CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY (CIPN): CLASSIFICATION AND INVESTIGATION OF ASSESSMENT TOOLS TO IDENTIFY DIFFERENT CIPN SUBGROUPS

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STATEMENT OF ORIGINALITY

This is to certify that to the best of my knowledge, the content of this thesis is my own work.

This thesis has not been submitted for any degree or other purposes.

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Signature:

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Date: 30 September 2023

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ABSTRACT

This thesis investigated assessment tools, including subjective and objective measures, to identify patient subgroups according to different symptom profiles of chemotherapy-induced peripheral neurotoxicity (CIPN), including neuropathic pain and small nerve fibre dysfunction. Furthermore, this thesis aimed to characterise the impact of CIPN on patient function, quality-of-life and sleep quality in neurotoxic chemotherapy-treated patients. The data chapters comprised in this thesis involved clinical observational cohort studies and recruited patients with multiple cancer types who had been treated with a range of neurotoxic chemotherapy drugs.

Chapter 3 identified the lack of routine assessment of autonomic dysfunction in the context of CIPN and examined the use of electrochemical skin conductance (ESC) via Sudoscan as a potential measure of autonomic function in patients with CIPN. While we did find evidence of ESC dysfunction in half of the cohort with CIPN, the ESC values did not associate with any CIPN severity measures or the autonomic outcome measure. This led us to question the utility of Sudoscan for the purpose of investigating autonomic neuropathy in neurotoxic chemotherapy-treated patients.

Chapter 4 compared a range of functional assessments and neurophysiological measures of CIPN severity, focusing on upper-limb symptoms. Overall, two-third of patients with CIPN reported the presence of upper-limb symptoms. Functional assessments of fine motor skills and sensory perception, and neurophysiological measures of the sensory median nerve were associated with global CIPN severity. This chapter also incorporated stimulated skin wrinkling (SSW) assessment, a proposed assessment small nerve fibre function, to assess CIPN severity and upper-limb symptoms for the first time. SSW assessment did not associate

with global CIPN severity measures. These results demonstrate the presence of long-term upper-limb CIPN symptoms, highlighting the need to improve rehabilitation programs in order to provide targeted interventions on upper-limb function that will help lessen the symptom burden on patient quality-of-life.

In addition, differences in clinical symptom profiles of non-painful and painful CIPN were examined in Chapter 5, including the impact on symptom burden in chemotherapy-treated patients. One quarter of patients reported painful CIPN symptoms, whereby these patients also reported worse CIPN severity and greater behavioural changes, including trouble sleeping, exercise intolerance and increased treatment-seeking behaviour, in comparison to patients with non-painful CIPN.

Finally, Chapter 6 explored the specific impact of CIPN on the sleep quality of patients with chronic CIPN. The results revealed three quarters of patients reporting poor sleep quality long after the completion of their chemotherapy treatment, with almost half of them attributing the sleep impairments to CIPN symptoms. Patients with CIPN-induced sleep impairments also reported worse CIPN severity and neuropathic pain, as well as worse quality-of-life, particularly physical, social and emotional functioning.

In summary, the studies involved in this thesis demonstrated the need for patient subgrouping and importance of identifying the impact of CIPN on patient function in hopes of informing better supportive care and symptom management options for patients with CIPN long after the completion of their neurotoxic chemotherapy treatment. This thesis explored a range of CIPN assessment tools, including potential measures of small nerve fibre dysfunction, and highlighted the presence of a subgroup of patients with upper-limb CIPN dysfunction who

reported high symptom burden of upper-limb CIPN symptoms on patient function, while still reinforcing the need for better and more sensitive measures of small nerve fibre function in the context of CIPN. This thesis also informed a better understanding of the different clinical subgroups of CIPN, particularly painful and non-painful CIPN profiles and provided recommendations for the inclusion of pain assessment tools alongside a comprehensive assessment of CIPN in hopes of informing personalised intervention options, particularly for patients with painful CIPN. Furthermore, given that the findings of this thesis demonstrated a high burden of sleep dysfunction a subgroup of chemotherapy-treated patients, incorporation of sleep assessments in this cohort is also highly recommended in hopes of also improving their function and overall quality-of-life.

PUBLICATIONS

The chapters presented in this thesis resulted from research undertaken at the University of Sydney. Chapters 3 – 6 in this thesis are separate studies that are published or submitted for publication in peer-reviewed journals.

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In addition to the prior statements, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Student name: Fawaz Mayez Mahfouz

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As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements are correct.

Supervisor name: A/Prof. Susanna B. Park

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ABBREVIATIONS

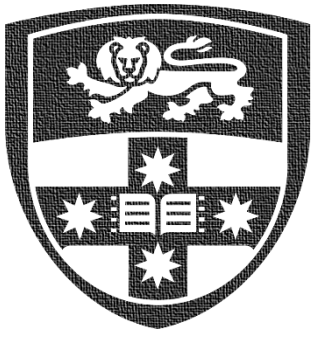
APB	Abductor Pollicis Brevis
ASP	Autonomic Symptom Profile
ATP	Adenosine Triphosphate
Aα	A-alpha
Aβ	A-beta
Aγ	A-gamma
Aδ	A-delta
BMI	Body Mass Index
BPI	Brief Pain Inventory
CAP-PRI	Chronic Acquired Polyneuropathy Patient-Reported Index
CIPN	Chemotherapy-Induced Peripheral Neuropathy
CMAP	Compound Muscle Action Potential
CNS	Central Nervous System
CSAP	Compound Sensory Action Potential
DN4	Douleur Neuropathique 4
DRG	Dorsal Root Ganglion
EORTC-QLQ-CIPN20	European Organisation for Research and Treatment for Cancer – Quality-of-Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy
ESC	Electrochemical Skin Conductance
GOT	Grating Orientation Task
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality-of-Life
IENFD	Intraepidermal Nerve Fibre Density

INFOCUS	Identifying Neurological and Functional Outcomes in Cancer Survivors Study
IQR	Interquartile Range
LANSS	Leads Assessment of Neuropathic Symptoms
mN	Milli-Newtons
MPQ	McGill Pain Questionnaire
Na^+	Sodium Ion
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Nerve Conduction Studies
NES	Nerve Excitability Studies
NPS-CIN	Neuropathic Pain Scale – Chemotherapy-Induced Neuropathy
NPSI	Neuropathic Pain Symptom Inventory
OIPN	Oxaliplatin-Induced Peripheral Neurotoxicity
PN	Peripheral Neuropathy
PNRS	Pain Numeric Rating Scale
PNS	Peripheral Nervous System
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PROMIS-PI	Patient-Reported Outcome Measure Information System – Pain Interference
PROMIS-SD	Patient-Reported Outcome Measure Information System – Sleep Disturbance
PSQI	Pittsburgh Sleep Quality Index
QSART	Quantitative Sudomotor Axon Reflex Test

QST	Quantitative Sensory Testing
PROMs	Patient-Reported Outcome Measures
ROS	Reactive Oxygen Species
RPAH	Royal Prince Alfred Hospital
SAS	Survey of Autonomic Symptoms
SD	Standard Deviation
SESLHD	South-Eastern Sydney Local Health District
SNAP	Sensory Nerve Action Potential
SSW	Stimulated Skin Wrinkling
TAPS	Taxane Acute Pain Syndrome
TNS	Total Neuropathy Score
TNSc	Total Neuropathy Score-clinical version
β-tubulin	Beta-tubulin
µS	Micro-Siemens
µV	Micro-Volts

CHAPTER 1

LITERATURE REVIEW



1.1 CANCER SURVIVORSHIP

While cancer is a leading cause of death in Australia [1], the 5-year survival rate of individuals with cancer between 2011 and 2015 has now improved to 69% [2]. With continuing advancements in early cancer diagnosis and treatment, it is expected that the number of cancer survivors will increase [3]. For this reason, cancer survivorship research is an essential and growing field, as it provides a focus on the health and wellbeing of a person living with and beyond cancer [4]. Long-term quality-of-life in cancer survivors is a current focus in survivorship research [5], and it is particularly important to understand potential long-term side effects of cancer treatments in survivors.

There are a range of current options available for the treatment of cancer, including a variety of different chemotherapy classes [6]. However, certain chemotherapies classes are neurotoxic in nature, which poses a significant limitation to their use [7]. Neurotoxicity refers to the toxic effects of chemotherapy on the nervous system, including the central nervous system (CNS) and the peripheral nervous system (PNS). The focus of this thesis is on the effect of neurotoxic chemotherapy on peripheral nerves, termed chemotherapy-induced peripheral neuropathy (CIPN) [8].

This introductory chapter will focus on providing an overview of the PNS, encompassing the different types of nerve fibres that may be susceptible to neurotoxic damage as well as the pathophysiological mechanisms of different chemotherapy classes. Furthermore, CIPN symptom profiles and the range of assessment tools that are currently utilised to assess CIPN symptoms will be introduced. Finally, the impact of CIPN on patient function and sleep quality will be addressed.

1.2 ANATOMY OF THE NERVOUS SYSTEM

The nervous system is comprised of two parts, the central nervous system (CNS), which includes the brain and spinal cord, and the peripheral nervous system (PNS) (Fig. 1.2.1). This section will focus on the anatomy of the PNS, including its components and nerve fibre types.

1.2.1 The neuron

The neuron is the main component of the PNS. It is a nerve cell that is responsible for detecting stimuli from the external environment and sending responses via the PNS to effector organs in the form of electrical impulses [9]. These electrical impulses travel down the axon of a neuron via saltatory conduction, which refers to the transmission of an action potential from one node to another (Fig. 1.2.1). The cell body, or soma, houses the nucleus and other organelles that are necessary for neuronal function [10]. Axons are the elongated cylindrical structures located between the cell body and the axon terminals [11]. Given their size, they may represent over 90% of the total volume of a neuron, and act as the main propagating vessel for electrical impulses [11]. The myelin sheath is a membranous material that insulates the axon to facilitate a more rapid conduction of the nerve impulse down the axon (Fig. 1.2.1) [12]; however, the myelin varies in composition, with some axons having no myelin at all, otherwise referred to as unmyelinated axons [11].

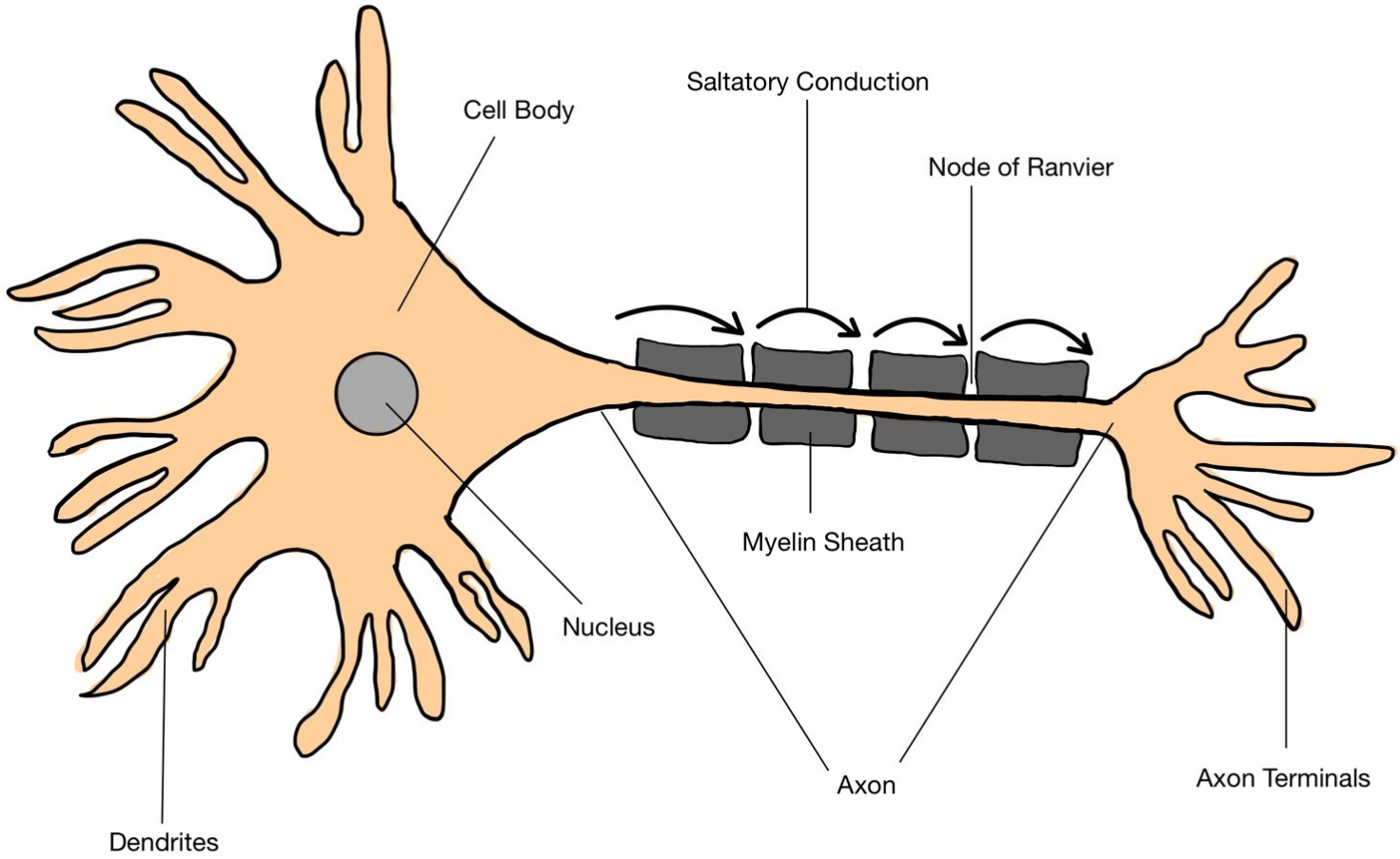


Figure 1.2.1. The major components of a neuron, including the dendrites, cell body, axon, myelin sheath and axon terminals. The saltatory conduction of a nerve impulse throughout the axon is also shown. Source: Original drawing, FM Mahfouz.

The neuron incorporates essential organelles, including the nucleus, endoplasmic reticulum, microtubules, and several others, as seen in Figure 1.2.2. Mitochondria are distributed throughout the cytoplasm and all over the neuron, including the axon [12]. They regulate various cellular processes, including the regulation of intracellular calcium ion signalling as well as the production of energy in the form of adenosine triphosphate (ATP) [12]. Microtubules are found as tightly packed structures in axons and dendrites (Fig. 1.2.2). They interact with a variety of proteins and act as information carriers in the axon and dendrites, including intracellular transport of organelles and cell locomotion [13].

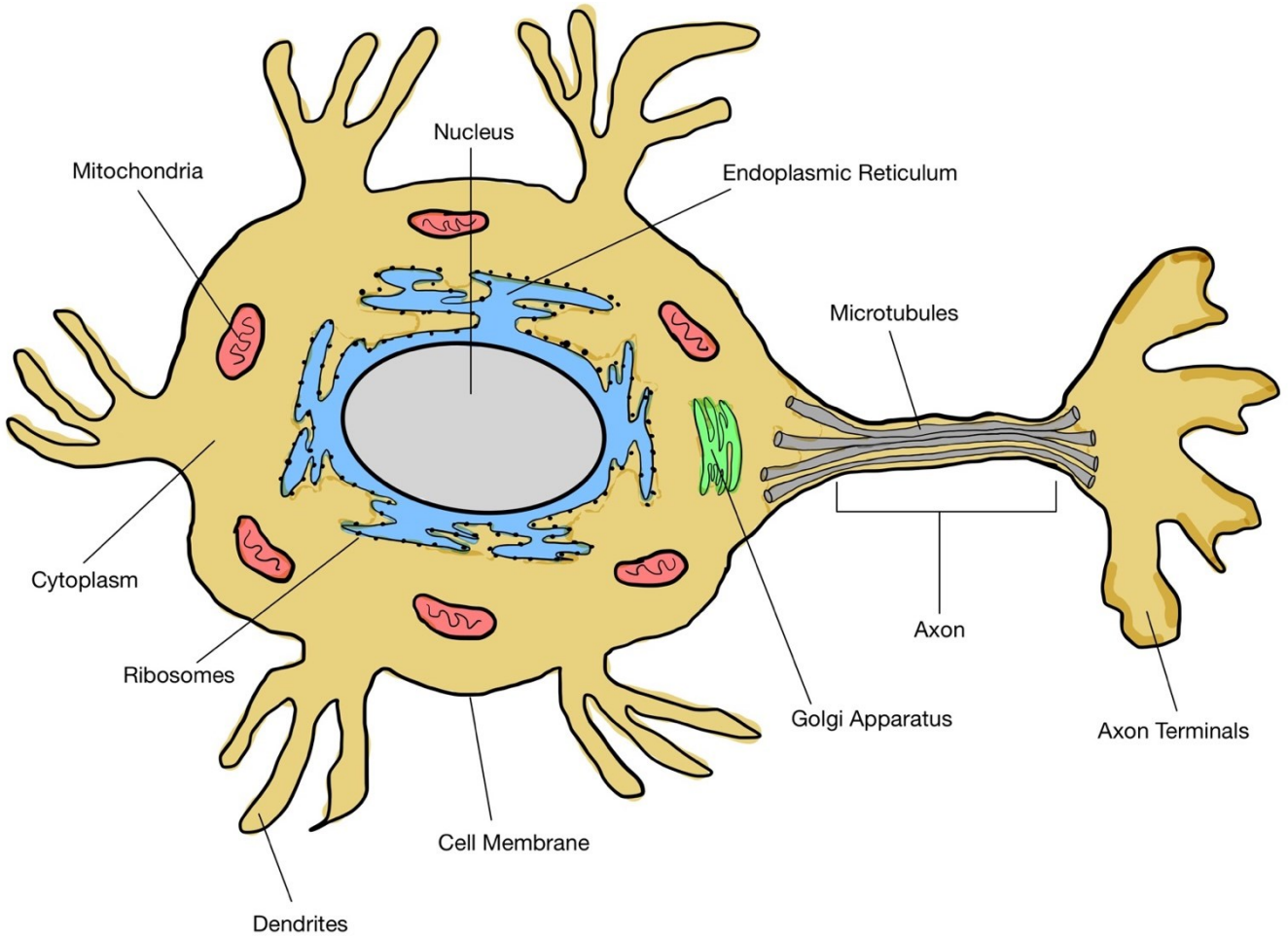


Figure 1.2.2. The organelles of a neuron, including the mitochondria, microtubules, endoplasmic reticulum, and ribosomes. Source: Original drawing, FM Mahfouz.

1.2.2 PNS

The PNS comprises 43 paired nerves, 12 of which are cranial nerve pairs, and 31 making up the spinal nerve pairs [14]. These nerves are subdivided into afferent and efferent divisions [15].

The afferent, or sensory division of the PNS stems from the dorsal root ganglion (DRG). DRG is a collection of sensory neurons of pseudo-unipolar cell bodies that emerges from the dorsal root of spinal nerves [16]. There are two branches of the axon arising from the cell body of each DRG sensory neuron, with one component forming the primary afferent sensory nerve while the other projects into the CNS [17]. The DRG relay somatic sensory messages from various receptors found in skin, muscle and joints, as well as visceral senses relating to the internal environment such as blood pressure, pH, and fullness of stomach, from the periphery to the central nervous system (Fig. 1.2.3) [15, 18]. The efferent, or motor division comprises preganglionic and post-ganglionic nerve fibres and are subdivided into the somatic and autonomic nervous system (Fig. 1.2.3) [18, 19].

While the somatic nervous system is responsible for voluntary movements, particularly skeletal muscle contractions, the autonomic nervous system is mainly responsible for the control of involuntary body functions, including perspiration, breathing, digestion and heartbeat [19].

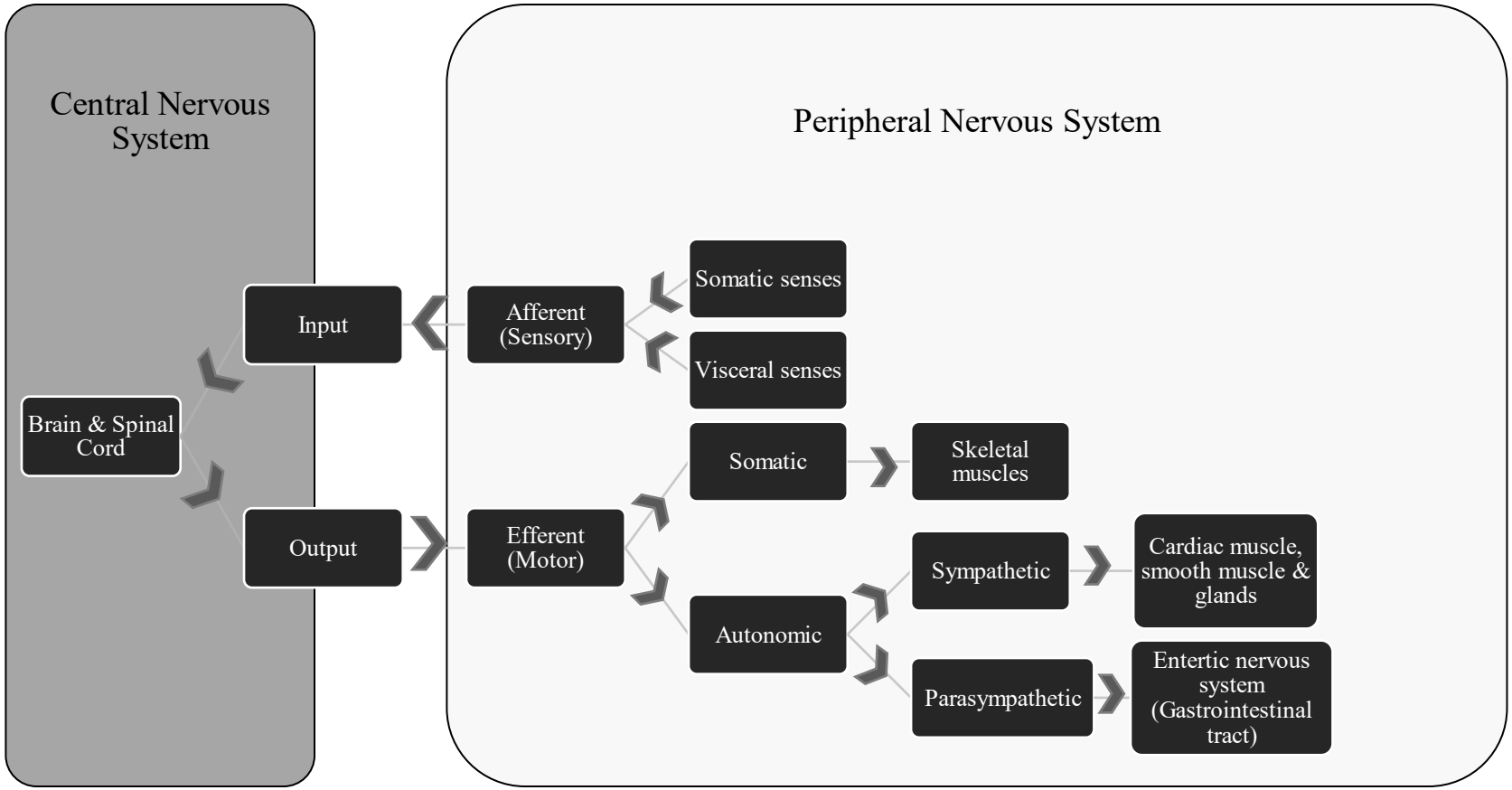


Figure 1.2.3. The nervous system and its organisation. The arrows indicate the direction of information flow via neurons (adapted from *Principles of Human Physiology*, 2014) [15].

1.2.3 Nerve fibre types

A nerve fibre is an enclosed, cable-like structure that is composed of a bundle of axons. In the PNS, nerve fibres can be classified into different types depending on their origin, structure, function, distribution, as well as their diameter and conduction velocity of the impulse. The three main types of peripheral nerve fibres are sensory, motor, and autonomic nerves.

Lower motor neurons originate in the anterior horn of the spinal cord and innervate muscles and glands [20]. Autonomic nerves control involuntary functions such as digestion, blood pressure, heart rate, and sweating, and are subdivided into the sympathetic, parasympathetic, and enteric autonomic nervous system (Fig. 1.2.3) [21].

There are three different types of nerve fibres, most commonly known as A, B and C fibres (Table 1.2.1). Overall, fibres of group A have characteristic larger diameters than B and C fibres, along with rapid conduction velocities and myelination [10, 22]. Group A fibres are divided into sub-grouped into the following: A-alpha (Aα) which comprises type Ia and Ib sensory fibres, A-beta (Aβ) which comprise type II sensory fibres, A-gamma (Aγ) and A-delta (Aδ), which comprise type III sensory fibres. Type Ia (Aα), Ib (Aα) and II (Aβ) sensory fibres innervate proprioceptors, which are sensory receptors that detect stimuli from within the body, particularly in response to movement and bodily position. This corresponds to muscle spindle, Golgi tendon and touch and pressure afferent fibres, respectively (Table 1.2.1) [23]. Furthermore, type II (Aβ) and III (Aδ) sensory fibres innervate mechanoreceptors, which are primarily involved in detecting and recognising different mechanical stimuli. This corresponds to detection of temperature, touch, vibration, pressure, and sound from the internal and external environments. More so, type III (Aδ) sensory fibres

innervate nociceptors, which are responsible for pain detection, and thermoreceptors, which are responsible for temperature detection (Table 1.2.1) [23].

Group B fibres have smaller diameters and lower conduction velocities than A, but larger diameters and are faster than C fibres. They are also myelinated and are primarily involved in transmitting autonomic information (Table 1.2.1) [10, 22].

Group C fibres are unmyelinated nerve fibres, which contributes to their slow conduction velocity compared to the other nerve fibre groups. Similar to type III (Aδ) sensory fibres, type IV (C) sensory fibres also innervate nociceptors and thermoreceptors, and respond to different stimuli, including thermal, chemical, and mechanical stimuli, making them polymodal in their response (Table 1.2.1) [10, 23].

Nerve fibre type	Erlanger-Gasser Classification	Sub-group	Receptor Type	Diameter	Relative Conduction Velocity	Modality
A	**A-alpha (Aα)**	Ia	Proprioceptor	Large	Rapid	Muscle spindle afferent fibres responsible for proprioception
		Ib	Proprioceptor	Large	Rapid	Golgi tendon organ afferent fibres
	A-beta (Aβ)	II	Proprioceptor & mechanoreceptor	Medium	Medium	Secondary afferents of muscle spindles, touch, and pressure
	A-gamma (Aγ)			Medium	Medium	Gamma motor neurons innervating intrafusal muscle fibres
	A-delta (Aδ)	III	Mechanoreceptor, nociceptor & thermoreceptor	Small	Medium	Temperature, fast pain, touch, and pressure
B				Small	Medium	Preganglionic nerve fibres of the autonomic nervous system
C		IV	Nociceptor & thermoreceptor	Smallest	Slow	Temperature, pain, and olfaction

Table 1.2.1. Sensory nerve fibre groups and their function in the peripheral nervous system [10, 22].

1.3 PERIPHERAL NEUROPATHY

This section will provide a broad overview of the causes and clinical characteristics of peripheral neuropathy (PN), with specific details of PN due to neurotoxic chemotherapy to be discussed in the next section.

PN represents a broad range of disorders that directly affect the peripheral nervous system. They are characterised by damage to the peripheral nerves, leading to a range of symptoms depending on the nerves affected, including weakness, sensory symptoms, and pain in the upper and lower extremities [24]. Based on the pathophysiology, PN may be classified as axonal or demyelinating neuropathy [25]. Axonal neuropathy results from damage to the axons, while demyelinating neuropathy manifests due to damage to the myelin sheath [25].

Different forms of PN are characterised by symptom onset (slowly progressive or subacute), progression rate, location (distal symmetric, lower limb predominant) and type of nerve fibres involved (sensory, motor, or autonomic dysfunction) [24]. PN may result in a range of symptoms, including paraesthesia, reduced vibration sense and proprioception, neuropathic pain, weakness and muscular atrophy [26].

Motor symptoms such as weakness and cramping may result from damage to large nerve fibre types, particularly group A fibres. Damage to Aα (Type Ia) fibres may result in the reduction or absence of tendon reflexes [27]. Damage to Aβ (Type II) fibres may result in reduced tactile sensation or vibration, which often occurs along with paraesthesia and numbness [28]. Damage to small nerve fibre types (C fibres) may lead to small fibre neuropathy, resulting in impairments of autonomic function and neuropathic pain [29]. The

most commonly identified subtype of PN is clinically presented as slowly progressive, distal symmetric and predominantly sensory neuropathy [24].

The prevalence of PN in the population generally ranges between 1 to 7%, with older people being at most risk [26]. While idiopathic PN is the most common with no identifiable cause, there are a range of triggers which can produce PN [26]. Diabetes is the most common aetiology of PN [30], followed by other identifiable causes such as hereditary diseases, nerve compression or injuries as well as neurotoxic drug exposure [26]. The focus of this thesis is on PN resulting from neurotoxic chemotherapy exposure, and accordingly further discussion of other aetiologies of PN will not be presented.

1.4 CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Chemotherapy-induced peripheral neuropathy (CIPN), also referred to as chemotherapy-induced peripheral neurotoxicity, is a disabling side effect of cancer treatment which occurs in approximately 50% to 90% of patients treated with neurotoxic chemotherapy agents [31]. CIPN produces peripheral nerve damage and dysfunction of sensory, motor, or autonomic nerves. Examples of neurotoxic chemotherapy agents that may induce CIPN include platinum-based agents, taxanes, bortezomib, vinca alkaloids and thalidomide (Table 1.4.1) [32]. Each of these chemotherapy drug classes have their own cumulative dose intensity regimens, which is accompanied by different risk profiles of CIPN symptom development; however, there is substantial inter-patient variability, with comorbidities such as diabetes, renal insufficiency, alcohol abuse, hypothyroidism and pre-existing neuropathy potentially leading to a higher risk [33].

The most common CIPN phenotype is sensory predominant but may be accompanied by motor or autonomic dysfunction [33]. Sensory CIPN may generate negative and positive symptoms. Negative sensory symptoms and signs encompass reduced responses to stimuli, or hypoalgesia, reduced vibration and proprioceptive sensations, as well as impaired fine motor skills. Positive sensory symptoms include paraesthesia, dysesthesia, hyperalgesia, and thermal and mechanical allodynia [33]. These symptoms may vary in duration and intensity, ranging from acute to chronic changes in peripheral nerves which, in some cases, may last for years [34]. Since the longest peripheral axons are more vulnerable to toxicity, these symptoms are typically more severe in the feet [33], but also occur in the hands [35]. The development of new CIPN symptoms or progression of already-established symptoms during treatment may occur in the months following treatment completion, a phenomenon known as

"coasting" [36]. Following this, CIPN may resolve with time, but in some cases, these symptoms may chronically persist for years post-neurotoxic chemotherapy treatment completion [37].

While numbness and tingling are the most commonly reported CIPN symptoms, there is a proportion of patients with CIPN who also report neuropathic pain [38]. This painful CIPN phenotype may manifest in 19% to 39% of patients, with incidence depending on the neurotoxic chemotherapy being administered [39]. However, to date, there remains a lack of understanding on the differences between painful and non-painful CIPN subgroups in terms of the differences in their clinical presentations and their impact on patient function and emotional well-being. In many assessment tools, the terms numbness, tingling and pain are often used interchangeably to describe neuropathic pain, making it difficult to distinguish between different clinical presentations. However, it is important to be able to identify subgroups with neuropathic pain. Current CIPN treatment guidelines from the American Society of Clinical Oncology and the European Society of Medical Oncology provide possible non-pharmacological interventions as well as pharmacological treatment options for patients who report painful CIPN [40, 41], however, the lack of appropriate subgrouping limits their success in clinical trials and research. The following section will present the currently-known CIPN symptom profiles of different neurotoxic chemotherapies, with particular focus on the reported prevalence, descriptors and location of neuropathic pain associated with each neurotoxic chemotherapy (Table 1.4.1).

1.4.1 TAXANES

Taxanes are most commonly used for the treatment of breast, ovarian and non-small cell lung cancer [42]. Taxanes were originally isolated from the bark of the pacific yew tree, otherwise known as *Taxus brevifolia*, and were first approved for the treatment of ovarian cancer in 1994 [43]. There are multiple taxanes which include paclitaxel, docetaxel and abraxane (also alternatively known as nab-paclitaxel). Taxane-induced PN is common and may impact 11% to 87% of taxane-treated patients [34]. Taxane-induced PN is usually a sensory dominant neuropathy which impacts mostly sensory fibres, particularly Aβ and Aδ fibres [44], along with the less frequent impairment of motor and autonomic or small nerve fibres. Symptoms are most commonly reported as numbness, dysesthesia, paraesthesia, altered proprioception as well as loss of dexterity in the upper and lower extremities [34]. These symptoms are dose dependent and may improve following treatment cessation, while some patients may continue to experience them for years post-completion [34].

Another debilitating symptom experienced by taxane-treated patients is neuropathic pain [45]. Taxane acute pain syndrome (TAPS) is associated with the onset of acute myalgia and arthralgia 24 to 72 hours post-taxane chemotherapy and may last between 3 to 7 days [46, 47]. It is reported by 69% to 88% of taxane-treated patients and primarily arises in the hips, knees, feet and back [48]. TAPS is described as a "diffuse aching discomfort" [45] as well as shooting or burning pain [49], with patients indicating higher pain severity compared to those without TAPS (Table 1.4.1) [50].

With an increase in cumulative dose exposure, patients may develop chronic taxane-induced neuropathy. Long-term chronic neuropathic pain induced by taxane may not resolve [45]. Painful symptoms are reported in the upper and lower limbs by 50% to 80% of patients with

established taxane-induced PN [51, 52], with some reports indicating a lower limb predominance [53]. These taxane-induced painful sensations as often described as burning, aching, prickling, numb and tingly (Table 1.4.1) [53, 54].

1.4.2 PLATINUM-BASED

Platinum-based agents are widely used for the treatment of digestive tract cancers, as well as other types of tumours, including lung, ovarian, uterine, testicular and bladder cancers [34]. The most commonly used platinum-based agents in cancer treatment are oxaliplatin, cisplatin and carboplatin [55]. Carboplatin produces less severe CIPN symptoms, affecting only 4% to 6% of patients [56]. However, cisplatin and oxaliplatin have more severe and distinct peripheral neurotoxic profiles. Neurotoxicity may lead to dose reductions, treatment delays, prolonged infusion times, and in some cases, cessation of platinum-based treatment [34].

1.4.2.1 Cisplatin

Cisplatin-induced neurotoxicity occurs following a cumulative dose of at least 350 mg/m^2 [34]. Depending on dose, cisplatin-induced neurotoxicity is prevalent in at least 49% of cisplatin-treated patients [34], with 5% to 20% experiencing progressively worsening symptoms post-treatment cessation; a phenomenon called “coasting” [57, 58]. Cisplatin-induced neurotoxicity predominantly presents as a sensory neuropathy in the distal extremities [42, 58], with symptoms of numbness and tingling (Table 1.4.1). Cisplatin may also induce ototoxicity, mainly tinnitus and hearing loss which may be permanent [57, 58]. However, reports of neuropathic pain induced by cisplatin is rare, and reported infrequently during treatment and follow-up [59].

1.4.2.2 Oxaliplatin

Similar to taxanes, treatment with the platinum-based agent oxaliplatin may induce either acute or chronic neurotoxicity [60]. This neurotoxicity may exhibit non-painful or painful symptoms. Oxaliplatin is associated with transient acute toxicity, otherwise called acute oxaliplatin-induced peripheral neurotoxicity (OIPN). This usually occurs immediately

following infusion [61, 62] and develops in 65% to 98% of patients [61-63], leading to symptoms that are mainly prevalent in the hands and feet, and less commonly in the throat [63, 64]. These symptoms are mostly characterised by dysesthesias and muscle cramps of the hands and feet, along with throat discomfort. However, over the course of treatment, 56% to 74% of patients may experience painful cold-induced paraesthesia [64], and describe sensations of tingling and freezing along with pain (Table 1.4.1). Most of these symptoms are usually transient in nature and tend to disappear within 2 to 4 days after drug infusion [65].

Chronic oxaliplatin neurotoxicity develops at higher cumulative doses in 48% to 70% of patients [63, 64, 66]. Patients who report more severe acute OIPN are more likely to develop severe chronic oxaliplatin neurotoxicity [57, 61, 67]. This form of toxicity is typically described as pure sensory axonal neuropathy [34]. Patients with chronic OIPN report experiencing symptoms of hypoesthesia, dysesthesia and distal paraesthesia [63]. The prevalence of painful chronic OIPN ranges from 5% to 44% of patients post-oxaliplatin treatment (Table 1.4.1) [68, 69]. While patients report numbness and tingling as more severe symptoms than neuropathic pain, pain is less likely to improve post-treatment completion [70].

1.4.3 BORTEZOMIB

Bortezomib is a proteasome inhibitor approved in 2003 for the treatment of multiple myeloma [55]. Patients who receive bortezomib may develop sensory PN, which is often described as painful [34]. These symptoms may manifest as a consequence of functional alterations observed in Aβ, Aδ and C fibres of bortezomib-treated patients [71]. Bortezomib-induced neuropathic pain may be severe and prolonged, developing as early as 2 months into treatment, which is also dependent on the dose and regimen of bortezomib being administered [72-74]. It affects up to 50% of all bortezomib-treated patients, with around 10% of those patients being clinically graded with more severe neuropathy (Table 1.4.1) [75, 76]. CIPN in bortezomib-treated patients usually manifests as a length-dependent axonal neuropathy [75], arising most prominently in the fingertips and toes, followed by a "border zone" in the palms of the hands and soles of the feet, which are more affected by the numbness rather than pain [77]. Bortezomib-induced neuropathic pain is mostly described as a burning, sharp, thermal [77], intense and stabbing due to the involvement of small nerve fibres (Table 1.4.1) [78]. Although reducing bortezomib dosage has been shown to reduce the incidence of symptoms [76, 79], some patients develop chronic symptoms, including reduced dexterity and ataxia, with persistent impact on daily activities [75].

1.4.4 THALIDOMIDE

Thalidomide is a synthetic glutamic acid derivative which was initially approved for the treatment of morning sickness in pregnancy, however, was later withdrawn due to its teratogenic implications [55]. Since the 1990s, it has been re-introduced for the treatment of severe inflammatory conditions such as Crohn's disease, as well as cancers, particularly multiple myeloma. Thalidomide-induced PN is commonly reported in patients who receive it long term. Similar to bortezomib, thalidomide also causes length-dependent axonal neuropathy [80], affecting mainly the feet [81, 82]. It is prevalent in 25% to 75% of patients, particularly those with a cumulative dose of 20g [34]. Its clinical features include numbness, tingling and painful distal paraesthesia [81, 82]. Although less frequent, motor and/or autonomic symptoms may arise, leading to muscle cramps, orthostatic hypotension, constipation or bradycardia [83]. The duration of exposure to thalidomide, particularly 12 months or more, as well as a high cumulative dose of > 20 g can predict the development and severity of thalidomide-induced neuropathic pain [83, 84]. This painful neuropathy may affect 20% of thalidomide-treated patients [85], mainly arising in the lower limbs (Table 1.4.1) [86].

