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PSYCHOSOCIAL PREDICTORS OF CHRONIC PAIN AND PAIN-RELATED DISABILITY 12 MONTHS AFTER LOWER EXTREMITY FRACTURE

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PSYCHOSOCIAL PREDICTORS OF CHRONIC PAIN AND PAIN-RELATED DISABILITY 12 MONTHS AFTER LOWER EXTREMITY FRACTURE

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Health Sciences
at the University of Kentucky

By
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2020

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ABSTRACT OF DISSERTATION

PSYCHOSOCIAL PREDICTORS OF CHRONIC PAIN AND PAIN-RELATED DISABILITY 12 MONTHS AFTER LOWER EXTREMITY FRACTURE

Over 700,000 lower extremity fractures occur each year with a large portion of these patients developing adverse long-term pain and disability outcomes. Current literature indicates that 39% to 62.7% of all patients report continued pain long after traumatic lower extremity fracture. Concurrent physical limitations and reduced quality of life are common, with nearly one-third of all patients reporting pain-related disability seven years after limb threatening trauma, and approximately 50% of these patients having limitations in functional mobility and activities of daily living at long-term follow-up. These poor long-term injury-related pain and disability outcomes are alarming and require further action to detect individuals at the greatest risk for detrimental outcomes in earlier stages of recovery.

Evidence for the important association psychosocial factors carry with suboptimal long-term outcomes after traumatic injury is lacking. Previous research has demonstrated that depression, self-efficacy, pain catastrophizing, and fear of movement are associated with pain and disability outcomes. However, no research has determined the earliest clinically meaningful timeframe possible to screen for these psychosocial measures. Furthermore, much of the research has only evaluated one psychosocial measure at a time, limiting our understanding of the most salient psychosocial measures associated with patient pain and physical function outcomes. Additionally, none of the past studies have excluded individuals with a history of chronic pain, which may enhance the association psychosocial measures have with adverse outcomes. Finally, no multidimensional screening tools exist to stratify patient risk for adverse long-term outcomes.

Therefore, the purpose of this dissertation was to evaluate how multiple psychosocial measures were associated with long-term patient outcomes after surgical fixation of lower extremity fracture. All studies included in this dissertation are based on the same cohort of 122 patients who did not have a history of chronic pain and were followed through their first 12 months of recovery from surgical fixation of a lower extremity fracture. Patients completed validated measures of depression, self-efficacy, pain catastrophizing, fear of movement, and pain intensity one week, six weeks, three

months, six months, and 12 months after definitive surgical fixation. At six weeks, each patient also completed the Subgroups for Targeted Treatment (STarT)-Lower Extremity Screening Tool (STarT-LE) with a retest completed one week later. At 12 months, patients completed validated, self-reported outcomes of chronic pain development, pain interference, and physical function.

The results of these studies indicate that six weeks after surgical fixation is the earliest time point psychosocial measures can be screened to determine risk for chronic pain, with large to very large effect sizes. Additionally, pain self-efficacy at six weeks was most strongly associated with chronic pain development and physical function at 12 months when accounting for depression and other important baseline variables. Pain catastrophizing at six weeks was most strongly associated with pain interference at 12 months when accounting for depression and other important baseline variables. Finally, we established the STarT-LE at six weeks as having strong reliability and predictive validity to stratify patients into low, medium, or high risk for each outcome at 12 months. The results of these studies objectively demonstrate that screening individuals with the STarT-LE, pain self-efficacy questionnaire, and pain catastrophizing scale six weeks after injury can inform the clinician with valuable information regarding the patient's long-term prognosis.

KEYWORDS: Chronic pain, Lower Extremity Fracture, Psychosocial, STarT-LE Screening Tool

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April 16, 2020
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PSYCHOSOCIAL PREDICTORS OF CHRONIC PAIN AND PAIN-RELATED DISABILITY 12 MONTHS AFTER LOWER EXTREMITY FRACTURE

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Introduction

Part I: The Psychosocial Variables of the Fear Avoidance Model and their Relationship to Patient Outcomes after Injury

Background: Pain and the Fear Avoidance Model

Over the last decade, there has been an increasing awareness of the tremendous economic and health care burden of chronic pain conditions.[1] Chronic pain is a world-wide epidemic with current epidemiologic data estimating that 20-30% of the world's population currently live with chronic pain.[2,3] The number one reason to seek out medical care in the United States (U.S.) is chronic pain,[4] resulting in $635 billion in medical expenses and lost work productivity annually.[5] This cost is greater than the U.S. combined annual cost of cancer and diabetes.[5] It is common for individuals suffering from chronic pain conditions to experience concomitant disability and reduced quality of life.[6] These secondary effects of chronic pain perpetuate patient suffering, health care utilization, and lost work time further extending the already significant burden of chronic pain. These data point toward a critical need to identify the modifiable factors that predispose an individual to developing chronic pain and subsequent disability after injury.

The biomedical model of healthcare states that disease is the result of underlying structural damage.[7] The insufficiency of this model has been highlighted by the fact that 37% of 20-year-olds and 96% of 80-year-olds with lumbar disk degeneration are asymptomatic,[8] and 28% of 70-year-olds and 56% of 80-year-olds have asymptomatic rotator cuff tears.[9] In-fact, chronic pain syndromes are rarely the direct result of an underlying lesion or tissue deformity.[10] Nociceptive signals, defined as the encoding of

damaging or potentially harmful noxious stimuli, are modulated by a number of subcortical structures to include the thalamus, hypothalamus, amygdala, anterior cingulate cortex (ACC), periaqueductal gray matter (PAG), and medulla before reaching the somatosensory cortex for interpretation.[11] The complex interaction between each of these inputs demonstrates the important contribution cognitive, emotional, and motivational factors carry in the modulation of noxious stimuli and ultimately in the perception of pain. While nociception is an objective response to noxious stimuli, pain is a subjective sensory experience influenced by past events, present situation, emotion, and psychosocial state.[10] There has been substantial evidence over the last few decades that indicates emotion and psychosocial state critically contribute to pain outcomes after injury.[12-15]

Some of the early evidence for how emotional and psychosocial factors contribute to pain modulation came from H.K. Beecher, an Army physician during the Second World War. He observed that 75% of alert and responsive soldiers with severe battlefield injuries denied the need for pain treatment, stating they had pain levels ranging from no pain to moderate pain.[16] Beecher concluded that the soldier experienced such mild levels of pain because the traumatic injury relieved the soldier from the fear provoking, exceedingly dangerous environment of the battlefield.[16] The noxious stimulus from the traumatic injury was therefore modulated by the "euphoria" of their newly found safety, and Beecher concluded that "strong emotion can block pain."[16] It became readily apparent that emotion and psychosocial state can also heighten awareness to sensory stimuli, which contributed to the development of the Fear Avoidance Model (FAM).[17]

The FAM is a theoretical framework originally developed to explain the transition from acute to chronic pain, although most of the research in this area has been conducted in patients with chronic pain.[13] The FAM states that after an acute pain experience, an individual will continue on either the confrontation or fear-avoidance pathway. The confrontation pathway consists of individuals that perceive the pain as non-threatening and maintain low fear avoidance beliefs. This increases the likelihood that these individuals confront their pain, engage in activity, and return to active participation in society (Figure 1.1).[13,18,19] The fear-avoidance pathway, however, consists of maladaptive thoughts toward the injury and low self-efficacy resulting in a perpetual cycle of fear, activity avoidance, disability, and pain (Figure 1.1).[18,20] Since its inception, there has been substantial evidence demonstrating the association between each psychosocial factor included in the FAM and the outcomes of heightened pain severity and disability in patients with chronic pain,[21-23] but has been understudied in regard to how these variables contribute to the transition from acute injury to the development of chronic pain.

Psychosocial Factors involved in the Fear Avoidance Model

Pain catastrophizing was originally proposed as the first psychosocial factor in the fear-avoidance pathway of the FAM. It is defined as "…an exaggerated negative mental state brought to bear during actual or anticipated painful experience."[24] Catastrophizing behavior causes an individual to perpetually dwell on the pain (rumination), maintain a position of hyperawareness of potentially painful stimuli (exaggeration), and feel that there is nothing that can be done to alleviate the pain (helplessness).[25,26] Therefore, an individual with high levels of catastrophizing tends to expect the worst possible outcome

in a painful or potentially painful circumstance.[27] Research to date demonstrates that high levels of catastrophizing are associated with increased pain intensity,[28-32] pain interference,[13,28] disability,[29,31,33] opioid use,[34] and risk of developing chronic pain.[30,35]

The FAM conceptualizes that pain related fear follows catastrophic thinking. This often presents in the form of kinesiophobia which can be defined as an individual with "…an excessive, irrational, and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or reinjury."[17] Fear of movement has been shown to be a significant predictor of disability[36-40] and pain intensity[36,40,41] in patients with acute and chronic pain. For example, Vlayaen et al. found that kinesiophobia is a better predictor of self-reported disability than physical examination findings and pain intensity in patients with low back pain.[17]

The final psychosocial factor included in the original FAM is depression. Depression is a mental health disorder characterized by sadness, hopelessness, irritability, guilt, fatigue, changes in appetite, and contemplation of death or suicide for at least two weeks.[42] As shown in the FAM, depression carries a strong relationship with disuse and disability (Figure 1.1). This has been supported in the literature in which higher levels of depression are associated with decreased physical function and persistent pain in patients with low back pain,[43,44] neck pain,[45] knee pain,[46] and orthopaedic trauma.[28,47]

While not included in the original FAM, self-efficacy is one of the key factors that has recently been added to the FAM.[20] The theory of self-efficacy was originally proposed by the psychologist Albert Bandura as a key determinant of whether or not an individual can accomplish and succeed in a task.[48] He theorized that an individual with higher self-efficacy would demonstrate a greater ability to cope with and persevere

through challenging or threatening circumstances.[48] As an individual engages in and confronts circumstances that were initially perceived as threatening, they gain experience and confidence. With persistence, the individual masters the task, the perceived threat is reduced, and the individual returns to a state of reduced fear. However, those individuals who prematurely discontinue the task will continue to perceive the task as threatening, resulting in continued fear and defensive postures that limit recovery potential.[48]

Self-efficacy can act as either a protective or risk factor for adverse outcomes. As a protective factor, high self-efficacy has been associated with reductions in disability,[49-53] pain intensity,[49,52,53] fear of movement and pain,[20,54,55] and affective distress in patients with chronic low back pain and fibromyalgia.[53] A recent meta-analysis of 86 publications (N=15,616) demonstrated that as self-efficacy increased impairment, affective distress, and pain severity decreased, each with medium to large effect sizes.[53] Low self-efficacy can also be a risk factor for activity avoidance and passive coping mechanisms (i.e. pain medication).[53] Recent studies have demonstrated that self-efficacy mediated the relationship between pain catastrophizing and pain intensity[56] as well as pain intensity and disability.[49] This research indicates that an individual with a lack of confidence to manage and work through symptoms plays a tremendous role in worse pain intensity and disability. These data suggest that self-efficacy may be a key psychosocial variable to evaluate in the transition from acute to chronic pain after injury.

Psychosocial Factor's Association with Outcomes after Traumatic Lower Extremity Injury

Over 700,000 lower extremity fracture occur each year[57] with a large portion of these patients developing adverse short and long-term pain outcomes. Archer et al. reported that 97% of patients with major trauma had pain at hospital discharge after

definitive surgical fixation, with 69% of these patients reporting at least moderate pain severity (≥4/10 on the brief pain inventory).[58] At six-month follow-up, 54% of individuals report persistent pain after non-life threatening lower extremity fracture or dislocation, with 87% of these reporting that pain interfered with daily living.[59] The Lower Extremity Assessment Project (LEAP) group found that 62.7% of patients reported injury-related pain at 12 months[60] and 39% Grade II or higher on the Chronic Pain Grade Scale 84 months after limb threatening lower extremity trauma.[61] The high prevalence of long-term pain outcomes makes patients who sustain a lower extremity trauma requiring surgical fixation a unique population to study the factors involved in the transition from an acute injury to chronic pain.

Patients that sustain a major trauma (injury severity score ≥16) have severe restrictions in long-term physical function as well. In-fact, disability 12 months post-traumatic injury is up to four times greater than community norms.[62] Holtslag et al. prospectively followed 335 patients who had sustained major trauma and reported that 48% had mobility limitations and 55% had limitations in activities of daily living at 18-month follow-up.[63] The LEAP group found that one-third of patients reported moderate to severe pain interference with daily activities seven years after limb-threating extremity trauma.[61] While these studies provide compelling data that major trauma often results in long-term functional impairment, it remains unclear the extent to which a lesser injury severity is associated with long-term physical function.

Given the adverse pain and disability outcomes patients with lower extremity trauma experience, there is a need to identify high risk individuals in the acute stages of recovery. This could allow for early targeted treatment strategies to improve long-term

outcomes. The psychosocial variables included in the FAM are a promising means to stratify patients into risk categories. However, research regarding psychosocial associations with long-term outcomes after trauma has many limitations that need to be addressed.

Pain catastrophizing has been shown to carry moderate to strong associations with both pain severity and pain interference after traumatic injury. A recent study in patients with orthopaedic trauma reported that pain catastrophizing one to two months after injury was the sole predictor of pain at rest, pain during activity, and disability at five to eight month follow-up.[64] Archer et al. determined that pain catastrophizing four weeks after definitive surgical fixation for lower extremity fracture carried strong associations with 12-month pain interference and pain severity after lower extremity fracture requiring surgical fixation;[28] in this study, each ten-point increase in PCS at four weeks was associated with a 6.7 point increase in pain intensity, and 3.8 point increase in pain interference at one year.[28] However, no other psychosocial variables were included in these statistical models; therefore, it is unknown whether another psychosocial variable may be more strongly associated with pain severity and pain interference.

Fear of movement has inconsistent associations with pain and disability outcomes after trauma. In a cross-sectional study two years after traumatic lower extremity fracture, fear was associated with worse pain intensity and physical health when controlling for age, sex, intensive care unit stay, and depression.[65] However, in a subsequent prospective study fear at four weeks was not associated with physical health at 12 months.[28] These results seem to indicate that fear is a learned response rather than an early predictor of pain and physical function outcomes after lower extremity fracture.

Depression has the most literature to support its important association with long-term pain and disability after trauma. The LEAP group determined that depression and anxiety measured at three months were strong predictors of persistent pain one and seven years after severe, limb threatening trauma.[60,61] Consistent with these findings, Jenewein et al. found depression, PTSD, and coping six months after trauma to carry the strongest association with persistent pain at 36 months.[66] A recent prospective study in 110 subjects with lower extremity fracture found depression carried a moderate association with 12-month pain severity, pain interference, and physical health when controlling for important baseline variables.[28] Depression has also been shown to play the strongest role in predicting disability 12 months after trauma,[62] and also mediates the relationship between pain severity and disability in patients with lower extremity trauma.[67] In fact, a recent systematic review found that depression was a consistent and significant predictor of both pain and disability outcomes after traumatic injury.[68] The diverse predictive role of depression indicates that this variable should be controlled for in all future studies evaluating how psychosocial variables are associated with both pain and physical function outcomes after traumatic lower extremity injury.

Self-efficacy has been associated with worse pain and disability outcomes after traumatic injury, although it has been grossly understudied in this patient population when compared to the mounting evidence in other patient populations. Cross-sectional studies in patients that sustain a traumatic injury demonstrate that lower levels of self-efficacy are associated with increased pain intensity at hospital discharge[58] and worse self-reported physical function.[69] The LEAP group reported that self-efficacy three months after limb threatening lower extremity trauma carried moderate associations with

the seven-year outcomes of worse pain interference and chronic pain,[61] severe physical and psychosocial disability,[70] and lower return to work.[71] The primary drawback of the LEAP studies was that they did not use a validated self-efficacy questionnaire, making it difficult to apply to the clinical population. Additionally, no studies have evaluated how early self-efficacy is associated with long-term outcomes of patients with a less severe lower extremity fracture. This points to the need to further evaluate how self-efficacy early after injury is associated with long-term patient outcomes.

There are two final limitations present in all of the research regarding each psychosocial factor's association with long-term outcomes after traumatic lower extremity fracture. First, none of the studies have accounted for individuals with a history of chronic pain. This is crucial to account for when evaluating the factors that specifically influence an acute to chronic pain transition. Additionally, patients with chronic pain have elevated psychosocial beliefs compared to individuals without chronic pain, which would further skew findings in this area of research.[50,72,73] Second, there is substantial heterogeneity in the timing by which psychosocial factors are screened for after definitive surgical fixation between studies. This makes it difficult for clinicians to know the earliest timeframe screening an individual's psychosocial profile can be implemented into the clinical setting. Research that addresses these limitations has the potential to significantly improve the delivery of care to this patient population.

Multidimensional Screening

While the individual psychosocial constructs of the FAM are related to long-term patient outcomes, it is clear that multiple factors contribute simultaneously to influence resultant pain and disability levels.[74] However, limited time and patient burden are

barriers that make screening for multiple, full-length psychosocial questionnaires difficult to incorporate into clinical practice.[75] Shortened screening tools that assess for multiple psychosocial and physical impairments simultaneously may help streamline clinical decision-making and patient risk stratification.[76,77]

Methods to screen patients with acute orthopaedic trauma for adverse outcomes have been gaining interest. Castillo et al. were able to successfully identify four distinct patient groups ranging from "low risk and high protection" to "high risk and low protection" for 12-month self-reported functional and health related outcomes after traumatic lower extremity fracture.[78] This was based on the presence of five risk factors (pain level, depression, post-traumatic stress, alcohol abuse, and tobacco use) and four protective factors (resilience, social support, self-efficacy for return to work, and self-efficacy to manage finances) measured six weeks after the traumatic injury.[78] This is the first work that has attempted to classify patients with orthopaedic trauma into risk categories with the goal to inform a stratified patient care approach. While promising, this work neglects the important contribution that pain catastrophizing, anxiety, fear, and current disability play in trauma outcomes.[28,65,69]

The Keele Subgroups for Targeted Treatment Back Screening Tool (STarT) is an easily modifiable nine-item tool that screens patients with low back pain for modifiable physical and psychosocial factors that are associated with long-term disability. The nine-items consist of referred leg pain, comorbid pain, disability (two-items), pain bothersomeness, pain catastrophizing, fear of movement, anxiety, and depression.[79] Patient responses on the STarT are used to categorize an individual with low back pain into low, medium, and high risk categories for disability. In a randomized controlled

trial, patients with low back pain stratified to care based on their STarT score reported less disability, improved health related quality of life, and decreased cost of care 12 months after injury when compared to the control group that received standard of care intervention.[80] While the STarT has a proven ability to stratify risk for patients with low back pain, the STarT has not been validated for use in other patient populations. However, the STarT has proven feasible to generalize to patients with other musculoskeletal conditions.[81]

Given that the STarT assesses multiple disability and psychosocial constructs associated with poor patient outcomes, it may prove worthwhile to modify the STarT for patients who sustain a traumatic lower extremity fracture (STarT-LE). This could result in a fundamental shift in the ability to detect individuals at risk for adverse outcomes resulting in improved post-operative trauma care and reductions in the long-term economic burden associated with traumatic lower extremity fracture requiring surgical fixation.

The Problem

Patients with lower extremity fracture requiring surgical fixation have adverse long-term pain and physical function outcomes. It is clear that psychosocial variables carry important associations with these outcomes, but the earliest time point to screen for psychosocial characteristics to assess long-term risk for adverse outcomes is currently unknown. Additionally, no research has evaluated multiple psychosocial factors simultaneously to determine the most salient characteristic associated with the transition from acute injury to chronic pain, severe pain interference, and poor physical function in this population. Finally, a critical need to develop a multidimensional screening tool for

adverse long-term pain and physical function outcomes after lower extremity trauma persists. The STarT-LE evaluates modifiable factors that are likely to influence the development of chronic pain, worse pain interference, and reduced physical function. Each of these limitations has important implications on risk stratification, clinical decision-making, and the development of future therapies to intervene and improve patient outcomes after lower extremity fracture requiring surgical fixation. In the absence of such knowledge, these patients will continue to have poor long-term pain and physical function outcomes, perpetuating the individual and societal burden of these injuries.

