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Research Article

CLINICAL & GENETIC RISK FACTORS CONTRIBUTION TO CIPN (CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY): A SYSTEMATIC REVIEW & META-ANALYSIS

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ABSTRACT

Background of study: Chemotherapy-induced peripheral neuropathy (CIPN) is an adverse effect of many chemotherapeutic agents and a major cause of pain in cancer survivors. Severe acute CIPN may require chemotherapy dose reduction or cessation. There is no effective CIPN prevention strategy; treatment of established chronic CIPN is limited, and risk factors of CIPN are also elusive.
Objectives of the study: To identify the clinical& genetic risk factors of chemotherapy induced peripheral neuropathy in adult population.
Research Methodology: The systematic review was used to identify studies reporting the risk factors of CIPN, searched Delnet, Remote XS (PGIMER), Ebsco, Willey online library, Medline, PubMed, and Web of Knowledge for relevant references and used random-effects meta-regression. Study quality assessed by using the CONSORT and STROBE guidelines, and PRISMA guidance.
Conclusion and Results: This systematic review included 133 studies with data from 12,378 patients in the meta-analysis. A qualitative summary of factors reported to alter the risk of CIPN provided. Out of 133, sixty eight studies explained various risk factors contributing to CIPN. Genetic risk factors were reported in 19 studies. Clinical risk factors, identified in 29 studies, included neuropathy at baseline, cumulative dose, double-crush syndrome, abnormal creatinine clearance, LDH variation, EEG changes, specific sensory changes during chemotherapy, and persistent muscle and joint pains.

INTRODUCTION

Neuropathy is a common, often enfeebled complication of cancer and its treatment.

"Peripheral neuropathy is a disorder that happens when peripheral nerves malfunction because these are damaged or destroyed and this disrupts the nerves proper functioning" **(**Morrison, 2016).

Chemotherapy-induced peripheral neuropathy (CIPN) is an adverse effect of many chemotherapeutic agents and becomes a cause of continuous pain in cancer patients (Smith & Brown, 2016).

Chemotherapy-induced peripheral neuropathy (CIPN) is that the commonest medical distinctive neurological impediment of cancer treatment (Kannarkat *et al*., 2007) causes severe symptoms which can result to dose reductions or premature terminations of chemotherapy. Moreover, effects on quality of life patient become worse and left patients with permanent neuropathic pain.

There is a triple fold increase in the number of cancer survivors since 1970s, now there are over 28 million cancer survivors worldwide. There is increased awareness and knowledge of long-term toxicities and effect on quality of life after treatment in cancer survivors (**Cancer J Clin. American Cancer Society, 2013)**.

Chemotherapeutic and Biologic Agents and Mechanisms of Neuropathy

Cause of neuropathy is damage to the peripheral nerves. Within the peripheral system a nervosum, the motor axons (nervefibers) area unit are giant and medullated, and also the sensory and involuntary axons area unit are tiny and unmyelinated or thinly medullated. The type of neuropathic symptom experienced depends on the type of nerve affected as follows:

Sensory nerves affect sensation, which may result in painful paresthesia, dysesthesia, cold sensitivity, tingling, numbness, alteration in vibration and proprioception, or a change in reflexes.

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Motor nerves affect muscles and motion e.g.muscle weakness.

Autonomic nerves affect internal organs, which may result in orthostatic hypotension, constipation, urinary retention, irregular h e a r t rate, and sexualdysfunction.
(JNCCN, Sep 2009)

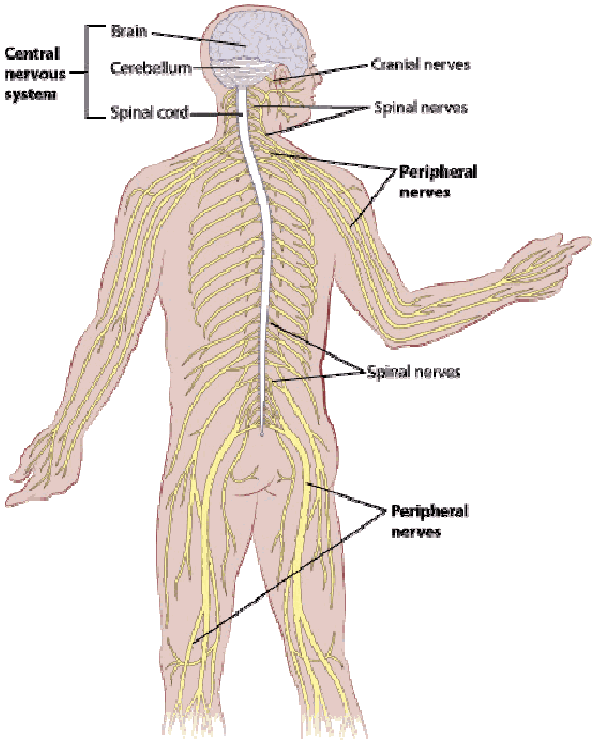

Figure 1: Body showing different nerves (Medline Plus, 2018)

Chemotherapeutic medications spread through entire body, and certain types of chemo agents will damage different nerves. Whether CIPN arises, and to what degree, is detected by the selection of drug, period of use, the full dose consumed and whether or not the patient already has peripheral pathology. Various chemo drugs are more often linked to CIPN. Chemotherapy drugs associated with CIPN include:

Table 1 Classification of Chemotherapeutic Drugs identified by Grisold, Oberndorfer&Windebank, Oncology Nursing Society 2012.

