ADDIS ABABA UNIVERSITY COLLEGE OF HEALTH SCIENCE AND SCHOOL OF MEDICINE DEPARTMENT OF NEUROLOGY

PREVALENCE AND ASSOCIATED RISK FACTORS OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY IN BREAST CANCER PATIENTS, TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

BY:

DR. HIWOT BERHANU- MD, NEUROLOGY RESIDENT

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A final research thesis submitted to Tikur Anbessa Specialized Hospital, Department of Neurology, in partial fulfillment of the requirements for the specialization certificate in neurology.

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Abstract

BACKGROUND -Breast cancer is the second leading cause of cancer deaths among women. The development of breast cancer is a multi-step process involving multiple cell types, and its prevention remains challenging to the world. Chemotherapy can be an integral component of the adjuvant management strategy. Chemotherapy-induced peripheral neuropathy (CIPN) describes the damage to the peripheral nervous system incurred by a patient who has received a chemotherapeutic agent that is known to be neurotoxic. Neurotoxic side effects are the second most common acute side effect, behind hematologic toxicity.

METHODS: The study will be conducted at the Department of Oncology at TASH, Addis Ababa, using a comparative cross-sectional study design. Data will be collected during the study period by face-to-face interviewing using a prepared questionnaire and physical examination from the modified total neuropathy score. The study population includes all breast cancer patients on chemotherapy at TASH during the study period. A total of 181 breast cancer will be included in the data collection & simple random sampling technique will be used to select the participants. The collected data will be analyzed using SPSS statistical software. Binary and multivariate logistic regression models will be used to examine the relationship between the explanatory variables and the outcome variable. A p-value of less than 0.05 will be considered statistically significant.

RESULTS: One hundred and eighty-one female breast cancer patients receiving chemotherapy were enrolled in the study. 45% of the participants' age group was between 36 -51 years. 69% of the study participants reported symptoms of CIPN at the end of chemotherapy. Although the majority of the patients, 90% with CIPN, experienced mild symptoms. In this cross-sectional study, most patients reported the onset of peripheral neuropathy (PN) symptoms beginning around the fifth chemotherapy cycle. Participants older than 35 were 5.6 times more likely to develop CIPN than those aged 35 and below. Patients with stage 3 or higher breast cancer were 3.31 times more likely to develop CIPN compared to those with lower stage cancers.

CONCLUSION: The prevalence of CIPN was 69% among the study participants. Tingling sensation was the most commonly reported symptom among the participants, and the majority of the participants experienced mild symptoms of peripheral neuropathy

Keywords: chemotherapy-induced peripheral neuropathy, CIPN, breast cancer patients, chemotherapy

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List of abbreviations

CIPN - chemotherapy-induced peripheral neuropathy

TASH - Tikur Anbessa specialized hospital

AAU- Addis Ababa University

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1. Introduction

1.1 Background

Breast cancer is the second most common cause of cancer-related mortality among women. Its development is a complex, multi-step process involving multiple cell types, and effective prevention remains a global challenge (1). Chemotherapy represents a key component of adjuvant treatment strategies (2).

The origins of chemotherapy can be traced back to the early 20th century, particularly during World War II. It was detected that individuals exposed to nitrogen mustard experienced a substantial decrement in white blood cell counts. This outcome led researchers to explore the potential use of mustard agents to inhibit the growth of rapidly dividing cancer cells. Following early studies using nitrogen mustard derivatives—substances termed *alkylating agents* due to their ability to alkylate proteins, DNA, and RNA—researchers demonstrated their cytotoxic effects on mice with lymphoma in 1943. These results gained wider attention after their publication in 1946 (3)

Over the following twenty years, combination chemotherapy regimens emerged as a prominent treatment approach, leveraging drugs with distinct mechanisms of action. . This approach contributed to improvements in patient survival and reductions in mortality. The recognition of chemotherapy-related neurological complications began with the documentation of vincristine-induced neurotoxicity in 1986. By the early 1990s, research expanded significantly, highlighting a broader spectrum of neurological side effects. These studies emphasized that such complications, though frequent, could be severe and might hinder the effective treatment of systemic or central nervous system cancers. Neurotoxicity was identified as stemming either from the direct effects of chemotherapeutic agents or interactions between them (4).

The effects of chemotherapeutic agents on the nervous system differ significantly depending on the drug class, influenced by their physical and chemical properties as well as dosage. Notably, unlike the central nervous system (CNS), the peripheral nervous system (PNS) is not shielded by the blood-brain barrier (BBB), rendering it more vulnerable to direct toxic effects from antineoplastic drugs. Indirect effects, such as inflammatory responses, play a major role in triggering chemotherapy-induced peripheral neuropathy (CIPN) (5).

Chemotherapy-induced peripheral neuropathy (CIPN) refers to the damage that occurs to the peripheral nervous system following the exposure of the patient to a chemotherapeutic agent that is known to have a neurotoxic side effect. Neurotoxicity is the second most frequent acute side effect of chemotherapy, only second to hematologic toxicity (6). A systematic review and meta-analysis, involving 4,179 patients who had been treated with various classes of neurotoxic agents, found that approximately 68.1% of patients developed CIPN within one month post-treatment (7).

1.2 Statement of the problem

Cancer remains a critical public health challenge in many low-income countries such as Ethiopia. According to the Addis Ababa cancer registry, roughly 64000 new cases of cancers are diagnosed annually nationwide, of which around 5500 new cases are managed at Addis Ababa University (AAU), Tikur Anbessa Specialized Hospital (TASH) oncology unit per year. From this high burden of cases, breast cancer patients account for the largest proportion of cancer patients. (8)

A 2017 study by Hanna Bandoz et al. explored the long-term peripheral neuropathy (PN) in breast cancer patients treated with adjuvant chemotherapy. According to the result, it was reported that peripheral neuropathy incidence was found to be 41.9% two years post-treatment. In contrast, research conducted in Ethiopia evaluating the toxicities of Adriamycin-Cyclophosphamide (AC) versus AC followed by Paclitaxel regimens documented a CIPN prevalence as high as 74%, highlighting a stark contrast with global data (9).