Purpose

There are three overarching purposes of this dissertation. The first purpose is to determine the earliest timeframe psychosocial variables can be effectively screened to assess risk for chronic pain after lower extremity fracture requiring surgical fixation. The second purpose is to determine which psychosocial factors six weeks after surgical fixation predict the transition from acute to chronic pain, pain interference, and physical function 12 months after lower extremity trauma requiring surgical fixation. The final purpose of this dissertation is to determine the reliability and validity of the STarT-LE for the 12-month outcomes of chronic pain, pain interference, and physical function. These purposes are addressed with the following specific aims for patients that sustained a lower extremity fracture requiring surgical fixation without a history of chronic pain:

1. To evaluate when the psychosocial profile stabilizes throughout the first 12 months of recovery.

2. To identify the earliest time of divergence in psychosocial profile between those individuals that do and do not develop chronic pain at 12 months.
3. To determine which psychosocial factors six weeks after definitive surgical fixation predict the transition to chronic pain, severe pain interference, and poor physical function at 12 months.
4. To assess the reliability and concurrent validity of the STarT-LE six weeks after definitive surgical fixation.
5. To establish the predictive validity of STarT-LE risk category at six weeks for chronic pain development, pain interference, and physical function at 12 months.

Overview

Each of the studies in this dissertation utilize the same sample of patients from a prospective cohort study of 122 patients that sustained a lower extremity fracture requiring surgical fixation. These patients were consented to participate within the first week after definitive surgical fixation and followed through their first 12 months of recovery. Chapter 2 will determine how responses on the Patient-Reported Outcomes Measurement Information System (PROMIS) Depression, pain self-efficacy questionnaire (PSEQ), pain catastrophizing scale (PCS), Tampa Scale of Kinesiophobia-17 (TSK-17), and brief pain inventory pain severity subscale (BPI) change over the course of the first 12 months of recovery (Specific Aims 1 and 2). Chapter 3 will determine how patient-reported psychosocial measures six weeks after definitive surgical fixation are associated with 12-month pain and physical function outcomes (Specific Aim 3). Lastly, Chapter 4 will determine the reliability, concurrent validity, and predictive

validity of the STarT-LE for use in patients that sustain a lower extremity fracture requiring surgical fixation (Specific Aims 4 and 5).

Operational Definitions

Throughout each Chapter, the following terminology will be utilized:

1. Chronic Pain: In these manuscripts, this will be defined as pain lasting greater than three months and bothersome at least half the days over the past six months.[82]
2. Pain: An unpleasant sensory and emotional experience caused by actual or potential tissue damage.
3. Pain Interference: The extent to which pain affects the social, cognitive, emotional, physical, and recreational activities of an individual's life.
4. Psychosocial: The relationship between psychological factors (i.e. self-efficacy, pain catastrophizing, fear) and social factors (i.e. social support) that can influence patient thoughts, behaviors, and outcomes after injury.
5. Pain Self-efficacy: This refers to the confidence an individual possesses in completing a task despite their pain.
6. Pain Catastrophizing: A negative mental mindset characterized by rumination, magnification, and helplessness during actual or anticipated pain experiences.
7. Fear: An unpleasant emotion caused by a specific actual or potential threat.
8. Fear-Avoidance Beliefs: An individual's fear that a particular activity is harmful and/or dangerous resulting in avoidance of the activity to prevent injury/reinjury.

Assumptions

The primary assumptions for this dissertation are as follows:

Chapters 2, 3, and 4:

1. Participants were honest that they did not have a past history of chronic pain at the time of consent.
2. Participants answered all PROs honestly and to the best of their ability.
3. The surgical techniques utilized were sound and comparable between patients.
4. Opioid prescription did not influence the patient's outcomes.

Delimitations

The delimitations of this dissertation are as follows:

Chapters 2, 3, and 4:

1. Participants were males and females between the ages of 18-70 years at the time of consent.
2. Participants did not have a past history of chronic pain.
3. Participants had an acute orthopaedic fracture to the pelvis, acetabulum, femur, patella, tibia, talus or foot requiring surgical fixation.
4. Participants had a Glasgow Coma Scale score of 15 at the time of hospital admission.
5. Participants were able to read and speak English.
6. Participants did not have a moderate or severe Traumatic Brain Injury as evidence via Computed Tomography Scan.
7. Participants did not have initial treatment requiring amputation.
8. Participants did not have an alcohol or drug addiction (self-identified and per medical record review).
9. Participants did not have a neurologic disorder diagnosed at the time of consent.

10. Participant's injury was not self-inflicted or the result of domestic violence.

Limitations

The limitations of this dissertation are as follows:

Chapter 2:

1. The manner by which psychosocial variables change at intervals other than one week, six weeks, three months, six months, and 12 months after surgical fixation cannot be positively affirmed.
2. Measures of the individual's psychosocial profile were not able to be assessed prior to injury.
3. All outcomes are self-reported which may not reflect objective functional measures.
4. The study was completed at a single center. This may decrease the generalizability of the findings.

Chapter 3:

1. Measures of the individual's level of function and psychosocial profile were not able to be assessed prior to injury.
2. Self-reported physical function was not collected at six weeks after surgical fixation.
3. All outcomes are self-reported which may not reflect objective functional measures.
4. The quality and quantity of rehabilitation received was not accounted for which may affect the outcomes.

5. The study was completed at a single center. This may decrease the generalizability of the findings.

Chapter 4:

1. Measures of the individual's level of function and psychosocial profile were not able to be assessed prior to injury.
2. Self-reported physical function was not collected at six weeks after surgical fixation.
3. All outcomes are self-reported which may not reflect objective functional measures.
4. The extent to which the STarT-LE risk categories predict outcomes when compared to individual psychosocial assessment tools cannot be inferred.
5. The study was completed at a single center. This may decrease the generalizability of the findings.

Abbreviations

FAM = Fear Avoidance Model

PRO = Patient Reported Outcome Measure

PCS = Pain Catastrophizing Scale

PSEQ = Pain Self-Efficacy Questionnaire

TSK-17 = Tampa Scale of Kinesiophobia-17

BPI = Brief Pain Inventory-Pain Severity Subscale

ISS = Injury Severity Score

BMI = Body Mass Index

STarT = Subgroups for Targeted Treatment Back Screening Tool

STarT-LE = STarT Lower Extremity Screening Tool

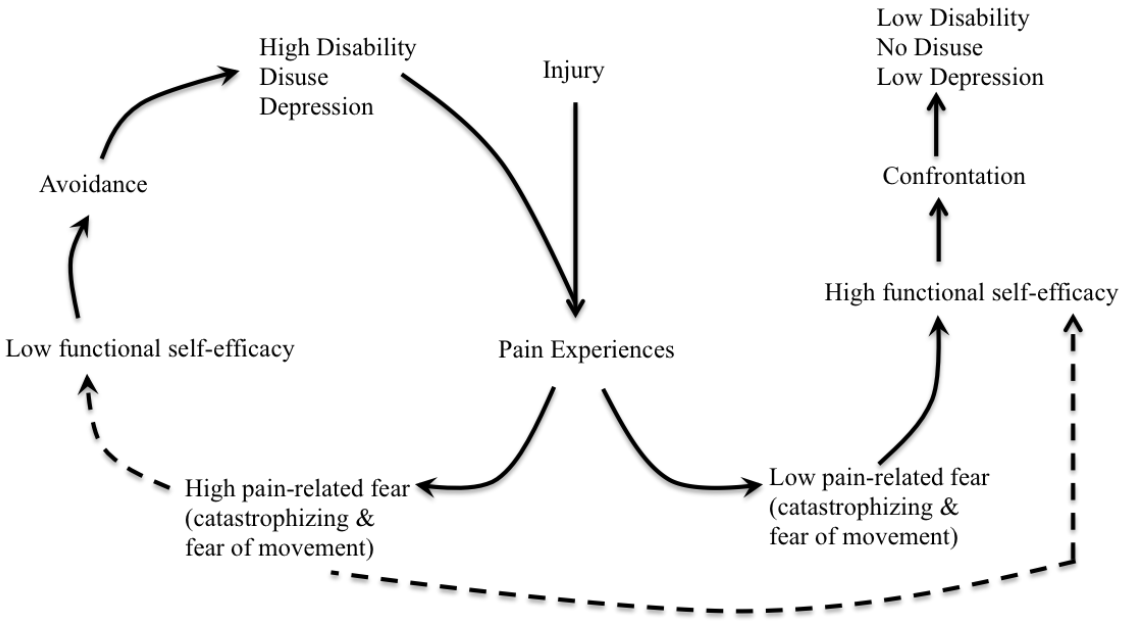
PROMIS Depression = Patient-Reported Outcomes Measurement Information System – Depression Scale

PROMIS Physical Function = Patient-Reported Outcomes Measurement Information System – Physical Function Scale

PROMIS Pain Interference = Patient-Reported Outcomes Measurement Information System – Pain Interference Scale

CAT = Computer Adaptive Test

Figure 1.1 Fear-Avoidance Model



From: Woby SR, et al. Self-efficacy mediates the relation between pain-related fear and outcome in chronic low back pain patients. *Eur J Pain.* 2007; 11(7): 711-718.
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Part II: Self-Efficacy and Pain Catastrophizing's Predictive Role for Pain Intensity, Disability and Chronic Pain after Orthopaedic Fracture: A Systematic Review

Introduction

Chronic pain has traditionally been defined as pain that persists beyond the normal course of tissue healing, generally accepted as greater than three months.[83] However, this definition is becoming obsolete as it only addresses the time component of chronic pain and fails to account for pain intensity and concomitant levels of disability. Pain intensity and disability play related but differing roles in the chronic pain epidemic. For example, an individual may have high pain intensity and relatively low interference with their daily activities. On the contrary, high levels of disability do not necessarily reflect the intensity of the pain. Therefore, accounting for each of these components of chronic pain has important implications on decreasing missed work time, reducing the number of outpatient hospital visits, and improving the quality of life in at risk patient populations.[84]

A patient population prime for studying chronic pain is the acute orthopaedic trauma population. Approximately 590,000 upper extremity fractures[85] and 730,000 lower extremity fractures occur in the United States each year.[57] Of these fractures, approximately 50% go on to develop chronic pain and concomitant disability.[59-61,86] Despite these poor outcomes, standard of care intervention remains unchanged and is grossly ineffective.[87] This is largely due to a limited understanding of the modifiable factors influencing the prognosis of patients that sustain a traumatic fracture. Previous research has identified smoking status, low education level, and high initial pain intensity

as risk factors for poor outcomes.[61,86] These non-modifiable factors are useful in predicting prognosis, but do not easily allow alternative intervention to change long-term outcomes.

Prognostic research on the modifiable factors that influence the outcomes of patients with orthopaedic trauma has been growing over the past decade. This research has largely focused on psychosocial factor's influence on patient outcomes after lower or upper extremity fracture. The most commonly reported psychosocial factors include pain catastrophizing (PCS),[28-31] fear of movement,[13,21,88] anxiety,[13] depression,[87,89,90] and self-efficacy.[20,53] Current evidence suggests that increased PCS may be the primary predictor of poor pain related outcomes after surgery,[31,91,92] while increased self-efficacy may protect from the development of adverse outcomes.[53,87] Understanding how these factors are associated with pain intensity, disability, and chronic pain development after orthopaedic fracture could have important clinical implications. Therefore, the specific aims of this study are to determine how pain catastrophizing and self-efficacy are associated with pain intensity, disability, and chronic pain among patients with lower and upper extremity fracture requiring definitive surgical fixation.

Methods

A systematic search was carried out through PubMed, MEDLINE, SportDiscus, CINAHL, Health Source-Consumer Edition, PsycINFO, and Psychology and Behavioral Science Collection databases for articles that evaluated the association between PCS and self-efficacy with pain and disability outcomes after orthopaedic fracture. Articles were limited to human subjects and those published in the English language. The search was carried out with MeSH terms and synonyms grouped together with Boolean operators on

March 8, 2018. A detailed list of the specific search terms utilized are highlighted in Table 1.1.

Inclusion and Exclusion Criteria

This systematic review included prospective longitudinal cohort, retrospective cohort, or cross-sectional studies. Articles were selected for inclusion based on the following criteria:

- Subjects sustained a fracture to the lower or upper extremity requiring definitive fixation.
- Statistical analysis included multivariate analysis to ensure the numerous prognostic factors were weighted appropriately against other predictive measures.
- Subjects were adults (18 years of age or older).
- The study achieved a "Strengthening the Reporting of Observational studies in Epidemiology" (STROBE) score ≥ 17/22.

The following were the exclusion criteria for study inclusion in this review:

- Studies related to spine-related injury or amputation.
- Presence of a fracture secondary to disease (pathologic fracture).
- Inadequate power to conduct an appropriate statistical analysis (<10 subjects per independent variable).
- Low follow-up rates affecting the ability to draw conclusions from the study (<65% follow-up).

Quality Assessment

The quality of the selected studies were assessed via the 22-item STROBE guidelines. One reviewer (J.V.) assessed the 17 full-text articles reviewed in full on each

STROBE criteria. Each of the 22-items were marked as “yes”, “no”, or “unsure”. Only those items that received a definitive “yes” were awarded a point toward the article’s final STROBE score. Only high quality articles were included in this systematic review. High quality articles were those that received a STROBE score of 17 or higher.

Data Extraction

All the data utilized in this systematic review were compiled into three article summary tables (Tables 1.3, 1.4, and 1.6). These data include the sample size, follow-up schedule and follow-up rate for prospective studies, nature of injury, study design, predictor and outcome variables evaluated, and the results from the multivariate analysis. Both statistically significant and non-significant results were reported from the multivariate analysis in each study. Level of statistical significance, percent variance, odds ratios, and relative risk ratios were extracted from each study. Factors were considered significant in this review if the 95% confidence interval did not include 1.00 for odds ratios and/or the significance level was $p<0.05$.

Level of Evidence Synthesis of Results

The strength of evidence synthesized in this systematic review was based on the Van Tulder Approach modified for observational studies. These criteria are outlined in Table 1.2. A “Strong” rating was offered when three or more high quality cohort studies had consistent findings. If two high-quality cohort studies yielded consistent findings, a “Moderate” score resulted. A “Limited” rating was provided for those studies that only had one study with statistically significant results in the multivariate model. Inconsistent findings among multiple studies were offered a “Conflicting” strength of evidence.

Finally, if all studies failed to find a statistically significant association or no articles were found the strength of evidence was marked as “No Evidence”.

Results

Study Selection

The search yielded 333 articles for consideration. All articles were downloaded into Endnote X8 and 101 duplicates were removed. Of the remaining 232 articles, 215 were removed based on the title and abstract. The full-text of the remaining 17 articles were retrieved for exhaustive examination and eight did not meet the inclusion criteria. Articles were excluded for possessing a STROBE<17 (3), possessing less than 65% follow-up (2), insufficient sample size (1), not evaluating pain catastrophizing or self-efficacy as a primary predictive measure (1), and the study population did not consist of patients with orthopaedic fracture (1). The article screening methodology is defined in Figure 1.2.

Summary of Included Studies

Of the nine studies included in this review six were prospective, two were cross-sectional, and one was retrospective. Four of the studies evaluated PCS’s role in predicting outcomes, four studies evaluated self-efficacy’s ability to predict outcomes, and one study evaluated the predictive role of both PCS and self-efficacy. Four of the studies used lower extremity fractures as the population of interest, three studies utilized upper extremity fractures, and two studies used patients with both lower and upper extremity fractures. The prospective cohort follow-up rate ranged from 72-93%, and terminal follow-up timeframe was a minimum of 5 months and as long as 84 months. The study characteristics are summarized in Table 1.3.

Assessment of Statistical Analysis

All selected studies were included if the author used a multivariate analysis plan necessary for large observation and prognostic studies. Each study performed preliminary bivariate statistical testing and progressed to a multivariate statistical analysis. Six of the studies included variables that carried $p<0.05$ in the bivariate model to the multivariate model,[28,58,64,70,93,94] and two studies included variables with $p<0.10$ in the bivariate model to the multivariate model.[61,69] One study, however, neglected to highlight the means by which multivariate hypothesis testing was completed.[71] Only one study was potentially underpowered resulting in the inability to determine the significance PCS plays alone in predicting upper extremity disability.[95]

Prognostic Factor's Strength of Recommendation:

A. *Self-Efficacy:* Four of the five studies evaluating the predictive role of self-efficacy utilized patients with lower extremity fracture, and the fifth study consisted of patients with both lower and upper extremity fracture. Refer to Table 1.4 for the self-efficacy results within each study.
    a. *Pain Intensity:* There is "Limited" evidence that self-efficacy predicts pain intensity after lower extremity fracture as only one Prognostic Level II study found an association,[65] while "No Evidence" exists for this association in upper extremity fracture as no studies were identified.
    b. *Disability:* There is "Strong" evidence that self-efficacy is associated with disability after lower extremity fracture as evidenced by three Prognostic Level II studies analyzing this relationship in lower extremity fractures and a fourth study which included both lower and upper extremity

fractures with statistically significant findings in the multivariate analysis.[28,70,71] "Limited" evidence exists for the relationship between self-efficacy and disability in upper extremity fracture as only one Prognostic Level II study with statistically significant findings was identified in this review, and this study included both lower and upper extremity fractures in the analysis.[69]

c. *Chronic Pain:* There is "Limited" evidence that self-efficacy is associated with chronic pain development after lower extremity fracture and "No Evidence" after upper extremity fracture. There was one Prognostic Level I study identified in patients with lower extremity fracture that found a statistically significant association between self-efficacy and chronic pain development in the multivariate model,[61] and no studies were identified evaluating this relationship in upper extremity fracture.

d. *Self-efficacy Summary:* Table 1.5 provides the strength of recommendation results for self-efficacy categorized by fracture location.

B. *Pain Catastrophizing (PCS):* Two of the five studies dealing with PCS utilized only patients with upper extremity fracture, two studies consisted of both lower and upper extremity fracture patients, and one study consisted of only lower extremity fractures. Refer to Table 1.6 for PCS results by study.

a. *Pain Intensity:* "Limited" evidence exists suggesting that PCS is associated with pain intensity in both lower and upper extremity fracture. This strength of evidence is based on one Prognostic Level II study comprised only of subjects with lower extremity fractures[28] and a

Prognostic Level I study population consisting of both lower and upper extremity fractures, both of which demonstrated a statistically significant relationship between PCS and pain intensity.[64]

b. *Disability:* "Limited" evidence exists for the association between PCS and disability after lower extremity fracture as only one Prognostic Level II study was identified as having a statistically significant association in this review.[28] "Conflicting" evidence exists for the association between PCS and long-term physical disability after upper extremity fracture as there was one Therapeutic Level IV and one Prognostic Level II study with inconsistent findings.[93,94]

c. *Chronic Pain:* There is "No Evidence" that PCS is associated with chronic pain development in either lower or upper extremity fracture as evidenced by no articles evaluating this association.

d. *PCS Summary:* Table 1.7 provides the strength of recommendation results for PCS categorized by fracture location.

Discussion

The number of studies evaluating how self-efficacy and PCS contribute to patient outcomes after traumatic fracture are lacking. Only four studies evaluated self-efficacy after lower extremity trauma, and three of these studies were based on the same cohort. One study evaluated the role of PCS in predicting pain intensity and disability after lower extremity fracture. Only one study assessed self-efficacy's role in predicting pain outcomes after upper extremity fracture, while four studies evaluated PCS's role in this population. There was only one study that evaluated chronic pain as a primary outcome

in either fracture population, and this study did not exclude individuals with a past history of chronic pain. This leaves a strong need for studies that evaluate how psychosocial factors influence the transition from acute injury to chronic pain after trauma.

Despite the limited literature, the studies in each fracture population show general agreement with one another. For example, the studies included in this review seem to indicate that self-efficacy carries important associations with disability and pain catastrophizing is associated with pain intensity after both upper and lower extremity fracture. However, most of these studies did not account for the role that other psychosocial factors, such as fear or depression, may carry in predicting patient outcomes. This introduces a fair amount of bias. It will not be possible to identify the primary psychosocial predictive measure for each outcome of interest if the study does not account for other important predictors based on prior literature. While it is not feasible to look at every predictive construct in one study, accounting for potential confounding variables is crucial to ensure accurate statistical reporting and clinical interpretation of the findings. For example, the LEAP group has identified depression three months after lower extremity trauma as carrying a strong association with seven-year pain outcomes.[61] Therefore, future studies should account for depression in their statistical models to determine if the psychosocial factor of interest carries further predictive capability for the outcome of interest. These data indicate the need for additional robust studies that evaluate the contribution multiple psychosocial factors carry in predicting long-term pain and disability outcomes after lower or upper extremity fracture.

