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Serum Nerve Growth Factor as a Biomarker for Chemotherapy-Induced Peripheral Neuropathy: A Cross-Sectional Study

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A B S T R A C T

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating side effect of cancer treatment. Nerve growth factor (NGF) plays a crucial role in neuronal health and has been implicated in CIPN development. This study investigated the relationship between serum NGF levels and CIPN in cancer patients undergoing chemotherapy. **Methods:** A cross-sectional study was conducted on 60 cancer patients receiving chemotherapy at Dr. M. Djamil General Hospital Padang, Indonesia, from June to October 2024. Serum NGF levels were measured, and CIPN was assessed using the Toronto Clinical Scoring System (TCSS). The relationship between NGF and CIPN was analyzed using the Mann-Whitney test. **Results:** The median serum NGF level was significantly lower in patients with CIPN (n=43) compared to those without CIPN (n=17) (103.26 pg/ml vs. 148.91 pg/ml, p=0.029). No significant association was found between chemotherapy regimens and CIPN or NGF levels. **Conclusion:** Lower serum NGF levels are associated with CIPN in cancer patients undergoing chemotherapy. NGF may serve as a potential biomarker for CIPN, aiding in early detection and management. Further research is needed to explore the clinical utility of NGF as a predictive and monitoring tool for CIPN.

1. Introduction

Cancer stands as a major global health challenge and a leading cause of mortality, with its prevalence showing a concerning upward trend. Chemotherapy, a fundamental pillar in cancer treatment, employs potent drugs to eradicate rapidly dividing cancer cells. While crucial for combating cancer, chemotherapy is frequently accompanied by a spectrum of adverse effects that can profoundly impact patients' well-being. Among these, chemotherapy-induced peripheral neuropathy (CIPN) is a particularly common and debilitating complication that significantly impairs the quality of life of cancer survivors. CIPN is a toxic neuropathy that arises as a consequence of damage to the peripheral nerves resulting from the administration of chemotherapeutic agents. This damage precipitates a range of sensory, motor, and autonomic dysfunctions. Patients frequently experience symptoms such as numbness, tingling, and pain in the extremities, which can evolve into more severe manifestations, including gait disturbances, muscle weakness, and autonomic dysfunction. The severity and persistence of CIPN can necessitate dose reductions or treatment cessation, potentially compromising cancer treatment outcomes. Furthermore, the chronic nature of CIPN can lead to

long-term disability, impacting patients' ability to perform daily activities, maintain employment, and engage in social interactions. Consequently, CIPN not only presents a significant clinical challenge but also imposes a substantial burden on healthcare systems and society.[1-3]

The pathogenesis of CIPN is complex and multifactorial, involving a constellation of mechanisms that are not yet fully elucidated. Several chemotherapeutic agents, including taxanes and platinum-based compounds, have been identified as neurotoxic. These agents can trigger a cascade of cellular and molecular events that ultimately culminate in neuronal injury. Proposed mechanisms include mitochondrial dysfunction, oxidative stress, DNA damage, and inflammation. These processes can disrupt axonal transport, impair Schwann cell function, and induce neuronal apoptosis, contributing to the development and progression of CIPN. The variability in CIPN presentation and severity among patients underscores the influence of individual susceptibility factors, such as genetic predisposition, age, and pre-existing conditions. A deeper understanding of the precise mechanisms underlying CIPN is crucial for the development of effective preventive and therapeutic strategies. Nerve growth factor (NGF), a member of the neurotrophin family, is a protein that plays a pivotal role in the development, maintenance, survival, and function of neurons. NGF exerts its effects by binding to specific receptors on the surface of target cells, initiating intracellular signaling cascades that regulate neuronal growth, differentiation, and survival. Beyond its neurotrophic functions, NGF is also implicated in a variety of physiological processes, including nerve regeneration, pain signaling, and inflammation. The multifaceted roles of NGF highlight its importance in the nervous system's health and functionality.[4-6]