Drug class	Drug name
Platinum drugs	Cisplatin, Carboplatin, and Oxaliplatin
Taxanes	Paclitaxel, Docetaxel, and Cabazitaxel
Epothiolones	Iixabepilone
Plant alkaloids	Vinblastine, Vincristine, Vinorelbine,and Etoposide
Protease Inhibitors	Bortezomib, and Carfilzomib
Immunomodulatory / Antiangiogenic agents	Thalidomide, Lenalidomide, and Pomalidomide

Symptoms of CIPN

The National Cancer Institute's Dictionary of Cancer Terms defined peripheral neuropathy as "a nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body. It usually begins within the hands or feet and gets worse over time".

Peripheral neuropathy is characterized by sensory symptoms which involve unusual or exaggerated responses to painful symptoms or painless symptoms. Motor symptoms affect the musculoskeletal system, and manifested by peripheral neuropathy and can be classified as painful (e.g. arthralgias) or painless (e.g. muscle weakness) **(Backonja, 2003)**.

Chemo medications unfold through the entire body, and bound sort of chemo will injury totally different nerves. Symptoms tend to start out farthest far from the pinnacle, but move closer over time. In most cases, patient can notice chemo-induced peripheral neuropathy (CIPN) symptoms within the feet and soon within the hands. Symptoms may begin within in the toes, but move on to the ankles and legs. Likewise, symptoms will move up from the fingers to the hands and arms. CIPN most frequently affects each side of the body within the same manner. When it affects both hands and both feet, may call it a stocking-glove distribution. CIPN can begin any time after treatment starts. It often gets worse as treatments go on. Symptoms of CIPN may include:

Table 2 Classification of CIPN associated symptoms identified by American Cancer Society, 2008

S.NO.	SYMPTOMS
1.	Pain of any type
2.	Burning sensation upper and lower limbs
3.	Tingling(Pins and needles feeling)
4.	Loss of feeling(which may be numbness or just less ability to sense pressure, touch , heat or cold)
5.	Balance problems (troubles with tripping or stumbling while walking)
6.	Generalized Muscle weakness

Pathogenesis of Chemotherapeutic Drugs

CIPN may develop as a result of nerve injury at various anatomic regions of the nerve depending on the specific drug as below:

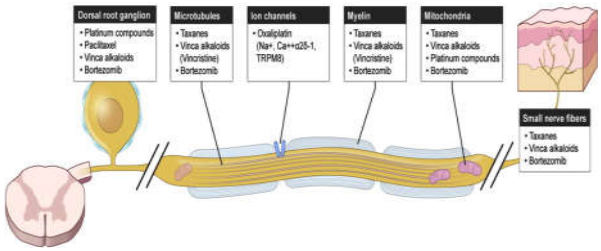

Figure 2 Pathogenesis of Antineoplastic drug induced CIPN (integrative oncology- essentials, 2013)

The myelin, a covering of nerves that protects nerves from damage and ensures their proper functioning. CIPN develops due to destruction of the myelin covering in nerves through drug-induced free radical production along the nerves. Nerves with damaged myelin won't able to send signals properly. This believed that symptom happens once nerves are not any longer functioning and transmit a signal, tingling happens if a false signal is conveyed and pain is felt once information overloads non-protected nerves.

Table 3 Common sites of involvement by neurotoxic drug classification concluded by Andreas &Argyriou, 2014

Agent	Sites of peripheral nerve damage
Cisplatin	Dorsal root ganglion
Oxaliplatin	Dorsal root ganglion; ion channels
Paclitaxel	Dorsal root ganglion; microtubules; nerve terminals
Docetaxel	Dorsal root ganglion; microtubules; mitochondria; nerve terminals
Epithilones	Dorsal root ganglion; microtubules; nerve terminals
Bortezomib	Microtubules; mitochondrial and endoplasmic reticulum; dysregulation of neurotrophins
Thalidomide	Dorsal root ganglion; nerve blood supply; dysregulation of neurotrophins
Lenalidomide	Dorsal root ganglion; nerve blood supply; dysregulation of neurotrophins
Pomalodomide	Dorsal root ganglion; nerve blood supply; dysregulation of neurotrophins
Vincristine	Dorsal root ganglion; microtubules; nerve terminals