Given the predominance of breast cancer patients receiving treatment at Tikur Anbessa Specialized Hospital (TASH) and the global recognition of CIPN as a frequent chemotherapy-related complication, this study aims to assess the prevalence and risk factors of CIPN among breast cancer patients at TASH Oncology Unit. Additionally, it seeks to identify potential contributors to the significant disparity in CIPN rates between Ethiopian and global findings (41% vs. 74%), offering insights to improve clinical management and patient outcomes.

1.3 Research objective

1.3.1. GENERAL OBJECTIVE

- To determine the prevalence and associated risk factors of chemotherapy induced peripheral neuropathy of breast cancer patients, TASH, Addis Ababa, Ethiopia, from September 1, 2024, to January 31, 2025

1.3.2. SPECIFIC OBJECTIVE

- ✓ To determine the prevalence of Chemotherapy induced peripheral neuropathy in breast cancer patients at TASH, Addis Ababa, Ethiopia.
- ✓ To assess the risk factors of Chemotherapy induced peripheral neuropathy in breast cancer patients at TASH, Addis Ababa, Ethiopia.

1.4 Significance of the study

Chemotherapy-induced peripheral neuropathy (CIPN) serves as a significant dose-limiting complication of many first-line chemotherapeutic agents. It impacts 20–50% of patients receiving standard doses and nearly all patients on high-dose regimens (10), resulting in long-term consequences for cancer survivors, including chronic pain, functional limitations, and psychological distress.

Investigating CIPN prevalence and risk factors within local clinical settings is critical to enhancing patient care, as it informs targeted interventions to improve quality of life. Furthermore, such research underscores the need for future studies to prioritize innovative strategies for CIPN prevention, management, and therapeutic development.

2. Literature review

Chemotherapy-induced peripheral neuropathy is a common and potentially debilitating side effect of chemotherapy treatment. This literature review aims to summarize recent research on the prevalence, risk factors, and clinical presentation of CIPN

Findings of this meta-analysis revealed critical insights into the prevalence and risk factors of chemotherapy-induced peripheral neuropathy (CIPN). on this metanalysis, on the within the first month of chemotherapy, 68.1% of patients had symptoms. This rate decreased to 60% by the third month and dropped further to 30% in patients undergoing treatment for six months or longer. This pattern suggests that CIPN may manifest acutely in many individuals but resolves or diminishes over time in a subset of patients, potentially due to dose adjustments, neuroadaptation, or discontinuation of neurotoxic agents. (7) Key risk factors—pre-treatment neuropathy, smoking, reduced creatinine clearance, and sensory disruptions—were noted in 4 out of 31 studies, which underscores the importance of baseline patient assessment and continuous monitoring during chemotherapy to mitigate CIPN risk.

A 2019 prospective multinational longitudinal cohort study evaluated methodological approaches for assessing neurotoxic chemotherapy-induced complications. The research involved a heterogeneous cohort of consecutively enrolled patients (N=342) receiving neurotoxic chemotherapy as outpatients or inpatients across three tertiary hospitals in Hong Kong, Singapore, and Manchester, UK, utilizing convenience sampling. Sensory neuropathy prevalence varied significantly among chemotherapy agents, with rates of 63% for paclitaxel and 71.4% for oxaliplatin, peaking at approximately six months post-treatment. Additionally, motor neurotoxicity was notably prevalent in

the docetaxel subgroup, affecting 22.1% (n=11) of patients. These findings underscore the differential neurotoxic profiles of chemotherapeutic agents and highlight temporal patterns in toxicity manifestation (11).

A 2017 study by Natan P. Staff and colleagues, published in a comprehensive review on chemotherapy-induced peripheral neuropathy (CIPN), highlighted that CIPN is a prevalent and dose-limiting adverse effect among cancer patients undergoing chemotherapy. Approximately 30-40% of the individuals receiving antineoplastic agents, which tend to be neurotoxic, experience chemotherapy-induced peripheral neuropathy (CIPN), with significant symptom severity varying widely among individuals. The condition typically manifests as sensory symptoms, such as pain, and may persist long-term, contributing to ongoing health complications in cancer survivors. As cancer treatments advance and survival rates climb, the prevalence of CIPN and its enduring effects are projected to grow, amplifying the need to address its impact on survivors' long-term well-being. (12)

A cross-sectional investigation conducted by Anna-Liisa Kautio and colleagues (2011) evaluated the prevalence and characteristics of chemotherapy-induced peripheral neuropathy (CIPN). Among 152 participants, 59% (n=90) exhibited persistent neuropathic symptoms at the screening phase. Predominant manifestations included tingling (71%), numbness (58%), sensory impairment (46%), and pain in the extremities (40%), with a median symptom intensity of 28 (interquartile range not specified) on a 100-mm visual analogue scale (VAS). Sensory neuropathy was graded as mild (Grade 1) in 21% (n=19), moderate (Grade 2) in 42% (n=38), and severe (Grade 3) in 37% (n=33) of symptomatic patients. Motor neuropathy severity was distributed as Grade 1 in 31% (n=28), Grade 2 in 16% (n=14), and Grade 3 in 1% (n=1), with no Grade 4 sensory or motor cases reported. Within the entire cohort, fatigue (66%), mucositis (61%), and neuropathic symptoms (59%) emerged as the most frequently reported adverse effects. Notably, 37% of participants with neuropathy identified these symptoms as their most debilitating clinical concern, underscoring their significant subjective burden. This study highlights the high prevalence and functional impact of CIPN, emphasizing the need for targeted management strategies in oncology care.