1.4.5 VINCA ALKALOIDS

Vinca alkaloids are molecules naturally derived from Madagascar periwinkle leaves (*Catharanthus roseus)* [55] and used for the treatment of cancers, including testicular and non-small cell lung cancer, as well as Hodgkin and non-Hodgkin lymphoma [34]. Vinca alkaloids include vincristine, vinblastine and vinorelbine. Vincristine is the most commonly used vinca alkaloid and is the most neurotoxic [55]. Vincristine may induce neurotoxicity at cumulative doses of 4 mg/m^2, producing both sensory and motor neuropathy [34]. Autonomic fibres may also be affected [65]. Patients receiving vincristine report distal paraesthesia and present with severe weakness [87], with the severity of symptoms remaining unchanged for up to 1-year post-treatment completion and may potentially persist for several years [87]. Typical clinical sensory symptoms reported following vincristine treatment are mainly in the fingertips, palms, and lower limbs [88]. Vincristine-induced neuropathic pain may also result from the treatment. It has an early onset, which may result in dose-limiting adverse effects, eventually ceasing treatment [44, 89, 90]. Higher cumulative doses and prolonged treatments seem to be associated with increasing its occurrence and severity [91]. Neuropathic pain may affect between 7% and 62% of patients (Table 1.4.1) [92, 93]. This prevalence is broad in range, which may be due to the variability in the assessment tools used to assess and measure neuropathic pain in vincristine-treated patients. Patients most commonly describe vincristine-induced neuropathic pain as numb, followed by tingling, throbbing, burning and sharp (Table 1.4.1) [88], which further demonstrates how painful and non-painful CIPN symptoms are difficult to distinguish due to interchangeable descriptors of neuropathic pain.

Articles	Classification of chemotherapy drugs	Chemotherapy agents	% of patients reporting painful symptoms		Main descriptors or clinical symptoms used to report neuropathic pain	Location of pain
[45-50]	*Taxanes*	Paclitaxel, Docetaxel, Abraxane	***Acute***	69% to 88%	Ache, shooting or burning pain	In feet, hips, knees, and back
			Chronic	50% to 80% of patients with established taxane-induced PN	Burning, aching, prickling, numb and tingly	In hands and feet (mostly lower-limb predominance)
[59, 64, 65, 68, 69]	*Platinum-based compounds*	Oxaliplatin	***Acute***	56% to 74%	Cold-induced paraesthesia, tingling, cold, freezing	In hands, feet, and throat.
			Chronic	5% to 44%	Numbness, tingling, pain	In hands and feet
		Cisplatin	No reported percentages		Numbness, tingling	In hands and feet (distal extremities)
[73, 75, 77, 78]	*Proteasome Inhibitor*	Bortezomib	Up to 50%		Burning thermal pain, sharpness, intense, stabbing, allodynia, tingling	In hands (‘border zone’ in palms) and feet (soles)
[81-85]	*Immunomodulatory drug*	Thalidomide	20%		Numbness, tingling, painful paraesthesia.	In feet
[87, 88, 92, 93]	*Vinca Alkaloid*	Vincristine	7% to 62%		Numbness, tingling, throbbing, burning, sharp	In hands (fingertips, palms), and feet.

Table 1.4.1. Neuropathic pain profile of different chemotherapies, including prevalence, main descriptors, and location of pain.

1.5 PATHOPHYSIOLOGICAL MECHANISMS OF CIPN

Different chemotherapies produce neurotoxic effects on multiple parts of the PNS, including the sensory cell bodies in the DRG, the components of the axon such as ion channels, mitochondria, and microtubules, as well as the myelin sheath [94]. Damage to these sites may collectively contribute to neuropathic symptoms and potential long-term changes to the nervous system. There has been a wide variety of studies and experimental models used to identify potential pathophysiological mechanisms of CIPN. This section will provide a brief overview of key pathophysiological mechanisms of neurotoxic chemotherapy treatment in producing PNS damage.

The cell bodies of sensory neurons in the **DRG** are vulnerable to neurotoxic damage due to being less protected by the blood-nerve barrier [95]. The selective vulnerability of these sensory neuron cell bodies compared to the motor neuron cell bodies which are located in the anterior horn may explain why CIPN manifests as a predominantly sensory deficit. Damage to DRG may occur as a consequence of treatment with neurotoxic chemotherapy drugs, including platinum-based agents and bortezomib (Fig. 1.5.1). Platinum-based agents result in the formation of DNA adducts which consequently accumulate in DRG, while bortezomib results in the accumulation of ubiquinated proteins in DRGs, both of which may lead to the death of sensory neurons, resulting in the manifestation of PN [65].

Treatment with neurotoxic chemotherapy drugs may also result in **axonal degeneration**, which is a common pathophysiological process resulting in the self-destruction of axons [96]. Multiple factors have been shown to trigger axonal degeneration, including disturbances to

mitochondrial function and calcium signalling, as well as altered axonal transport and altered ion channel function [96]. **Microtubules** are important structures in the axon that are essential for axonal transport of proteins from the cell body to the axon terminals (Fig. 1.5.1) [95]. Disruption to axonal transport due to damage of microtubules may trigger axonal degeneration, and has been described following treatment with different chemotherapies, including taxanes, vinca alkaloids and bortezomib. Taxanes bind to beta-tubulin (β-tubulin) components involved in the assembly of microtubules, which results in the disruption of axonal transport [95], whereas vinca alkaloids impact axonal transport by destabilising microtubule formation. Bortezomib also leads to increasing polymerisation of microtubules, which results in decreased axonal transport, and eventually, decreased function in sensory neurons [65].

Another major mechanism that contributes to the development of CIPN is damage and impairment of **mitochondria** (Fig. 1.5.1). Damage to mitochondria may lead to the generation of reactive oxygen species (ROS) which may also induce axonal degeneration [97]. Neurotoxic chemotherapy drugs, particularly platinum-based agents, can bind to mitochondrial DNA, leading to impaired physiological function and resulting in oxidative stress [98]. More so, paclitaxel administration may cause axonal mitochondria abnormalities, while bortezomib directly affects mitochondrial and endoplasmic reticulum integrity [95]. Overall, mitochondrial dysfunction due to neurotoxic chemotherapy drugs may trigger axonal degeneration and contribute to the development of neurotoxicity [95].

Ion channels have also been described in experimental models to be involved in the pathogenesis of CIPN. For example, the phenomena of acute oxaliplatin-induced neurotoxicity [99] may be linked to the action of oxaliplatin on the axonal membrane and

voltage gated sodium (Na^+) ion channels (Fig. 1.5.1), which results in hyperexcitability of the peripheral nerves [100, 101]. This hyperexcitability may produce symptoms such as cold-induced dysesthesia and paraesthesia [65]. These acute symptoms have been linked to higher risk of chronic CIPN. Potentially, altered ion channel function may trigger axonal degeneration, contributing to the pathophysiology of CIPN.

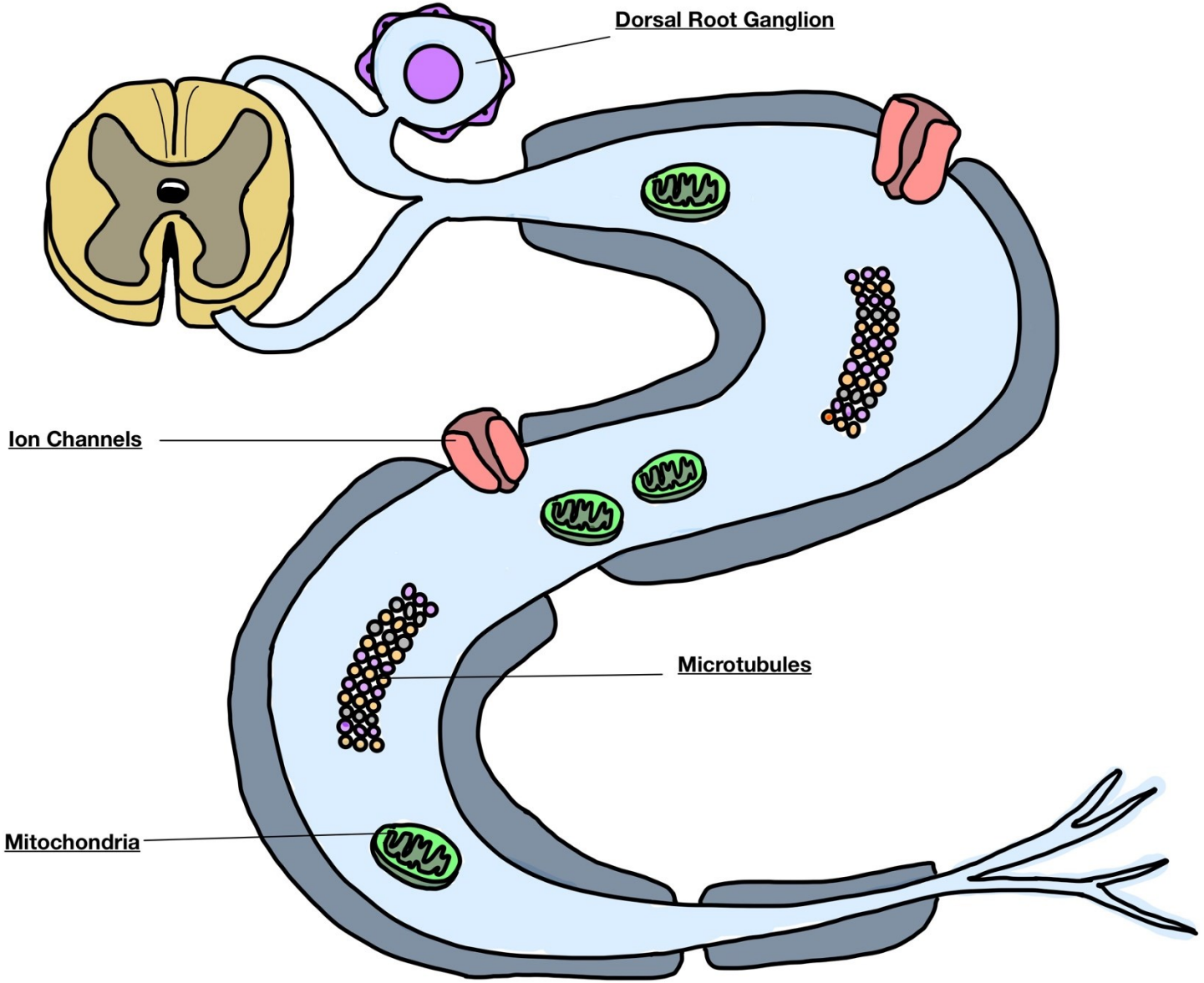


Figure 1.5.1. Potential key targets of neurotoxic chemotherapy agents on the peripheral nerve. Source: Original drawing, FM Mahfouz.

1.6 ASSESSMENT OF CIPN

To date, there is a lack of consensus on the ideal methods to quantify and assess CIPN [102], including chemotherapy-induced neuropathic pain. Current tools that are utilised in clinical settings often lack a sensitivity to change [103]. Furthermore, there are gaps in identifying different CIPN subgroups and phenotypic profiles which are not explicitly addressed in assessment tools. Despite the lack of consensus on CIPN assessment [104], a range of assessment tools and methods have been developed and utilised in CIPN research to aid in assessing and measuring the extent of symptom severity. This section will focus on key assessment tools utilised in the context of CIPN assessment.

1.6.1 Clinically-Graded Scale

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) is the most common clinical grading scale to assess general toxicity [105]. It is a 4-point scale that measures the severity and interference of neurotoxicity with activities of daily living. Due to the ease of administration, it is utilised more favourably in clinical settings, including clinical trials [106]. Despite being used extensively in CIPN, it is limited by the lack of objective thresholds to reliably determine CIPN severity [107, 108]. More so, there remains discrepancies between the patient's and the clinician's perceived CIPN symptom severity, despite reports showing improved reliability following clinician training in using the tool [108].

1.6.2 Total Neuropathy Score (TNS)

The Total Neuropathy Score (TNS) is a composite tool that incorporates patient symptom report, clinical examinations and objective neurophysiological measures of nerve function [109]. It is a sensitive measure of CIPN as it allows for greater responsiveness to change due to the use of a larger scoring range (0 to 28) than other scales [110]. The TNS, as well as its multiple versions, have been validated in patients with CIPN [111, 112]. The TNS-clinical version (TNSc©, John Hopkins University), which excludes the neurophysiological measures, is commonly utilised. Despite having a limitation in assessing only large fibre neuropathy, the TNS is used as a primary outcome measure for the assessment of CIPN in clinical studies and clinical trials [97, 113].

1.6.3 Neurophysiological measures

1.6.3.1 Nerve conduction studies (NCS)

The gold standard for the diagnosis of large fibre neuropathy are nerve conduction studies (NCS), which can be used to non-invasively investigate compound action potential amplitudes, conduction velocity and latency [114]. These data provide insight into the extent of axonal loss [94]. Patients treated with neurotoxic chemotherapy, particularly taxanes and platinum-based agents, often demonstrate reduction in compound sensory action potential (CSAP) amplitudes, which is indicative of the presence of sensory axonal polyneuropathy [115, 116]. NCS may confirm the presence of CIPN but have limited ability to identify specific pathophysiological mechanisms linked to CIPN [117]. They also lack sensitivity as they identify dysfunction in patients who are further into the treatment course [118]. Given that they only assess large fibre neuropathy, they are limited by their lack of ability to measure small nerve fibre damage [119]. NCS may be used to quantify axonal damage in neurotoxic chemotherapy-treated patients [120], but there remains the need for a gold standard to objectively assess CIPN more broadly.

1.6.3.2 Nerve Excitability Studies (NES)

Another neurophysiological method of assessing large fibre neuropathy in CIPN are nerve excitability studies (NES). NES provide information about the function and membrane properties of peripheral nerves, and indirect assays of ion channel function as well as membrane potential [121]. However, similar to NCS, NES do not measure small nerve fibre function. NES can provide more insight into nerve function changes than NCS, depending on the type of chemotherapy agent being used for treatment [122]. For example, changes in nerve excitability were observed in oxaliplatin-treated patients prior to any changes being visible on NCS, suggesting that NES could be utilised to determine the onset of oxaliplatin-induced neurotoxicity [94]. This suggests that NES are more sensitive and may potentially be used as a biomarker for patients who may be at risk of developing CIPN [94].

1.6.4 Small Nerve Fibre Assessment

Assessment of small nerve fibre damage in the context of CIPN is a challenge. In patients with suspected damage to small nerve fibres, large fibre measures such as NCS appears normal [119]. Current Neuropathic Pain Special Interest Group (NeuPSIG) guidelines state that Quantitative Sensory Testing (QST) and skin biopsies may be used to diagnose patients with small fibre neuropathy [123]. However, assessment of small nerve fibre damage in the context of CIPN is a challenge, particularly in a clinical setting. Multiple tools have been used to measure and quantify CIPN-associated small fibre neuropathy, including skin biopsy, Quantitative Sudomotor Axon Reflex Test (QSART) and QST.

1.6.4.1 Skin Biopsy

Skin biopsy is an assessment method that allows for the objective quantification of small nerve fibre damage via measurement of intraepidermal nerve fibre density (IENFD). Once a sample is biopsied, usually from the lower limb, epidermal nerve fibres and innervated structures such as sweat glands and vessels, may be used to identify small nerve fibre dysfunction [61]. Reduced IENFD has been identified in skin biopsies from bortezomib, docetaxel and oxaliplatin-treated patients [52, 124]. However, when investigated in a larger prospective cohort of oxaliplatin-treated patients, there was no evidence of reduced IENFD throughout treatment [125]. Furthermore, there was also no association between IENFD and CIPN severity in a longitudinal cohort of patients treated with either taxane, bortezomib or platinum-based drugs [126]. In addition, skin biopsy is invasive in nature and not suited to longitudinal clinical assessment, which poses limitations to its use in clinical practice.

1.6.4.2 QSART

The Quantitative Sudomotor Axon Reflex Test (QSART) is another test of small nerve fibre via assessment of sudomotor function [127]. Unlike skin biopsy, it is a non-invasive technique that quantifies sudomotor function. It has good sensitivity in diagnosing small nerve fibre dysfunction [128] and has shown good concurrence with skin biopsy and QST (discussed below in section 1.6.4.3) [129]. However, in the context of CIPN, only one study utilised QSART in a sample of patients who were treated with a range of neurotoxic and non-neurotoxic chemotherapies [130]. Furthermore, it is technically challenging to perform and requires extensive patient preparation time [131], which makes it not ideal for the assessment of small nerve fibre damage in a clinical setting, including assessment of chemotherapy-treated patients.

1.6.4.3 Quantitative Sensory Testing (QST)

Quantitative Sensory Testing (QST) is a non-invasive, quantitative test comprised of a panel of tests administered to the patient who is asked to respond to different stimuli that examine mechanical, thermal, and vibration sensations [132]. The sensory stimuli administered are objective; however, patient responses are subjective. This variability, along with the variability in examiner training, location of testing, skin temperature and use of different instruments may make QST unreliable in diagnosing small nerve fibre damage when used alone [133]. Studies have shown that taxane and platinum-treated patients showed no changes in QST modalities of detecting cold or heat pain stimuli which is suggestive of small, unmyelinated C fibre dysfunction, but rather, they had impairments in QST modalities of detecting vibration thresholds that are suggestive of Aβ fibre dysfunction [134]. However, other studies have demonstrated increased thresholds in heat, touch and sharpness in vincristine and bortezomib-treated patients, which is suggestive of Aβ, Aδ and C fibre dysfunction [88, 135]. Further clarification on the use of QST in evaluating small nerve fibre damage in CIPN is still needed.

1.6.5 Patient-reported outcome measures (PROMs)

Patient-reported outcome measures (PROMs) are subjective measures that can be used to assess neuropathy in a clinical setting. PROMs often identify more symptoms in patients with CIPN than identified by clinicians. For example, a study involving oxaliplatin-treated patients described that while clinicians only identified symptoms in 10% of patients with CIPN, PROMs such as patient interviews and self-report questionnaires were able to identify significant neuropathic symptoms in up to 60% of patients [136]. Therefore, PROMs are continuously used in the assessment of CIPN symptoms because they allow patients to subjectively report their own perceived symptom severity, independent from the clinician's interpretation and diagnosis, which allows for better quantification of the patient's experience with CIPN [137].

One of the most frequently used PROMs in CIPN research is the European Organisation for Research and Treatment of Cancer – Quality-of-Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy (EORTC-QLQ-CIPN20) scale [138]. It is a 20-item questionnaire, with each item utilising a Likert scale to rate the symptom severity from 'not at all' to 'very much'. The EORTC-QLQ-CIPN20 has been extensively investigated in CIPN research, and its psychometric properties have demonstrated reliability in grading CIPN symptoms [138, 139], and greater sensitivity than the NCI-CTCAE [138].

While the majority of patients with CIPN most commonly report symptoms of numbness and tingling, there is a proportion of patients who report neuropathic pain [38]. Currently, there is a lack of specific PROMs that assess neuropathic pain and its impact in the context of CIPN. CIPN PROMs such as EORTC-QLQ-CIPN20 include items that assess CIPN-related pain but

lack the ability to distinguish its impact from non-painful symptoms, which limits our understanding of the differences between painful and non-painful CIPN subgroups [140].

There are a range of tools that are validated for the assessment of neuropathic pain in other conditions, such as diabetic painful neuropathy, that have been utilised in CIPN studies. However, each of these tools has a different definition of neuropathic pain and different scoring system, which further contributes to the inability to consistently subgroup or phenotype patients across studies.

The following section will investigate these pain PROMs according to the way they define neuropathic pain, their overall scoring system used to confirm the presence of neuropathic pain, as well as the evidence of their efficacy in CIPN research.

1.6.5.1 Pain PROMs

1.6.5.1.1 Definition of pain

A key issue arising from the assessment of neuropathic pain in CIPN is the lack of tools that are capable of distinguishing painful symptoms, such as burning, electric shock and shooting pain, from non-painful symptoms, such as numbness, tingling and pins and needles. There are a number of tools that have been used to distinguish between neuropathic pain and other pain syndromes. For example, the Leads Assessment of Neuropathic Symptoms and Signs (LANSS) [141] and ID Pain [142] were both developed to distinguish between neuropathic and nociceptive pain through the use of descriptors such as 'tingling', 'electric shocks', 'numb', 'pins and needles' and 'pricking'. In contrast, the Neuropathic Pain Scale for Chemotherapy-Induced Neuropathy (NPS-CIN) [143] separates sensory descriptors such as 'numb' and 'tingly' from pain descriptors such as 'sharp' and 'intense' to assess neuropathic pain. While this tool was designed to separate the painful descriptors from the non-painful descriptors, other tools focus on assessing the components of neuropathic pain, particularly its distribution, progression, severity, and interference with the patient's daily activities, as evident in PainDETECT [144] as well as the Brief Pain Inventory (BPI) [145]. Nevertheless, the differing definitions neuropathic pain found across these tools further contributes to the inability to consistently identify subgroups of patients with painful CIPN.

1.6.5.1.2 Scoring of pain

Each of these pain tools have different scoring schemes. Some tools are designed to identify the absence or presence of pain, such as ID Pain and LANSS, while other tools utilise a scale to assess pain, such as PainDETECT [144] and the Patient-Reported Outcome Measure Information System – Pain Interference (PROMIS-PI) [146].

Overall, the total score of each of these tools will allow for the identification of neuropathic pain by the use of a cut-off score. For example, the LANSS, Douleur Neuropathique 4 (DN4) [147], ID Pain [142] and PainDETECT [144] all have a cut-off score that identifies patients who are likely to have neuropathic pain. Meanwhile, other tools such as the McGill Pain Questionnaire (MPQ) [148], the Neuropathic Pain Symptom Inventory (NPSI) [149], and PROMIS-PI [146] indicate that higher scores are equivalent to increased severity of neuropathic pain. Unlike all of these tools, the BPI scores the pain intensity separately from the pain interference for a better understanding of the patient's experienced neuropathic pain [145]. Discrepancies in scoring methods may add to the difficulty in accurately identifying subsets of patients with painful CIPN.

1.6.5.1.3 Use of pain PROMs in CIPN research

Whilst many of these pain tools have been utilised in CIPN research, there is a lack of specific psychometric studies to evaluate their efficacy in people with CIPN, particularly whether tools were capable of distinguishing between painful and non-painful CIPN symptoms.

As an example, a clinical trial of duloxetine utilised the BPI as its primary outcome measure and demonstrated a decrease in BPI scores in those treated with duloxetine compared to placebo [150], which suggests its potential use in the monitoring of chemotherapy-induced neuropathic pain. Furthermore, ID Pain scores were shown to significantly correlate with a clinical diagnosis of neuropathic pain. However, this was only examined in a cohort of breast-cancer patients receiving taxane chemotherapy [151], with no evidence of its efficacy in other cancer or chemotherapy types. Hence, the efficacy of the standalone use of these pain

tools and scales in CIPN research remains limited, particularly in the identification and assessment of the painful CIPN subgroup.

Overall, the collective use of both subjective and objective measurements in CIPN assessment may help better our understanding of the different CIPN subgroups, including the impact of CIPN on the quality-of-life of cancer survivors' post-neurotoxic chemotherapy treatment.

1.7 IMPACT OF CIPN ON PATIENT FUNCTION & SLEEP QUALITY

The associated side effect profile of neurotoxic chemotherapy treatment, including CIPN symptoms such as numbness, tingling, neuropathic pain, and reduced function, have shown to significantly affect the physiological and psychological state of patients, ultimately reducing their overall quality-of-life [152]. This section will explore the impacts of these symptoms on patient function, including activities of daily living and emotional well-being, as well as sleep quality.

People with CIPN may experience greater-than-normal hypersensitivity coupled with paraesthesia, dysesthesia and neuropathic pain [153]. These symptoms may significantly interfere with the patient's activities of daily living [154]. Upper-limb CIPN symptoms may interfere with typing, writing and household chores such as opening jars or using the remote control, as well as dressing, particularly fastening buttons and using zippers [154, 155], whereas lower-limb CIPN symptoms may lead to instability when walking, climbing stairs or performing physical activity [155].

Patients who deal with CIPN symptoms often express significant impacts on their mood, particularly frustration, anger, irritability, and depression [155]. The presence of these symptoms may act as a constant reminder of having cancer, which may contribute to worsening anxiety and depression [66]. Furthermore, changes in physical function, including the inability to stand or walk for long periods of time may lead to the inability for the patient to participate in activities, which may lead to exacerbated psychological distress and feelings of social isolation [155].

Sleep problems are common in chemotherapy-treated patients, with reported prevalence in 30% to 88% of cancer patients [156, 157]. The development of sleep-related problems in chemotherapy-treated patients range from difficulty falling asleep, to short sleep duration and poor sleep quality [157]. Descriptors such as waking up at night or early mornings as well as the inability to fall asleep in 30 minutes are reported by two-thirds of patients during their chemotherapy treatment [158]. However, sleeping problems may persist for years post-chemotherapy completion, and this often leads to increased levels of psychological distress and fatigue, and is associated with increased levels of pain [158].

Poor sleep quality remains highly prevalent and greatly reduces the quality-of-life of chemotherapy-treated patients. When assessing the sleep quality of patients before, during and after completion of chemotherapy treatment, higher levels of sleep disturbance and poorer sleep quality were identified during treatment [159]. However, a meta-analysis revealed that the sleep quality of breast cancer patients improved in the first few months after treatment initiation, but eventually got worse between 4 and 12 months after completion [160]. Therefore, while there is a high number of patients with sleep disturbance during chemotherapy treatment, it is possible that sleep may not recover and potentially worsen post-treatment completion.

Cancer studies have reported the presence of multiple factors that may contribute to a worsening sleep quality of patients with CIPN, particularly neuropathic pain. Neuropathic pain has been reported to significantly associate with increased sleep disturbance, making it a potential risk factor of poorer sleep quality [66, 155, 156, 158]. This was shown by a study on breast cancer survivors, whereby those who had neuropathic pain were more likely to develop poor sleep quality than those without pain [156]. Whilst depression and anxiety were shown

to be significant predictors of insomnia and sleep disturbances, the literature remains limited on the association between neuropathy, neuropathic pain, and sleep quality of chemotherapy-treated patients [157]. More so, there remains a difficulty in isolating the specific impact of CIPN on sleep quality in cancer survivors, especially since the majority of CIPN assessment tools do not address it. Therefore, this warrants further investigation of patient subgroups who present with sleep problems due to CIPN, as well as investigate the burden of poor sleep quality on their function and overall quality-of-life post-neurotoxic chemotherapy treatment.

1.7.1 Current treatment and management options for CIPN

Given that CIPN can markedly affect the quality-of-life of neurotoxic chemotherapy-treated patients, it is essential that treatment or management options are available to help lessen its burden on their function, their daily activities, their emotional wellbeing as well as their sleep quality. Unfortunately, to date, the current American Society of Clinical Oncology (ASCO) as well as the European Society for Medical Oncology (ESMO), the European Oncology Nursing Society (EONS) and the European Association of Neuro-Oncology (EANO) CIPN guidelines report limited options available for CIPN, with only duloxetine being moderately recommended for a subgroup of patients who report painful neuropathy [40, 41].

Despite numerous clinical trials being undertaken to investigate a variety of treatment options, there remains a lack of evidence supporting their efficacy in treating CIPN-associated symptoms. A potential factor that may be attributing to the lack of efficacy of these treatment options in clinical trials is the broad inclusion of patients who report general CIPN symptoms, including numbness, tingling and pain, rather than including patients who present with specific symptom subgroups [161]. Furthermore, another contributing factor to the lack of efficacy in published CIPN trials may pertain to the type of primary outcome measures used for the assessment of neuropathy symptoms [162]. This includes measures that assess general CIPN symptoms collectively, rather than separately. These factors may limit our ability to identify if pharmacological therapies are beneficial for subgroups of patients with different CIPN symptom profiles, such as those with neuropathic pain.

A randomised, phase III double-blind trial of a large sample size (n=220) managed to successfully demonstrated the efficacy of duloxetine in the treatment of CIPN in patients who reported painful symptoms [150], leading to uptake by ASCO and ESMO-EONS-EANO

guidelines [40, 41]. This clinical trial utilised a pain score cut-off for the identification and inclusion of the subgroup of patients who reported neuropathic pain (PNRS score of ≥ 4 of 10) [161], as well as the use of the BPI short form as the primary outcome measure for neuropathic pain. Nevertheless, despite duloxetine's success in clinical trials, data from real-world practice has shown that it has numerous side-effects and is not tolerated well by patients [163]. Therefore, there remains a gap in CIPN symptom treatment, which more broadly underscores the need for appropriate patient subgrouping in order to identify those who may benefit from these treatment options.

Non-pharmacological interventions such as exercise and rehabilitation may be more acceptable and feasible for patients than pharmacological treatment. There is a growing body of evidence suggesting that exercise may reduce CIPN symptoms and improve fine motor skills, sensory perception as well as balance and coordination; however, the evidence remains insufficient and larger sample-sized studies are still needed to confirm its efficacy [40, 41]. With appropriate patient subgrouping, this type of intervention can be tailored according to specific symptom profiles to help improve functional deficits and overall quality-of-life.

Besides exercise, there are currently other promising non-pharmacological interventions for the management of CIPN symptoms. In addition, methods such as cognitive behavioural therapy and acupuncture have been shown to alleviate pain and improve sleep quality in patients with sleep disorders [164], which may be applicable to sleep dysfunction in the context of CIPN. However, there remains a need for appropriate outcome measures for patient subgrouping in the context of CIPN. Because of that, currently, there are insufficient clinical trials that investigate the efficacy and feasibility of these technique in treating or managing CIPN symptoms [40, 41], including neuropathic pain [165].

Therefore, this reinforces the importance of identifying ways to appropriately subgroup patients according to their symptom profiles to guide appropriate selection of eligible participants for relevant therapies. Improved investigation of these options may also help guide appropriate treatment and management interventions of CIPN symptoms, as well as improve overall function and quality-of-life.

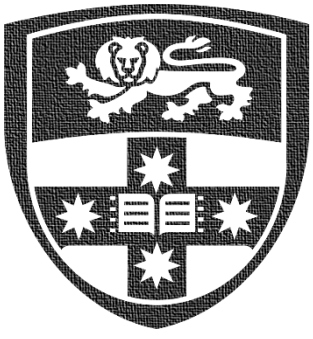
1.8 AIMS AND OBJECTIVES

The overarching aims and objectives of this thesis are to address current limitations in defining patient subgroups according to CIPN symptom profiles, as well as investigate the clinical assessments available for measuring these different subgroups, including the use of current and novel, non-invasive methods for the assessment of CIPN.

The studies comprised in this thesis will address multiple aspects of CIPN, particularly investigating clinical subgroups of CIPN, including those with small nerve fibre dysfunction, upper-limb dysfunction, painful CIPN as well as sleep dysfunction. Furthermore, this thesis will examine the impact of these CIPN subgroups on symptom burden, particularly patient function and quality-of-life of chemotherapy-treated patients, in hopes of guiding appropriate symptom management and treatment selection.

CHAPTER 2

METHODOLOGY



2.1 PATIENTS AND CHEMOTHERAPY REGIMENS

Included patients were ≥ 18 years-of-age and were referred by medical oncologists or oncology nursing staff from the Chris O'Brien Lifehouse, Royal Prince Alfred Hospital, Prince of Wales Hospital, Sydney Adventist Hospital, Northern Cancer Institute and Mater Hospital in New South Wales, as well as Royal Brisbane and Women's Hospital in Queensland, Australia. All studies included in this thesis were data collected as part of the INFOCUS (Identifying Neurological and Functional Outcomes in Cancer Survivors Study) Research Program and were approved by Sydney Local Health District (RPAH zone) Human Research and South-Eastern Sydney Local Health District (SESLHD) Ethics Committee. Written informed consent was obtained from each patient. Clinical data was collected from medical notes.

All patients were treated with a neurotoxic chemotherapy-containing regimen, including taxanes, platinum-based agents, bortezomib, thalidomide or vinca alkaloids. Patients were eligible for inclusion in the study if they were assessed between 1 week and 5 years after completion of their neurotoxic chemotherapy treatment (Fig. 2.1), with the specific inclusion criteria for each study discussed in individual chapters.

Each patient undertook a comprehensive neuropathy assessment incorporating CIPN symptom questionnaires to assess CIPN severity as well as neurological assessments of peripheral nerves in the upper and lower-limbs. This included administering a range of patient-reported outcome measures (PROMs), clinical neuropathy assessments, functional assessments of fine motor skills, sensory perception, and small nerve fibre assessment, as

well as neurophysiological measures of nerves in the upper and lower limbs, as described in detail below. Study-specific details related to methods and statistical analyses are presented in each data chapter (Chapters 3 to 6).

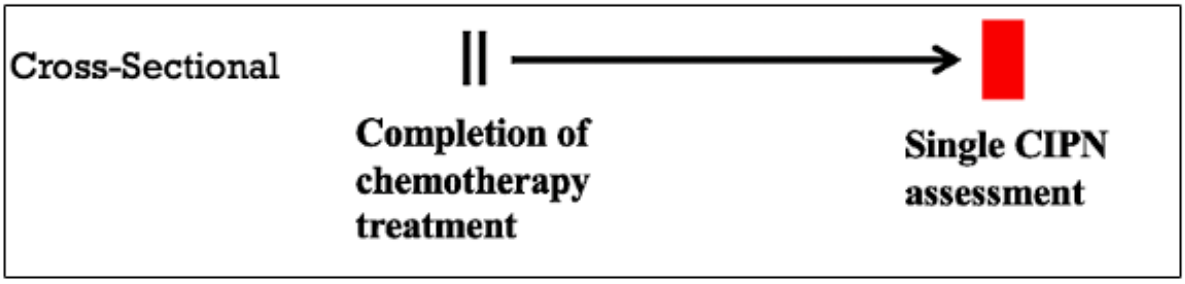


Figure 2.1. Timeline of the INFOCUS Study. A) Cross-sectional patients were assessed once post-neurotoxic chemotherapy treatment completion.

2.2 PATIENT-REPORTED OUTCOME MEASURES (PROMs)

The studies described in this thesis utilised a broad range of PROMs for assessment of CIPN severity and its associated symptoms, including autonomic dysfunction, pain, and sleep, as detailed below.

2.2.1 CIPN Severity PROMs

2.2.1.1 EORTC-QLQ-CIPN20

The European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy module (QLQ-CIPN20) is a validated PROM that was designed to assess CIPN severity, particularly the impact of sensory, motor, and autonomic symptoms of CIPN on patient's quality-of-life in the past week. It comprises of 20 items, and each item is rated on a 4-point Likert scale consisting of 1 'not at all', 2 'a little bit', 3 'quite a bit' and 4 'very much'. The total score was then converted to a linear scale from 0 to 100. Higher scores indicated worse CIPN severity. In this thesis, a male-specific question was omitted from the assessment (Q20) to avoid missing data from female participants [138].

2.2.1.2 PRO-CTCAE

The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a 2-item questionnaire that was used for the assessment of the severity and interference of the numbness and tingling in the hands and feet over the past week. For the severity of symptoms, patients were asked to rate it on a scale of "none", "mild", "moderate", "severe" or "very severe". Whereas for the interference of symptoms,

patients were asked to rate it on a scale of "not at all", "a little bit", "somewhat", "quite a bit" or "very much". Each item response was scored from 0 to 4, with higher scores reflecting greater severity and interference of neuropathy symptoms [166].

2.2.1.3 CAP-PRI

The Chronic Acquired Polyneuropathy Patient-Reported Index (CAP-PRI) scale is a disease-specific health-related quality-of-life measure that was used to assess the patient's physical and social functioning, emotional well-being, and pain severity over the past few weeks. It consists of 15 items with response categories of 0 'not at all', 1 'a little bit' and 2 'a lot'. The sum of all items led to a score ranging from 0 'the best score' to 30 'the worst score'. [167].

2.2.1.4 Structured-Interview Questions

A semi-structured qualitative interview was conducted with patients who were asked open-ended questions relating to CIPN including descriptors of the symptoms and impact on quality-of-life. Patients used their own words to describe their experiences to each question and their responses were recorded verbatim. Responses to three questions were used in this thesis. This includes "do you have trouble sleeping because of your CIPN symptoms", "does CIPN affect your ability to exercise" and "have you tried anything to treat the CIPN symptoms". Answers to these questions were transcribed to 'yes' or 'no' for statistical analyses [136].

2.2.2 Autonomic Outcome Measure

2.2.2.1 SAS

The Survey of Autonomic Symptoms (SAS) is a questionnaire that was used to measure autonomic symptoms experienced by patients. It is an 11-item questionnaire with each item having two scores: total number of symptoms (SAS symptom score) and total impact score (SAS impact score) with each reported symptom being graded from 1 'least severe' to 5 'most severe'. In this thesis, the items were grouped into autonomic symptom domains including sudomotor, gastrointestinal, vasomotor, orthostatic, and urinary function. The sum of total reported symptoms was calculated from the total number of symptoms, and the total burden from each reported symptom resulted in the total impact score [168].

2.2.3 Pain Outcome Measures

2.2.3.1 PNRS

The Pain Numeric Rating Scale (PNRS) was used to assess the intensity of nerve pain experienced by patients. The scale comprises a single-item scale ranging from 0 ‘no pain’ to 10 ‘worst pain possible’ [169]. Patients were asked to rate the intensity of nerve pain experienced either in the past 24 hours or past 7 days prior to assessment day (as specified in individual results chapters).

2.2.3.2 DN4

The Douleur Neuropathique 4 (DN4) is a screening tool that estimates the probability of neuropathic pain. The DN4 interview was used in this thesis to report the characteristics of pain and its associated symptoms, while the bedside clinical examination items were omitted, in line with previous studies [170]. The DN4 includes 7 items that relate to the characteristics of pain and its associated symptoms, including burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching. The items were used to report the most common descriptors of pain in patients who had neuropathic pain across different chemotherapy types [147].

2.2.4 Sleep Outcome Measures

2.2.4.1 PSQI

The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate overall sleep quality, including sleep latency, duration, efficiency, disturbances, medication, and daytime dysfunction in the past month. It is a 19-item questionnaire that comprises of 7 domains which include subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, the use of sleep medications and daytime dysfunction. Each item has a 4-point score of 0 'no trouble on sleep', 1 'trouble less than once a week', 2 'trouble once or twice a week', and 3 'trouble three or more times a week'. A global PSQI score was generated from the sum of all 7 domains, with scores ranging from 0 to 21. Higher scores indicated worse sleep quality [171].