Risk factors of CIPN

The biggest risk factor for the development of CIPN is treatment with neurotoxic anti-cancer drugs (Wickham & Wilkes, 2007). Several risk factors will promote CIPN as an operate of the antitumour drug thought of likeaccumulative dose, treatment period, history of neuropathology, combination of therapies and genetic polymorphisms. CIPNs are frequent in cancer patients with an overall incidence of approximately 38% (possibly up to 90% of patients treated with oxaliplatin) (Kerckhove&Collin, 2017). Risk of developing CIPN rises as the cumulative dose of chemotherapy escalates (Jandolo & Garufi, 2006; Quasthoff & Hartung, 2002). People who receive two or more neurotoxic chemotherapy drugs are at higher risk as are those with preexisting neuropathy (Badros *et al*., 2007; Cella & Fleming, 2007).

Peripheral Neuropathy can be Caused by Other Things besides Chemo, Such as

- Other cancer treatments, like surgery or radiation
- Tumors pressing on nerves
- Infections that affect the nerves
- Spinal cord injuries
- Diabetes and Alcohol abuse
- High Serum Creatinine levels
- Shingles (post herpetic neuralgia)
- Low vitamin B levels
- Some autoimmune disorders
- HIV (human immunodeficiency virus) infection
- Kidney, liver or thyroid disorders
- Exposure to toxins, such as heavy metals, gold compounds, lead, arsenic, mercury, and organophosphate pesticides (**William & Shiel, 2001)**
- Poor circulation (peripheral vascular disease)
- The cancer itself (for instance, multiple myeloma can cause peripheral neuropathy including multiple body aches.)
- CIPN might last a short-time, or it can become a long-term problem, depending on factors like:
- Age of patient
- Having other medical conditions that cause neuropathy
- Prescription drugs patients are taking
- If others in patient's family have neuropathy
- The drug or combination of chemo drugs used (including those used in the past)
- The drug dose (some drugs only cause CIPN at high doses)
- How often the drug is given?
- The total dose of chemo given over time

So it's very important to know what's causing peripheral neuropathy so that the right treatment can be given. The focus here will be on peripheral neuropathy that's a side effect of chemotherapy – CIPN.

Treatments associated with chemotherapy-induced peripheral neuropathy and details of clinical presentations are shown, with an indication of the frequency of the presentation in sensory, motor, and autonomic neuropathy categories shown in following table.

Table 4 Chemotherapies Associated with Peripheral Neuropathy with their threshold dose identified by Cancer Journal for Clinicians, Susanna B. Park, 2013

Type	Class	Threshold Dose	Sensory Neuropathy	Motor Neuropathy	Autonomic Neuropathy
Paclitaxel	Taxane	>300 mg/m^2	Predominantly sensory neuropathy	At higher doses, myalgia and myopathy	Rare
Docetaxel	Taxane	>100 mg/m^2	Predominantly sensory neuropathy	At higher doses, myalgia and myopathy	Rare
Oxaliplatin	Platinum	>550 mg/m^2	Acute sensory symptoms and chronic sensory neuropathy	Acute cramps and fasciculations	Rare
Cisplatin	Platinum	>350 mg/m^2	Acute sensory symptoms and chronic sensory neuropathy	Rare	Rare
Vincristine	Vinca alkaloid	>2-6 mg/m^2	Sensory neuropathy	Muscle cramps and mild distal weakness	Yes
Thalidomide	Immunomodulatory/ antiangiogenic agent	>20 mg/m^2	Sensory neuropathy	Mild distal weakness and cramps	Rare
Thalidomide	Proteasome inhibitor	>16 mg/m^2	Painful, small-fiber sensory neuropathy	Rare	Yes

This data suggest that a threshold for the earliest signs of cisplatin-induced CIPN is 250–350 mg/m^2, with increasing incidence and severity with higher doses. Oxaliplatin-induced CIPN is frequently persistent and dose-dependent, with a threshold dose of 500–600 mg/m^2. The severity of vincristine-induced CIPN is dose-related, ensuing in most patients after the administration of 4 mg/m^2 of the drug. Sensory signs are the earliest; with doses >6–8 mg/m^2. Vinblastine and vinorelbine

are less neurotoxic. The neurotoxic threshold is around 1000 mg/m^2 for paclitaxel and 400 mg/m^2 for docetaxel. The risk of developing severe taxane-induced CIPN is related to treatment interval.

Factors Predisposing to CIPN are Pre-existing neuropathy, such as diabetes mellitus, alcohol, or inherited neuropathies and related comorbidities may predispose to more severe neuropathy. Age-related axonal loss may also predispose to more severe symptoms from CIPN. Prior chemotherapy can also be predisposing towards CIPN. The pre-chemotherapy analysis identifies patients with pre-existent peripheral neuropathy that will place them at higher risk for the event of CIPN. This clinical analysis ought to embrace a history specializing in symptoms and practical activities yet as a physical examination that objectively assesses the patient's strength, sensation, reflexes, and gait. Ongoing investigation following the initiation of a toxin agent is vital to observe for the event and progression of symptoms related to CIPN, and to make sure its resolution over the long term.