A multicenter, cross sectional study of long-term prevalence of sensory chemotherapy-induced peripheral neuropathy for 5 years after adjuvant FOLFOX chemotherapy was done by Merie Selvy and co , in 2020.This prospective multicenter study, conducted across 16 French centers, evaluated the prevalence of chemotherapy-induced peripheral neuropathy (CIPN) and its associated long-term sequelae—including neuropathic pain, anxiety, depression, and diminished quality of life—in cancer survivors during the five-year period following adjuvant oxaliplatin chemotherapy. Findings revealed that 30-40% of patients treated with neurotoxic chemotherapeutic agents developed CIPN, with marked interindividual variability in symptom severity. Sensory-predominant manifestations, particularly chronic pain, were prominent, contributing to persistent morbidity among survivors. The study further highlighted that CIPN-related neuropathic pain and psychosocial comorbidities, such as clinically significant anxiety and depression, correlated with reduced quality

of life. These outcomes underscore the necessity for targeted interventions to mitigate CIPN's enduring burden, particularly as advances in oncology prolong survival and amplify the clinical and societal impact of long-term treatment-related toxicities.

Among a cohort of 406 patients, the prevalence of chemotherapy-induced peripheral neuropathy (CIPN) was 31.3% (95% confidence interval [CI]: 26.8–36.0). Longitudinal assessment revealed minimal improvement in CIPN symptomatology over a five-year period, with neuropathic pain concurrently affecting 36.5% of CIPN cases. The condition demonstrated significant associations with comorbid anxiety, depressive symptoms, and diminished quality of life. Notably, no patients diagnosed with CIPN received duloxetine, a therapeutic agent endorsed by the American Society of Clinical Oncology (ASCO) guidelines. Furthermore, only 3.2%, 1.6%, and 1.6% of affected individuals were administered pregabalin, gabapentin, or amitriptyline, respectively. The study further revealed persistent CIPN morbidity, with 25% of the cohort exhibiting symptoms five years post-chemotherapy cessation. These findings highlight substantial psychological morbidity and systemic inadequacies in the clinical management of CIPN, underscoring a critical gap between evidence-based recommendations and real-world therapeutic practices. (14)

A 2018 longitudinal cohort analysis by Bandos et al. examined the persistence of chemotherapy-induced peripheral neuropathy (PN) and its association with quality of life (QOL) in breast cancer survivors receiving adjuvant chemotherapy. Among 1,512 patients evaluated, 41.9% (n=634) reported PN symptoms two years post-treatment initiation. Multivariable analysis identified preexisting neuropathy, advanced age, obesity, mastectomy, and a higher number of positive lymph nodes as significant predictors of long-term PN development. Furthermore, patients with more severe PN symptoms at the 24-month follow-up demonstrated a statistically significant deterioration in QOL metrics compared to those with milder or absent symptoms.

The study underscores the clinical relevance of sustained neurotoxic effects in survivorship care, emphasizing the need for proactive monitoring of high-risk patients and integration of PN management strategies to mitigate long-term functional and QOL impairments. These findings highlight the enduring burden of chemotherapy-related neuropathies and their critical role in shaping post-treatment health outcomes in oncology populations.

According to SWOG S1714 clinical trial which was reported in 2023 annual meeting of the American society for Clinical Oncology, by Michael J, Fisch , emphasized the clinical significance of its findings, noting that taxanes (e.g., paclitaxel, docetaxel) are cornerstone agents in breast cancer therapy, yet the mechanisms and outcomes of taxane-induced peripheral neuropathy (TIPN) remain incompletely characterized. To address this gap, a prospective observational cohort study was conducted, enrolling 1,336 patients diagnosed with non-small cell lung cancer (NSCLC), breast cancer, or ovarian/fallopian tube cancer, all undergoing taxane-based chemotherapy. Of these, a subset of 1,103 breast cancer patients was prospectively monitored for neuropathic sequelae over a 24-week post-registration follow-up period. The research aimed to delineate the incidence,

progression, and clinical burden of TIPN, with a focus on its impact on functional outcomes and quality of life in a population heavily reliant on taxane regimens. This longitudinal cohort design highlights the critical need to elucidate the pathophysiological mechanisms and clinical trajectory of taxane-induced peripheral neuropathy (TIPN). All participants underwent baseline pre-treatment evaluations for peripheral neuropathy symptoms, followed by serial assessments at 4, 8-, 12-, 24,52,104-, and 156-weeks post-registration. Evaluations included standardized neurosensory examinations, functional assessments, and clinician-rated CIPN symptom grading via the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE). By the 24-week follow-up, quantitative analysis revealed that over 40% of patients administered paclitaxel or docetaxel exhibited a clinically meaningful progression of CIPN symptoms, as defined by validated thresholds in sensory function and patient-reported outcomes. These findings underscore the high prevalence and early onset of taxane-related neurotoxicity, emphasizing the imperative for systematic surveillance and mechanistic research to refine risk stratification and therapeutic interventions in populations reliant on taxane-based regimens. The study's longitudinal framework provides a robust platform for characterizing CIPN's dynamic evolution and its correlation with cumulative dose exposure, functional impairment, and quality-of-life metrics. (17)