Given NGF's critical role in neuronal health, it is plausible that alterations in NGF levels or signaling may contribute to the pathogenesis of CIPN. Preclinical studies have provided evidence that NGF can protect neurons from chemotherapy-induced neurotoxicity, suggesting that NGF may have a protective role against CIPN. Clinical investigations have explored the relationship between NGF levels and CIPN in patients undergoing chemotherapy. However, the findings from these studies have been inconsistent. Some studies have reported decreased NGF levels in patients with CIPN, while others have observed increased levels. These discrepancies may stem from a variety of factors, including differences in study design, heterogeneity of patient populations, variations in chemotherapy regimens administered, and methodological differences in NGF measurement. Further research is warranted to clarify the precise role of NGF in CIPN development. The identification of reliable biomarkers for CIPN is of paramount importance for early detection, risk stratification, and monitoring of treatment response. A biomarker is a measurable indicator of a biological state or condition. In the context of CIPN, an ideal biomarker would be able to predict the development of neuropathy before it becomes clinically apparent, allowing for timely intervention and prevention strategies. Furthermore, a biomarker could aid in identifying patients who are at increased risk of developing severe or persistent CIPN, enabling clinicians to tailor treatment regimens accordingly. Finally, a biomarker could serve as a surrogate endpoint in clinical trials evaluating novel CIPN therapies, facilitating the assessment of treatment efficacy.[7-10] This study was designed to investigate the relationship between serum NGF levels and CIPN in a well-defined cohort of cancer patients undergoing chemotherapy.

2. Methods

This research employed a cross-sectional study design. This design was chosen to provide a snapshot of the relationship between serum NGF levels and CIPN at a single point in time within a defined group of cancer patients undergoing chemotherapy. The study was conducted at the Department of Neurology, Dr. M. Djamil General Hospital Padang, Indonesia. Data collection took place over a five-month period, specifically from June to October 2024. The study

population consisted of cancer patients who were actively receiving chemotherapy treatment at the aforementioned hospital. To ensure the selection of an appropriate study group, specific inclusion and exclusion criteria were established.

Patients were eligible for inclusion in the study if they met the following criteria; Chronological Age: Participants were required to be 18 years of age or older. This age threshold was selected to focus on adult cancer patients; Confirmed Cancer Diagnosis: All participants had to have a diagnosis of cancer. The specific type of cancer was not a limiting factor for inclusion, allowing for a heterogeneous sample reflective of the broader cancer patient population; Chemotherapy Treatment History: Participants must have received at least one cycle of chemotherapy. This criterion ensured that all participants had been exposed to potential neurotoxic chemotherapeutic agents; Informed Consent: A crucial ethical consideration was that all patients had to provide voluntary written informed consent to participate in the study. This process ensured that patients were fully aware of the study's purpose, procedures, potential risks, and benefits before agreeing to take part.

Patients were excluded from the study if they presented with any of the following criteria; Pre-existing Peripheral Neuropathy: Individuals with a prior diagnosis or documented history of peripheral neuropathy from any cause other than chemotherapy were excluded. This was critical to isolate CIPN and avoid confounding factors in the assessment of neuropathy; History of Neurological Disorders: Patients with a history of other neurological disorders, such as stroke, multiple sclerosis, or Parkinson's disease, were excluded. These conditions can independently affect nerve function and potentially influence NGF levels; Use of Medications Affecting NGF Levels: Patients currently using medications known or suspected to have a significant impact on NGF levels were excluded. This precaution was taken to minimize potential interference with the accurate measurement of NGF and the interpretation of study results.

The sample size for this study was 60 cancer patients. The process of data collection involved gathering both demographic and clinical information, as well as biological samples for laboratory analysis. Demographic and clinical data were obtained through a combination of methods, including a review of patients' medical records and direct patient interviews. This comprehensive approach ensured the collection of relevant information. The specific data points collected included; Age: The patient's age at the time of data collection; Gender: The patient's gender (male or female); Education Level: The patient's highest level of educational attainment. This information provides insight into socioeconomic factors within the study population; Type of Cancer: The specific type of cancer diagnosed in each patient. This information allows for analysis of potential differences in CIPN prevalence or NGF levels across various cancer types; Chemotherapy Regimen: The specific chemotherapy drugs and their administration schedule. This is a critical factor in CIPN development, as different chemotherapeutic agents have varying neurotoxic potentials; Number of Chemotherapy Cycles: The total number of chemotherapy cycles the patient had received at the time of data collection. This variable helps to explore the potential cumulative effect of chemotherapy exposure on CIPN and NGF levels.