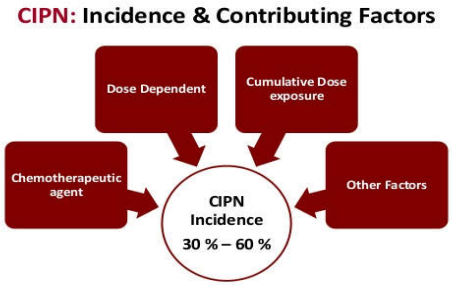

Figure 3 CIPN Incidence and contributing factors (bing.com/images)

Incidence of Neuropathic Pain (NeP) Related to Risk Factors

Ne P affects up to 8% of the population (Torrance *et al*., 2005). It is relatively common in people with certain conditions. For example:

20-40% of people with diabetes experience NeP (painful diabetic neuropathy) (Serpell, 2004)

25-50% of patients aged over 50 years with herpes zoster infection develop post-herpetic; neuralgia three months after the rash recovery (Rice & Maton, 2001)

30% of people with cancer reported NeP(Davies and Walsh, 2004)

20% of women develop neuropathic pain post-surgery (mastectomy) (Bowsher, 1991).

Peripheral neuropathy is common and can be long lasting according to the specific characteristics of chemotherapeutic agent. There is significant difference in reported incidence and natural history, related to challenges in clinical examination and diagnosis. Confounding risk factors for CIPN include treatment factors such as dose, duration and concurrent medication and patient factors such as age and inherited susceptibilities. Recent identification of individual genetic variations has advanced understanding of pathomechanisms and may direct future treatment modalities for better management of CIPN (Kandula, 2016).

Table 5 Risk factors of CIPN by neurotoxic drug classification (cancer management and research; Andreas A., 2014)

Agent	Risk Factors
Cisplatin	Prior or concomitant administration of taxanes, single and cumulative dose level, pre-existing peripheral neuropathy
Oxaliplatin Acute form	Cold, duration of infusion (2-hour vs 4- or 6-hour infusion)
Chronic form	Single and cumulative dose level, severity of the acute form of neurotoxicity, time of infusion, pre-existing peripheral neuropathy, treatment duration.
Paclitaxel	Single and cumulative dose level, prior or concomitant administration of platinum compounds, pre-existing peripheral neuropathy, duration of infusion (1- to 3-hour vs 24-hour infusion).
Docetaxel	Single and cumulative dose level, prior or concomitant administration of platinum compounds, pre-existing peripheral neuropathy.
Epothilones	Single and cumulative dose level, prior or concomitant administration of platinum compounds, pre-existing peripheral neuropathy.
Bortezomib	Single and cumulative dose level, pre-existing peripheral neuropathy.
Thalidomide	Single and cumulative dose level, pre-existing peripheral neuropathy
Lenalidomide	Single and cumulative dose level, pre-existing peripheral neuropathy
Pomalodomide	Single and cumulative dose level, pre-existing peripheral neuropathy
Vincristine	Single and cumulative dose level, pre-existing peripheral neuropathy

Researcher is looking at, which predictor and risk-factor contributes to chemotherapy induced peripheral neuropathy for cancer patients. While going through literature, researcher will try to find the variations in studies with help of meta-analysis and systematic reviews.

The purpose of this study is to find out the most frequently reported clinical and genetic risk factors.

Objectives of the study

- To identify the predictors and risk factors of CIPN in adult cancer patients.
- To compile the clinical and genetic risk factors contributing to CIPN in adult cancer patients.

Significance of the study: This review paper intends to put together and discuss the spectrum of chemotherapy-induced peripheral neuropathy (CIPN) characteristics so as to highlight areas of future research to pursue on the topic. Current knowledge shows that the predictors and risk factors of CIPN still remain elusive.

Background

The present study will include systematic review and meta-analysis. The investigator did an extensive research & systematic review literature related to the present study & made an attempt through search strategies include offline and online sources which contribute to a deep insight into the problem area & methodology.

Online Resources: Delnet, Remote X Spgimer, Ebsco, Willey online library

Offline Resources: Dr.Tulsi Das Library PGIMER, Chandigarh and National Library, Banglore.

Systematic review of literature for the present study have been collected, organized& presented under the following heading.

Literature related to predictors and risk-factors of Chemotherapy Induced Peripheral Neuropathy (CIPN).

