An Exploration of Severe Peripheral Nerve Injuries: Barriers to Timely Surgical Intervention

By

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Abstract

Introduction: The timing of nerve transfer or graft after peripheral nerve injury is critical, and accepted to be approximately 3 to 6 months. However, in practice, patients often present in a delayed manner for surgical intervention.

This study describes the timing of surgery after peripheral nerve injury for adult patients in Alberta, and explores factors influencing time to surgical intervention and clinical outcomes.

Design and Methods: A retrospective analysis of adult patients undergoing peripheral nerve transfer or grafting in Alberta from 2005 to 2017 was completed. One hundred and sixty-six patients who underwent distal nerve transfers or grafts for either upper or lower limb peripheral nerve injuries were included in the analysis of time to surgery. One hundred and twenty-nine patients with a minimum of one year follow up, after peripheral nerve surgery, were included in the analysis of factors affecting clinical outcomes.

Additionally, qualitative semi-structured interviews were conducted with patients who underwent surgery through the Northern Peripheral Nerve Clinic in order to explore patient perceived barriers and experiences accessing care for severe peripheral nerve injuries.

Intervention(s) and Outcome Measures: A Cox Proportional Hazard Regression was completed to determine correlation of patient, injury and systemic factors with time to surgical intervention. Additionally, a clustered multivariable logistic regression analysis was completed to examine the association of time to surgery, patient, injury and operative characteristics on MRC strength outcomes. Thematic analysis was utilized to examine the qualitative data collected from the semi-structured interviews.

Results: The mean (SD) time to surgery was 221 (118.1) days. A referral made by a surgeon approximately doubled the hazard of earlier surgery as compared to a general practitioner ($p=0.006$). An increase in one comorbidity resulted in the adjusted hazard of earlier surgery decreasing by 16% ($p=0.014$).

Patients identified three main themes of concern: delays in diagnosis, issues with resource accessibility, and lack of support as barriers to accessing the Peripheral Nerve Clinic and subsequent surgery.

Numerous factors are associated with post-operative strength outcomes including: time to operative intervention, operative procedure, and injury. For every week increase from injury to time of surgery, the adjusted odds of the patient achieving a MRC strength grade $\geq$ 3 decreases by 3% ($p=0.02$). If a patient received a nerve transfer instead of a nerve graft the adjusted odds of the patient achieving a MRC strength grade $\geq$ 3 was 388% ($p=0.003$). The adjusted odds of achieving a MRC $\geq$ 3 decreased 65% if the injury sustained had a component of pre-ganglionic injury ($p=0.05$).

Conclusions: The timing of operative intervention after peripheral nerve injury is critical, and delays in surgical intervention are best explained by both patient and systemic factors. These areas of deficiency in the peripheral nerve injury service pathway require further exploration and improvement in order to optimize patient care.

Preface

This thesis is an original work by Julie Beveridge. The quantitative work in Chapter 2 and 4 received research ethics approval from the University of Alberta Health Research Ethics Board, Project Name “Peripheral Nerve Injury in Northern Alberta”, No. Pro00081170, April 12, 2018. Additionally, the quantitative work in chapters 2 and 4 received research ethics approval from the University of Calgary Conjoint Health Research Ethics Board, Project Name “Identifying Barriers to Care to Peripheral Nerve Injury Surgical Intervention”, No. REB18-0138, April 10, 2018.

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The identification and design of the research was done in collaboration with Dr. KM Chan, Dr. RT Tsuyuki, Dr. J Olson and Dr. M Morhart. Dr. J Olson and Dr. M Morhart facilitated the identification of, and access to data for the Edmonton patients. Dr. Midha provided the identification of, and access to data for the Calgary patients. Analysis of data from the Calgary patients was done in part by Allison Beveridge, an undergraduate research assistant from the University of Calgary, and by the main author, Julie Beveridge. Bo Pan completed the Cox Proportional Hazard Regression analysis and independently verified that the logistic regression analysis was performed correctly. Julie Beveridge completed the statistical analysis, other than the Cox Proportional Hazard Regression analysis.

Yazid Al Hamarneh offered expert guidance in the design and analysis of the qualitative component of this dissertation. McNiel Keri conducted the semi-structured interviews, as well as acted as the second independent research assistant who participated in the initial coding of the thematic analysis. Julie Beveridge completed all other data processing and analysis.

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List of Abbreviations

PNS - Peripheral Nervous System

PNI – Peripheral Nerve Injury

DRG - Dorsal Root Ganglion

ECM - Extracellular Matrix

BPI – Brachial Plexus Injury

RAGs – Regeneration Associated Genes

GAP-43 – Growth Associated Protein 43

MVC – Motor Vehicle Collision

USA – United States of America

SCa - Slow Component A

SCb - Slow Component B

NRG - Neuregulin

MRC – Medical Research Council Strength Grade

DASH – Disabilities of the Arm, Shoulder and Hand Questionnaire

SF-36 – Short Form Health Survey (36 Item Questionnaire)

UK – United Kingdom

BMI – Body Mass Index

IBR – Immediate Breast Reconstruction

PNI – Peripheral Nerve Injury

EMG - Electromyography

EDX – Electrodiagnostic testing

SD – Standard deviation

AIC – Akaike Information Criterion

SES – Socioeconomic Status

SEP – Socioeconomic Position

MRI – Magnetic Resonance Imaging

PAC – Pre-Anesthetic Consultation

aHR – adjusted Hazard Ratio

Chapter 1: Introduction to Peripheral Nerve Injuries

1.1 The Peripheral Nerve and Injuries

The peripheral nervous system (PNS) refers to the components of the nervous system outside of the brain and spinal cord. Peripheral nerves may have a combination of motor, sensory or autonomic functions. Dysfunction of, or injury to, a motor nerve results in weakness, while dysfunction of, or injury to, a sensory nerve results in abnormal or decreased sensation. The motor neuron cell bodies are located in the anterior horn cells of the grey matter of the spinal cord, while the dorsal root ganglion (DRG), outside the spinal cord, house the cell bodies of the sensory nerves (Zochodne, 2008). Schwann cells wrap themselves around the length of the axon, making up the myelin sheath (Zochodne, 2008). The degree of myelination varies dependent on the axonal class and function (Zochodne, 2008). The conduction velocity of an axon is dependent on the degree of myelination as well as the diameter of the axon (Zochodne, 2008). Nodes of Ranvier are spaces between the Schwann cells that contain ion channels to allow for depolarization and resultant salutatory conduction, which facilitates a high conduction velocity (Kandel et al., 2013). It should be noted that Schwann cells play many roles including, but not limited to, acting as an electrical insulators; they are metabolically active, communicate with the neuron, and facilitate regeneration in the case of peripheral nerve injury (Kandel et al., 2013).

A peripheral nerve may be comprised of motor, sensory, and autonomic neurons in various combinations. Axons are classified according to their diameter and degree of myelination into – A, B and C fibers. The unmyelinated small diameter C fibers conduct slowest, followed by B fibers, and finally the large myelinated A fibers conduct the fastest (Kandel et al., 2013). There are seven different types of nerve fibers each with unique properties: Aα, Aβ, Aγ, Aδ, B, sC, and dC (Zochodne, 2008). Aα nerve fibers run efferently to provide voluntary motor control of muscle (Zochodne, 2008). Aβ fibers run afferently from skin and joints providing tactile sensation and proprioception, as well as autonomic functions (Zochodne, 2008). Aδ fibers are thinly myelinated and run afferently providing sensation (Zochodne, 2008). Aγ fibers provide muscle tone. B fibers run afferently as visceral sensory fibers and are involved in the autonomic nervous system. Finally, the small unmyelinated C fibers participate in autonomic functions, contribute to pain, temperature, and touch sensation (Menorca et al., 2013b).

1.1.1 Peripheral Nerve Injuries

An understanding of the composition of a nerve is critical in order to understand the pathophysiology and classification of nerve injuries. A nerve is comprised of bundles of axons, known as fascicles, that run together surrounded by perineurium – a protective sheath of connective tissue (Figure 1.2). Each fascicle contains endoneurium within it, a collagen rich connective tissue (Zochodne, 2008). The extracellular matrix (ECM) is contained between individual nerve fibers and comprised of collagen, laminin, and fibronectin (Gonzalez-Perez et al., 2013). The ECM contains components that contribute to cell differentiation, migration and proliferation (Gonzalez-Perez et al., 2013). Thus, the ECM plays a role in cellular communication and guidance of axonal outgrowth during regeneration after injury (Gonzalez-Perez et al., 2013). The epineurium is the outermost, loose connective tissue layer that encloses the fascicles (Zochodne, 2008).

A peripheral nerve injury is classified by the extent of the damage sustained to component nerve tissues (Sunderland, 1951, Seddon, 1943). Seddon and Sunderland developed histologically based classification systems for peripheral nerve injuries (Sunderland, 1951, Seddon, 1943). Seddon classified nerve injuries into three distinct categories, i) neuropraxia, ii) axonotmesis in which axonal damage is sustained and subsequent degeneration occurs but the endoneurium and surrounding connective tissue elements remain intact, and iii) neurotmesis or total disruption of the nerve fiber and all its component tissues (Seddon, 1943). Sunderland expanded Seddon's classification developing a classification system in which there are five types of nerve injury: i) grade one - neurapraxia, ii) grade two – axonal disruption, iii) grade three – axonal and endonerial disruption, iv) grade four - axonal, endonerial and perineurial disruption, and v) grade five – axonal, endonerial, perineurial and epineurial disruption (Figure 1.3) (Sunderland, 1951). Sunderland grade 5, and 4 lesions, and in some cases grade 3, require surgical intervention in order to restore reinnervation of target tissues and ultimately peripheral nerve function (Boyd et al., 2011).

Glial and stromal non-neuronal cells, are also involved in the maintenance and function of the peripheral nerves (Zochodne, 2008). The stromal connective tissue scaffold is made up of non-neuronal cells and the connective tissues that surround axons. This stromal scaffold is important in the understanding of the regeneration of peripheral nerve injuries (Menorca et al., 2013b, Zochodne, 2008). The regenerative ability of the peripheral nervous system is inherently great, however, despite decades of research being devoted to improving functional outcomes clinical gains remain minimal (Kubiak et al., 2018).

1.1.2 Epidemiology of Peripheral Nerve Injury

The majority of peripheral nerve injuries, 50-83%, are sustained by young males between the ages of 18 and 35 (Noble et al., 1998, Taylor et al., 2008). Patients sustaining a trauma, admitted to a level one trauma center, have a concomitant peripheral nerve injury (excluding minor nerve injuries) in 2-3% of cases; if this definition is expanded to include brachial plexus injuries the incidence of peripheral nerve injury is 5% (Noble et al., 1998, Selecki et al., 1982, Midha, 1997a). The above estimation is the most accurate estimation of the frequency of peripheral nerve injury in Canada (Noble et al., 1998, Midha, 1997a). The most common etiology of peripheral nerve injury is trauma; traumatic mechanisms of injury include motor vehicle collisions (MVC), laceration, fractures, and crush injuries (Robinson, 2000). Approximately, 50% of peripheral nerve injuries are due to MVCs (Noble et al., 1998).

Peripheral nerve injuries are common and most frequently affect the upper extremity (60.5%) (Noble et al., 1998, Forli et al., 2017). The most commonly injured upper extremity nerves are the radial, ulnar, median, and axillary nerves respectively (Noble et al., 1998, Selecki et al., 1982, Lad et al., 2010). However, lower extremity peripheral nerves, namely the peroneal, tibial and sciatic nerves may also be injured via trauma mechanisms

(Noble et al., 1998). Injuries to peripheral nerves may be sustained as a result of sharp, penetrating, or blunt traumatic mechanisms resulting in nerve laceration, traction and/or compressive injury (Zochodne, 2008). Although, the endoneurium of the nerve is highly elastic due to the collagen content, excessive traction forces may induce proximal nerve root avulsion or rupture; this injury pattern is commonly referred to as a pre-ganglionic injury (Zochodne, 2008).

Peripheral nerve injuries often occur concurrently with other traumatic injuries, specifically orthopedic and central nervous system injuries (Noble et al., 1998). A study examining the frequency of peripheral nerve injury associated with any extremity trauma found that 1.64% of extremity traumas had an associated nerve injury; in particular crush injuries of the extremities had the highest rate of associated nerve injury at 1.91%, followed by dislocations in 1.46% of cases (Taylor et al., 2008). The prevalence of peripheral nerve injuries sustained in upper extremity trauma is dependent on the type of trauma sustained; a peripheral nerve injury was found in association with any upper extremity trauma in 3.3% of cases (Taylor et al., 2008, Huckhagel et al., 2018). Dislocation was the most common traumatic extremity injury (49% of all extremity trauma) associated with peripheral nerve injury (Taylor et al., 2008). A humeral fracture accompanied 72% of radial nerve injuries, and radius/ulna injuries accompanied 45% of ulnar and median nerve injuries (Noble et al., 1998). Additionally, 10% of traumatic brain injury rehabilitation inpatients had an associated peripheral nerve injury (Stone and Keenan, 1988, Cosgrove et al., 1989). Conversely, approximately 60% of peripheral nerve injuries admitted to a Canadian trauma centre had an associated head injury, 10% an associated thoracic or lumbar spine injury, and 30% fractured ribs (Noble et al., 1998). Lower extremity fractures were associated with approximately 60% of tibial and 40% of peroneal nerve injuries (Foster et al., 2018). Peripheral nerve injuries often occur in patients who have sustained multisystem traumas, or associated regional musculoskeletal injuries; these concomitant injuries serve to compound the difficulties with diagnosis and may complicate the recovery and treatment of the injury (Midha, 1997a, Brogan et al., 2014, Rhee et al., 2011).

Brachial plexus injuries (BPIs) are a particular subset of peripheral nerve injuries that may result in potentially devastating functional deficits. The brachial plexus is comprised of a series of nerves formed by the ventral rami of cervical segments 5 to 8 (C5–C8) as well as the first thoracic nerve (T1); it may also contain partial innervation from C4 (prefixed) or T2 (postfixed) (Figure 1.4) (Zochodne, 2008). The brachial plexus provides efferent and afferent (motor and sensory) innervation to the skin and muscles of the chest, shoulder, arm and hand (Zochodne, 2008). The spinal nerves exit the spinal foramina and form the brachial plexus between the anterior and middle scalene muscles, then extend distally down the proximal arm. The brachial plexus is divided into five roots, three trunks, six divisions, three cords and five terminal branches, with numerous pre-terminal branches. Upper trunk brachial plexus injuries grossly affect shoulder abduction, elbow flexion/extension and the wrist extensors. Conversely, lower trunk brachial plexus injuries grossly affect hand function (Zochodne, 2008). Adult brachial plexus injuries are mainly due to traumatic events, most commonly MVCs, which lead to traction or compressive injury of the roots, trunks, divisions, or cords of the brachial plexus (Arzillo et al., 2014, Midha, 1997b).

It is estimated that 0.36 to 6.3 cases of traumatic adult brachial plexus injury occur per 100,000 inhabitants in the USA, per year (Kalsbeek et al., 1980). The epidemiology of adult brachial plexus injuries was examined in trauma patients presenting to a Canadian trauma center as well as in a large Brazilian metropolis (Midha, 1997a, Faglioni et al., 2014). The reported incidence of traumatic brachial plexus injury in polytrauma patients is 1.2% (Midha, 1997a). The majority of patients whom sustained a brachial plexus injury associated with a polytrauma were male (89%) with a mean age of 29 years (Midha, 1997a). Approximately, 4% of motorcycle collisions presenting to a major trauma centre had an associated brachial plexus injury in Canada, whereas 79% of adult plexus injuries were caused by motorcycle collisions in Brazil (Midha, 1997a, Faglioni et al., 2014, Flores, 2006). Additional causes of traumatic brachial plexus injury, in order of most to least common, include: motor vehicle collisions, vehicle versus pedestrian collisions, firearm injuries, industrial accidents, bicycle accidents, and falls from a height (Faglioni et al., 2014, Midha, 1997a).

1.1.3 Impact of Peripheral Nerve Injury

Traumatic peripheral nerve injury can result in permanent disability and loss of independence and function, despite treatment (Novak et al., 2011). Adult peripheral nerve injuries most often affect young, otherwise healthy individuals, thus creating a lifelong disability (Midha, 1997a). The socioeconomic burden of peripheral nerve injuries has yet to be fully quantified in the literature but is likely substantial. The estimated cost of an ulnar or median nerve injury, in the forearm, including loss of work, was 51,238 and 31,186 euros respectively (Rosberg et al., 2005). The mean cost of one year of treatment post peripheral nerve injury, in the USA, for an ulnar nerve injury is $42,852, while a brachial plexus injury cost $77,485 (Karsy et al., 2018). Similarly, the mean cost of treatment one year after tibial nerve injury was found to be $74,468.80 (Foster et al., 2018). However, the true societal and personal cost of a peripheral nerve injury is likely much higher than the quoted numbers.

Quality of life assessments conducted many years after peripheral nerve injury and reconstruction demonstrate significant persistent disabilities post injury and surgical treatment (Novak et al., 2009, Choi et al., 1997). Choi et al administered a quality of life questionnaire to a patients with brachial plexus injuries, a mean of 7 years post injury, 75% of patients reported significant pain, only 54% returned to work, and 25% were unsatisfied with their overall quality of life (Choi et al., 1997). Similarly, only 59% of patients had returned to work one year after operative intervention for median and ulnar nerve injury (Bruyns et al., 2003). Additionally, the majority of patients reported dissatisfaction with their financial situations (Choi et al., 1997). Patients who reported increased pain levels, older age, and brachial plexus injuries had higher long-term disability scores (Novak et al., 2009). In a more recent study, 68% of patients with a brachial plexus injury reported pain prevented them from participating in activities that they would have liked (Gray, 2016).

Likely, the personal and socioeconomic effects of peripheral nerve injuries are underestimated both by the literature and practitioners working in the area (Gray, 2016). Appropriate medical and timely operative interventions must be employed in order to maximize patient quality of life, minimize morbidity, and decrease the negative personal and socioeconomic impact of these potentially devastating peripheral nerve injuries (Wali et al., 2017). Given the specialized surgical expertise required to effectively treat peripheral nerve injuries and the variability of injury patterns, peripheral nerve injuries are treated at dedicated peripheral nerve injury centres.

1.2 Basics of Nerve Regeneration

After proximal peripheral nerve injury, regeneration over long distances is required in order to reinnervate target musculature. The rate of peripheral nerve regeneration is generally accepted to be between 1–3 mm/day (Seddon et al., 1943, Fu and Gordon, 1997, Sunderland, 1947b). Despite the amazing capacity of injured peripheral nerves to regenerate, reinnervation and functional recovery are often incomplete after injury, particularly in the case of a proximal injury when reinnervation must occur over long distances (Fu and Gordon, 1997). In order to truly understand the challenges of peripheral nerve regeneration, one must first understand the mechanism of peripheral nerve regeneration under ideal circumstances.

A well characterized pattern of events take place after a peripheral nerve injury is sustained: a) depolarization of ion gated channels, and calcium efflux from the endoplasmic reticulum, b) calcium mediated retrograde signaling to the cell body, c) up regulation of mRNA at the cell body resulting in translational products, and d) anterograde transport of these up regulated products to the site of injury to facilitate regeneration (Rishal and

Fainzilber, 2014, Zochodne, 2008). The initial peripheral nerve injury results in an efflux of calcium ions from the endoplasmic reticulum, triggering a retrograde signaling process that progresses towards the cell body (Zochodne, 2008). The dynein motor system facilitates this retrograde signaling; retrograde signaling results in up regulation of regeneration-associated genes (RAGs) (i.e. c-JUN, ATF-3, BDNF, and GAP-43); the products of these genes are subsequently involved in anterograde transport (Ben-Yaakov and Fainzilber, 2009, Richardson et al., 2009, Zochodne, 2008). The anterograde response phase is divided into the slow component A (SCa) and slow component B (SCb) pathways (Hoffman and Lasek, 1980). The SCa pathway transports neurofilament, and facilitates the development of the microtubule neurofilament network (Hoffman and Lasek, 1980). The SCb pathway transports cytoskeleton proteins including: tubulin, neurofilament proteins, actin/actin-associated proteins, and spectrin distally to the site of injury (Black and Lasek, 1979, Roy, 2014). The SCb pathway provides critical tubulin and actin to the developing growth cone at the site of injury in order to facilitate axonal outgrowth (Wujek and Lasek, 1983, McQuarrie and Grafstein, 1982). The SCb pathway is considered a rate-limiting step in peripheral nerve regeneration, since the delivery of tubulin, actin and neurofilament to the developing growth cone is crucial for axonal outgrowth and regeneration (Zochodne, 2008).

Additionally, Wallerian degeneration of the distal stump occurs following a peripheral nerve injury (Zochodne, 2008). Wallerian degeneration is important as it allows for the removal and recycling of axonal material (Zochodne, 2008). In the first days after injury Schwann cells divide, proliferate, and phagocytize myelin and axonal debris present in the distal stump (Gordon, 2016). As well, axonal injury causes inflammatory changes that promote macrophage invasion; macrophages phagocytize the remaining axonal debris in the distal stump (Bruck, 1997). Additionally, macrophages also express pro-inflammatory cytokines (Bruck, 1997). The Schwann cells in distal stump themselves are not phagocytized, instead they remain viable, undergo mitosis, proliferate, and change from myelinating Schwann cells to dedifferentiated type cells capable of guiding regeneration (Sulaiman and Gordon, 2000). The transition of Schwann cells to a dedifferentiated type after injury occurs through neuregulin (NRG) signaling via the erbB2 Schwann cell tyrosine kinase receptor (Birchmeier and Nave, 2008, Hall, 1999, Sulaiman and Gordon, 2000). Bands of Bunger are formed in the distal stump by the dedifferentiated Schwann Cells, this occurs approximately two days after injury; these Bands of Bunger serve to guide the neurite outgrowth, thus enabling axonal regeneration (Fu and Gordon, 1997, Fawcett and Keynes, 1990, Rotshenker, 2011). Bands of Bunger play an crucial role in directing and guiding regenerating axons across the injury site and in the distal stump (Fu and Gordon, 1997). Furthermore, axonal regeneration across the site of nerve injury and/or site of coaptation occurs in a “staggered” manner (Brushart et al., 2002). Brushart et al found that in a rat model it took up to one month before all regenerating axons crossed the surgical coaptation site (Brushart et al., 2002). Due to axonal stagger and non-optimal conditions for regeneration, the time it takes for axons to regenerate in the distal nerve stump, and subsequently reinnervate target tissues after injury is longer than predicted based solely on the regeneration rate (Brushart et al., 2002, Al-Majed et al., 2000).