2.2.4.2 PROMIS-SD

PROMIS Sleep Disturbance (PROMIS-SD) Short Form 8a version was used to assess the patient's perception of sleep quality and depth, as well as sleep restoration in the past 7 days. It comprises of 8 items, whereby each item has a 5-point Likert scale of 1 'not at all', 2 'a little bit, 3 'somewhat', 4 'quite a bit' and 5 'very much'. The sum of all 8 items generated a raw score, which was then converted to a standardised T-score according to the conversion tables published on the PROMIS website (nihpromis.org). Higher T-scores indicated greater sleep disturbance [172].

2.3 CLINICAL NEUROPATHY ASSESSMENT

2.3.1 Clinically-Graded Scale (NCI-CTCAE)

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 is a clinically-graded scale that was utilised to grade the CIPN severity of patients with one of the following grades: Grade 0 – no symptoms, Grade 1 – symptoms not interfering with function, Grade 2 – moderate symptoms, Grade 3 – severe symptoms or Grade 4 – disabling (Table 2.3.1). In order to improve consistency [173], in the studies in this thesis, the NCI-CTCAE was scored by the trained research team following the completion of comprehensive patient testing.

Grade	0	1	2	3	4
NCI Common Terminology Criteria for Adverse Events	None	Asymptomatic; loss of deep tendon reflexes or paraesthesia (including tingling) but not interfering with function	Sensory alteration or paraesthesia (including tingling), interfering with ADL Moderate symptoms; limiting instrumental ADL	Sensory alteration or paraesthesia with ADL. Severe symptoms; limiting self-care ADL.	Disabling

Table 2.3.1. The NCI-CTCAE V4.0 Scale [105].

2.3.2 Neurological Examination Score (TNSc)

The Total Neuropathy Score-clinical version (TNSc ® John Hopkins University) is a validated neurological examination score grading CIPN severity across 6 domains that assess upper and lower limb deep tendon reflexes, vibration sensibility, strength assessment and pin-prick sensibility and patient-reported sensory and motor symptoms. Each domain has severity grades ranging from 0 – none to 4 – severe [109, 110], for a total score range of 0 to 24 with higher scores indicating more severe neuropathy. The scoring of the TNSc domains is found in Table 2.3.2 and summarised below. All of the assessments described below were conducted and scored by the trained research team.

1. The presence of sensory symptoms was investigated by asking patients if they had experienced any changes to sensation, including numbness, tingling and pins and needles (Domain 1, Table 2.3.2).
2. The presence of motor symptoms was investigated by asking patients if weakness was present in the arms or legs and graded according to the severity of the impairment (Domain 2, Table 2.3.2).
3. Pinprick sensibility task was completed using disposable pins (Neurotips, Owns Mumford, Woodstock, UK), with a sharp and dull end. Patients were asked to close their eyes prior to commencing. Five randomised applications of the dull/sharp end were administered on digit 2 and digit 5 of the dominant hand and left foot. The pinprick assessment progressed proximally (wrist/ankle → elbow/knee → above elbow/knee) if impairments were identified. If patients scored < 9 out of 10 correct, the testing progressed to the wrist/ankle. If patients scored < 5 correct, then the testing progressed to elbow/knee. The progression of the testing ceased once patients score 5/5 correct. Overall, the results were graded according to the Pinprick Sensibility domain in Table 2.3.2.

4. Vibration sensibility task was completed by using a semi-quantitative Rydel-Seiffer tuning fork (64 Hz). Along the surface of the weights of the tuning fork, there are 2 upward-facing triangles with eight intersections on each side, ranging from 0 at the bottom to 8 at the top. Once struck, the tuning fork vibrations will create an optical overlap of the triangles on each side. For clinical examination, the black side of the two triangles was read for scoring. Patients were first given an example of the vibration sensation on their collarbone. Then, while the patients' eyes were closed, the vibrating tuning fork was placed at the interphalangeal joint of digit 1 of the dominant hand and then on the distal phalanx of the large toe on the left foot. Patients were asked to indicate when the vibrating sensation ceased in each test. A vibration threshold was then identified by the examiner on the tuning fork between 0 (no vibration perception) to 8 (complete vibration perception), and the score was compared to age-specific normative values [174, 175]. The task progressed proximally (bony prominences at wrist/ankle and elbow/knee) if the vibration threshold was lower than normative values.
5. Muscle strength testing was conducted manually on the foot to test the strength of ankle and toe flexion and dorsiflexion against the examiner's hand [176]. The strength task was then graded according to the scoring manual in Table 2.3.2.
6. Deep tendon reflexes of the knee and ankle were assessed using a tendon hammer and were conducted in line with standard clinical practice [177]. If both lower limb reflexes were absent, the task was repeated with reinforcement. If both reflexes were absent with reinforcement, the bicep reflex was then investigated. The deep tendon reflex task was graded according to the scoring manual in Table 2.3.2.

Domain	0	1	2	3	4
1) Sensory symptoms	No symptoms	Affect only fingers and toes	Affect up to ankles or wrists	Extend up to knees and elbows	Extend higher than knees and elbows
2) Motor symptoms	No symptoms	Slight difficulty	Moderate difficulty	Require help or assistance	Part of body paralysed
3) Pinprick sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
4) Vibration sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
5) Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
6) Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent

Table 2.3.2. The domains of the Total Neuropathy Score-clinical version (TNSc) [109, 110].

2.4 FUNCTIONAL ASSESSMENTS

2.4.1 Upper-limb Assessments

2.4.1.1 Grating Orientation Task (GOT)

Sensory perception was assessed via the Grating Orientation Task (GOT). This task involves the use of JVP domes (Johnson-Van Boven-Philips (JVP) Domes, Stoelting Co., IL, USA) with gratings that range between 0.35 mm to 12 mm. These domes were applied on the distal tip of the index finger, with orientations of vertical (down the finger) or horizontal (across the finger) were randomly applied for a total of 20 applications. Patients were instructed to close their eyes and report whether the orientation of the dome was pressed vertically or horizontally. The task aimed to identify the smallest grating size that patients could discriminate. If 15 out of 20 applications were correct, the task progressed to a smaller size. The GOT threshold was then calculated according to the scoring protocol [178].

2.4.1.2 Von Frey Monofilaments

Von Frey Monofilaments (Optihair2-Set, Marstock, Nervtest, Germany) were used to evaluate upper limb mechanical detection thresholds. The monofilaments exert a force that range from 0.125 to 512 millinewtons (mN). The task was applied 5 times on the distal tip of digit 2 and patients had to report the presence of the sensation from the monofilament. The weight was increased if 3 out of 5 applications were not identified. In total, 5 trials were conducted using a series of descending and ascending stimulus intensities. The mechanical detection threshold was calculated according to the scoring protocol [179].

2.4.1.3 Grooved Pegboard Task

The Grooved Pegboard Task (Lafayette Instruments, IN, USA) was used to assess manual dexterity of the patient's dominant hand. By using only their dominant hand, patients were asked to place 25 grooved pegs into grooved holes with different orientations on the board. Two attempts were completed by each patients, with the averaged time being calculated. The number of peg drops were also recorded, and the trial was stopped if the completion time exceeded 5 minutes [180].

2.4.1.4 Stimulated Skin Wrinkling (SSW)

A proposed non-invasive measure of upper-limb small nerve fibre function is the stimulated skin wrinkling (SSW) assessment [181], which utilises EMLA cream (lidocaine 2.5% and prilocaine 2.5%, AstraZeneca), a topical anaesthetic [182] to produce skin wrinkling as a result of vasoconstriction of the glabrous skin of the digit tips mediated by sympathetic or small nerve fibres of the autonomic nervous system [183]. The distal digit tips of the 3rd, 4^{th,} and 5th digits [184] of the non-dominant hand were sterilised with alcohol wipes and photographed using an iPad Pro 11-inch (3rd generation – Model MHQV3X/A) at a distance of approximately 20 cm away from the fingertips against a blue background [182, 184-186]. EMLA cream sufficient to thickly cover each distal digit pulp was applied (~1g) and sealed with transparent film tape (Opsite Flexifix, Smith & Nephew, UK) for 30 minutes [182, 186]. After the 30-minute application time, the EMLA cream was removed, and post-EMLA photographs were taken.

The number of wrinkles per digit were noted through live examination of the fingertips and graded independently by two assessors based on a previously published scale [182, 184-186]. The grading of the degree of wrinkles was as follows: **Grade 0** – wrinkling absent; **Grade 1**

– just perceptible wrinkling with the fingertip not completely smooth; **Grade 2** – 2 or less lines of superficial wrinkling on the fingertip; **Grade 3** – 3 or more lines of deep wrinkling on the fingertip; **Grade 4** – wrinkling completely distorts the pulp of the fingertip (Fig. 2.4.2.1).

The grades for digits 3, 4 and 5 were then added and averaged (÷ 3) by each assessor. An average score of < 3 is considered as abnormal stimulated skin wrinkling (SSW) while a score of ≥ 3 is considered as normal SSW. If the independent grading of both assessors differed (one normal and one abnormal), an additional grading was then completed based on the post-EMLA photographs by a third assessor, and the average of all 3 assessors was used to obtain the final SSW status.

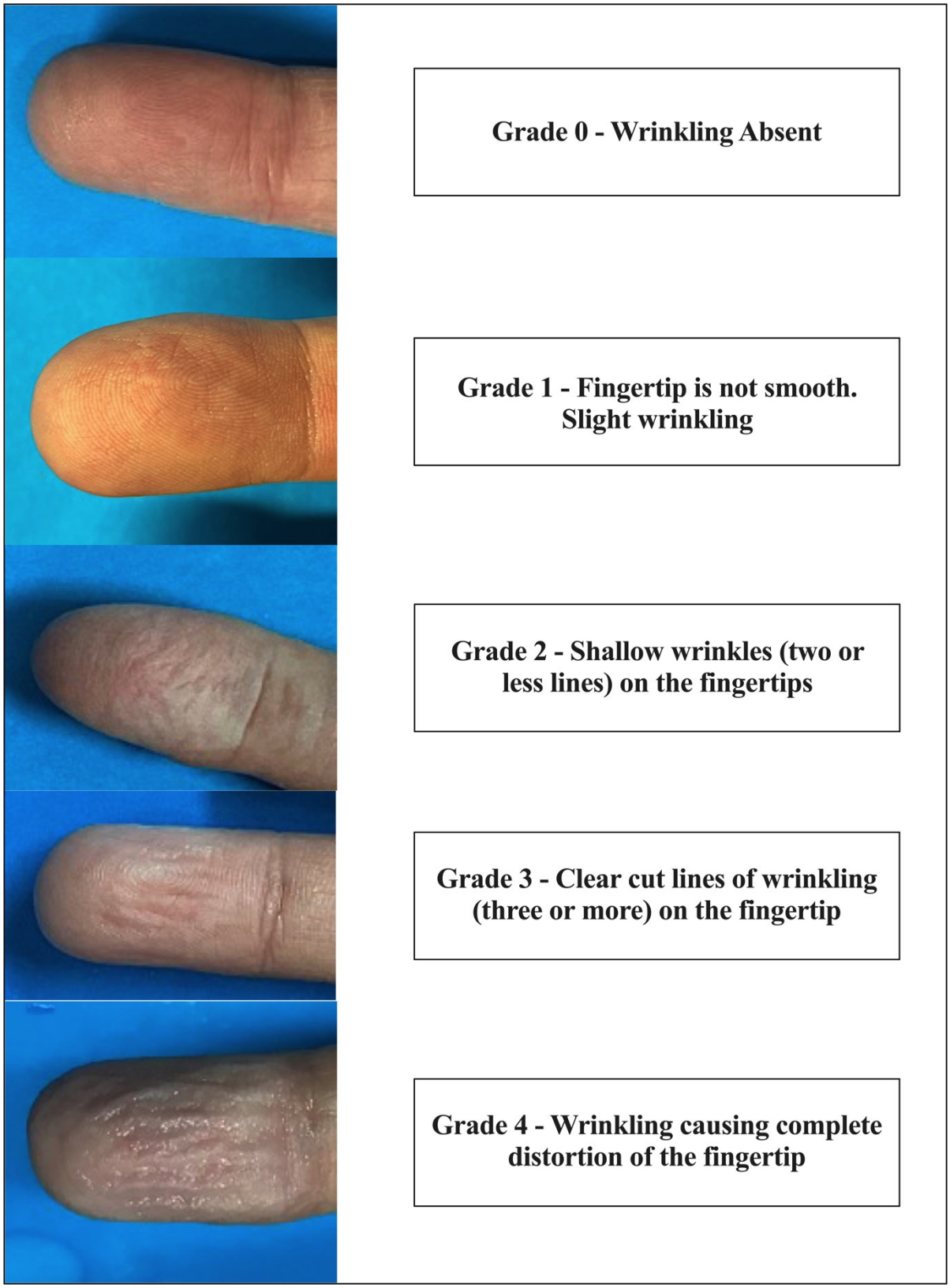


Figure 2.4.2.1. The SSW grading scale. Source: Original pictures compiled from our patients.

2.4.1.5 Electrochemical Skin Conductance (ESC)

The Sudoscan device (Impeto Medical, Paris, France) was designed to evaluate electrochemical skin conductance (ESC) by assessing sweat gland function [187]. The device consists of 2 sets of stainless-steel electrodes for the palms (hands) and soles (feet) and are connected to a computer for data management and recording (Fig. 2.4.2.2). A direct current of ≤4 volts is applied through the electrodes by chronoamperometry and generate a current relative to the chloride ions extracted from the skin through the mechanism of reverse iontophoresis [187-191]. Since volts being applied by the device are very low, the stratum corneum insulates the skin from electric current, causing only the sweat glands to be conductive [187].

The ESC values were quantified in micro-Siemens (μS) based on the reaction between chloride ions from the sweat glands and the direct current generated from the electrodes [187]. During the test, patients placed their hands and feet on the electrodes and stood for 2 to 3 minutes, for a total of 2 trials. Then, the device generated individual ESC values for the left and right hands and feet and calculated an average score for hands and feet. Average ESC values were categorised as no dysfunction (≥60 μS) or dysfunction (<60 μS), in line with prior studies [188, 190].

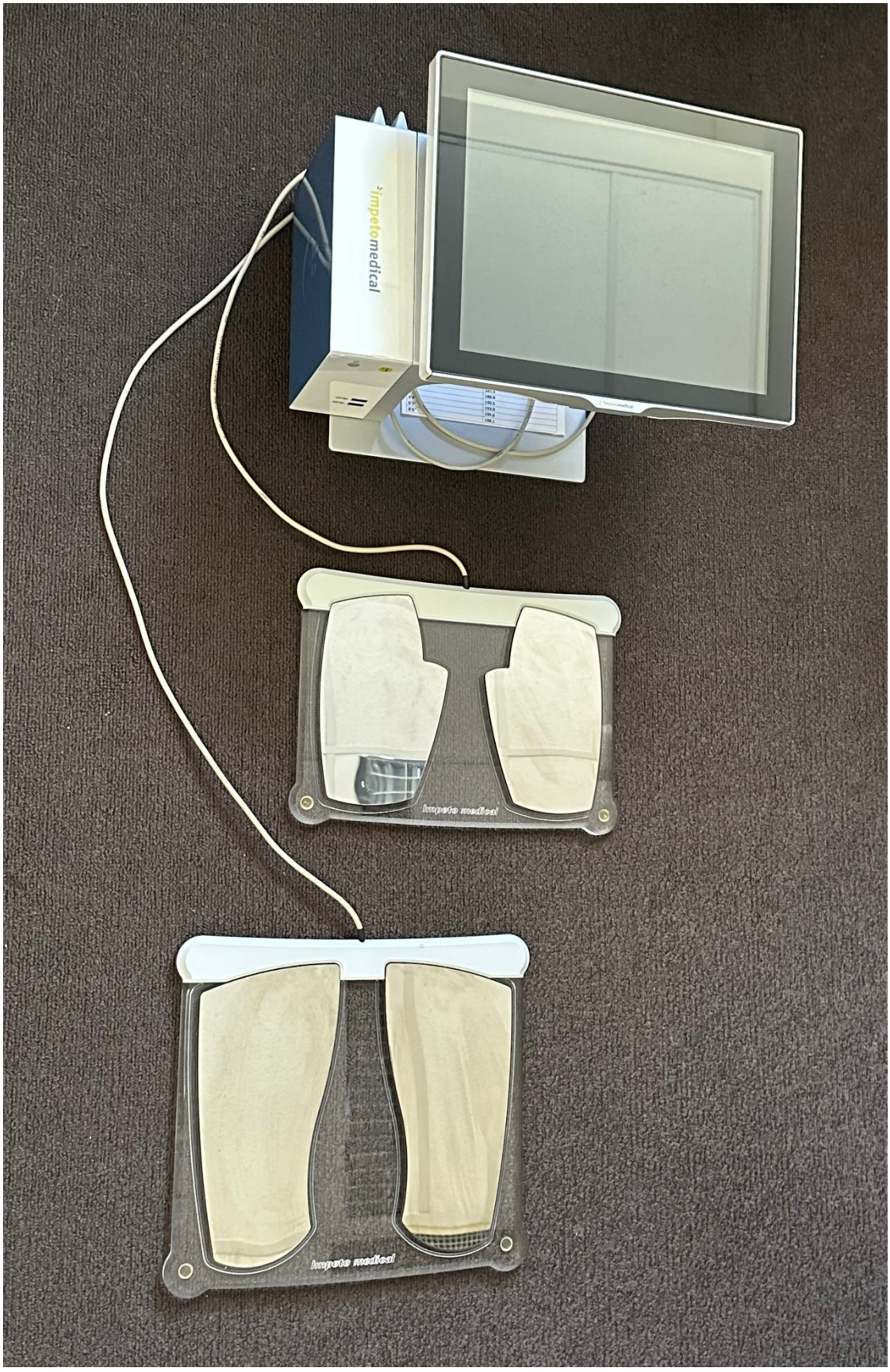


Figure 2.4.2.2. The Sudoscan device set-up consisting of a computer that is connected to the hands and feet stainless steel electrodes. Source: Original photograph, FM Mahfouz.

2.4.2 Lower-limb Assessment

2.4.2.1 Two-Point Discrimination

The two-point discriminator task (Touch Test® Two-Point Discriminator, North Coast Medical, Inc., California, USA) was used to assess the ability of patients to discriminate between one or two close points touching a small area on the first left metatarsus [192]. The gaps between the two points on the discriminator disc range from 2 to 15 millimetres (mm). The task commenced when the disc was positioned perpendicular to the sole of the toe in an antero-posterior direction. Pressure was then applied in a series of ten random trials of one or two points being administered for each distance. The patient was tasked to identify the correct number of points for each application. The smallest distance (mm) in which at least 7 out of 10 correct trials were identified was recorded as the two-point discrimination threshold.

2.5 NEUROPHYSIOLOGICAL MEASUREMENTS

2.5.1 Lower-limb Nerve Conduction Studies (NCS)

Nerve conduction studies (NCS) of the sural and tibial nerves were undertaken using the Nicolet® VikingQuest™ system (Natus® Neurology, USA). The sural nerve was stimulated unilaterally at the left posterior calf using a stimulating probe, and the compound sensory action potentials (CSAPs) was recorded at active and reference electrodes placed just behind the lateral malleolus (Fig. 2.5.1A). The tibial nerve was stimulated by the stimulating probe at the ankle posterior to the medial malleolus. The compound muscle action potentials (CMAPs) were recorded at the active and reference electrodes placed on the abductor hallucis muscle (Fig. 2.5.1B). Stimulus current was increased until amplitude was maximal, and maximal CMAP or CSAP values and onset latencies were recorded for each nerve. Both sural and tibial nerve amplitudes were compared with lower limit of age-matched normative values [193-195].

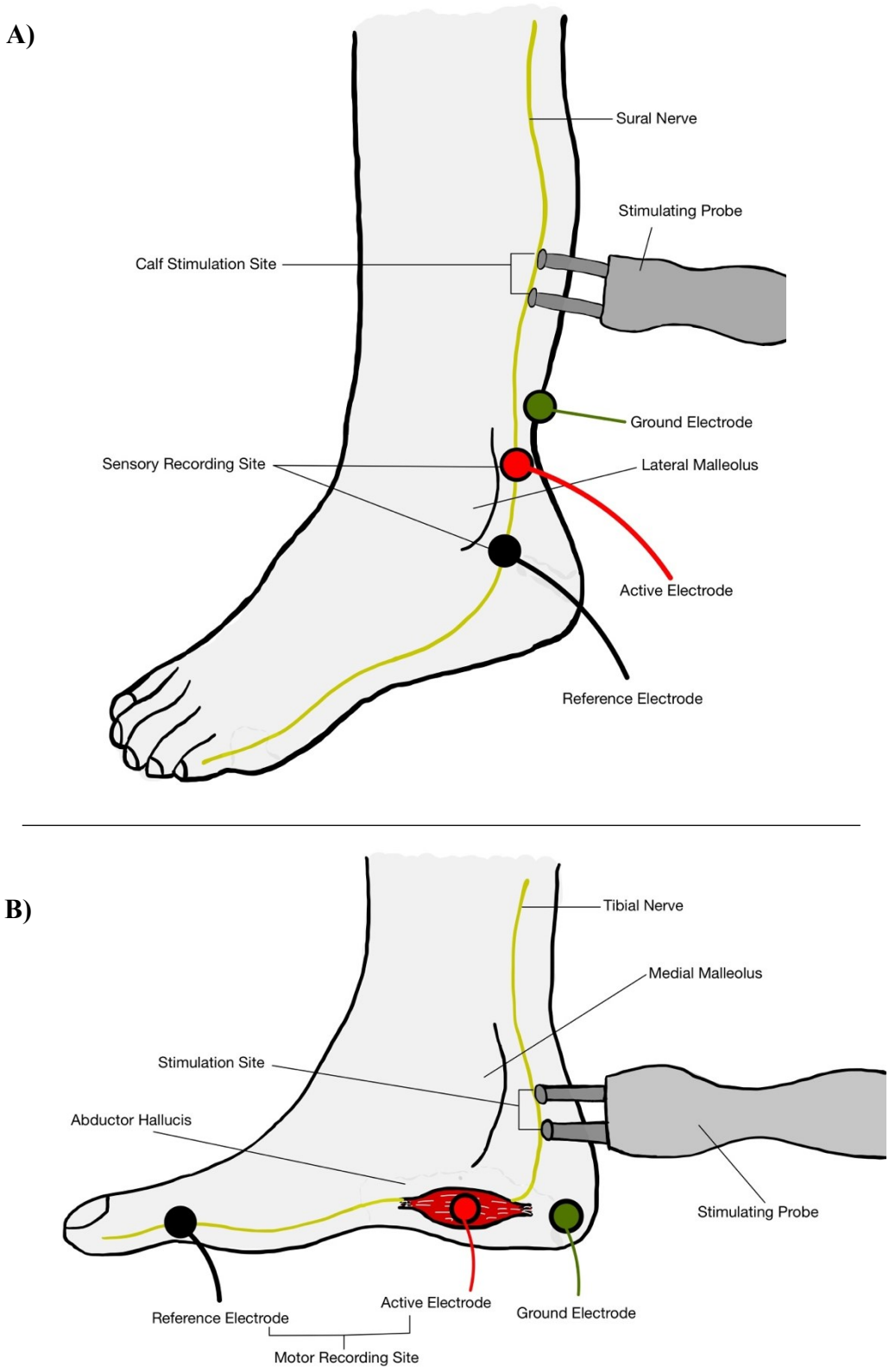


Figure 2.5.1. The NCS recording set-up for (A) the sural nerve and (B) the tibial nerve.

Source: Original drawing, FM Mahfouz.

2.5.2 Upper-limb NCS

Sensory and motor median nerve amplitudes were recorded, using equipment and protocols for nerve excitability studies (NES). A breakdown of the equipment, set-up and protocol of the parameters being measured are listed below. The list of equipment used for the nerve excitability protocol is found in table 2.5.2.

Equipment	Function
Control & Acquisition	
QTrac Software *(Institute of Neurology, Queen Square, UK)*	*QTracS* – runs the TROND protocol for axonal excitability.
	QTracP – used to access and analyse axonal excitability data generated from QTracS
National Instruments *(NI USB-6341 Data Acquisition Board, National Instruments Corporation, Austin, Texas)*	Data acquisition system.
Stimulation	
Digitimer DS5 Stimulator *(DS5, Digitimer Ltd. Hertfordshire, UK)*	Constant current stimulator, maximal output of ± 50mA.
Repositionable Bipolar Electrode	Used to search for the median nerve response along the wrist.
Amplification	
Low Noise Isolated Amplifier *(GRASS LP511 AC Amplifier, Astro-Med®, Inc.)*	Used to amplify sensory and motor nerve responses (10,000x and 25x, respectively).
HumBug 50/60Hz Noise Eliminator *(HumBug, Quest Scientific Instruments, North Vancouver, CA)*	Used to remove electrical noise in the recording setup.

Table 2.5.2. List of equipment used for the nerve excitability protocol [121].

2.5.2.1 Set-up & Protocol

The following excitability set-up was done on each patient prior to commencing the protocol. The patient's dominant hand was prepared by exfoliating the skin at the forearm and wrist using Abrasive pad (3M™ Red Dot™ Trace Prep 2236, CA) to reduce skin resistance, followed by alcohol wipes (Medi-Swab, BSN Medical, Victoria, AU) to sterilise the skin. A thermometer (Oakton® Acorn® Thermocouple Digital Thermometer, Oakton Instruments, IL, USA) was attached close to the wrist and was used throughout the protocol to ensure the patient's wrist temperature was ≥ 32°C. Two ground surface electrodes (Ambu® WhiteSensor WS-00-S/50, Medico Electrodes Ltd, UK) were placed on the dorsal surface of the hand. The median nerve was then stimulated at the wrist using a bipolar electrode. Once the stimulation site was located, a stimulating surface electrode (cathode) (Ambu® WhiteSensor 4500M-H, Medico Electrodes Ltd, UK) was then placed along with an anode electrode approximately 10cm proximal, on the ventral surface of the forearm (Fig. 2.5.2.1 & 2.5.2.2). Two excitability protocols were conducted: a motor and sensory motor median excitability protocol. The set-up for each of these protocols is discussed in section 2.5.2.1.1 and 2.5.2.1.2, respectively.

2.5.2.1.1 Motor Median Nerve

The motor median excitability protocol was undertaken following the set up in Figure 2.5.2.1. The median nerve was stimulated at the wrist between the flexor digitorum superficialis and flexor carpi radialis tendons (cathode in Fig. 2.5.2.1A) [196]. Recording of the compound motor action potential (CMAP) was done by placing motor recording surface electrodes (Ambu® WhiteSensor WS-00-S/50, Medico Electrodes Ltd, UK) at the muscle belly of the Abductor Pollicis Brevis (APB) and a reference electrode at the distal tip of digit 1 (Fig. 2.5.2.1A). A stimulus-response curve was then recorded by increasing the current in increments. A maximal response was found, which was indicated by the response not increasing as the stimulus intensity was further increased [197], and maximal CMAP amplitude was recorded. In this thesis, only stimulus-response parameters obtained from nerve excitability studies were used for analysis.

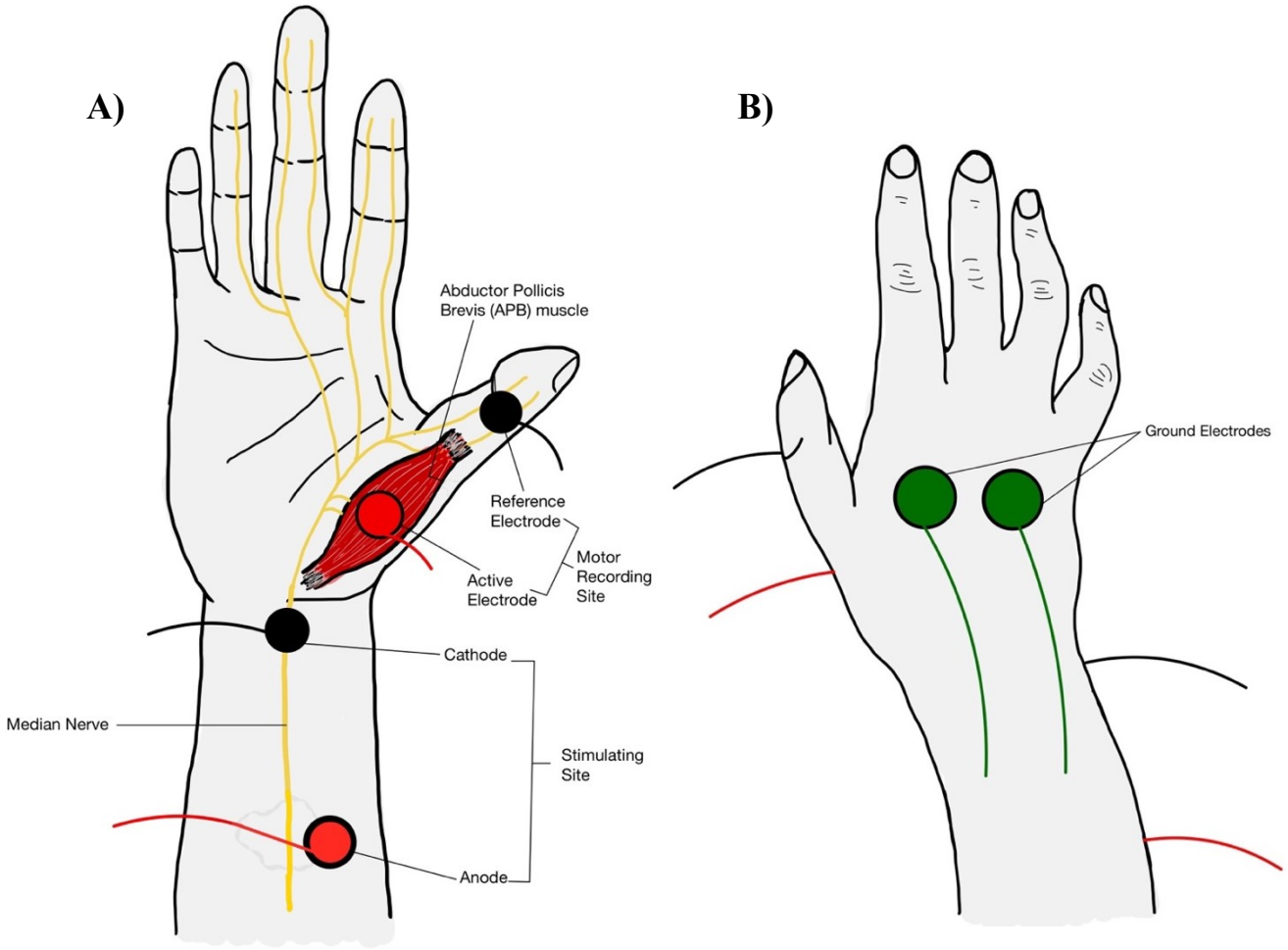


Figure 2.5.2.1. The motor NES set-up on the A) ventral and B) dorsal surface of the hand. Source: Original drawing, FM Mahfouz.

2.5.2.1.2 Sensory Median Nerve

The sensory median excitability protocol was undertaken following the set-up in Figure 2.5.2.2. The median nerve was stimulated similarly to the median motor protocol (cathode in Fig. 2.5.2.1A). Recording of the sensory nerve action potential (SNAP) was undertaken by placing the active and reference electrodes sensory recording ring electrodes (R-ED Disposable Hydrogel Ring Electrodes, Enumclaw, WA, USA) on the proximal and distal interphalangeal flexion creases of digit 2, with a distance of 3 cm in between the active and reference electrodes (Fig. 2.5.2.2A) [196]. Two ground electrodes were placed on the dorsal surface of the hand (Fig 2.5.2.2B). Similar to the motor median excitability protocol, a maximal amplitude was obtained by recording the stimulus-response curve and maximal CSAP amplitude was recorded for analysis.

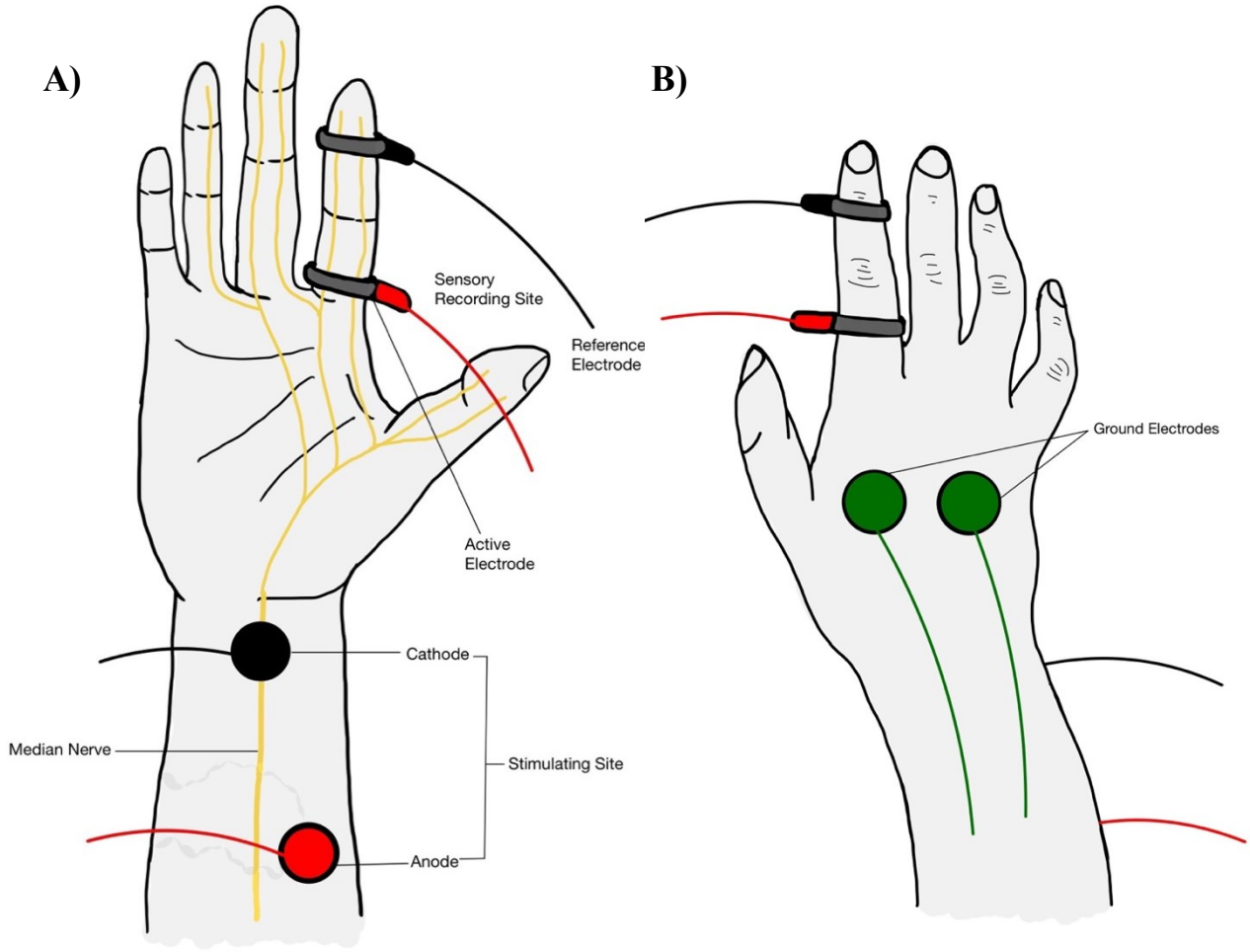
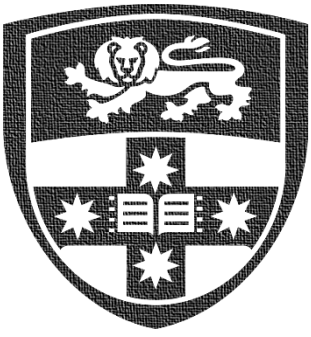


Figure 2.5.2.2. The sensory NES setup on the A) ventral and B) dorsal surface of the hand. Source: Original drawing, FM Mahfouz.

CHAPTER 3

Association of Electrochemical Skin Conductance with Neuropathy in Chemotherapy-Treated Patients



ABSTRACT

Purpose. Chemotherapy-induced peripheral neuropathy (CIPN) is an adverse event of cancer treatment that can affect sensory, motor, or autonomic nerves. Assessment of autonomic neuropathy is challenging, with limited tools available. Accordingly, it is not routinely assessed in chemotherapy-treated patients. In this study, we aimed to examine whether electrochemical skin conductance (ESC) via Sudoscan, a potential measure of autonomic function, associates with subjective and objective measures of CIPN severity and autonomic neuropathy. **Methods**. A cross-sectional assessment of patients who completed neurotoxic chemotherapy 3-to-24 months prior was undertaken using CIPN patient-reported outcomes (EORTC-QLQ-CIPN20), clinically-graded scale (NCI-CTCAE), neurological examination score (TNSc), autonomic outcome measure (SAS) and Sudoscan. Differences in CIPN severity between participants with or without ESC dysfunction were investigated. Linear regression analyses were used to identify whether ESC values could predict CIPN severity. **Results**. 130 participants were assessed, with 93 participants classified with CIPN according to the clinically-graded scale (NCI-CTCAE/grade ≥1). 49% demonstrated hands or feet ESC dysfunction (n=46). Participants with ESC dysfunction did not significantly differ from those with no dysfunction on multiple CIPN severity measures (clinical-grade, patient-report, neurological examination), and no differences on the autonomic outcome measure (SAS) (all $p>0.0063$). Linear regression analyses showed that CIPN could not be predicted by ESC values. **Conclusions**. The inability of ESC values via Sudoscan to predict clinically-graded and patient-reported CIPN or autonomic dysfunction questions its clinical utility for chemotherapy-treated patients. The understanding of autonomic neuropathy with chemotherapy treatment remains limited and must be addressed to improve quality-of-life in cancer survivors.

3.1 INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect of numerous neurotoxic chemotherapy agents, including vinca alkaloids, taxanes, platinum compounds, bortezomib and thalidomide [94]. The pathophysiological mechanisms of CIPN remain ill-defined; however, off-target effects of chemotherapy on peripheral nerve fibres may trigger its manifestation in patients [198]. CIPN produces symptoms of sensory loss, paraesthesia, poor dexterity, and pain, which may significantly impact the patient's quality-of-life [199]. Although CIPN predominantly affects large sensory nerve fibre function [200], small sensory fibres may also be affected, resulting from damage occurring to unmyelinated C-fibres and thinly myelinated A-delta fibres [201]. Small fibre neuropathy may be accompanied by symptoms of sporadic burning and shock-like pain [202], as well as impairment of autonomic function [8], including blood pressure, digestion and perspiration [130].