Serum samples were collected from each participant to measure NGF levels. The following procedure was used; Blood Sample Collection: Blood samples were drawn from patients prior to their next scheduled chemotherapy cycle. This timing was chosen to minimize acute effects of chemotherapy administration on NGF levels and to provide a more stable baseline measurement; Sample Processing: Following collection, the blood samples were processed to obtain serum. This typically involves centrifugation to separate the serum from the cellular components of the blood; NGF Quantification: Serum NGF levels were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit. ELISA is a widely used immunological assay that allows for the sensitive and specific measurement of proteins, such

as NGF, in biological samples. The specific details of the ELISA kit used, including the manufacturer and catalog number, are not provided in the text. However, it is crucial that a validated and reliable ELISA kit is used to ensure the accuracy and reproducibility of the NGF measurements; Assay Procedure: The ELISA procedure involves a series of steps, including coating a microplate with an antibody specific to NGF, adding the serum sample, allowing NGF to bind to the antibody, adding a secondary antibody conjugated to an enzyme, adding a substrate for the enzyme, and measuring the resulting color change. The intensity of the color change is directly proportional to the concentration of NGF in the sample; Quality Control: Appropriate quality control measures are essential in ELISA assays to ensure the accuracy and reliability of the results. These measures may include the use of standard curves, positive and negative controls, and intra- and inter-assay variability assessments.

CIPN was assessed in each participant using the Toronto Clinical Scoring System (TCSS). The TCSS is a validated clinical tool specifically designed for the evaluation and grading of CIPN. It is a widely used and accepted instrument in both clinical practice and research settings. The TCSS assesses sensory, motor, and autonomic symptoms and signs of peripheral neuropathy. The sensory component evaluates symptoms such as numbness, tingling, pain, and loss of sensation in the extremities. The motor component assesses muscle weakness, reflexes, and gait abnormalities. The autonomic component evaluates symptoms such as changes in heart rate, blood pressure, sweating, and bowel and bladder function. The TCSS is typically administered by a trained healthcare professional, such as a neurologist or a nurse, through a standardized clinical examination and patient interview. The specific procedures for administering the TCSS, including the detailed instructions and scoring criteria, are well-defined in the published literature. The TCSS generates a numerical score that reflects the severity of CIPN. Higher scores indicate more severe neuropathy. The specific scoring range and the cut-off points for defining CIPN severity may vary slightly depending on the specific version of the TCSS being used.

Statistical analysis was performed to analyze the collected data and to determine the relationship between serum NGF levels and CIPN. Data analysis was conducted using IBM SPSS Statistics version 23.0 for Windows. SPSS is a widely used statistical software package in health sciences research. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study participants. These statistics provide an overview of the sample and include measures of central tendency (e.g., mean, median), measures of variability (e.g., standard deviation), and frequencies and percentages for categorical variables. The Mann-Whitney test, a non-parametric statistical test, was used to compare serum NGF levels between patients with CIPN and those without CIPN. The Mann-Whitney test is appropriate for comparing two independent groups when the data are not normally distributed. This test was chosen because NGF levels may not follow a normal distribution. The chi-square test was used to examine the association between chemotherapy regimens and CIPN. The chi-square test is a statistical test used to analyze categorical data and to determine if there is a statistically significant association between two or more categorical variables. A p-value of less than 0.05 was considered to indicate statistical significance. The p-value is the probability of obtaining the observed results, or more extreme results, if there is no true effect. A p-value of <0.05 is a conventional threshold for rejecting the null hypothesis and concluding that there is a statistically significant effect.