1.2.1 Effect of Chronic Axotomy and Denervation on Nerve Regeneration

Chronically axotomized peripheral nerves demonstrate a reduction in regenerative capabilities over time after injury, due to a decrease in the expression of regeneration-associated genes and viable Schwann cells in the distal stump (Chen et al., 2007, Gordon et al., 2011). There is also a progressive increase in fibrosis and proteoglycan scarring that occurs in the distal axon stump, particularly three months post injury (Jonsson et al., 2013). Thus, the pro-regenerative environment that is necessary to support axonal outgrowth and regeneration deteriorates over time after axonal injury; therefore, regeneration and subsequent reinnervation of tissues is often incomplete after peripheral nerve injury (Gordon et al., 2011). Establishing the optimal timing of nerve-based reconstruction after peripheral nerve injury is paramount in order to facilitate successful axonal regeneration and obtain functional reinnervation.

Fu and Gordon examined the impact of chronic denervation and axotomy independently in a rat model. An exponential reduction of motor units was observed with prolonged axotomy prior to nerve reconstruction, less than 35% of motor units reinnervated as compared to the control group when chronic axotomy was prolonged for 3 months before the injury was reconstructed (Fu and Gordon, 1995a). Individual motor unit force and innervation ratio increased in order to compensate for the decreased number of motor units that resulted from prolonged axotomy (Fu and Gordon, 1995a). Chronic axotomy reduces the regenerative capability of motor axons, thus leading to poor reinnervation and poor functional recovery after delayed nerve reconstruction (Fu and Gordon, 1995a).

Additionally, Fu and Gordon examined the impact of isolated chronic denervation in the paradigm of loss of nerve supply to target musculature independent of chronic axotomy. With chronic denervation, longer than 6 months, less than 50% of the muscle fibers reinnervated, after repair of the nerve injury (Fu and Gordon, 1995b). Chronic denervation not only results in a reduced number of motor axons reinnervating the target musculature, it also decreases the ability of those axons that do reinnervate the musculature to form hypertrophied motor units in order to compensate for the decreased number of motor units secondary to poor reinnervation (Fu and Gordon, 1995b). Prolonged denervation, over 6 months, ultimately resulted in a 90% reduction in motor unit number (Fu and Gordon, 1995b). Impaired regeneration and reinnervation is in part due to the failure of chronically denervated Schwann cells to sustain the necessary trophic support to maintain prolonged axonal regeneration after proximal injury (Hoke et al., 2002, Sulaiman and Gordon, 2000). However, Schwann cells retain the capacity to remyelinate those axons that do regenerate (Hoke et al., 2002).

1.3 Peripheral Nerve Surgical Interventions

Clinical decision making with regards to surgical reconstruction varies dependent on mechanism of injury and suspected Sunderland injury grade (Sunderland, 1951). In the case of sharp penetrating or transection injuries, immediate exploration and repair should be undertaken as there is no reasonable potential for spontaneous regeneration (Giuffre et al., 2010). However, in the case of closed proximal peripheral nerve injuries, the potential for spontaneous recovery is less clear as the severity of injury to the nerve may not be immediately apparent (Giuffre et al., 2010). It is generally accepted that if timely spontaneous recovery does occur, patient outcomes are equal to or improved compared to those where surgical intervention is required (Lim et al., 2017). Currently, optimal timing of surgical intervention in a closed peripheral nerve injury, if there is no clinical or EMG confirmation of spontaneous recovery, to perform either nerve transfer or nerve grafting based on expert consensus is thought to be within 3 to 6 months of injury (Giuffre et al., 2010, Shin et al., 2005, Lim et al., 2017, Bertelli et al., 2016, Martin et al., 2018).

Reconstructive options for a severe proximal peripheral nerve injury requiring operative intervention include early reconstructive options: nerve grafting, and nerve transfers, as well as late reconstructive options: free functioning muscle transfers, tendon transfers, and arthrodesis (Giuffre et al., 2010). Nerve grafts may be used to bridge a gap between distal and proximal nerve ends that are no longer in continuity due to transection injury, or in cases where excision of irreversibility damaged nerve is necessary, for example when there is severe scarring or a neuroma in continuity as a result of injury (Tung and Mackinnon, 2010). Nerve transfers may also be utilized in case of irrecoverable proximal peripheral nerve injury to effectively bypass the injured segment of nerve, rather than replace it (Tung and Mackinnon, 2010).

1.3.1 Potential for Spontaneous Recovery of Peripheral Nerve Injuries

Recovery of traumatic peripheral nerve injuries without intervention may occur in the case of Sunderland grade 1, 2 or 3 injuries (Zochodne et al., 2008). Spontaneous recovery may be possible even in the setting of an initially severe appearing brachial plexus injury (Lim et al., 2017). Motor recovery is clinically classified using the MRC Strength grading scale (Figure 1.1) (Van Allen, 1977). Nagano et al examined 198 cases of post-ganglionic brachial plexus lesions serially over time; 44% had functional recovery (MRC ≥3), 38% of these injuries demonstrated functional recovery in the upper trunk only (Nagano et al., 1984). Nagano found that if an MRC ≥1 was seen in upper trunk injuries before 9 months after injury, and 12 months for lower trunk injuries, in the majority of cases, the final result was an MRC grade of at least 3 (Nagano et al., 1984). Kline et al observed approximately 40% of C5-6 injuries, 15% of C5-7 injuries, and only 5% of pan plexus injuries (C5-T1) demonstrated signs of spontaneous recovery on EMG testing by 3 to 4 months after injury (Kline, 2009).

Radial nerve injuries, when associated with a closed humeral fracture, are reported to spontaneously recover in 60% to 92% of cases (Pollock et al., 1981, Shaw and Sakellarides, 1967, Papasoulis et al., 2010, Shao et al., 2005, DeFranco and Lawton, 2006). Functional spontaneous recovery of the triceps branch of the radial nerve in upper trunk (C5-C7) brachial plexus injuries occurred in 33% of patients within two years of injury (Flores, 2012). The ability of nerves to spontaneously recover after injury only serves to increase the controversy surrounding the optimal timing for surgical intervention; clinical diligence is required to ensure that the opportunity for intervention is not missed if spontaneous recovery does not occur (Kline, 2009). The decision to operate on a peripheral nerve injury is a complex balance between the potential for spontaneous recovery and the benefits of surgery. Thus, the timely diagnosis of irrecoverable peripheral nerve injury is essential to allow for surgical intervention in the event that recovery does not occur (Kline, 2009).

1.3.2 Nerve Reconstruction Techniques: Nerve Grafting

Nerve grafts may be used to reconstruct nerve defects when the distal and proximal nerve ends are no longer in continuity due to injury or surgical resection (Figure 1.5) (Trehan et al., 2016). A potential benefit of using a nerve graft is the ability to reinnervate multiple target tissues distal to the graft site, with a single nerve graft, allowing for the recovery of multiple target muscles (Bertelli and Ghizoni, 2008). As well, nerve grafts have the potential to restore both sensory and motor function, as the graft facilitates regeneration of the injured nerve to its natural targets both skin and muscle (Bertelli and Ghizoni, 2008).

The nerve graft is classically coapted to both the proximal and distal ends of the recipient nerve via epineurial suturing (Trehan et al., 2016). The autologous nerve graft undergoes Wallerian degeneration providing a mechanical scaffold that includes the Schwann cells, basal laminae, and neurotrophic factors necessary to facilitate nerve regeneration (Ide et al., 1983). Donor nerves utilized for nerve grafting are selected for minimal donor site morbidity, and are typically sensory in nature, given the graft provides only a structural framework for the proximal stump to regenerate through, and does not provide axons for regeneration (Ide et al., 1983). Sural nerve grafts are the most commonly employed free nerve graft and are used in majority of nerve grafting cases (Chuang, 2010). However, the medial and lateral cutaneous nerves of the forearm, as well as the long saphenous nerve may also be used as donor nerves for nerve grafting (Poppler et al., 2015).

However, there are multiple potential pitfalls in utilizing nerve grafts for the reconstruction of nerve injuries. The pitfalls of nerve grafting include the potential biological difficulties of having two separate coaptation sites through which the proximal nerve stump must grow, as well as dependant on the extent and site of injury, the length of the graft needed, and the distance from the proximal nerve stump to target tissues may be long (Trehan et al., 2016). Short nerve grafts typically reinnervate better than longer grafts (Hentz and Narakas, 1988, Chuang et al., 1993). Therefore, if an injury is sustained in a manner where optimal conditions for peripheral nerve regeneration are not met, an alternative nerve reconstruction technique, such as a nerve transfer, should be considered if possible.

Chuang et al demonstrated that reconstruction of upper extremity peripheral nerve injuries with nerve grafts resulted in better functional results than tendon transfers, and reconstruction with nerve grafts <10cm had better functional outcomes than those >10cm (85% vs. 66%, respectively) (Chuang, et al. 1993). Additionally, nerve grafts longer than 7cm utilized for proximal peripheral nerve injury reconstruction (above the elbow) have been associated with worse outcomes (Grinsell and Keating, 2014). This finding that shorter nerve grafts result in improved outcomes over longer grafts is supported consistently throughout the literature (Chuang et al., 1993, Bentolila et al., 1999, Samii et al., 1997, Hentz and Narakas, 1988). Bertelli et al reported results of nerve grafting for reconstruction of upper trunk brachial plexus injuries; grafting of the anterior division of the upper trunk resulted in 32% of patients regaining pectoralis major and biceps function (Bertelli and Ghizoni, 2008). However, nerve grafting of the posterior division did not result in reliable functional recovery of shoulder abduction, but did restore elbow extension in 67% of patients (Bertelli and Ghizoni, 2008). Similarly, proximal nerve grafting did not reliably restore elbow or forearm flexion and extension, or hand function (Bertelli and Ghizoni, 2008, Ochiai et al., 1996). Based on their experience Bertelli et al suggest that functional reconstruction of upper trunk injuries is most reliably achieved through a combination of distal nerve transfers and grafts (Bertelli and Ghizoni, 2010).

1.3.3 Nerve Reconstruction Techniques: Nerve Transfers

Historically peripheral nerve injuries have been preferentially reconstructed with nerve grafts; however, over the past decades the nerve reconstruction paradigm has shifted toward the use of nerve transfers in proximal adult peripheral nerve injuries (Ray et al., 2011, Mackinnon et al., 2005, Fox and Mackinnon, 2011). The paradigm of nerve transfers for reconstruction is of particular utility in proximal peripheral nerve injuries (Baltzer et al., 2017). A lack of available nerve roots for grafting, long nerve defects, and long distances from injury to the target musculature mean that nerve grafts are frequently inadequate to restore function for adult patients with severe proximal peripheral nerve injuries (Tung and Mackinnon, 2010).

Potential benefits of utilizing nerve transfers for reconstruction of peripheral nerve injuries are the effect of redirection of an intact uninjured motor nerve to a distal undamaged nerve segment close to the target muscle for reinnervation, effectively bypassing the injured segment of nerve (Rohde and Wolfe, 2007). In other words, the donor nerve is moved distally and coapted to the recipient nerve close to the target muscle, bypassing the area of injury (Figure 1.6) (Ladak et al., 2013). Thus, in nerve transfers there is only one coaptation site that must be overcome and the target muscle for reinnervation is the shortest possible distance from the coaptation site, facilitating the shortest possible time to functional recovery (Hems, 2011). Nerve transfers are designed to solely restore motor function, as the donor nerve is a motor nerve branch and is coapated to a recipient motor branch, likely any sensory restoration that results is a consequence of cortical plasticity (Sun et al., 2014, Yoshikawa et al., 2012).

Potential pitfalls of nerve transfers include the potential for donor site morbidity due to sacrificing a physiologically intact but functionally redundant donor nerve branch, in order to reinnervate a functionally more important target (Tung and Mackinnon, 2010). When choosing a donor nerve for distal nerve transfer, care is taken by the surgeon to minimize donor site morbidity. The ability to achieve optimal outcomes with a nerve transfer is in part dependant on the axonal composition of the donor nerve, specifically the match of the number of motor axons between the donor and recipient nerve (Schreiber et al., 2015, White et al., 2012). Motor axon count ratios below 0.7:1 (donor to recipient) are associated with poorer outcomes (Schreiber et al., 2015). In addition to reinnervation, the functional success of distal nerve transfers is reliant on cortical plasticity and the patients' ability to recruit the newly reinnervated muscle group often in a way that is not typical (Socolovsky et al., 2017, Midha, 2004).

Efforts have been made to evaluate the functional outcomes of nerve transfers for reconstruction of adult traumatic peripheral nerve injury. Nerve transfer reconstruction aimed at restoring elbow flexion, in brachial plexus injuries, produced better motor results than nerve grafts (Yang et al., 2012). Oberlin's procedure, utilizing a branch of the ulnar nerve to flexor carpi ulnaris to a motor branch of the musculocutaneous nerve, resulted in the best functional outcomes for restoration of elbow flexion, as compared to alternative nerve transfers (Yang et al., 2012). Utilizing nerve transfers for restoration of shoulder abduction was more effective than reconstruction with nerve grafting (Ali et al., 2015). After nerve transfer reconstruction aimed at functional restoration of the supraspinatus, biceps, triceps, and finger flexors anti-gravity strength was achieved in 54%, 86%, 46% and 43% of cases respectively (Liu et al., 2013). Despite the promising nature of nerve transfers, high quality prospective trials directly comparing the outcomes of nerve transfers and grafts for specific functional restoration are needed to confirm their ultimate utility.

The published outcomes of these nerve transfers provide a benchmark against which surgeons may assess their individual outcomes and if necessary make changes to their practice in order to continually strive for improved patient care. There is no definitive consensus in the literature regarding the best surgical reconstructive option when primary repair using direct epineurial coaptation is not a possibility, particularly regarding the use of nerve grafts or transfers when both are viable reconstructive techniques.

1.4 Factors Affecting Outcomes of Peripheral Nerve Surgical Interventions

The outcomes of nerve reconstruction procedures are determined by a number of variables including surgical technique, patient factors, injury factors, time from injury to surgery, and post-operative rehabilitation (Socolovsky et al., 2011, Bertelli and Ghizoni, 2010, Lee et al., 2012, Ruijs et al., 2005, Trehan et al., 2016). Despite extensive clinical and surgical experience with the evaluation and management of severe peripheral nerve injury, there remain limitations in diagnosis and determination of optimal timing of surgical intervention (Simon et al., 2016).

1.4.1 Timing of Peripheral Nerve Surgery

Timely surgical intervention results in the best possible outcomes for patients with irrecoverable peripheral nerve injuries (Hems, 2015, Birch, 2015). However, functional motor outcomes may also be observed due to spontaneous axonal regeneration in patients with Sunderland grade ≤ 3 injuries (Lim et al., 2017). Due to current diagnostic limitations, the determination of the severity of a peripheral nerve injury and potential for recovery must be made over time, based upon serial electrodiagnostic testing and clinical exams (Ferrante, 2012). Thus, the decision to intervene surgically must be measured and allow time for the nerve to demonstrate signs of spontaneous recovery, while still leaving time for surgical intervention to be performed while the regenerative capabilities of axons persist (Tung and Mackinnon, 2010).

Currently, the optimal time of surgical intervention in the context of closed peripheral nerve injury, based on expert consensus, is accepted to be approximately 3 to 6 months after injury, if there is no clinical or EMG evidence of spontaneous recovery (Giuffre et al., 2010, Shin et al., 2005, Lim et al., 2017, Bertelli et al., 2016, Martin et al., 2018). Historically, operative intervention less than six months following peripheral nerve injury has been viewed as producing favourable results (Narakas, 1982, Narakas, 1985, Narakas and Hentz, 1988). A recent meta-analysis found that the best outcomes for surgical reconstruction of brachial plexus injury are observed when surgery is performed within 4 months (Martin et al., 2018). In the same review, patients who did not obtain anti-gravity results had a mean time of 7 months from injury to operative intervention (Martin et al., 2018). Bhandari et al demonstrated that operative intervention within 3 months resulted in the best functional outcomes, followed by operative intervention within 3 to 6 months, with a sharp decline in functional outcomes if nerve based reconstruction of brachial plexus injury was performed after 6 months in a military population (Bhandari and Bhatoe, 2012). Significantly better strength outcomes have been observed in patients who underwent surgery prior to 6 months from injury (Flores, 2011). Functional outcomes, as measured by DASH and SF-36, were significantly improved when patients underwent nerve transfer surgery less than 6 months from injury as opposed to later (Ahmed-Labib et al., 2007). Other groups have demonstrated improved outcomes when surgical intervention is performed within 9 months of injury (Songcharoen et al., 1996, Terzis and Barbitsioti, 2012).

There has been a recent move in the UK towards very early exploration and reconstruction, within the first two weeks after injury, of all brachial plexus injuries regardless of whether a closed or open injury was sustained (Hems, 2015, Birch, 2015). These groups argue functional results are improved after early operative intervention and reconstruction (Birch, 2009, Jivan et al., 2009). Kato et al found that a shorter interval between injury and operative repair led to lower pain scores post brachial plexus injury, and proposed that exploration and repair of brachial plexus injuries should ideally occur within one month of injury (Kato et al., 2006). There are a number of groups that have found early surgery resulted in significantly better motor outcomes (Jivan et al., 2009, Liu et al., 2014). These groups advocate for very early surgical intervention, with definitive reconstruction within two weeks of injury (Birch, 2015, Hems, 2015, Jivan et al., 2009). Outcomes of brachial plexus reconstruction with nerve grafts are significantly improved if the nerve graft procedure is completed less than one month from the time of injury (Jivan et al., 2009). However, early interventions (within 1 month) or very early (within 2 weeks) interventions, fail to take into account the inherent regenerative capacity of the peripheral nervous system, as well as the ability to make an accurate diagnosis of injury severity based on EMG studies (Ferrante, 2012). It is prudent to remember that spontaneous recovery of brachial plexus injury does occur even in cases that are may initially appear severe (Kline, 2009, Lim et al., 2017).

In contrast, other groups propose long delays prior to surgical reconstruction may still result in acceptable results (Sedain et al., 2011, Narakas and Herzberg, 1985, Khalifa et al., 2012). Khalifa et al examined the outcomes of patients who underwent nerve-based reconstructions of peripheral nerve injury longer than one year after injury. An MRC strength grade ≥ 3 resulted in 67% procedures after an average delay of 18 months (Khalifa et al., 2012). Similarly, Narakas found that reinnervation may be obtained even after a delay in 24 months from time of injury (Narakas and Herzberg, 1985). Sunderland reported functional outcomes (MRC strength grading and active range of motion) for patients who underwent nerve reconstruction; demonstrating that functional recovery may occur after surgical delays of 6 to 11 months (Sunderland, 1947a). However, most groups advocate waiting a minimum of three months to allow for signs of spontaneous recovery on EMG, but operating prior to six months if a nerve reconstruction is required (Chuang et al., 1993, Kim et al., 2001, Samii et al., 1997, Martin et al., 2018). Despite the frequent use of nerve based reconstructive procedures the ideal time to operative intervention is not clear in the literature.

In a systematic review examining late surgical intervention (>12months) aimed at restoring elbow flexion after peripheral nerve injury, it was found that free muscle transfer procedures resulted in MRC strength grade 3 or greater more reliably than purely nerve based reconstructions, such as a nerve transfers or grafts (Hoang et al., 2018). Once 12 months after injury has passed, free functioning muscle transfer should be the preferred reconstructive procedure (Bishop, 2005). Although, it is apparent that late nerve based operative reconstruction does not produce reliable results, reinnervation may still result, and therefore the optimal timing of nerve-based reconstruction is still debated in the literature.

Given these findings, the exact timing of surgery producing the optimal balance of early intervention while allowing sufficient time to evaluate the injury for spontaneous recovery has yet to be fully elucidated. Outside of the UK, there is relative consensus that a decision regarding operative intervention should be made 3 to 4 months after injury, and the potential for reinnervation producing functional outcomes is significantly worse if operative intervention is performed after 6 months (Giuffre et al., 2010, Shin et al., 2005, Lim et al., 2017, Bulstra and Shin, 2016, Nath and Mackinnon, 2000, Martin et al., 2018). To date there have been no high quality prospective studies conducted correlating timing of intervention and functional outcome.

1.4.2 Additional Factors Impacting Operative Motor Outcomes

A number of factors, in addition to time to operative intervention, which may impact the success of operative nerve based reconstruction for peripheral nerve injury, have been identified (Ruijs et al., 2005, Trehan et al., 2016). Not only does the timing of surgery affect nerve transfer outcomes, as discussed earlier, injury characteristics (i.e. lower trunk injuries have worse prognosis), level of injury (proximal vs. distal), the nerve(s) injured, the presence of the associated arterial and bony injury, surgical technique, patient factors, and post-operative rehabilitation also impact functional outcomes (Socolovsky et al., 2011, Bertelli and Ghizoni, 2010, Lee et al., 2012, Jivan et al., 2009, Trehan et al., 2016, Ruijs et al., 2005, Rosen and Lundborg, 2001).

Patient variables reported to negatively correlate with operative nerve reconstruction outcomes include older age, increased BMI, and female gender (Lee et al., 2012, Socolovsky et al., 2014, Terzis and Konofaos, 2011, Trehan et al., 2016, Osborne et al., 2000, Roganovic, 2004, Martin et al., 2018). In reconstructions utilizing extraplexal, primarily intercostal donor nerves patients less than 30 years old had better MRC strength grade outcomes (Coulet et al., 2010, El-Gammal and Fathi, 2002, Nagano, 1998). Similarly, an examination of the outcomes of both nerve grafting and transfer procedures found patients younger than 20 years old were associated with better motor outcomes (Terzis and Barbitsioti, 2012). Poorer post-operative function is thought to be associated with older age due to reduced cortical plasticity, and thus decreased ability to recruit muscles in an atypical fashion (Socolovsky et al., 2017). In addition to reinnervation occurring, the functional success of distal nerve transfers is also reliant on cortical plasticity and the patients' ability to learn to consciously, and eventually unconsciously, to recruit the newly reinnervated muscle group (Socolovsky et al., 2017, Midha, 2004). However, worse post-operative outcomes have not been associated with older age when patients over the age of 50 are examined (Gillis et al., 2019). The impact of BMI is particularly associated with motor outcomes from reinnervation procedures aimed at restoring the proximal shoulder musculature (Socolovsky et al., 2014). Additionally, Socolovsky et al examined a series of reconstructions using sural nerve grafts (>10cm long) and determined the most important factors associated with achieving a functional outcome were: time from injury to surgery and the quality of postoperative rehabilitation (Socolovsky et al., 2011).

Injury factors that have been observed to negatively correlate with operative nerve reconstruction outcomes include: anatomic location of the injury (i.e. lower trunk injuries have worse prognosis), level of injury (proximal vs. distal), associated boney and arterial injury, multiple nerve injuries, and whether or not a nerve root avulsion is sustained (Socolovsky et al., 2011, Bertelli and Ghizoni, 2010, Lee et al., 2012, Jivan et al., 2009, Trehan et al., 2016, Ruijs et al., 2005, Rosen and Lundborg, 2001, Osborne et al., 2000). Upper trunk injuries are reported to have better outcomes than lower trunk or pan-plexus injuries, and isolated nerve injuries better prognosis than multiple nerve injuries (Kline, 2009, Terzis et al., 1999, Martin et al., 2018). Nerve root avulsions are associated with poorer overall functional outcomes, likely due to the severity of the initial injury, as a large amount of force is required to sustain this type of injury, and the limited potential for reconstruction using intraplexal donors (Tu et al., 2014, Ahmed-Labib et al., 2007).