Table 6 Overview of included studies

S.NO.	AUTHOR	YEAR	STUDY TYPE
1	Kiser DW	2010	Observational descriptive study
2	Agryriou A	2010	Review
3	Velasco R	2010	Review
4	Nurgalieva Z	2010	Cohort study
5	Glendenning	2010	cross-sectional cohort
6	Johnson	2011	RCT
7	Diamopoulos	2011	RCT
8	Balayssac D	2011	Review
9	Baldwin	2012	Prospective cohort study
10	Kawakami	2012	Prospective cohort study
11	Won	2012	Prospective cohort study
12	Park SB	2012	NM*
13	Tofthagen C	2012	Descriptive study
14	Stubblefield MD	2012	Prospective study
15	Argyriou	2013	Prospective cohort study
16	Gewandter JS	2013	Phase III RCT
17	Hertz DL	2013	Cohort study
18	Cindy Tofthagen	2013	Assessment study
19	Zedan AH	2014	Mini review
20	Travis LB	2014	NM*
21	Mols F	2014	Population-based sample study
22	Sisignano M	2014	NM*
23	Ezendam NP	2014	Population-based profile regisrty
24	Hong JS	2014	Interview based survey
25	Kim HY	2014	Questionnaire survey
26	Scheel A	2014	NM*
27	Okada N	2014	Patient records study
28	Bhatnagar B	2014	Cancer clinic chart review
29	Miltenburg NC	2014	Comprehensive survey
30	Seretny M	2014	Systematic review and meta-analysis
31	Saad M	2014	Review
32	Beijers AJ	2016	Evaluative study
33	Tian	2015	Population survey
34	Pereira S	2015	Prospective cohort study
35	Schneider BP	2015	Literature review
36	Ewertz M	2015	Review
37	Kim KY	2015	Cross-sectional survey design
38	Taniguchi H	2015	Questionnaire survey
39	Chen EI	2015	Cohort study
40	Eckhoff L.	2015	Evaluative study
41	Emily L Chen	2015	Evaluative study
42	Johnson	2015	Pathway study
43	Bao T	2016	Cross-sectional analyses
44	Izycki D	2016	NM*
45	Dawn L	2016	Phase II and III trials
46	Bhugwandass CS	2016	Population-based profile regisrty
47	Schwenk M	2016	RCT
48	Ventzel L	2016	Prospective study
49	Matsuoka A	2016	Quantitative assessment
50	Wang XS	2016	Descriptive study
51	Majithia	2016	Trial study
52	Floortje	2016	Prospective study
53	Nho JH	2017	Cross-sectional study design
54	Kerckhove	2017	Comprehensive literature review
55	Derksen TM	2017	Systematic review
56	Cox-Martin E	2017	Comparative study
57	Prinsloo S	2017	RCT
58	Greenlee H	2017	The pathways study
59	Hough SW	2017	Evaluative study
60	Cliff J	2017	Critical review
61	Chan	2017	Clinical details
62	Jeonghwan	2017	Prospective study
63	Lucia V	2017	Prospective cohort study
64	Dr. Marshall Pitz	2017	NM*
65	Velasco R	2017	Prospective observational study
66	Clermont-Ferrand	2017	Monocentric observational study
67	Karafiath S	2017	Prospective study
68	Cioroiu C	2017	Review

NM*- Not Mentioned in the study

Study Characteristics

Of the 133 studies included, 17 were prospective cohort studies, 12 were RCTs, and 14 were cross-sectional cohort study. Eight of 12 RCTs (82%) reported investigator blinding of some type. Blinded assessment of outcome was reported in 3 of 14 prospective cohort studies. All studies reporting CIPN risk factors described methods used to identify these predictors and risk factors. Total 68 risk factor studies were included; out of them twenty nine were Clinical risk factors studies and nineteen genetic risk factors studies, included in this paper.

MATERIAL AND METHODS

Research design: The present study has Non-experimental quantitative (casual-comparative research design).

Area of study: The present study has two sources/ search strategy of data collection which further dividing into following:

Online Resources: Delnet, RemoteXS pgimer, Ebsco, Willey online library

Offline Resources: Dr. Tulsi Das Library PGIMER, Chandigarh and National Library Banglore.

The selection of the search strategies was done on the basis of feasibility of conducting the study and availability of studies in particular resources.

Population: The population of the present study include all the research studies related to adult patients receiving any type of chemotherapy from 2010 to 2017 year.

The samples of the present study include adult cancer patients receiving any type of chemotherapy. Total numbers of adult cancer patients from 133 studies are 12,378.

The sampling technique used in this study was purposive non probability sampling technique based on inclusive criteria.

Criteria for the Selection of Studies

Inclusion Criteria: prospective observational studies including

a. Clinically controlled studies
b. Randomized controlled trials
c. Systematic reviews of prospective studies.
d. Any other type of study deemed fit while doing review of literature
e. Adult cancer patients receiving any type of chemotherapy.