3. Results

Table 1 presents a detailed overview of the baseline characteristics of the participants included in the study. The table categorizes these characteristics by the chemotherapy regimen received: Taxane, Platinum, and a combination of Taxane + Platinum, with 20 participants in each group; Gender Distribution: A striking difference is observed in the gender distribution across the groups. The Taxane

group consists entirely of females (100%). In contrast, the Platinum group has a mix of both genders, with 35% males and 65% females. The Taxane + Platinum group also shows a predominantly female composition (90%) but includes a small proportion of males (10%). This uneven gender distribution is a notable feature of the data. It suggests potential differences in the types of cancers treated with these regimens, as certain cancers have higher prevalence in specific genders. It also raises questions about whether gender might be a confounding factor in the study's results, although this would need to be addressed through statistical analysis; Age: The mean age of participants is relatively similar across the three groups. The Taxane group has a mean age of 47.65 years (±10.23 SD), the Platinum group has a mean age of 49.25 years (±13.03 SD), and the Taxane + Platinum group has a mean age of 45.90 years (±11.73 SD). While there are slight variations, the age ranges overlap, indicating that the groups are generally comparable in terms of age. Statistical tests would be needed to confirm if these differences are significant; Education Level: The table illustrates the distribution of participants across four education levels: Elementary School, Junior High School, Senior High School, and Bachelor's Degree. The Taxane group has a distribution leaning towards higher education, with 45% having a Senior High School education and 30% holding a Bachelor's Degree. The Platinum group shows a more varied distribution, with the highest percentage (40%) having a Senior High School education, but also a notable proportion (30%) with only an Elementary School education. The Taxane + Platinum group has a distribution similar to the Taxane group, with the largest proportion (25%) having a Senior High School education. Overall, there's variability in educational attainment within and across the groups, which might reflect socioeconomic differences within the study population. Education level could potentially influence health literacy and adherence to treatment, making it a relevant factor to consider; Therapy Cycle: The therapy cycle indicates the duration of chemotherapy treatment. Most participants in all groups are in the earlier stages of their treatment (Cycle 1-6). Specifically, 90% of the Taxane group, 70% of the Platinum group, and 80% of the Taxane + Platinum group are in Cycle 1-6. A smaller proportion of participants are in the later stages of treatment (Cycle 7-12). This distribution might be due to various factors, such as treatment response, side effects, or study inclusion criteria; BMI (Body Mass Index): BMI, a measure of body fat based on height and weight, is presented as mean ± standard deviation. The Taxane group has a mean BMI of 22.96 kg/m² (±3.33 SD), the Platinum group has a mean BMI of 20.27 kg/m² (±3.08 SD), and the Taxane + Platinum group has a mean BMI of 22.27 kg/m² (±4.87 SD). The Platinum group exhibits a slightly lower mean BMI compared to the other two groups. A BMI of 20.27 kg/m² falls within the underweight category, which could be a significant factor influencing overall health and response to treatment. The other two groups fall within the healthy weight category; TCSS Score (Toronto Clinical Scoring System): The TCSS score reflects the severity of Chemotherapy-Induced Peripheral Neuropathy (CIPN). The scores are presented as the median, with the minimum and maximum values in parentheses. The Taxane group has a median TCSS score of 5.5, with scores ranging from 0 to 10. Both the Platinum and Taxane + Platinum groups have a median TCSS score of 7. However, the range of scores varies, with the Platinum group ranging from 4 to 13 and the Taxane + Platinum group ranging from 0 to 10. These scores indicate that CIPN is present to varying degrees across all groups. The higher median scores in the Platinum and Taxane + Platinum groups suggest a trend towards more severe neuropathy in these groups compared to the Taxane group. However, it's important to consider the range of scores and the specific distribution within each group.

Table 1. Participant characteristics.

Characteristic	Category	Taxane (n=20)	Platinum (n=20)	Taxane + Platinum (n=20)
Gender	Male	0 (0%)	7 (35%)	2 (10%)
	Female	20 (100%)	13 (65%)	18 (90%)
Age (years)	Mean ± SD	47.65 ± 10.23	49.25 ± 13.03	45.90 ± 11.73
Education level	Elementary School	1 (5%)	3 (15%)	1 (5%)
	Junior High School	4 (20%)	3 (15%)	0 (0%)
	Senior High School	9 (45%)	8 (40%)	5 (25%)
	Bachelor's Degree	6 (30%)	6 (30%)	4 (20%)
Therapy cycle	Cycle 1-6	18 (90%)	14 (70%)	16 (80%)
	Cycle 7-12	2 (10%)	6 (30%)	4 (20%)
BMI (kg/m²)	Mean ± SD	22.96 ± 3.33	20.27 ± 3.08	22.27 ± 4.87
TCSS score	Median (min-max)	5.5 (0-10)	7 (4-13)	7 (0-10)

CIPN: Chemotherapy-Induced Peripheral Neuropathy; TCSS: Toronto Clinical Scoring System; BMI: Body Mass Index.