One of the major limitations of the studies included in this review were the varied predictive and outcome measures used. There was no consistency in the outcome measures used, and considerable inconsistency in the predictive measures given only two psychosocial constructs were evaluated in this systematic review. This significantly limits the interpretability and comparability of the results between studies.

The quality of study design was inconsistent between studies in this review. Predictive measures were typically taken only at initial intake and outcomes at terminal follow up. Repeated measures along the timeline is crucial to establish a temporal relationship between predictive and outcome measures. This may help with understanding the optimal sampling times to develop intervention studies. Comparing fractures of the upper and lower extremity in the same cohort may confound the results and should be avoided. Individualized consideration of specific fracture locations is important to ensure proper reporting of the statistical findings. Subgroup analysis by fracture location should be considered to improve the specificity of the findings. This is admittedly difficult and would require a very large sample size to evaluate subgroups in this manner.

Finally, there was inconsistent means of conducting the statistical analysis and reporting the findings. Many of the authors failed to report the final results of each variable included in the multivariate analyses. Only effect sizes from statistically significant variables were reported. This made it impossible for the reviewer to determine whether the statistically non-significant variables were a result of too low power or small effect sizes. This may have resulted in missed clinically significant results worthy of continued study.

Future Research

This review shows the critical need for further research evaluating the role of self-efficacy and PCS in predicting pain and disability outcomes after fracture. More rigorous studies with multiple follow-ups and at least 12-month terminal follow-up are indicated.[87] Standardizing predictive and outcome measures is crucial to improve interpretability between studies. The National Institutes of Health (NIH) have recently developed the PROMIS health measures in order to standardize reporting of patient outcomes. Future research should consider using these patient reported outcome measurement tools. Additionally, consistent reporting of the significant and non-significant statistical findings through odds ratios and effect sizes will aid with clinical interpretation and developing future study protocols. Studies should also resolve to have more homogenous study populations to increase ease of applying the clinically relevant findings. Reporting threshold cut-off scores for each predictive measure to deduce individual risk for good and poor outcomes would allow for further clinical applicability.

While meta-analysis was not possible due to the substantial heterogeneity between studies, careful examination of Tables 1.4 and 1.6 seems to indicate that lower extremity fractures have worse outcomes than upper extremity fractures. This agrees with other research indicating lower extremity fractures possessing greater risk for adverse patient outcomes than other traumatic injuries.[59] This further indicates the need for studies that evaluate the factors predictive of chronic pain after lower extremity trauma. Only one study identified in this review assessed chronic pain as an outcome after lower extremity trauma, and this study did not account for prior existing chronic pain. Studies evaluating the transition from acute to chronic pain in this population may

not only help with clinical decision making after lower extremity trauma, but also identify risk factors of interest in other populations with high rates of chronic pain.

Strengths and Limitations of this Review

There are a number of strengths inherent to this review. The primary strength is that only studies that included multivariate results were utilized. This was done to limit the effect confounding variables had in influencing the interpretability of the results. Additionally, this review utilized the STROBE guidelines to ensure high-quality observational studies were included.

This systematic review is not without limitations. First, while the search terms were carefully constructed, there is a chance an article was missed with the search strategy and databases utilized. Second, data of potential significance may have been missed by excluding studies with a STROBE<17. These STROBE scores were only assessed by one reviewer, which may result in a biased exclusion of certain studies. Additionally, while all studies included were observational in nature, there was still a wide variety of observational studies included. Directly comparing a prospective cohort study to a retrospective study neglects the importance of the inherent biases each study design possesses. Finally, the results of this review may not be applicable to those with concomitant spine related injury, amputation, or pathologic fracture. These were exclusion criteria for most of the studies reviewed, and therefore the results presented in this review may not be generalizable to these populations.

Conclusions

There remains a need for more high-quality studies evaluating the role self-efficacy and pain catastrophizing play in predicting pain and disability outcomes in

patients with lower and upper extremity fracture requiring definitive fixation. These studies should be more rigorous in design, consistent in reporting effect sizes, and consider more factors in the statistical analysis to ensure predictive measure evidence reporting is not biased.

Table 1.1 Search strategy.

Step	Search terms	Boolean Operator
1	Lower/upper extremity fracture Lower/upper extremity trauma Orthopaedic trauma/fracture Femur/tibia/ankle/foot trauma Femur/tibia/ankle/foot fracture Radius/ulna/humerus/wrist/hand trauma Radius/ulna/humerus/wrist/hand fracture	OR
2	Pain catastrophizing Catastrophic thoughts Catastrophizing Catastrophizing behaviors Rumination Self-efficacy	OR
3	Disability Pain Interference Pain-related disability Quality of Life Pain Intensity Persistent/Chronic pain Pain severity Pain prevalence	OR
4	1+2+3	AND
5		Limited to ALL ADULT
6		Limited to English

Table 1.2 Strength of Evidence per Modified Van Tulder Approach for Observational Studies.

Level of Evidence	**Criteria for evidence level**
Strong	Consistent findings among 3 or more high-quality cohorts
Moderate	Consistent findings among 2 high-quality cohorts
Limited	One high-quality cohort
Conflicting	Inconsistent findings among multiple cohorts
No Evidence	No studies identified or no statistically significant findings

Table 1.3 Characteristics of Included Studies

Author, year	Sample Size	Prospective Follow-up Rate	Nature of Injury	Study Design	Predictor variable	Outcome variable	Prospective Follow-up time-point(s)
Archer, 2012	233	N/A	Lower Extremity Trauma	Cross-sectional	Chronic Pain Self-Efficacy Scale	Pain intensity and interference via Brief Pain inventory	N/A
Castillo, 2006	550	72.20%	Lower Extremity Trauma	Prospective	Self-efficacy for return to activity	Graded Chronic Pain Questionnaire	84 months
MacKenzie, 2005	569	72.6%	Lower Extremity Trauma	Prospective	Self-efficacy for return to activity	Physical and psychosocial scores of Sickness Impact Profile	84 months
MacKenzie, 2006	433	97.70%	Lower Extremity Trauma	Prospective	Self-efficacy for return to activity	Work Limitations Questionnaire	84 months
Van Leeuwen, 2016	124	N/A	Orthopaedic Trauma	Cross-sectional	Pain Self-efficacy Questionaire-2 and Pain Catastrophizing Scale-4	PROMIS Physical Function and PROMIS Pain Intensity	N/A

Table 1.3 Continued

Author, year	Sample Size	Prospective Follow-up Rate	Nature of Injury	Study Design	Predictor variable	Outcome variable	Prospective Follow-up time-point(s)
Roh, 2014	129	93.80%	Distal Radius Fracture	Prospective	Pain Catastrophizing Scale	Michigan Hand Questionnaire (patient perceived disability), wrist ROM, Grip strength	4, 12, and 24 weeks
Vranceanu, 2014	152	89.50%	Orthopaedic Trauma	Prospective	Pain Catastrophizing Scale	Short Musculoskeletal function assessment questionnaire (Disability) and pain intensity (NRS)	5-8 months
Bot, 2011	71	N/A	Radius and Ulna Fracture	Retrospective	Pain Catastrophizing Scale	Disabilities of the Arm, Shoulder, and Hand	N/A
Archer, 2015	134	82.1%	Lower Extremity Trauma	Prospective	Pain Catastrophizing Scale	Pain intensity and interference via Brief Pain inventory, Short Form-12	12 months

Table 1.4 Self-Efficacy Results by Study.

Author, year	STROBE Score	Level of Evidence	Pain/Disability (mean ± SD or %)	Multivariate Results
Archer, 2012	19/22	Prognostic Level II	**BPI Pain interference:** 6.3 ± 2.4 with 69% of subjects reporting moderate to severe pain interference (on 0-10 scale) **BPI Pain Intensity:** 5.2 ± 2.2 with 73% of subjects reporting moderate to severe pain intensity (on 0-10 scale)	Self-efficacy had a moderate negative effect on pain interference (OR: 0.91; 95% CI: 0.82–1.01) Lower self-efficacy was statistically associated with pain intensity (OR: 0.87; 95% CI: 0.78–0.98)
Castillo, 2006	20/22	Prognostic Level I	**Graded Chronic Pain Questionnaire:** 77.1% of all subjects had chronic pain 84 months post-injury	High self-efficacy was moderately associated with lower rates of Graded Chronic Pain Level IV
MacKenzie, 2005	21/22	Prognostic Level II	**Sickness Impact Questionnaire:** 84 months after injury, 49.4% had a score of 10 or higher indicating severe disability while only 34.5% had disability comparable to the US population	Low self-efficacy was significantly associated with a lower psychosocial and physical subscore on the SIP. When comparing low self-efficacy to high self-efficacy: OR: 2.2 for severe physical disability OR: 2.5 for severe psychosocial disability

Table 1.4 Continued

Author, year	STROBE Score	Level of Evidence	Pain/Disability (mean ± SD or %)	Multivariate Results
MacKenzie, 2006	20/22	Prognostic Level II	**Work Limitations Questionnaire:** cumulative proportion returning to work at 12, 24, and 84 months were 42%, 51%, and 58%.	Greater self-efficacy resulted in improved RTW rates and lower disability. When compared to low self-efficacy the Relative Rate Ratio (RRR) for RTW was: Average self-efficacy RRR: 2.58 (95% CI: 1.68-3.95) [p<0.01] High self-efficacy RRR: 3.88 (95% CI: 2.45-6.16) [p<0.01]
Van Leeuwen, 2016	19/22	Prognostic Level II	**PROMIS Physical Function:** 36 ± 9.6 (95% CI: 35-38)	Higher self-efficacy predicted higher physical function (PSEQ-2; b = 0.93, p < 0.001, 95% CI: 0.48–1.4) --Caucasian, employed work status, injury from anything other than sports, MVC or fall, and higher self-efficacy explained 35% of the variance in PROMIS Physical Function

Table 1.5 Strength of Evidence for Self-efficacy by Fracture Location.

	Lower Extremity Fracture	**Upper Extremity Fracture**
Pain Intensity	**Limited** --1 Prognostic Level II	**No Evidence** --No studies Identified
Disability	**Strong** --3 Prognostic Level II --1 Prognostic Level II (mixed population)	**Limited** --1 Prognostic Level II (mixed population)
Chronic pain	**No Evidence** --1 Prognostic Level II	**No Evidence** --No studies Identified

Table 1.6 Pain Catastrophizing results by study.

Author, year	STROBE Score	Level of Evidence	Pain/Disability (mean ± SD)	Multivariate Results
Roh, 2014	18/22	Prognostic Level II	**Michigan Hand Questionnaire** (lower score means greater disability): 4 weeks: 58 ± 11 12 weeks: 75 ± 11 24 weeks: 82 ± 12	Pain catastrophizing was associated with decrease in grip strength, ROM, and MHQ score at 4 weeks. Pain catastrophizing was not significant with any outcomes at 12 and 24 weeks.
Vranceanu, 2014	18/22	Prognostic Level I	**Short Musculoskeletal Function Assessment questionnaire (0-100 with higher score indicating greater disability):** 1-2 months: 98.5 ± 32.6 5-8 months: 79.4 ± 38.3	Catastrophic thinking at Time 1 was the sole significant predictor of pain at rest, pain during activity, and disability ($p<0.01$) at Time 2.
Bot, 2011	20/22	Therapeutic Level IV	**Dutch version of the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire (0-100 with higher scores indicated greater disability):** 21 (Range: 13 to 33)	Grip strength, pain, pain catastrophizing, and ipsilateral injury accounted for 55.9% of the variation in DASH ($p<0.001$)

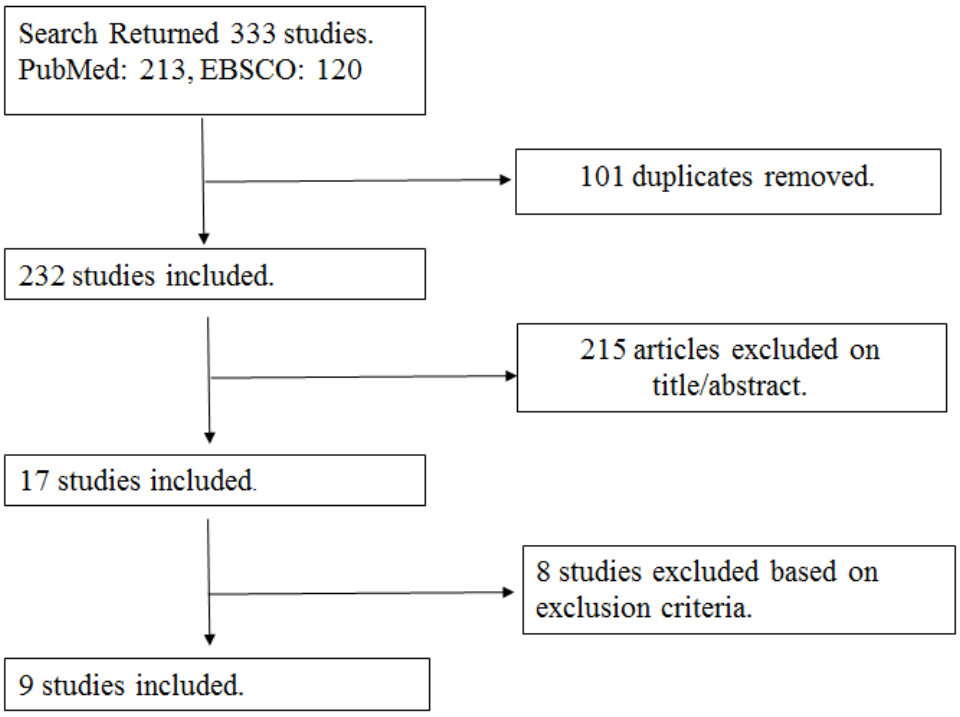
Table 1.6 Continued

Author, year	STROBE Score	Level of Evidence	Pain/Disability (mean ± SD)	Multivariate Results
Archer, 2015	20/22	Prognostic Level II	**BPI Pain interference:** 6.0 ± 3.0 (on 0-10 scale) **BPI Pain Intensity:** 4.0 ± 2 .0 (on 0-8 scale)	Pain catastrophizing at 4 weeks was associated with pain intensity (b = 0.67; p< 0.001) and pain interference (b = 0.38; p = 0.03) at 12 months A 10-point increase in pain catastrophizing scores (range, 0-52) at 4 weeks results in a 6.7-point and 3.8-point increase in pain intensity and pain interference (range, 0–10), respectively, at 1 year.
Van Leeuwen, 2016	19/22	Prognostic Level II	**PROMIS Pain Intensity:** 49 ± 8.4 (95% CI: 48-51)	Higher degrees of catastrophic thinking was the only variable significantly associated with higher PROMIS Pain Intensity (b = 1.2, P < 0.001, 95% CI: 0.99 to 1.5) --Catastrophic thinking explained 44% variance in pain intensity

Table 1.7 Strength of Evidence for Pain Catastrophizing by Fracture Location.

	Lower Extremity Fracture	**Upper Extremity Fracture**
Pain Intensity	**Limited** --1 Prognostic Level II --1 Prognostic Level I (mixed population)	**Limited** --1 Prognostic Level I (mixed population)
Disability	**Limited** --1 Prognostic Level II	**Conflicting** --Inconsistent findings between a Level IV and Level II
Chronic pain	**No Evidence** --No studies Identified	**No Evidence** --No studies Identified

Figure 1.2 Flow Diagram of Search Strategy.



CHAPTER TWO:

Individuals that Develop Chronic Pain have Increased Psychosocial Distress Six Weeks After Lower Extremity Fracture

Abstract of Chapter Two

Background: Approximately 50% of patients with a lower extremity fracture requiring surgical fixation develop chronic pain. Current evidence has associated early psychosocial beliefs with long-term pain outcomes. However, there is substantial heterogeneity in injury severity and the timing by which psychosocial factors have been assessed between studies.

Objective: To determine the earliest time in recovery that depression, pain self-efficacy, pain catastrophizing, fear of movement, and pain intensity can be screened to determine risk for the development of chronic pain after definitive surgical fixation for lower extremity fracture when controlling for injury severity score (ISS).

Design: Single center, prospective cohort study.

Methods: 122 patients (41.7 ± 14.7 years, 93.3 ± 28.5 Kg) with a lower extremity fracture requiring surgical fixation and no history of chronic pain consented to this study. Patients completed validated measures of depression, pain self-efficacy, pain catastrophizing, fear of movement, and pain intensity. Chronic pain development was assessed at 12 months after surgical fixation. A one-way repeated measures analysis of variance was used to evaluate the change in each psychosocial measure over time of the entire cohort. A two-way repeated measures analysis of covariance was subsequently utilized to determine the change in each psychosocial measure over time between those individuals with and without chronic pain at 12 months when controlling for ISS. Effect sizes were used to quantify the magnitude of change in the psychosocial profile over time between individuals with and without chronic pain. Odds ratios (ORs) for chronic pain

development were calculated by dichotomizing psychosocial variable using established reference standards.

Results: 114 patients (93.4%) completed this study. Evaluating the entire cohort over time demonstrated that pain catastrophizing and pain intensity stabilized six weeks after surgical fixation while depression, pain self-efficacy, and fear stabilized at three months. Individuals reporting chronic pain at 12 months had significant differences on all psychosocial measures starting at six weeks that persisted through 12-month follow-up with large to very large effect sizes (Cohen's d range: 0.79 to 1.96). Finally, dichotomized six-week psychosocial variables carried medium to large ORs to develop chronic pain at 12 months (OR range: 3.4 to 6.7).

Conclusion: The earliest time psychosocial variables can be effectively screened is six weeks after definitive surgical fixation. These results may prove useful in providing early targeted intervention to higher risk subgroups to decrease the incidence of chronic pain after lower extremity fracture.

Individuals that Develop Chronic Pain have Increased Psychosocial Distress Six Weeks After Lower Extremity Fracture

Introduction

Chronic pain is a world-wide epidemic with an estimated prevalence of 20-30%[1] and an annual incidence as high as 10%.[2] In the United States alone, chronic pain is the number one reason to seek out medical care,[3] resulting in $635 Billion in medical expenditure and lost wages due to missed work.[4] This cost is greater than that of heart disease, cancer, and diabetes.[4] Therefore, identifying the modifiable risk factors associated with the acute to chronic pain transition has become a public health priority.[2]

An important cohort to study these modifiable risk factors is the lower extremity trauma population. Approximately 50% of all patients that sustain a lower extremity fracture requiring surgical fixation develop chronic pain.[5-7] This results in high levels of concomitant disability, patient suffering and psychosocial distress, and health care utilization.[8] These burdens continue to grow in this patient population due to a limited understanding of how and when to screen for risk factors that may contribute to the development of chronic pain after injury.

Over the last two decades, a number of research groups have shown that psychosocial factors carry important associations with pain outcomes after lower extremity fracture. Specifically, depression,[5,7-9] self-efficacy,[6,10,11] pain catastrophizing,[12-14] fear of movement,[13] and pain severity[6,11,15] were shown to carry moderate associations with long-term pain intensity and pain interference after traumatic lower extremity injury. These studies indicate that screening for psychosocial factors in

recovery from a traumatic lower extremity fracture may identify those individuals at the greatest risk for adverse long-term pain outcomes.

Research evaluating psychosocial factor's association with pain is limited as there is substantial heterogeneity in both the severity of lower extremity injuries between studies and the timing by which psychosocial assessment was performed after injury. For example, Archer et al. identified depression and pain catastrophizing four weeks after definitive surgical fixation were associated with 12-month pain severity and pain interference in patients with lower extremity fracture.[12] The Lower Extremity Assessment Project (LEAP) found that depression/anxiety, pain severity, and self-efficacy three months after injury were associated with seven-year outcomes in patients with limb threatening lower extremity trauma.[6] Finally, a number of cross-sectional studies indicate that fear of movement and self-efficacy are associated with greater pain severity and pain interference in patients with a lower extremity fracture requiring surgical fixation, but the study design limits the ability to draw causal inferences.[10,13] Understanding how psychosocial factors change throughout the course of recovery from a lower extremity trauma while accounting for injury severity will allow for informed psychosocial screening to be implemented in the clinical setting. See Table 1.1 for a comprehensive summary of what is known regarding psychosocial assessment following lower extremity trauma.