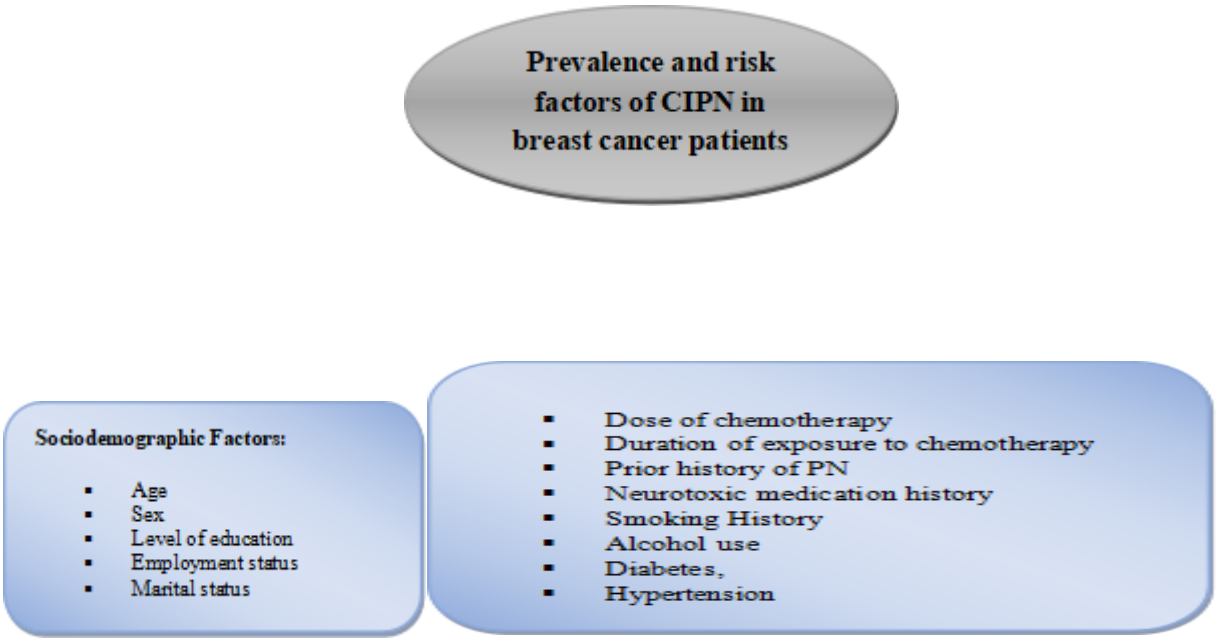
In a comprehensive investigation of risk factors associated with chemotherapy-induced peripheral neuropathy (CIPN), Alex Molassiotis and colleagues conducted a prospective observational study to evaluate the relative contributions of diverse risk factors in patients undergoing taxane- and platinum-based chemotherapy. Leveraging data from a six-month prospective follow-up nested within a parent study investigating chemotherapy-induced peripheral neuropathy (CIPN) risk, prevalence, and quality-of-life (QOL) outcomes, this retrospective analysis explored covariates encompassing pre-existing neuropathic conditions, history of infectious diseases (current/past), concurrent or historical neurotoxic pharmacotherapy, sociodemographic and clinical treatment parameters, behavioral factors (tobacco use, alcohol consumption), and dietary habits, with emphasis on vegetable and fruit consumption. The study aimed to identify modifiable and non-modifiable predictors of CIPN incidence and its longitudinal impact on functional and QOL metrics.. The cohort comprised 255 patients recruited from three oncology centers in Hong Kong, Singapore, and the United Kingdom, with breast cancer representing the predominant diagnosis (followed by lung and gynecological malignancies).

Multivariate logistic regression analysis identified several independent predictors of CIPN. Older age exhibited a significant association (adjusted odds ratio [OR] = 1.08 per year, $p < 0.01$, using the WHO grading scale), while platinum-based chemotherapy regimens demonstrated a reduced likelihood of CIPN compared to taxane-based treatments (OR = 0.20–0.27, $p < 0.01$). A history of neuropathy was strongly linked to motor CIPN (OR = 8.36, $p < 0.01$), and higher symptom burden (OR = 1.06, $p < 0.05$), increased chemotherapy cycles (OR = 1.19–1.24 per cycle, $p < 0.01$), and alcohol consumption (OR = 0.32, $p < 0.05$) also emerged as significant factors. In univariate

analyses, statin use demonstrated a statistically significant association with CIPN across multiple assessment tools ($p = 0.03–0.04$), while diabetes mellitus approached statistical significance ($p = 0.09$) as a potential contributor.

This study underscores the multifactorial etiology of CIPN, highlighting modifiable and non-modifiable risk factors that may inform clinical risk stratification and preventive strategies in patients receiving neurotoxic chemotherapeutic agents. (18)

2. CONCEPTUAL FRAMEWORK



3. METHODS AND MATERIALS

3.1 STUDY SETTING AND PERIOD

The Department of Oncology at Addis Ababa University, Tikur Anbessa Specialized Hospital, a leading and pioneering referral hospital in Ethiopia, will be the place of conduct for this study. The hospital, which opened in 1972, became a university teaching hospital under Addis Ababa University in 1998 after the federal Ministry of Health transferred it to the school of medicine.

Specialty clinics and inpatient service departments at Addis Ababa hospital provide comprehensive health care services to about half a million patients every year. The hospital has more than 700 beds and around 1,700 staff members who work in inpatient, outpatient, and emergency units. It also offers specialized clinical services that are not available elsewhere in the country. The hospital is a teaching institution for the School of Medicine, where various departments, faculties, and residents under specialty training provide patient care.

The department of oncology is one of the pioneering departments in the country dedicated to the vast majority of the country's oncology services, including chemotherapy and adjuvant radiotherapy, in in service out patients' services. of the 700 hospital beds, 18 are dedicated to the oncology department inpatient service.

The data will be collected from September 1, 2024, to January 31, 2025, at the department of oncology, from patients treated or on treatment with chemotherapy for breast cancer at both inpatient and outpatient services

3.2 STUDY DESIGN

A cross-sectional study design will be used.

3.3. POPULATION

3.3.1. SOURCE POPULATION

All adult breast cancer patients at TASH, during the study period, with histologically confirmed breast cancer undergoing chemotherapy that met the inclusion criteria.

3.3.2. STUDY POPULATION

All adult patients on chemotherapy treatment for breast cancer who meet the inclusion criteria.

3.4. ELIGIBILITY CRITERIA

3.4.1. INCLUSION CRITERIA

- Patients must have a histopathology report of breast cancer
- Patients must consent to the study

- All stages of breast cancer
- Breast cancer patients who completed chemotherapy during the study period and consented to be included in this research, in TASH, Addis Ababa, Ethiopia.

3.4.2. EXCLUSION CRITERIA

- Age less than 18 years
- Underlying psychiatric illness
- Patients with recurrence who have received a neurotoxic chemotherapy previously.
- Patients who don't complete the chemotherapy regimen during the study period
- Patients who discontinued from treatment

3.5. SAMPLE SIZE DETERMINATION

The sample was calculated by assuming a Confidence interval of 95%.

A single population proportion formula

$$[n = (Z\ \alpha/2)^2\ p\ (1-p)\ /\ d2]$$, will be used to estimate the sample size.