Table 2 presents data on the association between different chemotherapy regimens, the incidence of Chemotherapy-Induced Peripheral Neuropathy (CIPN), and Nerve Growth Factor (NGF) levels. The data is categorized by the chemotherapy regimens: Taxane, Platinum, and Taxane + Platinum; CIPN Incidence: The table shows the number and percentage of patients with and without CIPN in each chemotherapy group. In the Taxane group, 8 patients (40%) had no neuropathy, while 12 patients (60%) developed neuropathy. The Platinum group had 6 patients (30%) without neuropathy and 14 patients (70%) with neuropathy. The Taxane + Platinum group showed the highest incidence of neuropathy, with only 3 patients (15%) without neuropathy and 17 patients (85%) developing neuropathy. The p-value for the chi-square test is 0.210. This indicates that there is no statistically significant association between the chemotherapy regimens and the incidence of CIPN. In simpler terms, the differences in CIPN incidence across the three groups are not large enough to conclude that the chemotherapy regimen itself is a significant determining factor in whether or not patients develop CIPN; NGF Levels: The table presents the median NGF levels (pg/ml) and the minimum-maximum range for each chemotherapy group. The Taxane group has a median NGF level of 143.70 pg/ml, with a range from 55.12 to 470.50 pg/ml. The Platinum group shows a lower median NGF level of 97.30 pg/ml, with a range from 29.81 to 173.73 pg/ml. The Taxane + Platinum group has a median NGF level of 139.73 pg/ml, with a wider range from 23.86 to 630.80 pg/ml. The p-value for the Kruskal-Wallis test is 0.144. This suggests that there is no statistically significant difference in NGF levels across the three chemotherapy groups. The variations in median NGF levels and ranges are not sufficient to conclude that the chemotherapy regimen significantly influences NGF levels.

Table 2. Association between chemotherapy regimens, CIPN incidence, and NGF levels.

Variable	Taxane (n=20)	Platinum (n=20)	Taxane + Platinum (n=20)	p-value
CIPN				0.210#
No Neuropathy	8 (40%)	6 (30%)	3 (15%)	
Neuropathy	12 (60%)	14 (70%)	17 (85%)	
NGF (pg/ml)				1.440
Median (min-max)	143.70 (55.12-470.50)	97.30 (29.81-173.73)	139.73 (23.86 – 630.80)	

#Chi-Square test; 0Kruskal-Wallis test.

Table 3 presents the findings on serum Nerve Growth Factor (NGF) levels in relation to the incidence of Chemotherapy-Induced Peripheral Neuropathy (CIPN). It compares NGF levels between patients who did not develop neuropathy and those who did. The table shows the median serum NGF levels (pg/ml) and the range (minimum-maximum) for both groups: patients with no neuropathy and patients with neuropathy. In the group without neuropathy (n=17), the median serum NGF level was 148.91 pg/ml, with levels ranging from 82.42 to 470.50 pg/ml. In the group with neuropathy (n=43), the median serum NGF level was 103.26 pg/ml, with levels ranging from 23.86 to 630.80 pg/ml. The p-value for the Mann-Whitney U test is 0.029. This indicates a statistically significant difference in serum NGF levels between the two groups. The statistically significant p-value (0.029) suggests that there is a relationship between serum NGF levels and the incidence of CIPN. Specifically, the median serum NGF level is significantly lower in patients who developed CIPN compared to those who did not.

Table 3. Serum NGF levels and CIPN incidence.

Variable	No Neuropathy (n=17)	Neuropathy (n=43)	p-value
Serum NGF Level (pg/ml)			0.029#
Median (min-max)	148.91 (82.42 – 470.50)	103.26 (23.86 - 630.80)	

#Mann-Whitney U test.