While there remains no gold-standard clinical outcome measures for CIPN [97], there are a range of validated methods examining large fibre dysfunction in CIPN, including neurophysiological assessments, clinical examination [203] and patient-reported outcome measures [103]. However, there is a lack of validated tools to measure small nerve fibre damage or autonomic neuropathy in CIPN [133]. Available techniques to examine small nerve fibre integrity, such as skin biopsy, have limited utility in clinical practice due to invasiveness, cost and delays in receiving results [204].

Since sudomotor sweat gland function is innervated by small nerve fibres [205], techniques have been developed to assess sudomotor function to provide an index of autonomic neuropathy. The Quantitative Sudomotor Axon Reflex Test (QSART) is a sensitive and

reproducible test of sudomotor function, but it is limited by cost and extensive patient preparation time [206, 207]. Since electrochemical skin conductance (ESC) depends on sweat gland function [208], its values may quantify sudomotor function and provide a surrogate marker for autonomic neuropathy. Sudoscan has been developed as a method to measure ESC, with preliminary findings suggesting its potential use as a measure of small nerve fibre function across disorders such as diabetic PN [207]. Nevertheless, the Sudoscan technique has been criticised as lacking evidence for a direct link between ESC and small nerve fibre or autonomic function, as well as discrepancies with normative datasets [209]. A blinded-prospective study demonstrated reduced intraepidermal nerve fibre density (IENFD) measured via skin biopsy was associated with lower ESC values via Sudoscan in small fibre neuropathy [210]. However, a subsequent cohort study of patients with polyneuropathy found that the association between ESC and IENFD was not strong and that additional mechanisms may be required to explain sweat gland dysfunction in PN [211].

Sudoscan techniques have only been utilised in three previous CIPN studies [206, 212, 213]. Although reduced ESC values were associated with CIPN severity [213], including the Total Neuropathy Score [206] and measures of neuropathic pain [212], broader comparisons of CIPN outcome measures and ESC values in patients with CIPN are needed to investigate the utility of Sudoscan in this population. Further, mechanistic understanding of the physiological contributors to ESC values are needed to determine the clinical significance of reduced ESC in the context of CIPN.

Therefore, the primary aim of this study was to examine the association of ESC dysfunction with clinical, patient-reported, and neurophysiological measures of CIPN among neurotoxic

chemotherapy-treated patients. Additionally, we aimed to identify whether ESC values via Sudoscan were predictive of CIPN severity, pain, and autonomic outcomes.

3.2 METHODS

3.2.1 Participants

Participants who completed neurotoxic chemotherapy (including taxanes, platinum-based agents, bortezomib, vinca alkaloids and thalidomide) were recruited cross-sectionally from Sydney, Australia, between June 2017 and March 2020. Participants who were aged ≥18-years and 3-24 months post-treatment were eligible. The study was approved by Sydney Local Health District (RPAH zone) Human Research Ethics Committee, with informed consent obtained from each participant.

3.2.2 Procedures

Clinical data (age, height, chemotherapy type, cancer diagnosis and stage) were retrieved from medical records. Participants' weight was assessed during their study visit. Body mass index (BMI) was calculated as kg/m^2.

3.2.3 Electrochemical skin conductance measurement

ESC was evaluated by assessing sweat gland function using the Sudoscan device (Impeto Medical, Paris, France) [187]. Participants placed their palms (hands) and soles (feet) onto the electrodes in a standing position for 2 to 3 minutes. A direct current of ≤4 volts was applied through the electrodes by chronoamperometry and generated a current relative to the chloride ions extracted from the skin through the mechanism of reverse iontophoresis [187-191]. The ESC values were quantified in microSiemens (μS) based on the reaction between chloride ions from the sweat glands and the direct current generated from the electrodes [187]. The electrodes were sterilised before each test, and the test was repeated twice for both the hands and feet, with the average ESC value taken separately for the hands and feet. Average ESC values were categorised as no dysfunction (≥60 μS) or dysfunction (<60 μS), as

in prior studies [188, 190]. Participants were classified with ESC dysfunction if they had dysfunction in the hands, feet, or both.

3.2.4 Clinical neuropathy assessment

CIPN severity was assessed using the Total Neuropathy Score-clinical version (TNSc© Johns Hopkins University), a composite tool of six domains including upper and lower limb pin-prick sensory and vibration sensibility, deep tendon reflexes, strength assessment and patient-reported sensory and motor symptoms [109, 110]. Each domain was graded between 0 'normal' and 4 'severe', with a total score ranging from 0 'no neuropathy' to 24 'severe neuropathy'; Researchers completed training to ensure reliability across assessors.

Researchers graded CIPN severity via the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) sensory neuropathy subscale Version 4.0 categorised: Grade 0 'no symptoms', Grade 1 'asymptomatic, not interfering with daily function', Grade 2 'moderate symptoms, limiting daily function', Grade 3 'severe symptoms, limiting daily function and self-care', and Grade 4 'disabling' [105]. Nerve conduction studies (NCS) were undertaken to record maximal amplitude of lower limb tibial and sural nerves, using methodology as reported in previous studies [214].

3.2.5 Patient-reported outcome measures

The European Organisation of Research and Treatment of Cancer Quality-of-Life Questionnaire-Core (EORTC-QLQ-CIPN-20) is a 20-item validated questionnaire assessing motor, sensory and autonomic PN symptoms, rating each item on a 4-point Likert scale from 1 ‘not at all’ to 4 ‘very much’, converted to a 0-100 scale, with higher scores indicating more severe CIPN [138].

The Survey of Autonomic Symptoms (SAS) questionnaire is an 11-item questionnaire to measure autonomic symptoms based on two scores including total number of symptoms (SAS symptom score), and total impact score (SAS impact score) graded from 1 ‘least severe’ to 5 ‘most severe’ for each reported symptom [168]. Questions assessing the following autonomic symptom domains were grouped: sudomotor, gastrointestinal, vasomotor, orthostatic, and urinary function. The total number of symptoms is calculated as the sum of total reported symptoms, whilst the total impact score is the sum of the total burden from each reported symptom. The SAS domains have been well validated with other measures of autonomic function, displaying strong correlations with Autonomic Symptom Profile (ASP) domains and QSART measurements [168]. Male specific questions (Question 20 EORTC-QLQ-CIPN20; question 12 SAS) were omitted from analysis.

The Pain Numeric Rating Scale (PNRS) was utilised to assess the worst neuropathic pain that participants have experienced in the last 24 hours prior to testing. The scale ranges from 0 to 10, with ‘0’ representing ‘no pain at all’ and 10 representing ‘the worst pain possible’ [215].

3.2.6 Statistical Analyses

All analyses were conducted using SPSS Statistics Software V27 (IBM; Armonk, NY) and followed the STROBE statement for observational studies [216]. Normality of data was assessed using the Shapiro-Wilk test. Normally distributed data ($p>0.05$) were presented as mean ± standard deviation (SD), while non-normally distributed data ($p<0.05$) were presented as medians and interquartile range (IQR). Independent sample t-tests or Mann-Whitney U tests were used, for normally and non-normally distributed data, respectively, to explore mean differences between clinical, neurophysiological and CIPN outcome measure scores of the two cohorts (participants with ESC dysfunction versus no-ESC dysfunction). The associations between ESC values via Sudoscan, clinical characteristics, CIPN, pain and autonomic outcome measures were calculated using Pearson's or Spearman's correlation coefficients for normally and non-normally distributed data, respectively. Where specified, Bonferroni correction was applied, modifying the significance level from $p<0.05$ to $p<0.0063$ due to the number of contrasts. Finally, we examined the ability of ESC values and clinical characteristics to predict patient scores on CIPN severity and autonomic outcome measures using linear regression. The independent variables were age, sex, BMI, hand ESC and feet ESC. Dependent variables were scores of patient-reported outcome measure (EORTC-QLQ-CIPN20), neurological examination score (TNSc), sural and tibial amplitudes as well as sudomotor dysfunction of the autonomic outcome measure (SAS). The independent variables of the model were checked for multicollinearity. Linear regression was bootstrapped to account for non-normal distribution of the residuals and to produce robust confidence intervals.

3.3 RESULTS

3.3.1 Demographics and clinical history

A total of 130 neurotoxic chemotherapy-treated participants were assessed cross-sectionally at a median of 6.0 (3.0 – 12.0) months post-treatment completion. Sixty-seven percent were female (n=87), and the median age at the time of assessment was 58.6 years (47.6 – 66.5) (Table 3.3.1). The most common cancer types were breast (33%, n=43) and gynaecological (21%, n=27) cancers. The most common chemotherapy types were taxanes (61%, n=79) and platinum-based (24%, n=31). Clinical and demographic information is displayed in Table 3.3.1.

	Total cohort (n=130)	
	n	**%**
Sex, Female	87	67
Cancer types		
Breast	43	33
Gynaecological	27	21
Haematological	19	15
GI/Colorectal	14	11
Testicular	12	9
Other (Prostate, Pancreatic & Urothelial)	15	11
Chemotherapy types		
Taxane	79	61
Platinum-based	31	24
Bortezomib	17	13
Thalidomide	2	1.5
Nab-paclitaxel	1	0.5
Cancer stage of solid tumours		
I	8	6
II	28	22
III	34	26
IV	38	29
Non-solid (no stage)	19	15
Undefined	3	2
	Median	**IQR (25^{th} – 75^{th} percentile)**
Age (years)	58.6	47.6 – 66.5
BMI (kg/m^2)	27.1	23.8 – 30.6
Months since treatment completion	6.0	3.0 – 12.0

Table 3.3.1. Clinical and demographic characteristics of participants.

3.3.2 Chemotherapy-induced peripheral neuropathy profile

Overall, 28% of participants (n=37) had no CIPN symptoms (Grade-0) at the time of assessment using a clinically-graded scale (NCI-CTCAE), while 72% (n=93) were graded with CIPN symptoms of any severity (Grade ≥1). Twenty three percent were classified with mild CIPN (Grade-1; n=30), 42% with moderate (Grade-2, n=54), and 7% with severe CIPN (Grade-3, n=9). Using the neurological examination score (TNSc), the median score of the cohort was 3.5(2.0-6.0) (out of 24). From the TNSc score, 62% had reduced pinprick sensation (Score≥1, n=81), 22% had reduced vibration sensation (Score≥1, n=29), 73% had abnormal tendon reflexes (Score≥1, n=95) and none had reduced ankle plantar flexor strength (Score=0, n=130). Seventeen percent (n=22) reported any nerve pain (≥1/10) in the 24 hours prior to the study visit. Based on the patient-reported autonomic neuropathy outcome measure (SAS), completed by 81 participants, 52% reported having sudomotor dysfunction (n=42), 45% reported vasomotor dysfunction (n=36), 36% reported orthostatic dysfunction (n=29), 28% reported gastrointestinal dysfunction (n=20) and 11% reported urinary dysfunction (n=9).

Participants with CIPN were older ($p<0.001$) and had significantly greater CIPN severity score on multiple CIPN outcome measures versus those without CIPN (Table 3.3.2), including the patient-reported outcome (EORTC-QLQ-CIPN20 ($p<0.001$)) and neurological examination scores (TNSc ($p<0.001$)). Sural and tibial amplitudes were significantly reduced in participants with CIPN compared to those without CIPN (all $p<0.002$) (Table 3.3.2). In patients with CIPN, higher scores on the patient-reported outcome measure (EORTC-QLQ-CIPN20) correlated with higher autonomic outcome measure (SAS) symptom score ($r=0.48$) and total impact score ($r=0.47$) (both $p<0.001$). However, despite this, there was no significant difference in the autonomic outcome measure (SAS) domain scores between

patients with and without CIPN (all p>0.0063) (Table 3.3.2). ESC values via Sudoscan, including average hand ESC and feet ESC, were also not statistically different between participants with or without CIPN (all p>0.0063) (Table 3.3.2).

Assessment tools	No CIPN (NCI-CTCAE grade 0) (n=37)		CIPN (NCI-CTCAE grade ≥ 1) (n=93)		P-value
	Median	IQR (25-75th percentile)	Median	IQR (25-75th percentile)	
Clinical characteristics					
Age (years)	**49**	**35.7-55.2**	**61.1**	**53.5-68.6**	**<0.001**
BMI (kg/m^2)	26.4	22.6-30.5	27.1	23.8-30.6	0.40
CIPN outcome measures					
EORTC-QLQ-CIPN20	**0**	**0-1.8**	**14.0**	**8.8-22.8**	**<0.001**
TNSc	**1**	**0-3**	**5**	**3-7**	**<0.001**
Neurophysiological measurements					
Tibial amplitudes (mV), mean (SD)*	**12.7**	**4.6**	**9.7**	**4.3**	**0.002**
Sural amplitudes (μV)	**18**	**10.3-22.0**	**7.5**	**4.5-12.0**	**<0.001**
Pain measures					
PNRS	0	0-0	0	0-0	0.02
Autonomic outcome measures					
Symptom score	1	0-2	2	1.0-3.3	0.02
Total impact score	1	0-5	4	1-8	0.03
Orthostatic dysfunction	0	0-0	0	0-1	0.29
Sudomotor dysfunction	0	0-1	1	0-1	0.03
Vasomotor dysfunction	0	0-1	1	0-1	0.04
Gastrointestinal dysfunction	0	0-0	0	0-1	0.42
Urinary dysfunction	0	0-0	0	0-0	0.67
Electrochemical Skin Conductance via Sudoscan					
Hands ESC (average)	70	60.8-78.0	66	51.8-73.5	0.17
Feet ESC (average)	74.5	69.5-79.8	71.0	56.3-78.3	0.04

Table 3.3.2. Comparison of neuropathy outcomes between patients with ESC and no ESC dysfunction. p<0.0063 was considered significant due to Bonferroni correction.

***Indicates p-values using independent sample t-tests.**

3.3.3 ESC dysfunction and CIPN severity in cancer survivors exposed to neurotoxic chemotherapy.

Of the 93 participants with CIPN, 49% (n=46) had any ESC dysfunction, while 51% (n=47) had no dysfunction. Thirty nine percent (n=36) experienced ESC dysfunction in their hands, 30% (n=28) experienced ESC dysfunction in their feet while 19% (n=18) had dysfunction in both their hands and feet. There were no significant correlations between clinical, neurophysiological, or autonomic outcome measures with ESC values for either hands or feet (all $p>0.0063$) (Table 3.3.3), including the patient-reported outcome measure (EORTC-QLQ-CIPN20) and the neurological examination score (TNSc) (Fig. 3.3.1).

CIPN severity from patient-reported outcome (EORTC-QLQ-CIPN20), clinically-graded scale (NCI-CTCAE) and neurological examination score (TNSc) were not significantly different between participants with and without ESC dysfunction (all $p>0.0063$) (Table 3.3.4). Neurophysiological measurements did not significantly differ between participants with and without ESC dysfunction ($p>0.0063$). None of the individual items or total scores of the autonomic outcome measure were different between participants with and without ESC dysfunction ($p>0.0063$) (Table 3.3.4).

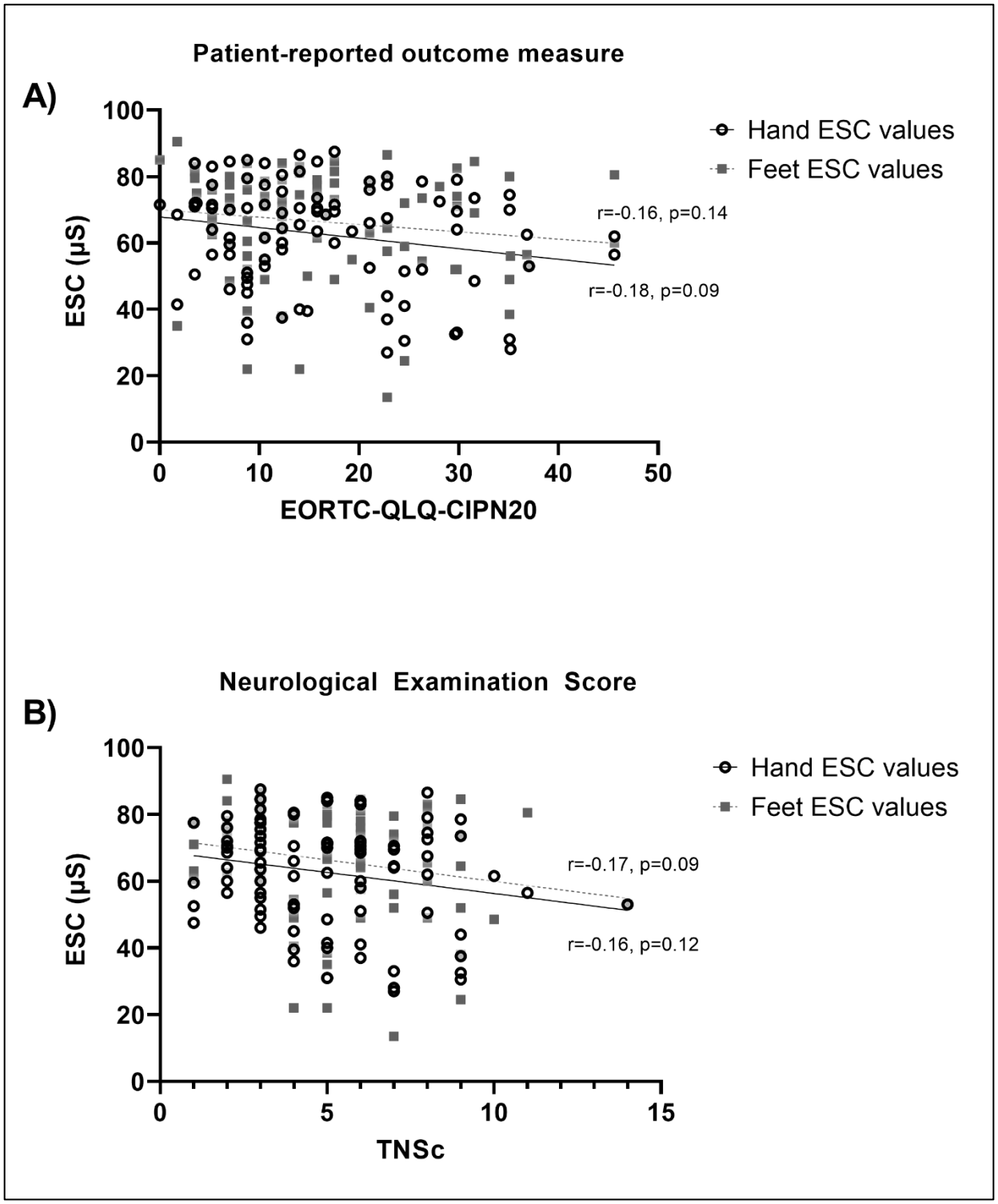


Figure 3.3.1. Scatterplot of ESC values (via Sudoscan) of the hands and feet with (A) patient-reported outcome measure (EORTC-QLQ-CIPN20) and (B) neurological examination score (TNSc). The unbroken line represents the line of best fit for hand ESC, and broken line represents feet ESC.

Assessment tools		Hands ESC (n=93)	Feet ESC (n=93)
Clinical characteristics			
	Age (years)	r_s=-0.19, p=0.06	r_s=-0.25, p=0.02
	BMI (kg/m^2)	r_s=0.14, p=0.19	r_s=-0.02, p=0.88
Neurophysiological measurements			
	Tibial amplitudes (mV)*	r=0.15, p=0.20	r=0.15, p=0.21
	Sural amplitudes (μV)	r_s=0.14, p=0.23	r_s=0.24, p=0.04
CIPN outcome measures			
	TNSc	r_s=-0.16, p=0.12	r_s=-0.17, p=0.09
	EORTC-QLQ-CIPN 20	r_s=-0.18, p=0.09	r_s=-0.16, p=0.14
	NCI-CTCAE	r_s=-0.19, p=0.07	r_s=-0.17, p=0.09
Pain measures			
	PNRS	r_s=0.01, p=0.96	r_s=-0.21, p=0.05
Autonomic outcome measures			
	Symptom score	r_s=0.02, p=0.91	r_s=-0.12, p=0.36
	Total impact score	r_s=-0.04, p=0.79	r_s=-0.12, p=0.35
	Orthostatic dysfunction	r_s=0.08, p=0.56	r_s=-0.03, p=0.85
	Sudomotor dysfunction	r_s=-0.09, p=0.49	r_s=-0.20, p=0.13
	Vasomotor dysfunction	r_s=-0.10, p=0.48	r_s=-0.06, p=0.66
	Gastrointestinal dysfunction	r_s=0.01, p=0.97	r_s=-0.14, p=0.31
	Urinary dysfunction	r_s=0.04, p=0.79	r_s=0.02, p=0.87

Table 3.3.3. Associations between clinical characteristics, neurophysiological measurements and CIPN outcome measures with hands and feet ESC in participants with CIPN. p<0.0063 was considered significant due to Bonferroni correction. The use of Pearson's r or Spearman's r_s was denoted in the table.

Assessment tools	ESC dysfunction (n=46)		No ESC dysfunction (n=47)		P-value
	Median	IQR (25-75th percentile)	Median	IQR (25-75th percentile)	
CIPN outcome measures					
EORTC-QLQ-CIPN20	16.2	8.8-27.1	14.0	5.3-17.5	0.07
NCI-CTCAE	2	1.75-2	2	1-2	0.02
TNSc	5	3-7	4	3-6	0.16
Clinical characteristics					
Age (years)	62.2	57.0-67.7	60.3	50.8-69.3	0.45
BMI (kg/m^2)	26.9	22.8-30.7	27.2	24.3-30.6	0.45
Neurophysiological measurements					
Tibial amplitudes (mV), mean (SD)*	8.7	3.9	10.6	4.4	0.06
Sural amplitudes (μV)	7.3	3.4-11.1	8	5.5-13.3	0.10
Pain measures					
PNRS	0	0-3	0	0-0	0.12
Autonomic outcome measures					
Symptom score	2	0.5-4.5	2	1.5-3.0	0.79
Total impact score	5	0.5-8.5	4	2.0-7.5	0.86
Orthostatic dysfunction	0	0-1	0	0-1	0.43
Sudomotor dysfunction	1	0-1	0	0-1	0.23
Vasomotor dysfunction	1	0-1	1	0-1	0.90
Gastrointestinal dysfunction	0	0-1	0	0-1	0.95
Urinary dysfunction	0	0-0	0	0-0	0.23

Table 3.3.4. Comparison of neuropathy outcomes between CIPN participants (NCI-CTCAE ≥1, n=93) with ESC and no ESC dysfunction. p<0.0063 was considered significant due to Bonferroni correction. *Indicates p-values using independent sample t-tests.

3.3.4 Predictive models of CIPN severity

Linear regression analyses revealed that age was a significant predictor of all clinically-graded and patient-reported CIPN severity measures, including the patient-reported outcome (EORTC-QLQ-CIPN20, p=0.002) and the neurological examination score (TNSc, p=0.001), but not of patient-reported sudomotor function (p>0.05) (Table 3.3.5). Sex was a predictor of sural amplitudes (p=0.001), while BMI was a predictor of tibial amplitudes (p=0.003) (Table 3.3.5). Neither hand ESC nor feet ESC values could predict CIPN severity with any measures, including the sudomotor dysfunction sub-scale of the autonomic outcome measure (all p>0.05) (Table 3.3.5).

Dependent variable	Independent variables	Parameter estimate [95% Confidence Interval]	P-value
CIPN outcome measures			
EORTC-QLQ-CIPN20	**Age**	**0.24 [0.09, 0.40]**	**0.002**
	Sex	0.04 [-4.6, 3.9]	0.99
	BMI	-0.02 [-0.4, 0.4]	0.93
	Hand ESC	-0.13 [-0.31, 0.04]	0.12
	Feet ESC	-0.02 [-0.21, 0.17]	0.82
TNSc	**Age**	**0.11 [0.08, 0.13]**	**0.001**
	Sex	-0.73 [-1.6, 0.11]	0.10
	BMI	-0.009 [-0.09, 0.08]	0.79
	Hand ESC	-0.02 [-0.06, 0.02]	0.39
	Feet ESC	-0.009 [-0.05, 0.02]	0.61
Neurophysiological measurements			
Sural Amplitudes	**Age**	**-0.26 [-0.41, -0.12]**	**0.001**
	Sex	**6.2 [3.06, 9.47]**	**0.001**
	BMI	-0.04 [-0.38, 0.27]	0.83
	Hand ESC	-0.16 [-0.38, 0.07]	0.12
	Feet ESC	0.14 [-0.01, 0.27]	0.07
Tibial Amplitudes	**Age**	**-0.14 [-0.20, -0.08]**	**0.001**
	Sex	1.48 [-0.23, 3.26]	0.10
	BMI	**-0.18 [-0.33, 0.0002]**	**0.03**
	Hand ESC	0.07 [-0.01, 0.16]	0.10
	Feet ESC	-0.04 [-0.12, 0.03]	0.28
Autonomic outcome measure			
SAS - Sudomotor dysfunction	Age	-0.005 [-0.02, 0.006]	0.37
	Sex	0.34 [-0.10, 0.70]	0.07
	BMI	-0.003 [-0.03, 0.02]	0.84
	Hand ESC	0.001 [-0.02, 0.02]	0.92
	Feet ESC	-0.01 [-0.03, 0.008]	0.33

Table 3.3.5. Linear regression analyses of Sudoscan ESC values and clinical characteristics to predict CIPN severity, neurophysiological outcomes or sudomotor dysfunction. $p<0.05$ indicates statistical significance.

3.4 DISCUSSION

There is a need to establish reliable and easily implementable measures of nerve dysfunction among patients treated with neurotoxic chemotherapy. In particular, assessment of autonomic neuropathy in the context of CIPN has been inadequately explored. This study investigated an easily implementable measure of autonomic and small nerve fibre neuropathy associated with patient-reported and clinical measures of CIPN severity. However, hands and feet Sudoscan ESC values were not associated with CIPN measures or autonomic outcome measures. More so, ESC values failed to predict CIPN severity or autonomic neuropathy using linear regression analyses.

While there are a range of assessment tools for large fibre neuropathy in chemotherapy-treated patients, assessment of small fibre neuropathy and autonomic dysfunction remains limited [133]. IENFD, assessed via skin biopsy, provides a diagnostic tool for small fibre neuropathy. However, while some studies have revealed reduced IENFD with neurotoxic chemotherapy, others have not found reduced IENFD following treatment [133, 217]. Further, routine use of skin biopsy in clinical settings is not practical. Accordingly, other methods have been developed to attempt to assess small nerve fibre integrity and autonomic function. These include measurement of sudomotor activity via ESC as a measure of electrically induced chloride ion conductance from the sweat glands on the skin surface [187]. However, it remains unclear if ESC reflects sudomotor fibre activity directly or is largely a measure of sweat gland activity [218].

Despite this lack of consensus, reduced ESC values have been found across a range of peripheral neuropathies, particularly in diabetic neuropathy [219]. Similarly, multiple studies have identified reduced ESC in hands and feet in chemotherapy-treated patients [206, 212,

213]. In concordance with these studies, we found evidence of reduced ESC values in a large proportion of our CIPN cohort, however, reduced ESC values were not associated with any CIPN outcome measures. More so, ESC values were not predictive of CIPN severity or autonomic function using linear regression analyses. Accordingly, our findings do not provide support for the utility of ESC measurement as a diagnostic tool in patients with established CIPN. In contrast, Saad et al. [206] examined longitudinal change in ESC values during neurotoxic chemotherapy treatment but did not examine the long-term effect of chronic CIPN on ESC values, as in the present study. Two smaller studies have demonstrated a link between CIPN severity and ESC values in 18 bortezomib-treated patients [213] and pain severity and reduced hands and feet ESC values in 36 oxaliplatin-treated patients [212]. In contrast, the current study showed no association of pain symptoms with reduced or increased hands or feet ESC values. Accordingly, the findings of these previous studies do not align with the results identified in the current study.

The inability for ESC values to accurately predict clinically-graded and patient-reported CIPN severity and autonomic function may relate to a lack of specificity in the ESC measurement. Initially, ESC values were used as an assessment of sweat function [187-191]. Gradually, it transitioned into a measure of sudomotor function [187-191] and finally into a measure of autonomic and small nerve fibre function in patients with underlying medical conditions, such as diabetes [219] and cystic fibrosis [187-191]. However, there remains a lack of evidence for a direct link between ESC and small nerve fibre function, as well as discrepancies with normative datasets, which greatly limits its clinical utility [209]. Overall, this study used a range of methods to measure CIPN severity, including patient-reported, clinically-graded, objectively measured, and neurophysiological measures. However, we did not have access to more objective quantification of autonomic or small

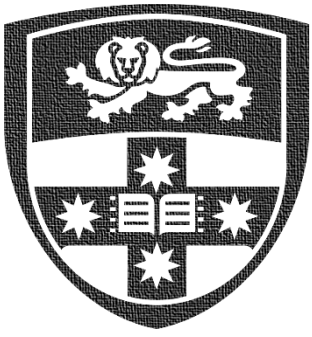
nerve fibre neuropathy such as skin biopsies, QSART [204] or autonomic reflex screen, and assessed autonomic neuropathy via a subjective patient-reported questionnaire. In our study, neither the autonomic outcome measure total score nor sub-scale scores were associated with ESC values. However, the SAS is a subjective tool for quantifying autonomic dysfunction and may be limited in this context due to the overlap between symptoms of CIPN and other effects of cancer and its treatment. Furthermore, the cross-sectional study design did not allow for examination of changes in ESC values and CIPN severity over time, including accounting for pre-treatment values. Additionally, our sample included a range of different cancer and treatment types which makes it challenging to determine if there were specific patterns of ESC changes in particular patient cohorts.

3.5 CONCLUSION

ESC values measured by Sudoscan were not associated with CIPN severity using multiple outcome measures and were not associated with patient-reported nor autonomic neuropathy measures. The discrepancies in the findings of prior studies and the inability of ESC values to predict clinically-graded and patient-reported CIPN or autonomic dysfunction may limit its utility in the clinic for assessing chemotherapy-treated patients. The results of our study highlight the need for a better measure of small nerve fibre and autonomic neuropathy with greater sensitivity in the context of CIPN. Understanding CIPN phenotype may inform appropriate treatment strategies to reduce neuropathy burden and promote a better quality-of-life for affected patients.

CHAPTER 4

Impact of Upper-Limb Dysfunction on Cancer Survivors with Chemotherapy-Induced Peripheral Neurotoxicity



ABSTRACT

Purpose. Upper-limb symptoms are often reported in the context of chemotherapy-induced peripheral neurotoxicity (CIPN), but objective quantification of functional deficits is often lacking. We examined and compared a range of neurophysiological and functional assessments of the upper-limb in the assessment of CIPN severity.

Methods. Cross-sectional assessment of neurotoxic chemotherapy-treated patients was undertaken using patient-reported and clinically-graded CIPN measures. Upper-limb functional assessments comprised of assessing fine motor skills, sensory perception, and neurophysiological measures of the median nerve. Group comparisons between participants who reported absence or presence of upper-limb functional deficits were investigated.

Results. 60 participants who were 11.5 (IQR=4.0-26.0) months post-neurotoxic chemotherapy treatment reported CIPN. 65% (n=39) reported upper-limb CIPN symptoms. Reduction in fine motor skills, sensory perception and median nerve SNAP amplitudes were associated with higher CIPN severity. Participants who self-reported presence of upper-limb functional deficits had worse CIPN severity across all measures, compared to participants who reported no upper-limb functional deficits.

Conclusions. Participants who reported upper-limb symptoms and functional deficits had worse CIPN severity and quality-of-life. There is a high burden of upper-limb dysfunction long after neurotoxic chemotherapy treatment cessation. Focus on research into supportive care and rehabilitation options to improve upper-limb function is warranted to improve patient quality-of-life.

4.1 INTRODUCTION

Chemotherapy-induced peripheral neuropathy, or CIPN, is a common side-effect resulting from treatment with taxanes, platinum-based agents, bortezomib, thalidomide and vinca-alkaloid chemotherapies [94]. CIPN affects both large sensory nerve fibres and small sensory nerve fibres including thinly myelinated A-delta (Aδ) fibres and unmyelinated C-fibres [201], leading to symptoms of numbness, tingling, and neuropathic pain [199]. Chronic CIPN symptoms are lower-limb predominant [38]. However, depending on the chemotherapy agent, a large proportion of patients also report upper-limb symptoms, including functional deficits in hand motor control, writing, typing, and buttoning clothes [220-222]. During neurotoxic chemotherapy, a similar proportion of patients report lower- and upper-limb symptoms [35], highlighting the importance of assessing upper-limb dysfunction given the significant functional consequences.

However, there has been a lack of focus on upper-limb assessments and the implications of upper-limb dysfunction on the quality-of-life of cancer survivors. The most common assessment modalities are patient-reported outcome measures (PROMs), clinician-graded scales, as well as neurophysiological measures such as nerve conduction studies (NCS) which provide information on axonal damage [103]. However, knowledge on the correspondence of upper-limb symptoms and functional deficits with these tools remain limited.

While NCS can quantify damage to large sensory axons, it lacks the ability to assess damage to small nerve fibres [133]. A potential assessment of upper-limb small nerve fibre dysfunction may be Stimulated Skin Wrinkling (SSW) [181], which utilises topical anaesthetic to induce skin wrinkling of the fingertips as a result of vasoconstriction of the glabrous skin mediated by sympathetic or small nerve fibres [183]. Reductions in SSW have

been identified in diabetic neuropathy [186], carpel tunnel syndrome (CTS) [223] and human immunodeficiency virus (HIV) neuropathy [185] and linked to small fibre neuropathy.

In this study, we aimed to characterise the impact of CIPN on upper-limb function and compare a range of neurophysiological and functional assessments to determine their association with self-reported upper-limb functional deficits in neurotoxic chemotherapy-treated patients.

4.2 METHODS

4.2.1 Participants

Participants who were aged ≥18-years and completed neurotoxic chemotherapy treatment (including taxanes, platinum-based agents, bortezomib, vinca alkaloids and thalidomide) were eligible and assessed on a single occasion. The study was approved by Sydney Local Health District (RPAH zone) Human Research Ethics Committee and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each participant. Clinical data were retrieved from medical records.

4.2.2 Clinically-graded CIPN

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) sensory neuropathy subscale Version 4.0 was used by researchers to clinically grade CIPN severity based on 4 categories: No symptoms = Grade 0; Asymptomatic, symptoms not interfering with activities of daily life = Grade 1; Moderate symptoms that interfere with activities of daily life = Grade 2; Severe symptoms that limit activities of daily life and self-care = Grade 3; Disabling symptoms = Grade 4 [105].

4.2.3 Neurologically-graded CIPN

Neurologically-graded CIPN severity was assessed using the Total Neuropathy Score-clinical version (TNSc©, John Hopkins University). It is a 6-domain composite tool that assesses patient-reported sensory and motor symptoms; and clinically-rated upper and lower-limb vibration and pinprick sensation, deep tendon reflexes and strength. Each domain is graded between 0 (normal) and 4 (severely abnormal) and all 6 domains sum to a total score between 0 (no CIPN) to 24 (severe CIPN) [109, 110].

4.2.4 Upper-limb functional assessments

Upper-limb sensory perception was assessed using the Grating Orientation Task (GOT) with Johnson-Van Boven-Philips (JVP) domes (Stoelting Co., IL, USA) with grating, between 0.35 mm and 12 mm. The domes were pressed on the distal tip of digit 2 of the dominant hand, with horizontal or vertical grating placement. Twenty random trials were administered, and participants had to identify the smallest grating size (mm) they could discriminate, with ≥ 75% accuracy [178].

Von Frey Monofilaments (Optihair2-Set, Marstock, Nervtest, Germany) assessed sensory perception via exertion of forces between 0.125 and 512 millinewtons (mN) upon bending. The monofilaments were applied on the distal tip of digit 2 of the dominant hand. To identify the mechanical detection threshold, 5 trials were administered in a sequence of descending and ascending stimulus intensities [179].

Assessment of fine motor skills was performed using the Grooved Pegboard task. With their dominant hand, participants were instructed to place 25 pegs into grooved holes of different orientations. The average time was calculated across two trials [180].

4.2.5 Patient-reported CIPN severity and upper-limb symptoms

The European Organisation of Research and Treatment of Cancer Quality-of-Life Questionnaire-Core (EORTC-QLQ-CIPN20) is a validated patient-reported outcome measure (PROM) comprising 20 items, with a 4-point Likert scale ranging from 1 ‘not at all’ to 4 ‘very much’. The score was converted to a 0-100 scale, with higher scores are indicative of more severe CIPN [138]. The male specific item was omitted from the final score (Q20).

Participants were characterised by the absence or presence of **upper-limb functional deficits** according to responses of "not at all" or "a little bit/quite a bit/very much", respectively, on items assessing difficulty writing (Q11) and difficulty manipulating small objects with the fingers (Q12). A sum score of these two items (Q11 & 12; score range: 2-8) was used as a composite measure of patient-reported upper-limb functional deficit severity.

Participants completed the 15-item Chronic Acquired Polyneuropathy Patient-Reported Index (CAP-PRI) to measure health-related quality-of-life (HRQOL) related to CIPN. The total score ranges between 0 (no impact of CIPN on HRQOL) and 30 (worst impact of CIPN on HRQOL) [167].

Patient-reported pain scores were measured using a modified version of the Pain Numeric Rating Scale (PNRS). Participants were asked to rate the intensity of neuropathic pain in the last 7 days prior to testing from 0 "no pain" to 10 "worst pain possible" [169]. Participants were sub-grouped into non-painful and painful CIPN groups according to PNRS scores of 0 or ≥1.

Researchers conducted a semi-structured qualitative interview with participants to assess CIPN severity [136]. Participants were asked "are the nerve symptoms worse in the hands or the feet?". Responses to this question were transcribed to "worse in hands", "worse in feet" or "same" for statistical analyses.

4.2.6 Neurophysiological measures

4.2.6.1 *Upper-limb neurophysiological measures*

Neurophysiological assessment of both sensory and motor components of the median nerve were undertaken, using a computerised system (QTracS–Institute of Neurology, Queen Square, UK), a constant current stimulator (Digitimer DS5 Stimulator–Digitimer Ltd., Hertfordshire, UK) and a low noise amplifier [224]. The median nerve was stimulated at the wrist with maximal compound motor action potential (CMAP) recorded at the Abductor Pollicis Brevis (APB) muscle and maximal sensory nerve action potential (SNAP) from digit 2 of the dominant hand [197]. Values were compared to lower-limit of age-matched normative values, as reported previously [193, 214].

4.2.6.2 Lower-limb neurophysiological measures

Nerve conduction studies were also undertaken in the lower-limb sural nerve using the Nicolet® VikingQuest™ (Natus® Neurology), stimulating at the posterior calf of the left foot and recording at the lateral malleolus [101]. The sural nerve amplitude was then compared to lower limit of age-matched normative values [194, 214].