Finally, an important variable that has not been accounted for in any studies to date is a past history of chronic pain. Individuals with chronic pain have elevated psychosocial profiles and will have much greater odds of reporting continued chronic pain after traumatic injury.[16-18] Therefore, a critical need exists to identify the earliest

time point each of these psychosocial factors can be effectively screened in a patient population without a history of chronic pain after lower extremity fracture. These data can be used to test targeted early intervention strategies in higher risk patient subgroups in order to reduce the incidence of chronic pain after lower extremity fracture.

Therefore, the primary purpose of this study is to determine the earliest time in recovery depression, pain self-efficacy, pain catastrophizing, fear of movement, and pain intensity can be screened to determine risk for the development of chronic pain after definitive surgical fixation for lower extremity fracture when controlling for injury severity score (ISS). We hypothesized *a priori* that six weeks after definitive surgical fixation will be the earliest point in recovery that each factor can be accurately assessed. The secondary purposes of this study were to determine how each psychosocial factor at the earliest time point identified is associated with the development of chronic pain, and to describe how psychosocial responses over time may inform rehabilitative efforts throughout patient recovery.

Patients and Methods

After this study was approved by the local institutional review board, patients admitted to a level 1 trauma center for a lower extremity fracture requiring open-reduction internal fixation to the pelvis, acetabulum, femur, tibia, patella, or foot/ankle were screened for inclusion between December 2017 and February 2019. Written and informed consent was obtained from each eligible and willing participant. Patients were deemed as eligible if they were between the ages of 18 and 70 years, sustained a primary injury consisting of a lower extremity fracture requiring surgical fixation, and did not sustain an upper extremity fracture requiring immediate surgical fixation. All patients

that met eligibility criteria were approached for consent while admitted to the hospital. The exclusion criteria were consistent with criteria from past studies after lower extremity fracture:[10,12] self-inflicted injury or injury resulting from domestic abuse, brain imaging demonstrating moderate to severe brain injury, current alcohol or drug abuse, initial treatment consisting of amputation, unreasonable follow-up expected (prisoner or homeless), medical diagnosis of Alzheimer's Disease or Dementia, and inability to complete the questionnaires (developmental disorder, non-English speaking, Glasgow Coma Score <15). Additionally, individuals that had current chronic pain were excluded. Chronic pain was defined as pain present greater than three months and bothersome at least half the days over the prior six months.[19]

Patients were approached within the first week after definitive surgical fixation. Demographic questions were completed at the time of consent while mechanism of injury, primary injury location, and ISS were extracted from each individual's medical record. Validated measures of depression, pain self-efficacy, pain catastrophizing, fear of movement, and pain intensity were collected at baseline (within the first week), six weeks, three months, six months, and 12 months after definitive surgical fixation. Additionally, at 12 months each participant was asked whether they had developed chronic pain. Individuals were provided a two-week window to complete the six-week and three-month surveys, and a four-week window to complete the six- and 12-month surveys. All questionnaires were administered via a secure internet application developed by Vanderbilt University for research (Research Electronic Data Capture [REDCap]).[20]

Validated Questionnaires Administered

Depressive symptoms were measured with the Patient-Reported Outcomes Measurement Information System (PROMIS) Depression. The PROMIS Depression was administered to each subject as a computer adaptive test (CAT), which is a valid means to assess for symptoms of depression in adults.[21] CAT modules efficiently and effectively measure a construct with high precision in as few as four question-items. The mean score of the U.S. general population on the PROMIS Depression is 50 with each 10-point change corresponding with one standard deviation from the population mean.[21] Higher scores indicate worse depressive symptoms.

The Pain Self-efficacy Questionnaire (PSEQ) was administered to each subject as it is a reliable and valid way to gauge an individual's beliefs that they can participate in social and physical activity despite having pain.[22-25] The PSEQ consists of 10 statements and the subject rates their confidence to complete each statement despite pain. Responses range from zero (Not at all confident) to six (Completely confident), with higher scores indicating better pain self-efficacy (range: 0-60). Based on normative data from other patient populations with chronic pain, a score >40 indicates high pain self-efficacy while a score ≤40 is consistent with low pain self-efficacy.[24,26]

The Pain Catastrophizing Scale (PCS) was used to assess the extent to which each individual catastrophized over their pain. The PCS is a reliable and valid method to assess whether an individual magnifies, ruminates, or feels helpless in the presence of pain.[27,28] It consists of 13-questions with responses ranging from zero (Not at all) to four (All the time), with higher scores indicative of worse catastrophizing (range: 0-52). A

score ≥20 is an established cuff-off that differentiates individuals with high catastrophizing from those with low catastrophizing.[26,29]

Kinesiophobia is an exaggerated fear of movement stemming from feelings of vulnerability to pain and subsequent injury.[30] The Tampa Scale of Kinesiophobia (TSK-17) is a reliable and valid means to assess for fear of movement in patients currently in pain.[17,24,31] This survey consists of 17-items in which patients can respond with one (Strongly disagree) to four (Strongly agree), with higher scores indicating worse fear of movement (range: 17-68). A score ≥41 is often used to differentiate individuals with high and low kinesiophobia.[24,26]

Pain intensity was measured with the first four question-items of the Brief Pain Inventory (BPI), which consists of asking the subject's worst, least, average, and best pain over the last week. Participants respond on a zero (No pain) to 10 (Worst pain you can imagine) scale for each question, and the average of all four measures was used as the individual's pain intensity (range: 0-10). The BPI is a valid and reliable method to assess for pain after a surgical procedure.[32,33] A score ≥5 is used to differentiate moderate-to-severe pain from lower pain intensity.[34-36]

Chronic Pain Assessment

At the 12-month follow-up, each participant was asked a two-part question following the recommendations of a recent NIH Task Force to determine the presence of chronic pain:[19] (1) "Over the last six months, how *long* has pain been an ongoing problem for you?" and (2) "Over the last six months, how *often* has pain been an ongoing problem for you?" Individuals were deemed as having chronic pain with responses greater than

three months to question one, and at least half the days over the last six months to question two.

Statistical Analysis

Parametric assumptions were evaluated for each continuous variable. Descriptive statistics (mean, SD, frequency, percentage) were used to summarize demographic, psychosocial, and pain variables. The baseline demographic and psychological characteristics of individuals who were lost to follow-up were compared to those who completed the study with independent t-tests and chi-square analysis. Missing data was less than 5% for those individuals who completed the study, and these data were imputed using multiple imputation in which five versions of the missing data were created and subsequently combined into one inferential analysis score.[37]

One-way repeated measures analysis of variance (ANOVA) with Bonferroni post-hoc correction was used to evaluate the change in each psychosocial measure (dependent variable [DV]) over time (independent variable [IV]) of the entire cohort. A 2x5 repeated measures analysis of covariance (ANCOVA) with Bonferroni post-hoc correction was subsequently utilized to determine the change in each psychosocial measure (DV) over time (IV) between those individuals with and without chronic pain at 12 months (IV) when controlling for ISS (covariate). Cohen's d effect sizes were used to quantify the magnitude of change in psychosocial profile over time, with effect sizes defined as small=0.20, medium=0.50, large=0.80, and very large=1.30.[38,39] Finally, each psychosocial variable was dichotomized using established reference standards (PROMIS Depression ≥1 SD above the mean,[40] PSEQ ≤40,[24,26] PCS ≥20,[26,29] TSK-17 ≥41,[26,29] and BPI ≥5).[34-36] Univariate odds ratios (OR) for each dichotomized measure's association

with the development of chronic pain were calculated with ORs defined as small=1.5, medium=2.5, and large=4.2.[41] All statistical analyses were made using IBM SPSS Statistics (Version 24). Significance level was set as $\alpha \leq 0.05$.

Results

Of the 122 subjects that consented and enrolled in this study, our follow-up rates at each time point were excellent, ranging from 91.8% to 95% (Figure 2.1). The total number of individuals that were screened, excluded, consented and enrolled, and completed the study at each follow-up time point are presented in Figure 2.1. Of the subjects that started this study but did not complete 12-month follow-up, five subjects were unable to be contacted and three subjects declined to participate. There were no significant differences in Injury Severity Score (ISS), education level, body mass index (BMI), age, smoking status, gender, or baseline psychosocial scores between those who completed the study and those who did not complete the 12-month follow-up. The majority of individuals in this study were males (55%), and had greater than High School education (60%). Current smokers made up 26% of the patients in this study. The mean ISS was 9.1 with 51% sustaining a primary injury to the tibia, 24% to the femur, and 18% to the pelvis or acetabulum (Table 2.2).

Evaluating the entire cohort over time demonstrated that PSEQ, PCS, TSK-17, and BPI changed significantly between baseline and six weeks (Table 2.3). Scores on the PCS and BPI did not change between six weeks and any subsequent time point. Depression, PSEQ, and TSK-17 carried a statistically significant change in score between six weeks and three months with scores not changing thereafter (Table 2.3).

Comparing scores on each psychosocial measure over time between individuals reporting chronic pain at 12-month follow-up and those that did not have chronic pain displayed no difference at baseline between groups. However, at six weeks, three months, six months, and 12 months there was a statistically significant difference between groups on all psychosocial measures with large to very large effect sizes and significant interaction effects (Table 2.4, Figure 2.1). Finally, dichotomized six-week psychosocial variables carried medium to large ORs to develop chronic pain at 12 months (Table 2.5).

Discussion

The main purpose of this study was to determine the earliest time point depression, pain self-efficacy, pain catastrophizing, fear of movement, and pain intensity can be effectively screened in order to assess risk for chronic pain. Each subject in this study completed validated psychosocial assessments at five time points throughout recovery and questioned whether or not they had developed chronic pain at 12-months follow-up. The novel findings of this study indicate that the earliest time point that psychosocial profile can be screened is six weeks after definitive fixation for a lower extremity fracture. These results provide evidence that screening psychosocial profile at six weeks after surgical fixation may help inform rehabilitation treatment efforts with the ultimate goal of reducing the incidence of chronic pain after lower extremity fracture.

The dynamic nature of the entire cohort's psychosocial profile during the first three months of recovery indicates that six weeks to three months post definitive surgical fixation is the earliest time point psychosocial factors can be effectively screened. The responses received from patients during these early stages of recovery are consistent with

an initial psychophysiological state response, which is common after injury.[42] State responses are not as conducive to screening for long-term risk because they tend to be transient and situationally dependent.[43] States are often contrasted with personality traits, which are longer-lasting, stable characteristics of an individual.[43] As time since injury elapses it is expected to observe improvement and stabilization in both pain intensity and psychological distress.[44] Our results indicate that as recovery from the lower extremity fracture progresses, the individual shifts from a transient state response to their psychosocial personality trait. In some cases, these psychosocial traits manifested at three months post-surgical fixation are elevated from that of their pre-injury traits. These newly formed traits are likely a result of the individual's injury, recovery experience, and recovery expectations.[45]

The order by which these variables stabilize over time in the entire cohort provides interesting insight into the recovery process after traumatic injury. Our data demonstrating that PCS and BPI scores stabilize simultaneously is consistent with a large body of literature establishing the strong association pain catastrophizing and pain intensity carry with one another.[12,46-49] It is interesting that the stability of these two constructs also corresponds with the timing that the majority of patients are cleared to begin full weight-bearing activity after surgery.[50,51] The majority of patients in this study that were not in an external fixator were cleared to begin weight bearing as tolerated approximately six weeks after surgical fixation, while patients in an external fixator were typically cleared at three months. Physical function, psychological distress, and pain intensity heavily influence each other.[6,7,52,53] Therefore, it is possible that individuals with higher pain intensity at six weeks will also have elevated psychosocial profiles

resulting in worse responses to initiating physical activity. These responses to physical activity should theoretically reflect in the patient's depression, pain self-efficacy, and fear of movement at three-month follow-up. This progression is consistent with the fear avoidance model demonstrating the strong interrelationship between low self-efficacy, high fear, depressive symptoms, and disability after painful injury.[54-56] These results may point to the importance of positive initial experiences with resuming weight-bearing activity through aggressive pain management techniques in the acute stages of recovery,[57] cognitive behavioral therapy intervention focused on building positive expectations and reducing fear,[18,58,59] and rehabilitative techniques focused on gradually improving tolerance to activity and exercise.

When comparing individuals that reported chronic pain at 12 months to those who did not report chronic pain, our results suggest that six weeks is the earliest time point that these maladaptive tendencies are able to be determined with medium to large univariate odds ratios. While the psychosocial trait is not manifested until three-months recovery for depression, PSEQ, and TSK-17, a clear divergence between patients with and without chronic pain presented six weeks after surgery and persisted through terminal follow-up for all psychosocial constructs measured. The fact that baseline measures were similar between patients with and without chronic pain indicates that heightened pain and psychosocial distress are normal and expected responses during the initial stages of recovery after lower extremity fracture. This agrees with other research demonstrating low self-efficacy and moderate-to-severe depressive symptoms, pain intensity, and pain interference within the first week after lower extremity trauma.[10] It is possible that elevated pain and psychosocial responses serve a protective role in the very early stages

of recovery from acute injury by preventing activity that may cause further harm. Psychosocial distress that persists past the acute phase of injury, however, can quickly become maladaptive and associated with worse long-term outcomes.[12,53,60-62]

Moreover, there is a clear interaction effect between group (chronic pain versus no chronic pain) and each psychosocial measure over time. The individuals that did not report chronic pain at 12 months manifested steady improvements on all psychosocial measures over time (Figure 2.2). However, those individuals with chronic pain had worse depressive symptoms and PSEQ scores at six weeks when compared to baseline responses. Similarly, PCS and BPI responses worsened between three and six months while TSK-17 scores did not demonstrate clinically meaningful improvement between any time point in recovery in the chronic pain group. These interactions clearly demonstrate the importance of evaluating psychosocial factors over the course of recovery to assess for risk of chronic pain after lower extremity trauma.

Our results also indicate the need to develop more sensitive cut-off scores on each of these psychosocial measures for the earlier stages of recovery after fracture. Many of the psychosocial score cut-offs were validated in patients with current chronic pain, and in many of these cases have had the chronic pain for many years.[24-26,63] Our data indicates that a population transitioning to develop chronic pain will have entirely different psychosocial manifestations in the earlier stages of recovery than those individuals that already have chronic pain (Figure 2.2). At 12-month follow-up, however, the individuals in this study with chronic pain report mean psychosocial scores consistent with established cutoff scores from other patient populations with chronic pain.[24-26,63]

These results have promising clinical applications that may help improve the outcomes of patients who sustain a lower extremity fracture. Screening individuals for a heightened psychosocial profile six weeks after surgical fixation may open avenues to test targeted intervention in order to reduce the number of individuals that transition to chronic pain. While psychological intervention and graded exercise progressions have demonstrated inconsistent effects in treating individuals with chronic pain,[64] it may be possible to optimize the outcomes of individuals manifesting maladaptive psychosocial tendencies prior to developing chronic pain. Research to date clearly demonstrates that it is much more challenging to decrease pain and disability levels once an individual has already developed chronic pain.[65,66] Physical therapy intervention beginning six weeks after injury that focuses on building patient confidence with a functional weight bearing progression and pain reduction techniques such as transcutaneous electrical nerve stimulation, manual therapy, and heat/ice may adjust maladaptive tendencies early in recovery and improve long-term outcomes.

This study is not without limitations. First, we were not able to determine if psychosocial screening earlier than six weeks post surgical fixation is an effective screen given that no assessments were conducted between baseline and six weeks. The large effect sizes present between groups at six weeks indicate that an earlier divergence may exist in the recovery process. Future studies may consider prospectively evaluating the differences at two weeks and four weeks to determine if that offers further resolution in assessing psychosocial differences. Additionally, the exclusion criteria of this study may limit the generalizability of these findings. Specifically, the psychosocial profile of individuals with chronic pain prior to sustaining a lower extremity fracture will likely be

different than those included in this study. Third, the odds ratios calculated in this study did not account for additional variables that may confound the results. Future studies that evaluate how early psychosocial factors are associated with chronic pain should be done with multivariate techniques accounting for important characteristics that may influence outcomes. This will allow clinicians to identify which psychosocial characteristics explain the most variance in long-term patient outcomes. Finally, this study was conducted at a single center further reducing the external validity of our findings. Larger, multicenter trials are needed to provide pragmatic evidence reflective of the U.S. population.

Conclusion

The results of this study demonstrate that there are no differences in any psychosocial variables directly after definitive surgical fixation between those individuals with and without chronic pain at 12 months. However, individuals with chronic pain have worse depression, pain self-efficacy, pain catastrophizing, fear of movement, and pain intensity at six weeks that persist through 12-months recovery when compared to individuals without chronic pain with large to very large effect sizes. The results of this study may prove useful in screening at-risk subgroups in order to provide targeted intervention and decrease the incidence of chronic pain after lower extremity fracture.

Table 2.1 Summary of what is currently known regarding psychosocial factors association with adverse outcomes after lower extremity trauma.

General knowledge of trauma outcomes: -Approximately 50% of all patients with lower extremity fracture report persistent pain.[5-7] -Psychosocial factors carry moderate associations with pain and disability. -Substantial heterogeneity exists in both the timing of psychosocial assessment and injury severity between studies. -No studies have accounted for individuals with history of chronic pain.
Pain Catastrophizing: -At 4-week follow-up associated with pain intensity and pain interference at 12 months after moderate-to-high energy lower extremity fracture.[12] -At 1-2 months follow-up associated with pain and disability 5-8 months after musculoskeletal trauma.[14] -Cross-sectional relationship to pain intensity an average of 3 months after lower or upper extremity trauma (91% fracture).[67]
Self-efficacy: -At 3 months associated with pain, disability and return to work at 7 years after limb threatening trauma.[6,68,69] -Cross-sectional relationship to pain intensity and pain interference when discharged from hospital for a lower extremity fracture.[10]
Fear: -At 4 weeks not associated with physical health at 12 months after moderate-to-high energy lower extremity fracture.[12] -Cross-sectional relationship to pain and physical health two years after severe trauma.[13]
Depression: -At 4 weeks associated with pain severity, pain interference, and physical health at 12 months after moderate to high energy lower extremity fracture.[12] -At 3 months associated with pain at 7 years after limb threatening trauma.[6] -At 6 months associated with pain at 3 years after severe trauma.[8]

Table 2.2 Characteristics of study population (N=122).[t]

Age	42.1 ± 14.6
Body Mass Index (BMI)	31.5 ± 9.5
Gender	
Female	55 (45)
Male	67 (55)
Education	
High School or less	50 (41)
Greater than High School	72 (59)
Current Smoker	33 (27)
Mechanism of Injury	
Motor Vehicle Accident	46 (38)
Motorcycle Accident	13 (11)
Pedestrian/cyclist hit by vehicle	9 (7)
Fall	36 (29)
Blunt Trauma	13 (11)
Other	5 (4)
Primary Injury Location	
Pelvis/Acetabulum	21 (17)
Femur	30 (25)
Tibia	63 (51)
Patella	2 (2)
Ankle/Foot	6 (5)
External Fixator used prior to definitive fixation	
Yes	28 (23)
No	94 (77)
Injury Severity Score	9.1 ± 6.6

[t] Values are listed as either frequency (percentage) or mean ± SD.

Table 2.3 One-Way repeated measures analysis of variance displaying the change in each psychosocial measure over time of the entire cohort (N=114). [t]

	Baseline	Six Weeks	Three Months	Six Months	12 Months
Depression [†]	55.8 ± 8.7	54.3 ± 9.2	51.4 ± 9.9	51.0 ± 9.8	50.7 ± 9.7
PSEQ* [†]	30.9 ± 15.0	38.2 ± 15.8	42.3 ± 15.2	44.7 ± 14.8	46.8 ± 13.3
PCS*	15.4 ± 10.5	9.4 ± 9.8	9.6 ± 10.7	11.5 ± 11.7	10.2 ± 11.4
TSK-17* [†]	43.1 ± 6.7	40.6 ± 6.7	38.9 ± 7.9	38.3 ± 7.2	38.2 ± 7.8
BPI*	5.9 ± 1.7	3.0 ± 2.1	2.8 ± 2.1	2.8 ± 2.2	2.6 ± 2.3

[t] Values presented as Mean ± SD

*Indicates statistically significant change between baseline and six weeks

[†] Indicates statistically significant change between six weeks and three months

Table 2.4 Psychosocial means over time between those who reported chronic pain at 12 months and those who did not.