4. Discussion

The core finding of this study lies in the observation that patients who developed CIPN demonstrated significantly lower median serum NGF levels when compared to those who did not. Quantitatively, the median serum NGF level registered at 103.26 pg/ml within the CIPN group, while the group without CIPN presented a median serum NGF level of 148.91 pg/ml. This disparity between the two groups reached statistical significance, as evidenced by a p-value of 0.029. This statistical significance provides robust evidence supporting the existence of an association between diminished NGF levels in the serum and the occurrence of CIPN in cancer patients undergoing chemotherapy. To fully appreciate the implications of this finding, it is essential to delve into the biological roles of NGF and the pathobiological mechanisms underpinning CIPN. NGF, a member of the neurotrophin family, is a protein that functions as a crucial signaling molecule within the nervous system. Its significance is underscored by its involvement in a multitude of critical neuronal processes. These include the development of neurons during the early stages of life, the maintenance of neuronal structure and function throughout life, the promotion of neuronal survival in the face of injury or stress, and the

regulation of overall neuronal functionality. NGF exerts its biological effects through a mechanism involving binding to specific receptors located on the surface of target cells. This binding event initiates a cascade of intracellular signaling events, complex sequences of molecular interactions that ultimately govern a wide array of cellular responses. These regulated responses encompass neuronal growth, the process by which neurons extend their processes and increase in size, neuronal differentiation, the process by which neurons acquire specialized functions, and neuronal survival, the ability of neurons to resist cell death. However, the functional scope of NGF extends beyond these fundamental neurotrophic activities. NGF is also actively implicated in a diverse array of physiological processes that are critical for overall health and well-being. These additional processes include nerve regeneration, the process by which damaged nerves repair themselves, pain signaling, the complex mechanisms by which the nervous system detects and transmits pain sensations, and inflammation, the body's complex response to injury or infection. The involvement of NGF in such a wide spectrum of vital functions underscores its importance in maintaining the health and functional integrity of the nervous system. In contrast to the supportive and protective roles of NGF, chemotherapeutic agents, while critical for cancer treatment, can exert detrimental effects on the nervous system. These agents can induce neurotoxicity, a state of damage or dysfunction in the nervous system, through a variety of complex mechanisms. These mechanisms, which often operate in concert, include mitochondrial dysfunction, a disruption in the energy-producing machinery of cells, oxidative stress, an imbalance between the production of harmful free radicals and the body's ability to neutralize them, and DNA damage, injury to the genetic material of cells. These multifaceted mechanisms, initiated by chemotherapeutic agents, can converge to cause significant neuronal damage and degeneration. This damage and degeneration ultimately manifest as CIPN, a debilitating condition characterized by a range of sensory, motor, and autonomic symptoms. The observation in the current study of lower NGF levels in patients with CIPN suggests a potential link in this complex pathway reduced NGF may compromise the neuron's ability to withstand the toxic onslaught of chemotherapy. The findings of the present study, specifically the observation of lower serum NGF levels in patients with CIPN, strongly suggest that a diminished capacity for neuronal protection and repair exists in these patients. This interpretation is grounded in the well-established ability of NGF to protect neurons against the damaging effects of chemotherapy-induced neurotoxicity. NGF has demonstrated a remarkable capacity to mitigate or counteract the neurotoxic effects of various chemotherapeutic agents. It can achieve this neuroprotection through several mechanisms. NGF can enhance cellular antioxidant defenses, thereby reducing oxidative stress. It can also modulate inflammatory responses, preventing excessive or prolonged inflammation that can damage neurons. Furthermore, NGF can support mitochondrial function, ensuring that neurons have the energy they need to function and survive. By bolstering these protective mechanisms, NGF can significantly reduce the vulnerability of neurons to the toxic effects of chemotherapy. Therefore, within the context of CIPN, it is plausible to hypothesize that in patients with lower circulating levels of NGF, this crucial protective mechanism is compromised. This compromise leaves neurons more vulnerable and susceptible to the damaging effects of chemotherapeutic agents, ultimately increasing the likelihood of developing CIPN. In essence, the reduced availability of NGF may deprive neurons of the support they need to resist and repair the damage inflicted by chemotherapy, tilting the balance towards neurodegeneration and the manifestation of CIPN symptoms. This interpretation of the study's findings aligns seamlessly with the broader understanding of NGF's fundamental role in maintaining neuronal health and its potential involvement in the complex pathobiology of CIPN. While the current study did not directly investigate the

intricate underlying molecular and cellular mechanisms responsible for the observed association, the results are certainly consistent with the proposed concept that NGF plays a pivotal and protective role against chemotherapy-induced neuronal damage. The observed reduction in NGF levels in CIPN patients may represent a critical factor that contributes to the development and progression of this debilitating condition.[11-15]