As well, surgical techniques such as ensuring donor recipient axon count match, utilization of an unaffected intraplexal donor, choosing a donor with a synergistic function, and establishing a tension free epineurial repair via microsurgical anastomosis maximize functional results (Schreiber et al., 2015, Snyder-Warwick et al., 2015). Motor axon count ratios below 0.7:1 (donor to recipient) are associated with poor reconstructive outcomes for elbow flexion (Schreiber et al., 2015). The quality of the donor nerve chosen is extremely importance, an unaffected donor nerve based on preoperative strength evaluation and EMG assessment is associated with better post-operative motor strength and range of motion (Schreiber et al., 2014). The donor nerve utilized for the nerve transfer should not only be unaffected by the initial injury, if possible it should be an intraplexal donor, as intraplexal donor nerves are associated with better motor outcomes than extraplexal donors (El-Gammal and Fathi, 2002, Narakas and Hentz, 1988, Terzis and Barbitsioti, 2012). A donor nerve with a synergistic function, to the paralyzed muscle, offer benefits over the utilization of an antagonistic donor, as cortical remapping and subsequent motor relearning after surgery are facilitated (Leechavengvongs et al., 1998, Isaacs and Cochran, 2019, Brown et al., 2009, Midha, 2004). When considering the use of nerve grafts, grafts longer than 7cm utilized for reconstruction above the above the elbow have been associated with worse outcomes (Grinsell and Keating, 2014). Shorter nerve grafts are consistently associated with faster time to reinnervation and better outcomes (Chuang et al., 1993, Bentolila et al., 1999, Samii et al., 1997, Hentz and Narakas, 1988). Finally, the choice of reconstruction of a proximal nerve injury with a nerve transfer or a graft, also impacts the post-operative outcome, with nerve transfers being associated with better motor outcomes (Garg et al., 2011, Yang et al., 2012, Ali et al., 2015).

1.5 Barriers of Access to Peripheral Nerve Surgery

1.5.1 Factors Impacting Time to Operative Intervention

Determinants impacting time to surgery for peripheral nerve reconstruction after injury have not been extensively studied. There is very limited information in the literature regarding barriers to accessing surgical care for peripheral nerve injury. Proposed explanations for delayed referral and/or subsequent delayed surgical intervention for peripheral nerve injuries include: missed diagnosis, inappropriate referral, or a delay for unknown reasons (McAllister et al., 1996). Similarly, a study examining spinal accessory nerve injuries found that poor recognition of injuries and delayed referral were often reasons for delayed treatment of these injuries (Camp and Birch, 2011). An observational series utilizing administrative data from the USA found that patients initially treated at small hospitals had a higher risk of surgery occurring greater than a year after injury (Dy et al., 2016). Patient insurance type, travel distance to the surgical site, distance between treating hospitals, and changing hospitals for surgery were not associated with surgical intervention occurring more than one year after injury (Dy et al., 2016). A qualitative study investigating factors that contribute to patients not undergoing surgical reconstruction of brachial plexus injuries revealed a number of issues: including delayed diagnosis, patients having insufficient access to information regarding surgical options, and lack of insurance coverage (Franzblau et al., 2015). Conversely, the implementation of effective information transfer systems has been demonstrated to improve the care of patients with peripheral nerve injuries (Giddins et al., 1998). These findings, paired with a lack of extensive studies in the area, point to the need for a dedicated study examining determinants of access to peripheral nerve surgery. Improved accessibility to peripheral nerve reconstruction specialists, efforts to improve education surrounding diagnosis, and timely referral of peripheral nerve injuries are likely required in order to alleviate barriers to surgical care.

1.5.2 Barriers to Specialist Access in the Literature

The Canada Health Act is meant to ensure equal access for all Canadians, regardless of ability to pay, to surgery and medically necessary health care services. Despite a single-payer health care system in Canada, research demonstrates persistent inequalities in access to health care between socioeconomic groups, and particular geographic areas (Curtis and MacMinn, 2008, Stirbu et al., 2011). Access to medical and surgical specialists in Canada is lacking when wait time are compared to other countries, more than 50% of Canadians wait over four weeks for an appointment with a specialist (Bichel and Conly, 2009). A study examining specialists wait times in Ontario found the median wait time for a surgical consultation was between 33 days to 66 days, with a median time of 49 days wait to see a plastic surgeon (Jaakkimainen et al., 2014). Females and those with lower incomes waited longer to see a plastic surgeon (Jaakkimainen et al., 2014). Given the time sensitive nature of nerve based reconstructions for treatment of severe peripheral nerve injury, timely access to appropriate specialists and surgical resources is critical. However, accessing specialist care, particularly subspecialist surgeons, can be difficult and filled with delays; a difficultly compounded for particular subgroups, often disadvantaged, that face even greater barriers to accessing specialist care (Harrington et al., 2013).

Referral to a specialist is reliant on a complex process, and any number of barriers may cause a delay from the time of injury to initial surgical consultation. System complexities in the referral process may include: the physical separation of general practitioners from specialists, and the fact that there is currently no standardized referral process in Alberta (Bichel and Conly, 2009). The process of referring a patient is often difficult, reliant on the referring physicians knowledge of available services, and ability to negotiate this process on their patients behalf. The implementation of a centralized access and triage system reduced patient wait times for medicine specialists, despite referral volumes increasing (Bichel and Conly, 2009). A centralized access system reduced duplicate referrals, standardized referral information, standardized the triage process, and confirmed that the referral was received, ultimately streamlining the process (Bichel and Conly, 2009). Additionally, the lack of a standardized referral form for peripheral nerve injuries means that the information contained within the referral is at the referring physicians discretion and may not be sufficient to allow for efficient and appropriate triaging of the patient's injury and assessment of urgency of care (Tobin-Schnittger et al., 2018).

Access to a surgeon for treatment of a peripheral nerve injury may be impeded at any number of points in the referral process. Firstly, a diagnosis of peripheral nerve injury must be established, a referral made to the correct surgical specialists' office, and finally based on the information contained within the referral the specialists' office must triage the referral and determine how quickly the patient requires an appointment. In a review of the referral process for patients that require hip and knee arthroplasty, 40-80% of the waiting time for surgery preceded the initial consultation (Fyie et al., 2014). Ultimately, long wait times for specialist appointments were thought to be due to discrepancy in referral processing by individual specialists offices (Fyie et al., 2014). In a study examining surgical wait times in patients requiring urological surgical intervention, 53% of the overall wait time occurred after the decision to operate was made by the surgeon (Cole et al., 2011). Predictors of a shorter wait time for surgery in multivariable analysis included a diagnosis of cancer, younger age, higher urgency score, repeat patient, and female gender (Cole et al., 2011). Similarly, 55% of patients who required a hysterectomy in Ontario waited longer than the recommended time for treatment of uterine cancer (O'Leary et al., 2013). Older age, particular geographical regions, lower income, a subspecialist surgeon, and having surgery in a teaching hospital were associated with longer wait times (O'Leary et al., 2013). It is likely that the referral system for severe peripheral nerve injury surgery in Alberta faces similar challenges and bottlenecks, as it involves a subspecialist referral and, to add a layer of complexity, EMG testing by a second medical specialist is a necessary component of diagnosis.

Inequities in access to plastic surgeons have been examined in the context of breast reconstruction (Potter et al., 2013, Vrouwe et al., 2017, Zhong et al., 2014). Immigrant women, and those who lived in areas with a lower median income demonstrated an association with not undergoing immediate breast reconstruction (IBR) (Zhong et al., 2014). In a different provincial setting, income did not impact breast reconstruction rates; however, patient age, stage of disease, and the year mastectomy was completed were associated with undergoing breast reconstruction (Barnsley et al.). A qualitative survey examined patients perceptions regarding barriers to breast reconstruction; despite 43% of patients potentially being interested in IBR prior to undergoing mastectomy, the option of IBR was only discussed by the treating physician in 14% of cases (Cheng et al., 2017). Patients stated reasons they did not undergo IBR were: inadequate knowledge of reconstructive options, the procedure not being offered, surgeon opinion regarding IBR, or long surgical wait times (Cheng et al., 2017). Access to plastic surgeons in Canada can likely be improved by improving referral systems as well as knowledge of surgical resources available (Cheng et al., 2017, Fyie et al., 2014).

Patients living in an urban area consistently report fewer difficulties, than those who live in rural areas, in obtaining a consultation with a specialist (Pong et al., 2011, Chan and Austin, 2003). This is particularly relevant in Canada, as approximately 30% of the Canadian population lives in areas with populations of less than 30,000 persons, based on the 2011 Canadian census data (Canada, 2011). In Saskatchewan, difficulty accessing specialist care increased with the distance the patient lived from the medical specialist (Karunanayake et al., 2015). Patients living in rural centers are less likely to access medical specialists and to compound difficulties with access less likely to have a family physician in order to obtain a referral to a specialist (Sibley and Weiner, 2011). The reasons underlying geographic disparity of specialist access are complex and may be in part due to significant travel, and other, costs incurred in order to attend a specialist consultation (Robb and Clapson, 2014, Mathews et al., 2009). Travel, child care costs, and other financial barriers influence patients' decisions regarding whether or not to attend a specialist appointment for those patients living in rural centers to a greater extent than patients living in urban centers (Mathews et al., 2009, Humber and Dickinson, 2010). In the plastic surgery literature, breast reconstruction rates have a negative correlation with increasing travel distance to the surgical centre (Albornoz et al., 2016, Roughton et al., 2016). In fact having to travel more than 20 miles for surgery was associated with patients not undergoing any type of breast reconstruction after mastectomy (Roughton et al., 2016). As well, patients who live farther from the operative site may have an increased number of post-operative complications, and inferior surgical outcomes (Etzioni et al., 2013). Systemic inequities influencing access to specialist care permeate the literature and highlight the need of healthcare policy to specifically target these areas of inequities in order to provide truly accessible and universal healthcare.

Socioeconomic inequity exists and persists in utilization of specialist resources (van Doorslaer et al., 2006, Vikum et al., 2013). Patients with a lower socioeconomic status are less likely to visit specialists, and have more difficulties accessing specialists when medically necessary (Schoen and Doty, 2004, Stirbu et al., 2011, Dunlop et al., 2000). Surgical specialists provide greater amounts of care to patients in higher income neighbourhoods, not necessarily those patients with the greatest medical need (Roos and Mustard, 1997). Additionally, patients who have greater socioeconomic resources may be better able to navigate the complexities of the health care system (Roos and Mustard, 1997). The correlation of lower SES and longer surgical wait times persists in other publically funded systems outside of Canada (Laudicella et al., 2012). Occupation is often used as an indicator of socioeconomic position (SEP) (Galobardes et al.,2007). Socioeconomic position is typically measured as a combination, of occupation, education and income. Occupation is closely related to income and education, thus an association of occupation with health care access may suggest a relationship between SEP and health care access (Galobardes et al., 2007). Differences in surgical specialist access according to occupation may reflect differential access to health care resources due to social standing and/or financial resources (Galobardes et al., 2007). Lower income and education are associated with longer surgical wait times (Laudicella et al., 2012). To complicate matters, geographic areas of low socioeconomic status are often associated with "surgical deserts", typically these "surgical deserts" are small centers or rural areas (Vora et al., 2018). “Surgical deserts” not only have less surgeons per capita, they are associated with low income households, and higher rates of medical comorbidities (Vora et al., 2018). Perversely, those patients with a greater number of chronic comorbidities report more difficulty with accessing specialist care (Harrington et al., 2013). This discrepant distribution of surgical specialists, with more specialists in areas of higher socioeconomic status, highlights the need of for interventions aimed at decreasing disparities in access due to socioeconomic status and health status.

1.5.3 Modified Penchansky and Thomas Access to Care Model

Barriers to accessing medical care can be characterized according to the modified Penchansky and Thomas six-domain model (Penchansky and Thomas, 1981, Saurman, 2016). Access to health care can be evaluated within this six-domain framework: availability, accessibility, accommodation, affordability, acceptability, and awareness (Penchansky and Thomas, 1981, Saurman, 2016). Accessing surgical specialist care may be due to difficulties in one or more of these six of these domains. Availability is defined as the relationship of the *volume and type* of relevant health care services available to those required by the patient, or client (Penchansky and Thomas, 1981). Issues with availability to care are demonstrated by the presence of surgical deserts (Vora et al., 2018). Accessibility is the relationship of the *location of services* provided by the health care system and where those services are required (Penchansky and Thomas, 1981). Accessibility is illustrated by the urban-rural disparity in specialist access (Karunanayake et al., 2015, Mathews et al., 2009, Humber and Dickinson, 2010, Harrington et al., 2013, Pong et al., 2011, Chan and Austin, 2003). Accommodation is the relationship between the *organization of resources* and the ability of the users, both clients and providers, to adapt to the organization of resources (Penchansky and Thomas, 1981). Reduced accommodation is illustrated by the prolonged waiting times due to variation in referral processing by specialists offices, as well as long surgical wait times due to limited operative theatre capacity (Fyie et al., 2014, Cheng et al., 2017). Affordability is characterized by the relationship of the *prices of necessary services and the users ability to pay* (Penchansky and Thomas, 1981). Lower income and socioeconomic status are associated with longer surgical wait times, and lack of insurance was associated with a decision not to undergo surgery for brachial plexus injuries, thus, highlighting issues with affordability (Laudicella et al., 2012, Franzblau et al., 2015). Acceptability is the relationship between the *users perceptions* regarding the characteristics of providers or procedures, as well as the *providers' perceptions* of acceptable personal characteristics of the user for eligibility of a particular service (Penchansky and Thomas, 1981). Patients who were initially treated at small hospital demonstrated a significant association with delay in surgery beyond one year (Dy et al., 2016). This delay may be in part due to the opinions and referral practices of the physicians practicing at these institutions, thus, relating to perceived acceptability of patient suitability for peripheral nerve surgery (Dy et al., 2016). Awareness is the *knowledge* of available services/resources and *indications* for use of a particular service (Saurman, 2016). Insufficient information in the community regarding treatment options for peripheral nerve injuries highlights a lack of awareness of surgical treatment options that may act as a barrier to access for surgical care of peripheral nerve injuries (Franzblau et al., 2015, Cheng et al., 2017).

Based on the identified barriers to care in the peripheral nerve injury, plastic surgery, and public health literature we aim to investigate factors, both system and patient related, that might be associated with patient difficulties accessing care, and consequently a prolonged time to operative intervention for peripheral nerve injury.

1.5.4 Patient Perceived Barriers to Accessing Surgical Care

The delivery of health services and creation of health policy should be informed by not only quantitative data but also patient experiences and opinions, in order to create a system that truly optimizes the patient care experience. Qualitative research offers the benefit of illustrating the patient viewpoint and enables providers to understand health service delivery challenges from the patient perspective (Leung, 2015). This essential in depth understanding of health care processes and patient experiences cannot be achieved through traditional quantitative methodologies (Shauver and Chung, 2010). Complex issues, such as the process of accessing surgical care for peripheral nerve injury, are best characterized by qualitative methodology, in order to ensure all aspects of the issue that are important to health care users are captured (Corbin, 2008). As a result, qualitative research methodology has the potential to influence health policy focussed on improving patient care, at a local and national level.

Unfortunately, literature elucidating patient experiences in the context of peripheral nerve reconstruction is sparse. The majority of qualitative peripheral nerve injury research focuses on patient satisfaction and patient reported outcomes post operative reconstruction of brachial plexus injuries (Franzblau et al., 2014, Novak et al., 2009). A Canadian analysis of patients with peripheral nerve injury who presented for initial surgical consultation in a delayed fashion, more than 6 months after injury, found that these patients reported higher levels of disability and lower overall health status (Novak et al., 2009). Patients are, for the most part, satisfied with the outcomes of brachial plexus surgery, with 78% of patients reporting they were at least moderately satisfied with their surgical outcomes (Kretschmer et al., 2009, Franzblau et al., 2014, Choi et al., 1997). Despite patient satisfication with surgical outcomes, Choi et al reported that only 54% of patients were able to return to work (Choi et al., 1997). Similarly, 75% of patients reported longstanding persistent pain (Choi et al., 1997). In addition, patient expectations of function post brachial plexus reconstruction have been characterized in the qualitative literature (Mancuso et al., 2015). Patients expected improvements in function, pain, as well as return to activity, particularly work, after surgery (Mancuso et al., 2015). Interestingly, these patient expectations of surgery were derived from Internet research and discussion with other patients, rather than the medical team directly (Mancuso et al., 2015). Post-operatively, patients reported impairments in essential activities, including work, school, and activities of daily living (Mancuso et al., 2015). While patient reported outcomes are important in improving care and outcomes of peripheral nerve injuries, these studies do not assess the patient perceptions of accessibility treatment, nor do they assess ways in which the care pathway can be improved.

Franzblau et al interviewed a number of patients with brachial plexus injuries regarding their decisions not to undergo surgical reconstruction. This group found that lack of insurance, delays in diagnosis, and insufficient information regarding treatment options prevented patients from receiving surgical care (Franzblau et al., 2015). Similarly, a study examining access to IBR found that a lack of information, limited availability of plastic surgeons, and difficulty with referrals were perceived to contribute to low rates of IBR after mastectomy (Cheng et al., 2017). It is feasible that a lack of information regarding treatment options, and delayed diagnosis of peripheral nerve injuries also present barriers to accessing surgical intervention in the publically funded Canadian system. A qualitative study examining wait times for surgery in the bariatric surgery population found patients perceived socioeconomic and regional inequities as affecting their ability to access bariatric surgery (Gregory et al., 2013). These perceived inequities in access, within a publicly funded system; likely represent systemic issues that persist across surgical specialities. Despite identifying a need for detailing patient perspectives and experiences no further work has been done examining the patient experience with regard to the accessibility of, and perceived barriers to, surgical care for peripheral nerve injury.

1.6 Objectives

Peripheral nerve transfers or grafts for reconstruction of severe proximal peripheral nerve injury are standard of care in the peripheral nerve injury field. We aim to address a number of current deficiencies in the literature through this dissertation. Although prolonged time prior to operative intervention is detrimental to reinnervation, the optimal time to operative intervention remains unclear in the literature (Fu and Gordon, 1995b). Additionally, the effect of patient, injury, and operative factors has not been adjusted for in previous examinations of the effect time to operative reconstruction, with nerve transfer or graft, has on strength outcomes. Thus, we aim to characterize the impact of time and other factors on post-operative strength outcomes. As well, dedicated analysis of factors associated with time to operative intervention is lacking in the literature. Last, but certainly not least, patient experiences during the process of accessing surgical care have not been explored or characterized in the peripheral nerve injury literature. Therefore we aim to explore factors associated with time to operative intervention, and patient perceptions regarding the process of accessing surgical care through a dedicated peripheral nerve clinic.

1.6.1 Aims

1) To characterize the time to operative intervention in Alberta, and explore potential system and patient factors that may be associated with a prolonged time to surgical intervention.
2) To understand patient experiences and perceived barriers to accessing peripheral nerve surgery through the Northern Alberta Peripheral Nerve Clinic.
3) To assess if time to intervention, as well as injury, surgery, and patient factors are associated with clinical outcomes strength outcomes as graded on the MRC scale.

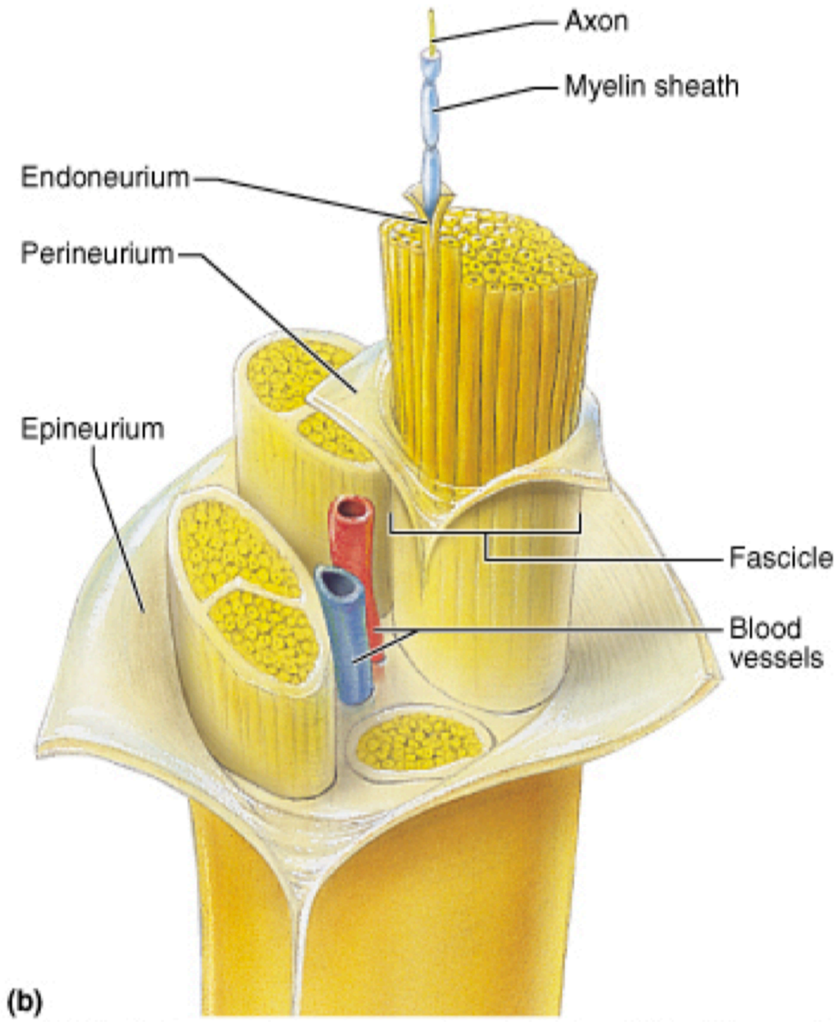
Figure 1.1: Medical Research Council (MRC) Motor Strength Grading Scale

Observation	Muscle Grade
No contraction	0
Flicker or trace of contraction	1
Active movement with gravity eliminated	2
Active movement against gravity	3
Active movement against gravity and resistance	4
Normal power	5

Data from Aids to the Investigation of Peripheral Nerve Injuries, ed 2. (Medical Research Council War Memorandum, vol 7.) London, His Majesty's Stationary Office, 1943, p 48.

