the results and should be perceived as preliminary only.
- Small sample size can again affect the generalizability of the results.
- Only three questions in EORTC were used to assess CIPN, including acute symptoms, which may have led to other CIPN symptoms being missed.
- Other factors may also contribute to weakness, such as cancer and lack of appetite and nutrition.

8. CONCLUSION

The present study showed that a significant proportion of patients with gynecological cancer receiving taxanes suffered from long-term residual neuropathy. The use of docetaxel and paclitaxel was associated with Sensory Peripheral Neuropathy.
Chemotherapy-induced peripheral neuropathy can significantly impact a large portion of the gynecologic oncology population. The clinician needs to have a fundamental understanding of clinical manifestations and treatment modalities available.
This study confirms the role of (older) age, the number of chemotherapy cycles received, and the type of chemotherapy as key CIPN risk factors.

The present study assessed CIPN clinical risk factors using a prospective design and a wide range of potential predictors. Overall, CIPN incidence was higher in this study than that reported in the literature, and this has to do with the scales used.
Identification of risk factors may assist the clinician in making chemotherapy treatment decisions accordingly to minimize the development of CIPN and the morbidity and health care utilization linked with a higher incidence of CIPN (while clinical effectiveness is not compromised).
However, science in this area is not yet optimal for such clinical decisions. More research elucidating strong CIPN related risk factors is needed, including developing predictive models. Other consistent risk factors, such as higher BMI and obesity, were not assessed in this study, and these should be included in future models.

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