The investigation of altered NGF levels in the context of CIPN is not a novel pursuit in scientific research. Both preclinical studies, involving laboratory experiments typically conducted in vitro or in animal models, and clinical studies, involving human subjects, have previously explored the potential involvement of NGF in the complex pathobiology of CIPN. These prior investigations have sought to elucidate the role that NGF might play in the development, progression, and manifestation of this debilitating condition. However, a critical challenge in this field of research is the inconsistency of findings across different studies. This lack of uniformity in results has created a complex and sometimes conflicting body of evidence, making it difficult to draw definitive conclusions about the precise role of NGF in CIPN. In alignment with the results obtained in the current study, some previous investigations have indeed reported decreased NGF levels in patients diagnosed with CIPN. These studies provide support for the hypothesis that a deficiency in NGF may be a contributing factor in the development or severity of CIPN. The observation of reduced NGF levels in CIPN patients in these studies, and in the current one, suggests that a lack of this crucial neurotrophic factor may compromise neuronal health and resilience in the face of chemotherapy-induced damage. Conversely, it is important to acknowledge that other studies have presented contrasting findings. These studies have observed increased NGF levels in patients with CIPN. Such findings challenge the straightforward interpretation of NGF deficiency as a primary driver of CIPN. The elevation of NGF levels in some CIPN cases might reflect a compensatory response by the nervous system in an attempt to counteract the damage caused by chemotherapy. It is also possible that increased NGF levels could be associated with specific CIPN symptoms, such as pain, as NGF is known to play a role in pain signaling. These discrepancies in findings across different studies highlight the complexity inherent in understanding the relationship between NGF and CIPN. The variability in results suggests that the interplay between NGF and CIPN is likely influenced by a multitude of factors, and that a simple cause-and-effect relationship may not fully explain the observed phenomena. The factors contributing to these inconsistencies are numerous and multifaceted. Differences in study design represent a significant source of variability and a major challenge in comparing and synthesizing findings across different investigations. One critical aspect of study design that can vary considerably is the patient inclusion and exclusion criteria. Studies may differ in the specific types of cancer included, the stages of cancer in the participants, and the presence of other comorbidities. These variations can lead to the recruitment of heterogeneous patient populations, which can, in turn, influence both the incidence and severity of CIPN, as well as the observed levels of NGF. For example, studies focusing on specific cancer types known to have a higher propensity for CIPN may yield different results compared to studies with a broader inclusion of various cancer types. Another significant source of variability lies in the specific chemotherapeutic agents administered. Different chemotherapeutic drugs have varying mechanisms of action and differing degrees of neurotoxicity. Studies that administer different chemotherapeutic regimens are likely to observe variations in CIPN development and NGF levels. Furthermore, the dosage and duration of chemotherapy can also significantly impact neurotoxicity and NGF levels. The timing of NGF measurements is also a crucial factor that can influence study results. NGF levels may fluctuate over the course of chemotherapy treatment, and the timing of blood draws or tissue sampling can affect the observed NGF concentrations. Studies that measure