	Baseline		Six Weeks		Three Months		Six Months		12 Months	
Chronic Pain at 12-mo	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Depression Mean ± SD	57.6 ± 8.1	54.1 ± 8.0	57.9 ± 8.2	51.5 ± 8.2	55.6 ± 9.4	48.0 ± 8.9	55.4 ± 9.0	47.3 ± 9.0	55.2 ± 8.3	46.9 ± 9.2
Cohen's d (95%CI)	*0.43 (0.05 to 0.81)*		*0.79 (0.39 to 1.17)**		*0.83 (0.43 to 1.22)**		*0.90 (0.50 to 1.29)**		*0.94 (0.53 to 1.33)**	
PSEQ Mean ± SD	29.1 ±12.7	32.3 ±17.1	29.9 ±14.1	44.7 ±13.7	33.7 ±15.1	49.4 ±10.8	36.5 ±13.6	51.4 ±12.1	37.1 ±12.2	54.2 ±8.6
Cohen's d (95%CI)	*0.21 (-0.17 to 0.58)*		*1.06 (0.65 to 1.45)**		*1.22 (0.80 to 1.62)**		*1.17 (0.75 to 1.56)**		*1.66 (1.21 to 2.08)**	
PCS Mean ± SD	16.5 ±10.5	14.2 ±10.1	14.5 ±11.4	6.1 ±6.3	14.3 ±12.1	5.7 ±7.5	18.2 ±11.9	6.2 ±8.4	17.7 ±11.9	4.2 ±6.1
Cohen's d (95%CI)	*0.23 (-0.15 to 0.60)*		*0.93 (0.53 to 1.32)**		*0.88 (0.47 to 1.26)**		*1.19 (0.78 to 1.59)**		*1.47 (1.04 to 1.89)**	
TSK-17 Mean ± SD	44.7 ±7.5	41.8 ±5.8	43.5 ±6.2	38.4 ±6.5	42.4 ±7.1	36.2 ±6.9	42.1 ±6.7	35.3 ±6.2	42.6 ±6.8	34.6 ±6.9
Cohen's d (95%CI)	*0.43 (0.04 to 0.81)*		*0.81 (0.42 to 1.20)**		*0.88 (0.48 to 1.27)**		*1.07 (0.66 to 1.46)**		*1.18 (0.77 to 1.58)**	
BPI Mean ± SD	6.2 ± 1.6	5.5 ± 1.8	4.2 ± 2.1	2.2 ± 1.7	3.9 ± 2.2	2.0 ± 1.6	4.3 ± 2.1	1.6 ± 1.4	4.5 ± 2.0	1.2 ± 1.4
Cohen's d (95%CI)	*0.39 (0.01 to 0.77)*		*1.03 (0.62 to 1.42)**		*0.95 (0.55 to 1.34)**		*1.50 (1.07 to 1.91)**		*1.96 (1.49 to 2.40)**	

*Indicated statistically significant effect size for the difference in the psychosocial measure at that time point between individuals with and without chronic pain.

Table 2.5 Univariate odds ratios for chronic pain for each psychosocial measure dichotomized at six weeks after definitive surgical fixation.*

Psychosocial measure	Chronic Pain
Depression	5.7 (95%CI: 2.3 to 13.9)
PSEQ	4.5 (95%CI: 2.0 to 10.0)
PCS	6.7 (95%CI: 1.8 to 25.2)
TSK-17	3.4 (95%CI: 1.6 to 7.4)
BPI	6.2 (95%CI: 2.1 to 18.3)

*Psychosocial measures were dichotomized using Depression ≥1SD from mean, PSEQ <40, PCS ≥20, TSK ≥41, BPI ≥5.0.

Figure 2.1 CONSORT Diagram depicting the total number of subjects screened, enrolled, and completed study.

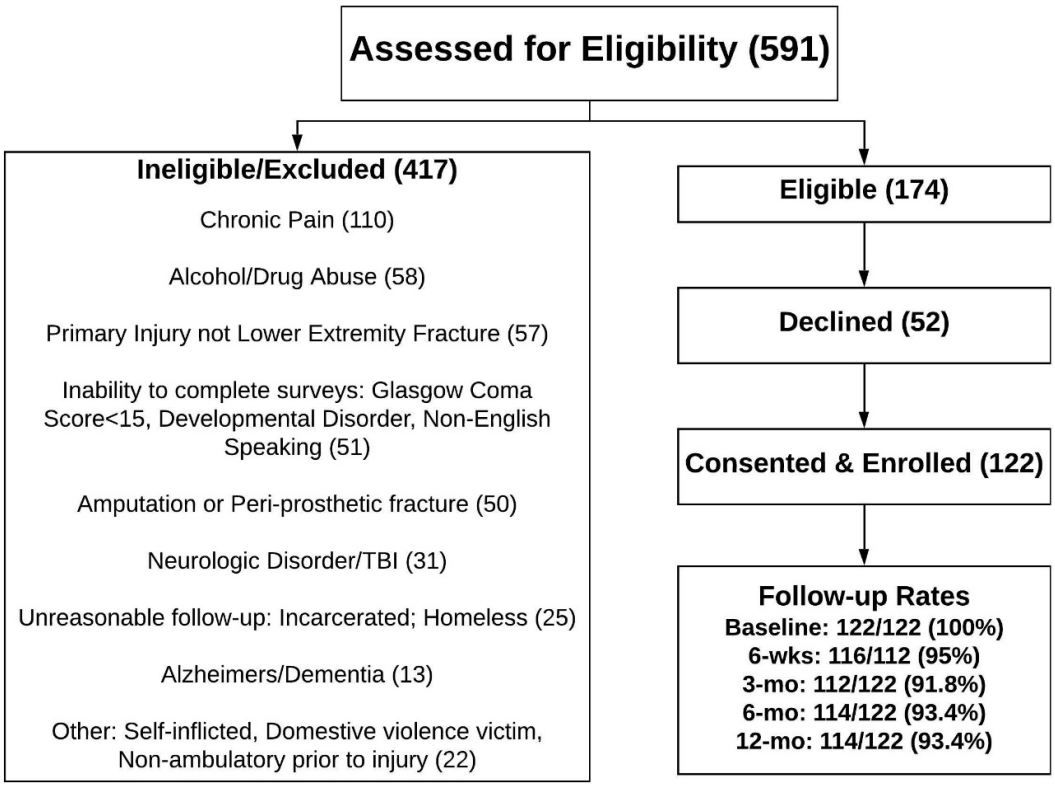
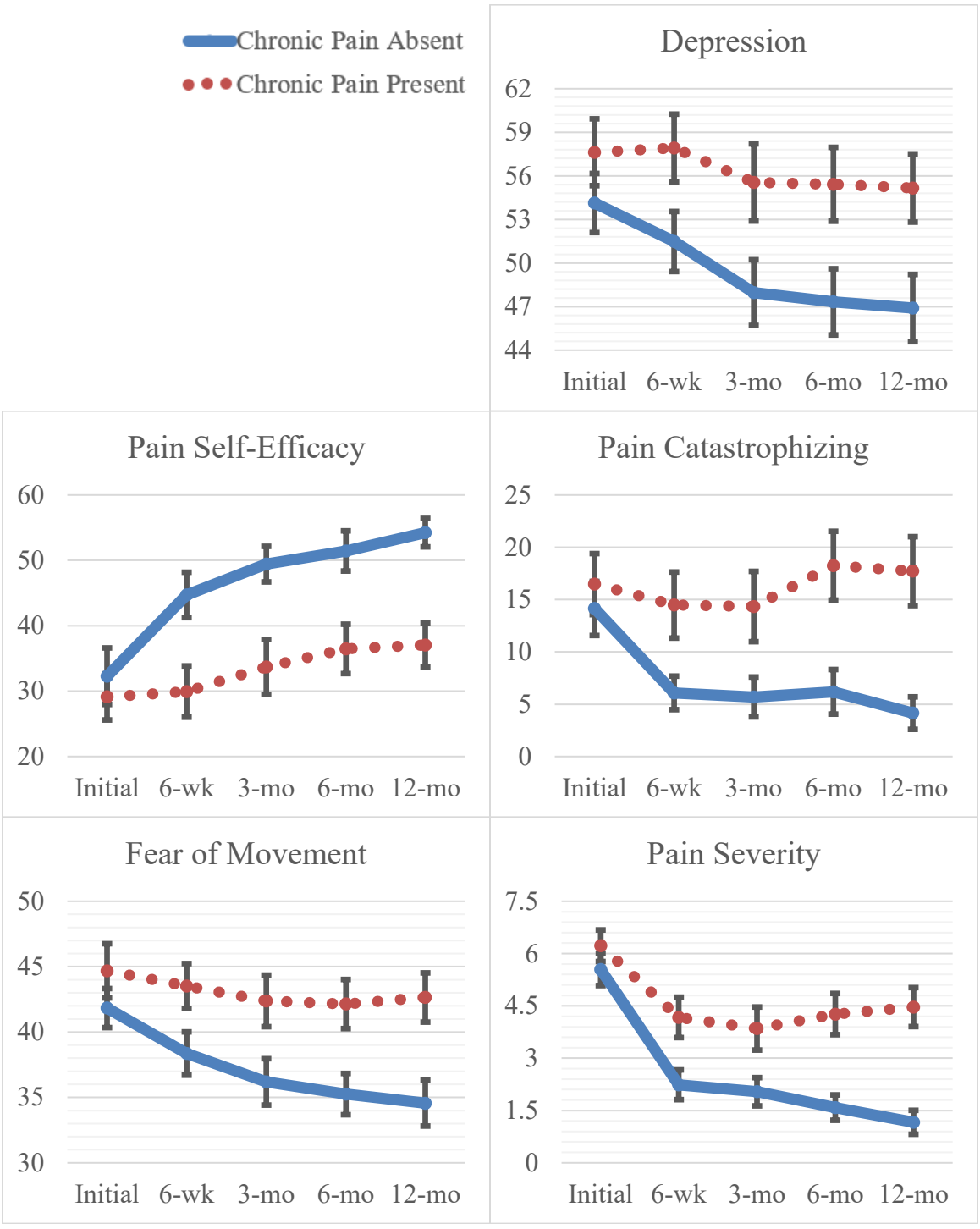


Figure 2.2 Mean psychosocial score over time between individuals with and without chronic pain. Error bars represent 95% Confidence Intervals.



CHAPTER THREE:

Self-efficacy and Pain Catastrophizing at Six Weeks are Associated with Chronic Pain and Pain-related Disability 12 Months After Lower Extremity Fracture

Abstract of Chapter Three

Background: Chronic pain and disability are common long-term outcomes after lower extremity fracture. Research to date has indicated that psychosocial factors early in recovery carry moderate to strong associations with long-term outcomes. However, much of this research has only evaluated one psychosocial factor at a time. This limits the ability to identify the most salient psychosocial variables associated with patient outcomes after a lower extremity fracture.

Objective: To determine how pain catastrophizing, pain self-efficacy, and fear of movement six weeks after definitive surgical fixation are associated with chronic pain development, pain interference, and physical function at 12 months when controlling for depression at six weeks and other important baseline variables.

Design: Single center, prospective cohort study.

Methods: 122 patients (41.7 ± 14.7 years, 93.3 ± 28.5 Kg) with a lower extremity fracture requiring surgical fixation and no history of chronic pain consented to this study. Six weeks after definitive surgical fixation, patients completed measures of pain catastrophizing, self-efficacy, fear of movement, and depression. Self-reported measures of chronic pain development, pain interference, and physical function were completed at 12 months after surgery. Multivariable hierarchical linear regression analyses determined if psychosocial variables at six weeks were associated with each outcome at 12 months when controlling for important baseline demographics.

Results: 114 patients (93.4%) completed this study. Of these patients, 51 (45%) reported chronic pain at 12 months. Self-efficacy at six weeks was the sole psychosocial variable associated with chronic pain development (odds ratio: 0.95; 95% CI: 0.91-0.99; p=0.02)

and physical function (β:0.134; p=0.048) at 12 months, while pain catastrophizing at six weeks was the sole psychosocial variable associated with pain interference (β:0.217; p=0.045) at 12 months.

Conclusion: Pain self-efficacy and pain catastrophizing at six weeks carry important associations with chronic pain and pain-related disability outcomes at 12 months after lower extremity fracture. These results indicate that screening for pain self-efficacy and pain catastrophizing in the early stages of recovery may help clinicians identify patients at heightened risk for adverse outcomes.

Self-efficacy and Pain Catastrophizing at six weeks are associated with Chronic Pain and Pain-related Disability 12 Months After Lower Extremity Fracture

Introduction

Persistent pain and disability outcomes are tremendous burdens after traumatic lower extremity fracture.[1,2] Current literature indicates that 39% to 62.7% of all patients report chronic pain long after traumatic lower extremity fracture.[3-5] Concurrent physical limitations and reduced quality of life are common,[5,6] with nearly one-third of all patients reporting pain-related disability seven years after limb threatening trauma.[5] In-fact, individuals that sustain a traumatic injury have disability levels four times greater than community norms one year after injury,[7] and are approximately 50% limited in both functional mobility and ability to complete activities of daily living at 18-month follow-up.[8] The high incidence of long-term injury-related pain and disability are alarming and require further action to detect individuals at the greatest risk for detrimental outcomes in earlier stages of recovery.

Evidence for the important association psychosocial factors carry with suboptimal long-term outcomes after traumatic injury has been growing. Pain catastrophizing, defined as an unhealthy disposition toward pain in which the individual ruminates, magnifies, and feels helpless during an actual or potential painful experience,[9,10] is consistently associated with adverse long-term pain-related outcomes after traumatic injury.[11,12] Archer et al. reported that higher pain catastrophizing in the acute stages of recovery has an important association with pain intensity and pain interference 12 months after lower extremity fracture.[13] Furthermore, pain catastrophizing two months after a motor vehicle accident was the strongest independent predictor of pain at 24-month

follow-up.[14] These data indicate that pain catastrophizing may be an important psychosocial variable to account for in predicting the development of chronic pain after lower extremity trauma. However, no research has evaluated the relationship between early levels of pain catastrophizing and the development of chronic pain in this patient population.

Self-efficacy is defined as the confidence an individual has to accomplish and succeed in a task, despite challenging or even threatening circumstances.[15] In patients with limb threatening lower extremity trauma, self-efficacy three months after injury demonstrated an important association with seven-year pain and disability outcomes.[5,16] A recent Major Extremity Trauma Research Consortium (METRC) study reported that higher self-efficacy in the early stages of recovery is protective of worse functional and health-related outcomes 12 months after major trauma.[17] Self-efficacy has been associated with diverse pain and disability outcomes in other patient populations,[18-22] and may be the most important psychosocial characteristic to consider when evaluating these outcomes after traumatic lower extremity fracture.

Fear of movement has inconsistent relationships with outcomes after lower extremity fracture. While a cross-sectional study in this patient population demonstrated that fear was associated with pain and physical health two years after injury,[23] a recent prospective study showed that acute fear is not related to these outcomes at 12-month follow-up.[13] Importantly, fear of movement has been associated with long-term physical function outcomes in patients with a variety of musculoskeletal conditions,[24-26] but no research to date has evaluated this association after traumatic injury.

Depressive symptoms in the acute stages of recovery have been widely studied and associated with worse long-term pain and disability after trauma.[2,5,27] A recent study determined that depressive symptoms mediated the relationship between acute pain severity and long-term disability in patients with traumatic lower extremity injury.[28] Archer et al. reported that depressive symptoms four weeks after surgical fixation was moderately associated with 12-month pain severity, pain interference, and physical health in patients with lower extremity fracture.[13] Finally, Jenewein et al. identified depression as one of the key factors that drive pain outcomes after traumatic injury.[29] These data indicate that depression is a crucial variable to account for when determining the influence of psychosocial variables on patient outcomes after trauma.

Despite the growing evidence to support the important role psychosocial variables carry with patient outcomes after traumatic injury, there are two important limitations that must be addressed. First, no research to date has evaluated how multiple psychosocial factors in the early stages of recovery influence long-term pain and physical function outcomes in this population. Therefore, the most relevant psychosocial characteristic associated with adverse outcomes after lower extremity fracture has yet to be determined. The second limitation is that none of the trauma studies accounted for individuals with a history of chronic pain. It is well established that patients with chronic pain have elevated psychosocial beliefs and will be much more likely to report persistent pain after a traumatic injury.[19,30,31] Excluding individuals with a history of chronic pain while accounting for multiple psychosocial factors will allow for a better understanding of the most salient variables clinicians should account for in the early stages of recovery that influence patient outcomes. This may open avenues to test alternate, targeted

interventions to higher risk patient subgroups in order to improve long-term pain and physical function outcomes.

Therefore, this study had three specific objectives in patients that sustained a lower extremity fracture requiring surgical fixation and without a history of chronic pain. The first aim was to determine whether self-efficacy, pain catastrophizing, and fear of movement at six weeks were associated with the development of chronic pain 12 months after definitive surgical fixation. The second aim was to determine whether self-efficacy and pain catastrophizing at six weeks were associated with pain interference at 12 months. The final aim was to determine whether self-efficacy and fear of movement at six weeks were associated with self-reported physical function at 12 months. We hypothesized *a priori* that self-efficacy at six weeks would be most strongly associated with each 12-month outcome when accounting for depression at six weeks and other important baseline patient characteristics.

Patients and Methods

This study was a prospective cohort study conducted in patients that sustained a lower extremity fracture requiring open reduction internal fixation to the pelvis, acetabulum, femur, tibia, patella, or foot/ankle at a Level I trauma center. Written and informed consent was obtained from all study participants after approval by the local institutional review board. Individuals with a primary injury of lower extremity fracture requiring surgical fixation, Glasgow Coma Score[32,33] of 15 upon hospital admission, and ages 18 to 70 years old met the eligibility criteria for this study. Patients with a medical diagnosis of Alzheimer's or Dementia, intracranial hemorrhage consistent with moderate to severe brain injury, current alcohol or drug abuse, treatment consisting of amputation,

self-inflicted injury, the victim of domestic violence, homeless, or incarcerated were excluded from this study. Additionally, individuals that reported current chronic pain were excluded from the study. Pain that had been present greater than three months and had been bothersome at least half the days over the last six months was used to define chronic pain.[34]

Individuals were approached for consent to the study within the first week after definitive surgical fixation between December 2017 and February 2019. Demographic questions such as smoking status, education level, race, age, body weight, and gender were completed at the time of consent. Mechanism of injury, primary injury location, and Injury Severity Score (ISS)[35] were collected from the patient's medical record. At six weeks after definitive surgical fixation each patient completed validated measures of pain catastrophizing, pain self-efficacy, fear of movement, depression, pain intensity, and pain interference. Twelve months after definitive surgical fixation, the self-reported outcomes of chronic pain development, pain interference, and physical function were collected. One researcher not involved in the patient's clinical care (J.V.) contacted individuals that did not complete the surveys within 7, 14, and 21 days via telephone to remind the patient to complete the surveys within the next 7 days. All surveys were administered via Research Electronic Data Capture (REDCap), a secure, web-based application developed by Vanderbilt University to collect data.[36]

Six-week Psychosocial Questionnaires Administered

The Pain Catastrophizing Scale (PCS) was used to measure whether individuals maintained an unhealthy disposition toward pain resulting in magnification, rumination, and helplessness. The PCS is a 13-item questionnaire with each individual question

scored on a 5-point Likert scale, and higher scores indicating worse catastrophizing (range: 0-52). Each question gauges the individual's disposition toward their pain with responses ranging from "not at all" to "all the time." The PCS has demonstrated strong internal consistency;[37,38] test-retest reliability;[37] and construct, criterion, concurrent, and discriminant validity.[38]

Pain self-efficacy is the confidence an individual has to complete a task despite their pain.[39] The Pain Self-efficacy Questionnaire (PSEQ) was used to gauge each patient's self-efficacy, which consists of 10-items each on a 7-point Likert scale.[39] Each question response ranges from 0 = "Not at all confident" to 6 = "Completely confident" with higher scores indicating better self-efficacy (range: 0-60). The PSEQ has demonstrated excellent reliability and validity for use in adult patients.[40-42]

Fear of movement was measured by the Tampa Scale of Kinesiophobia (TSK-17). This consists of 17-items on a 4-point Likert scale with responses ranging "strongly disagree" to "strongly agree". Higher scores indicate worse fear of movement (range: 17-68). The TSK-17 has demonstrated excellent reliability and validity for use in adults with pain.[30,42,43]

The Patient-Reported Outcomes Measurement Information System (PROMIS) Depression computer adaptive test was used to measure depressive symptoms.[44] A score of 50 on any PROMIS computer adaptive test is consistent with the mean score of the United States (U.S.) general population, with each 10-point deviation indicating a one standard deviation shift from the mean. Higher scores on the PROMIS Depression indicate worse depressive symptoms.[45]

The pain intensity subscale of the Brief Pain Inventory (BPI) was used to measure pain intensity.[46,47] This consists of four items: worst, least, average, and best pain over the last week. Each of these four items are measured on a 0 = "No pain" to 10 = "Worst pain you can imagine" scale, and the mean of all four measures is used to gauge overall pain intensity. The BPI is reliable and valid for use in post-surgical adults.[46,48]

12-month Outcome Measures

Consistent with recommendations from a recent National Institutes of Health (NIH) Task Force,[34] the development of chronic pain was measured in each patient with two questions: (1) "Over the last six months, how *long* has pain been an ongoing problem for you?" and (2) "Over the last six months, how *often* has pain been an ongoing problem for you?". Patients were categorized as having chronic pain with responses of greater than three months to question one and at least half the days over the last six months for question two.