4.2.6.3 Upper-limb Stimulated Skin Wrinkling (SSW) assessment

The distal digit tips of the 3rd, 4th and 5th digits [184] of the non-dominant hand were sterilised with alcohol wipes and photographed (iPad Pro, Model MHQV3X/A) at a distance of approximately 20 cm away from the fingertips against a blue background, consistent with previous studies [182, 184-186]. EMLA cream (lidocaine 2.5% and prilocaine 2.5%, AstraZeneca) sufficient to thickly cover each distal digit pulp was applied (~1g) and sealed with transparent film tape (Opsite Flexifix) for 30 minutes [182, 186]. Following 30-minutes, the cream was removed, and photographs were taken and the number of wrinkles per digit

were graded independently by two assessors based on a previously published scale [182, 184-186] : **Grade 0** – wrinkling absent; **Grade 1** – just perceptible wrinkling with the fingertip not completely smooth; **Grade 2** – 2 or less lines of superficial wrinkling on the fingertip; **Grade 3** – 3 or more lines of deep wrinkling on the fingertip; **Grade 4** – wrinkling completely distorts the pulp of the fingertip (Fig. 4.2.1). Grades were averaged for each assessor. An average score of < 3 was noted as abnormal stimulated skin wrinkling (SSW) while a score of ≥ 3 was noted as normal SSW, as per prior studies [185, 186]. If the independent grading between each assessor differed, an additional grading was done based on the post-EMLA photographs by a third assessor.

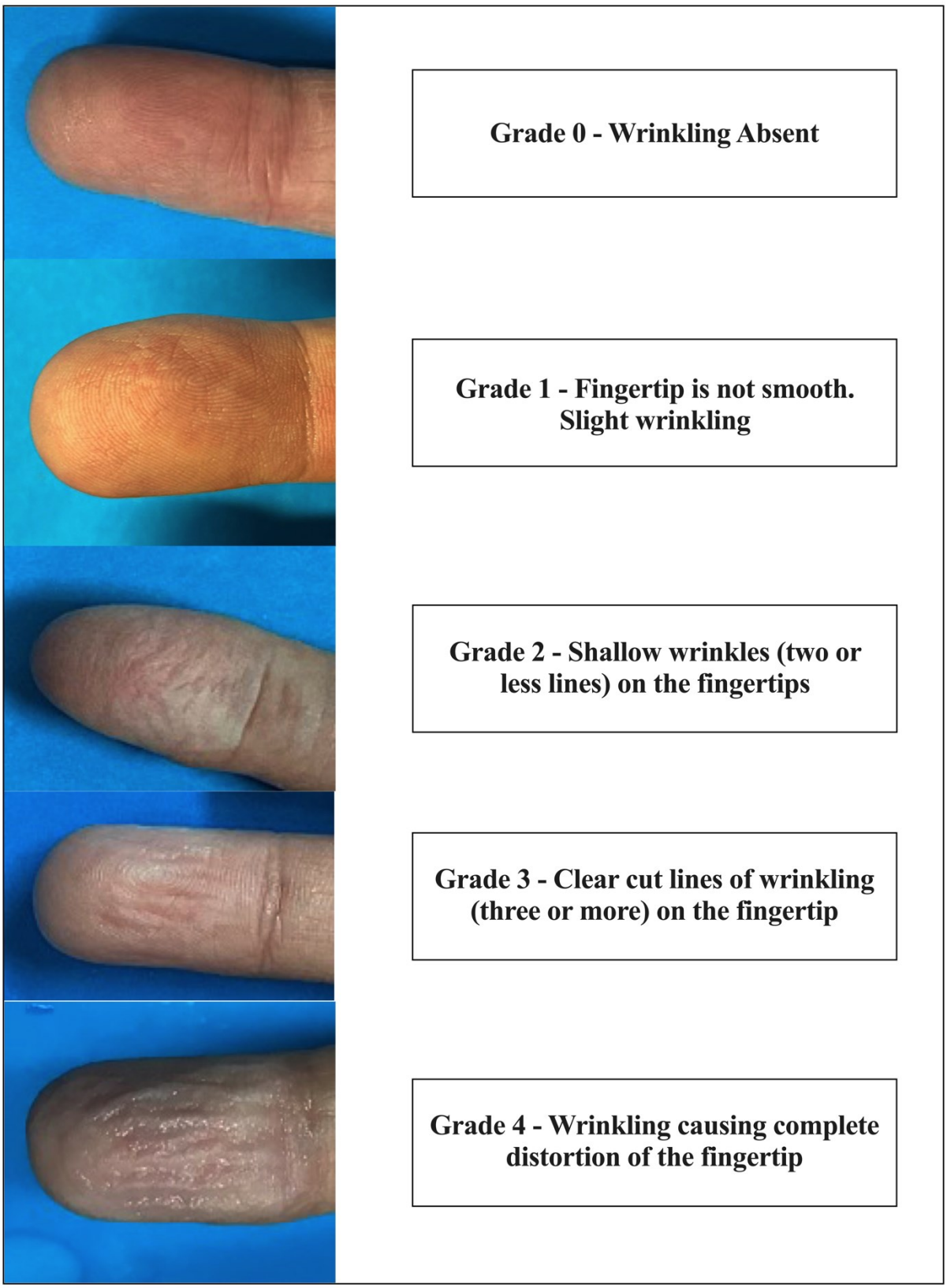


Figure 4.2.1. Grading scale based on scale utilised in [185, 186]. Original photographs utilised.

4.2.7 Statistical Analyses

All statistical analyses were completed using SPSS Statistics Software V27 (IBM; Armonk, NY). The Shapiro-Wilk test was applied to assess the normality of the data. Non-normally distributed data ($p<0.05$) were presented as medians and interquartile range (IQR; 25%-75%), while normally distributed data ($p>0.05$) was presented as mean ± standard deviation (SD).

The associations between all upper-limb assessments, clinical characteristics and CIPN outcome measures were done using Spearman's or Pearson's correlation coefficients, for non-normally and normally distributed data, respectively. Group comparisons were done using Mann-Whitney U tests or independent sample t-tests for non-normally and normally distributed data, respectively.

4.3 RESULTS

4.3.1 Demographics and clinical history

A total of 68 participants with a mean age of 61±12 (SD) years were assessed cross-sectionally 8.5(IQR=4.0-26.0) months following completion of neurotoxic chemotherapy. Eight of 68 participants (12%) reported no CIPN at the time of assessment and were excluded from further analyses, while the remaining 60 (88%) with at least Grade 1 CIPN were included in the analyses.

These 60 participants had a mean age of 62±12 years and were assessed 11.5(4.0-26.0) months post-neurotoxic chemotherapy treatment. Seventy-three percent (n=44) were female, mostly diagnosed with gynaecological (40%, n=24), gastro-intestinal (17%, n=10) or haematological cancers (20%, n=12). The most common chemotherapy drugs administered were taxanes (57%, n=34), followed by platinum-based drugs (21%, n=13) and bortezomib (18%, n=11) (Table 4.3.1). All clinical and demographic information is found in table 4.3.1.

	Participants with CIPN (n=60)
	n (%)
Female sex	44 (73%)
Cancer types	
Breast	5 (8%)
Gynaecological (Cervical, Endometrial & Ovarian)	24 (40%)
Haematological (Myeloma & Hodgkin's Lymphoma)	12 (20%)
GI/Colorectal & Pancreatic	10 (17%)
Testicular & Prostate	4 (7%)
Other	4 (7%)
Missing	1 (1%)
Chemotherapy types	
Taxane	34 (57%)
Platinum	13 (21%)
Bortezomib	11 (18%)
Vincristine	1 (2%)
Thalidomide	1 (2%)
Cancer stage of solid tumours	
0	1 (2%)
I	7 (12%)
II	13 (22%)
III	18 (30%)
IV	8 (13%)
Non-solid (no stage)	12 (20%)
Undefined	1 (1%)
Age (years)* (mean, SD)	62.0 ± 12.0
BMI (kg/m^2)* (mean, SD)	26.6 ± 5.7
Months since treatment completion (median, IQR)	11.5 (4.0-26.0)

Table 4.3.1. Clinical and demographics table of participants.

4.3.2 Patient-reported upper-limb symptoms

Overall, 65% of participants (n=39/60) reported upper-limb symptoms on the patient-reported outcome measure (EORTC-QLQ-CIPN20). Of these, half reported both numbness and tingling in the figures or hands (51%, n=20), while 33% (n=13) reported only numbness and 16% (n=6) reported only tingling in the fingers or hands. When participants were asked on the qualitative interview if their symptoms were more severe in the upper or lower-limbs, only 15% (n=9/60) of participants reported that the neuropathy severity was worse in the upper-limb, while 73% (n=44) of participants reported more severe lower-limb neuropathy, and 12% (n=7) reported equal severity.

The additional burden of upper-limb symptoms on patient function was investigated. Of the participants who reported upper-limb symptoms, 56% reported difficulty manipulating small objects with their fingers (n=22/39) and 28% reported difficulty with writing (n=13) on the patient-reported outcome measure (EORTC-QLQ-CIPN20).

4.3.3 Upper-limb functional assessments of fine motor skills and sensory perception

Fine motor skills and sensory perception assessments were undertaken in all participants (n=60). Reduced sensory perception in the fingertips assessed via GOT correlated with higher neurologically-graded CIPN severity (TNSc; r_s=0.4; p=0.002) (Fig. 4.3.1A) and patient-reported pain scores (PNRS; r_s=0.3; p=0.02) (Fig. 4.3.1B). Reduced fine motor skills (Grooved Pegboard Task) also correlated with higher neurologically-graded CIPN severity (TNSc; r_s=0.3; p=0.04) (Fig. 4.3.1C). However, there were no significant correlations between fine motor skills or sensory perception with clinically-graded CIPN (NCI-CTCAE) and overall patient-reported CIPN severity, including patient-reported outcome (EORTC-QLQ-CIPN20) and health-related quality-of-life measure (CAP-PRI) (all p>0.05).

Correlations were also undertaken in the cohort reporting upper-limb CIPN symptoms (n=39). Similarly, reduced sensory perception (GOT threshold) was associated with worse neurologically-graded CIPN severity (TNSc; r_s=0.5, p=0.002). In addition, reduced fine motor skills (Grooved Pegboard Task) was significantly associated with worse health-related quality-of-life (CAP-PRI; r_s=0.5, p=0.003) and with reduced sensory perception (GOT threshold; r_s=0.5, p=0.003).

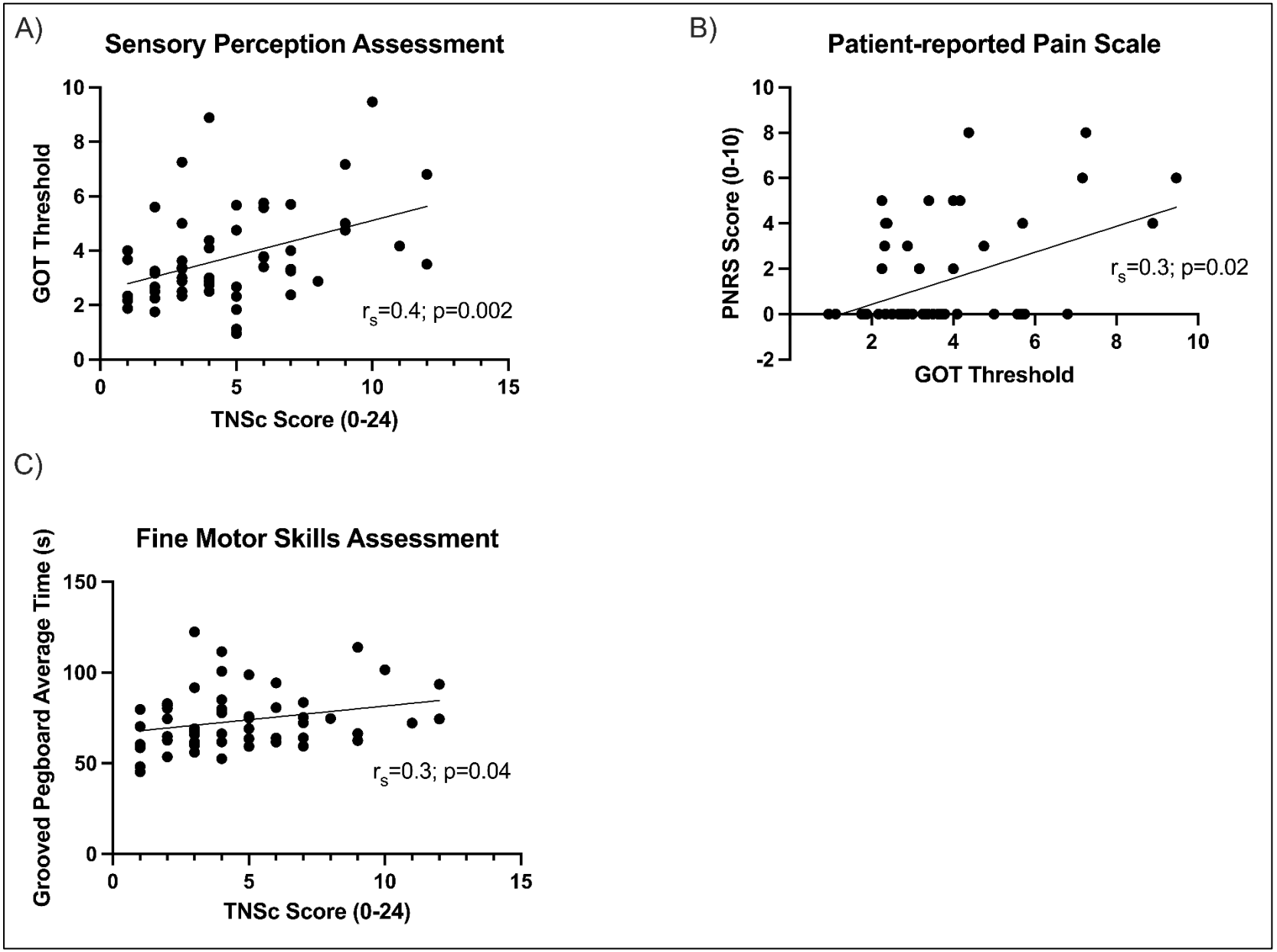

A)
Sensory Perception Assessment
GOT Threshold
TNSc Score (0-24)
r_s=0.4; p=0.002
B)
Patient-reported Pain Scale
PNRS Score (0-10)
GOT Threshold
r_s=0.3; p=0.02
C)
Fine Motor Skills Assessment
Grooved Pegboard Average Time (s)
TNSc Score (0-24)
r_s=0.3; p=0.04

Figure 4.3.1. Scatterplots of the upper-limb functional assessments, including sensory perception assessment (GOT Threshold) and (A) neurological examination score (TNSc) and (B) patient-reported pain scale . Figure (C) shows the scatterplot between fine motor skills assessment (Grooved Pegboard Time) and neurological examination score (TNSc). The solid line represents the line of best fit. r_s denotes the use of Spearman's correlations. $p<0.05$ indicates significance.

4.3.4 Upper-limb neurophysiological measures

Neurophysiological studies of the sensory and motor median nerve were conducted in 43 participants, with the remaining unavailable due to participant preference or discomfort, time or technical constraints.

The median nerve SNAP amplitude ranged between 4.0 microvolts (μV) and 66.0 μV and the median nerve CMAP amplitude between 3.0 millivolts (mV) and 14.0 mV. Despite the prevalence of upper-limb symptoms, only 12% (n=5) of participants had median nerve SNAP amplitudes below the lower limit of normal (LLN) values (Table 4.3.2). However, a higher proportion of participants had reduced lower-limb sensory amplitudes in the sural nerve (32%, n=14). Median nerve CMAP amplitudes were below the LLN in only 2% (n=1) of participants (Table 4.3.2).

Correlations between upper-limb neurophysiological measures with upper-limb functional assessments were investigated. Lower median nerve SNAP amplitude significantly correlated with higher neurologically-graded CIPN severity (TNSc; $p=0.003$) (Fig. 4.3.2A) and reduced sensory perception (GOT Threshold; $p=0.006$) (Fig. 4.3.2B). Upper and lower-limb sensory amplitudes (median nerve and sural nerve SNAP amplitudes) were also significantly correlated ($p<0.001$) (Fig. 4.3.2C). However, there were no significant correlations between median nerve SNAP or CMAP amplitudes with clinically-graded CIPN (NCI-CTCAE) or overall patient-reported CIPN severity as measured by the patient-reported outcome (EORTC-QLQ-CIPN20) and health-related quality-of-life measure (CAP-PRI) (all $p>0.05$).

Similarly, in participants reporting upper-limb CIPN symptoms who had undertaken neurophysiological measures (n=28), significant associations between median nerve SNAP

amplitudes and neurologically-graded CIPN severity (TNSc; r=-0.6, p=0.002), sensory perception (GOT threshold; r=-0.5, p=0.02) and lower-limb sensory amplitudes (sural nerve SNAP amplitude; r=0.6, p=0.001) were evident.

Neurophysiological Parameter	LLN	Age range (years)	Maximal amplitude (mean, SD)	Total cases (n)	Abnormal cases (n(%))
Upper-limb Neurophysiological Measures					
Median nerve SNAP amplitude	≥ 11 μV	19 – 49	21.9 ± 13.1 μV	43	5 (12%)
	≥ 7 μV	50 – 79	24.4 ± 15.7 μV		
Median nerve CMAP amplitude	≥ 5.9 mV	19 – 39	7.4 ± 1.7 mV	43	1 (2%)
	≥ 4.2 mV	40 – 59	9.7 ± 3.2 mV		
	≥ 3.8 mV	60 – 79	7.3 ± 2.6 mV		
Lower-limb Neurophysiological Measure					
Sural nerve SNAP amplitude	≥ 9 μV	21 – 40	2.3 ± 3.2 μV	44	14 (32%)
	≥ 7 μV	41 – 60	14.3 ± 7.9 μV		
	≥ 6 μV	61 – 80	6.0 ± 5.3 μV		

Table 4.3.2. Neurophysiological measures of the median nerve SNAP and CMAP amplitudes, as well as sural nerve SNAP amplitude, according to age-adjusted lower limit of normal (LLN) from previous studies [193, 194, 214].

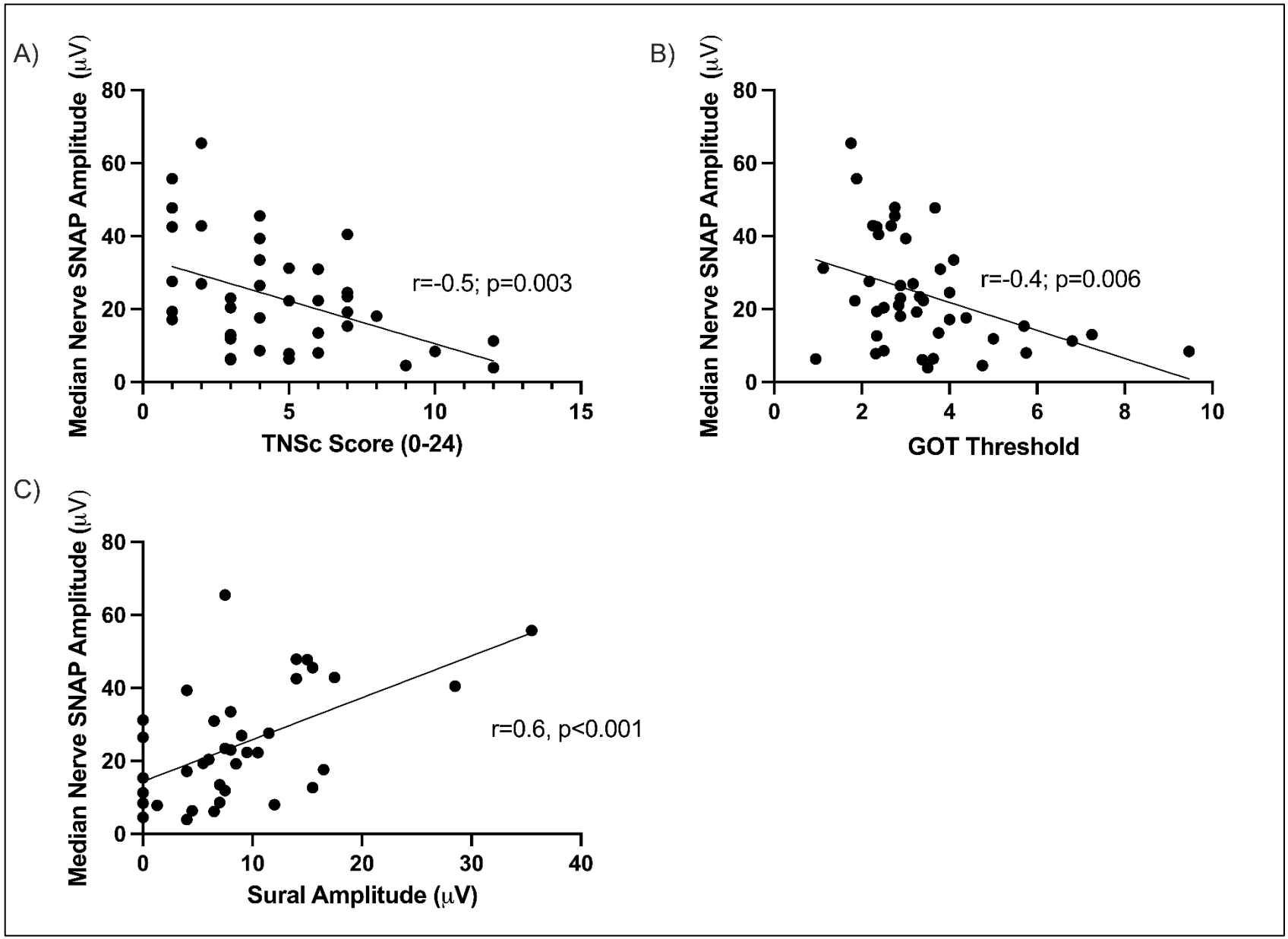

A)
Median Nerve SNAP Amplitude (μV)
80
60
40
20
0
0
5
10
15
TNSc Score (0-24)
r=-0.5; p=0.003
B)
Median Nerve SNAP Amplitude (μV)
80
60
40
20
0
0
2
4
6
8
10
GOT Threshold
r=-0.4; p=0.006
C)
Median Nerve SNAP Amplitude (μV)
80
60
40
20
0
0
10
20
30
40
Sural Amplitude (μV)
r=0.6, p<0.001

Figure 4.3.2. Scatterplots of the neurophysiological measures, including median nerve SNAP amplitude with (A) neurological examination score (TNSc), (B) sensory perception assessment (GOT Threshold) and (C) sural amplitude. The solid line represents the line of best fit. R denotes the use of Pearson's correlations. P<0.05 indicates significance.

4.3.5 Upper-limb Stimulated Skin Wrinkling (SSW) assessment

Participants were classified according to the presence of normal or abnormal EMLA-induced SSW, and group comparisons were undertaken (Table 4.3.3). Overall, 78% (n=47) had normal SSW while 22% (n=13) had abnormal SSW, potentially indicating the presence of small nerve fibre dysfunction. Participants who had abnormal SSW were older than participants with normal SSW (p=0.03) and had significantly reduced fine motor skills (Grooved Pegboard Task; p=0.04) and sensory perception (Von Frey Monofilaments; p=0.004). However, there were no significant differences in any of the clinically-graded, neurologically-graded or patient-reported CIPN severity measures between both groups (all p>0.05) (Table 4.3.3).

	Normal SSW (n=47)	Abnormal SSW (n=13)	P-value
	Median (IQR)	**Median (IQR)**	
Demographic characteristics			
Age (years) (mean, SD)*	**60.0 ± 12.0**	**68.0 ± 10.0**	**0.03**
BMI (kg/m^2) (mean, SD)*	27.2 ± 5.8	24.2 ± 4.8	0.1
Months since treatment completion	13.0 (4.0-26.0)	11.0 (1.5-14.0)	0.3
CIPN Outcome Measures			
Neurological Examination Score (TNSc) (mean, SD)*	4.6 ± 2.8	4.9 ± 3.1	0.8
Patient-Reported Outcome (EORTC-QLQ-CIPN20)	10.5 (7.0-19.3)	14.0 (8.8-26.2)	0.3
Upper-limb Functional Deficit Score	2.0 (2.0-3.0)	2.0 (2.0-4.0)	0.8
Health-Related Quality-of-Life Outcome (CAP-PRI score)	2.0 (0-6.0)	4.0 (1.0-7.5)	0.3
Patient-Reported Pain Scale (PNRS)	0 (0-3.0)	0 (0-2.5)	0.9
Clinically-Graded Scale (NCI-CTCAE)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	0.3
Upper-limb Functional Assessments			
EMLA-Induced SSW Average Score	**3.9 (3.5-4.0)**	**1.9 (1.2-2.5)**	**<0.001**
Average Pegboard Time (secs)	**67.5 (60.5-78.7)**	**80.0 (65.3-97.2)**	**0.04**
Von Frey Threshold (mN)	**0.2 (0.2-0.7)**	**0.7 (0.3-2.8)**	**0.004**
Grating Orientation Task (GOT) Threshold (mm)	3.3 (2.4-4.2)	3.0 (2.5-5.8)	0.9
Neurophysiological Measures			
Median Nerve SNAP Amplitude (μV) (mean, SD)*	22.2 ± 14.1	30.1 ± 17.9	0.2

Median Nerve CMAP Amplitude (mV) (mean, SD)*	7.9 ± 3.1	8.5 ± 2.7	0.7

Table 4.3.3. Comparison of neuropathy outcomes as well as upper-limb functional and neurophysiological measures between participants with normal and abnormal SSW, using Mann-Whitney U tests. $p<0.05$ indicates significance. Lower scores on SSW, higher scores on all sensory and functional assessments, as well as CIPN outcome measures and lower sensory and motor median nerve amplitudes indicate greater impairment. *Indicates p-values using independent sample t-tests.

4.3.6 Upper-limb functional deficits

To understand the additional burden of upper-limb CIPN symptoms on CIPN severity and patient function, we compared participants who reported the presence of upper-limb functional deficits on the patient-reported outcome measure (EORTC-QLQ-CIPN20) (n=27) with those who did not report upper-limb functional deficits (n=33). Overall, there were no differences in age, BMI, or months since treatment completion between groups (all $p>0.05$) (Table 4.3.4). Participants who reported upper-limb functional deficits had significantly worse clinically-graded CIPN (NCI-CTCAE), worse neurologically-graded CIPN (TNSc) as well as overall worse patient-reported CIPN severity, including higher scores on patient-reported outcome (EORTC-QLQ-CIPN20) and health-related quality-of-life measure (CAP-PRI) (all $p<0.05$) (Table 4.3.4).

Group comparison of upper-limb functional assessments and neurophysiological measures were also undertaken (Table 4.3.4). Overall, there were no differences in fine motor skills (Grooved Pegboard Task) or sensory perception assessment (GOT threshold; Von-Frey Monofilaments) between participants with or without upper-limb functional deficits (all $p>0.05$). Also, assessment of small nerve fibre dysfunction via SSW was not significantly different between both groups ($p=0.2$). Neurophysiological measurements of median nerve SNAP or CMAP amplitudes also did not significantly differ between both groups (both $p>0.05$) (Table 4.3.4), despite the presence of higher overall CIPN severity.

	Absence of Upper-limb Functional Deficits (n=33)	**Presence of Upper-limb Functional Deficits (n=27)**	**P-value**
	Median (IQR)	**Median (IQR)**	
Demographic characteristics			
Age (years) (mean, SD)*	62.0 ± 13.0	61.0 ± 10.0	0.8
BMI (kg/m^2) (mean, SD)*	25.7 ± 5.1	28.1 ± 6.5	0.2
Months since treatment completion	7.0 (4.0-24.0)	14.0 (4.0-27.0)	0.4
CIPN Outcome Measures			
Neurological Examination Score (TNSc) (mean, SD)*	**4.0 ± 2.3**	**5.5 ± 3.2**	**0.03**
Patient-Reported Outcome (EORTC-QLQ-CIPN20)	**8.8 (4.6-12.3)**	**19.3 (10.5-31.6)**	**<0.001**
Health-Related Quality-of-Life Outcome (CAP-PRI score)	**1.0 (0-4.0)**	**5.0 (1.0-12.0)**	**0.003**
Patient-Reported Pain Scale (PNRS)	0 (0-1.5)	0 (0-4.0)	0.2
Clinically-Graded Scale (NCI-CTCAE)	**1.0 (1.0-2.0)**	**2.0 (2.0-2.0)**	**<0.001**
Upper-limb Functional Assessments			
EMLA-Induced SSW Average Score	3.5 (3.0-3.9)	3.7 (3.2-4.0)	0.2
Average Pegboard Time (secs)	66.5 (60.6-82.0)	73.9 (61.8-80.7)	0.6
Von Frey Threshold (mN)	0.5 (0.2-0.7)	0.3 (0.2-0.7)	0.7
Grating Orientation Task (GOT) Threshold (mm)	3.0 (2.4-4.1)	3.4 (2.5-4.8)	0.2
Neurophysiological Measures			

Median Nerve SNAP Amplitude (μV) (mean, SD)*	24.8 ± 14.8	23.2 ± 16.0	0.7
Median Nerve CMAP Amplitude (mV) (mean, SD)*	8.1 ± 2.9	8.2 ± 3.1	0.9

Table 4.3.4. Comparison of neuropathy outcomes as well as upper-limb functional and neurophysiological measures between participants with absence or presence of upper-limb functional deficits, using Mann-Whitney U tests. $p<0.05$ indicates significance. Lower scores on SSW, higher scores on all sensory and functional assessments, as well as CIPN outcome measures and lower sensory and median nerve amplitudes indicate worse impairment. *Indicates p-values using independent sample t-tests.

4.4 DISCUSSION

This study characterised the impact of CIPN on upper-limb function and compared neurophysiological and functional assessments of the upper-limb in neurotoxic chemotherapy-treated patients. Overall, upper-limb CIPN symptoms were prevalent in 65% of participants with CIPN. Reduced sensory perception, reduced fine motor skills, and reduced median nerve SNAP amplitudes significantly correlated with worse neurologically-graded CIPN severity (TNSc). Participants who reported upper-limb functional deficits also had worse clinically-graded CIPN, worse neurologically-graded CIPN severity, and worse patient-reported CIPN severity across multiple measures. However, there were no significant differences in upper-limb functional assessments or neurophysiological measures compared to participants who did not report upper-limb functional deficits.

CIPN is typically described as lower-limb predominant [38]. In the present study, lower-limb neuropathy was also described as more severe than upper-limb symptoms by the majority of participants. However, the majority of participants (65%) in our study also reported persistent upper-limb symptoms. This is in line with a prior study which reported associations between the severity of upper and lower-limb CIPN symptoms [225]. Given that participants with upper-limb functional deficits in this study reported overall worse CIPN severity and reduced quality-of-life compared to participants without upper-limb functional deficits, this further highlights the significant additional burden of the presence of upper-limb CIPN symptoms in patients with chronic CIPN.

Limited previous studies have highlighted the impact of upper-limb CIPN symptoms, reporting persistent deficits in skilled hand functions, such as writing and typing on a keyboard post-neurotoxic cancer treatment [221, 222]. Other studies have focused on

comparing upper and lower-limb symptoms during neurotoxic chemotherapy treatment. In oxaliplatin and paclitaxel treated patients, upper and lower-limb neuropathy symptoms occurred with similar incidence and severity during treatment, but upper-limb symptoms demonstrated better reversibility [35]. However, despite the potential for recovery, in this cohort we demonstrated that patients still report burden of upper-limb CIPN symptoms at a median of 11.5 months post-neurotoxic treatment completion, highlighting its potential persistence in the long-term.

Despite this burden, there remains no gold standard for the assessment of CIPN [103]. The currently-utilised tools, including functional assessments, are often used to investigate lower-limb symptoms, with only a few studies specifically looking at upper-limb symptoms [220-222]. We focused on comparing upper-limb functional assessments, including assessment of fine motor skills via Grooved Pegboard Task as well as sensory perception via Grating Orientation Task (GOT) and Von-Frey Monofilaments, to determine which tools were associated with CIPN severity. Overall, assessment of fine motor skills via Grooved Pegboard and sensory perception assessment via Von Frey Monofilaments were significantly associated with neurologically-graded CIPN severity as measured by the TNSc.

Furthermore, investigation of upper-limb neurophysiological measures was undertaken to determine their association with upper-limb functional assessments and CIPN severity. Overall, reduction in median nerve SNAP amplitude was significantly associated with reduced sensory perception via GOT and higher neurologically-graded CIPN severity. Previous work has demonstrated strong associations between lower-limb clinical examination including vibration and light touch, with reduced sural amplitudes [107]. Similarly in this study, we found strong associations between upper-limb examinations via GOT with reduced

median nerve SNAP amplitude. Reduced median nerve SNAP amplitude was also significantly associated with reduced lower-limb sural SNAP amplitude, highlighting the links between lower-limb and upper-limb nerve damage in chronic CIPN.

Overall, none of the functional assessments or neurophysiological measures were associated with patient-reported upper-limb functional deficit severity, including difficulty writing and manipulating objects with fingers. A lack of association between patient-report and other measures of CIPN has been identified previously [226-228]. This lack of association potentially reflects differences in the specificity of these assessment tools. PROMs assess symptoms and their impact more broadly while functional assessments and neurophysiological assessment tools often assess focal locations. While these functional assessments and neurophysiological measures provide specific quantification of sensory loss and axon damage, they often lack sensitivity to capture global impacts of neurotoxicity that are relevant to patient function and quality-of-life, and which are readily identified by PROMs [103, 228]

Another upper-limb parameter that was investigated in this study pertains to small nerve fibre dysfunction. Validated tools that are used to measure upper-limb small nerve fibre dysfunction, such as intraepidermal nerve fibre density (IENFD) measured via skin biopsy, may have limited utility in a clinical setting due to cost and invasiveness [133]. Accordingly, there remains a need for a quick and non-invasive measure of small nerve fibre dysfunction in patients with CIPN. In this study, assessment of upper-limb small nerve fibre dysfunction was investigated via EMLA-induced SSW. SSW is a proposed assessment tool of small nerve fibre dysfunction, as skin wrinkling of the digit tips occurs due to vasoconstriction of the glabrous skin, mediated by small nerve fibres [183]. SSW scores have been shown to

associate with IENFD via skin biopsy in patients with neuropathy [184, 229]. Furthermore, the simple administration, low cost and non-invasiveness makes EMLA-induced SSW assessment favourable to use in a clinical setting [186]. However, SSW largely remains unvalidated as a measure of small nerve fibre dysfunction. In addition, there is a lack of pre-defined thresholds for abnormal skin wrinkling, which limits ability to determine age matched cut-off values for normal and abnormal SSW status [230].

In limited previous studies, SSW was able to predict abnormalities in NCS in patients with diabetic sensorimotor polyneuropathy [186]. Furthermore, in CTS studies, SSW status demonstrated better association with CTS severity than NCS [223]. To our knowledge, this study is the first to investigate the use of EMLA-induced SSW as an upper-limb assessment of small nerve fibre dysfunction in patients with CIPN. In contrast to these findings, in this study, SSW did not associate with any CIPN severity or neurophysiological measures. Rather, the presence of abnormal SSW was associated with reduced fine motor skills and sensory perception, which could be related more broadly to age. Abnormal SSW only occurred in less than a quarter of participants with CIPN. However, we could not determine the exact association of EMLA-induced SSW with small nerve fibre dysfunction in patients with CIPN because skin biopsy was not an available technique in this study. Therefore, more studies, particularly of prospective cohorts, are needed to trace the trajectory of change in SSW scores along with CIPN development throughout chemotherapy treatment to confirm if EMLA-induced SSW is an appropriate marker of small nerve fibre dysfunction in neurotoxic chemotherapy-treated patients.

This study underscores the need for improved focus on the assessment of upper-limb CIPN symptoms to determine their impact on overall function and quality-of-life in neurotoxic

chemotherapy-treated patients. We included a range of assessments of fine motor skills, sensory perception and neurophysiological measures of median nerve SNAP and CMAP amplitudes. However, this study was cross-sectional in nature, which limits our ability to investigate the trajectory and potential changes in upper-limb assessments and CIPN symptoms over time. Further, we included participants of multiple cancer types who were treated with different chemotherapy drugs, which limits our ability to investigate cancer- or chemotherapy-specific characteristics. In addition, given that our cohort was predominantly female, this may limit the generalisability of our study. Also, there was a small sample size in the group comparisons between patients with normal and abnormal SSW, which could account for the lack of statistical significance observed.

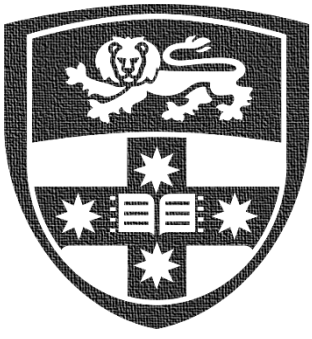
Overall, given the findings of this study, we recommend that upper-limb function be comprehensively assessed in both CIPN research and oncology clinical settings. Items on the patient-reported outcome measure EORTC-QLQ-CIPN20 that pertain to upper-limb assessment may be used to identify clinical subgroups of patients with CIPN who have upper-limb functional deficits. Given the association of upper-limb CIPN with overall worse CIPN severity, it is likely that patients with more severe lower-limb CIPN also have upper-limb dysfunction. Hence, this clinical subgroup of patients with worse neuropathy may benefit from referral to physical therapy or rehabilitation which targets both upper and lower-limbs.

4.5 CONCLUSIONS

Upper-limb symptoms are common and those with upper-limb functional deficits have overall worse CIPN severity. Upper-limb CIPN symptoms are associated with significant burdens on upper-limb function, including deficits in writing and manipulating objects with fingers. While there are multiple current rehabilitation programs that focus on improving or managing lower-limb CIPN symptoms, the results of this study highlight the need to phenotype and subgroup patients with upper-limb functional deficits in order to provide supportive care and rehabilitation options to help improve upper-limb function.

CHAPTER 5

Impact of Pain on Symptom Burden in Chemotherapy-Induced Peripheral Neurotoxicity



ABSTRACT

Background. Chemotherapy-induced peripheral neurotoxicity (CIPN) affects the quality-of-life of cancer survivors. However, the impact of pain on symptom burden remains undefined. This study aimed to define differences in the clinical symptom profile of patients with painful and non-painful CIPN. **Patients and Methods**. 579 participants (median age=59; IQR=(19)years; F=66%) were assessed cross-sectionally 6.0(6) months post-treatment. CIPN severity was graded using multiple methods including patient-reported outcome measures, a clinically-graded scale (NCI-CTCAE), and a neurological examination score. Participants were classified into subgroups based on patient symptom report, with painful CIPN characterised by the presence of shooting/burning pain, and non-painful CIPN by the presence of numbness or tingling without shooting/burning pain. Behavioural changes were assessed by structured-patient interview regarding symptom impact on sleep, exercise, and treatment-seeking. **Results.** Among 579 participants, 24% (n=140) reported painful CIPN, 48% (n=280) reported non-painful CIPN and 28% (n=159) had no CIPN. Participants with painful CIPN demonstrated higher CIPN severity than participants with non-painful CIPN across multiple measures, including NCI-CTCAE, neurological grading and patient-report (all $p<0.05$). Participants with painful CIPN were more likely to report that their symptoms affected their ability to exercise ($p=0.007$), produced sleep impairment and increased treatment-seeking behaviour due to their symptoms (both $p<0.001$), compared to participants with non-painful CIPN. **Discussion and Conclusions**. Overall, participants with painful CIPN reported higher scores across all CIPN severity measures, including behavioural changes. This study underlines the need for accurate identification of different CIPN subgroups, in hopes of informing better treatment and rehabilitation options for cancer survivors with painful CIPN.