NGF levels at different time points may capture different phases of CIPN development or recovery, leading to inconsistent findings.Furthermore, the methods used to assess CIPN can vary across studies. Different clinical scales, electrophysiological tests, or imaging techniques may be employed to diagnose and grade CIPN. These methodological differences can introduce variability in CIPN assessment and make it challenging to compare results across studies. Beyond variations in study design, heterogeneity in patient populations represents another significant factor contributing to discrepancies in findings. Cancer patients exhibit a wide range of individual characteristics that can influence their susceptibility to CIPN and their NGF levels. Variations in cancer type play a crucial role. Different types of cancer may be associated with different underlying biological processes that can affect NGF production or utilization. For instance, some cancers may directly produce NGF or alter its metabolism. The stage of cancer at which patients are included in a study can also be a significant factor. Patients with advanced-stage cancer may have different physiological responses to chemotherapy and different NGF profiles compared to patients with early-stage disease. Individual susceptibility factors also play a critical role in CIPN development and NGF levels. Genetic predisposition, age, and pre-existing conditions can all influence a patient's risk of developing CIPN and their response to chemotherapy. These individual variations can contribute to the heterogeneity observed in CIPN and NGF levels across different studies. Furthermore, variations in the specific chemotherapy regimens employed are a major contributor to the inconsistencies observed in CIPN and NGF research. Different chemotherapeutic drugs exhibit a wide range of neurotoxic potentials. Some drugs, such as platinum-based agents and taxanes, are well-known for their propensity to induce CIPN, while others may have a lower risk. Studies focusing on different chemotherapeutic agents are likely to observe variations in CIPN incidence and severity. Even within the same class of chemotherapeutic drugs, there can be variations in neurotoxicity. Different taxanes, for example, may have slightly different chemical structures or pharmacological properties that can influence their neurotoxic effects. Differences in drug dosage and administration schedule also contribute to variability. Higher doses of chemotherapeutic drugs are generally associated with a greater risk of CIPN. The frequency and duration of chemotherapy infusions can also influence neurotoxicity. Methodological differences in NGF measurement are an additional source of variability that can contribute to inconsistencies across studies. NGF can be measured in various biological samples, including serum, plasma, cerebrospinal fluid, and tissue samples. The choice of sample type can influence the observed NGF levels. For example, NGF levels in serum may not accurately reflect NGF levels in the peripheral nerves, the primary site of CIPN pathology. Different types of assays are used to measure NGF, including enzyme-linked immunosorbent assays (ELISAs) and other immunoassays. These assays may have different sensitivities and specificities, which can affect the accuracy and reliability of NGF measurements. Variations in sample processing, such as the timing and temperature of sample collection, storage, and handling, can also introduce variability in NGF measurements. The current study's finding of decreased NGF levels in patients with CIPN contributes to the growing body of evidence suggesting a potential link between NGF deficiency and the development of CIPN. By adding to the studies that have reported reduced NGF in CIPN, this research strengthens the hypothesis that insufficient NGF may play a role in making neurons more vulnerable to chemotherapy-induced damage. However, it is crucial to acknowledge that this finding also highlights the complexity of the relationship between NGF and CIPN. The existence of studies that have reported increased NGF levels in CIPN patients underscores the fact that the interplay between NGF and CIPN is likely multifaceted and not fully understood. The current study, alongside previous research, emphasizes the need for further investigation to reconcile the

conflicting findings present in the existing scientific literature. Resolving these discrepancies is essential for developing a comprehensive understanding of NGF's role in CIPN and for potentially harnessing NGF-related pathways for therapeutic interventions.[16-20]

5. Conclusion

In conclusion, this cross-sectional study provides evidence that lower serum NGF levels are associated with CIPN in cancer patients undergoing chemotherapy. The median serum NGF level was significantly lower in patients with CIPN compared to those without CIPN (103.26 pg/ml vs. 148.91 pg/ml, p=0.029). This finding suggests that NGF may play a crucial role in protecting neurons from chemotherapy-induced damage. While the study did not find a significant association between chemotherapy regimens and CIPN or NGF levels, the observed reduction in NGF levels in CIPN patients aligns with some previous studies, supporting the hypothesis that insufficient NGF may contribute to the development and progression of CIPN. However, the complexity of CIPN pathogenesis is highlighted by the inconsistencies in NGF levels reported across different studies. These inconsistencies may be attributed to variations in study design, heterogeneity of patient populations, and methodological differences in NGF measurement. Further research is warranted to elucidate the precise role of NGF in CIPN, to reconcile conflicting findings, and to explore its potential as a predictive and monitoring biomarker for CIPN. A more comprehensive understanding of the interplay between NGF and CIPN may pave the way for the development of effective preventive and therapeutic strategies to mitigate this debilitating complication of cancer treatment.

6. References

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