Exclusion Criteria: The present study will excluding

Table 7 CIPN risk factors (Clinical)

S.N.	Study	Category of Risk factor reported	Data source of study	Sample size of study	Predictors & Risk factor details
1	Agryriou A (2010)	Clinical	Review	NM*	Single dose per course, cumulative dose, treatment schedule, age, prior or con-comitant administration of neurotoxic agents, Baseline Neuropathy
2	Glendenning (2010)	Clinical and Treatment-related	Cross-sectional cohort	293	Cisplatin dose increase, Carboplatin dose increase
3	Nurgalieva Z (2010)	Clinical	Cohort study	65316 (breast Ca), 9242(ovarian), 86278(non-small cell lung cancer)	Increasing no. of chemo cycles
4	Dimopoulous (2011)	Clinical	RCT	340	Baseline neuropathy
5	Park SB (2012)	Clinical		NM*	During early treatment
6	Stubblefield MD (2012)	Clinical	Prospective study	NM*	Agents used, dose and schedule
7	Kawakami (2012)	Clinical	Prospective cohort	50	Smoking history back years Decreased creatinine clearance
8	Gewandter JS (2013)	Clinical	Phase III RCT	421	Motor neuropathy
9	Kim HY (2014)	Clinical	Questionnaire survey	249	Peripheral neurotoxic chemotherapeutic agents
10	Sisignano M (2014)	Clinical		NM*	High doses
11	Bhatnagar B (2014)	Clinical & Racial	Cancer clinic chart review	123	African-American pts, diabetics, Paclitaxel use pts
12	Okada N (2014)	Epidemiological & Clinical	Patient records study	41	Age(upto 65 yrs), drug dose, concomitant use of aprepitant
13	Kim HY (2014)	Clinical	Questionnaire survey	249	Peripheral neurotoxic chemotherapeutic agents
14	Scheel A (2014)	Clinical	Review	NM*	Drug dose
15	Ezendam NP (2014)	Clinical	Population-based profile regisrty study	191	More cycles of chemotherapy, shorter period since last treatment
16	Zedan AH (2014)	Clinical	Mini review	NM*	Type of chemotherapy drug
17	Beijers (2015)	Clinical	Population-based registry	207	Cumulative dose
18	Tian, Jun (2015)	Epidemiological & Clinical	Population survey	142	High distress score, depression, anxiety, chemo+radiotherapy simultaneous
19	Taniguchi H (2015)	Clinical	Questionnaire survey	147	Adjuvant chemotherapy
20	Ewertz M (2015)	Clinical & Physical	Review	NM*	Dose per cycle, cumulative dose, duration of infusion, exposure to cold
21	Johnson (2015)	Epidemiological & Genetical	Pathway-based study	400	Genetic risk factors (SNPs-single nucleotide polymorphisms include glutathione peroxidase 7(GPX7) gene, ATP-binding cassette sub-family C member 4(ABCC4) gene, methyl-o-guanine-methyl-transferase(MGMT) and glutathione-S-transferase (GST) isoforms. Epidemiologic risk factors (no. of chemo cycles, type of concurrent chemotherapy).
22	Dawn L. Hershman (2016)	Clinical	Phase II and III trials	1401	Drug related factors
23	Ventzel L (2016)	Clinical	Prospective study	174	Cumulative doses, endocrine therapy
24	Izycki D (2016)	Clinical	Review	NM*	Repeated cycles of chemotherapy
25	Matsuoka A (2016)	Epidemiological & Clinical	Quantitative assessment	50	Cumulative dose, Age, Height
26	Wang XS (2016)	Clinical	Descriptive study	NM*	Pre-chemotherapy screening
27	Prinsloo S (2017)	Clinical	RCT	NM*	EEG changes
28	Chan (2017)	Epidemiological & Clinical	Clinical details	NM*	Age, Gender, Adverse effects of medications and other comorbidities
29	Dr. Marshall Pitz (2017)	Clinical	Review	NM*	Combined chemotherapy (double-crush syndrome)

NM* - Not Mentioned in the study

Table 8 CIPN risk factors (Genetic)