Considering a previous prevalence study at 35%, P= 0.74, at 95% confidence interval, and a margin of error of 5% were used for sample size calculation

$$n = (1.96)^2(0.74)\ (1-0.74)/\ (0.05)2 = 295$$

Considering the 10% non-response rate, it will be 324, but since the population size is <10000, the following formula will be used for the final sample size calculation.

Nfinal = n/(1+n/N), since 100-140 breast cancer patients visit the 5th oncology center per month, N=360

Nfinal =181

A simple random sampling technique will be used to select the participants

3.6. DATA COLLECTION PROCEDURE

3.6.1. DATA COLLECTION TOOLS

In 2017, a systematic review was done for the CIPN assessment tool by Haryani and co, A total of 19 studies describing 20 tools were reviewed, and considering the easy administrability and accessibility, the modified TNS score will be used.

For this study will be using the modified total neuropathy score, which has 5 parameters, graded from 0--4. parameters include symptom extension of tingling sensation, numbness symptom extension. neuropathic pain symptom extension. tendon reflexes, vibration sensibility. A cumulative number > 1 will be considered as the presence of CIPN

A comprehensive clinical evaluation for neuropathy necessitates the identification of predisposing factors, including acquired or hereditary neurological disorders (e.g., diabetes mellitus, chronic renal disease, hypothyroidism, connective tissue disorders), a personal history of neuropathy, familial predisposition to neuropathic conditions, or metabolic deficiencies such as vitamin B12 insufficiency (20). Additionally, infectious etiologies linked to neuropathy, including HIV, poliomyelitis, and hepatitis B or C, must be systematically assessed (21). Furthermore, a detailed pharmacological history is critical to identify prior or ongoing exposure to neurotoxic agents, such as chemotherapeutic regimens, antiretroviral therapies, or other medications with established neuropathic side effects (22).

Personal and treatment characteristics

Age, (23) disease site, (7) chemotherapy type, cycle, and cumulative dosage (24), smoking history (7), alcohol history(25)

3.6.2. DATA QUALITY CONTROL

To guarantee the accuracy of the data, a one-day training session will be held for data collectors and supervisors. They will learn about the study's purpose and how to handle the data properly. The training group will consist of six data collectors and two supervisors.

A standard instrument for data collection will be employed. The language clarity and the questionnaire will be tested in other hospitals with five percent of the samples. The main researcher will supervise the activity closely every day. The researcher will also examine the filled questionnaires and checklists for clarity, consistency, completeness, and skip patterns at the end of each day of data collection. The researcher will also verify that the recorded information is sensible to ensure the quality of the data collected. Meetings with the data collectors will be held as needed to resolve any ambiguity through discussion.

3.7. STUDY VARIABLES

3.7.1. DEPENDENT VARIABLES

- The prevalence of chemotherapy-induced peripheral neuropathy
- Risk factors of Chemotherapy induced peripheral neuropathy

3.7.2. INDEPENDENT VARIABLES

Age, Sex, Level of education, Employment status, Marital status,

Stage of breast cancer, Type of chemotherapy, cycle, cumulative dosage

Diabetes mellitus, renal disease, hypothyroidism, and connective tissue disease.

Prior history of neuropathy, family history of neuropathy, and vitamin B12 deficiencies,

Diagnosis with infectious disease, eg, HIV, poliomyelitis, hepatitis b and c, syphilis. Neurotoxic medication history, smoking history, and alcohol history

3.8. DATA PROCESSING AND ANALYSIS

The association between risk factors and other variables will be determined by using binary and multiple logistic regression. The odds ratios with 95% confidence interval, both crude and adjusted, will be used to measure the strength of the association between the dependent and independent variables. Variables with a P-value < 0.05 will be regarded as significant.

3.9. ETHICAL CONSIDERATION

The study will be conducted after obtaining ethical clearance from the Research and Publication Committee (RPC) of the Department of Neurology, TASH. The participants will be informed about the purpose and significance of the study and their rights. They will be assured that their responses will be anonymous and that no identifying information will be collected. They will also be told that their participation is voluntary and that they can withdraw at any time without affecting their care or rights. Their privacy will be respected throughout the study.

4. DISSEMINATION OF RESULTS

Study findings will be disseminated to key stakeholders, including CHS, AAU, TASH, the Department of Neurology, and relevant academic institutions. Broader scientific dissemination will occur via conference presentations and publication in a peer-reviewed journal to ensure accessibility to the academic and clinical communities.

5. Result

All of the study participants were female patients who completed chemotherapy for breast cancer. Most of the participants' ages were between 36 and 51 years old. The symptoms of chemotherapy-induced neuropathy appeared from the 5th cycle of chemotherapy onward, with most participants reporting symptoms at the 6th cycle. All participants were on the AC-Taxol regimen for their entire treatment plan. The average duration from breast cancer diagnosis to completion of chemotherapy was 6.6 months. The median duration to completion of chemotherapy was 6 months, with an interquartile range of 2 months.

Sociodemographic characteristics		Frequency	Percent
Age	18-35	43	23.8
	36-51	82	45.3
	>51	56	30.9
Educational level	No formal education	27	14.9
	Primary school	58	32.0
	Secondary school	61	33.7
	College/University	35	19.3
Marital Status	Never married	29	16.0
	Married	135	74.6
	Separated	3	1.7
	Divorced	10	5.5
	Widowed	4	2.2
Employment status	Paid work	56	30.9
	Self employed	56	30.9
	Student	2	1.1
	Home maker	64	35.4
	Unemployed due to health reasons	3	1.7

Table 1 Sociodemographic characteristics of patients enrolled for studying the prevalence of chemotherapy induced peripheral neuropathy, Addis Ababa Ethiopia (n=181)