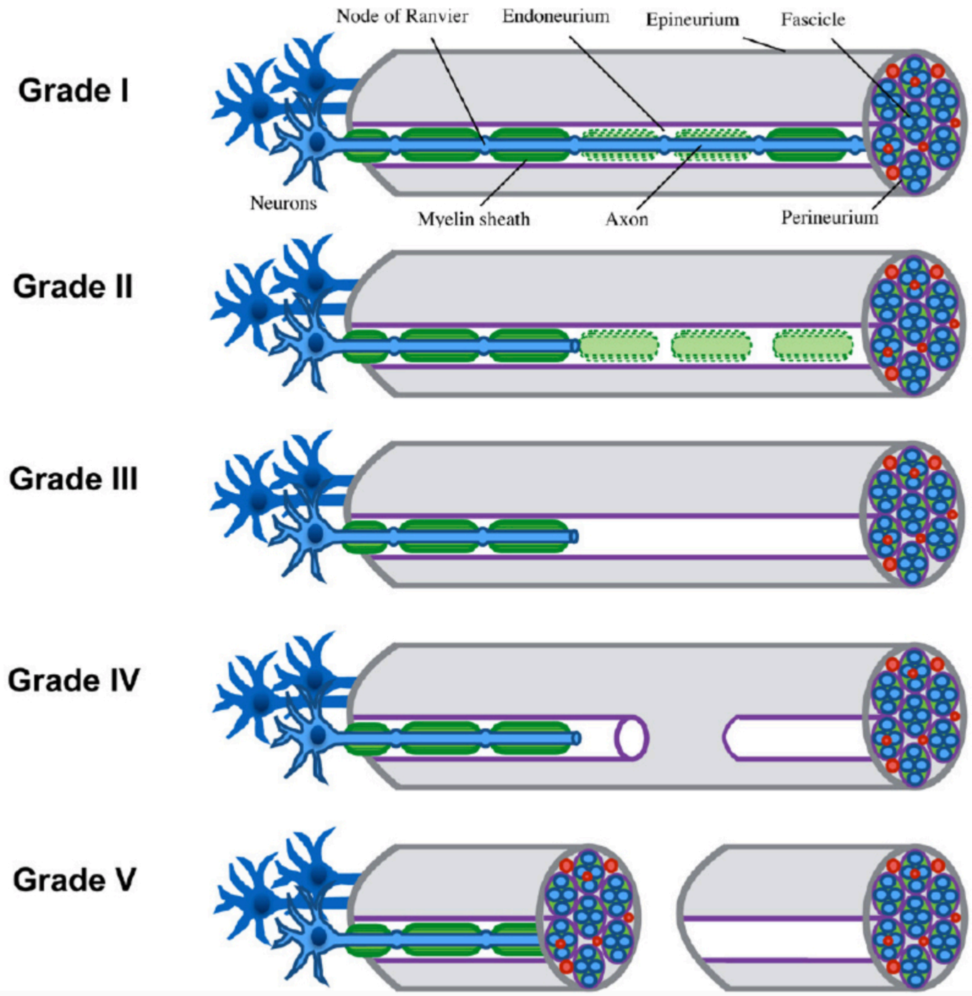
(Van Allen, 1977)

Figure 1.2 Layers of Connective Tissues Surrounding Peripheral Nerves



(Cummings, 2011)

Figure 1.3 Sunderland Classification of Peripheral Nerve Injury



(Menorca et al., 2013a)

Figure 1.4 Anatomy of the Brachial Plexus

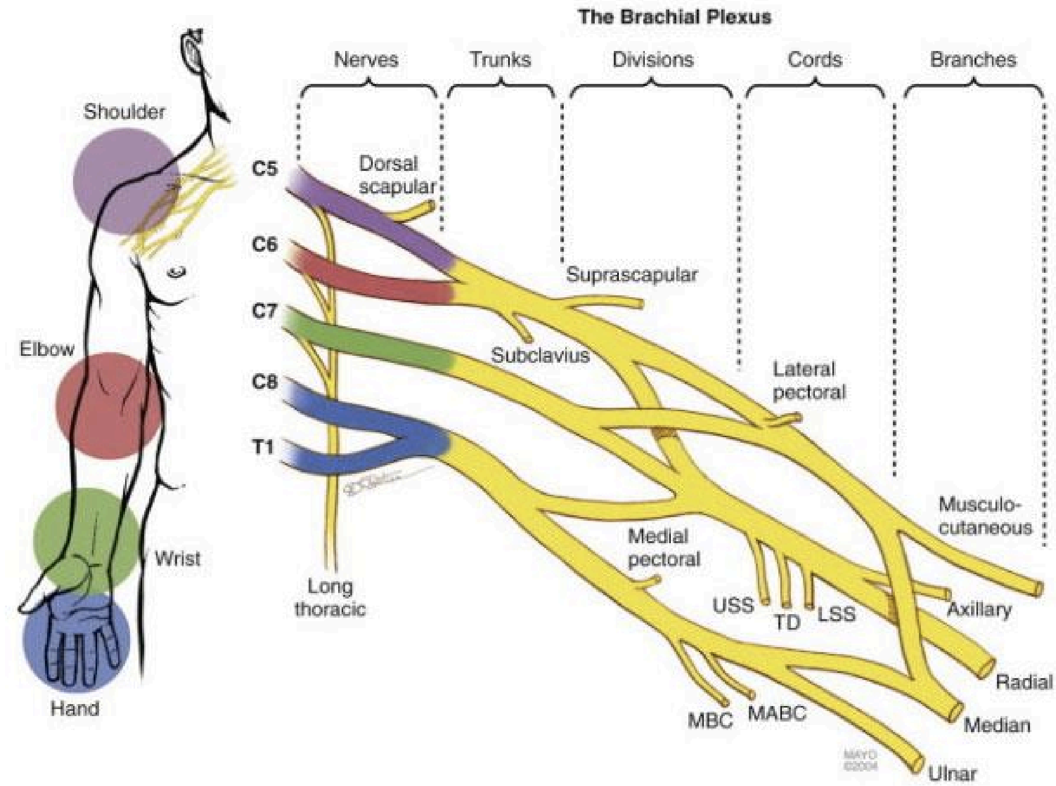


Figure 1.5: Nerve Grafting of the Upper Trunk of the Brachial Plexus

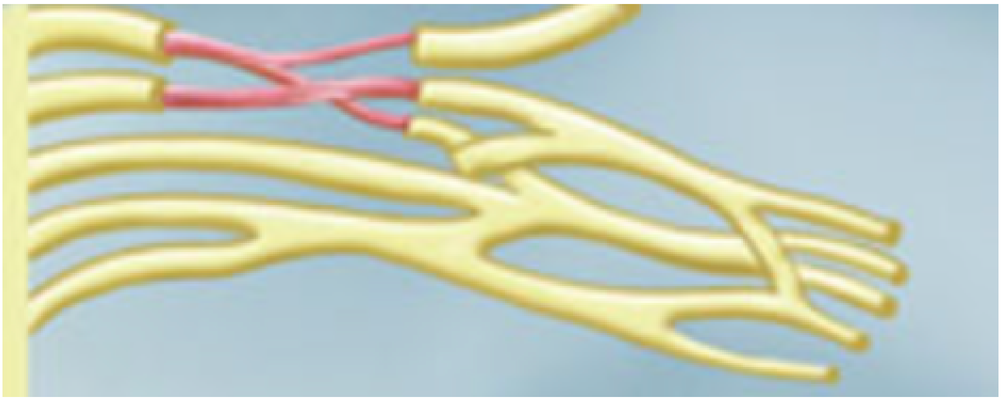
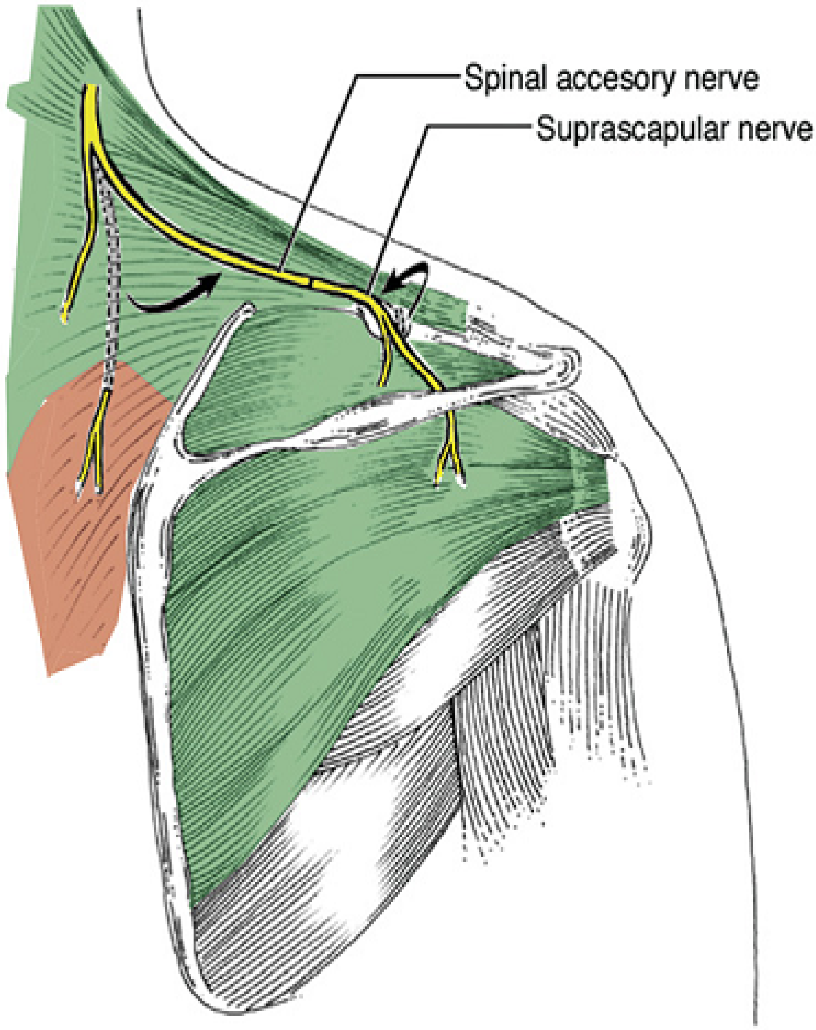


Figure 1.6 Example of a Distal Nerve Transfer



1.7 Introduction References

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Chapter 2: Severe Peripheral Nerve Injury: Factors Associated with Time to Surgical Intervention

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2.1 Introduction

Depending on the severity of the peripheral nerve injury, surgical intervention may be required to restore function. Reconstructive options for proximal peripheral nerve injuries include nerve grafts and transfers; and timing of surgery plays a critical role in patient outcomes, with earlier intervention resulting in better outcomes (Jivan et al., 2009). Optimal timing of nerve reconstruction is generally accepted to be 3 to 6 months after injury (Martin et al., 2018). However, clinically patients often undergo reconstruction outside of this 3 to 6 month window for a variety of reasons (McAllister et al., 1996, Camp and Birch, 2011, Franzblau et al., 2015). The median time to surgery in a large observational study from the USA was 7.6 months after injury (Dy et al., 2016).

There is very limited information in the literature regarding factors associated with time to definitive surgical care for peripheral nerve injury. In a study by Dy et al., treatment of the initial injury at a smaller hospital (less than 400 beds) was significantly associated with a delay in surgery over a year after injury (Dy et al., 2016). In contrast, insurance type, travel distance, and distance between the presenting and surgical centre were not associated with time to surgical intervention (Dy et al., 2016). While this study is valuable, nerve based reconstruction likely should not be performed beyond one year from injury (Hoang et al., 2018). Thus, it is essential to delineate the factors that impact the time to surgery within the first year of injury, as the majority of nerve reconstruction surgery is conducted within that time frame.

The reasons for delayed surgical intervention in severe peripheral nerve injury have not been well investigated in the literature. Specifically, an examination of patient, injury and system factors that impact the time to surgery utilizing a multivariable model has not been completed. Thus, we aimed to investigate patient, injury, and system factors that are associated with time to operative intervention in an effort to identify potentially modifiable factors that may be addressed to reduce delays in surgery.

2.2 Methodology

This study describes the timing of surgery for adult patients in Alberta who underwent operative reconstruction of a proximal peripheral nerve injury with a nerve transfer or graft. We conducted a retrospective chart review of patients who underwent nerve grafting or transfer in the province between 2005 and 2017, for reconstruction of severe peripheral nerve injury. Factors associated with time to surgical intervention for nerve reconstruction were explored. The study was conducted in adherence with the ethical principles outlined in the Declaration of Helsinki and was approved by the human research ethics boards at the University of Alberta and the University of Calgary.

2.2.1 Inclusion Criteria

Adult patients who had underwent peripheral nerve reconstruction with either a nerve transfer or graft by an experienced peripheral nerve surgeon in either Calgary or Edmonton, the only centres in Alberta that perform major peripheral nerve reconstruction surgery, were included. Inpatient and outpatient charts, using operative codes, associated with peripheral nerve surgeries, were identified (Figure 2.1 & 2.2). In Calgary the patient records were identified using operative codes for peripheral nerve surgery and then screened for those patients undergoing nerve transfer or graft, whereas in Edmonton charts associated with nerve grafting and transfer were identified directly. In Calgary a single neurosurgeon specializing in peripheral nerve reconstruction was involved in all surgeries. In Edmonton a team of two plastic surgeons specializing in peripheral nerve surgery performed all of the peripheral nerve reconstructions.

2.2.2 Exclusion Criteria

Pediatric patients, and patients who required a primary free muscle based reconstruction, primary nerve repair, or did not undergo surgical reconstruction of their peripheral nerve injury were excluded from analysis.

2.2.3 Predictor Variables Examined

Demographic information including: patient age at the time of surgery, gender, side of injury, smoking status, alcohol use, pre-injury employment, number of pre-injury comorbidities, peripheral nerve injury requiring operative intervention, and surgery performed, along with a number of other variables were collected (Table 2.1). Excessive alcohol use was included as it is well known that substance users have higher rates of non-attendance at all appointments (Milward et al., 2014). Alcohol use was defined as a self reported or documented alcohol use disorder or intake beyond that of the recommended daily limit: two drinks a day, or 10 drinks per week for women, and three drinks a day, or 15 drinks per week for men (Bondy et al., 1999). The type of pre-injury employment the patient was working in was classified as intellectual employment, manual employment, or unemployed. This classification of employment is pertinent as manual labor is associated with higher incidence of work place injury (Piha et al., 2013, Rommel et al., 2016). Manual labor was defined as a physically demanding occupational activity or one involving low-level service activities, while intellectual labor was defined as occupational activities that involved mostly intellectual work, office work, or the pursuit of education (Galobardes et al., 2007). The number of pre-injury comorbidities was also documented as proxy of overall pre-injury health status. Patients with a greater number of chronic comorbidities are more likely to report difficulties accessing specialist care (Harrington et al., 2013).

Additionally, we examined whether the patient lives in an urban or rural location, sustained a polytrauma, the duration of acute care hospital stay at time of injury, the distance the patient lived from the surgical centre, if the patient was insured privately by the workers compensation board, and the specialty of the physician referring the patient to the peripheral nerve clinic. A rural area was defined based on the Canadian census definition as small population centre (population less than 30,000) (Canada, 2011). The driving distance of the patient's home to the centre performing surgery was calculated using the patients' postal code when available, or the distance from the surgical site to the location of residence.

Peripheral nerve injuries are often associated with concomitant trauma (Noble et al., 1998). The presence of comorbid injuries may influence the timing of surgery for multiple reasons. A patient in this study was defined as having sustained a polytrauma if the person sustained moderately severe injuries in two or more different anatomic regions, or had a calculable injury severity score >/= 16 (Pape et al., 2014, Baker et al., 1974, Butcher and Balogh, 2012).

We investigated if a prolonged length of stay in an acute care facility was associated with time to peripheral nerve surgery, as the length of acute stay is a proxy of the severity of injury over a discrete period of time (Cryer et al., 2010, Newgard et al., 2010). Additionally, the medical specialty referring the patient to the peripheral nerve clinic may impact the time to surgery, as specialist care arguably is more difficult and time consuming to access than a general practitioner. We aimed to determine if patient referral by a specialist is associated with a delay in peripheral nerve surgery.

2.2.4 Statistical Analysis

There were 19 potential predictor variables (Table 2.1) of interest identified *a priori* based on clinical knowledge and previous work examining reasons for delayed referral of peripheral nerve injuries, and determinants of accessibility to surgical specialists.

A univariate comparison of the patient and injury characteristics between surgical site was completed using Student t-tests (mean (standard deviation)) for parametric, Mann-Whitney U tests (median (interquartile range)) for nonparametric data, and Chi-squared or Fischer Exact testing for frequency data, in order to examine the differences between sites (Table 2.3). Post hoc testing when necessary was conducted by utilizing the Bonferroni adjustment method. The Jarque-Bera test was used in order to test for normality.

A univariate Cox proportional hazard analysis was conducted for each potential predictor variable of interest to obtain the unadjusted hazard ratio and to evaluate whether each candidate variable independently met the proportional hazard assumption (Table 2.1). A multivariable Cox Proportional Hazard Regression model was chosen to evaluate the adjusted effect of selected predictor variable on time to operative intervention (Grambsch and Therneau, 1994). Given the limited body of work examining determinants of access to peripheral nerve surgery we chose to perform variable selection according to the Akaike Information Criterion (AIC) best subset variable selection method (Akaike, 1975). In addition to the advantage of allowing for selection of variables that balance model fit with the least number of parameters, the AIC variable selection method offers a number of benefits over stepwise modeling procedures, especially when clinically important parameters are relatively unknown. Since there is a comparison of models to one another, in AIC variable selection the "best model" is identified (Akaike, 1975). Best subset variable selection avoids the bias and validity issues introduced by selecting variables based solely on p-values (Steyerberg et al., 1999). The final multivariable Cox model was established by the AIC best subset selection approach and included four variables (Wen et al., 2017).

Patients with missing data in the final model were eliminated from the Cox Proportional Hazard regression analysis, resulting in the final model including 144 patients.

The final model was further examined to ensure that all assumptions were fulfilled for time to event analysis. The proportional hazard assumption was tested for the global model and each of the predictor variables in the selected model using the "phtest" based on Schoenfeld residuals (Grambsch and Therneau, 1994, Therneau, 2015). Statistical analysis was performed on R version 3.4.0 (Wen et al., 2017, Therneau, 2015, Team, 2017).

2.3 Results

2.3.1 Patient Demographics

There were 166 patients identified, 97 from Edmonton and 69 from Calgary who underwent a nerve graft or transfer for treatment of severe proximal peripheral nerve injury between 2005 and 2017 that met the inclusion criteria (Figure 2.1 & 2.2). The majority of patients who underwent surgery were male (81.8%) and the median age at time of surgery was 34 (IQR: 25) years (Table 2.2). The time to surgical intervention ranged from 0 to 633 days after injury, 17 patients underwent operative intervention greater than 365 days from injury, and 13 received surgery within 2 weeks of injury. The characteristics of the patients undergoing surgery in Edmonton and Calgary were examined in a univariate analysis for significant differences between locations (Table 2.3 & 2.4). There were statistically significant differences between the two surgical centres with Calgary performing more grafts, operating on more brachial plexus injuries, injuries with a pre-ganglionic component, and fewer lower extremity injuries. Additionally, in Calgary there were more polytrauma patients. However, the length of acute stay in hospital did not differ between centres.

2.3.2 Treatment Pathway

In order to undergo reconstructive peripheral nerve surgery a patient must receive i) a referral to the peripheral nerve clinic, ii) an EMG study diagnosing and documenting the extent of injury, and iii) attend a surgical consultation appointment in the peripheral nerve clinic. The median time to a referral being made to a peripheral nerve clinic was 66 (IQR: 116) days after injury, time to initial EDX testing was 84 (IQR: 99.5) days, and the median time initial consultation was 135 (IQR: 111) days. The mean time to operative intervention was 221.9 (SD: 118) days (Table 2.5).

The waiting time for a referral to a peripheral nerve surgeon accounts for 30% of the overall waiting time, and 38% of the total time waited was prior to receiving an EMG study. Patients waited approximately 51 days from their initial EMG, 135 days after injury, and 69 days after referral for their initial consultation with a peripheral nerve surgeon. Finally, 36% of the total waiting time prior to surgery occurred after the initial consultation in peripheral nerve clinic.

2.3.3 Cox Proportional Hazard Regression

The unadjusted univariate hazard ratios for all potential predictor variables considered are illustrated in Table 2.1. The year of surgery and location of surgical site did not demonstrate any association with time to surgical intervention (Table 2.1). The final Cox Proportional Hazard Regression model, based on variable selection according to the Akaike Information Criterion (AIC) best subset variable selection method contained the predictor variables of injury to the dominant limb, whether or not the patient lived in an urban or rural location, number of pre-injury comorbidities, and the medical specialty that referred the patient (Table 2.6) (Akaike, 1975). An increase in pre-injury comorbidities was associated with longer overall time to surgery (aHR 0.84, 95% CI 0.74 - 0.95). An increase of one comorbidity decreased the instantaneous risk of surgery by 16% after controlling for involvement of the dominant limb, where the patient lived, and referring specialty (p=0.006). A referral to the peripheral nerve clinic made by a surgeon was associated with a shorter overall time to surgery, when compared to a referral made by a general practitioner (aHR 1.87, 95% CI 1.14 – 3.06). The expected instantaneous risk of surgery for a patient referred by a surgeon is 87% greater than if a general practitioner made the referral, after controlling for the other variables in the model (p=0.014). Thus, a referral to the peripheral nerve clinic by a surgeon increased the potential that a patient undergoes surgery in a timely fashion. There was a non-significant association of patients living in an urban centre having a shorter overall time to surgery as compared to those living in a rural centre, when all other factors remain the same (aHR 1.39, 95% CI 0.98 - 2.01, p=0.072). Involvement of the dominant limb did not statistically significantly impact the overall time to operative intervention.

2.4 Discussion

Having a greater number of comorbidities was significantly associated with an overall increased time to operative intervention for patients with a severe peripheral nerve injury. A referral by a surgeon was significantly associated with overall decreased time to operative intervention. As well, there was also a non-significant association with overall increased time to operative intervention for patients who lived in small centres.

2.4.1 Comorbidities

An increased number of comorbidities have been associated with a longer overall time to operative intervention, independent of surgical specialty (Zeltzer et al., 2014, Vergara et al., 2011, Kwon et al., 2007). In this analysis the number of comorbidities is a proxy for overall health status, as the severity of individual comorbidities was not considered due to sample size constraints. To minimize peri-operative risk, optimization of medically modifiable co-morbidities prior to surgery is critical (Fong and Sweitzer, 2014). Any patient whom is deemed at risk for a peri-operative adverse event should be referred for evaluation by a multi-disciplinary pre-anesthetic consultation (PAC) team. Referral and intervention to decrease rates of adverse peri-operative events understandably takes time.