5.1 INTRODUCTION

Chemotherapy-induced peripheral neurotoxicity (CIPN) is associated with treatment with neurotoxic chemotherapies including platinum-based agents, taxanes, vinca-alkaloids, bortezomib and thalidomide [94]. Because there are no preventative or treatment measures for CIPN, symptoms may require chemotherapy dose modification which could reduce effectiveness [231]. Further, CIPN symptoms affect quality-of-life in cancer survivors, often producing long-term disability, including impact on fine motor skills, walking and gait [232]. The core symptoms associated with CIPN are sensory disturbances including numbness and tingling [222, 233, 234]. Neuropathic pain, often described as shooting or burning pain, is less common [38], with only 33% of patients with CIPN reporting burning pain, compared to 77% reporting severe numbness and tingling [38]. This discrepancy occurs for multiple neurotoxic drugs, with patients treated with taxanes [35, 233, 235], bortezomib [170], and platinum-based agents [35, 59, 231, 233] all reporting more severe tingling and numbness compared to neuropathic pain.

However, our understanding of the impact of painful CIPN on chemotherapy-treated patients is inadequate. In limited previous studies, participants with painful CIPN reported worse health-related quality-of-life (HRQoL) than those with non-painful CIPN [235]. Furthermore, painful CIPN may be associated with comorbidities, including fatigue, anxiety and sleep impairments [140]. However, assessment of neuropathic pain in the context of CIPN remains a challenge. There is a lack of validated diagnostic tools that address pain and its impacts separately from non-painful CIPN symptoms. Multiple studies utilise the clinically-graded scale the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) for the quantification of neuropathy severity [236], which does not include

neuropathic pain. Further, few patient-reported outcome measures (PROMs) for CIPN evaluation focus on identifying pain and its impact [140]. The aim of this study was to understand the differences in prevalence and symptom burden between painful and non-painful CIPN.

5.2 METHODS

5.2.1 Participants

Eligible participants were cancer survivors aged ≥18-years of age and were 3-12 months post-treatment with neurotoxic chemotherapy (including taxanes, platinum-based agents, bortezomib, thalidomide & vinca alkaloids). Participants were assessed cross-sectionally on a single occasion. Relevant clinical data were retrieved from medical records. This study was approved by Sydney Local Health District (RPAH zone) and South Eastern Sydney Local Health District Human Research Ethics Committees and informed consent was obtained from each participant.

5.2.2 CIPN and Pain assessment: Patient-reported outcome measures

Assessment tools are briefly described below, with further details available in Appendix 1, Supplementary Methods 1.1.1.

The European Organisation of Research and Treatment of Cancer Quality-of-Life Questionnaire-Core (EORTC-QLQ-CIPN20), a validated 20-item questionnaire that assesses CIPN [138], was utilised. Total score as well as individual item scores assessing the impact of CIPN symptoms on patient function were investigated.

The Pain Numeric Rating Scale (PNRS) was used to assess the intensity of nerve pain experienced by participants in the 24-hours prior to testing [169]. A modified Douleur Neuropathique 4 (DN4) was used to report the most common descriptors of pain in participants who had neuropathic pain, including a comparison of pain descriptors reported across different chemotherapy types [147].

A semi-structured qualitative interview was conducted to collect information about participant symptoms and their impact, similar to previously conducted interviews [136].

5.2.3 Clinical neuropathy assessment

Trained researchers undertook a comprehensive neuropathy assessment protocol to grade CIPN severity, including clinical neuropathy grading scales and functional assessments. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) sensory neuropathy subscale Version 4.0 [105] and the Total Neuropathy Score-clinical version (TNSc© John Hopkins University) were undertaken [109, 110]. Nerve conduction studies (NCS) were undertaken in the lower-limb sural and tibial nerves, as per previous studies [101]. (Detailed in Appendix 1, Supplementary Methods 1.1.2).

Functional assessments on participant's dominant hand assessed sensory perception via Von-Frey monofilaments [179] and Grating Orientation Task (GOT) [178], as well as fine motor skills via the Grooved Pegboard Task [180]. (Detailed in Appendix 1, Supplementary Methods 1.1.3).

5.2.4 Participant classification

Participants were classified based on CIPN symptoms reported in the patient-reported outcome measure (EORTC-QLQ-CIPN20), as in previous studies [231]. Participants who did not report any painful or non-painful CIPN symptoms were placed in the "No CIPN" group and were excluded from further analyses. From the remaining cohort, the presence of painful CIPN was characterised using either EORTC-QLQ-CIPN20 items or PNRS score (Detailed in Appendix 1, Supplementary Methods 1.1.4).

5.2.5 Statistical analyses

Data analysis was undertaken using SPSS Statistics Software V27 (IBM; Armonk, NY). Data was assessed for normality using the Shapiro-Wilk test, and non-normally distributed data ($p<0.05$) were presented as median (interquartile range(IQR)). Mann-Whitney U tests were used to explore differences between CIPN outcome measure scores, clinical characteristics, neurophysiological measurements, and treatment factors of painful and non-painful CIPN cohorts. Chi-square tests were used to explore group differences between taxane and platinum-based participants in the painful CIPN cohort and to investigate behavioural changes associated with CIPN subgroups. Statistical significance was considered when $p<0.05$.

5.3 RESULTS

5.3.1 Demographics and clinical history

A total of 579 participants with median age of 59(IQR=19) years were assessed cross-sectionally 6.0(6) months post neurotoxic chemotherapy treatment. In total, 66% of the cohort were females (n=384). The most common cancer types were breast (32%, n=184), gastrointestinal (28%, n=162) and gynaecological (18%, n=102). The most common chemotherapy types were taxanes (57%, n=329) and platinum-based (33%, n=194).

Overall, 28% (n=159) reporting no CIPN, 33% (n=140) reporting painful CIPN and 67% (n=280) reported non-painful CIPN. Participants not reporting CIPN at the time of assessment were excluded from the analysis (n=159). Of those with CIPN (n=420), females were more likely to report painful CIPN than males (p=0.02). However, there were no differences in cancer type, cancer stage or chemotherapy type between painful and non-painful CIPN (all p>0.05) (Table 5.3.1).

There were no demographic differences between both groups in age and BMI (both p=0.4). However, participants reporting painful CIPN were significantly farther from treatment completion (6(5) months) than participants with non-painful CIPN (4(3) months) (p=0.02) (Table 5.3.1). Clinical and demographic information is found in Table 5.3.1.

	Painful CIPN (n=140)	Non-Painful CIPN (n=280)	Total (n=420)	P-value
	n (%)	n (%)	n (%)	
Clinical characteristics				
Female sex	**105 (75%)**	**177 (63%)**	**282 (67%)**	**0.02**
Diabetes	13 (9%)	34 (12%)	47 (11%)	0.4
Cancer Type				
Breast	49 (35%)	80 (29%)	129 (31%)	0.3
Gynaecological (Cervical, Endometrial & Ovarian)	29 (21%)	43 (15%)	72 (17%)	
Haematological	10 (7%)	20 (7%)	30 (7%)	
GI/Colorectal & Pancreatic	38 (27%)	106 (38%)	144 (34%)	
Testicular, Prostate, Lung & Urothelial	9 (6%)	21 (7%)	30 (7%)	
Other	5 (4%)	10 (4%)	15 (4%)	
Chemotherapy Type				
Taxanes	85 (61%)	143 (51%)	228 (54%)	0.3
Platinum-based	45 (32%)	114 (41%)	159 (38%)	
Bortezomib	4 (3%)	12 (4%)	16 (4%)	
Other	6 (4%)	11 (4%)	17 (4%)	
Cancer Stage				
0	0 (0%)	3 (1%)	3 (1%)	0.7
I	13 (9%)	26 (9%)	39 (9%)	
II	42 (30%)	59 (21%)	101 (24%)	
III	48 (34%)	89 (32%)	137 (33%)	
IV	26 (19%)	75 (27%)	101 (24%)	
No stage (non-solid tumours)	10 (7%)	20 (7%)	30 (7%)	
Missing	1 (1%)	8 (3%)	9 (2%)	
Neuropathy during treatment				
No	12 (9%)	19 (6%)	31 (7%)	0.6
Yes	108 (77%)	206 (74%)	314 (75%)	
Missing	20 (14%)	55 (20%)	75 (18%)	
Demographic characteristics				
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**P-value**
Age (years)	61.0 (18.0)	60.0 (18.0)	60.5 (18.0)	0.9
BMI (kg/m^2)	26.9 (6.1)	26.3 (6.4)	26.7 (7.0)	0.4
Months since treatment completion	**6.0 (5.0)**	**4.0 (3.0)**	**4.0 (4.0)**	**0.02**

Table 5.3.1. Clinical and demographics table of Painful CIPN and Non-Painful CIPN. Comparisons between both groups were performed using Chi-square tests. Demographic characteristics were compared using Mann-Whitney U tests. $p<0.05$ was considered significant.

5.3.2 Neuropathy profiles and subgroups

Participants with painful CIPN had a greater symptom burden than those with non-painful CIPN across multiple measures, including the clinically-graded scale (NCI-CTCAE; $p<0.001$) (Table 5.3.2) and the patient-reported outcome (EORTC-QLQ-CIPN20; $p<0.001$) (Fig. 5.3.1A) (Table 5.3.2; Appendix 1, Supp. Table 1.3.1). Participants with painful CIPN also had worse neurological examination scores (TNSc; $p<0.001$) (Fig. 5.3.1B), including higher report of sensory ($p=0.003$) and motor ($p=0.001$) symptoms in the extremities (Table 5.3.2). However, there were no significant differences in pinprick or vibration scores, no differences in functional assessments (all $p>0.05$) or sural ($p=0.1$) or tibial amplitudes ($p=0.06$) between the groups (Table 5.3.2).

Items assessing impact of symptoms on function on the patient-reported outcome measure (EORTC-QLQ-CIPN20) were investigated. Participants with painful CIPN reported significantly more functional impairments across all these items in comparison to those with non-painful CIPN (all $p\leq0.003$) (Fig. 5.3.2).

The severity of neuropathic pain was reported by patients with painful CIPN on the PNRS, focused on the shorter recall period of 24-hours. The median PNRS score was 4(IQR=6) out of 10, with 31% (n=44) reporting no pain in the 24-hours prior to testing (Score 0/10). Overall, the level of neuropathic pain on PNRS was significantly correlated with CIPN severity across all measures (all $p<0.05$), including the patient-reported outcome (Fig. 5.3.3A), the neurological examination score (Fig. 5.3.3B), and the clinically-graded scale ($r=0.3$, $p=0.002$). Similarly, those who reported more severe pain in the past week (EORTC-QLQ-CIPN20) had worse CIPN severity across all measures compared to those reporting

lower pain severity (all p<0.05). Common descriptors of pain are reported in Appendix 1, Supplementary Results 1.2.1.

Assessment tools	**Painful CIPN (n=140)**	**Non-painful CIPN (n=280)**	**P-value**
	Median (IQR)	**Median (IQR)**	
CIPN outcome measures			
Clinically-Graded Scale (NCI-CTCAE)	**2.0 (1.0)**	**1.0 (1.0)**	**<0.001**
Patient-Reported Outcome (EORTC-QLQ-CIPN20)	**22.8 (19.0)**	**12.3 (12.0)**	**<0.001**
Neurological Examination Score (TNSc)	**5.0 (4.0)**	**4.0 (3.0)**	**<0.001**
TNS – Sensation	**1.0 (1.0)**	**1.0 (1.0)**	**0.003**
TNS – Weakness	**0 (1.0)**	**0 (0)**	**0.001**
Sensory and Functional Assessments			
Average Pegboard Time (secs)	77.9 (25.6)	73.9 (25.4)	0.4
Grating Orientation Task (GOT) Threshold (mm)	3.7 (2.6)	3.8 (2.6)	0.8
Two-Point Discrimination Distance	15.0 (6.0)	13.0 (6.0)	0.09
TNS – Pinprick	1.0 (2.0)	1.0 (1.0)	0.2
TNS – Vibration	0 (1.0)	0 (1.0)	0.3
Neurophysiological measures			
Tibial amplitudes (mV)	8.9 (5.8)	9.3 (6.7)	0.3
Sural amplitudes (µV)	6.0 (6.9)	7.3 (7.8)	0.1

Table 5.3.2. Comparison of neuropathy outcomes between participants with painful and non-painful CIPN, using Mann-Whitney U tests. p<0.05 was considered significant. Higher scores on CIPN outcome measures and sensory and functional assessments, as well as lower amplitudes of neurophysiological measures indicate worse impairment.

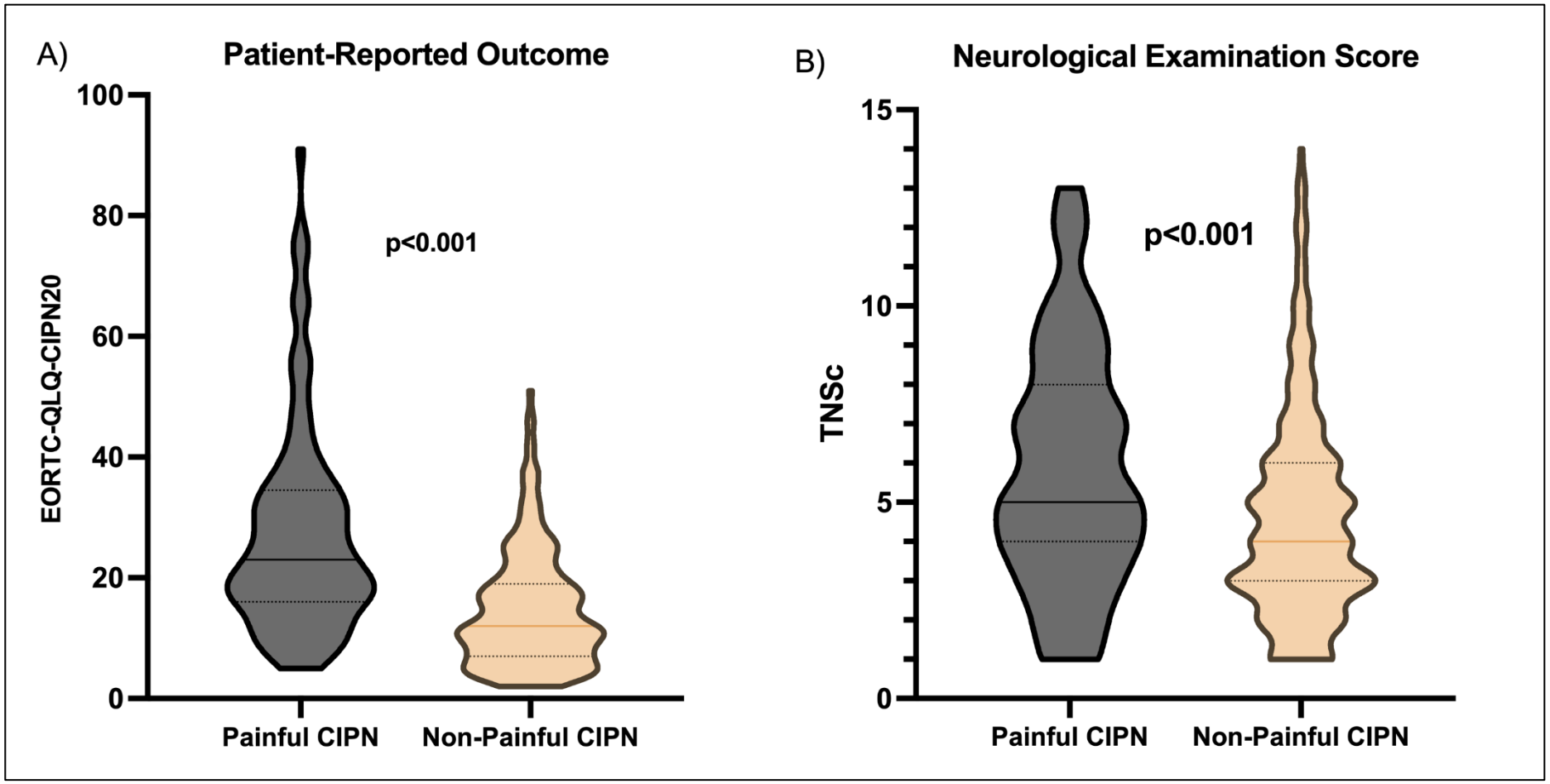


Figure 5.3.1. Violin plots showing the differences between Painful CIPN group and Non-Painful CIPN group on A) Patient-reported outcome measure (EORTC-QLQ-CIPN20) and B) Neurological examination score (TNSc). Solid line represents median, and dotted lines represent 25%-75% percentile. Higher scores indicate worse symptom burden.

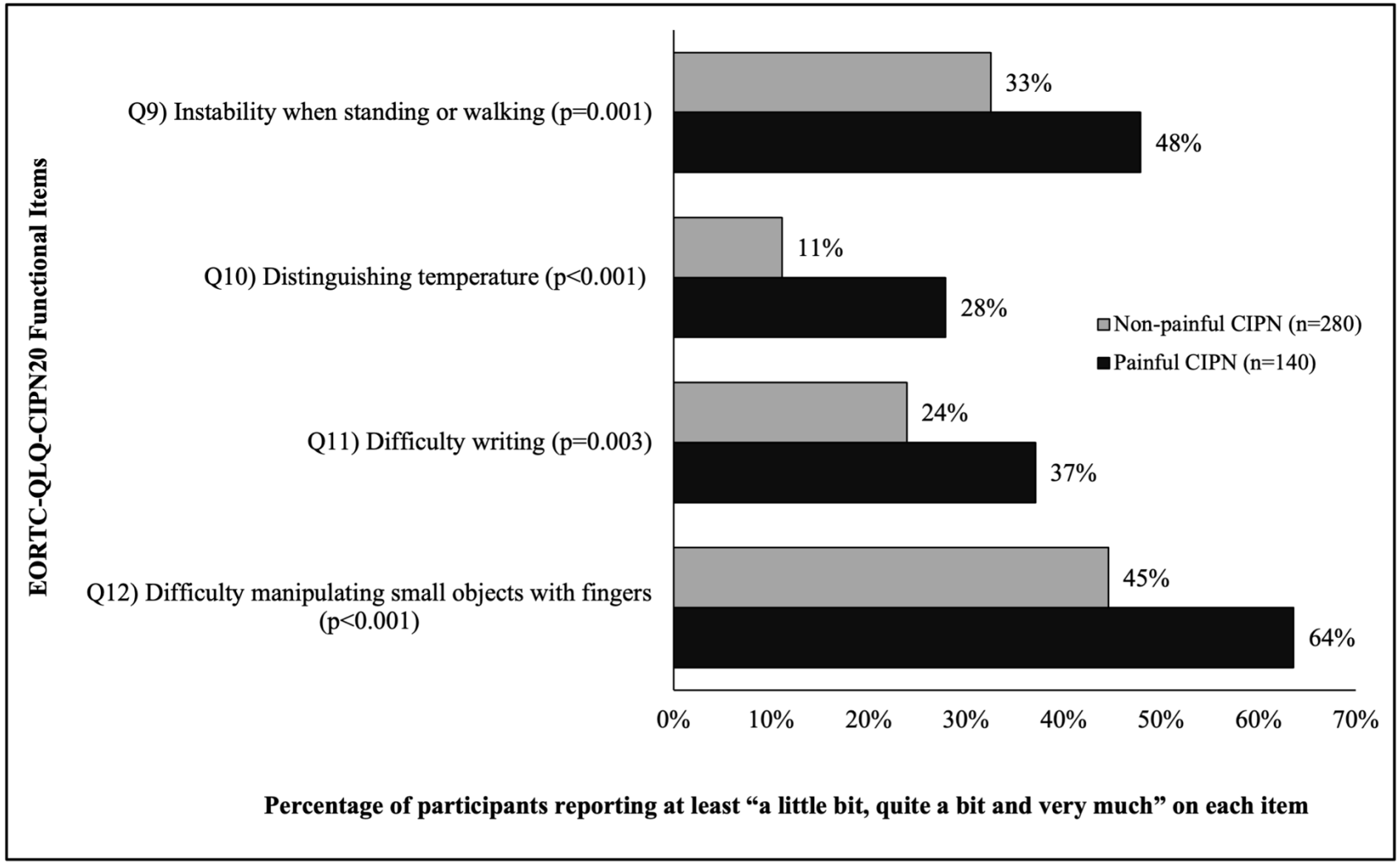


Figure 5.3.2. Percentage of participants painful and non-painful CIPN reporting at least "a little but, quite a bit" and "very much" on EORTC-QLQ-CIPN20 functional items (Q9, 10, 11 &12). p<0.05 was considered significant.

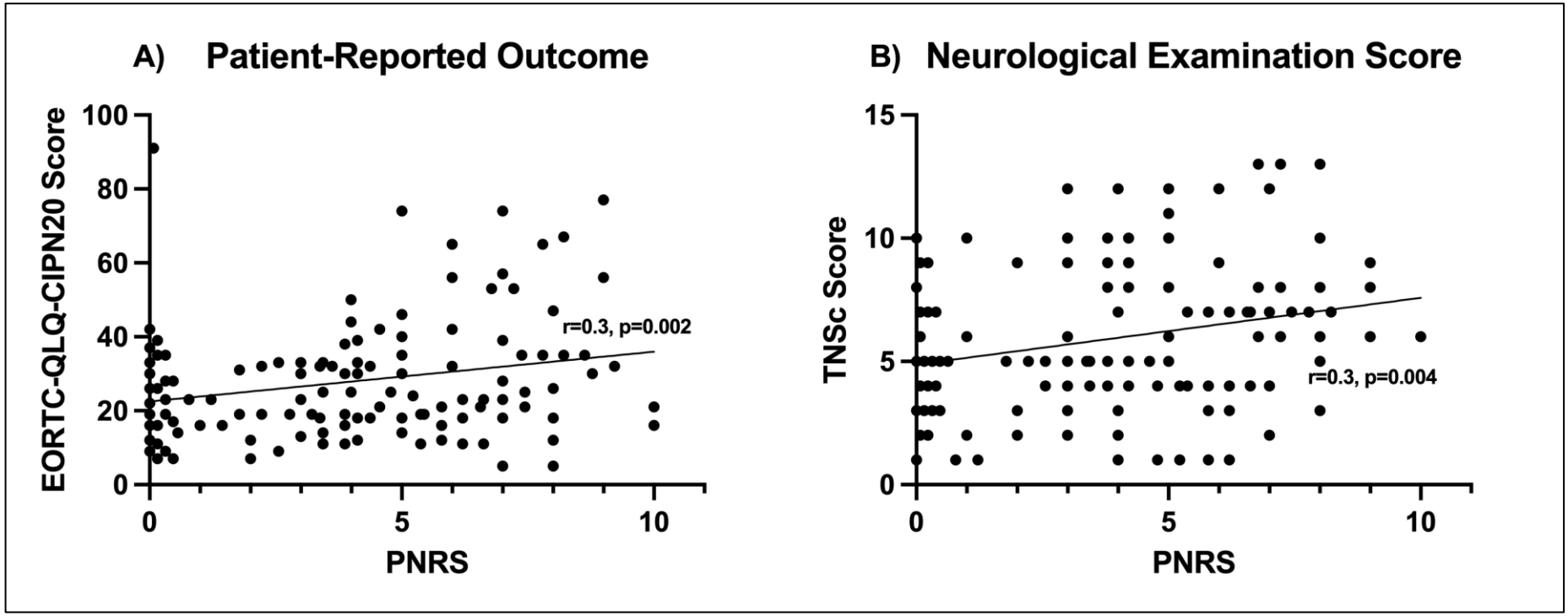


Figure 5.3.3. Scatterplots of the patient-reported pain scale (PNRS) of the Painful CIPN group with (A) patient-reported outcome measure (EORTC-QLQ-CIPN20) and (B) neurological examination score (TNSc). The solid line represents the line of best fit.

5.3.3 Subgroups within moderate-to-severe CIPN cohort

In order to examine further subgroup differences, comparisons were undertaken between participants with moderate-to-severe CIPN symptoms with pain (n=102) and without pain (n=121). Even within the moderate-to-severe CIPN cohort, those with painful CIPN symptoms had worse impairments across all CIPN severity measures, including the patient-reported outcome, the clinically-graded scale, and the neurological examination score (all $p<0.05$) (Table 5.3.3). However, there were no demographic, neurophysiological, or functional differences between both groups ($p>0.05$) (Table 5.3.3).

Assessment tools (NCI-CTCAE cut-off ≥ 2)	Moderate-to-severe CIPN without Pain (n=121)	Moderate-to-severe CIPN with Pain (n=102)	P-value
	Median (IQR)	Median (IQR)	
CIPN outcome measures			
Clinically-Graded Scale (NCI-CTCAE)	**2 (0)**	**2 (0)**	**0.009**
Patient-Reported Outcome (EORTC-QLQ-CIPN20)	**17.5 (12.0)**	**27.9 (18.0)**	**<0.001**
Neurological Examination Score (TNSc)	**5.0 (5.0)**	**6.0 (5.0)**	**0.01**
TNS – Sensation	2.0 (1.0)	2.0 (1.0)	0.5
TNS - Weakness	**0 (1.0)**	**0 (1.0)**	**0.006**
Sensory and Functional Assessments			
Average Pegboard Time (secs)	81.0 (30.2)	79.7 (27.3)	0.5
Grating Orientation Task (GOT) Threshold (mm)	4.8 (3.5)	3.8 (3.0)	0.1
Two-Point Discrimination Distance	15.0 (5.0)	16.0 (5.0)	0.4
TNS – Pinprick	1.0 (2.0)	1.0 (1.0)	0.2
TNS – Vibration	0 (2.0)	0 (2.0)	0.9
Demographic characteristics			
Age (years)	61.0 (17.0)	61.0 (18.0)	0.7
BMI (kg/m^2)	26.6 (7.2)	27.2 (7.9)	0.7
Neurophysiological measures			
Tibial amplitudes (mV)	8.9 (6.5)	8.5 (5.4)	0.7
Sural amplitudes (μV)	6.0 (7.1)	5.0 (7.0)	0.2

Table 5.3.3. Comparison of neuropathy outcomes, sensory and functional assessments, neurophysiological measures, and demographic characteristics between participants with worse CIPN (NCI-CTCAE ≥ 2) and report no pain vs participants with worse CIPN and report pain, using Mann-Whitney U tests. $p<0.05$ was considered significant. Higher scores on CIPN outcome measures and sensory and functional assessments, as well as lower amplitudes of neurophysiological measures indicate worse impairment.

5.3.4 Comparison of CIPN subgroups among different chemotherapy types

The two largest chemotherapy type cohorts (paclitaxel and oxaliplatin) were selected for group comparisons. There were significant differences in the prevalence of pain between the paclitaxel and oxaliplatin chemotherapy cohorts (39% vs 28% respectively; p=0.03) (Appendix 1, Supp. Fig. 1.3.1). Group comparisons between paclitaxel- and oxaliplatin-treated patients can be found in supplementary results (Appendix 1, Supp. Results 1.2.2).

5.3.5 Impact of painful CIPN on sleep, exercise, and treatment-seeking behaviour

To characterise the impact of painful CIPN on behaviour and patient function, we compared the painful (n=87) and non-painful CIPN (n=193) cohorts who completed the structured-interview in terms of self-reported sleep dysfunction, exercise impairment and treatment-seeking behaviour.

Participants with painful CIPN were more likely to report that their symptoms affected their ability to exercise (OR=2.1; p=0.007) than those without pain, with 43% (n=37) of participants in the painful CIPN group reporting impact on exercise ability, compared to 26% (n=51) of those without pain. Similarly, participants with painful CIPN were more likely to report that they had trouble sleeping (OR=2.8; p<0.001), with 47% (n=41) of the painful CIPN cohort reporting sleep dysfunction due to CIPN, compared to 24% (n=46) of those with non-painful CIPN (Appendix 1, Supp. Table 1.3.4).

In addition, participants with painful CIPN were more likely to report seeking treatment for their symptoms than the non-painful CIPN group (OR=3.2; p<0.001) (Appendix 1, Supp. Table 1.3.4), with 69% (n=60) of the painful CIPN cohort reporting trying to find treatment

options, compared to 41% (n=79) of those with non-painful CIPN. Further, participants with painful CIPN were four-times-as-likely to report the use of medications to ameliorate neuropathy than the non-painful CIPN cohort ($p<0.001$; Appendix 1, Supp. Table 1.3.5). These medications included anticonvulsants (pregabalin and gabapentin) and antidepressants (duloxetine and amitriptyline). In total, 12% (n=17) of the painful CIPN cohort were receiving medication for CIPN at the time of assessment, compared to 3% (n=9) of the non-painful CIPN cohort.

5.4 DISCUSSION

This study investigated neuropathic pain and its impact on symptom severity, sensory function, and behaviour in participants with CIPN. Overall, 33% of participants with CIPN reported painful CIPN, which was associated with higher symptom severity across all CIPN outcome measures. The participants with painful CIPN reported more functional consequences than those without pain and were more likely to take neuropathy medications and report sleep dysfunction and exercise intolerance. Pain descriptors were similar between paclitaxel and oxaliplatin-treated cohorts, however, pain was more prevalent in oxaliplatin-treated cohort.

Other cohort studies have reported similar prevalence of neuropathic pain, ranging between 20% to 33% of patients [108, 126, 143], in line with these results. Participants with painful CIPN had worse global CIPN severity across all measures compared to participants with non-painful CIPN. The presence of painful CIPN was linked to worse impairment to activities of daily life, particularly reduced ability to distinguish temperature, more instability when standing or walking, as well as difficulty writing and manipulating small objects with fingers.

However, there were no group differences in performance on functional assessments and NCS. This suggests a potential separation between the perception of overall symptom burden and objective measures of neuropathy severity. Discrepancies between patient-reported symptoms of CIPN and neurological examination have been previously identified [237], suggesting that these assessment tools address different aspects of CIPN [228]. Patient report of CIPN symptom severity and impact often provide a broader perspective compared to focal quantification of neurological status. In addition, most neurophysiological measures of CIPN,

including NCS, measure large nerve fibre function, whereas small nerve fibre dysfunction is less accessible to measure, presenting a potential limitation in fully capturing objective deficits [133]. Importantly, patient report remains a key metric of CIPN severity, particularly given the lack of efficacy of measures such as NCS to identify differences between CIPN cohorts.

Participants with painful CIPN may be higher symptom reporters due to their increased symptom severity. A previous study found that participants who reported painful CIPN also reported higher anxiety and depression [238], suggesting that there may be a modulating effect of psychological factors on pain perception in patients with CIPN. However, the direction of this association remains uncertain, as patients with painful CIPN were more likely to have persisting anxiety and depression following treatment, in contrast to patients with non-painful CIPN who demonstrated greater improvements in anxiety and depression following treatment cessation [235].

The presence of neuropathic symptoms, including pain, negatively impacts quality-of-life of cancer survivors. In this study, the presence of painful CIPN affected patient-reported sleep, exercise, and treatment-seeking behaviour and functional capacity. Although one previous study also highlighted the association between painful CIPN and comorbidities, including increased sleep dysfunction, fatigue, anxiety, and depression [239], research on the comorbidities associated with painful CIPN remains limited [140] and represents a gap in enabling personalised management strategies for people with CIPN.

This study also found that oxaliplatin-treated patients had overall worse CIPN symptoms, significantly lower sural amplitudes and greater functional changes in sensory perception and

fine motor skills than those treated with paclitaxel. The different CIPN profiles of taxane and platinum-based chemotherapies have been previously reported [53, 240, 241], with similar reports at 1 year follow-up [240], while there were no differences in subjective or objective measures of CIPN between taxane or platinum-treated patients at 5 years follow-up [241]. With regards to pain, it was significantly more prevalent in oxaliplatin-treated patients than paclitaxel-treated patients. Interestingly, oxaliplatin-treated patients with painful CIPN also benefitted the most from duloxetine treatment in clinical trials, suggesting that different pain phenotypes may guide treatment responsiveness between chemotherapy types [150, 242]. Understanding differences in chemotherapy-specific profiles of CIPN are important to guide patients and clinicians in understanding the likelihood of symptom recovery and adaptation over time [228].

To date, treatment options recommended for the management of painful CIPN remain limited [150]. In this study, only 12% of participants with CIPN reported taking anticonvulsants or antidepressants for neuropathy treatment. This reflects similar experiences with low medication uptake in Australia [232] and international settings [163, 243]. Although duloxetine is recommended for the treatment of painful CIPN by international guidelines [40], in real-world practice, duloxetine treatment for painful CIPN is limited – with high rates of non-response and side-effects leading to lack of tolerability [163]. Better phenotyping of patients to determine who is most responsive to duloxetine and other therapies will likely improve real-world outcomes [150, 242].

While there are emerging strategies for the management of neuropathic pain, including both pharmacological and non-pharmacological approaches [165, 244], both will require identification of patient subgroups likely to benefit most. Novel therapies, such as targeted

drug delivery and neurostimulation methods hold promise to reduce neuropathic pain but require additional testing and validation[165]. Preliminary findings suggest that non-pharmacological approaches such as cognitive behavioural therapy might improve quality-of-life in patients with neuropathic pain [244] and be more acceptable to patients.

Overall, this study provides a clearer understanding of differing symptom patterns in a large cohort. We used a combination of subjective and objective measures of CIPN, as well as the combination of patient-reported and clinically-graded outcome measures of CIPN. An issue limiting previous understanding of painful CIPN is the use of combined descriptors of CIPN, collapsing sensory and painful symptoms of CIPN into a singular measure [245]. For this reason, we used specific PROM items that assessed numbness, tingling and shooting or burning pain in the last 7 days, to capture a broader recall period and separate patients into groups according to neuropathic pain [38, 231, 240]. However, these measures are not specifically validated to identify neuropathic pain. While we did utilize validated neuropathic pain tools to assess pain intensity and descriptors, we did not utilise them for the purpose of participant classification due to the recall period only pertaining to the last 24-hours prior to participant testing.

Given that prior studies have demonstrated a “coasting” effect for up to 3 months post-treatment completion [246], we chose to look at a cross-sectional cohort between 3-and-12 months post-treatment completion. However, the cross-sectional nature of this study may be a limitation, and future prospective analyses will provide insights into the development of painful CIPN over time. Further, we included multiple cancer and chemotherapy types in the analysis and did not control for all pre-existing conditions that cause PN or pain. However, more than 70% of this cohort developed neuropathy during treatment, suggesting that the

CIPN symptoms identified were related to treatment-emergent toxicity, rather than other factors. Further, the inclusion criteria were deliberately broad to capture a naturalistic cohort reflecting patients receiving chemotherapy in a clinical setting. Although participants were asked about functional limitations, this study did not quantify the number of falls or participant balance performance. In addition, participants did not report if they had tried medications to treat neuropathic symptoms previously and why these were discontinued.

Overall, given the outcomes of this study, we recommend that neuropathic pain be assessed in research and clinical settings as part of a comprehensive CIPN assessment. Tools used for this purpose should utilize a longer recall period than 24-hours, such as the patient-reported outcome measure EORTC-QLQ-CIPN20. Other CIPN outcome measures, including the clinically-graded scale (NCI-CTCAE) and the neurological examination score (TNSc) which are used for assessment of CIPN severity, do not include questions to address neuropathic pain severity and require additional tools to address this. Finally, we recommend the assessment of the impact of neuropathic pain on patient function and behaviour, as our study has highlighted the long-term and deleterious consequences of pain on cancer survivors with CIPN.

Current guidelines for CIPN discuss assessment of CIPN and include potential treatment options [40, 41]. However, these guidelines lack information relevant to patient subgrouping and phenotyping, particularly those with neuropathic pain. The use of PROMs remains important in identifying clinically-relevant symptom patterns, while NCS may not provide useful information in the classification of CIPN subgroups. Critically, the lack of accurate assessment of painful and non-painful CIPN symptoms in clinical trials may lead to

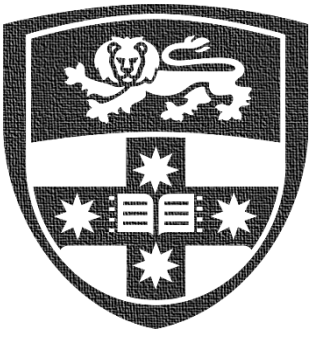
inaccurate results regarding intervention efficacy. Accordingly, it is essential that appropriate outcome measures be used to enable differentiation of painful and non-painful symptoms.

5.5 CONCLUSION

Although the pathophysiological mechanisms underlying the differences in symptom expression within CIPN remains unclear, improved screening for pain and associated functional changes will allow a better appreciation of symptom burden and encourage more tailored intervention strategies to improve the quality-of-life of cancer survivors.

CHAPTER 6

Sleep Dysfunction Associated With Worse Chemotherapy-Induced Peripheral Neurotoxicity Functional Outcomes



ABSTRACT

Purpose. Sleep problems are commonly reported by cancer survivors. However, knowledge of the impact of chemotherapy-induced peripheral neurotoxicity (CIPN) on sleep quality remains limited. In this study, we explored the impact of CIPN on sleep quality, as well as identified clinical characteristics associated with poor sleep quality. **Methods**. Participants were assessed cross-sectionally post-neurotoxic chemotherapy. CIPN severity was graded using a range of questionnaires that assessed CIPN severity and quality-of-life, as well as neurological grading scales. Sleep quality was assessed using a self-rated questionnaire (Pittsburgh Sleep Quality Index, PSQI). Participants with poor sleep quality were further grouped according to whether sleep impairment was due to CIPN or other factors. **Results**. Among 77 participants who reported CIPN, 75% (n=58) reported poor sleep quality. Of those, 41% (n=24) reported CIPN as contributing to sleep impairment, while 59% (n=34) reported other causes. Participants with CIPN-induced sleep impairments had higher CIPN severity across all outcome measures, as well as greater neuropathic pain (all $p<0.05$). Furthermore, participants with CIPN-induced sleep impairments reported worse impact of neuropathy on physical and social functioning, as well as emotional well-being (all $p<0.05$). **Conclusions**. Participants with CIPN-induced poor sleep quality reported worse scores across all CIPN severity measures. This emphasises the negative impacts of CIPN symptoms on quality-of-life of chemotherapy-treated patients and highlights the importance of sleep quality assessment in cancer survivors.