Sr. No.	Study	Category of Risk factor reported	Data source of study	Sample size of study	Predictors & Risk factor details
1	Velasco R (2010)	Genetical	Review	NM*	Patient Genotype
2	Johnson (2011)	Genetic	RCT	970+550	ABCA1, ICAMI1, PPARD, SERPINB2, SLC12A6
3	Baldwin (2012)	Genetic	Prospective cohort	855	FGD4
4	Won (2012)	Genetic	Prospective cohort	96	TAC1, FOXC1, ITGA1, ACYP2, DLEU7
5	Hertz DL (2013)	Genetic & Racial	Cohort study	209 European pts, 107 African-American pts	Genotype CYP2C8*3 , Non - Europeans(higher risk) African-American pts
6	Argyriou (2013)	Genetic	Prospective cohort	200	SNC4A, SNC10A
7	Travis LB (2014)	Genetical		NM*	Translational genomics including cell-based model
8	Seretny M (2014)	Genetical and Bioochemistry changes	Systematic review	4179	Baseline neuropathy, smoking, abnormal creatinine clearence, sensory changes during chemotherapy, genetic risk factors
9	Saad M (2014)	Genetical	Review	NM*	Genetic factors (candidate genes, single nucleotide polymorphisms), combination of chemotherapies
10	Miltenburg NC (2014)	Epidemiological &Genetical	Comprehensive survey	NM*	Dose per cycle, cumulative dose, treatment schedule, duration of infusion, administration of other chemotherapeutics, comorbidity, GENETIC (exploration of polymorphisms in genes.)
11	Schneider BP (2015)	Genetical	Literature review	NM*	Host specific factors (race and genetics)
12	Emily L Chen (2015)	Genetical	Evaluative study	NM*	Serum exosomes (protein biomarkers) associate with severity of CIPN
13	Chen EI (2015)	Genetical	Cohort study	NM*	Protein content in serum exosomes
14	Johnson (2015)	Epidemiological &Genetical	Pathway-based study	400	Genetic risk factors (SNPs-single nucleotide polymorphisms include glutathione peroxidase 7(GPX7) gene, ATP-binding cassette sub-family C member 4(ABCC4) gene, methyl-o-guanine-methyl-transferase(MGMT) and glutathione-S-transferase (GST) isoforms. Epidemiologic risk factors (no. of chemo cycles, type of concurrent chemotherapy).
15	Majithia, Neil (2016)	Genetical	Trial Study	NM*	Molecular genetic study for CIPN predictors
16	Kerckhove N (2017)	Genetical and Epidemiological	Comprehensive literature review	NM*	Older adults, several comorbidities, cumulative dose, treatment duration, history of neuropathy, combination of therapies and genetic polymorphisms
17	Kerckhove N (2017)	Genetical and Epidemiological	Comprehensive literature review	NM*	Older adults, several comorbidities, cumulative dose, treatment duration, history of neuropathy, combination of therapies and genetic polymorphisms
18	Cliff J. (2017)	Genetical	Critical review	93	Polygenic phenotype risk, SNPs in CYP2C8, CYP3A4, ARHGEF10, EPHA and TUBB2A genes (Taxanes), FARS2, ACYP2 and TAC1 (Oxaliplatin), and CEP75, CYP3A5 (Vincristine)
19	JeonghwanYou k (2017)	Genetical	Prospective study	45	Depletion of nerve growth factor (NGF)

NM* - Not Mentioned in the study

a. Retrospective studies
b. Case reports
c. Non-systematic reviews
d. Studies including paediatric population
e. Animal models of chemotherapy induced peripheral neuropathy
f. Studies investigating other causes of neuropathy in cancer patients (pre-existing neuropathy, diabetic).
g. Studies based on data patients receiving chemotherapy and radiotherapy simultaneously
h. Any other type of study not deemed fit while doing review of literature

Data Items: Description of data items given as below:

Demographic data of subjects

a. Age
b. Gender
c. Type of cancer
d. Chemotherapy type
e. Drug dose
f. Number of chemotherapy cycles

- Time frame over which CIPN symptoms were assessed in each study
- Methods used to identify risk factors for chemotherapy induced peripheral neuropathy

Study Characteristics

a. Author
b. Design
c. Publication year
d. Sample size
e. Type of chemotherapeutic drug and its dose
f. Duration of study
g. Predictors/ risk factors related to chemotherapy induced peripheral neuropathy
h. Methods used to calculate data analysis (incidence and prevalence rates)

Analysis and Estimation: The present study will include systematic review and meta-analysis method of data analysis and data estimation. Steps of Meta-analysis:

- Formulation of Problem
- Search of Literature
- Selection of studies based on inclusion criteria
- Decide which dependent variables or summary measures are allowed
  - Differences (discrete data)
  - Means (continuous data)
- Selection of meta-regression statistical model.

This study includes selection of meta-regression statistical model based on Simple regression; and Random effects meta-regression **(**Peck & Roxy, 2008).

Testing Hypothesis

This study testing hypothesis may show significant difference between the tested parameters of chemotherapy induced peripheral neuropathy (CIPN) based on systematic review and meta-analysis.

RESULTS

Researcher identified 4047 potentially relevant studies, and examined the full text of 326. A total of 133 studies (involving 12378 patients) met inclusion criteria. 68 studies assessed for risk factor study and 29 of which were of clinical risk factors. Genetic risk factors were reported in 19 studies.

CIPN Predictors and Risk Factors

Sixty eight of the included studies assessed risk factors for CIPN. Twenty nine clinical factor studies include disease duration, cumulative doses, increased and repeated number of chemo cycles, double-crush syndrome, persistent muscle and joint pains, decreased creatinine clearance and EEG changes. Pre-chemotherapy screening was also contributed to the development of CIPN.