Typically, an increased number of comorbidities correlate with older age (Davis, Chung et al. 2011). However, age was not found to be a significant factor impacting time to operative intervention in the univariate analysis, nor did it demonstrate collinearity with the presence of increasing comorbidities. This is likely due to the fact that the patients who sustain severe peripheral nerve injuries are young, with a median age of 34 years. Thus, the finding of an increase in comorbidities being associated with a longer overall time to surgery represents an accessibility problem, in which those patients with a lower pre-injury health status wait longer for surgery.

2.4.2 Referral Source

The association of a referral made by a surgeon with a shorter overall time to surgery has not been previously reported in the literature. This finding suggests access to surgery is biased towards a patient population who already has access to a surgical specialist. There are a number of possible reasons why referrals made by surgeons may be associated with a shorter time to operative intervention. First, currently there is no standardized referral system for peripheral nerve injuries in Alberta. Thus, the referring physician decides what information is included, to whom, and how the referral is sent. Incomplete referral letters have been associated with poor patient outcomes (Jiwa et al., 2009, Akbari et al., 2008). It is possible that surgeons' referrals contain more clinically pertinent and complete information allowing for more expedient and accurate triaging of referral. Second, appropriate referral is reliant on the referring physicians knowledge of local resources, thus it may be surgeons are more aware of other surgical resources. A centralized referral system, and the implementation of a standardized referral form would likely improve access to peripheral nerve specialists (Naseriasl et al., 2015, Bichel et al., 2009, Tobin-Schnittger et al., 2018).

Finally, it is likely surgeons and general practitioners have different experiences diagnosing peripheral nerve injuries, as these injuries commonly present to tertiary care centres (Noble et al., 1998). Physicians who encounter peripheral nerve injuries less frequently may have challenges diagnosing and thus referring patients with peripheral nerve injuries. Hence, targeted education to increase awareness of patterns of peripheral nerve injuries may serve to reduce diagnostic challenges. Ultimately, this discrepancy in access due to referring physician specialty is likely multi-factorial. The implementation of a standardized referral process, enhancing clinicians knowledge regarding resources available, and/or an increased emphasis of peripheral nerve injury diagnosis patterns may serve to alleviate the association between time to surgery and referral source.

2.4.3 Geographic Disparity

Living in an urban area has consistently been associated with improved access to medical specialists (Pong et al., 2011, Chan and Austin, 2003). This is of particular relevance in Canada as 31% of Canadians live in small centres with populations less than 30,000 people (Canada, 2011). Patients living in rural centres are less likely to use specialist services and/or have a regular physician (Sibley and Weiner, 2011). Factors influencing geographic disparity of specialist access are complex, and in part may be due to the significant costs incurred by rural patients when accessing non-local specialist care (Robb and Clapson, 2014, Mathews et al., 2009). Transportation and finances were identified as barriers to accessing specialist care; multiple visits further compounded these barriers (Humber and Dickinson, 2010). The burden of travel may be alleviated by the utilization of tele-health services when possible (Kruse et al., 2017). The idea of systemic inequities, such as geographic location, influencing access to peripheral nerve surgery is troublesome and needs to be addressed by improving the current care pathway.

2.4.4 Delays in Surgical Intervention

Of all the patients admitted to a Canadian level one-trauma centre approximately 5% have an associated peripheral nerve injury (Noble et al., 1998, Selecki et al., 1982). It is widely accepted that closed peripheral nerve injuries requiring surgical intervention should be explored and repaired at the earliest possible time, while still allowing for the evaluation of spontaneous recovery (Dahlin, 2013). Although the optimal balance of early surgery and spontaneous recovery is not entirely clear, operative intervention is generally considered at 3 to 6 months after injury (Martin et al., 2018). The mean time to operative intervention in Alberta is 7.5 months. Similarly, the median time to surgery in a large observational study from the USA is 7.6 months (Dy et al., 2016). These time frames fall outside of the recommended 3 to 6 month timeframe in which peripheral nerve surgery should be performed (Martin et al., 2018). Therefore, the clinical care pathway and factors associated with delayed operative intervention warrant further consideration.

We found that patients waited 135 days after injury, and 69 days after referral for their initial consultation with a peripheral nerve surgeon. In comparison, the median wait time to see a plastic surgeon in Ontario was 49 days from time of referral (Jaakkimainen et al., 2014). [43]. An examination of arthroplasty referrals found the majority of the total wait time was prior to the initial consultation with an orthopaedic surgeon, likely due to variations in referral processing [44]. Given the longer than 2 month wait time from referral to initial consultation, it is very likely that there are similar challenges with referral processing in peripheral nerve surgery (Fyie et al., 2014, Camp and Birch, 2011). Additionally, 36% of the overall time waiting time for peripheral nerve surgery occurs after the initial consultation. This finding is similar to delays in other surgical specialities (Cole et al., 2011). The delay in surgery after consultation may be due to insufficient operating room time, redundant diagnostic testing, and/or a clinically ambiguous picture regarding whether or not the nerve injury will recover without intervention.

What is clear is that the subspecialized nature and complex care pathway for the treatment of peripheral nerve injuries results in difficulties delivering timely surgical intervention (Camp and Birch, 2011). Based on these findings, we must work to improve clinical pathways for peripheral nerve injury referrals, and enhance awareness of injury patterns and clinical resources. We must also work to improve access to peripheral nerve surgery for patients living in small centres, and those with a greater number of comorbidities.

2.5 Limitations

Limitations of this study include its retrospective nature. We were constrained by the information available in patient charts as recorded by the clinicians in a non-standardized manner; thus, all possible confounders may not have been examined. Additionally, it is possible that there are other surgeons conducting peripheral nerve surgery outside of the confines of the two academic peripheral nerve clinics in Alberta, and these patients were not identified. However, given the limited availability of peripheral nerve surgical expertise, the number is likely very small.

Finally, we have combined the populations of two large academic centres with geographically different catchment areas, patients, injuries, and operative techniques in order to represent the provincial data. This utilization of provincial data is important as the findings reflect practices for the province rather than a single centre. In order to assess the effect of location on the fit of the model, we compared the AIC values of the chosen model and the model including an additional location variable; the AIC scores differed by 0.06. When comparing models, a lower AIC score indicates a model that better balances goodness of fit and number of parameters. An expert statistician determined that including location in the model did not enhance the fit of the model nor provide additional explanatory value over the chosen model.

2.6 Conclusion

The Canada Health Act mandates equal access to health care, including surgery, for all Canadians. Despite publicly funded health care, research has shown persistent systemic inequalities in access to specialist care (Harrington et al., 2013, Curtis and MacMinn, 2008). Similarly, our research demonstrates systematic inequalities in access to timely surgical intervention for peripheral nerve injuries. Factors that are associated with a shorter time to peripheral nerve surgery are fewer comorbidities, and referral by a surgical specialist. Understanding the factors that play a role in preventing timely access to surgery is important for clinicians and policymakers, as barriers to peripheral nerve surgery have the potential to directly negatively impact the functional outcomes of surgery. These findings should be used to guide future health care policies, and streamline care pathways in order to improve accessibility to surgical care for all patients with peripheral nerve injury.

	Unadjusted Hazard ratio (95% CI)	P-value	P-value (checking proportional hazard assumption)
Male	1.42 (0.94 to 2.14)	0.094	0.411
Age	0.995 (0.99 to 1.01)	0.371	0.987
Dominant hand	0.84 (0.60 to 1.17)	0.292	0.636
Polytrauma	1.03 (0.76 to 1.41)	0.840	0.666
Length of stay	0.998 (0.994 to 1.002)	0.378	0.895
Pre Ganglionic	1.04 (0.70 to 1.55)	0.835	0.171
Urban	1.12 (0.82 to 1.52)	0.477	0.502
Distance	1.0 (0.99 to 1.0)	0.486	0.340
Drinking	0.83 (1.2 to 0.59)	0.283	0.51
Smoking	0.86 (0.63 to 1.18)	0.352	0.171
WCB	0.78 (0.52 to 1.18)	0.237	0.373
Employment			
Intellectual labor	Reference		
Manual labor	0.91 (0.65 to 1.29)	0.607	0.045
Unemployed	0.81 (0.52 to 1.28)	0.369	0.052 (0.072 global)
Comorbidity	0.91 (0.82 to 1.01)	0.073	0.289
Injury BPI	1.29 (0.94 to 1.78)	0.116	0.638
Specialty			
General Practitioner	Reference		
Surgical Specialty	1.48 (0.94 to 2.33)	0.087	0.530
At time of EMG	1.29 (0.77 to 2.16)	0.333	0.577
Other	2.11 (0.98 to 4.56)	0.057	0.097 (global: 0.143)
Year of Injury	0.99 (0.95 to 1.04)	0.766	0.362

Table 2.1: Univariate Analysis of All Potential Independent Variables

Figure 2.1 Flow Chart of Edmonton Patient Selection & Chart Review

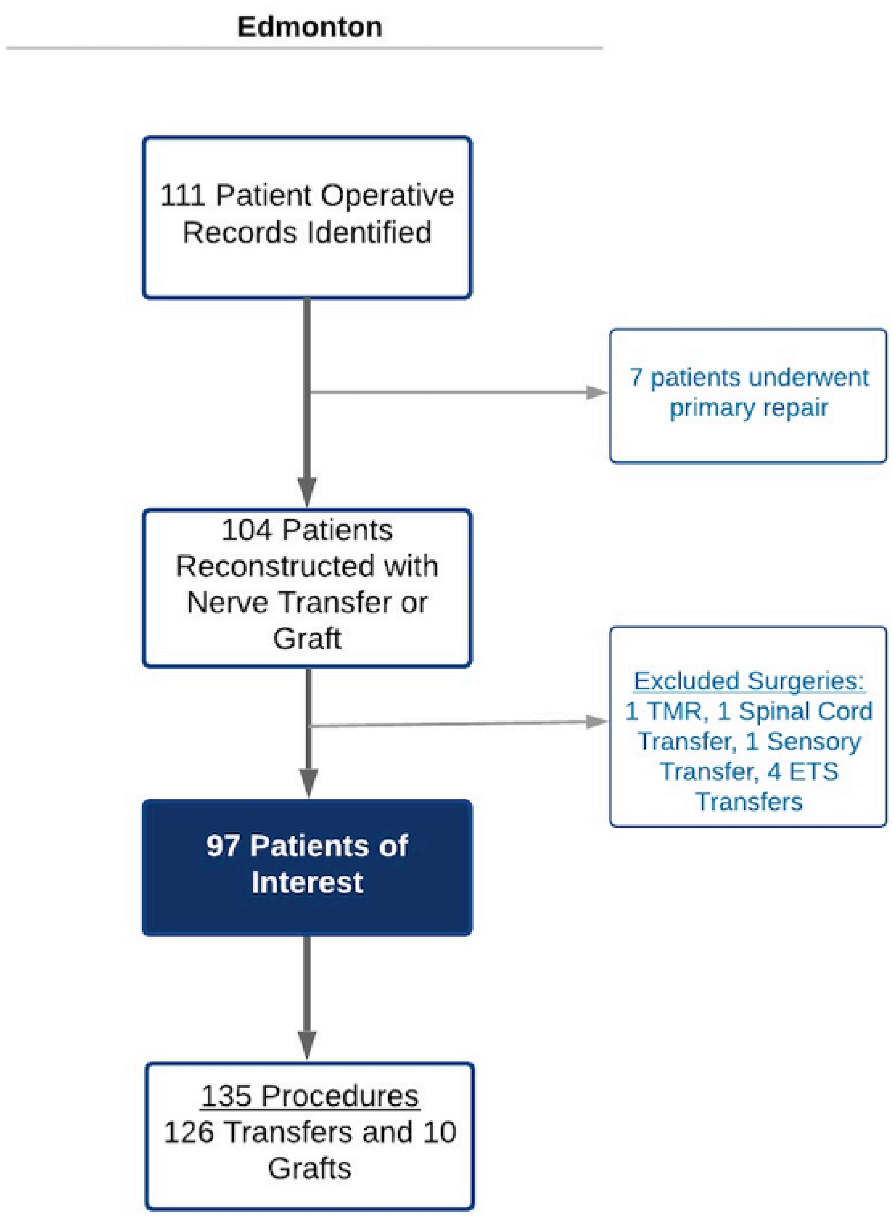
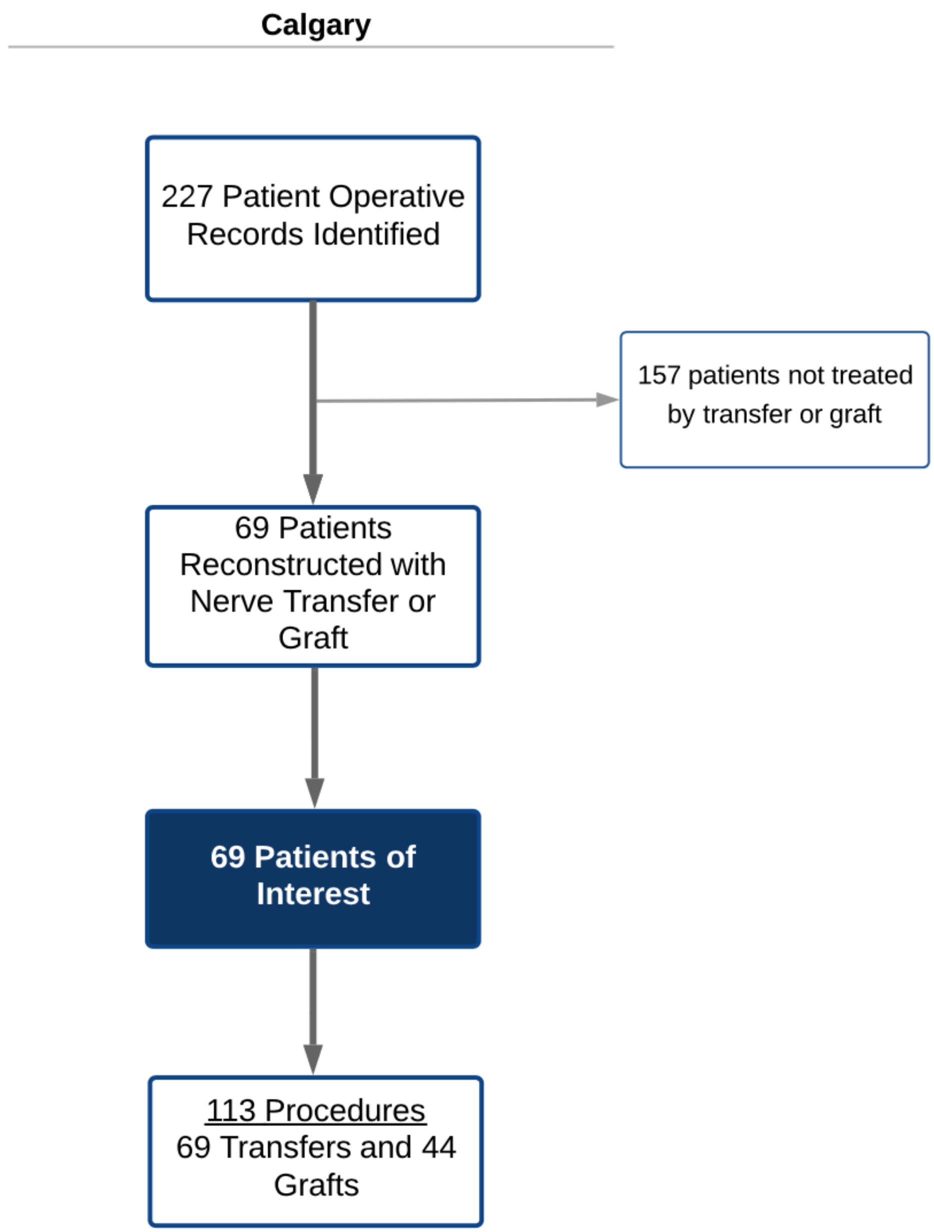


Figure 2.2 Flow Chart of Calgary Patient Selection & Chart Review



		Frequency	Percentage (%)
Gender	Female	31	18.2%
	Male	139	81.8%
Injury Requiring Operative Intervention	Brachial Plexus Injury	63	37.1%
	Isolated Upper Extremity	79	51.3%
	Lower Extremity	28	16.5%
Side of Injury	Right	90	52.9%
	Left	80	47.1%
Dominant Limb	Dominant	82	56.6%
	Non Dominant	63	43.4%
Surgical Intervention	Nerve Transfer	194	78.2%
	Nerve Graft	54	21.8%
Location	Rural	71	41.8%
	Urban	99	58.2%
Polytrauma	Yes	76	44.7%
Specialty Referring	Surgical	97	57.4%
	General Practioner	25	14.8%
	Neurology or PMR	38	22.5%
	Other	9	5.3%
Alcohol use	Yes	47	27.6%
Smoking	Yes	64	37.6%
Employment	Intellectual	53	31.2%
	Manual	86	50.6%
	Unemployed	31	18.2%
Workers Compensation Board	Yes	28	16.5%
BPI with pre-ganglionic component	Yes	31	18.2%

Table 2.2: Patient & Injury Characteristics

	Calgary		Edmonton				
	Median	IQR	Medial	IQR	Range	p-value	Statistical Test
Number of Comorbidities	1	1	1	2	0 to 8	0.002	Mann-Whitney U
Follow Up (days)	497.5	395.0	536.0	436.5	2 to 3840	0.287	Mann-Whitney U
Length of Acute Stay (days)	8.0	16.0	4.0	16.0	0 to 249	0.1256	Mann-Whitney U
Distance from Surgical Site (km)	50.0	214.0	66.0	239.0	0 to 5041	0.7244	Mann-Whitney U
Time to Referral (days)	78.5	109.0	54.0	122.0	0 to 431	0.5781	Mann-Whitney U
Time to Initial EMG (days)	77.0	67.0	96.0	126.0	7 to 437	0.0492	Mann-Whitney U
Time to Clinic (days)	135.0	102.0	129.0	123.0	1 to 437	0.8147	Mann-Whitney U
Age (years)	33.0	26.0	36.0	23.0	17 to 72	0.5841	Mann-Whitney U

	Mean	SD	Mean	SD	Range	p-value	Statistical Test
Time to OR (days)	212.1	95.9	265.8	242.4	0-633	0.0824	Student t-test

Table 2.3: Comparison of Patient Characteristic and Care Pathway Timelines Between Surgical Sites

Female	14.5	20.79	0.296	χ2
Surgical Intervention			<0.0001	χ2
Transfer	61.1	92.8	<0.0001	χ2
Graft	38.9	7.2	<0.0001	χ2
Injury Type			0.002	χ2
Isolated Upper Extremity	39.1	51.5	0.113	
Brachial Plexus	52.2	26.7	0.001	
Lower Extremity	8.7	21.8	0.024	
Component of Pre-Ganglionic Injury	31.9	10	<0.0001	χ2
Injury to Right Side	49.3	56.4	0.358	χ2
Dominant Limb	49.3	46.5	0.128	χ2
Rural Patients	34.8	48.5	0.076	χ2
Polytrauma	49.3	32.7	0.03	Fischers Exact
Specialty referring			0.009	χ2
GP	7.2	18.8	0.036	
Surgeon	53.6	58.4	0.607	
Neurology & PMR	34.8	15.8	0.004	
Other	2.9	6.9	0.257	
Alcohol use	15.9	35.6	0.005	χ2
Smoking	45.5	24.6	0.006	χ2
Employment			0.020	χ2
Intellectual	34.8	28.7	0.402	
Manual	56.5	45.5	0.160	
Unemployed	8.7	25.7	0.005	
Workers Compensation Board	22.8	8.7	0.017	χ2

Table 2.4: Comparison of Patient & Injury Characteristics Between Surgical Sites

	Combined		Calgary		Edmonton	
	Median	IQR	Median	IQR	Median	IQR
Time to Referral (months)	2.2	3.8	2.6	3.6	1.8	4.0
Time to EMG (months)	2.8	3.3	2.5	2.2	3.2	4.1
Time to Clinic (months)	4.4	3.7	4.4	3.4	4.2	4.0
Time to OR (months)	7.0	4.3	6.6	3.4	7.5	5.2

Table 2.5: Summary of Critical Time Points in the Peripheral Nerve Care Pathway

	Hazard ratio (95% CI)	P value	P-value (checking proportional hazard assumption)
Dominant limb	0.85 (0.61 – 1.19)	0.336	0.94
Urban	1.39 (0.98 to 2.01)	0.072	0.55
Comorbidity	0.84 (0.74 – 0.95)	0.006	0.22
Specialty Referring			0.21
GP	Reference		
Surgeon	1.87 (1.14 – 3.06)	0.014	
Neurology & PMR	1.35 (0.79 – 2.29)	0.273	
Other	3.46 (1.52 – 7.91)	0.003	

AIC score: 1143.272

Table 2.6: Cox Proportional Hazard Regression Analysis Results

2.7 References

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Chapter 3: Barriers to Surgery for Peripheral Nerve Injury: Patient Perspectives and Experiences

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3.1 Background

Accessing specialist care can be fraught with delay in publicly funded health care systems, and difficulties accessing care are increased for already disadvantaged subgroups (Harrington et al., 2013). Wait times for peripheral nerve surgery after injury, at our centre and in the USA, are longer than 7 months (Dy et al., 2016). The accepted time frame for nerve based reconstructive surgery after peripheral nerve injury is 3 to 6 months (Martin et al., 2018). Delayed referrals of peripheral nerve injuries are thought to be due to missed diagnoses, inappropriate referrals, or unknown reasons (McAllister et al., 1996, Camp and Birch, 2011). Delays in referral ultimately result in delays in appropriate surgical care. Delays are especially troubling in the context of a peripheral nerve injury; as the time in which nerve based surgical reconstruction can be performed after a severe peripheral nerve injury is limited (Martin et al., 2018). Thorough characterization of factors contributing to surgical delays is necessary to ameliorate any potential negative effects of delayed surgical intervention.

Qualitative methodology is not commonly employed in the surgical literature despite the many benefits of this methodology. The benefits of qualitative methodology include the characterizing of patient perceptions that cannot be captured by quantitative methodology, as participants are free to express their views in their own terms (Creswell, 2013). Qualitative research can be utilized to provide insights into unequal surgical accessibility, for treatment of peripheral nerve injury, as perceived by patients (Creswell, 2013). This methodology offers a means of understanding patient concerns as well as illustrating potential ways to improve surgical access from a patient perspective (Maragh-Bass et al., 2016). Qualitative research has the potential to make significant contributions to our understanding of the process of accessing surgical services through peripheral nerve clinics (Lewis, 2015).

Literature elucidating patient experiences in the context of peripheral nerve reconstruction is sparse. Franzblau et al interviewed a number of patients who did not receive surgical treatment of brachial plexus injuries. Lack of insurance, delays in injury diagnosis, and insufficient information regarding treatment options were reasons patients were unable to access surgical care (Franzblau et al., 2015). Similarly, patients awaiting bariatric surgery perceived socioeconomic and regional inequities as reasons that contributed to their wait times for surgery (Gregory et al., 2013). As well, poor access to breast reconstruction after mastectomy was perceived to be due in part to a lack of information regarding the procedure(s), and long surgical wait times (Potter et al., 2013). These perceived inequities and difficulties with access to surgery likely represent persistent systemic inequities across surgical specialties.