The Chronic Pain Grade Scale (CPGS) was a secondary outcome used to measure the presence of chronic pain. This scale consists of seven questions that gauges an individual's overall pain intensity and pain-related disability.[49] Patient responses are subsequently used to place the individual into one of five ordinal categories: Grade 0: no pain in last six months; Grade I: low disability-low pain intensity; Grade II: low disability-high pain intensity; Grade III: high disability-moderately limiting; and Grade IV: high disability-severely limiting.[49] Scores greater than Grade II have been used to identify individuals with disabling chronic pain after traumatic lower extremity injury.[5] The CPGS is a reliable and valid tool,[49] and has been used to measure chronic pain in the general population and after lower extremity trauma.[5,49-52]

The PROMIS Pain Interference and Physical Function computer adaptive tests were administered to each patient. As in the PROMIS Depression, a score of 50 is consistent with the mean score of the U.S. general population, with higher scores on each respective questionnaire indicating worse pain interference and better physical function. The PROMIS Pain Interference is a valid means to assess the extent to which pain limits an adult's ability to engage in social, cognitive, and physical activity.[53] The PROMIS Physical Function is a valid method to determine self-reported ability to complete physical activities of daily living and aerobic activities in patients with lower extremity trauma.[54]

Statistical Analysis

Descriptive statistics (means, medians, standard deviations, frequencies) were used to summarize all demographic, psychosocial, and outcome variables. Parametric assumptions were evaluated for all continuous variables. Bivariate testing consisted of testing differences between those that did and did not complete 12-month follow-up with Independent t-tests and Fischer's exact tests. Additionally, Pearson's product-moment and point-biserial correlation analyses were used to compare PCS, PSEQ, TSK-17, and PROMIS Depression at six weeks to chronic pain development, CPGS Grade >II, PROMIS Physical Function, and PROMIS Pain Interference at 12 months.

Multivariable hierarchical logistic and linear regression analyses were used to determine the association between baseline psychosocial variables (PCS, PSEQ, TSK-17, and PROMIS Depression) and the outcome measures of chronic pain (yes/no), CPGS Grade >II, PROMIS Pain Interference, and PROMIS Physical Function. In Step 1 of each regression model, depression and other relevant baseline variables determined *a*

priori from a thorough literature review were entered. These variables included ISS, age, smoking status, depression, pain catastrophizing, fear of movement, and pain intensity at six weeks. Step 2 entered the psychosocial predictor variables of interest, and Step 3 included the outcome measure at baseline.[55] Given that PROMIS Physical Function was not measured at six weeks, PROMIS Pain Interference was used as a surrogate.[56] Additionally, given no individuals with a history of chronic pain were included in this study, pain intensity at six weeks was controlled for in each logistic regression model. Adjusted total variance for each overall model was reported. Variance inflation factors greater than 10 and Pearson correlations coefficients ≥0.7 were the criteria used to check for multicollinearity of data.[57-59] Statistical analyses were completed using IBM SPSS Statistics (Version 24). Significance level was a priori set as $p \leq 0.05$.

The minimum number of participants required for this study was 81 subjects. This estimate was based on including up to eight independent variables in each multivariable regression model with an estimated overall model variance of 0.30, individual variance of 0.10 for the psychosocial predictor variables of interest, and a power of 0.8.[60] With a conservative 30% dropout rate through terminal follow-up, a sample of 122 subjects were recruited to participate. Power analysis calculations were completed with nQuery (Version 8.4).

Results

Of the 519 patients screened, 174 (29.4%) met the inclusion criteria. One hundred twenty-two (70.1%) of these patients consented to participate and 12-month follow-up was completed by 114 (93.4%) of the study participants (Figure 2.1). There were no differences in age, sex, education, injury severity score (ISS), body weight, or

smoking status between those that did and did not complete the study. The study population was 41.7 ± 14.7 years old and the majority were males (54%). Most of the primary injuries were tibia (51%) or femur (25%) fractures. The average ISS and length of hospital stay after definitive surgical fixation were 9.1 ± 6.6 and 3.5 ± 3.4 days, respectively (Table 3.1). The incidence of chronic pain at 12 months was 45% in this study (Table 3.2), while the average pain interference and physical function at 12 months was approximately half a standard deviation worse than that of the U.S. population (Table 3.3).

Our results indicated that moderate correlation existed between each psychosocial variable at six weeks and outcomes at 12 months (range: 0.38-0.56, $p<0.001$, Table 3.4). PSEQ carried the strongest bivariate association with chronic pain development (r=-0.49), CPGS Grade >II (r=-0.56), and Physical Function (r=0.53), while PCS was most strongly associated with Pain Interference (r=0.49).

The multivariable logistic regression results indicated that pain self-efficacy was most strongly associated with chronic pain development (OR: 0.95, 95%CI: 0.91-0.99) and CPGS Grade >II (OR: 0.95, 95%CI: 0.91-0.99) when accounting for ISS, age, smoking status, depression, pain catastrophizing, fear of movement, and pain intensity at six weeks (Table 3.5). Each 10-point increase in pain self-efficacy at six weeks was associated with 50% decrease in odds of reporting chronic pain and a CPGS Grade >II at 12 months. Pain intensity at six weeks was the only other statistically significant predictor of CPGS Grade >II, but was not statistically associated with chronic pain development (Table 3.5).

We found that pain catastrophizing at six weeks was the sole psychosocial variable associated with pain interference at 12 months when accounting for age, body weight, ISS, smoking status, depression, pain self-efficacy, and pain interference at six weeks (Table 3.6). Each 10-point increase in catastrophizing was associated with a 2.17 point increase in pain interference at 12 months (β=0.217, 95%CI: 0.01 to 0.43). Body weight was the only other variable significantly associated with pain interference at 12 months (β=0.07, 95%CI: 0.01 to 0.12).

Finally, pain self-efficacy at six weeks was the sole psychosocial variable associated with physical function at 12 months when accounting for age, body weight, ISS, smoking status, depression, fear of movement, and pain interference at six weeks (Table 3.6). Each 10-point increase in self-efficacy was associated with a 1.34 point increase in physical function at 12 months (β=0.134, 95%CI: 0.01 to 0.27). Age (β= -0.12, 95%CI: -0.22 to -0.03) and body weight (β= -0.06, 95%CI: -0.11 to -0.02) were the only other variables significantly associated with physical function at 12 months (Table 3.6).

Discussion

The purpose of this study was to determine whether pain catastrophizing, pain self-efficacy, and fear of movement at six weeks were associated with the development of chronic pain, pain interference, and physical function at 12 months after accounting for depression and other important baseline variables. The results indicated that pain self-efficacy was the sole psychosocial predictor of chronic pain and physical function at 12 months, while pain catastrophizing was the sole psychosocial predictor of pain interference at 12 months. These findings indicate that screening for pain self-efficacy

and pain catastrophizing early in recovery from a lower extremity fracture may help identify individuals at greatest risk for adverse pain and disability outcomes.

In this study, approximately 45% of the subjects reported chronic pain at 12 months. Clay et al. reported a 54% incidence of persistent pain six months after traumatic injury.[61] This agrees with our results given that pain levels generally reduce as time post trauma increases.[1] Our frequency of chronic pain is slightly lower than that reported by the LEAP group at 12 months.[4] The LEAP group only included patients with limb threatening lower extremity trauma, indicating that the injury severity likely played a role in the difference between LEAP's results and our results. Additionally, our study is the first to evaluate the incidence of chronic pain by excluding patients with a history of chronic pain, which likely further contributed to the lower frequency reported in our study compared to LEAP. Regardless, the high incidence of chronic pain development in our study agrees with other research indicating that lower extremity fractures requiring surgical fixation have adverse long-term pain outcomes.[1,61]

Our findings support a large systematic review indicating the important role that self-efficacy contributes to persistent pain outcomes.[22] The results of our study build on the cross-sectional findings by Archer et al. which reported that low self-efficacy at hospital discharge is concurrently associated with worse pain intensity.[6] These data are also consistent with those of the LEAP group, which reported that early self-efficacy is associated with persistent pain.[4,5] It is important to note that the agreement between the NIH definition of chronic pain development[34] and the CPGS >II[49] multivariable results further validates our findings that pain self-efficacy carries an important association with chronic pain outcomes. While there is a large body of literature indicating the important

role acute pain intensity carries with chronic pain development,[1,2,4,5] pain intensity was not consistently associated with each chronic pain outcome in this study. Therefore, the patient's confidence to successfully recover and persevere early after injury is one of the most important factors to consider when developing a patient prognosis and treatment plan.

Contrary to our hypothesis, pain catastrophizing was the sole significant psychosocial variable associated with pain interference. These results agree with the findings of Archer et al., which reported that pain catastrophizing four weeks after lower extremity fracture was associated with 12-month pain interference.[13] Recent work has reported that pain catastrophizing 1-2 months after injury was significantly associated with pain related disability at 5-8 month follow-up.[11,62] Catastrophizing has been associated with long-term pain, worse disability, and higher health care costs in a variety of patient populations.[63] These data indicate that magnifying, ruminating, and feeling helpless in the presence of pain has important long-term implications on pain-related disability.[64] Finally, it is important to note that increased body weight carried an important association with worse pain-related disability, which agrees with other research demonstrating the important association between greater body mass and pain.[65-67]

Our results supported our hypothesis that self-efficacy would carry important associations with long-term physical function. This agrees with a systematic review with meta-analysis that indicated that self-efficacy is associated with functional limitations with moderate to large effect sizes in patients with chronic pain.[22] A subsequent systematic review determined that high self-efficacy is associated with lower disability.[63] Self-efficacy has relatively few studies to date that demonstrate the important association

it carries with long-term physical function after traumatic injury, but our results agree with the research that has been conducted to date in this population.[27,68] As expected, increasing age[69,70] and body weight[71] carried important associations with long-term physical function. Even when accounting for these baseline characteristics, self-efficacy at six weeks carried a statistically significant relationship with 12-month self-reported physical function.

Interestingly, depression was not associated with any of the outcomes in this study in the final multivariable regression models. This is contrary to a large body of research indicating the important role depressive symptoms contribute to long-term pain and disability outcomes after traumatic injury.[2,5,13,28] Our study included multiple psychosocial factors simultaneously into the regression models in order to identify the most salient variables to consider when developing a patient prognosis. Therefore, it is possible that prior research identified depression as carrying an important association with patient outcomes because other psychosocial variables were not accounted for. Another possible explanation is that our cohort is different than that of other studies given that patients with a history of chronic pain were excluded. Future studies that do not exclude individuals with a history of chronic pain would be required to determine whether depressive symptoms carry stronger associations with outcomes in patients that have concurrent chronic pain at the time of injury.

This study possessed a number of strengths. First, the follow-up rate was excellent (93.4%) which limits the confounding effect of patient dropout. Secondly, our regression models accounted for multiple baseline variables that have been previously associated with pain and disabilities outcomes. This helps with determining the variables

that are most important to consider when developing early screening platforms for higher risk patient groups. Third, no patients with a history of chronic pain were included in this study. This prevented the elevated psychosocial beliefs of patients in chronic pain from inflating the strength of association between these early beliefs and patient long-term outcomes. Excluding individuals with chronic pain also allowed us to determine the factors most strongly associated with the acute to chronic pain transition after lower extremity fracture.

This study is not without limitations. First, this study was completed at a single center which may limit the generalizability of the findings. Additionally, there were a variety of fracture types included in this study. Future studies may consider evaluating outcomes of specific bone fractures to improve the recommendations that can be offered to specific injuries. Third, the PROMIS Physical Function was not collected at baseline. The findings of this article would be improved if baseline Physical Function were collected. Finally, no studies to date have evaluated how early psychosocial characteristics are associated with objective physical performance outcomes (i.e. six-minute walk test, single-leg step-down, single-leg calf raises) after lower extremity fracture requiring surgical fixation. Future research should consider evaluating these relationships.

The results of this study have important implications on the post-surgical management of patients with lower extremity fracture requiring surgical fixation. Screening for self-efficacy early in recovery may identify the patient subgroups that are protected from and at greatest risk for adverse pain and disability outcomes. Targeting high risk subgroups early in recovery with graded exposure and cognitive behavioral

strategies to improve patient confidence may help improve long-term outcomes. This could be followed with more intensive, skilled physical therapy intervention to further improve confidence and function. However, additional research is needed before these strategies can be recommended for clinical practice.

Conclusion

We have prospectively determined that pain self-efficacy at six weeks is most strongly associated with chronic pain development and physical function at 12 months while pain catastrophizing at six weeks is associated with pain interference at 12 months. This is the first study to evaluate the most salient psychosocial factor associated with outcomes of patients with lower extremity trauma without a history of chronic pain. These results indicate that screening for pain self-efficacy and pain catastrophizing in the early stages of recovery may help clinicians identify patients at heightened risk of chronic pain and pain-related disability outcomes.

Table 3.1 Characteristics of study population 6 weeks after definitive surgical fixation for lower extremity fracture (N=122).*

Injury Characteristics	Mean ± SD or N (%)
Age	41.7 ± 14.7
Body Weight (Kg)	93.3 ± 28.5
Height (cm)	172.9 ± 10.7
Gender	
Female	56 (46)
Male	66 (54)
Race	
White	110 (90)
Nonwhite	12 (10)
Education	
High School or less	50 (41)
Greater than High School	72 (59)
Current Smoker	33 (27)
Mechanism of Injury	
Motor Vehicle Accident	46 (38)
Motorcycle Accident	13 (11)
Pedestrian/cyclist hit by vehicle	9 (7)
Fall	36 (29)
Blunt Trauma	13 (11)
Other	5 (4)
Primary Injury Location	
Pelvis/Acetabulum	21 (17)
Femur	30 (25)
Tibia	63 (51)
Patella	2 (2)
Ankle/Foot	6 (5)
Articular Injury	
Yes	55 (45)
No	67 (55)
Injury Severity Score	9.1 ± 6.6
Length of Hospital Stay	3.5 ± 3.4

Table 3.2 Frequency of individuals that report chronic pain at 12 months (N=114).

12-month Outcome	Frequency (%)
Chronic Pain	
Yes	51 (45%)
No	63 (55%)
Chronic Pain Grade Scale	
No pain in last 6-mo	17 (15%)
Grade I	44 (38.6%)
Grade II	4 (3.5%)
Grade III	12 (10.5%)
Grade IV	37 (32.5%)

Table 3.3 Descriptive statistics of psychosocial variables at 6 weeks and continuous outcomes at 12 months.

	Mean ± SD	Median	Range
Psychosocial at 6 weeks			
Depression	54.3 ± 9.2	55.0	34 to 71
Pain Catastrophizing	9.5 ± 9.8	7.0	0 to 44
Pain Self-Efficacy	38.2 ± 15.9	38.5	4 to 60
Fear of Movement	40.7 ± 6.7	40.5	24 to 63
Outcomes at 12 months			
Pain Interference	55.0 ± 9.7	56.0	39 to 75
Physical Function	44.1 ± 9.1	43.5	25 to 73

Table 3.4 Correlation between psychosocial variables measured at six weeks and chronic pain (yes/no), CPGS >II,[†] Pain Interference, and Physical Function at 12 months.*

	Chronic Pain	CPGS	Pain Interference	Physical Function
Pain Catastrophizing	0.43	0.42	0.49	-0.46
Pain Self-Efficacy	-0.49	-0.56	-0.48	0.53
Fear of Movement	0.38	0.44	0.46	-0.47
Depression	0.40	0.39	0.44	-0.44

[†]CPGS >II: Chronic Pain Grade Scale dichotomized (Grade >II).

*All correlations significant at $p<0.001$.

Table 3.5 Multivariable logistic regression with psychosocial variables at six weeks predicting chronic pain at 12 months.*

	Chronic Pain		CPGS†	
Baseline Predictor Variables	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Injury Severity Score	0.97 (0.89-1.06)	0.51	0.996 (0.92-1.08)	0.93
Age	0.97 (0.94-1.00)	0.06	0.97 (0.94-1.01)	0.12
Smoking Status	1.08 (0.36-3.29)	0.89	1.36 (0.47-3.96)	0.57
Depression	1.07 (1.0-1.14)	0.06	1.03 (0.97-1.10)	0.37
Pain Catastrophizing	1.01 (0.93-1.10)	0.82	0.94 (0.87-1.02)	0.16
Pain Self-Efficacy	0.95 (0.91-0.99)	0.02	0.95 (0.91-0.99)	0.018
Fear of Movement	1.02 (0.92-1.13)	0.77	1.04 (0.94-1.15)	0.43
Pain Intensity	1.28 (0.91-1.81)	0.15	1.59 (1.12-2.27)	0.01

*Nagelkerke R^2 for each model. Chronic Pain Development: R^2=0.44; CPGS: R^2=0.40.

†CPGS: Chronic Pain Grade Scale dichotomized (Grade >II)

Table 3.6 Multivariable linear regression with psychosocial variables at six weeks predicting pain interference and physical function at 12 months.*

12-mo Outcome Variables	Baseline Predictor Variables	Final β Coefficient (95%CI)	p-value
Pain Interference	Age	-0.038 (-0.14 to 0.07)	0.470
	Body Weight	0.068 (0.14 to 0.12)	0.014
	Injury Severity Score	0.079 (-0.16 to 0.32)	0.511
	Smoking Status	0.464 (-3.16 to 4.08)	0.800
	Depression	0.155 (-0.07 to 0.38)	0.166
	Pain Self-Efficacy	-0.072 (-0.22 to 0.08)	0.336
	Pain Catastrophizing	0.217 (0.01 to 0.43)	0.045
	Outcome at Baseline	0.296 (-0.01 to 0.60)	0.058
Physical Function	Age	-0.122 (-0.22 to -0.03)	0.011
	Body Weight	-0.064 (-0.11 to -0.02)	0.008
	Injury Severity Score	-0.182 (-0.39 to 0.03)	0.088
	Smoking Status	0.469 (-2.72 to 3.66)	0.771
	Depression	-0.156 (-0.35 to 0.04)	0.109
	Pain Self-Efficacy	0.134 (0.01 to 0.27)	0.048
	Fear of Movement	-0.208 (-0.48 to 0.06)	0.130
	Outcome at Baseline	-0.184 (-0.46 to 0.09)	0.180

*Final Adjusted R^2 for each model. Pain Interference: R^2=0.35; Physical Function: R^2=0.41.

CHAPTER FOUR:

STarT-Lower Extremity Screening Tool

Part I: Reliability and Concurrent Validity of the STarT-Lower Extremity Screening Tool for Patients with Lower Extremity Fracture: A Cross-Sectional Study

Abstract of Chapter Four Part I

Objectives: Given that nearly half of all patients that sustain a lower extremity fracture requiring surgical fixation develop chronic pain and disability, the objective of this study was to determine whether a modified version of the STarT Back Screening Tool produces reliable and valid scores in this patient population.

Design: Single center, cross-sectional study.

Setting: Level I Trauma Center.