Pre-chemotherapy screening was also contributed to the development of CIPN. Nineteen epidemiological factor studies include age (>50 years), females were more prone to develop CIPN, BMI (obesity), African-American patients were likely to develop CIPN. Physical/General factors include smoking history, exposure to cold, shorter and heavier patients, life style (low QOL), nutritional deficiency (lack of vitamin B1, B6, D), MVPA (LOW moderate-to-vigorous physical activity).

In this article, Researcher discussed only clinical & genetic risk factors responsible for CIPN as following:

Table 9 Frequency and percentage distribution of risk factors contributing CIPN

Factors	Mean	N	Std. Deviation	% of Total Sum	% of Total N
Clinical	40.00	1	.	41.7%	25.0%
Epidemiological	19.00	1	.	19.8%	25.0%
Genetic	20.00	1	.	20.8%	25.0%
Physical	17.00	1	.	17.7%	25.0%
Total	24.00	4	10.739	100.0%	100.0%

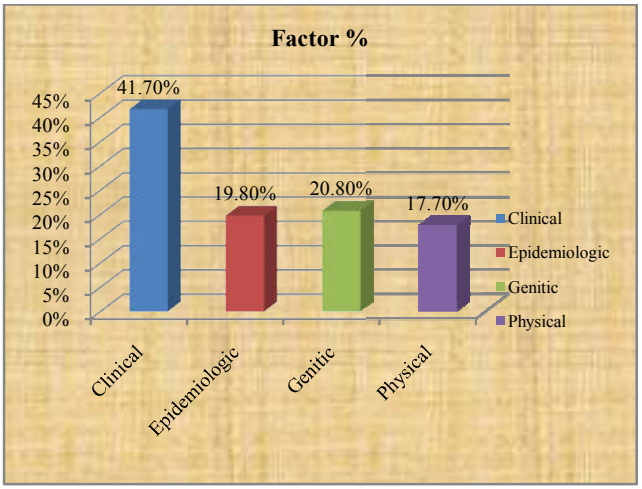

Figure 5 Percentage distributions of risk factors contributing CIPN

Regarding the risk factors contribution to CIPN under study evident that majority of clinical factors (41.7%) has significant role followed by genetic factors (20.8%) and epidemiological factors (19.8%) and less likely for physical factors (17.7%).

Hence it has been concluded that clinical factors and genetic factors were more responsible for CIPN occurrence than other factors.

CONCLUSION

Risk factors for CIPN

This systematic review and meta-analysis provide a qualitative summary of factors reported the risk of CIPN, which include 68 risk factor studies, out of sixty eight, twenty nine reported clinical risk factors, studies showed the 41.7% of clinical factors contributing CIPN occurrence. Nineteen genetic risk factors studies showed the 20.8% of genetic factors contributing CIPN occurrence.

A comprehensive literature review which provided a conclusion on risk factors contributed to CIPN are older adults, several comorbidities, cumulative dose, treatment duration, history of neuropathy, combination of therapies and genetic polymorphisms by the use of platinum based drugs, proteasome/angiogenesis inhibitors, taxanes, vinca alkaloids showing incidence 38% (overall) to 90% (oxaliplatin) of CIPN (Kerckhove, N. 2017).

A critical review of 93 studies based on predictors and risk factors of peripheral neuropathy showing the contribution of genetic factors such as polygenic phenotype risk, SNPs in CYP2C8, CYP3A4, ARHGEF10, EPHA and TUBB2A genes (taxanes), FARS2, ACYP2 and TAC1 (oxaliplatin), and CEP75, CYP3A5 (vincristine) (Cliff, J. 2017).
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A meta-analysis and systematic review provide a qualitative summary of factors reported to alter the risk of CIPN which included 31 studies with data from 4179 patients in the analysis. CIPN prevalence was 68.1% (57.7–78.4) when measured in the first month after chemotherapy. Various chemotherapy drugs were associated with differences in CIPN prevalence rate (Seretny, M. 2014).

Contribution and Future Prospects of this Paper

Different chemotherapy drugs were associated with differences in CIPN prevalence. Different studies showed that severe acute CIPN may require chemotherapy dose reduction or cessation. There is no effective CIPN prevention strategy; treatment of established chronic CIPN is limited, and risk factors of CIPN are also elusive. This paper contributes following:

- An implication for nursing practice is to improve the knowledge of chemotherapy causing CIPN in oncology settings and better understanding or consideration of clinical and genetic factors responsible for CIPN occurrence.
- The findings will help the nursing personnel to assess the clinical risk factors and their emergency situations which require CIPN management.
- This review helps to health care providers in clinical management of CIPN by knowing the risk factors responsible for CIPN occurrence.
- This paper will help all oncology clinical community for better consideration of predictors and risk factors contributing to CIPN whether they are clinical the most important risk factor or other like genetic, epidemiological and physical risk factors.

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