In light of the difficulties accessing peripheral nerve specialists, as evidenced by the prolonged time to surgery, it is our aim to determine patient perceived barriers to surgical intervention for treatment of peripheral nerve injuries (Dy et al., 2016). Ultimately, the goal of this study is to identify areas in which we can potentially intervene upon to improve the patient care experience.

3.2 Methods

To explore patient perceived barriers to accessing clinical, surgical, and post-operative care we conducted in depth semi-structured telephone interviews with participants who had undergone reconstructive surgery for peripheral nerve injury.

An inductive thematic analysis methodology was used to inform the study design, research questions, data collection, analysis, and interpretation (Nowell et al., 2017). A theoretical sampling process was used to select patients for interviews, as it allows for an open unbiased investigation of the experience of accessing the peripheral nerve surgery and facilitates the construction of a unified analysis (Butler et al., 2018). Our theoretical sampling process initially identified patients whom underwent delayed surgery (>6 months after injury). Based on analysis of these interviews, patients who underwent timely surgical intervention were subsequently identified and interviewed in an effort to attempt to disprove or confirm our initial findings. Selection of patients for interview was based on the need to further examine identified categories and relationships between these categories; as they related to participant experiences of accessing and being treated at the peripheral nerve injury clinic (Butler et al., 2018). The study was conducted in adherence to the ethical principles outlined in the Declaration of Helsinki and was approved by the human research ethics boards at the University of Alberta.

3.2.1 Inclusion Criteria

English speaking adult patients (age > 17 years) whom had previously undergone surgery through the Northern Alberta Peripheral Nerve Clinic, in Edmonton, were included in this study. Participants were recruited by the primary researcher at peripheral nerve injury clinic and if amenable to participate were contacted by an independent research assistant who conducted the interviews. By utilizing an interviewer independent of clinical care, the participants were able to speak freely and be assured that no repercussions to their care would occur as a result of the views expressed during the interview process.

Using theoretical sampling, we initially focused on those patients who underwent surgery in a delayed fashion, and later included patients who received their surgery in a timely fashion. Having undergone timely surgery does not preclude participants from difficulties with access to surgical care. The expansion of inclusion criteria allowed us to compare and contrast the experiences of patients who received surgery in different time frames.

3.2.2 Interview Process

Interview questions were developed with the guidance of a clinical content expert and a qualitative methodologies expert from the Strategy for Patient-Oriented Research (SPOR) Support unit at the University of Alberta. The interview questions were piloted and revised. Three domains of interest were assessed during the semi-structured interview: i) the process of accessing the peripheral nerve clinic after injury, ii) the process of accessing surgery through the clinic, iii) difficulties accessing necessary post-operative services, and any consequences experienced as a result of perceived difficulties or barriers. Additional interview questions were developed and explored in response to themes emerging from the data. The initial interview schedule is presented in Appendix 3.1.

A single qualitative researcher conducted phone interviews, which were approximately 30-60 minutes in duration. All interviews were audio-recorded and subsequently transcribed verbatim. Care was taken to ensure initial participants interviewed were representative of the demographics of those patients who underwent peripheral nerve reconstruction (i.e. urban vs. rural areas, gender, and age). Demographic information collected at the time of interview included participant age, gender, injury sustained, location lived in, and referring physician.

3.2.3 Coding and Analysis

In keeping with thematic analysis an iterative process of collecting, coding and analyzing the data was used. The data collection process was halted when there was felt to be saturation (no new perspectives and explanations emerging from the data) of the concepts or themes emerging from the data (Saunders et al., 2018, Bowen, 2008). The point of saturation defines the point where enough data has been obtained to ensure that the research question can be answered (Bowen, 2008).

After every interview, the interviewer and primary researcher conducted initial coding of the interviews independently. The initial codes were examined and all discrepancies in codes discussed, considered and revised. If consensus regarding codes could not be reached a third qualitative methodology expert was employed as an arbitrator. Ideas that were identified as requiring further exploration after each interview were acknowledged and subsequently explored in further interviews through supplementary questions based on new themes emerging from the data (Draucker et al., 2007). In all interviews, we kept the five guiding questions constant and explored emerging themes through asking supplementary questions.

Iterative comparison of the initial codes resulted in consolidation and refinement of codes based on patterns observed across interviews (Nowell et al., 2017). The process of coding and memo'ing allowed for continuous examination of the collected data, facilitating identification of new ideas, and consolidation of themes emerging after each interview (Figure 3.1) (Nowell et al., 2017). This process of coding and memo'ing enabled the inductive identification of core themes. Finally, exploring the relationships between the core categories and their characteristics, completed thematic analysis. Guidance by an experienced qualitative researcher was sought when developing conclusions in order to ensure the process remained inductive and introduction of researcher bias was minimized.

3.3 Results

3.3.3 Participant Demographics

Eleven participants who underwent nerve transfers for severe peripheral nerve injury were enrolled and interviewed for this study. One of the interviews was non-informative, as the participant had sustained a severe traumatic brain injury concomitantly with peripheral nerve injury. Seventy-three percent of participants were male and participants ranged in age from 20-65 years. This sample is reflective of the predisposition of males to peripheral nerve injuries (Noble et al., 1998). Two lived in rural communities, two lived in urban areas outside of the surgical centre, and six lived in close proximity to the surgical centre. The demographic details of the participants are listed in Table 3.1.

3.3.2 Core Themes

Despite the participants having diverse injuries, experiences, and demographic backgrounds, the findings highlighted three main areas in which patients experienced difficulties with access to care: i) delays in diagnosis, ii) difficulties accessing care, and iii) a lack of supports (Figure 3.2). Delayed injury identification and diagnostic testing contributed to delays in diagnosis of peripheral nerve injuries. Delays in identification of a peripheral nerve injury were due in part to the presence of concomitant injuries. Delays in confirmatory diagnostic testing were due to long wait times, participants having to travel long distances in order to undergo testing, and undergoing unnecessary tests. Delays in diagnosis of peripheral nerve injury resulted in emotional turmoil and distress. Additionally, issues with accessibility to surgical specialists, rehabilitation services and physical facilities/resources were identified. Difficulties stemmed from having to travel long distances, limited mobility secondary to injury, lack of awareness of health care resources for peripheral nerve injuries, financial barriers, and poor communication. Finally, participants lacked peer support and support in the process of navigating third party insurers.

3.3.2.1 Delays in Diagnosis

Participants experienced delays in diagnosis due to a delay in identification of peripheral nerve injury, and/or a delay in diagnostic testing being performed. Participants who experienced a delay in recognition of their peripheral nerve injury describe having another injury to the ipsilateral affected limb. Interview participants described more obvious injuries, typically orthopedic in nature, such as dislocations or fractures being recognized and addressed prior to recognition of the peripheral nerve injury. Often the peripheral nerve injury was only recognized weeks or months after the initial trauma when rehabilitation recovery did not progress as expected.

Participant 5: "…I was doing some of my exercises, I was kinda progressing but not really…. So that is when the physiotherapist had a talk with my doctor."

Participant 10: "So it wasn't until I recovered from all the surgeries that they realized that the nerve is not coming back."

Participants also experienced a delay in undergoing diagnostic testing after the identification of possible of peripheral nerve injury. Participants expressed that electrodiagnostic (EDX) testing was often performed in a delayed manner or found they had difficulty accessing the testing. In particular, those participants who had long wait times prior to undergoing EDX tests, or had to travel long distances recognized diagnostic testing as a barrier to accessing care, as well a source of stress and frustration.

Participant 10: "We didn't really have questions but it was quite frustrating waiting for the appointment and getting the nerve study done."

A number of participants discussed undergoing multiple diagnostic tests prior to being seen by the surgical team in the peripheral nerve clinic. Multiple tests were frustrating, burdensome from a travel perspective and contributed to increased participant stress. Participants undergoing multiple EDX studies before being referred to the peripheral nerve clinic only delayed the development of a treatment plan by a dedicated peripheral nerve surgery team.

Participant 7: "I think I was more frustrated that I had to have like three EMG studies."

Consequently, a delay in diagnosis of a peripheral nerve injury not only presented a barrier to timely surgical care for peripheral nerve injury, it resulted in emotional distress due to a sense of uncertainty as participants struggled to understand why they weren't progressing appropriately post injury and waited for definitive diagnosis.

3.3.2.2 Difficulties Accessing Care

Access to surgical specialists at the peripheral nerve clinic was hindered due to a lack of awareness regarding the availability of peripheral nerve surgery, and the long travel distances participants had to travel. Participants' initial physicians often lacked awareness of the peripheral nerve clinic and surgical options for treating peripheral nerve injury. Participants expressed concerns over the lack of knowledge in the medical community regarding surgical reconstruction options for peripheral nerve injuries. Additionally, participants feared the limited awareness of the peripheral nerve clinic might impede future patients' recovery.

Participant 10: "…but they still did not know that the surgery to fix the nerve was being offered in Alberta. It's just the reason we found out about the surgery is because the nerve testing was done in Edmonton."

Participants who lived outside of the surgical centre often did not receive a referral to the peripheral nerve clinic until examination by a specialist with greater familiarity of peripheral nerve injuries and awareness of the peripheral nerve clinic. Referral to the peripheral nerve clinic often occurred at the time of EDX testing.

Participant 2: "…and uh I am really grateful for that (EMG) appointment because that was the one that got the ball rolling for me to have surgery."

In order to access necessary medical services patients with peripheral nerve injuries are expected to navigate numerous medical appointments. Travelling for appointments places a substantial burden on those patients that have sustained concomitant injuries and may have limited mobility. These burdens disproportionately affect those participants who have to travel long distances to access physicians, diagnostic testing, and rehabilitation.

Participant 7: "….the doctor sent me to Calgary for the first one (EMG appointment) and then two months later I had another EMG. I am not sure why they sent me to Calgary. It would have been great if I could have had that done in (a smaller centre) because that's a lot closer. But bigger cities have more experience."

Participant 8: "…it would have been nice if it had been closer to home it's a little bit more of a drive in the winter."

Despite outpatient rehabilitation services not being publicly funded, only a minority of participants mentioned finances as a major barrier to rehabilitation. Instead participants cited failures in communication between members of the healthcare team as the greatest difficulty in accessing timely and appropriate rehabilitation after surgery. Participants discuss not being provided with adequate guidance regarding physiotherapy after surgery and not having physician orders nor up-to-date test results appropriately communicated to allied health staff.

Participant 9: "I went in and had the assessment done at the nerve clinic and ….the hand therapist did not have access to those results...To me perhaps there could be better communication between the physician and the physiotherapist."

3.3.2.3 Lack of Supports

Instead of feeling supported by third-party insurance companies, such as the Workers Compensation Board or private disability insurance, participants often felt that their functional difficulties were minimized and they were forced to return early to work. In contrast, participants noted that physician supplied letters for insurance purposes were incredibly helpful and eased their burden.

Participant 3: "My life insurance people wanted me to get back to work so they didn't have to pay me, but that is kinda the story and the way it goes."

Participant 6: "I am on long-term disability… my first experience with the insurance companies were just hell."

Additionally, participants felt they lacked a forum for sharing their experiences, information, and learning from peers practical lived experiences. The lack of peer connection was isolating and contributed to feelings of stress and uncertainty surrounding surgery and recovery. The suggestion of a peer support group was proposed by a participant and put forth to the other interviewees. Participants were supportive of the idea and felt that it would have been a useful tool prior to surgery and early in their recovery.

Participant 1: "Or even if they could have connected me with someone who had already had the surgery before, that would have been helpful I think. To at least talk to someone who had gone through it, and knowing what to expect."

3.3.2.4 Negative Consequences of Delays in Care

The impact of the delay in care has a profound negative effect on the participants' mental health, and the potential to negatively impact participant's physical recovery after surgery. Participants discuss feeling a sense of urgency regarding the need to undergo surgery; resulting in stress, uncertainty, and the perception of having limited time to make decisions regarding major surgery.

Participant 1: "I think it could have been faster, because when I first met with the doctors...they like right away told me like I had to have surgery as soon as possible…. like my nerve transfer. And I wasn't really expecting that at all."

Participant 7: "And (the doctors) basically said you are going to need surgery and you are going to need it pretty quick…. all of a sudden its like oh we have to operate and it's a pretty serious operation."

3.3.2.5 Patient Expectations of Specialist Accessibility

Finally, the expectation that waiting months before being seen by a specialist in the peripheral nerve clinic was normal and "part of the process" was a reoccurring theme voiced by participants.

Participant 7: "I think I was pretty lucky to get in as quickly as I did, to pretty much get everything that I had to have done…. I mean I don't expect to be seen right away, its just part of the process."

Participant 2: "Only other than long wait time. And I…again I am quoting and you can't see me. Because again this has all happened within a year and that is not that long."

3.4 Discussion

Assessments of health care quality in surgical literature focus on patient outcomes and safety (Cooperberg et al., 2009). However, the hallmark of high quality health care should not only be to deliver superior outcomes but also to ease the patient burden and increase accessibility of services. Health care access may be thought of as an interface between patients (heath care users) and health care resources and/or providers (Penchansky and Thomas, 1981). Access to care is influenced by both the characteristics of the users, providers, and the system itself (Penchansky and Thomas, 1981). According to the modified Penchansky and Thomas framework access-to-care can be divided into six dimensions: availability, accessibility, affordability, accommodation, acceptability, and awareness (Penchansky and Thomas, 1981, Saurman, 2016). When examined within this access-to-care framework our participants discuss four of the six domains: availability, accessibility, affordability, and awareness (Penchansky and Thomas, 1981, Saurman, 2016). Targeting identified access-to-care domains may allow for directed interventions to address barriers that impact access to peripheral nerve surgery.

3.4.1 Availability

The timing of operative peripheral nerve reconstruction via nerve transfer or grafting plays a critical role in patient outcomes, with earlier intervention generally resulting in better outcomes (Martin et al., 2018, Giuffre et al., 2010, Narakas, 1982, Narakas, 1985, Narakas and Hentz, 1988). Access to Canadian specialists is poor with over 50% of Canadians waiting four or more weeks for specialist care (Bichel and Conly, 2009). Wait times are further increased for surgical specialists (Jaakkimainen et al., 2014).

Availability is determined by the relationship of the volume and type of services and the client's, or patient's, needs (Penchansky and Thomas, 1981). Limited availability of peripheral nerve surgery is evident as there is a prolonged waiting time for surgery following a severe peripheral nerve injury (Dy et al., 2016). Participants believed waiting months to be seen by a specialist in the peripheral nerve clinic was "part of the process" of accessing a subspecialist surgeon. The limited availability of surgical subspecialists is so prevalent in our health care system that prolonged wait times for surgery are perceived as normal by users.

Additionally, physician knowledge and familiarity with peripheral nerve injuries is deficient, thus resulting in delayed identification of peripheral nerve injuries. For our participants a delay in diagnosis of peripheral nerve injury seems to be particularly notable when associated traumatic injuries were sustained, most commonly humeral fractures, shoulder dislocations, or orthopedic lower extremity injuries. This suggests that when confronted with these orthopedic injuries physicians often fail to diagnose an associated radial, axillary or common peroneal peripheral nerve injury. The availability of physicians with experience diagnosing peripheral nerve injuries must be increased in order to decrease the currently difficulties with delayed diagnosis.

3.4.2 Awareness

Awareness refers to the knowledge of health care resources, such as the peripheral nerve clinic, and indications for the use of a particular resource (Penchansky and Thomas, 1981). Difficulty accessing specialist care was in part attributed to lack of knowledge regarding the availability of peripheral nerve surgery. Awareness of the peripheral nerve clinic and the surgeries performed is insufficient in the medical community. The physician who initially identified the peripheral nerve injury in many cases did not make the referral to the peripheral nerve clinic. This may due to a lack of knowledge regarding: peripheral nerve injuries, the timeline that nerve reconstructive surgery must be performed in, or the existence of the peripheral nerve clinic. Insufficient information regarding diagnosis and treatment of peripheral nerve injury is not unique to our institution (McAllister et al., 1996, Franzblau et al., 2015). This lack of education and awareness surrounding peripheral nerve injury needs to be rectified in order to mitigate delays in the referral process. These findings point to the need for efforts to improve education surrounding diagnosis, treatment and prognosis of peripheral nerve injuries.

3.4.3 Accessibility

Accessibility is the relationship between the location of health care service in comparison to the location of the user or patient. Specialist access is consistently determined by whether or not the patient lives urban area (Pong et al., 2011, Chan and Austin, 2003). This urban-rural disparity is particularly problematic as Canada is geographically the second largest country in the world. Difficulty accessing medical specialist care increased with the distance the patient lived from the required specialist (Karunanayake et al., 2015). Rural patients struggle more with issues surrounding transportation and finances than those that lived in urban centres (Humber and Dickinson, 2010). Treatment of the initial peripheral nerve injury at a smaller hospital was significantly associated with surgery beyond 365 days after injury (Dy et al., 2016). Our study reinforces the idea that living a long distance from a major surgical centre, and travel for diagnostic testing and specialist appointments is a burden for patients. The burden of travel in order to access care is increased with multiple appointments, longer and poor driving conditions.

3.4.4 Affordability

Although, health care in Canada is a publicly funded service, there are a number of expenses that patients must pay for out of pocket in the process of seeking treatment for peripheral nerve injury. Out-of-pocket expenses include, but are not limited to, travel to appointments, and outpatient rehabilitation services and implements. Outpatient rehabilitation services are not fully covered under public health care, in particular splints and other rehabilitation equipment are not paid for. As well, participants discussed financial difficulties of being unable to work, and feeling forced to return to work by third party insurers. Stress and frustration were the result of being unemployed and negotiating with third-party insurers.

Affordability of health care services has a profound impact on the ability of patients to access care. Patients with a lower socioeconomic status are less likely to access specialists (Schoen and Doty, 2004, Stirbu et al., 2011, Dunlop et al., 2000). A greater amount of surgical care is provided in high-income neighborhoods (Roos and Mustard, 1997). Patients were unable to undergo reconstruction for brachial plexus injuries due to lack of insurance coverage (Franzblau et al., 2015). This correlation of lower SES and difficulty accessing surgical specialist care persists even in publicly funded systems (Laudicella et al., 2012).

3.4.5 Future Implications

To improve healthcare delivery for patients with severe peripheral nerve injuries, participants outlined a number of deficiencies that need to be addressed. The need for efforts to improve physician education surrounding diagnosis, treatment, and prognosis of peripheral nerve injuries is clear. In light of this, we recommend targeted education regarding the presentations of peripheral nerve injuries for frontline physicians and at an undergraduate medical education level (Jonas et al., 2017). As well, awareness of the peripheral nerve clinic needs to be enhanced. A centralized electronic referral system may improve awareness regarding surgical resources for peripheral nerve injury as well as facilitate efficient and effective information transfer (Hazlewood et al., 2016).

A centralized multi-disciplinary clinic composed of surgeons, physiatrists or neurologists to conduct EDX testing, physiotherapists and social workers would alleviate a number of accessibility issues highlighted by our participants. A centralized clinic would lessen the travel burden experienced by patients living outside of the surgical site, as multiple visits for diagnostic testing and rehabilitation would be reduced. As well, the implementation of a tele-health program for routine postoperative monitoring would reduce the burden of travel for patients living outside of the surgical site (Kruse et al., 2017).

The formation of a peer support group for patients with severe peripheral nerve injuries has the potential to make a large positive impact on patient wellbeing and is in theory easily implemented in the context of a peripheral nerve clinic (Dennis, 2003). Peer support programs provide emotional support; enhance coping, and facilitate sharing of practical experiences (Dennis, 2003, Gottlieb and Wachala, 2007). A thematic analysis of online brachial plexus injury support groups recognizes the value of sharing disease related experiences, as well as information (Morris et al., 2016). A face-to-face, or virtual, peer support group would offer the benefit of enhancing social supports, decreasing isolation, and increasing awareness of the disease, and recovery process (Dennis, 2003).

3.5 Limitations

In qualitative studies, researcher bias due to preconceived ideas may be introduced to the data and influence the analysis and outcomes. We attempted to alleviate the potential for researcher bias by utilizing an independent impartial interviewer. A theoretical sampling strategy was utilized in order to explore themes as they emerge from the interviews; however, this means the generalizability of our findings to other contexts may be limited. Nonetheless, the themes our participants discussed fit well with previously established access-to-care frameworks (Penchansky and Thomas, 1981). Similarities of our participants' experiences with those in the literature offer reassurance that these experiences may be used to offer guidance to health care providers seeking to assess and improve surgical specialist accessibility.

3.6 Conclusion

Using a qualitative methodology to examine and explore barriers to peripheral nerve surgery offers the unique benefits of identifying barriers to care from a patient perspective and illustrating patient experiences. Patients expressed delays in diagnosis, difficulty accessing resources, and a lack of support contributed to difficulties with accessing care. These findings suggest that barriers to timely surgical intervention for peripheral nerve injury are multi-dimensional and that difficulties accessing the peripheral nerve clinic are related to systemic deficiencies in the care pathway. In order to reduce barriers to accessing peripheral nerve surgery, delays in diagnosis, difficulties with accessibility to care, and lack of supports need to be addressed at a system level.

Appendix 3.1: Basic Interview Question Schedule

Demographic Questions:

- How old were you when you were injured?
- What was your injury?
- Where do you live?
- What physician referred you to the Peripheral Nerve Clinic?

In order to explore potential barriers *to accessing the Northern Peripheral Nerve Clinic* we would like to ask you some questions regarding your experience leading up to your first clinic appointment.

1. What was your opinion of the process of getting into the clinic?
2. Do you think there were any consequences to this process to you?