6.1 INTRODUCTION

Sleep problems are prevalent in cancer patients, but often overlooked. Approximately 25% to 60% of chemotherapy-treated patients report poor sleep quality, particularly experiences of sleep disturbance, early awakening, difficulty falling asleep, and excessive sleepiness during the day [247, 248]. More so, several studies have reported the association between poor sleep and fatigue, anxiety, as well as depression in cancer survivors [249-251]. There are multiple causes of sleep dysfunction in chemotherapy-treated patients, including cancer-related symptoms and treatment side effects such as pain, nausea, altered bowel and bladder function, and mood disturbance [252].

One common consequence of chemotherapy treatment is chemotherapy-induced peripheral neurotoxicity (CIPN), which produces symptoms of numbness, tingling, neuropathic pain and functional loss, which reduces quality-of-life of cancer patients [158]. Worse CIPN severity has been associated with increased sleep disturbance and depression in colorectal cancer survivors 1 to 7 years post-chemotherapy [66]. Similarly, a longitudinal study of colorectal cancer patients demonstrated that the development of sensory or motor PN was significantly associated with poor sleep quality with no improvements at 1 to 2 years post-cancer diagnosis [253].

There may be multiple contributors to poor sleep quality in patients with CIPN. Neuropathic pain has been reported to closely associate with declining sleep quality status in chemotherapy-treated patients [254, 255]. Accordingly, patients with painful CIPN may be at higher risk of developing anxiety, depression, and sleep disturbance [256]. In a cohort of 501 breast cancer patients, the occurrence of severe neuropathic pain was associated with a deteriorating global sleep quality from baseline to 1-year follow-up, particularly shorter sleep

duration, increased use of sleep medication, as well as trouble staying awake in social events and a lack of enthusiasm to get things done [257]. However, there is a lack of understanding of the specific impact of CIPN on sleep quality in cancer survivors and despite the potential interaction between CIPN severity and sleep quality, the impact of CIPN symptoms on sleep is not addressed in the majority of CIPN assessment tools.

Therefore, to help better understand the impact of CIPN on sleep quality [257], it is important that the specific impacts of CIPN on sleep quality are investigated. Accordingly, the aims of this study were to explore the impact of CIPN on sleep quality by identifying clinical characteristics of CIPN associated with sleep disturbance.

6.2 METHODS

6.2.1 Participants

This study was approved by the Sydney Local Heath District (RPAH zone) Human Research Ethics Committee and conducted in accordance with the Declaration of Helsinki. Consenting participants with cancer who were ≥ 18 years and who had completed their neurotoxic chemotherapy treatment (including taxanes, platinum-based, bortezomib, vinca alkaloids and thalidomide) were eligible for the cross-sectional study. Clinical data were retrieved from patient medical records. Informed consent was obtained from each participant.

6.2.2 Sleep assessment: Patient-reported outcome measures

Assessment of sleep quality and patterns were undertaken via the Pittsburgh Sleep Quality Index (PSQI). PSQI is a 19-item questionnaire comprised of seven subdomains: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, the use of sleep medications as well as daytime dysfunction over the past month. Each component has a 4-point score, with 0 indicating 'no trouble on sleep during the past month', 1: 'trouble less than once a week', 2: 'trouble once or twice a week', and 3: 'trouble three or more times a week'. Each subdomain was broken down into components of varying severity and dysfunction, according to a publicly available algorithm. All seven components sum up to provide a global PSQI score ranging from 0 to 21, with higher scores indicating worse sleep quality [171].

Sleep disturbance was measured using the Patient Reported Outcomes Measurement Information System (PROMIS-SD) 8-item short form (v. 1.0; 8a) [172]. It consists of 8-items that measure self-reported perceptions of sleep depth, restoration, and quality in the past week prior to testing. Each item has a 5-point Likert scale, and the sum of all 8-items

generated a raw score, which was then converted to a standardised T-score according to the conversion tables published on the PROMIS website (nihpromis.org). Higher T-scores indicated greater sleep disturbances.

6.2.3 Patient-reported outcome measures, clinical neuropathy assessment & functional assessment

Assessment tools are briefly described below with further details available in Appendix 2, Supplementary Methods 2.1.

The Chronic Acquired Polyneuropathy Patient-Reported Index (CAP-PRI) is a health-related quality-of-life (HRQoL) measure that were used to assess patient's emotional well-being, pain severity and social and physical functioning, including trouble sleeping due to neuropathy [167]. The European Organisation of Research and Treatment of Cancer Quality-of-Life Questionnaire-Core (EORTC-QLQ-CIPN20) was used to assess autonomic, motor, and sensory PN symptoms [138]. The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) was used to assess the severity and interference of the numbness and tingling in the hands and feet [166]. A modified version of the Pain Numeric Rating Scale (PNRS) was used for the assessment of the intensity of neuropathic pain experienced [169]. (Detailed in Appendix 2, Supp. Methods 2.1.1)

The severity of CIPN was clinically graded by research assistants using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) sensory subscale Version 4.0 with CIPN severity graded on a scale from Grade 0 = no CIPN to Grade 4= disabling. Total Neuropathy Score-clinical version (TNSc©, John Hopkins University) which

comprised patient report, sensory and neurological examination also graded CIPN severity [105, 109, 110]. (Detailed in Appendix 2, Supp. Methods 2.1.2)

Assessment of sensory acuity in the fingers of the dominant hand was undertaken by identifying the perception threshold for the Grating Orientation task (GOT) and Von Frey monofilament task [178, 179]. Assessment of fine motor skills and manual dexterity was undertaken via time taken to complete the Grooved Pegboard Task [180]. (Detailed in Appendix 2, Supp. Methods 2.1.3)

Neurophysiological measurements, including nerve conduction studies measuring sural and tibial nerve amplitudes of the lower limb as well as sensory and motor median nerve amplitudes of the upper limb were undertaken, following methodologies as per previous studies [214].

6.2.4 Participant classification

Participants with no CIPN (NCI-CTCAE grade 0) were excluded from further analysis of the effects of CIPN on sleep quality. The remaining participants were classified based on their global PSQI score. Participants who had a global PSQI score of ≥ 5 were placed in the 'Poor Sleep Quality' group, while those with a score of < 5 comprised the 'Good Sleep Quality' group, as per previous work [258].

Participants in the 'Poor Sleep Quality' group were further classified to determine the cause of sleep impairment according to their responses to the CAP-PRI item 'do you have trouble sleeping due to your neuropathy'. Responses of "A little bit" or "A lot" were placed in the 'CIPN-induced sleep impairments' group, while a "Not at all" response comprised the 'Sleep impairment due to other factors' group. Furthermore, factors causing sleep impairments in participants with poor sleep quality were identified by reporting percentage of participants with sleep dysfunction ("less than once a week" OR "once or twice a week" OR "three or more times a week") to each item of the sleep disturbance subdomain of the PSQI (Q5a to Q5j), as well as participant responses to the semi-structured interview question "do you have trouble sleeping due to neuropathy symptoms?"

6.2.5 Statistical Analyses

SPSS Statistics Software V27 (IBM, Armonk, NY) was used for all analyses in this study. Normality of data was evaluated using the Shapiro-Wilk test. A p-value of >0.05 highlights the normally distributed data which were presented as mean ± standard deviation (SD), while a p-value of <0.05 highlights the non-normally distributed data which were presented as medians and interquartile range (IQR). The associations between sleep outcome measures, demographic characteristics, functional assessments, CIPN severity and pain outcome measures were undertaken using Pearson's or Spearman's correlation coefficients, for normally and non-normally distributed data, respectively. Group comparisons were also investigated using Mann-Whitney U, independent sample t-tests or Chi-square tests.

6.3 RESULTS

6.3.1 Demographic and clinical history

A total of 87 participants were assessed cross-sectionally post-neurotoxic chemotherapy treatment. Out of 87 participants, 11% (n=10) reported no CIPN at the time of assessment and were excluded from further analyses.

The remaining 89% (n=77) reported CIPN. They had a mean age of 63.4 ±11.3 years and were 13.0(IQR=21.0) months post-neurotoxic chemotherapy treatment completion. Of those, 68% (n=52) were female participants, mostly diagnosed with gynaecological (29%, n=38) or haematological cancers (20%, n=26). Taxane (50%, n=38), platinum-based agents (25%, n=19) or bortezomib (23%, n=18) were the most common chemotherapy types administered to participants (Table 6.3.1). Overall, 39% (n=30 of 77) of participants graded with mild CIPN (NCI-CTCAE Grade 1) while 61% (n=47) were graded with moderate-to-severe CIPN (NCI-CTCAE Grade ≥2).

6.3.2 Sleep Quality Profile in Chemotherapy-Treated Patients

Of the 77 participants who reported CIPN, 75% (n=58) reported poor sleep quality, while 25% (n=19) reported good sleep quality (Table 6.3.1). Participants who reported poor sleep quality were younger than those who reported good sleep quality ($p=0.02$), however, there were no differences in sex, BMI, cancer type, cancer stage or chemotherapy type between the two groups (all $p>0.05$) (Table 6.3.1). All demographic and clinical information for participants is found in Table 6.3.1.

The outcomes of the subdomains of the self-reported sleep questionnaire (PSQI) are reported in Figure 6.3.1. Overall, more than 70% of all participants reported poor subjective sleep quality (Fig. 6.3.1A), increased time taken to fall asleep (sleep latency) (Fig. 6.3.1B), shorter sleep duration (Fig. 6.3.1C) and mild-to-severe daytime dysfunction (Fig. 6.3.1D). More so, 60% of participants reported moderately-to-greatly reduced sleep efficiency (Fig. 6.3.1E), while 69% reported moderate-to-great sleep disturbance (Fig. 6.3.1F). However, only 30% of participants reported using sleep medications in the past month prior to testing (Fig. 6.3.1G).

Participants with poor sleep quality had greater impact on all components of their sleep, including worse subjective sleep quality, increased sleep latency, shorter sleep duration, greater sleep disturbance, and reduced sleep efficiency compared to participants with good sleep quality (all $p\leq0.005$) (Table 6.3.2).

6.3.3 Impact of CIPN severity on Sleep Quality

Associations between CIPN severity measures and sleep quality of all participants were assessed. Overall, greater CIPN interference on participant's activities of daily living (PRO-CTCAE) was associated with worse sleep quality (higher PSQI global scores) (r_s= 0.2, p=0.03), including increased reported daytime dysfunction, as assessed by trouble staying awake and problems with keeping up enthusiasm (r_s=0.3, p=0.002). In addition, the severity of neuropathic pain (PNRS) was also associated with increased reported daytime dysfunction (r_s=0.2, p=0.03). Furthermore, increased CIPN severity, as assessed on the patient-reported outcome (EORTC-QLQ-CIPN20), was associated with reduced reported hours of sleep (subjective sleep quality subdomain) (r_s=0.2, p=0.04). However, there were no associations with other CIPN severity outcome measures and sleep parameters, including health-related quality-of-life (CAP-PRI), clinically-graded CIPN (NCI-CTCAE), and neurologically graded CIPN (TNSc, all p>0.05).

Similarly, there were no significant differences on CIPN severity measures between participants with poor and good sleep quality. This included the patient-reported outcome measures, the clinically-graded scale, and the neurological examination score (all p>0.05) (Table 6.3.2). Participants with poor sleep quality had significantly higher sural and tibial amplitudes (both p≤0.01) as well as better fine motor skills (Grooved Pegboard Task; p=0.02) than those with good sleep quality, but they were also older than participants with poor sleep quality (Table 6.3.1).

Participants with CIPN (n=77)	Good Sleep Quality (n=19)		Poor Sleep Quality (n=58)		Total (n=77)		P-value
	n	%	n	%	n	%	
Clinical characteristics							
Female Sex	11	58	41	71	52	68	0.3
Cancer Type							
Breast	1	5	5	9	6	8	0.9
Gynaecological (Cervical, Endometrial & Ovarian)	9	48	20	35	29	38	
Haematological (Myeloma & Hodgkin's Lymphoma)	5	26	15	26	20	26	
GI/Colorectal & Pancreatic	2	11	10	17	12	15	
Testicular & Prostate	1	5	2	3	3	4	
Other	1	5	3	5	4	5	
Missing	0	0	3	5	3	4	
Chemotherapy Type							
Taxane	9	48	29	50	38	50	0.2
Platinum-based	4	21	15	26	19	25	
Bortezomib	4	21	14	24	18	23	
Vincristine	1	5	0	0	1	1	
Thalidomide	1	5	0	0	1	1	
Cancer Stage							
0	0	0	1	2	1	1	0.9
I	3	16	6	10	9	12	
II	3	16	11	19	14	18	
III	6	32	15	26	21	27	
IV	2	10	6	10	8	10	
No stage (non-solid tumours)	5	26	15	26	20	26	
Missing	0	0	4	7	4	5	
Demographic characteristics							
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P-value**
Age (years)	**68.3**	**11.8**	**61.7**	**10.7**	**63.4**	**11.3**	**0.02**
BMI (kg/m^2)	25.3	4.4	26.4	5.5	26.2	5.3	0.5
Months since treatment completion; median (IQR)	14.0	24.0	12.5	20.0	13.0	21.0	0.3

Table 6.3.1. Demographic and clinical history of participants with good sleep quality vs poor sleep quality. Comparisons between both groups were performed using Chi-square tests. Demographic characteristics were also compared between good and poor sleep quality groups using independent sample t-tests. *Indicates p-values using Mann-Whitney U tests. $p<0.05$ was considered significant.

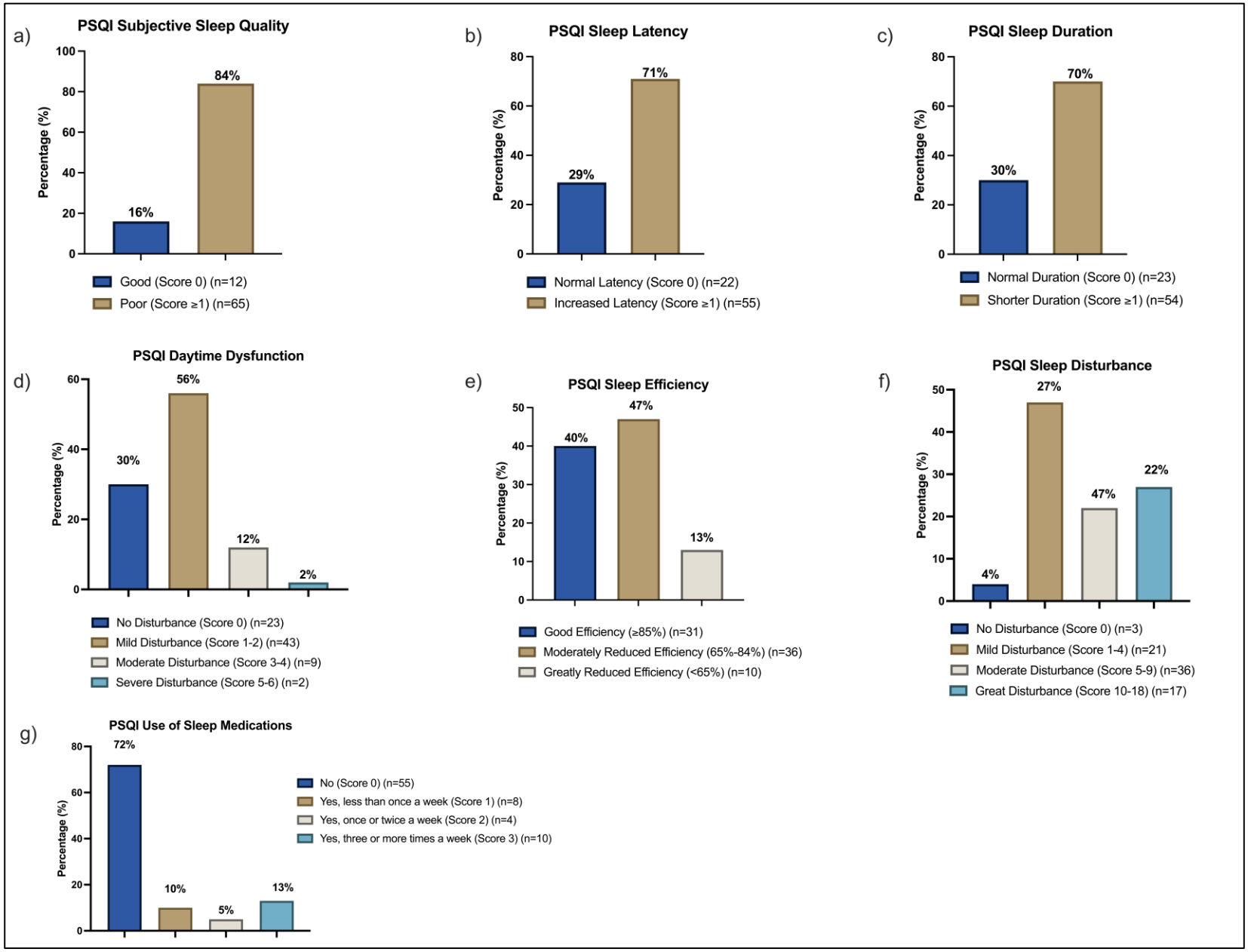

a)
PSQI Subjective Sleep Quality
Percentage (%)
16%
84%
Good (Score 0) (n=12)
Poor (Score ≥1) (n=65)
b)
PSQI Sleep Latency
Percentage (%)
29%
71%
Normal Latency (Score 0) (n=22)
Increased Latency (Score ≥1) (n=55)
c)
PSQI Sleep Duration
Percentage (%)
30%
70%
Normal Duration (Score 0) (n=23)
Shorter Duration (Score ≥1) (n=54)
d)
PSQI Daytime Dysfunction
Percentage (%)
30%
56%
12%
2%
No Disturbance (Score 0) (n=23)
Mild Disturbance (Score 1-2) (n=43)
Moderate Disturbance (Score 3-4) (n=9)
Severe Disturbance (Score 5-6) (n=2)
e)
PSQI Sleep Efficiency
Percentage (%)
40%
47%
13%
Good Efficiency (≥85%) (n=31)
Moderately Reduced Efficiency (65%-84%) (n=36)
Greatly Reduced Efficiency (<65%) (n=10)
f)
PSQI Sleep Disturbance
Percentage (%)
4%
27%
47%
22%
No Disturbance (Score 0) (n=3)
Mild Disturbance (Score 1-4) (n=21)
Moderate Disturbance (Score 5-9) (n=36)
Great Disturbance (Score 10-18) (n=17)
g)
PSQI Use of Sleep Medications
Percentage (%)
72%
10%
5%
13%
No (Score 0) (n=55)
Yes, less than once a week (Score 1) (n=8)
Yes, once or twice a week (Score 2) (n=4)
Yes, three or more times a week (Score 3) (n=10)

Figure 6.3.1. Percentage of all participants reporting sleep problems across PSQI subdomains, including (A) subjective sleep quality, (B) sleep latency, (C) sleep duration, (D) daytime dysfunction, (E) sleep efficiency, (F) sleep disturbance and (G) the use of sleep medications in the past month prior to testing. Blue indicates normal responses and absence of dysfunction, while other colours indicate the presence of varying severity and dysfunction (indicated in key legend of each figure).

Participants with CIPN (n=77)	Good Sleep Quality (n=19)		Poor Sleep Quality (n=58)		P-value
	Median	IQR	Median	IQR	
Functional assessments					
Grating Orientation Task (GOT) Threshold (mm)	3.9	3.1	3.3	1.2	0.3
Average Pegboard Time (secs) (mean, SD)*	**84.2**	**16.3**	**70.9**	**14.7**	**0.002**
Von Frey Threshold (mN)	0.4	0.7	0.4	0.5	0.8
Sleep outcome measures					
PSQI Global Score	**3.0**	**2.0**	**8.0**	**4.0**	**<0.001**
PSQI Subjective Sleep Quality	**1.0**	**1.0**	**1.0**	**1.0**	**<0.001**
PSQI Sleep Latency	**1.0**	**2.0**	**2.0**	**3.0**	**0.005**
PSQI Sleep Duration	**0**	**1.0**	**1.0**	**1.0**	**<0.001**
PSQI Sleep Efficiency (%) (mean, SD)*	**90.3**	**6.5**	**75.3**	**14.6**	**<0.001**
PSQI Sleep Disturbance (mean, SD)*	**3.8**	**2.8**	**7.7**	**3.7**	**<0.001**
PSQI Use of Sleep Medications	**0**	**0**	**0**	**1.0**	**0.002**
PSQI Daytime Dysfunction	**0**	**1.0**	**1.0**	**1.0**	**0.005**
PROMIS Sleep Disturbance (T-score)	47.9	1.2	50.8	6.4	0.07
CIPN outcome measures					
Patient-Reported Outcome (PRO-CTCAE) Severity score	1.0	1.0	2.0	1.0	0.6
Patient-Reported Outcome (PRO-CTCAE)	0	1.0	1.0	1.0	0.1

Interference score					
Neurological Examination Score (TNSc)	5.0	3.0	4.0	4.0	0.5
Patient-Reported Outcome (EORTC-QLQ-CIPN20) score	12.3	10.5	15.3	14.0	0.2
Health-Related Quality-of-Life Measure (CAP-PRI) score	2.0	4.0	3.5	8.0	0.3
Clinically-Graded Scale (NCI-CTCAE)	2.0	1.0	2.0	1.0	0.6
Neurophysiological measurements					
Sural Amplitude (μV)	**3.0**	**7.2**	**7.8**	**9.5**	**0.009**
Tibial Amplitude (mV)	**5.7**	**6.8**	**9.9**	**9.6**	**0.01**
Pain outcome measures					
Patient-Reported Pain Scale (PNRS)	0	3.0	0	3.0	0.9

Table 6.3.2. Comparison of neuropathy outcome measures between participants with good and poor sleep quality, using Mann-Whitney U tests. $p<0.05$ was considered significant. *Indicates p-values using independent sample t-tests. Higher scores on CIPN outcome measures and function assessments, including lower amplitudes on neurophysiological measures, indicates worse impairment.

6.3.4 Comparing Sleep Quality affected by CIPN vs Other Factors

Participants who reported poor sleep quality (n=58) reported which factors affected their sleep. Overall, more than 50% reported trouble sleeping due to not being able to sleep within 30 minutes (66%, n=38), waking up in the middle of the night or early morning (88%, n=51), getting up to use the bathroom (64%, n=37) or feeling too hot (55%, n=32) (Appendix 2, Supp. Fig. 2.2.1). Other reasons for sleep disturbance included pain, anxiety, stress, and overthinking (detailed in Appendix 2, Supp. Fig. 2.2.1). However, 41% (n=24) reported that CIPN symptoms were a factor contributing to their poor sleep quality. Participants reported that CIPN-related discomfort or pain led to trouble getting to sleep or caused early waking.

Group comparisons between participants who reported CIPN-induced sleep impairments (n=24) and sleep-impairments due to other factors (n=34) were undertaken. There were no demographic differences between both groups, including age, BMI, sex, as well as cancer type, cancer stage and chemotherapy type (all $p>0.05$) (Table 6.3.3). More so, overall sleep quality did not differ between both groups ($p>0.05$), as well as no significant differences in functional assessments or neurophysiological measures between groups (all $p>0.05$) (Table 6.3.4). However, participants with CIPN-induced sleep impairments had significantly higher CIPN severity, including higher scores on patient-reported outcome measures (EORTC-QLQ-CIPN20), HRQoL measure (CAP-PRI), clinically-graded scale (NCI-CTCAE) and the neurological examination score (TNSc) (all $p\leq0.01$). Furthermore, participants with CIPN-induced sleep impairments had greater perceived CIPN severity (PRO-CTCAE Severity) and greater CIPN interference on activities of daily living (PRO-CTCAE Interference) (both $p<0.01$) (Table 6.3.4).

To examine the impact of neuropathy on the quality-of-life of participants with poor sleep quality, specific items of the HRQoL measure (CAP-PRI) were investigated including physical functioning, social functioning, emotional well-being, and pain (Fig. 6.3.2). Overall, participants with CIPN-induced sleep impairments compared to other factors had significantly greater impacts of CIPN on physical functioning, particularly being bothered by limitations in doing work ($p=0.03$) and trouble getting dressed ($p=0.002$) (Fig. 6.3.2A) as well as greater decline in social functioning, including being dependent on others ($p=0.04$) and unable to do leisure activities due to their CIPN ($p=0.01$) (Fig. 6.3.2B). They reported being significantly more frustrated, depressed, worn-out, and pre-occupied with their CIPN (all $p<0.05$) compared to participants with sleep impairments due to other factors (Fig. 6.3.2C).

The impact of pain on participants with poor sleep quality was also investigated between both groups. In total, 63% (n=15) of participants with CIPN-induced sleep impairments reported feeling bothered by pain due to CIPN (CAP-PRI Q2), compared to only 15% (n=5) of participants with sleep impairments due to other factors ($p<0.001$) (Fig. 6.3.2D).

Poor Sleep Quality Group (n=58)	Sleep impairments due to other factors (n=34)		CIPN-induced sleep impairments (n=24)		Total (n=58)		P-value
	n	%	n	%	n	%	
Clinical characteristics							
Female Sex	26	77	15	63	41	71	0.3
Cancer Type							
Breast	3	9	2	8	5	9	0.8
Gynaecological (Cervical, Endometrial & Ovarian)	10	29	9	38	19	33	
Haematological (Myeloma & Hodgkin's Lymphoma)	11	32	4	17	15	26	
GI/Colorectal & Pancreatic	5	15	5	21	10	17	
Testicular & Prostate	1	3	1	4	2	3	
Other	2	6	1	4	3	5	
Missing	2	6	2	8	4	7	
Chemotherapy Type							
Taxane	18	53	11	46	29	50	0.2
Platinum-based	6	18	9	38	15	26	
Bortezomib	10	29	4	16	14	24	
Cancer Stage							
I	4	12	2	7	6	10	0.6
II	7	21	3	13	10	18	
III	7	21	8	33	15	26	
IV	3	9	3	13	6	10	
No stage (non-solid tumours)	11	32	4	17	15	26	
Missing	2	5	4	17	6	10	
Demographic characteristics							
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P-value**
Age (years)	61.0	12.2	62.8	8.4	61.7	10.7	0.5
BMI (kg/m^2)	26.1	5.3	27.1	6.1	26.4	5.5	0.6
Months since treatment completion; median(IQR)	13.0	20.0	9.0	16.0	12.5	20.0	0.2

Table 6.3.3. Demographic and clinical history of poor sleep quality cohort who had trouble sleeping due to CIPN vs due to other factors. Comparisons between both groups were performed using Chi-square tests. Demographic characteristics were compared using independent sample t-tests. *Indicates p-values using Mann-Whitney U tests. $p<0.05$ was considered significant.

Poor Sleep Quality Group (n=58)	Sleep impairments due to other factors (n=34)		CIPN-induced sleep impairments (n=24)		P-value
	Median	IQR	Median	IQR	
Functional assessments					
Grating Orientation Task (GOT) Threshold (mm)	3.2	1.3	3.4	1.2	0.1
Average Pegboard Time (secs) (mean, SD)*	69.5	13.7	73.0	16.2	0.4
Von Frey Threshold (mN)	0.2	0.6	0.6	0.6	0.07
Sleep outcome measures					
PSQI Global Score	8.0	4.0	8.0	4.0	0.9
PSQI Subjective Sleep Quality	1.0	1.0	1.5	1.0	0.06
PSQI Sleep Latency	2.0	2.0	2.0	4.0	0.5
PSQI Sleep Duration	1.0	1.0	1.0	1.0	0.6
PSQI Sleep Efficiency (%) (mean, SD)*	74.1	13.2	77.0	16.5	0.5
PSQI Sleep Disturbance (mean, SD)*	7.2	3.4	8.4	3.6	0.2
PSQI Use of Sleep Medications	0	2.0	0	1.0	0.1
PSQI Daytime Dysfunction	1.0	1.0	1.0	1.0	0.4
PROMIS Sleep Disturbance (T-score)	49.1	5.9	52.9	6.2	0.09
CIPN outcome measures					
Patient-Reported Outcome (PRO-CTCAE) Severity score	**1.0**	**1.0**	**2.0**	**1.0**	**<0.001**
Patient-Reported Outcome (PRO-CTCAE) Interference score	**0**	**1.0**	**1.0**	**2.0**	**0.008**
Neurological Examination Score (TNSc)	**3.0**	**4.0**	**5.0**	**3.0**	**0.01**
Patient-Reported Outcome	**10.5**	**10.9**	**22.8**	**11.4**	**<0.001**

(EORTC-QLQ-CIPN20) score					
Health-Related Quality-of-Life Measure (CAP-PRI) score	**1.0**	**4.0**	**6.0**	**6.0**	**<0.001**
Clinically-Graded Scale (NCI-CTCAE)	**1.0**	**1.0**	**2.0**	**0**	**0.001**
Neurophysiological measures					
Sural Amplitude (μV)	10.5	10.5	7.3	6.2	0.3
Tibial Amplitude (mV)	10.3	10.9	9.8	6.7	0.9
Pain outcome measures					
Patient-Reported Pain Scale (PNRS)	**0**	**0**	**2.5**	**5.0**	**0.007**

Table 6.3.4. Comparison of sleep outcome measures between participants with trouble sleeping due to CIPN or due to other factors, using Mann-Whitney U tests. $p<0.05$ was considered significant. *Indicates p-values using independent sample t-tests. Higher scores indicate worse impairment on sleep quality.

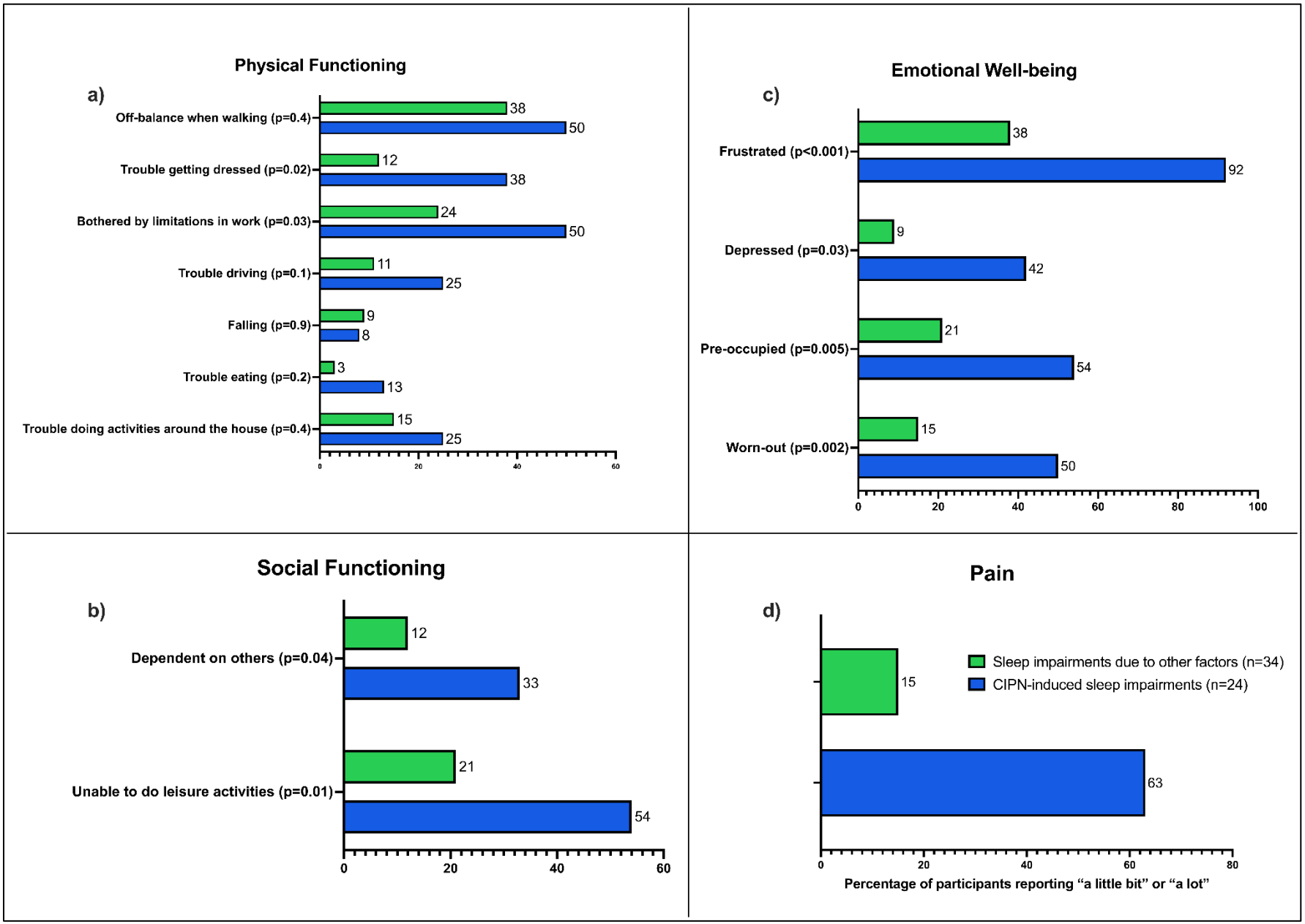

Physical Functioning
a)
Off-balance when walking (p=0.4)
38
50
Trouble getting dressed (p=0.02)
12
38
Bothered by limitations in work (p=0.03)
24
50
Trouble driving (p=0.1)
11
25
Falling (p=0.9)
9
8
Trouble eating (p=0.2)
3
13
Trouble doing activities around the house (p=0.4)
15
25
0
20
40
60
Emotional Well-being
c)
Frustrated (p<0.001)
38
92
Depressed (p=0.03)
9
42
Pre-occupied (p=0.005)
21
54
Worn-out (p=0.002)
15
50
0
20
40
60
80
100
Social Functioning
b)
Dependent on others (p=0.04)
12
33
Unable to do leisure activities (p=0.01)
21
54
0
20
40
60
Pain
d)
Sleep impairments due to other factors (n=34)
CIPN-induced sleep impairments (n=24)
15
63
0
20
40
60
80
Percentage of participants reporting “a little bit” or “a lot”

Figure 6.3.2. Comparison of percentage of poor sleep quality participants with sleep impairments due to CIPN (n=24) vs other factors (n=34) reporting at least "a little bit" or "a lot" on items of (A) physical functioning, (B) social functioning, (C) emotional well-being and (D) pain on the HRQoL measure (CAP-PRI), using Mann-Whitney U tests. $p<0.05$ was considered significant.

6.4 DISCUSSION

This study investigated the sleep quality of neurotoxic chemotherapy-treated patients. Overall, 75% of participants with CIPN reported poor sleep quality, particularly poor subjective sleep quality, increased sleep latency, shorter sleep duration, reduced sleep efficiency and greater sleep disturbance. Participants reported multiple factors contributing to their poor sleep quality, including difficulty falling asleep, inappropriate waking, getting up to use the bathroom and temperature disturbance. Importantly, 41% of these participants with poor sleep quality reported CIPN as the cause of their sleep impairments. People with CIPN-induced sleep disturbance reported worse CIPN severity, worse physical and social functioning, as well as worse emotional well-being and higher incidences of neuropathic pain when compared to participants with sleep impairments attributed to other factors.

Overall, there is a high burden of sleep dysfunction in cancer survivors, even following treatment completion. In our study, three quarters of our participants with CIPN reported poor sleep quality. This is comparable to previous studies on cancer survivors, with percentages ranging from 59% to 80% [157, 249, 259]. There were no differences in CIPN severity between participants with poor sleep quality and participants with good sleep quality. Interestingly, participants with poor sleep quality were younger in age than participants with good sleep quality, in line with previous studies [260, 261]. Although it remains unclear as to why younger patients are at greater risk of developing sleep problems, it could be that they may have better tolerance of treatment, leading to higher doses delivered [262]. They also may have higher levels of psychological distress, which may contribute to a worsening quality-of-life, in comparison to older patients [263]. However, since our cohort were assessed after chemotherapy treatment completion, the reason for this finding remains unclear.

There have been a number of studies that have investigated sleep quality of cancer patients throughout their chemotherapy treatment, but only a few have investigated the association between sleep quality status and chronic CIPN post-chemotherapy completion. A systematic review and meta-analysis of sleep quality in cancer patients indicated that patients reported poorer sleep quality during their chemotherapy, compared to before commencement and after completion [159]. More so, studies have suggested that patients experience improvements in their overall sleep quality after treatment completion, particularly between 3 to 12 months [264, 265]. However, our study revealed that poor sleep quality persists in neurotoxic chemotherapy-treated patients at a median of 13 months post-neurotoxic chemotherapy.

A limited number of previous studies have described the impact of chronic CIPN on sleep quality, particularly indicating that patients with more severe neuropathy report greater depression, insomnia, and worse health-related quality-of-life [66, 253]. Our study conducted group comparisons between participants with poor sleep quality due to CIPN versus other factors. In this study, we demonstrated that participants who report poor sleep quality due to CIPN have greater CIPN severity, with significantly more negative impacts on their quality-of-life, including worse physical, social, and emotional well-being.

Neuropathic pain was also investigated as a potential factor impacting the sleep quality of chemotherapy-treated patients. Among the 7 subdomains of the PSQI, higher incidence of neuropathic pain was significantly associated with daytime dysfunction, which is consistent with previous findings [257]. With a growing body of evidence suggesting that the presence of neuropathic pain may exacerbate poor sleep quality [266], we further investigated patient-reported neuropathic pain in the poor sleep quality cohort and found those with CIPN-

induced sleep impairments were substantially more likely to report painful CIPN than those with sleep impairments due to other factors (63% vs 15%, respectively). This finding suggests that painful CIPN adds an additional burden on sleep and quality-of-life of cancer survivors.

To date, there have been over 100 tools developed and validated for the assessment of CIPN [267]. This includes a range of patient-reported outcome measures, clinician-based measures, and neurological examination measures, which all aim to assess the severity and degree of CIPN. Unfortunately, the majority of these tools do not contain items designed to assess the presence and severity of sleep problems due to CIPN. Importantly, the most commonly used patient-reported outcome measures for CIPN (reviewed in [236]) do not encompass sleep dysfunction. As evident in the current study, sleep problems due to CIPN exist in a large proportion of neurotoxic chemotherapy-treated cancer survivors. Given that the presence of sleep dysfunction in people with CIPN is associated with worse physical, social, and emotional wellbeing, it is important to utilise tools that recognise sleep dysfunction to identify patient subsets with different clinical characteristics and allow for targeted referral and treatment optimisation.