Participants: Patients with lower extremity fracture without a history of chronic pain (N=116).

Interventions: N/A

Main Outcomes: Six weeks after surgical fixation, consenting subjects completed the STarT-Lower Extremity Screening Tool (STarT-LE) and the following validated questionnaires: Pain Catastrophizing Scale, Pain Self-efficacy Questionnaire, Tampa Scale of Kinesiophobia, Brief Pain Inventory pain intensity subscale, and PROMIS Depression and Pain Interference computer adaptive testing modules. A sub-sample completed the STarT-LE again one week later. Reliability was evaluated with intraclass correlation coefficients (ICCs) and Cronbach's alpha (α). Floor and ceiling effects were analyzed by summing the total number of responses that achieved the minimum and maximum STarT-LE score. Convergent validity was determined by Spearman's rho correlation. Criterion validity was evaluated by area under the curve analysis (AUC) and discriminant validity was evaluated by one-way analysis of variance.

Results: The results of this study indicate that the STarT-LE has good test-retest reliability (total: ICC=0.85, 95% CI: 0.78-0.91; psychosocial subscale: ICC=0.79, 95% CI: 0.68–0.87) and acceptable internal consistency (α=0.74). Additionally, the STarT-LE does not demonstrate floor/ceiling effects (<15%), moderate to strong convergent validity (r=0.48-0.75, p<0.001), acceptable to excellent criterion validity (AUC=0.75-0.89), and excellent discriminant validity.

Conclusions: The STarT-LE produces reliable and valid scores for patients with lower extremity fracture requiring surgical fixation. Individuals screened into the high-risk category had worse pain and psychosocial reports than those in lower risk categories at six weeks post definitive surgical fixation. Future investigations should determine the tool's predictive validity.

Abbreviations: BPI (Brief Pain Inventory Pain Severity Scale); PCS (Pain Catastrophizing Scale); PSEQ (Pain Self-Efficacy Questionnaire); STarT-LE Screening Tool (Subgroups for Targeted Treatment of Lower Extremity injury Screening Tool); TSK-17 (Tampa Scale of Kinesiophobia-17 item)

KEYWORDS: Screening; STarT; risk factors; psychosocial; lower extremity; fracture; pain

STarT-Lower Extremity Screening Tool

Part I: Reliability and Concurrent Validity of the STarT-Lower Extremity Screening Tool for Patients with Lower Extremity Fracture: A Cross-Sectional Study

Introduction

Approximately 700,000 individuals sustain a lower extremity fracture requiring surgical fixation in the United States each year.[1] It is not surprising that many of these patients have significant and disabling pain in the early stages of recovery;[2-4] however, persistent pain, symptoms, and/or functional limitations six to 18 months after trauma are not uncommon.[3,5,6] Long-term results are also alarming as 39% of patients who sustain severe lower extremity trauma report persistent pain and one-third report moderate to severe pain interference seven years after injury.[7]

Despite these poor outcomes, no screening tools have been validated to assess patient risk for these adverse outcomes after trauma. There is considerable research demonstrating how psychosocial factors such as anxiety, depression, pain catastrophizing, and fear of movement are independently associated with pain and disability after trauma.[7-10] However, administering multiple full-length psychosocial questionnaires is not practical nor is it easy to synthesize into clinical practice. Therefore, a need remains to develop a simple, multidimensional screening tool that can assess risk for long-term pain and disability after traumatic injury.

The Keele Subgroups for Targeted Treatment (STarT) Back Screening Tool is a 9-item prognostic screening tool developed for patients with low back pain;[11] however, the tool is easily modified and may prove useful in the trauma population for risk stratification. The STarT is comprised of four physical questions (referred leg pain,

comorbid pain, and two disability questions) and five psychosocial questions (pain bothersomeness, pain catastrophizing, fear of movement, anxiety, and depression). Each question is dichotomized, and the sum of all nine questions yields the STarT total score (range: 0-9) while the sum of the five psychosocial questions yields the psychosocial subscale score (range: 0-5). Those individuals with a total score ≤3 are categorized as low risk, a total score ≥4 and a psychosocial subscale score ≤3 are medium risk, and a score ≥4 on the psychosocial subscale are categorized as high risk.[11]

A modified version of the STarT Screening Tool for use in patients with lower extremity (LE) fractures requiring surgical fixation (STarT-LE) has the potential to inform clinical decision making through risk stratification and targeted treatment strategies in order to improve long-term outcomes. Therefore, the purpose of this study is to determine whether the STarT-LE produces scores that are reliable and valid in patients who sustain a lower extremity (LE) fracture requiring surgical fixation (STarT-LE). We hypothesized that the STarT-LE Screening Tool would demonstrate: (1) good test-retest reliability (Intraclass Correlation Coefficient ≥0.75), (2) adequate internal consistency (Cronbach's alpha >0.7), (3) no floor/ceiling effects (minimum and maximum score achieved in <15% of total responses), (4) moderate to strong convergent validity (spearman rho >0.4), (5) acceptable criterion validity (Area Under the Curve (AUC) >0.7), and excellent discriminant validity.

Patients and Methods

This study was a cross-sectional study conducted in 116 patients admitted to a Level I trauma center for surgical fixation of a lower extremity fracture between December 2017 and February 2019. Inclusion criteria included: (1) 18 to 70 years of age;

(2) primary injury annotated as a lower extremity fracture to the pelvis, femur, tibia, patella, or foot/ankle requiring open reduction internal fixation; (3) Glasgow Coma Score of 15 on hospital admission;[12,13] and (4) no fracture above the pelvis requiring immediate surgical fixation. Patients with self-inflicted injury, a history of schizophrenia or other psychotic disorder, intracranial hemorrhage consistent with moderate to severe brain injury, amputation, peri-prosthetic fracture, current alcohol or drug abuse, or those incarcerated or homeless were excluded. In addition, patients with a past history of chronic pain were not included in the study. Chronic pain was defined as pain present greater than 3 months and bothersome at least half the days over the last 6 months.[14]

Written informed consent was obtained from all study participants after approval by the local institutional review board. Eligible participants were approached in the hospital after definitive surgical fixation. Six weeks after definitive surgical fixation patients completed demographic questions, the STarT-LE Screening Tool, and validated measures of pain catastrophizing, pain self-efficacy, fear of movement, pain severity, depression, and pain interference. Mechanism of injury, primary injury location, and Injury Severity Score (ISS)[15] were extracted from the medical record. A convenience sample of 80 subjects were approached to complete the STarT-LE Screening Tool again one week later to establish the test-retest reliability.

Modifications for the STarT-LE Screening Tool were completed in a manner that ensured each question was applicable to patients with lower extremity fracture while keeping consistent with the original intent of each question. The first two question-items required the most substantial modifications, with question one asking whether the patient has experienced neurogenic symptoms in the leg and question two whether the pain has

spread to another body location other than the leg over the last two weeks (Figure 4.1). Questions 3, 4, 7, and 9 required minimal modification in which the words "back pain" on the original STarT tool were changed to "leg pain". Questions 5, 6, and 8 did not require modification.

Validated Questionnaires Administered Six Weeks Post-surgery

The Pain Catastrophizing Scale (PCS) assessed pain catastrophizing, which is a tendency to magnify, perpetually dwell on, and feel helpless in the presence of a pain experience.[16] The PCS consists of 13 questions with each question on a 5-point Likert scale and higher scores indicating worse catastrophizing (range: 0-52). A score greater than or equal to 20 differentiates between catastrophizers and noncatastrophizers.[11,17] The PCS has demonstrated strong internal consistency;[18,19] test-retest reliability;[18] and construct, criterion, concurrent, and discriminant validity.[19]

The Pain Self-Efficacy Questionnaire (PSEQ) was used to gauge the individual's confidence and beliefs regarding their ability to participate in social activity and accomplish their goals despite the presence of pain.[20] This questionnaire consists of 10-items, each scored on a 7-point Likert scale, with greater scores indicating better pain self-efficacy (range: 0-60). A score less than or equal to 40 differentiates individuals with low and high pain self-efficacy.[17,21] The PSEQ has demonstrated excellent internal consistency,[21-23] test-retest reliability,[22,24] and construct validity.[23]

The 17-item Tampa Scale of Kinesiophobia (TSK-17) was used to measure fear of movement. Each question is scored on a 4-point Likert scale, with greater scores indicating higher fear (range: 17-68).[25-27] Scores greater than or equal to 41 differentiate individuals with low and high fear of movement.[11,17] The TSK-17 possesses adequate

internal consistency,[21,28,29] excellent test-retest reliability,[30] and good construct validity.[28,29]

Pain Severity was assessed with the first 4-items of the Brief Pain Inventory (BPI): worst and least pain in the last 24 hours, average pain, and current pain. The mean of these four items is used to determine pain severity. Individuals that score greater than or equal to 5 indicates moderate to severe pain intensity.[31-33] The BPI has been found produce reliable and valid scores in post-surgical patients.[34,35]

The Patient-Reported Outcomes Measurement Information System (PROMIS) computer adaptive tests (CAT) were used to assess depression and pain interference. The PROMIS Depression is a validated method to measure depressive symptoms in adults[36] while the PROMIS Pain Interference produces reliable and valid scores to assess the extent to which pain prevents social, cognitive, emotional, and physical engagement in adults.[37] A score of 50 reflects the mean of the U.S. general population with each 10-point deviation from 50 indicating one standard deviation from the mean. Higher scores indicate worse depression and pain interference.[38]

While there are no established methods to conduct a power analysis to determine sample size in establishing the concurrent validity of a screening tool, a general rule is to have at least 100 subjects.[39,40]

Statistical Analysis

Demographic information, prevalence of each risk profile, and psychosocial characteristics were summarized with descriptive statistics (frequency, percentages, means, and standard deviations). Test-retest reliability of the STarT-LE Screening Tool total and 5-item psychosocial subscale scores (1 week apart) were assessed with

Intraclass Correlation Coefficients (ICC 3,1). Internal consistency of the STarT-LE Screening Tool total and psychosocial subscale scores were evaluated with Cronbach's alpha (α). Good test-retest reliability was defined as ICC≥0.75[41] and acceptable internal consistency was defined as α>0.70.[42] Floor and ceiling effects of the STarT-LE Screening Tool total score were also tested. Floor and ceiling effects are present when more than 15% of the patients score the lowest or highest possible score on a questionnaire.[43]

The validity of the STarT-LE Screening Tool was assessed via convergent, criterion, and discriminant validity. Convergent validity was evaluated with Spearman's rho correlation of the STarT-LE Screening Tool total and psychosocial subscale scores with the PCS, PSEQ, TSK, BPI, and PROMIS Depression and Pain Interference. Moderate and strong correlations were defined as r=0.40-0.59 and r=0.60-0.79, respectively.[44] Criterion validity was evaluated using receiver operating characteristics (ROC) curves and area under the curve (AUC) analysis. STarT-LE Screening Tool total and psychosocial subscale scores were compared to established physical (BPI ≥ 5[31-33] and PROMIS Pain Interference ≥ 1 SD above the mean[38]) and psychosocial (PCS ≥ 20,[11,17] PSEQ ≤ 40,[17,21] TSK ≥ 41,[11,17] and PROMIS Depression ≥ 1 SD above the mean[38]) reference standards. Sensitivity and specificity were subsequently calculated by comparing the low risk group relative to the medium/high risk groups and the high risk group relative to the low/medium risk group against these established reference standards. Strength of criterion validity was classified as 0.7 to 0.79 indicating acceptable criterion validity, 0.8 to 0.89 indicating excellent criterion validity, and ≥0.9 indicating outstanding criterion validity.[45] Discriminant validity was evaluated with a

one-way analysis of variance (ANOVA) and chi-square testing using STarT-LE Screening Tool risk category (low, medium, or high) as the independent variable and demographic, psychosocial, or pain characteristics as the dependent variables. Excellent discriminant validity was defined as no overlap in 95% confidence intervals for continuous outcomes or $p<0.05$ for dichotomous outcomes across STarT-LE Screening Tool risk categories.

Results

There were 591 subjects assessed for eligibility, of which only 174 met inclusion criteria. Of the 174 eligible patients, 122 consented to participate after surgical fixation and 116 patients completed the study (Figure 2.1). Of the 116 subjects, 35 (29%) were categorized as low risk, 61 (50%) as medium risk, and 20 (16%) as high risk 6 weeks after definitive surgical fixation for lower extremity fracture (Table 4.1). The mean age of the patients involved in this study was 42.1 years (SD: 14.6), and there were more males than females who participated (55% males, 45% females).

Reliability

A total of 67 subjects out of 80 (83.8%) completed the re-test of the STarT-LE Screening Tool at 7 weeks after surgical fixation. There were no differences in age, body mass index (BMI), gender, education; smoking status; Injury Severity Score (ISS); STarT-LE Screening Tool total score, psychosocial subscale score, and risk category; PCS; PSEQ; TSK; BPI; PROMIS Depression; and PROMIS Pain Interference between those who completed the re-test (N=67) and those that did not (N=49) ($p>0.05$). The STarT-LE Screening Tool total and psychosocial subscale scores demonstrated good test-retest reliability (total: ICC=0.85, 95% CI: 0.78-0.91; psychosocial: ICC=0.79, 95% CI:

0.68–0.87). The internal consistency of the STarT-LE Screening Tool total score was acceptable (α=0.74), while the psychosocial subscale Cronbach's alpha was slightly below acceptable criteria (α=0.62).

Validity

Of the 116 subjects, four patients (3.4%) reported a STarT-LE Screening Tool total score of zero, and 4 patients (3.4%) reported a STarT-LE Screening Tool total score of nine. This indicates that no floor or ceiling effects exist with the STarT-LE Screening Tool.

Correlation analyses demonstrated that both the STarT-LE Screening Tool total and psychosocial subscale had strong convergent validity with the PCS, PSEQ, and PROMIS Pain Interference and moderate convergent validity with the BPI and PROMIS Depression. The TSK demonstrated moderate convergent validity with the STarT-LE Screening Tool total score and strong convergent validity with the psychosocial subscale score. Correlation coefficients ranged from r=0.48 (BPI) to r=0.75 (PCS), with each correlation significant at $p<0.01$ (Table 4.2).

The criterion validity of the STarT-LE Screening Tool ranged from acceptable for depression (AUC=0.75) to excellent for self-efficacy (AUC=0.89) (Table 4.3). Importantly, STarT-LE Screening Tool total scores best categorized the physical standards of pain interference (AUC=0.88) and pain intensity (AUC=0.85) while the psychosocial subscale best categorized the psychosocial reference standards of pain catastrophizing (AUC=0.88) and fear of movement (AUC=0.78). Evaluating the STarT-LE by risk category demonstrated that the low risk group had high sensitivity (sensitivity

range: 82.9%-100%) and the high risk group had high specificity (specificity range: 87.8%-98.2%) for each reference standard (Table 4.4).

Chi square and ANOVA analyses were used to assess discriminant validity and found that demographic characteristics demonstrated poor discrimination, while psychosocial and pain characteristics demonstrated excellent discrimination by STarT-LE Screening Tool risk category (Table 4.5). The low risk group had a lower age when compared to the medium risk group but not the high risk group. The high risk group had a significantly higher percentage of smokers compared to the low and medium risk groups. There were no differences in BMI, sex, education, or ISS between risk categories ($p > 0.05$). Worse pain catastrophizing, pain self-efficacy, fear of movement, pain intensity, depression, and pain interference were noted with each increase in STarT-LE Screening Tool risk category (Table 4.5).

Discussion

The purpose of this study was to determine whether the STarT-LE Screening Tool produces reliable and valid scores in patients following surgical fixation of lower extremity fractures. The results indicate that the STarT-LE Screening Tool has good test-retest reliability, acceptable internal consistency, no floor or ceiling effects, moderate to strong convergent validity, and acceptable to excellent criterion and discriminant validity. These findings provide evidence that the STarT-LE Screening Tool has adequate properties for use in patients with lower extremity fracture requiring surgical fixation.

Results support our *a priori* hypothesis that the STarT-LE Screening Tool would possess good test-retest reliability (STarT-LE Screening Tool total ICC=0.85, psychosocial subscale ICC=0.79) and adequate internal consistency (total score α=0.74,

psychosocial subscale α=0.62). Our test-retest reliability results are consistent with prior work establishing the test-retest reliability of the STarT tool in patients with low back and neck pain.[11,46] It is generally accepted that internal consistency should be between α=0.8-0.9, but statisticians agree that diverse, multidimensional assessment tools are still useful with Cronbach's alpha as low as 0.6.[42] The lower internal consistency for the STarT-LE psychosocial subscale may be explained by its multidimensionality since the subscale measures five different constructs simultaneously. Our internal consistency was slightly lower than that of Hill's original validation of the STarT tool.[11] This may be partially explained by the fact that the original validation of the STarT Screening Tool included patients with a history of chronic pain, while our sample consists of patients with acute pain and a diverse group of injuries involving the lower extremity.

The convergent validity of this study was moderate (BPI, TSK-17, PROMIS Depression) to strong (PCS, PSEQ, TSK-17, PROMIS Pain Interference) which supported our *a priori* hypotheses. These results agree with those of Butera et al., in which a modified version of the STarT tool demonstrated convergent validity ranging from moderate to strong correlation with pain intensity, disability, PCS, depression, and PSEQ scores in patients with neck, shoulder, and knee pain.[47] Additionally, although self-efficacy is not directly measured by the STarT-LE Screening Tool, the strong negative association suggests that the tool may indirectly measure positive coping strategies. However, additional studies are needed to follow-up on this interesting finding.

The criterion validity of our AUC analysis ranged from acceptable to excellent which is consistent with our hypothesis and Hill's original validation of the STarT in

patients with low back pain.[11] Our results indicate that the STarT-LE Screening Tool total score best distinguished the physical standards of pain interference and pain intensity, while catastrophizing and fear of movement are best distinguished by the psychosocial subscale. This indicates that the STarT-LE Screening Tool total and psychosocial subscale scores are accurately measuring what they are intended to measure. Interestingly, the STarT-LE Screening Tool total score distinguished pain self-efficacy better than the psychosocial subscale score. These results are consistent with prior studies reporting self-efficacy's strong association with physical function after traumatic injury.[48,49] Finally, the high sensitivity of the low risk group and specificity of the high risk group for each reference standard were excellent. Our results are higher than those highlighted in Hills original validation.[11]

The STarT-LE Screening Tool risk category strongly discriminated psychosocial and pain characteristics, which is indicated by distinct separation of 95% Confidence Intervals between risk categories for each measure. This suggests that the STarT-LE Screening Tool accurately reflects multiple full-length psychosocial and pain questionnaires simultaneously. The lack of demographic differences between the STarT risk groups was consistent with previous studies. Smoking status has been identified as a consistent risk factor for adverse long-term outcomes in the lower extremity trauma population,[7,50,51] so it was not surprising that the high risk group had a higher frequency of current smokers than the low and moderate risk group. Similar to our results, prior literature supports inconsistent relationships between age,[3,52] BMI,[6,53] ISS,[6,54] and sex[3,52] and risk for adverse long-term outcomes in patient with traumatic injury.

Study Limitations

This study is not without limitations. The cross-sectional nature of this study does not provide any evidence that the STarT-LE Screening Tool is useful in predicting long-term outcomes. Therefore, the STarT-LE Screening Tool is not valid for use in clinical practice until future studies determine the predictive validity in patients with lower extremity fracture. Second, our study population did not include patients with a past history of chronic pain, moderate to severe TBI, limb salvage, amputation, or a current history of drug use. This may limit the generalizability of the findings to these patient populations. Finally, this study was conducted at a single center which may further limit the generalizability of our findings.

Conclusion

In conclusion, the STarT-LE Screening Tool risk categories appear to accurately reflect multiple physical and psychosocial domains simultaneously in patients six weeks after lower extremity fracture requiring surgical fixation. Future longitudinal risk stratification studies are needed to determine whether the STarT-LE Screening Tool is able to identify patients at-risk for long-term pain and disability after lower extremity fracture requiring surgical fixation.