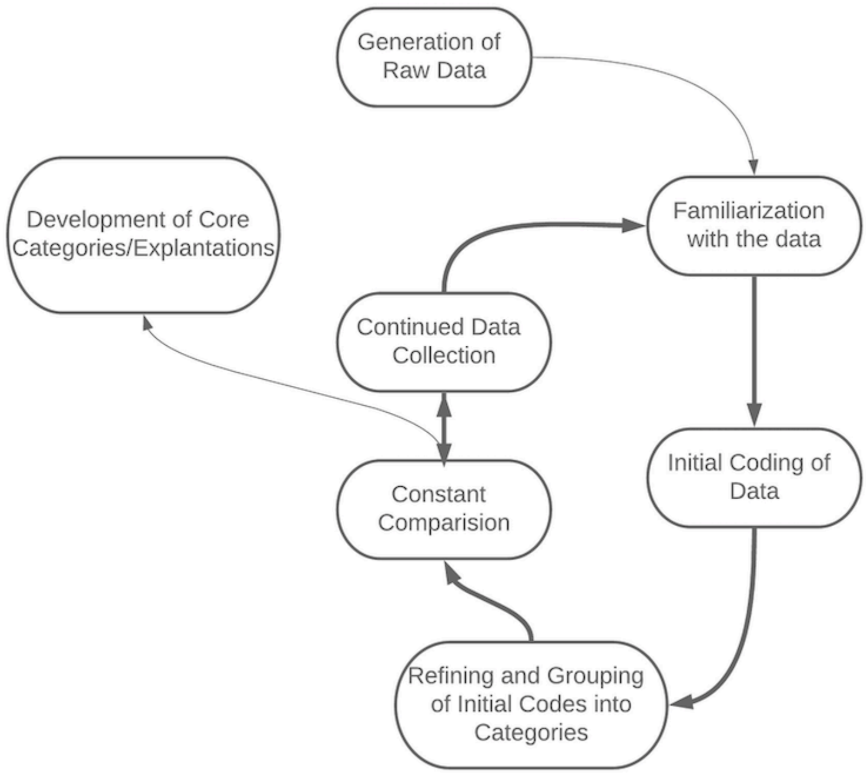
In order to explore potential barriers to *accessing surgery* for your nerve injury we would like to ask you some questions regarding your experiences at the clinic.

1. What was your opinion of the process of accessing the surgery through the clinic?
2. Do you think there were any consequences to that process to you?
3. Post-operatively did you feel you had any difficulties accessing services you required, and if you did what services were problematic to access?

ID	Sex	Injury	Specialty Referring	Large Centre	Polytrauma
1	Female	Common Peroneal Nerve	Orthopaedic Surgery	Yes	No
2	Female	Radial Nerve Injury	General Surgery	Yes	Yes
3	Male	Common Peroneal Nerve	Orthopaedic Surgery	No	No
4	Male	Ulnar Nerve	Orthopaedic Surgery	Yes	Yes
5	Male	Axillary Nerve	Orthopaedic Surgery	No	No
6	Male	Brachial Plexus Injury	Neuro Surgery	Yes	Yes
7	Female	Phrenic Nerve Palsy	General Practitioner	No	No
8	Male	Phrenic Nerve Palsy	Thoracic Surgery	No	No
9	Male	Brachial Plexus Injury	Neurosurgery	No	No
10	Male	Common Peroneal Nerve	Neurology	Yes	No

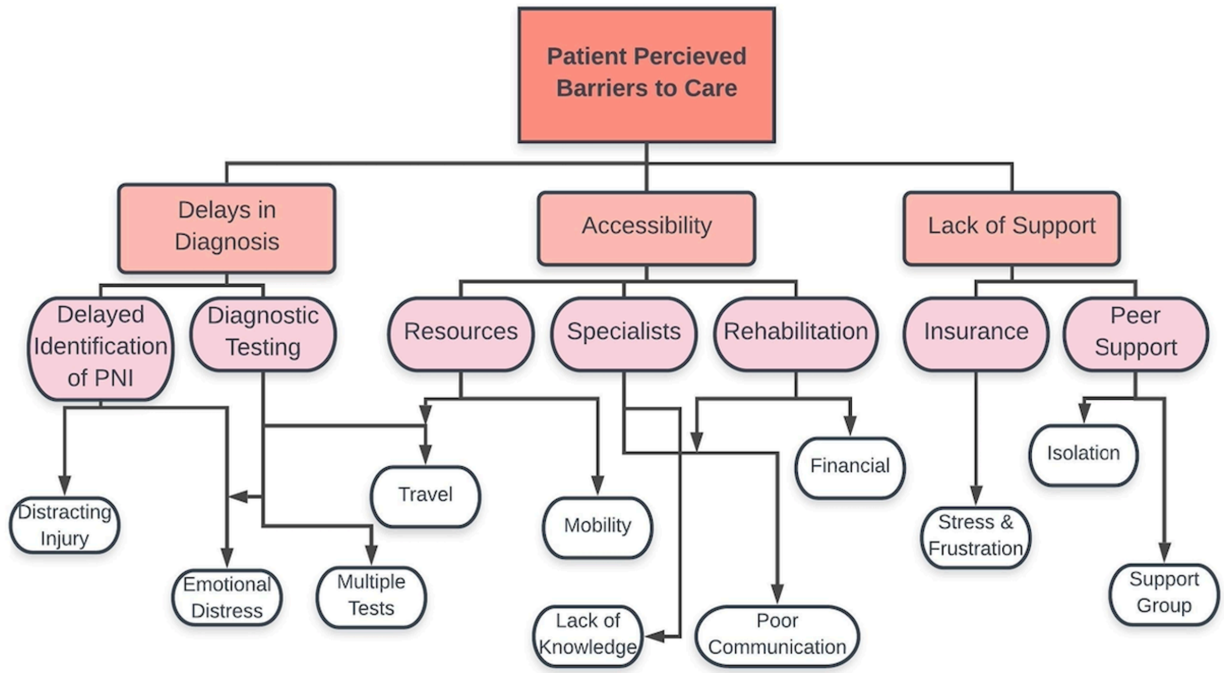
Table 3.1: Demographic Characteristics of Participants Interviewed

Figure 3.1 Thematic Analysis Methodology Flow Chart



(adapted from Nowell et al., 2017)

Figure 3.2 Thematic Analysis Flow Chart



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Chapter 4: Severe Peripheral Nerve Injury: Factors Associated with Post-Operative Motor Outcomes

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4.1 Introduction

Optimization of surgical outcomes for severe peripheral nerve injuries remains a challenge for the peripheral nerve surgeons. Recovery from proximal peripheral nerve injury requires regeneration over long distances to reach target musculature. Regeneration rates of 1–3 mm/day limit successful reinnervation, thus functional recovery is often incomplete and less than predicted (Seddon et al., 1943, Fu and Gordon, 1997, Sunderland, 1947, Sunderland, 1990). The high incidence of peripheral nerve injuries and the fact that they most often affect young, healthy individuals results in substantial lifelong disability (Noble et al., 1998, Selecki et al., 1982, Midha, 1997). Thus, identifying potentially modifiable factors to optimize surgical outcomes is essential.

It is currently accepted that nerve reconstruction in closed post-ganglionic injury should be performed within 3 to 6 months of injury if there is no clinical or EMG evidence of spontaneous recovery (Giuffre et al., 2010, Shin et al., 2005, Lim et al., 2017, Bertelli et al., 2017, Martin et al., 2018, Bertelli and Ghizoni, 2016). However, there are many potentially confounding factors that may influence the clinical outcomes of nerve reconstruction surgery. These factors include the timing of surgical interventions, patient age, donor nerve source, distance to target tissue, presence of nerve root avulsions, the length of nerve grafts, and quality of post-operative rehabilitation (Coulet et al., 2010, El-Gammal and Fathi, 2002, Nagano, 1998, Terzis and Barbitsioti, 2012, Tu et al., 2014, Dolan et al., 2012, Martin et al., 2018, Kline, 2009, Narakas, 1982, Chuang et al., 1993, Socolovsky et al., 2011).

Given the ambiguity regarding ideal time to operative intervention and limited investigation of other associated factors; we aimed to determine the association of time to operative intervention, as well as patient and injury characteristics with Medical Research Council strength outcome (MRC< 3 or MRC $\geq$ 3) (Sperandei, 2014, Zhang, 2016, Hosmer, 2000). The dichotomization of MRC strength outcome, into above or below antigravity strength outcomes, is commonly used to distinguish between outcomes that are functionally useful. Since individual factors do not act independently but rather interact with each other to influence strength outcomes, univariate analysis could potentially be misleading, as the confounding effects would not be accounted for. To mitigate the risk of erroneous associations, we carried out a multivariable logistic regression analysis to evaluate a number of factors that could potentially impact strength outcomes. This allows us to examine the effect of individual variables while holding the other predictor variables in the model constant. To our knowledge, outcomes of nerve reconstruction surgery have not been examined in this manner, which represents a major void in the literature (Terzis and Barbitsioti, 2012, Flores, 2011).

4.2 Methods

Data for adult patients who underwent a nerve graft or transfer for treatment of a severe proximal peripheral nerve injury between 2005 and 2017 in Alberta, was obtained through a retrospective review of all inpatient and outpatient records. In Calgary, a single neurosurgeon specializing in peripheral nerve reconstruction was involved in all surgeries.

In Edmonton a team of two plastic surgeons specialized in peripheral nerve surgery performed all the peripheral nerve reconstructions. This study was conducted in adherence to the ethical principles outlined in the Declaration of Helsinki and was approved by the human research ethics boards at the University of Alberta and the University of Calgary.

4.2.1 Inclusion Criteria

All patients over the age of 17 years, who had undergone peripheral nerve reconstruction with either a nerve transfer or graft by an experienced peripheral nerve surgeon in either Calgary or Edmonton, were identified based on operative booking codes. Patients were included in the analysis if they had a minimum of 12 months documented follow up or demonstrated reinnervation, resulting in MRC strength grade ≥3, prior to 12 months. At least one EMG study confirmed the presence of reinnervation if an MRC grade was documented.

4.2.2 Predictor Variables

The outcome variable of interest was whether or not the patient achieved an MRC ≥3 at the last documented follow up. Demographic information recorded included characteristics of the patients, injuries sustained, and operative interventions performed. The predictor variables collected and examined are listed in Table 4.1.

Rural areas was defined as small population centres; with a population less than 30,000; based on the 2011 Canadian census data (Canada, 2011). The driving distance of the patient's home to the surgical centre was computed using the patient's postal code, or the distance from the surgical centre to the epicenter of the location the patient lived.

A patient was defined as having sustained a polytrauma at the time of peripheral nerve injury if moderate injuries in two or more different anatomic regions, or injuries resulting in a calculable injury severity score ≥16 were sustained (Pape et al., 2014, Baker et al., 1974, Butcher and Balogh, 2012). The number of pre-injury comorbidities was documented; increased comorbidities are associated with increased surgical complications (Kim et al., 2008). Alcohol use was defined as a self reported or documented alcohol use disorder, or alcohol use beyond that of the recommended daily limit, two drinks a day, 10 drinks per week for women, and three drinks a day, 15 drinks per week for men (Bondy et al., 1999).

The patients' pre-injury employment was classified as intellectual or manual employment, or unemployed. Manual labor was defined as a physically demanding occupational activity or one involving low-level service activities. Intellectual labor was defined as occupational activities that involved mostly intellectual work, office work, or the pursuit of education (Galobardes et al., 2007). If patients were not working, or enrolled in educational pursuits, at the time of injury they were classified as unemployed.

4.2.3 Statistical Analysis

There were 19 potential predictor variables of interest identified *a priori* based on clinical knowledge and previous work examining outcomes of peripheral nerve injuries after nerve transfer or graft. The unit of analysis in this study was the surgical procedure and respective outcome.

A descriptive analysis of patient and injury characteristics, and time to operative intervention was completed. Mean and standard deviation (SD) were reported for parametric data and median and interquantile range (IQR) for non-parametric data. An examination of patient and injury characteristics from Edmonton and Calgary was completed using student T-testing for parametric data and Mann Whitney-U testing for non-parametric data. Chi-squared testing was used to compare frequency data between the two sites. Post hoc testing when necessary was conducted by utilizing the Bonferroni adjustment method. The Jarque-Bera test was used in order to test for normality.

A univariate logistic regression analysis was first performed to obtain the unadjusted coefficient and p-value of each potential predictor variable being considered for inclusion in the model (Table 4.1). A clustered multivariable logistic regression model was used to evaluate the association of the identified variables with a binary MRC strength outcome (MRC< 3 or MRC ≥ 3) (Sperandei, 2014, Zhang, 2016, Hosmer, 2000). A robust clustered analysis was used in order to account for the correlation of predictor factors within individual patients who received multiple procedures at the same time. Due to missing data the final model included 184 procedures and 127 patient clusters.

The method of purposeful variable selection was used to ensure that all *a priori* identified clinically relevant variables were included in the model, in addition to significant and confounding variables (Hosmer, 2000, Bursac et al., 2008, Zhang, 2016). Location of surgical site, age, time from injury to operation, and follow up time after surgery were the clinically relevant variables that were retained in the model regardless of statistical significance. Whether or not the patient sustained an isolated upper extremity injury, brachial plexus injury, or lower extremity injury that underwent operative intervention confounded the effect of follow up and age on MRC outcome, and thus was also retained in the model. The year of in which surgery was performed was not statistically significant and thus was not included in the final model. Biologically plausible interactions were checked, and none demonstrated a significant effect modification. The assumptions underlying the application of a logistic regression model were checked: i) the data was examined for outliers, using Cook's distance plots and values, ii) multicollinearity of the variables was assessed using the variable inflation factor index, iii) a visual inspection of scatter plots was done for the logit transformation of the continuous variables to ensure the linearity assumption was met, iv) a Hosmer-Lemeshow test for goodness of fit was performed for the final model to ensure the model fit the data well (p=0.19). Statistical Analysis was performed using STATA 15.

4.3 Results

4.3.1 Patient Demographics

One hundred and twenty nine patients were identified: 79 from Edmonton and 50 from Calgary who met the inclusion criteria. A total of 186 procedures were performed, and 39 patients underwent multiple procedures (Figure 4.1 & 4.2). The mean time to surgery was approximately 31 weeks (SD: 15.3) or 7.3 months. Ten patients underwent surgery within 2 weeks of injury and 15 underwent surgery over a year from injury. The majority of patients were males (85.4%) and the median age at time of surgery was 36 years (IQR: 24). Details of the patients and their injury characteristics are summarized in Table 4.2. Characteristics of the patients from Edmonton and Calgary were examined to determine whether there were differences in patient and injury characteristics according to location (Table 4.3). We found significant differences between the two surgical centres in the type of surgical intervention performed, with Calgary performing significantly more grafts. As well, Calgary operated on a significantly greater proportion of brachial plexus injuries, injuries with a pre-ganglionic component, and fewer lower extremity nerve injuries. Patients from Calgary sustained significantly higher rates of concomitant polytrauma at the time of injury than those in Edmonton. The time to operative intervention was significantly longer in Edmonton than Calgary.

4.3.2 Multivariable Regression Analysis

The unadjusted beta coefficients and respective p-values for all potential explanatory variables are listed in Table 4.1. The final logistic regression model, based on purposeful selection, contained the predictor variables of: location, age, follow up time after surgery, time to operative intervention, injury, whether there was a pre-ganglionic component to the injury, and if the patient received a nerve transfer or a graft (Appendix 4.1). The regression analysis demonstrated that the surgical site location, patient age, and follow up time were not associated with MRC strength outcome. As well, the MRC outcomes for brachial plexus injuries (BPI), and lower extremity nerve injury were not significantly different from those of an isolated upper extremity nerve injury when adjusted for other variables in the model (p=0.36 & 0.45, respectively).

4.3.3 Factors Associated with Strength Outcomes

Overall, 63% of patients achieved an antigravity strength outcome after surgery. If the patient received a nerve transfer rather than a nerve graft for reconstruction of a severe peripheral nerve injury, the estimated odds of achieving an MRC strength grade ≥ 3 increased by 388%, if all other variables remained constant (aOR=4.88, p=0.003). If the patient sustained a pre-ganglionic injury the estimated adjusted odds of the patient achieving an MRC strength grade ≥ 3 decreased by 65% (aOR= 0.35, p=0.05). For every one-week increase from injury to time of surgery, the estimated adjusted odds of the patient achieving an MRC strength grade ≥ 3 decreased by 3% (aOR=0.97, p=0.02) (Appendix 4.1). Thus, for an operative intervention with delay of 1, 3, 5, or 6 months after injury the adjusted odds of the a patient achieving greater than antigravity strength decreased by 22% (aOR =0.88), 31% (aOR=0.69), 47% (aOR = 0.53), and 53% (aOR = 0.47), respectively (Appendix 4.1). Perhaps most clinically relevant is that for a delay of 5.5 months the adjusted odds of achieving greater than antigravity strength decreased by 50% (OR=0.50). In other words, the estimated probability of achieving a good outcome 5.5 months after injury is only 33%.

4.4 Discussion

These results suggests that utilizing nerve transfers when possible, and operative intervention at the earliest possible time, while still allowing for assessment of spontaneous recovery, are critical factors in obtaining the best possible MRC outcome after surgery. The majority of patients who sustain a peripheral nerve injury are male (50-94.6%) between the ages of 18 and 35, and the consequences of peripheral nerve injury can be functionally devastating (Noble et al., 1998, Taylor et al., 2008, Faglioni et al., 2014, Ahmed-Labib et al., 2007, Choi et al., 1997, Novak et al., 2009). Thus, careful clinical monitoring and individual assessment of patients with peripheral nerve injuries is essential when making decisions regarding the need for, and timing of, surgical intervention in order to maximize functional recovery.

4.4.1 Time to Operative Intervention

The ideal timeline for surgical reconstruction of closed peripheral nerve injuries is not definitively established in the literature. Spontaneous recovery of traumatic peripheral nerve injuries is possible and it is generally accepted that if timely spontaneous recovery does occur patient outcomes are equal or better than those if surgical intervention is required (de Laat et al., 1994, Simon et al., 2016, Shao et al., 2005). Despite this, some groups advocate for very early surgical intervention, with definitive reconstruction within two weeks of injury; while other groups propose long delays may still result in acceptable results (Birch, 2015, Hems, 2015, Jivan et al., 2009, Sedain et al., 2011, Narakas and Herzberg, 1985, Khalifa et al., 2012). However, most groups advocate for waiting a minimum of three months to allow sufficient time to pass for the assessment of spontaneous recovery, via sequential EMG studies, but operating prior to six months if a nerve transfer or graft is required (Chuang et al., 1993, Kim et al., 2001, Samii et al., 1997, Martin et al., 2018).

We demonstrated that for every week that passes from injury to time of surgery, the adjusted odds of the patient achieving an MRC strength grade ≥ 3 decreased by 3%. The adjusted odds of a patient achieving antigravity function decreased by 50% by 5.5 months after injury. Similarly to findings in the literature, significantly better strength outcomes were observed in patients who underwent surgery prior to 6 months from injury (Flores, 2011). In a systematic review, the median time to surgery was four months for patients achieving anti-gravity strength, and approximately seven months for those who achieved less than antigravity function (Martin et al., 2018). Functional outcomes of nerve transfers, as measured by DASH and SF-36, were better when patients underwent surgery less than 6 months from injury as opposed to after 6 months (Ahmed-Labib et al., 2007). Other groups have demonstrated improved outcomes when surgery is performed within 9 months of injury (Songcharoen et al., 1996, Terzis and Barbitsioti, 2012).

The negative association of time to operation and MRC strength outcome, as demonstrated in our analysis, is substantiated by the knowledge that the regenerative capacity of axotomized peripheral nerves decline with time, due to decreased expression of regeneration-associated genes and viable Schwann cells in the distal stump (Chen et al., 2007, Gordon et al., 2011, Fu and Gordon, 1995b, Fu and Gordon, 1995a). The progressive increase in fibrosis and proteoglycan scarring in the distal nerve stump with prolonged time to repair may also contribute to poor outcomes after delayed surgery (Jonsson et al., 2013). Fewer axons regenerating and reinnervating the denervated muscle fibers, due to chronic denervation and axotomy, result in poor functional outcomes (Fu and Gordon, 1995b, Fu and Gordon, 1995a).

Given that by 5.5 months after injury the adjusted odds of achieving greater than antigravity strength decreased by 50% (OR=0.50), operative reconstruction should be undertaken as early as possible after spontaneous recovery is deemed improbable. Our analysis serves as a reminder that the determination of optimal time for surgical reconstruction requires balancing the potential for spontaneous recovery with possible functional recovery post-surgical reconstruction (Giuffre et al., 2010, Shin et al., 2005, Lim et al., 2017, Martin et al., 2018). Surgical decision-making may be particularly challenging and pertinent in closed traction injuries and thus timing of operative interventions must be made on an individual basis (Simon et al., 2016).

4.4.3 Injury

When adjusted for the other variables in the model, brachial plexus injuries, isolated upper extremity injuries, and lower extremity peripheral nerve injuries do not have significantly different associations with MRC strength outcomes after surgical intervention. However, if the brachial plexus injury has a component of a pre-ganglionic injury (nerve root avulsion or rupture) as documented on pre-operative MRI, EMG, or operative visualization, this was associated with a decreased odds of achieving a functional MRC grade. Although this negative association may seem intuitive, as a substantial force is needed to sustain an injury of this severity, this relationship was not well established in the literature (Martin et al., 2018). Avulsion type injuries have been associated with decreased DASH scores and increased pain scores (Ahmed-Labib et al., 2007). The finding that pre-ganglionic injuries are associated with worse strength outcomes may be due to the nature of the donor nerves utilized for reconstruction, often non-synergistic with a less ideal motor axon count, and longer distance for target reinnervation, and/or the severity of the initial injury (Forli et al., 2017). In this study extraplexal donor nerves, namely intercostal and spinal accessory, were used for the reconstruction of pre-ganglionic injuries when intraplexal donor nerves were not available. Extraplexal donors are associated with worse outcomes, when compared to reconstructions with intraplexal donor nerves (El-Gammal and Fathi, 2002, Terzis and Barbitsioti, 2012, Tu et al., 2014).

4.4.4 Operative Technique

If the patient received a nerve transfer rather than a nerve graft for reconstruction of a proximal peripheral nerve injury, they had a 388% greater adjusted odds of achieving at least anti-gravity strength. This finding is in keeping with a systematic review comparing outcomes of nerve transfer to nerve grafts for upper trunk brachial plexus injuries (Ali et al., 2015). Due to the concerns regarding model over-fitting given our relatively limited sample size we were unable to account for the effect of individual types of nerve transfers, or graft lengths and the distinct functional outcomes of these procedures.

Potential benefits of utilizing nerve transfers for reconstruction of traumatic proximal peripheral nerve injuries include minimizing regenerative distance, a single coaptation site, and the use of a healthy uninjured donor motor nerve (Ladak et al., 2013, Rohde and Wolfe, 2007). Minimizing regenerative distance and number of coaptation sites should result in a shorter time to reinnervation thus improved functional outcomes (Seddon et al., 1943, Sunderland, 1947). In contrast, potential pitfalls of nerve grafting include the biological difficulties of having two separate coaptation sites through which the proximal nerve stump must grow (Garg et al., 2011). As well, the length of the nerve graft plays a role, with short nerve grafts reinnervating better than longer grafts (Hentz and Narakas, 1988, Chuang et al., 1993). Thus, in cases where the conditions for optimal peripheral nerve regeneration are not met, especially when surgical intervention is postponed in order to assess for spontaneous regeneration, and long regeneration distances are required nerve transfer should be utilized preferentially.

4.4.5 Age & Follow up

The belief that younger age is associated with better post-operative outcomes permeates the literature. Younger patients are thought to have a greater capacity for cortical plasticity, faster axon growth, and a stronger regenerative capacity; while older patients often have comorbid illnesses that may impair regeneration such as vascular insufficiency and poor nutritional status (Brown, 1972, Socolovsky et al., 2017).