Overall, this study improves our understanding of the impact of CIPN on the sleep quality of chemotherapy-treated cancer survivors. We used a validated sleep assessment tool with index cut-offs to identify cohorts with poor sleep quality. Although we used a validated measure, it was self-reported which may introduce bias compared to polysomnography [268]. Further, due to the cross-sectional nature of this study, we are limited in our understanding of the progression and impact of CIPN symptoms on sleep quality during treatment. In addition, the low sample size of patients with good sleep quality may have led to low statistical power of

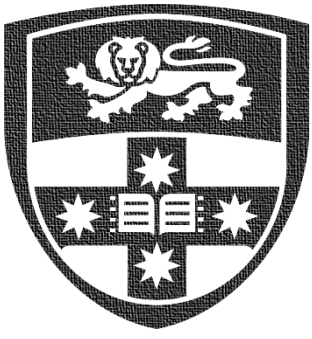
the group comparison. Therefore, a larger sample size may be required to confirm the results that were found in this study. Given that our cohort was assessed around 13 months post-neurotoxic chemotherapy treatment, additional comorbidities may have developed that could impact sleep. However, a specific question related to impact of CIPN on sleep was used to categorise participants and attribute the cause of sleep impairment, making it more likely that CIPN was related to sleep dysfunction. Because our study included a mix of cancer and chemotherapy types, this also limits our understanding of the impact of specific cancer and chemotherapy types on overall sleep quality.

6.5 CONCLUSIONS

There is a high burden of sleep dysfunction in neurotoxic chemotherapy-treated cancer survivors. These results highlight the persistence and impact of sleep problems due to CIPN long after treatment completion, which contribute to a worsening quality-of-life. Poor sleep quality was associated with worse CIPN and neuropathic pain, which may impose a great burden on quality-of-life. Our results reinforce the need to improve the currently-used tools to incorporate more focused assessment of sleep quality, which may ultimately help lessen the impact of chronic CIPN on patient function and improve their quality-of-life.

CHAPTER 7

SUMMARY AND CONCLUSIONS



7.1 SUMMARY & CONCLUSIONS

The studies contained in this thesis were focused on the classification and investigation of the impact of CIPN and delineation of phenotypic subgroups, including those with neuropathic pain, sleep dysfunction or upper-limb dysfunction. This necessitated utilisation of a range of assessment tools to appropriately assess CIPN, including novel tools potentially examining autonomic and small nerve fibre dysfunction. Taken together, this work investigated assessment strategies to quantify the impact of CIPN-associated symptoms on the quality-of-life of cancer survivors.

In summary, Chapter 3 examined the association of subjective and objective measures of CIPN severity with ESC values via Sudoscan, a potential measure of autonomic function. Chapter 4 compared these subjective and objective measures of CIPN severity to a range of upper-limb measures and assessment tools in order to identify associations with upper-limb CIPN, including the burden of upper-limb CIPN symptoms on patient function. Following the investigation of CIPN severity assessment tools, Chapter 5 then clinically characterised the differences between painful and non-painful CIPN subgroups, including the impact of pain on symptom burden in chemotherapy-treated patients. Finally, sleep dysfunction, which is an under-investigated comorbidity in chemotherapy-treated patients, was investigated in Chapter 6, including the specific impact of CIPN on the sleep quality of cancer survivors with CIPN.

To improve CIPN assessment, there remains a need for a fast, easy, reliable, and implementable measure of small nerve fibre dysfunction in chemotherapy-treated patients. Chapters 3 and 4 of this thesis investigated the clinical utility of two proposed measures of autonomic and small nerve fibre dysfunction: ESC via Sudoscan and EMLA-Induced SSW.

Both of these measures have previously been assessed in comparison to IENFD via skin biopsy, a validated measure of small nerve fibre dysfunction. Findings have demonstrated that reduced IENFD was associated with lower ESC values [210] and lower SSW scores [184, 229], which further highlights their potential use as tools to assess small nerve fibre dysfunction. However, the findings in presented in this thesis do not support their utility in neurotoxic chemotherapy-treated patients.

As reported in Chapter 3, ESC values via Sudoscan revealed that sudomotor dysfunction was prevalent in 49% of patients with CIPN. Although this is in line with previously reported findings of ESC dysfunction in chemotherapy-treated cohorts [206, 212, 213], there was a lack of association of ESC values with any CIPN severity measures or the autonomic outcome measure, suggesting their lack of ability to predict any patient-reported and clinically-graded CIPN severity or autonomic dysfunction. Chapter 4 was the first study to investigate the utility of EMLA-induced SSW as a measure of small nerve fibre dysfunction in chemotherapy-treated patients. Given its association to IENFD via skin biopsy as well as its purported utility in identifying small nerve fibre dysfunction in diabetic [186], CTS [223] and HIV neuropathy [185], investigation of its utility in CIPN was pursued. Only 22% of patients with CIPN demonstrated abnormal SSW and there were no associations between SSW scores and global CIPN severity. Given that there were no other CIPN studies that investigated this tool to date, comparison of these findings was not possible. Overall, the proportion of patients with CIPN who have small nerve fibre dysfunction remains unknown. There have been inconclusive findings from skin biopsy studies in CIPN research, including its variability across different chemotherapy agents [96]. Therefore, by investigating the use of EMLA-induced SSW on a homogeneous cohort who were treated with a single

chemotherapy type may help address the aforementioned limitations in understanding its clinical utility in patients with CIPN.

There have been several criticisms pertaining to the use of Sudoscan, as well as EMLA-induced SSW. Firstly, there is a lack of evidence that ESC values via Sudoscan directly measure small nerve fibre dysfunction, with concerns over the biological plausibility of this method [209]. Furthermore, both SSW [230] and Sudoscan [209] lack of pre-defined thresholds for normative data to suggest the presence of dysfunction, which further adds to their inconsistent and unreliable use as small nerve fibre measures. Therefore, the results of these chapters highlight the remaining need for a better measure of CIPN-associated autonomic or small nerve fibre function. Furthermore, investigating these novel small nerve fibre measures revealed the difficulty of assessing their efficacy in a cohort of patients that present with various symptom profiles. Hence, it was important that patients were sub-grouped based on their clinical symptom profiles to identify different characteristics, with a particular focus on upper-limb function, pain, and sleep quality, for a better assessment of symptoms.

The vast majority of CIPN research focuses on assessment of lower-limb CIPN symptoms. While lower-limb symptoms are typically more severe and prevalent than upper-limb CIPN symptoms [38], the impact of upper-limb CIPN symptoms has been less examined. Therefore, Chapter 4 compared a range of functional assessment tools and neurophysiological measures, with a particular focus on their ability to assess upper-limb CIPN symptoms and functional deficits. After the completion of chemotherapy treatment, 65% of patients with CIPN reported chronic upper-limb symptoms. More so, this study demonstrated the presence of high symptom burden of upper-limb CIPN symptoms on

patient function, including difficulty in writing and manipulating small objects with their fingers. This is in line with prior findings, whereby a large proportion of chemotherapy-treated patients reported functional deficits in typing, writing and buttoning clothing items [220-222]. This highlights the need to clinically phenotype patients according to the presence or absence of these symptoms, in order to guide appropriate upper-limb targeted rehabilitation options and supportive care management alongside lower-limb interventions, to potentially aid in lessening overall symptom severity and improve quality-of-life.

To further phenotype CIPN symptom burden, Chapter 5 compared the prevalence and symptom burden between CIPN subgroups with neuropathic pain and without pain. This investigation involved a large cohort study that provided a clearer understanding of differing symptom patterns of painful and non-painful CIPN by using a combination of patient-reported and clinically-graded outcome measures of CIPN. The study identified 33% of patients with painful CIPN, in line with prior studies [108, 126, 143], which was also associated with higher CIPN severity and more functional consequences in comparison to patients with non-painful CIPN. Furthermore, the presence of painful CIPN led to patient-reported exercise intolerance, sleep dysfunction and reduced functional capacity, as well as increased treatment seeking. Investigation of symptom burden of specific chemotherapy drugs revealed that painful CIPN was significantly more prevalent in oxaliplatin-treated patients, in addition to worse CIPN symptoms, greater functional changes in sensory perception and fine motor skills, as well as lower sural amplitudes, in comparison to paclitaxel-treated patients.

The most commonly-used screening tools in CIPN research have limited ability to identify the symptom burden of painful CIPN. For instance, the clinically-graded scale NCI-CTCAE

is the most frequently-used tool for CIPN grading [94], however it does not include neuropathic pain in its grading criteria. The patient-reported outcome measure EORTC-QLQ-CIPN20 contains two items that assess shooting or burning pain in the upper and lower extremities, but these are not specifically validated to identify neuropathic pain. Other neuropathic pain tools, such as the PNRS [169] and the DN4 [147], may not be appropriate tools due to the short recall period, as well as the lack of separating non-painful from painful symptoms, such as numbness and tingling from burning pain and electric shock sensations, respectively. Therefore, the results of Chapter 5 recommended that painful symptoms should be assessed in research and clinical settings as part of a comprehensive CIPN assessment, which includes assessment tools with a recall period of longer than 24 hours, as well as additional tools to the CIPN outcome measures currently utilised, in order to address it.

Based on the behavioural changes investigated in Chapter 5, sleep dysfunction was identified as one of the major factors associated with painful CIPN. However, the existing CIPN literature lacked data on demonstrating the specific impact of chronic CIPN on the sleep quality of chemotherapy-treated patients. Therefore, Chapter 6 used a validated sleep assessment tool with index cut-offs that helped to identify the prevalence of sleep dysfunction in the cohort. In total, 75% of patients with CIPN reported poor sleep quality, which is comparable to previous studies [157, 249, 259]. Furthermore, responses to a specific question related to impact of CIPN on sleep revealed that 41% of patients with poor sleep quality attributed it to CIPN symptoms. Patients with CIPN-induced sleep impairments reported worse CIPN severity and worse neuropathic pain, in comparison to patients with poor sleep quality due to other factors. Furthermore, this study revealed that CIPN-induced poor sleep quality can persist up to 2 years post-neurotoxic treatment cessation. Patients with CIPN and sleep dysfunction reported worse physical and social functioning, as well as worse emotional

well-being than those without sleep impairments. These results reinforce the need to improve the currently-used tools for CIPN assessment to incorporate items assessing sleep quality and sleep dysfunction, as it has been shown to be a significant contributing factor to worsening the quality-of-life of cancer survivors with CIPN.

7.2 FUTURE DIRECTIONS

The studies in this thesis incorporated cross-sectional data collected from a single timepoint post-neurotoxic chemotherapy treatment cessation. Therefore, future studies of prospective cohorts will assist in investigating the utility of novel CIPN assessment tools in a clinical setting. Although our findings did not reveal any associations between ESC via Sudoscan or EMLA-induced SSW with CIPN severity, investigation of these tools in a prospective cohort may demonstrate their trajectory of change during the course of chemotherapy treatment, which may provide insight into their potential associations with the development of CIPN. Furthermore, given that some group comparisons had low sample sizes, cohorts of larger sample sizes may help clarify results and yield higher statistical power.

Studies in this thesis have also identified subgroups of patients who reported upper-limb CIPN symptoms and brought attention to the presence of the additional burden of these upper-limb CIPN symptoms on patient function such as writing and manipulating small objects with the fingers, including worse global CIPN severity as well as reduced health-related quality-of-life in patients with chronic CIPN. Therefore, it may be beneficial to identify these patient subgroups earlier during treatment, preferably when CIPN symptoms originally manifest, in order to investigate the potential association of progression of neuropathy severity with a range of upper-limb functional assessments and neurophysiological measures throughout the course of treatment.

There is a need to subgroup patients in order to personalise rehabilitation strategies based on their symptom profiles and functional issues. Therefore, future studies should focus on appropriate ways to identify clusters of patients with upper-limb CIPN symptoms, as this may help clinicians match patients with appropriate upper-limb rehabilitation options and

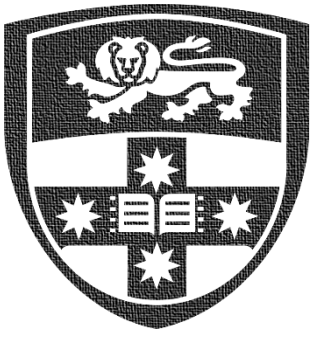
intervention strategies that may be successfully implemented to help lessen their symptom severity and improve their overall function.

Studies of this thesis have also demonstrated the importance of subgrouping patients based on the presence of painful or non-painful symptoms of CIPN. However, the main issue pertains to the outcome measures used to identify these subgroups. This has also been suggested as a reason for the lack of success of prior clinical trials that investigated a range of pharmacological and non-pharmacological interventions to help treat neuropathic pain in patients with CIPN [161]. Therefore, future studies should focus on developing outcome measures for the assessment of painful neuropathy, including items separating numbness and tingling from pain, longer recall periods, as well as items investigating behavioural changes. Such tools may then be incorporated for assessment of patients in a clinical setting, as well as help guide clinical trials in selecting eligible participants to investigate the efficacy of potential pharmacological and non-pharmacological interventions in the treatment of painful and non-painful CIPN symptoms.

This thesis has also demonstrated the presence of sleep dysfunction in patients with chronic CIPN. However, due to the cross-sectional nature of our study, it still remains unknown whether these sleep problems were chronic or developed throughout the treatment along with CIPN development. Therefore, future studies should improve or modify the currently-used CIPN assessment tools to incorporate items that will help identify the presence of sleep problems in patients prior to commencement of chemotherapy treatment, and also assess its trajectory of change throughout their treatment. This will assist with early identification of patients with poor sleep quality due to CIPN, with a focus on further assessing the burden of poor sleep quality in the context of CIPN.

Overall, the findings of this thesis provide an important contribution to global cancer survivorship research by addressing important and under-reported topics. Studies of this thesis have addressed several current limitations in CIPN research, including the following: limitation in appropriate assessments of upper-limb CIPN symptoms, including small nerve fibre function, limitation in methods of identification and management of neuropathic pain in the context of CIPN, as well as limitations in our understanding of the impact of CIPN on the sleep quality of cancer survivors. While these comprehensive assessments may not yet be suitable for translational clinical practice, selection of particular items from currently-used assessment tools may help future studies to identify particular subgroups. It is also important to note that clinical significance is separate from statistical significance, and the specific clinical significance of these tools remains under investigated. Further, these items may assist clinicians in identifying suitable interventions for patients, as well as guide clinical trials in appropriate participant selection in hopes of developing appropriate intervention strategies and treatment options. Ultimately, this will aid in lessening the significant burden of CIPN on daily function and improve the quality-of-life of cancer survivors worldwide who are living with CIPN.

APPENDIX



1. APPENDIX 1

Chapter 5: Impact of Pain on Symptom Burden in Chemotherapy-Induced Peripheral Neurotoxicity

1.1 Supplementary Methods

1.1.1 CIPN and Pain assessment: Patient-reported outcome measures

Each item of the EORTC-QLQ-CIPN20 is rated on a 4-point Likert scale consisting of 1 (not at all), 2 (a little bit), 3 (Quite a bit) and 4 (very much), and the total score was converted to a scale from 0 to 100, whereby higher scores indicate worse CIPN. A male specific question was omitted from the assessment (Q20 of EORTC-QLQ-CIPN20). Two items (Q5&6) assess the presence of pain in the extremities. Individual items assessing the impact of CIPN symptoms on patient function, including instability when standing or walking (Q9), difficulty distinguishing temperature (Q10), difficulty writing (Q11), and difficulty manipulating small objects with their fingers (Q12) were investigated.

The PNRS scale ranges from 0 (no pain at all) to 10 (worst pain possible) [169]. The modified DN4 includes seven items relating to the characteristics of pain (burning, painful cold, electric shocks) and its associated symptoms (tingling, pins and needles, numbness, itching) [147].

A semi-structured qualitative interview was conducted whereby participants were asked to describe their symptoms, including: “do you have trouble sleeping because of your CIPN symptoms”, “does CIPN affect your ability to exercise” and “have you tried anything to treat the CIPN symptoms”. Participants were also asked if they were taking neuropathy

medications at the time of testing. Answers were also transcribed to “yes” or “no” for statistical analyses.

1.1.2 Clinical neuropathy assessment

The NCI-CTCAE was used by researchers to grade CIPN severity according to the following categories: Grade 0 – no symptoms; Grade 1 – asymptomatic, not interfering with daily function; Grade 2 – moderate symptoms, limiting daily function; Grade 3 – severe symptoms, limiting daily function and self-care; and Grade 4 – disabling [173].

The TNSc was also used by researchers to assess CIPN severity. It comprises of six domains, whereby each domain is graded between 0 (normal) and 4 (severe), summing up to a total score ranging from 0 (no neuropathy) to 24 (severe neuropathy). The domains include upper and lower limb vibration sensibility, pin-prick sensibility, strength assessment, deep tendon reflexes and patient-reported sensory and motor symptoms [109, 110].

1.1.3 Functional assessments

Mechanical detection threshold was measured using a standardised set of Von Frey monofilaments (Optihair2-Set, Marstock, Nervtest, Germany) that exert forces upon bending between 0.125 and 512 millinewtons (mN). Five applications were administered on the distal tip of digit 2 of the dominant hand. The weight of the monofilament was increased if participants failed to identify 3 of the 5 applications. A total of 5 trials were administered in a sequence of ascending and descending stimulus intensities [179].

The Grating Orientation Task (GOT) was applied for the assessment of sensory perception. JVP domes with gratings between 0.35 mm and 12 mm were placed on the distal tip of digit 2

of the dominant hand. The domes were placed with the gratings going down the finger (vertical) or across the finger (horizontal) in random order to identify the smallest grating size that could be discriminated. Twenty trials were administered for each grating size. If participants scored at least 15 correct, they progressed to a smaller size [178].

The Grooved Pegboard task was used to assess fine motor skills. Participants were asked to use their dominant hand only and place 25 pegs into grooved holes of different orientations. The task was repeated twice and an averaged time was calculated [180].

1.1.4 Participant classification

Participants were classified into painful and non-painful CIPN according to items evaluating shooting or burning pain in the fingers/hands and toes/feet. If participants answered at least one of the items with "a little bit", "quite a bit" or very much", they were placed in the "Painful CIPN" group, with the other participants comprising the "non-painful CIPN" group. Participants were further characterised by the presence of more severe neuropathic pain within the painful CIPN group, which was determined by having a response of "quite a bit" or "very much" on shooting or burning pain items (EORTC-QLQ-CIPN20).

Participants were also classified according to PNRS scores of 0 or ≥4 to identify participants with non-painful or painful CIPN, respectively [269].

Participants with moderate-to-severe CIPN symptoms were determined according to the clinically-graded scale score (NCI-CTCAE ≥ 2) and group comparisons were done to examine the impact of CIPN severity between painful and non-painful CIPN.

1.2 Supplementary Results

1.2.1 Neuropathy profiles and subgroups

Participants were also classified into painful or non-painful CIPN groups according to the validated neuropathic pain questionnaire cut-off scores (PNRS). 71% (n=277) reported non-painful CIPN, while 29% (n=113) reported neuropathic pain (Supp. Table 2.3.1). Overall, similar to the results of table 5.3.2 in Chapter 5, participants with painful CIPN still reported worse CIPN severity across all neuropathy measures, with no significant differences in functional assessments or neurophysiological measures of sural or tibial amplitudes between both groups (all $p>0.05$) (Supp. Table 2.3.1).

According to the DN4, the most common descriptors of pain reported by participants with painful CIPN (n=140) were numbness (51%, n=72), followed by tingling (44%, n=61), pins and needles (42%, n=59), burning (36%, n=51) and electric shock (35%, n=49). The least reported symptoms were painful cold (19%, n=26) and itching (11%, n=15) .

1.2.2 Comparison of CIPN subgroups among different chemotherapy types

Group comparisons between paclitaxel- and oxaliplatin-treated patients revealed worse CIPN symptoms in the oxaliplatin-treated cohorts, according to all CIPN severity measures (all $p<0.05$), except the clinically-graded scale ($p=0.06$) (Supp. Table 2.3.2). In addition, oxaliplatin-treated patients had reduced sensory and functional performance, including slower average pegboard time, higher grating orientation task threshold (both $p<0.001$) and larger two-point discrimination distance ($p=0.03$) (Supp. Table 2.3.2). Also, sural amplitudes were significantly reduced in oxaliplatin-treated patients compared to paclitaxel-treated patients ($p<0.001$) (Supp. Table 2.3.2). There was a significant difference in cumulative dose ($p<0.001$), despite no differences in age, BMI, or months since treatment completion between both groups (both $p>0.05$).

In terms of pain descriptors, paclitaxel-painful CIPN group reported similar pain descriptors to the oxaliplatin-painful CIPN group, particularly "*burning*" ($p=0.7$), "*painful cold*" ($p=0.2$) and "*electric shocks*" ($p=0.5$) (Supp. Table 2.3.3).

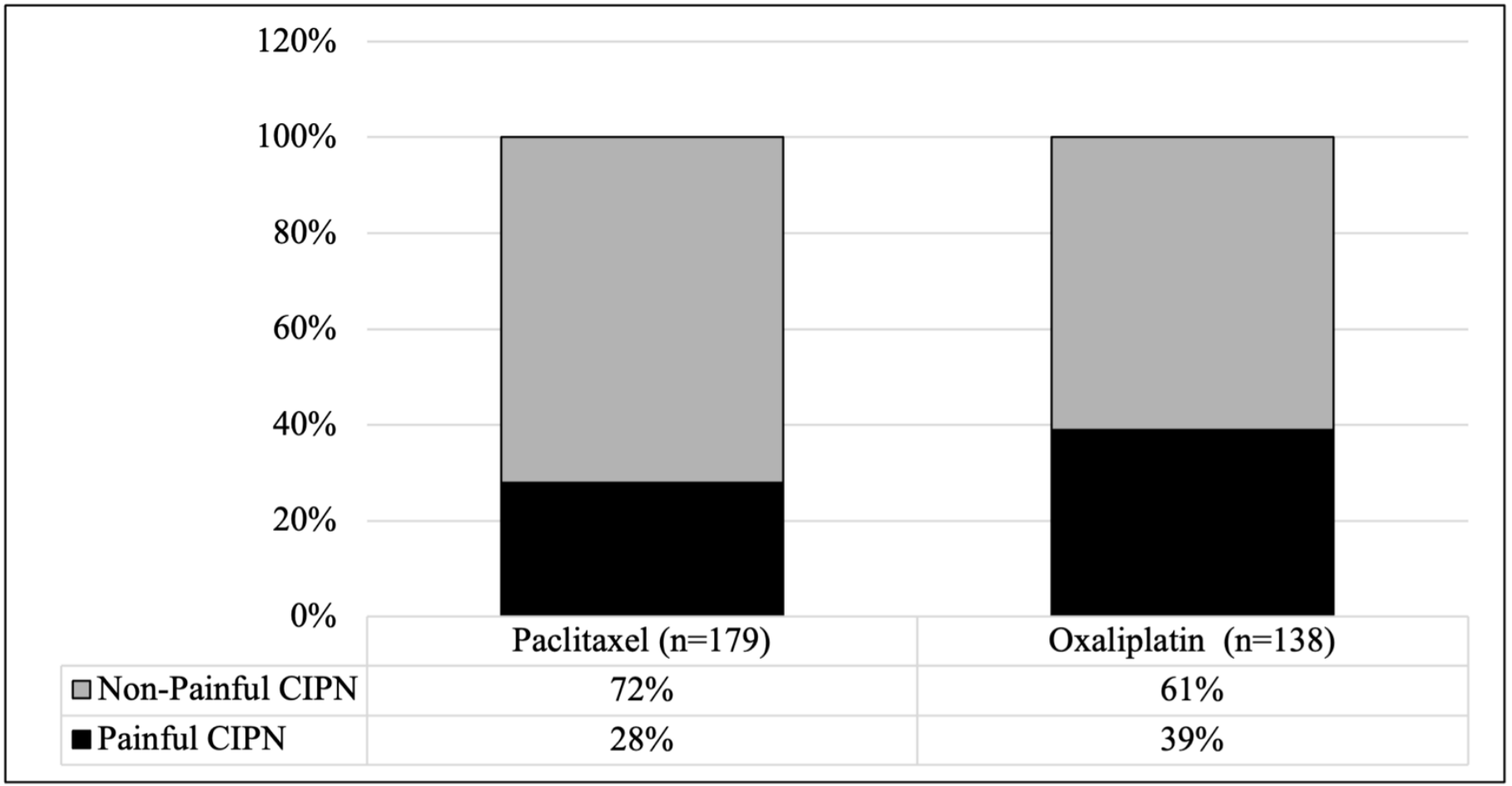
1.3 Supplementary Tables & Figures

Assessment tools	Painful CIPN (n=113) (PNRS ≥ 4)	Non-painful CIPN (n=277) (PNRS=0)	P-value
	Median (IQR)	Median (IQR)	
CIPN outcome measures			
Clinically-Graded Scale (NCI-CTCAE)	**2.0 (1.0)**	**1.0 (1.0)**	**<0.001**
Patient-Reported Outcome (EORTC-QLQ-CIPN20)	**21.1 (23.0)**	**12.3 (14.0)**	**<0.001**
Neurological Examination Score (TNSc)	**5.0 (4.0)**	**4.0 (3.0)**	**0.001**
TNS – Sensation	**2.0 (1.0)**	**1.0 (1.0)**	**<0.001**
TNS - Weakness	**0 (1.0)**	**0 (0)**	**<0.001**
Sensory and Functional Assessments			
Average Pegboard Time (secs)	74.9 (22.6)	74.8 (26.1)	0.4
Grating Orientation Task (GOT) Threshold (mm)	3.6 (2.3)	3.7 (2.7)	0.8
Two-Point Discrimination Distance	16.0 (6.0)	13.0 (6.0)	0.2
TNS – Pinprick	1.0 (2.0)	1.0 (1.0)	0.3
TNS – Vibration	0 (1.0)	0 (1.0)	0.9
Neurophysiological measures			
Tibial amplitudes (mV)	8.7 (7.8)	9.2 (5.8)	0.8
Sural amplitudes (μV)	7.0 (7.9)	7.1 (7.1)	0.6
Demographic characteristics			
Age (years)	59.0 (18.0)	61.0 (18.0)	0.2
BMI (kg/m^2)	**27.5 (8.6)**	**26.3 (5.9)**	**0.02**
Months since treatment completion	5.0 (4.0)	4.0 (3.0)	0.4

Supplementary Table 1.3.1 Comparison of neuropathy outcomes between participants with painful and non-painful CIPN according to the PNRS classification, using Mann-Whitney U tests. p<0.05 was considered significant. Higher scores on CIPN outcome measures and sensory and functional assessments, as well as lower amplitudes of neurophysiological measures indicate worse impairment.

Assessment tools	Paclitaxel-treated participants (n=179)	Oxaliplatin-treated participants (n=139)	P-value
	Median (IQR)	Median (IQR)	
CIPN outcome measures			
Clinically-Graded Scale (NCI-CTCAE)	2.0 (1.0)	2.0 (1.0)	0.06
Patient-Reported Outcome (EORTC-QLQ-CIPN20)	**15.8 (16.0)**	**19.3 (19.0)**	**0.02**
Neurological Examination Score (TNSc)	**4.0 (3.0)**	**5.0 (4.0)**	**0.02**
TNS – Sensation	**1.0 (1.0)**	**1.0 (1.0)**	**0.02**
TNS - Weakness	0 (1.0)	0 (0)	0.2
Sensory and Functional Assessments			
Average Pegboard Time (secs)	**71.6 (23.5)**	**83.0 (35.2)**	**<0.001**
Grating Orientation Task (GOT) Threshold (mm)	**3.5 (2.0)**	**5.2 (3.7)**	**<0.001**
Two-Point Discrimination Distance	**13.0 (7.0)**	**15.0 (5.0)**	**0.03**
TNS – Pinprick	1.0 (2.0)	1.0 (1.0)	0.8
TNS – Vibration	**0 (1.0)**	**1.0 (2.0)**	**<0.001**
Demographic characteristics			
Age (years)	60.0 (17.0)	60.5 (18.0)	0.7
BMI (kg/m^2)	27.2 (8.6)	26.3 (5.4)	0.09
Months since treatment completion	4.0 (4.0)	4.5 (3.0)	0.7
Cumulative Dose (mg/m^2)	**918.8 (223.1)**	**748.0 (280.5)**	**<0.001**
Neurophysiological measures			
Tibial amplitudes (mV)	9.4 (6.7)	9.3 (5.8)	0.8
Sural amplitudes (µV)	**9.5 (7.8)**	**4.3 (5.0)**	**<0.001**

Supplementary Table 1.3.2. Comparison of neuropathy outcomes, sensory and functional assessments, neurophysiological measures, and demographic characteristics between Paclitaxel-treated participants and Oxaliplatin-treated participants, using Mann-Whitney U tests. $P<0.05$ was considered significant. Higher scores on CIPN outcome measures and sensory and functional assessments, as well as lower amplitudes of neurophysiological measures indicate worse impairment.



Supplementary Figure 1.3.1 Prevalence of participants with painful and non-painful CIPN across paclitaxel and oxaliplatin chemotherapy drugs. Oxaliplatin-treated participants were more likely to have painful CIPN than paclitaxel-treated patients (p-value=0.03, which indicates significance)

Painful CIPN			P-value
Chemotherapy Types	**Paclitaxel (n=53)**	**Oxaliplatin (n=21)**	
	n (%)	**n (%)**	
Characteristics of pain (DN4)			
Burning	26 (49%)	11 (52%)	0.8
Painful Cold	14 (26%)	7 (33%)	0.6
Electric Shocks	25 (47%)	13 (62%)	0.3

Supplementary Table 1.3.3. Comparison of characteristics of pain via DN4 between participants in painful paclitaxel and painful oxaliplatin CIPN groups, using Chi-square tests. $p<0.05$ indicates significance.

Cohort	Structured-Patient Interview Questions & Responses		Test for differences between yes vs no groups		
	Does it affect your ability to exercise?				
	Yes	No	Test	Risk (Odds ratio)	P-value
	n (%)	n (%)			
Painful CIPN (n=87)	37 (43%)	50 (57%)	Chi-square	2.1	0.007
Non-painful CIPN (n=193)	51 (26%)	142 (74%)			
	Have you tried anything to treat the symptoms?				
	Yes	No	Chi-square	3.2	<0.001
	n (%)	n (%)			
Painful CIPN (n=87)	60 (69%)	27 (31%)			
Non-painful CIPN (n=193)	79 (41%)	114 (59%)			
	Do you have any trouble sleeping?				
	Yes	No	Chi-square	2.8	<0.001
	n (%)	n (%)			
Painful CIPN (n=87)	41 (47%)	46 (53%)			
Non-painful CIPN (n=193)	46 (24%)	147 (76%)			

Supplementary Table 1.3.4. Comparison of responses to structured-interview questions between painful and non-painful CIPN groups, using Chi-square tests. $p<0.05$ indicates significance.

Cohort	Neuropathy Medication at Time of Testing		Test for differences between yes vs no groups		
	Yes	No	Test	Risk (Odds ratio)	P-value
	n (%)	n (%)			
Painful CIPN (n=140)	**17 (12%)**	**123 (88%)**	Chi-square	**4.2**	**<0.001**
Non-painful CIPN (n=280)	**9 (3%)**	**271 (97%)**			

Supplementary Table 1.3.5. Comparison of neuropathy medication intake (anticonvulsants and antidepressants) at the time of assessment between participants with non-painful CIPN and participants with painful CIPN using Chi-square tests. $p<0.05$ indicates significance.

2. APPENDIX 2

Chapter 6: Sleep Dysfunction Associated With Worse Chemotherapy-Induced Peripheral Neurotoxicity Functional Outcomes

2.1 Supplementary Methods

2.1.1 CIPN and pain assessment: Patient-reported outcome measures

To assess health-related quality-of-life, the CAP-PRI included 15 items addressing impact of neuropathy on physical, social, and emotional function. Each item was graded on a 3-point scale comprising of: 0 'not at all'; 1 'A little bit'; 2 'A lot'. A total score was generated, ranging from 0 to 30, with higher scores indicating worse quality-of-life in the 7 days prior to testing [167].

For the assessment of CIPN severity, the validated 20-item patient-reported questionnaire EORTC-QLQ-CIPN20 was used. It assessed PN symptoms in participants over the 7 days prior to testing. A 4-point Likert scale was used for each item, consisting of the following: 1 'Not at all'; 2 'A little bit'; 3 'Quite a bit'; 4 'Very much'. The total score was then converted to a scale ranging from 0 to 100, with higher scores indicating the presence of severe CIPN [138].

The PRO-CTCAE is a 2-item questionnaire. Each item response was scored from 0 to 4, with higher scores reflecting greater severity and interference of neuropathy symptoms in the 7 days prior to testing [166].

The PNRS was used to determine the presence of neuropathic pain. A score of 0 indicated no pain at all, while a score of 10 indicated the worst pain possible in the 7 days prior to testing [169].

2.1.2 Clinical neuropathy assessment

Researchers used the NCI-CTCAE to grade participants based on the extent of their CIPN symptoms. The following grades comprise the NCI-CTCAE scale: Grade 0 = no neuropathy symptoms; Grade 1 = asymptomatic, but not interfering with function; Grade 2 = moderate neuropathy symptoms, limiting instrumental activities of daily life (ADL); Grade 3 = severe neuropathy symptoms, limiting self-care ADL; Grade 4 = disabling [105].

The Total Neuropathy Score-clinical version (TNSc©, John Hopkins University) is a composite instrument that comprised the following six domains: patient reported (1) sensory & (2) motor neuropathy symptoms, upper and lower-limb (3) pinprick, (4) vibration, (5) strength and (6) tendon reflex assessments. The grade of each domain ranges from 0 'normal' to 4 'severe impairment' and the sum of these 6 domains ranges from 0 'no neuropathy' to 24 'severe neuropathy symptoms' to generate a neurological examination score [109, 110].

2.1.3 Functional assessments

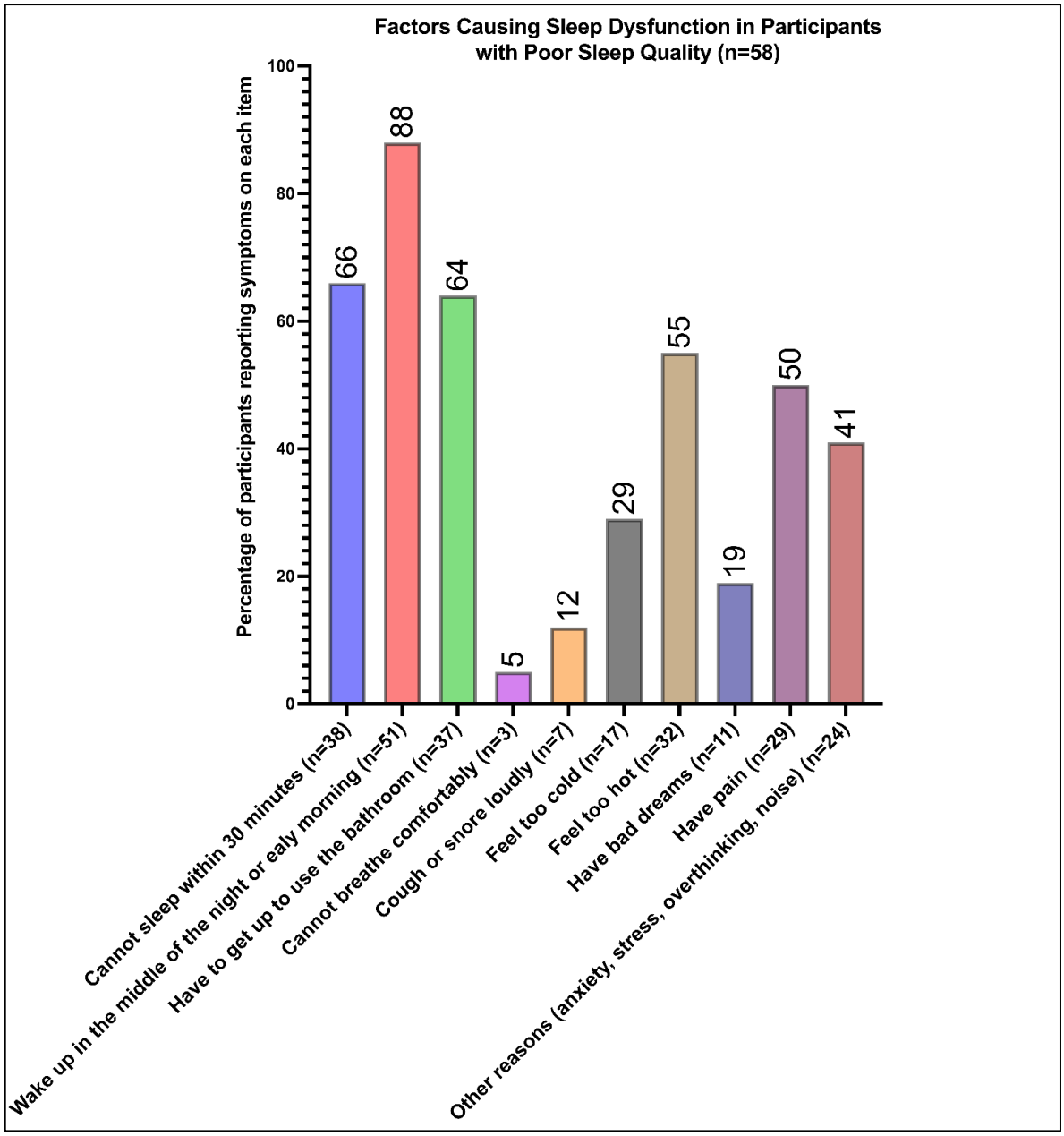
The Grating Orientation Task (GOT) was used to assess sensory perception of participants. The task was conducted on the distal tip of the dominant index finger, using JVP domes with gratings ranging from 0.35 mm to 12 mm in width. The examiner placed the dome with the gratings either vertical or horizonal in a series of 20 random applications. The aim of the task was to identify the smallest grating size that participants could discriminate. A score of at least 15 out of 20 correct was counted as correct identification and subsequent trials were

undertaken with a smaller grating size. A GOT threshold was generated according to the scoring protocol. [178].

Upper-limb mechanical detection threshold was measured using the Von Frey monofilaments (Optihair2-Set, Marstock, Nervtest, Germany). A range of monofilament hairs that exert a bending force between 0.125 and 512 millinewtons (mN) were used. The distal tip of the dominant index finger was used for this task, whereby 5 applications were administered. If participants failed to identify 3 out of the 5 applications, then the weight of the monofilament was increased. A total of 5 trials were conducted in a series of increasing and decreasing stimulus intensities, and a final threshold score was generated according to the scoring protocol [179].

The Grooved Pegboard Task was used to assess fine motor skills and manual dexterity. Participants were instructed to place a total of 25 pegs, using their dominant hand only, into grooved holes that are orientated differently along the board. The task was done twice, and a score was calculated in the form of an average time of both trials [180].

2.2 Supplementary Figure Legend



Supplementary Figure 2.2.1. Percentage of participants with poor sleep quality (n=58) reporting symptoms on each item of the sleep disturbance subdomain of the PSQI (Q5a to 5j). Percentages are displayed on top of the column graph.

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