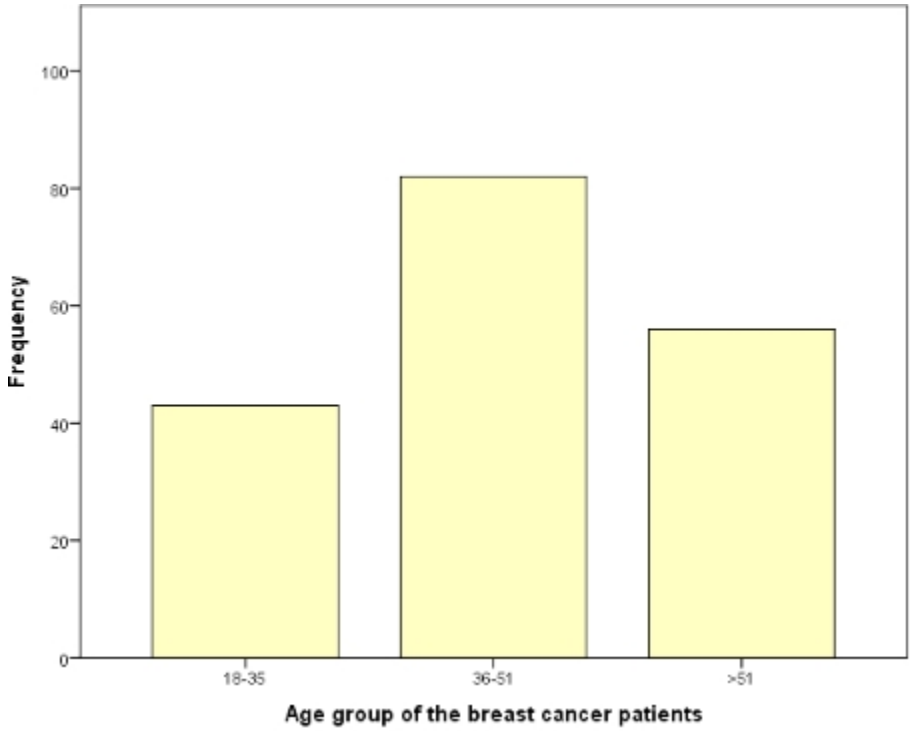


Figure 1 The distribution bar graph for age group of breast cancer patients that underwent chemotherapy, Addis Ababa Ethiopia (n= 181)

Of the study participants, 9 (5%) reported a history of alcohol abuse, while most (95%) reported no such history. None of the patients reported a history of cigarette smoking or the use of neurotoxic drugs.

Table 2 Frequency of comorbidities (Diabetes Mellitus, Hypertension and Human Immunodeficiency Virus) on participants with breast cancer, Addis Ababa Ethiopia (n=181)

Comorbidities		Frequency	Percent
Diabetes Mellitus	Yes	22	12.2
	No	159	87.8
Hypertension	Yes	32	17.7
	No	149	82.3
HIV	Yes	1	0.6
	No	180	99.4

The majority of participants (68%) were diagnosed at stage 2b, while a smaller proportion (4.4%) presented at stage 3b or higher. For statistical analysis, participants were categorized as below stage 3a or at stage 3a and above.

Table 3 Breast cancer stage at diagnosis distribution, Addis Ababa Ethiopia (n=181)

Breast Cancer staging	Frequency	Percent
Stage 2a	8	4.4
Stage 2b	123	68
Stage 3a	42	23.2
Stage 3b	2	1.1
Stage 4	6	3.3

Chemotherapy-induced peripheral neuropathy (CIPN) is defined as a total score of >1. Accordingly, 68.5% of the study participants had CIPN. The most affected parameter in the CIPN assessment tool was tingling, which was observed in 21 (11.6%) participants. In contrast, tendon reflexes were the least affected parameter, with no participants exhibiting any abnormalities in this category. Approximately 90% of the participants had mild CIPN, while 10% had moderate CIPN. None of the participants had severe CIPN.

Table 4 Frequency and Percentage of Tingling symptoms, Addis Ababa, Ethiopia (n=181)

Item 1	Symptom extension (tingling)	Frequency	Percent
0	None	57	31.5
1	Symptoms from toes to midfoot (not including heel)	5	2.8
2	Symptoms from midfoot to ankle	97	53.6
3	Symptoms extend above ankle to knee without upper extremity symptoms	1	0.6
4		21	11.6

	Symptoms above knee or concurrent lower and upper extremity symptoms		

Table 5 Frequency and Percentage of Numbness symptoms, Addis Ababa, Ethiopia (n=181)

Item 2	Symptom extension (numbness)	Frequency	Percent
0	None	79	43.6
1	Symptoms from toes to midfoot (not including heel)	13	7.2
2	Symptoms from midfoot to ankle	72	39.8
3	Symptoms extend above ankle to knee without upper extremity symptoms	1	0.6
4	Symptoms above knee or concurrent lower and upper extremity symptoms	16	8.8

Table 6 Frequency and Percentage of Neuropathic pain symptoms, Addis Ababa, Ethiopia (n=181)

Item 3	Symptom extension (neuropathic pain)	Frequency	Percent
0	None	101	55.8
1	Symptoms from toes to midfoot (not including heel)	30	16.6
2	Symptoms from midfoot to ankle	33	18.2
3	Symptoms extend above ankle to knee without upper extremity symptoms	1	0.6

4	Symptoms above knee or concurrent lower and upper extremity symptoms	16	8.8

Table 7 Frequency and Percentage of Tendon reflex examinations, Addis Ababa, Ethiopia (n=181)

Item 4	Tendon reflexes	Frequency	Percent
0	Normal	181	100
1	Ankle reflex reduced	0	0
2	Ankle reflex absent	0	0
3	Ankle reflex absent or others reduced	0	0
4	All reflexes absent	0	0

Table 8 Frequency and Percentage of Vibration sensibility examinations , Addis Ababa, Ethiopia (n=181)

Item 5	Vibration Sensibility	Frequency	Percent
0	Normal	122	67.4
1	Absent or decreased from toes to midfoot (not including heel)	58	32.0
2	Absent or decreased from midfoot to ankle	1	0.6
3	Absent or decreased above ankle to knee	0	0

4	Absent or decreased above knee or in lower and upper extremities concurrently	0	0

Factors associated factors with chemotherapy induced peripheral neuropathy on breast cancer patients

Each independent variable was individually entered into bivariate analyses. Age (≤35 and >35), educational status (below and above higher education), employment status (self-employed or not), and breast cancer stage (<3a and ≥3a) were significantly associated with the presence of CIPN. In a multivariable binary logistic regression model that included all covariates, age, employment status, and breast cancer stage remained significantly associated with CIPN. Participants older than 35 years were 5.6 times more likely to have CIPN (AOR 5.6, 95% CI [2.5-12.8]). Participants who were not self-employed were 4.4 times more likely to have CIPN (AOR 4.4, 95% CI [2-9.7]). Participants with breast cancer stage 3a and above had 3.3 times the odds of having CIPN compared to those with earlier stages (OR 3.3, 95% CI [1.3-8.3]).