However, data regarding the effect of age on outcomes after peripheral nerve surgery has been contradictory (Martin et al., 2018, Coulet et al., 2010, El-Gammal and Fathi, 2002, Nagano, 1998, Lee et al., 2012). In reconstructions using intercostal donor nerves patients less than 30 years old had better MRC strength grade outcomes (Coulet et al., 2010, Nagano, 1998). Similarly, in a large series examining outcomes of intra and extra-plexal donor nerve transfers and grafts for elbow reconstruction, age less than 20 years old was found to be associated with better motor outcomes in a univariate analysis (Terzis and Barbitsioti, 2012). Lee et al observed patients less than 40 years old achieved an MRC≥3 for shoulder abduction after a radial to axillary nerve transfer in 92% of cases and those between 40 to 50 years achieved anti-gravity strength in only 56% of cases (Lee et al., 2012). In contrast, a meta-analysis of upper trunk brachial plexus injuries (reconstructed with nerve transfer or graft) found age was not a significantly associated with motor outcome (Ali et al., 2015). A large meta-analysis of nerve repair outcomes found older age was associated with negative MRC outcomes in a univariate analysis but not in a multivariate analysis (He et al., 2014). Similarly, in our model, age is not significantly associated with MRC outcome, when adjusted for the other variables in the model. The inconsistent relationships between age and outcome after peripheral nerve surgery in the literature may be explained by the fact that univariate comparisons do not identify or adjust for confounding factors, thus potentially overstate the effect of age on outcomes (Martin et al., 2018, Coulet et al., 2010, El-Gammal and Fathi, 2002, Nagano, 1998).

Additionally, the median patient age in our population is 36 years, substantially older than the identified age associated with improved MRC outcomes (Terzis and Barbitsioti, 2012, Coulet et al., 2010). Reports of older patients (over 50 years) who underwent nerve transfers for reconstruction of shoulder abduction or elbow flexion, found age was not significantly associated with MRC grade (Gillis et al., 2019a, Gillis et al., 2019b). Additionally, Bonnard et al. found that there was no difference in success of axillary nerve repair in patients under versus those over 40 years (61% versus 77%) (Bonnard et al., 1999).

Finally, in this model, follow up has no association with MRC outcome, when adjusted for the other variables in the model. It was previously believed motor recovery after surgical reconstruction plateaus 2 to 3 years after surgery (Narakas and Hentz, 1988). However, recently it has become evident that MRC strength outcomes do continue to improve beyond two-years post surgical intervention (Wang et al., 2016). However the mean follow up in this study was only 1.9 years; thus these patients may not have been followed long enough for their strength grade to significantly improve over time after reinnervation. Thus, the relatively short follow up in this study may explain why there is not a positive association between follow-up time and MRC outcome in this model.

4.5 Limitations

Limitations of this study include the retrospective nature of the chart review, potential for recall bias, and the inability to account for all potential confounding variables. Also, it should be emphasized that the retrospective nature of this study does not establish causation, only associations. There is heterogeneity of the procedures included in the analysis. However, this heterogeneity is necessary in order to give a realistic determination of factors that impact outcomes of severe peripheral nerve injury following operative intervention and increase generalizability of the results.

Additionally, MRC strength grade, although ubiquitous in the clinical assessment of peripheral nerve injury, is an imperfect measure of functional outcome (Wankhar et al., 2017). MRC scoring is subjective, and there is variability between examiners (Paternostro-Sluga et al., 2008). MRC testing does not account for weakness due to pain; it is not uncommon for peripheral nerve injured patients to have significant neuropathic pain. Ultimately the MRC score is dependant on patient effort, which may be compromised for multiple reasons including pain, comprehension of instructions, or motivation for secondary gains (a factor that may be particularly relevant in the case of workplace injuries). Finally, the MRC grading system classifies strength into discrete categories but does not quantify strength, range of motion, or offer a functional assessment of strength. In future prospective studies, we recommend that a combination of patient-reported-outcomes, quantitative force measurements, and range of motion data be used.

4.6 Conclusion

The timing of operative intervention after a severe peripheral nerve injury plays an important role in post-surgical strength outcomes when adjusted for injury and patient characteristics. However, whether or not a pre-ganglionic injury was sustained, and if a nerve transfer or graft was performed, were also associated with the MRC strength outcome achieved post-operatively. These associations require further investigation in prospective fashion. These findings suggest that proximal injuries with long regeneration distances should be reconstructed preferentially with nerve transfers, when possible. Finally, delays in operative intervention need to be mitigated in order to achieve optimal patient strength outcomes after peripheral nerve surgery.

Figure 4.1 Flow Chart of Edmonton Patient Selection & Chart Review

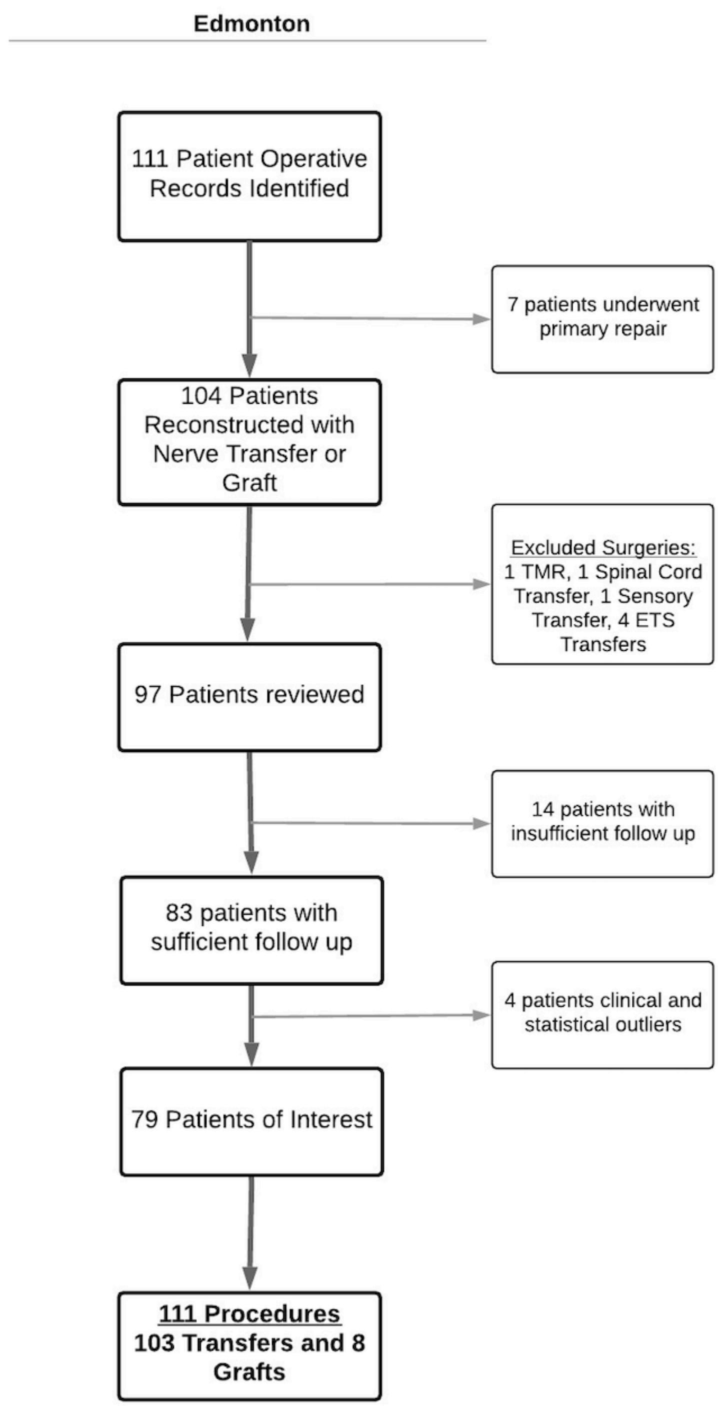
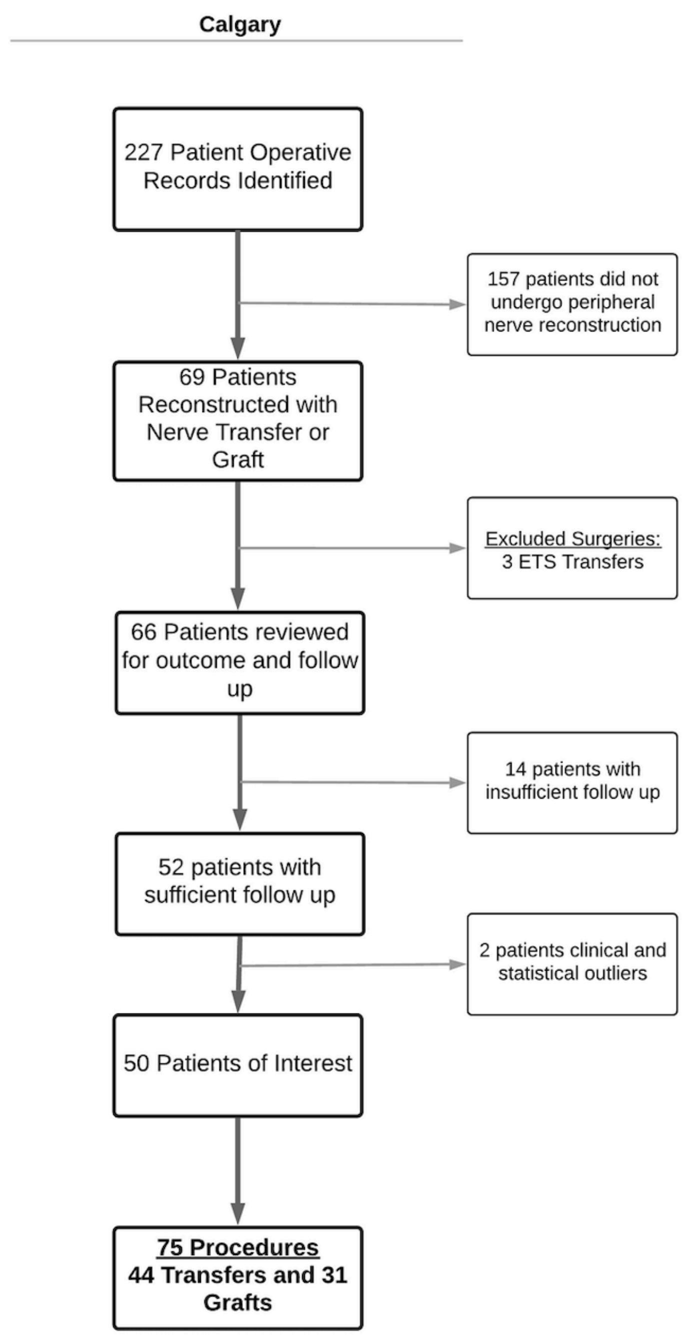


Figure 4.2 Flow Chart of Calgary Patient Selection & Chart Review



		Beta coefficient (95% CI)	P-value	Odds Ratio
Male		-0.166 (-1.028 to 0.697)	0.707	0.847
Age		0.013 (-0.009 to 0.034)	0.249	1.013
Polytrauma		-0.364 (-0.965 to 0.237)	0.235	0.695
Urban		-0.101 (-0.700 to 0.499)	0.742	0.904
Distance		-0.0002 (-0.0006 to 0.0002)	0.387	1.000
Drinking		-0.004 (-0.685 to 0.677)	0.991	0.996
Smoking		-0.683 (-1.301 to -0.064)	0.030	0.505
WCB		-0.484 (-1.296 to 0.327)	0.242	0.616
Comorbidity		-0.072 (-0.249 to 0.104)	0.422	0.930
Injury	Isolated Upper Extremity	Reference		
	BPI	-0.769 (-1.479 to -0.060)	0.033	0.463
	Lower Extremity	-0.811 (-1.760 to 0.139)	0.094	0.444
Follow Up (weeks)		-0.004 (-0.004 to 0.003)	0.163	0.996
Location		-0.247 (-0.853 to 0.359)	0.424	0.781
Transfer		1.044 (0.322 to 1.767)	0.005	2.841
Time to OR (weeks)		-0.019 (-0.0399 to 0.001)	0.064	0.981
Pre ganglionic		-0.802 (-1.486 to -0.119)	0.021	0.045
Year of Surgery		-0.002 (-0.008 to 0.005)	0.613	0.998

Table 4.1: Univariate (unadjusted) Analysis of all Potential Independent Variables

		Frequency	Percentage
Gender	Female	27	14.5%
	Male	159	85.5%
Operative Intervention	BPI	98	52.7%
	Isolated Upper Extremity	60	32.3%
	Isolated Lower Extremity	28	15.1%
Side of Injury	Right	109	58.6%
	Left	77	41.4%
Dominant Limb	Dominant	103	63.6%
	Non Dominant	59	36.4%
Surgical Intervention	Nerve Transfer	147	79.0%
	Nerve Graft	39	21.0%
Location	Calgary	75	40.3%
	Edmonton	111	59.7%
Polytrauma	Yes	96	51.6%
	Other	90	48.4%
Alcohol use	Yes	49	26.3%
Smoking	Yes	75	40.3%
Workers Compensation Board	Yes	28	15.1%
Urban or Rural	Urban	101	54.3%
	Rural	85	45.7%
Pre Ganglionic Component	Yes	45	24.2%

Table 4.2: Patient and Injury Characteristics

	Edmonton (%)	Calgary (%)	p-value	Statistical Test
Polytrauma	42.3	65.3	0.002	X^2 test
WCB	18.9	9.3	0.073	X^2 test
Urban Location	49.5	41.4	0.114	X^2 test
Male	82	90.7	0.099	X^2 test
Transfer	92.8	58.7	<0.0001	X^2 test
Injury			0.006	X^2 test
Upper Extremity Injury	35.1	28	0.307	
BPI	44.1	65.3	0.005	
Lower Extremity Injury	20.7	6.7	0.009	
Smoking	45	33.3	0.095	X^2 test
Alcohol	33.3	16	0.006	X^2 test
Dominant Side Affected	62.1	65.3	0.667	X^2 test
Pre-ganglionic	16.2	36	0.002	X^2 test

	Edmonton		Calgary				
	Median	IQR	Median	IQR	p-value	Range	Statistical Test
Time to OR (weeks)	33.4	16.5	27.3	14.7	0.0043	0-90	Man-U Whitney
Follow Up (weeks)	79.6	55.1	83.0	63.2	0.499	29.7-260.7	Man-U Whitney
Distance (km)	101.0	340.0	62.0	214.0	0.3577	0-5041	Man-U Whitney
Age	33.0	22.0	39.0	24.0	0.1459	17-72	Man-U Whitney
Comorbidities	1	2	1	1	<0.0001	0-8	Man-U Whitney

Table 4.3: Differences in Baseline Demographic Data Between Calgary and Edmonton

Outcome: MRC ≥ 3	**Regression Coefficient (SE)**	**Odds Ratio (95% CI)**	**P-value**
Intercept	1.228	-	0.726
Age (years)	0.011 (0.0150)	1.01 (0.981 to 1.041)	0.47
Follow up (weeks)	-0.0001 (0.004)	1 (0.991 to 1.007)	0.87
Time to Surgery (weeks)	-0.030 (0.0127)	0.97 (0.947 to 0.995)	0.02
Surgical Site	0.410 (0.448)	1.51 (0.625 to 3.63)	0.33
Transfer	1.586 (0.524)	4.88 (1.744 to 13.687)	0.003
Pre-ganglionic Component	-1.062 (0.545)	0.35 (0.119 to 1.01)	0.051
Injury			
Isolated Upper Extremity	Reference		
BPI	-0.561 (0.505)	0.63 (0.234 to 1.695)	0.36
Lower Extremity	-0.467 (0.624)	0.63 (0.184 to 2.131)	0.45

Table 4.4: Multivariable Logistic Regression Analysis Results

Odds ratio for an increase "c" in weeks, when all other variables held constant:

$$\textbf{OR of MRC} \geq \textbf{3} = e^{c\beta_{\text{time to OR}}}$$

Logit [P(MRC ≥3 given age, follow up, time to surgery, location, transfer, pre-ganglionic injury, BPI, lower extremity injury)] = 0.314 + 0.011(age) - 0.0001(follow up) - 0.030(time to surgery) + 0.410(location) + 1.649(transfer) – 1.063(pre-ganglionic) - 0.505(BPI) - 0.579(lower extremity injury)

Appendix 4.1: Multivariable Logistic Regression Analysis Equations

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Chapter 5: Final Conclusions & Future Directions

5.1 Final Conclusions

Injuries to peripheral nerves may be sustained as a result of sharp penetrating or blunt trauma resulting in nerve laceration, traction, and/or compressive injury. The consequences of peripheral nerve injuries can be devastating to independence and function (Choi, et al. 1997). Adult peripheral nerve injuries most often affect young, otherwise healthy individuals, thus creating a lifelong disability (Midha 1997). Approximately 2-5% of patients admitted to a level one-trauma centre have an associated peripheral nerve injury (Noble, et al. 1998; Midha 1997; Selecki, et al. 1982). Peripheral nerve injuries most commonly affect the hand and upper extremity thus intensifying functional difficulties (Forli, et al. 2017; Novak, et al. 2009). Given the potential morbidity of peripheral nerve injuries, the specialized surgical expertise required, and the wide variation of injury patterns; peripheral nerve injuries are best treated at dedicated peripheral nerve injury centre.

An important missing piece in understanding the burden of peripheral nerve injury is the quantification of the resultant socioeconomic burden of the injury on the individual, their family, and society. The socioeconomic burden of peripheral nerve injury is likely substantial, given that a simple digital nerve laceration is estimated to result 59 lost days of work (Thorsen, et al. 2012). After median or ulnar nerve injury, only 59% of patients had returned to the workplace one year after operative intervention (Gray 2016). The personal and socioeconomic burden of all peripheral nerve injuries is likely underestimated in the literature. Since appropriate medical and timely operative interventions are important determinants of functional outcomes, they have a major potential to improve quality of life and reduce the personal and socioeconomic costs of this potentially devastating injury (Wali, et al. 2017).

This dissertation addresses three deficiencies in the peripheral nerve injury literature. First, the literature examining barriers to timely surgical intervention for treatment of peripheral nerve injury is sparse. Reasons for delayed referral and subsequent surgical delays include missed diagnosis and inappropriate referrals (Camp and Birch 2011; McAllister, et al. 1996). Treatment of initial peripheral nerve injury at a small hospital was associated with peripheral nerve surgery being delayed for longer than a year after injury (Dy, et al. 2016). Additionally, reasons patients do not undergo surgical reconstruction of peripheral nerve injuries are delayed diagnosis, insufficient information regarding surgical options, and lack of insurance coverage (Franzblau, et al. 2015). We aimed to establish if patients in Alberta experienced similar barriers resulting in delayed surgical intervention by describing the timing of surgery for adult patients with a peripheral nerve injury, necessitating a nerve transfer or graft. As well, we explored factors that are associated with prolonged time to surgery. The mean time from injury to operative intervention in Alberta was approximately 7.5 months, thus surgery was being performed in a delayed manner (Martin, et al. 2018). The major findings from our multivariable Cox Proportional Hazard analysis are that the number of pre-injury comorbidities and the specialty referring were both associated with time to operative intervention. The subspecialized nature of the treatment of peripheral nerve injuries likely contributes to delayed surgical intervention, beyond 6 months, a timeline not in keeping with the standard of care according to current evidence (Fu and Gordon 1995; Martin, et al. 2018). Based on these findings, we must work to improve clinical pathways for peripheral nerve injury referrals, and enhance education surrounding peripheral nerve injury and surgical resources.

Barriers to accessing appropriate care are especially troubling in the context of a peripheral nerve injury as the window in which nerve based surgical reconstruction can be performed is limited. Given, the paucity of qualitative research in the area of access-to-care for peripheral nerve injury we elicited patient perspectives through semi structured interviews in order to explore patient opinions and perceived barriers to timely care. Thematic analysis results point to delays in care, difficulties with accessibility to care, and lack of patient supports that need to be addressed on both a local and systemic basis.

Finally, although many authors have examined the timing of surgical interventions after proximal peripheral nerve injury few have quantified the relationship of time to operative intervention and MRC strength outcomes adjusted for patient and injury characteristics (Wang, et al. 2017). We characterized a number of factors, including time to operative intervention, which are associated with functional outcomes. The major findings of our multivariable logistic regression analysis are that the odds of achieving an MRC strength grade ≥ 3 decreased with every week after injury surgery was delayed, if the patient received a nerve graft rather than transfer, and if the patient sustained a pre-ganglionic injury. Given the paramount importance of optimizing outcomes after peripheral nerve surgery we recommend the use of peripheral nerve transfers when possible, and earlier operative intervention, particularly prior to 5.5 months elapsing after injury as this is at this point that the adjusted odds of achieving a MRC ≥ 3 outcome decreased by 50%.

5.2 Future Directions

To expand on the work in this thesis, a prospective study to examine quantitative strength outcomes of patients undergoing nerve reconstruction surgery is necessary to control for potential confounders and validate our results. A collaborative nation wide database would provide a powerful dataset and allow for subgroup analysis of individual nerve transfers and assessment of the respective impact on time to operative intervention by procedure. As there has recently been strong interest expressed by all the major peripheral nerve surgical centers across Canada to participate in a national collaborative, this idea of forming a national registry in order to further our work is timely and our findings may provide the catalyst for the initiation of a nation wide project.

Furthermore, this work may pave the way to facilitate changes enhancing access to peripheral nerve surgery in Alberta. There is a need to improve referral processing as well as education surrounding diagnosis, treatment and prognosis of peripheral nerve injuries. Establishing an efficient centralized referral intake system would likely help to alleviate waiting times from referral to initial appointment. A central access and triage system serves to eliminate duplicate referrals, and standardize referrals as well as the triage process (Bichel and Conly 2009). In particular, a standardized electronic referral form would alleviate discrepancy in information between referrals and possibly reduce the inconsistency of wait times for surgery by referral specialty (Tobin-Schnittger et al., 2018).

The diagnosis of peripheral nerve injury is challenging for a number of reasons: injury patterns vary depending on the anatomical location of injury and these injuries commonly occur with other traumatic injuries that may mimic functional deficits to some extent. Increased education regarding the presentations of peripheral nerve injuries for frontline physicians and at an undergraduate medical education level is likely necessary, given that delayed diagnosis of peripheral nerve injuries is common.

As well, the implementation of a peer support group for peripheral nerve injury has the potential to positively impact patient wellbeing, and enhance health care experiences. Peer support programs provide a venue for obtaining emotional support, and sharing of practical experiences and information among patients (Dennis 2003). As well, participants in peer support programs have been shown to gain confidence and a sense of control over their disability and recovery process (Dennis 2003; Gottlieb and Wachala 2007). We are hopeful that this work may help to guide improvements in the access to surgical treatment of peripheral nerve injuries.

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