In the initial bivariate analyses, perfect separation was observed for diabetes mellitus (DM) and hypertension (HTN), as all patients with DM and HTN also had CIPN. This perfect separation prevented the estimation of odds ratios for DM and HTN in the bivariate models. While these variables were included in the multivariable logistic regression model, the perfect separation persisted, resulting in unstable and unreliable estimates for DM and HTN. Therefore, the odds ratios and confidence intervals for DM and HTN are not presented. The multivariable model, which included all covariates, provided stable estimates for the remaining variables, allowing for a more accurate assessment of their independent relationships with CIPN.

Table 9 Factors associated factors with chemotherapy induced peripheral neuropathy on breast cancer patients, their COR, AOR, and p-values, Addis Ababa Ethiopia (n=181)

Variables	Chemotherapy induced neuropathy		COR	AOR	P value
	Yes	No			
Age					
≤ 35	16	27	1	1	
>35	108	30	6.08 (2.9, 12.2)	***5.63 (2.5, 12.77)***	***0.00***

Educational Status					
College/University	19	16	1	1	
Below higher education	105	41	2.16 (1.01, 4.6)	1.34 (0.53, 3.39)	0.53
Employment					
Self employed	28	28	1	1	
Others	96	29	3.3 (1.7, 6.46)	***4.4 (2.01, 9.69)***	***0.00***
Stage of Breast CA at diagnosis					
< 3a stage	84	47	1	1	
≥ 3a stage	40	10	2.23 (1.03, 4.88)	***3.31 (1.32, 8.31)***	***0.011***

Discussion

This study aimed to assess the prevalence and associated factors of chemotherapy-induced peripheral neuropathy (CIPN) among 181 breast cancer patients. Our findings revealed a CIPN prevalence of approximately 69%, a result consistent with the 68% prevalence reported in a meta-analysis of CIPN incidence and prevalence measured after the first month of chemotherapy (12). However, our prevalence rate is higher than the 42% incidence reported in another study of CIPN among breast cancer patients. (16) This 69% prevalence in our setting emphasizes the significant impact of CIPN on this patient population. While this study successfully demonstrated the prevalence of CIPN, it did not assess the condition's impact on patients' quality of life.

Understanding the subjective effects of CIPN is crucial for comprehending the true burden it places on patients. Although the majority of patients (90%) with CIPN experienced mild

symptoms, the actual effect of even mild CIPN on quality of life is essential for fully understanding the clinical significance of our prevalence findings. Further research is needed to explore the relationship between CIPN severity and its impact on patients' daily lives.

Consistent with the findings of the meta-analysis (12), which also reported sensory-predominant CIPN with pain, our study found that 50-70% of patients experienced sensory disturbances, including tingling, numbness, or neuropathic pain. All patients in our study received the AC-T chemotherapy regimen (Adriamycin, cyclophosphamide, and paclitaxel). A study evaluating this specific regimen reported CIPN prevalence rates as high as 74% (9). Therefore, the higher prevalence observed in our study (69%) may be attributable to the use of this particular, potentially more neurotoxic regimen.

In this cross-sectional study, most patients reported the onset of peripheral neuropathy (PN) symptoms beginning around the fifth chemotherapy cycle. This observation suggests a possible link between the cumulative chemotherapy dose at the fifth cycle and the development of PN, representing a potential area for future research to explore a dose-response relationship. A study of breast cancer patients receiving a Taxane-based regimen reported a 40% incidence of clinically significant CIPN at 24 weeks. (17) This finding aligns with our observation of increased PN effects in the majority of our patients around the sixth cycle (approximately 20 weeks) after treatment initiation. Although the mechanisms by which Taxanes induce PN are not fully understood, these findings may provide insights into identifying a potential neurotoxic cumulative dose for these drugs.

Our study identified three significant factors associated with the development of CIPN. Specifically, participants older than 35 were 5.6 times more likely to develop CIPN than those aged 35 and below (AOR = 5.6, 95% CI: 2.5-12.77). This finding aligns with a study conducted in specialist oncology clinics across Hong Kong, Singapore, and UK, which also demonstrated an association between older age and CIPN. (18) While that study did not explicitly define "older age," our data suggest that 35 years may be a relevant threshold for increased risk in our population.

Participants who were not self-employed were 4.4 times more likely to develop CIPN than those who were self-employed (AOR = 4.4, 95% CI: 2.01 - 9.69). Within the non-self-employed group, the majority were homemakers (35%) and paid workers (31%). This observed association may be explained by several factors. One possibility is that the types of work typically held by non-self-employed individuals involve higher physical demands, greater psychological stress, and less control over work environment which could contribute to CIPN risk. It is also possible that differences in lifestyle, nutrition, and access to healthcare between these groups play a role.

However, our study did not directly assess these factors, so further research is needed to explore these potential explanations.

Patients with stage 3 or higher breast cancer were 3.31 times more likely to develop CIPN compared to those with lower stage cancers (AOR = 3.31, 95% CI: 1.32 - 8.31). This translates to a CIPN prevalence of 80% in patients with stage 3 and above, compared to 64% in those with lower stage cancers. While our study found a statistically significant association between advanced cancer stage and CIPN, the results of other studies have been inconsistent. (18) These discrepancies may be due to variations in sample size, patient characteristics or CIPN assessment methods. Therefore, further research with larger sample sizes and rigorous control for potential confounders is warranted to clarify the relationship between cancer stage and CIPN.

6. Conclusion

The prevalence of CIPN was 69% among the study participants. Tingling sensation was the most commonly reported symptom among the participants and the majority of the participants experienced mild symptoms of peripheral neuropathy

7. Recommendation and limitations

This study has a cross-sectional study design hence it fails to show causality.

This study included only patients from Tikur Anbessa Specialized Hospital (TASH), Addis Ababa. Future research with a more diverse patient population from other Ethiopian hospitals is needed to improve generalizability.

Despite efforts to account for known confounders, residual confounding by unmeasured factors may have influenced the observed associations. In addition, this research was not able to correlate the effect CIPN and degree of severity with QOL measures, which have predicted the effect of CIPN .

As a recommendation, considering the investigative tool (modified TNS) is easily reproducible and can be done with oncology nurses who spend the majority of the time during chemotherapy infusion, training them would be the fastest way to identify CIPN and act effectively to avoid long-lasting effects on their quality of life.

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9. Annex

ANNEX I: Participant Information Sheet and Informed Consent

Dear study Participant,

- My Name is Hiwot Berhanu I am a second-year postgraduate Neurology Resident in Addis Ababa University College of Health Science. I am doing a research as a completion for my residency program on my topic of interest prevalence and associated risk factors of chemotherapy induced peripheral neuropathy of breast cancer patients, TASH, Addis Ababa, Ethiopia In Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia
- The purpose of this study is to assess the prevalence and associated risk factors of chemotherapy induced peripheral neuropathy of breast cancer patients, TASH, Addis Ababa, Ethiopia. I am going to give you information and invite you to be part of this research. Before you decide, you can talk to anyone you feel comfortable with about the research.
- Your personal data used in the study, as detailed in the information sheet will be handled in a strictly confidential way. It will take about 15 minutes of your time for interview. I request you to answer as truthfully as possible. Your willingness and participation in the study is very helpful in identifying the problem related to the issue. There is no payment in participating in the research. You have a right to withdraw at any time you want without any repercussion.

  So do you agree to participate in this study? Yes/No
- Thank you in advance for your cooperation.
- Data collectors Name_____sign: _____
- Name of the principal Investigator: Hiwot Berhanu
- Mobile no: +251911691330
- E-mail: hiwotbgizaw@gmail.com

ANNEX II: Assessement TOOL -

- Table10ModifiedTNS

Item	0	1	2	3	4
Symptom extension (tingling)	None	Symptoms from toes to midfoot (not including heel)	Symptoms from midfoot to ankle	Symptoms extend above ankle to knee without upper extremity symptoms	Symptoms above knee or concurrent lower and upper extremity symptoms
Symptom extension (numbness)	None	Symptoms from toes to midfoot (not including heel)	Symptoms from midfoot to ankle	Symptoms extend above ankle to knee without upper extremity symptoms	Symptoms above knee or concurrent lower and upper extremity symptoms
Symptom extension (neuropathic pain)	None	Symptoms from toes to midfoot (not including heel)	Symptoms from midfoot to ankle	Symptoms extend above ankle to knee without upper extremity symptoms	Symptoms above knee or concurrent lower and upper extremity symptoms
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent or others reduced	All reflexes absent
Vibration sensibility	Normal	Absent or decreased from toes to midfoot (not including heel)	Absent or decreased from midfoot to ankle	Absent or decreased above ankle to knee	Absent or decreased above knee or in lower and upper extremities concurrently

Note. Based on information from Chaudhry et al., 1994; Cornblath et al., 1999; Lavoie Smith et al., 2011; Smith et al., 2008, 2010.

ANNEX III: QUESTIONER

Table 11

Section 1 - Face sheet				
Complete items F1–F5 before starting each interview				
F1	Respondent identity number			
F2	Interviewer identity number			
F3	Assessment time point (1, 2, etc.)			
F4	Interview date	/day	/month	/year
F5	Living situation at time of interview (circle only one)	Independent in community		1
		Assisted living		2
		Hospitalized		3

Section 2 - Demographic and background information			
A1	**Record sex as observed**	Female	1
A2	How old are you now?	_____years	
A3	How many years in all did you spend studying in school, College or university?	_____years	
A4	What is your current marital status? **(Select the single best option)**	Never married	1
		Currently married	2
		Separated	3
		Divorced	4
		Widowed	5
		Cohabiting	6
A5		Paid work	1

	Which describes your main work status best? **(Select the single best option)**	Self employed, such as own your business or farming	2
		Non-paid work, such as volunteer or charity	3
		Student	4
		Keeping house/ homemaker	5
		Retired	6
		Unemployed (health reasons)	7
		Unemployed (other reasons)	8
		Other (specify)_____	9
A6	When were you diagnosed with breast cancer ?	Time completed in years	
A7	Did you start chemotherapy	Exposed	1
		Not exposed	2
A8	Type of chemotherapy regimen	Currently taking	
A9	Cycle of chemotherapy	In number	1 2
A10	Cumulative dosage of chemotherapy	Dosage	
A11	Presence of diabetes mellitus	Yes	1
		No	2
A12	Presence of Hypertension	yes	1
		no	2

A13	Presence of renal disease	yes	1
		no	2
A14	Presence of hypothyroidism	yes	1
		no	2
A15	Presence of known connective tissue disease	yes	1
		no	2
A16	Prior History of neuropathy	yes	1
		no	2
A17	Family history of neuropathy	yes	1
		no	2
A18	Presence of vitamin B12 deficiency	yes	1
		no	2
A19	Presence of infectious disease A-HIV, B-polyomyelitis,C-hepatitis B,D-hepatitis c,E-syphilis	yes	1(A-HIV, B-polyomyelitis,C-hepatitis B,D-hepatitis c,E-syphilis)
		no	2
A20	neurotoxicity medication history	yes	1
		no	2
A21	smoking history	yes	1
		no	2
A22	alcohol history	yes	1
		no	2