Table 4.1 Characteristics of study population 6 weeks after definitive surgical fixation for lower extremity fracture.*

Age	42.1 ± 14.6
Body Mass Index (BMI)	31.5 ± 9.5
Gender	
Female	52 (45)
Male	64 (55)
Education	
High School or less	46 (40)
Greater than High School	69 (60)
Current Smoker	30 (26)
Mechanism of Injury	
Motor Vehicle Accident	43 (37)
Motorcycle Accident	13 (11)
Pedestrian/cyclist hit by vehicle	9 (8)
Fall	34 (30)
Blunt Trauma	13 (11)
Other	4 (3)
Primary Injury Location	
Pelvis/Acetabulum	20 (18)
Femur	28 (24)
Tibia	60 (51)
Patella	2 (2)
Ankle/Foot	6 (5)
Articular Injury	
Yes	52 (45)
No	64 (55)
Injury Severity Score	9.1 ± 6.6
mSBT Risk Category	
Low Risk	35 (30)
Moderate Risk	61 (53)
High Risk	20 (17)
Pain Catastrophizing Scale (PCS)	9.4 ± 9.8
Pain Self-Efficacy Questionnaire (PSEQ)	38.2 ± 15.8
Tampa Scale of Kinesiophobia (TSK)	40.6 ± 6.7
Brief Pain Inventory Pain Severity subscale (BPI)	3.0 ± 2.1
Depression (PROMIS)	54.2 ± 9.1
Pain Interference (PROMIS)	59.1 ± 7.7

Higher PCS (range: 0-52), TSK (range: 17-68), BPI (range: 0-10), Depression (range: 20-80), and Pain Interference (range: 20-80) indicate worse levels of each respective construct. Higher PSEQ (range: 0-60) indicates better self-efficacy.

*Values are listed as either frequency (percentage) or mean ± SD.

Table 4.2 Convergent Validity: Spearman rho correlation between STarT-LE total and psychosocial subscale score and reference questionnaires.*

	PCS	PSEQ	TSK	BPI	Depression	Pain Interference
STarT-LE Total	0.75	-0.68	0.59	0.59	0.55	0.67
Psychosocial Subscale	0.68	-0.66	0.60	0.48	0.53	0.61

*Values reported are correlation coefficients (r). All correlations are significant at $p<0.01$ level (2-tailed). See Table 1 for abbreviation definitions.

Table 4.3 Criterion validity area under the receiver operating characteristics curve comparing STarT-LE Screening Tool total and psychosocial subscale scores against established reference case standards 6 weeks after definitive surgical fixation.*

Reference Standards	STarT-LE Total score AUC (95% CI)	STarT-LE Psychosocial subscale score AUC (95% CI)
Pain Interference (1SD above mean)	0.88 (0.82-0.94)	0.85 (0.79-0.92)
Pain Intensity (BPI ≥ 5)	0.87 (0.79-0.94)	0.81 (0.71-0.90)
Self-Efficacy (PSEQ ≤ 40)	0.89 (0.83-0.95)	0.85 (0.78-0.92)
Catastrophizing (PCS ≥ 20)	0.87 (0.80-0.95)	0.88 (0.80-0.96)
Fear (TSK ≥ 41)	0.77 (0.69-0.86)	0.78 (0.70-0.87)
Depression (1 SD above mean)	0.75 (0.66-0.84)	0.75 (0.66-0.84)

*95% CI = 95% Confidence Interval, SD=Standard Deviation, AUC=Area Under the Curve.

Table 4.4 Sensitivity and Specificity of the STarT-LE Screening Tool Risk categories against established reference case standards 6 weeks after definitive surgical fixation.*

Reference Standard	STarT-LE Risk Cutoff	Sensitivity: % (95% CI)	Specificity: % (95% CI)
Pain Interference (1SD above mean)	L v M/H	97.14 (85.1-99.9)	64.2 (52.8-74.6)
	H v M/L	35.9 (23.1-50.2)	98.4 (91.5-99.9)
Pain Intensity (BPI ≥ 5)	L v M/H	100 (90.0-100.0)	28.4 (18.9-39.5)
	H v M/L	47.8 (26.8-69.4)	90.3 (82.4-95.5)
Self-Efficacy (PSEQ ≤ 40)	L v M/H	94.3 (80.8-99.3)	74.1 (63.1-83.2)
	H v M/L	30.7 (19.6-43.7)	98.2 (90.1-99.9)
Catastrophizing (PCS ≥ 20)	L v M/H	100 (90.0-100.0)	19.8 (11.7-30.1)
	H v M/L	68.8 (41.3-89.0)	91.0 (83.6-95.8)
Fear (TSK ≥ 41)	L v M/H	82.9 (66.4-93.4)	64.2 (52.8-74.6)
	H v M/L	25.9 (15.3-39.0)	91.4 (81.0-97.1)
Depression (1 SD above mean)	L v M/H	91.4 (76.4-98.2)	38.3 (27.7-49.7)
	H v M/L	29.4 (15.1-47.5)	87.8 (78.7-94.0)

*95% CI = 95% Confidence Interval, SD=Standard Deviation, L=Low Risk, M=Medium Risk, H=High Risk.

Table 4.5 Discriminant Validity of STarT-LE Risk Categories. One-way Analysis of Variance was used to assess differences in continuous variables and chi-square testing was used to assess dichotomous variables by risk category.

	Low Risk Group	Medium Risk Group	High Risk Group
N	35 (30%)	61 (53%)	20 (17%)
Age†	36.80 ± 15.87 (31.35-42.25) †	45.18 ± 13.70 (41.67-48.69)	42.20 ± 12.83 (36.19-48.21)
BMI	29.75 ± 9.01 (26.65-32.85)	32.96 ± 9.18 (30.61-35.31)	30.39 ± 11.04 29.80-33.30
Female	15 (42.9%)	27 (44.26%)	10 (50%)
≤ HS Education	15 (42.86%)	23 (37.7%)	8 (40%)
Current Smoker†	6 (17.1%)	14 (23.0%)	10 (50%) †
ISS	10.66 ± 8.63 (7.69-13.62)	8.51 ±5.31 (7.15-9.87)	7.90 ± 5.54 (5.31-10.49)
PCS*	2.5 ± 3.5 (1.3-3.7)	9.3 ± 7.1 (7.5-11.1)	22.2 ± 11.8 (16.7-27.7)
PSEQ*	52.1 ± 8.2 (49.3-54.9)	35.0 ± 14.3 (31.4-38.7)	23.4 ± 11.8 (17.9-28.9)
TSK*	35.3 ± 5.3 (33.5-37.2)	41.7 ± 4.9 (40.4-43.0)	46.7 ± 7.2 (43.3-50.1)
BPI*	1.6 ± 1.3 (1.1-2.0)	3.3 ± 1.9 (2.8-3.8)	4.9 ± 1.9 (4.0-5.8)
Depression†	47.0 ± 8.9 (44.0-50.1) †	56.2 ± 6.9 (54.4-58.0) †	60.5 ± 7.4 (57.1-64.0)
Pain Interference*	52.8 ± 5.8 (50.8-54.8)	60.4 ± 7.1 (58.6-62.2)	66.0 ± 3.7 (64.3-67.8)

Displayed as Mean ± Standard Deviation (95% Confidence Interval) or frequency (%). Low risk is defined as STarT-Trauma total score ≤ 3, Medium risk as STarT-Trauma total score ≥ 4 and psychosocial subscale score ≤ 3, and High risk as STarT-Trauma psychosocial subscale score ≥ 4. See Table 1 for abbreviations.

*indicates significant difference between each risk category

† indicates significantly different than at least one of the other risk categories

Figure 4.1 STarT-LE Screening Tool Questions.

Please mark whether you agree or disagree with the following 8 statements and circle one response for item 9.

	Disagree	**Agree**
	0	1
1) I have had numbness, tingling, electric sensations, or burning sensations in my leg at some point in the last 2 weeks.	☐	☐
2) I have had pain spread from the original site of injury to another portion of my leg, hip, or back at some point in the last 2 weeks.	☐	☐
3) I have only walked short distances because of my leg pain.	☐	☐
4) In the last 2 weeks, I have dressed more slowly than usual because of leg pain.	☐	☐
5) It's not really safe for a person with a condition like mine to be physically active.	☐	☐
6) Worrying thoughts have been going through my mind a lot of the time.	☐	☐
7) I feel that my leg pain is terrible and it's never going to get any better.	☐	☐
8) In general I have not enjoyed all the things I used to enjoy.	☐	☐

9) Overall, how bothersome has your leg pain been in the last 2 weeks?

Not at all	Slightly	Moderately	Very much	Extremely
0	0	0	1	1

Total score (all 9): _____ **Psychosocial Subscale Score (Q5-9):**_____

Part II: STarT Screening Tool at Six Weeks Predicts Pain and Physical Function 12 Months after Traumatic Lower Extremity Fracture

Abstract of Chapter Four Part II

Background: Patients with lower extremity fracture requiring surgical fixation have been found to have poor long-term pain and disability outcomes. The STarT tool has been adapted to help identify patients with lower extremity (LE) trauma at-risk for poor outcomes. The STarT-LE Screening Tool has shown to be reliable and valid in a cross-sectional study in this patient population. However, the predictive validity of the STarT-LE has yet to be established.

Objective: To determine the predictive validity of the STarT-LE in patients with lower extremity fracture requiring surgical fixation.

Design: Single center, prospective cohort study.

Methods: 122 patients (41.7 ± 14.7 years, 54% male) with lower extremity fracture and no history of chronic pain were enrolled in this study. Six weeks after definitive fixation, patients completed the STarT-LE. Validated measures of chronic pain development, pain interference, and physical function were collected at 12-month follow-up. STarT-LE risk subgroups were compared against each outcome measure with chi-square, one-way analysis of variance, and sensitivity and specificity analyses. Multivariable hierarchical linear regression analyses determined if STarT-LE risk subgroups at six weeks were associated with each outcome at 12 months when controlling for important baseline demographics.

Results: 114 patients (93.4%) completed 12-month follow-up. The increase in STarT-LE risk subgroup was associated with higher frequency of developing chronic pain, worse pain interference, and worse physical function at 12 months ($p<0.05$). The low risk subgroup had high sensitivity (sensitivity range: 84.9%-93.9%) and the high risk

subgroup had high specificity (specificity range: 87.7%-95.2%) for dichotomized 12-month outcomes. The multivariable results showed that medium and high-risk STarT-LE risk categories at six weeks were associated with chronic pain development (OR: 4.24, 95% CI: 1.21-14.94; and 13.51, 95% CI: 2.32-78.60), increased pain interference (β: 4.38 and β: 7.03), and worse physical function (β: -3.77 and β: -7.51) at 12 months, respectively.

Conclusion: The STarT-LE Screening tool has the potential to identify patients at-risk for poor pain and functional outcomes following traumatic lower extremity injury. Implementing this short screening instrument into clinical practice may help inform the post-surgical management of this patient population.

STarT-Lower Extremity Screening Tool

Part II: STarT Screening Tool at Six Weeks Predicts Pain and Physical Function 12 Months after Traumatic Lower Extremity Fracture

Introduction

Many patients who sustain a lower extremity fracture requiring surgical fixation have poor long-term pain[1-3] and physical function[4, 5] outcomes. This has resulted in a heightened interest to identify risk factors associated with adverse outcomes after traumatic injury over the last decade.[6] Clinicians are inconsistent in their ability to independently identify patient subgroups at risk for chronic pain and disability,[7, 8] perpetuating adverse long-term outcomes and higher healthcare utilization.[9, 10] Therefore, a critical need exists for a brief screening tool that can be integrated into clinical practice. A validated tool that can stratify patients early in recovery into risk categories has the potential to inform clinical decision-making and a comprehensive treatment approach after surgical fixation.[7, 11]

The Keele Subgroups for Targeted Treatment (STarT) Back Screening Tool is a concise nine-item screening instrument validated for use in patients with low back pain.[12] The STarT Tool places individuals into one of three risk categories, with each increase in risk associated with worse long-term disability in patients with low back pain.[12] Van Wyngaarden et al. adapted the STarT Tool for patients with lower extremity fractures requiring surgical fixation (STarT-LE).[13] The tool was found to have good test-retest reliability (ICC=0.85, 95% CI: 0.78-0.91), acceptable internal consistency (Cronbach alpha = 0.74), and moderate to strong convergent validity with pain and psychosocial measures.[13] Similar to the original instrument, the STarT-LE has three risk categories

(low, medium, and high risk) with each increase in risk category increasingly associated with measures of pain catastrophizing, pain self-efficacy, fear, depression, pain intensity, and pain interference at six weeks after surgery.[13] Given that each of these constructs carry important associations with long-term patient outcomes,[1, 14-17] the STarT-LE is a promising multidimensional screening tool for use in patients with lower extremity injuries.

The purpose of this study was to further examine the validity of the STarT-LE in patients with traumatic lower extremity fracture requiring surgical fixation. More specifically, we aimed to determine whether the STarT-LE administered six weeks after surgical fixation was associated with the development of chronic pain, pain interference, and physical function at 12 months after surgery. We hypothesized that each increase in the STarT-LE risk category six weeks after surgical fixation would be associated with higher rates of chronic pain development, worse pain interference, and worse physical function at 12 months.

Patients and Methods

This study was a prospective cohort study conducted in patients admitted to a Level I trauma center between December 2017 and February 2019. Written and informed consent was obtained from all study participants after approval by the local institutional review board. Eligibility criteria were as follows: (1) 18 to 70 years of age; (2) lower extremity fracture to the pelvis, acetabulum, femur, tibia, patella, or foot/ankle requiring open reduction internal fixation; and (3) Glasgow Coma Score of 15 upon admission to the hospital.[18, 19] Patients with self-inflicted injury, a medical diagnosis of schizophrenia or other psychotic disorder, computed tomography scan consistent with moderate to

severe brain injury, current alcohol or drug abuse, homeless, incarcerated, or treated with amputation were excluded from this study. Additionally, those individuals who reported having chronic pain prior to injury were excluded from the study. Chronic pain was defined as pain present for more than three months and bothersome at least half the days over the preceding six months.[20]

Patients were approached and enrolled during the initial hospital stay after definitive surgical fixation. Demographic characteristics such as age, gender, smoking status, education level, and race were collected at the time of consent. Mechanism of injury, primary injury location, and Injury Severity Score (ISS)[21] were extracted from the medical record. Each patient completed the STarT-LE Screening Tool, a pain intensity scale, and a pain interference scale at an outpatient clinic visit six weeks after definitive surgical fixation. At 12 months after definitive surgical fixation, patients completed a Research Electronic Data Capture (REDCap)[22] web-based survey to assess the outcomes of chronic pain development, pain interference, and physical function. Those individuals that did not complete the surveys within 7, 14, and 21 days were contacted via telephone by research personnel not involved in the patient's clinical care to complete the survey through an interview.

STarT-LE Screening Tool and Pain Intensity Scale Administration

The STarT-LE was administered to each subject six weeks after definitive surgical fixation. This is a nine-item multidimensional screening tool that consists of four physical function and five psychosocial questions. Each question is dichotomized and the sum of all nine questions yields the STarT-LE total score (range: 0-9) while the sum of the psychosocial questions makes up the psychosocial subscale score (range: 0-5).

Individuals with a total score ≤3 are low risk, a total score ≥4 and a psychosocial subscale score ≤3 are medium risk, and a score ≥4 on the psychosocial subscale are categorized as high risk.[12] The STarT-LE has demonstrated good test-retest reliability, adequate internal consistency, moderate to strong convergent validity, acceptable to excellent criterion validity, and excellent discriminant validity in patients with lower extremity fracture requiring surgical fixation.[13]

Pain intensity was also assessed at six weeks with the first four items of the Brief Pain Inventory (BPI).[23, 24] These questions consist of the worst pain, least pain, average pain and current pain the individual experienced over the last week, with "0" being no pain and "10" being the worst pain you can imagine. The average of all four items is used to determine pain intensity.[24-26] The BPI has been found to be reliable and valid for use in post-surgical patients.[23, 27]

Pain and Physical Function Outcomes assessed at 12 months

Chronic pain development was determined by administering each patient two questions: (1) "Over the last six months, how *long* has pain been an ongoing problem for you?" and (2) "Over the last six months, how *often* has pain been an ongoing problem for you?" Only those individuals that responded with greater than three months to question one and at least half the days over the last six months to question two were categorized as having chronic pain. This is the method by which chronic pain was defined by a recent National Institutes of Health (NIH) Task Force whose goal was to standardize the definition of chronic pain for patients with low back pain.[20]

The Chronic Pain Grade Scale (CPGS) was also used to measure the presence of chronic pain. The CPGS consists of seven-items that measure the individual's pain

intensity and pain-related disability.[28] Responses are used to categorize individuals into one of five hierarchical categories: Grade 0, no pain in the last six months; Grade I: low disability-low pain intensity; Grade II: low disability-high pain intensity; Grade III: high disability-moderately limiting; and Grade IV: high disability-severely limiting.[28] A cut-off of greater than Grade II can be used to indicate individuals with disabling chronic pain.[1] The CPGS is a reliable and valid tool to measure chronic pain in diverse patient populations,[28-31] including patients with traumatic lower extremity injury.[1]

The Patient-Reported Outcomes Measurement Information System (PROMIS) computer adaptive tests (CAT) were used to assess pain interference and physical function. These are dynamic question banks that allow for efficient self-reporting of each respective construct with reduced patient burden and high precision.[32] A score of 50 reflects the mean of the U.S. general population with higher scores indicating worse pain interference and better physical function. Each 10-point deviation from 50 reflects a one standard deviation shift from the mean. The PROMIS Pain Interference is a valid means to measure limitations in cognitive, social, emotional, and physical activities as a direct result of their pain in adults[33] and more specifically after lower extremity trauma.[34] The PROMIS Physical Function is a valid method to assess self-reported physical function and ability to complete activities in patients with lower extremity trauma.[35]

Statistical Analysis

Descriptive statistics were used to summarize all demographic information and patient outcomes (frequency, percentages, means, and standard deviations). All continuous variables were examined to ensure they met the assumptions required for parametric testing. T-test and Fisher's Exact Tests were used to compare baseline

responses between individuals that completed 12-month follow-up and those that did not complete 12-month follow-up.

Bivariate analysis was conducted via two different methods. First, chi-square and one-way analysis of variance (ANOVA) with Tukey post hoc correction analyses were carried out with STarT-LE risk categories as the independent variable and each outcome measure as the dependent variable. Sensitivity, specificity, and negative and positive likelihood ratios were subsequently calculated using STarT-LE risk category cutoffs (high vs low/medium and low vs medium/high) and dichotomized 12-month outcomes (chronic pain development,[20] GCPS Grade > II,[1] pain interference and physical function ≥ 1SD worse than the mean).[36]

Multivariable hierarchical logistic and linear regression (HLR) analyses were used to determine if STarT-LE risk category was independently associated with each outcome when accounting for important demographic characteristics that have been associated with each outcome based on prior literature review (body mass index (BMI),[37] ISS,[3] age,[3, 4, 38] smoking status[4, 39, 40]). Baseline demographic variables were entered first into the HLR (Step 1), followed by the outcome measure at baseline (Step 2), and finally the STarT-LE risk category (Step 3).[41] In the logistic regression models predicting the development of chronic pain, there was no outcome measure at baseline as individuals with a history of chronic pain were excluded from this study; therefore, pain intensity at six weeks was controlled for in the logistic regression model. Additionally, the PROMIS Physical Function was not collected at baseline so the PROMIS Pain Interference at baseline was used as a surrogate.[42] Variance inflation factor values greater than 10 and independent variables with Pearson correlation coefficients ≥0.7 were used to check for

multicollinearity of data.[43-45] All statistical analyses were conducted using IBM SPSS Statistics (Version 24). Significance level was a priori set as $p \leq 0.05$.

The number of study participants for this study was based on a sample size calculation for multivariable regression modeling.[46] Using an estimated R^2 of 0.30 for each individual model, an R^2 of 0.10 for the STarT-LE, and a power of 0.80, a sample of at least 81 subjects was required. To account for a 70% follow-up rate through 12 months, a sample of 122 subjects were recruited. Power analysis calculations were completed with nQuery (Version 8.4).

Results

Five hundred ninety-one patients were examined for eligibility, of which 417 (70.6%) did not meet the inclusion or exclusion criteria. Of the remaining 174 eligible patients, 122 (70.1%) patients agreed to participate and were enrolled into this study. One hundred fourteen (93.4%) patients completed 12-month follow-up (Figure 2.1). There were not significant differences in age, sex, ISS, level of education, smoking status, BMI, or initial pain severity between those that completed the study and those that did not. The mean age of the entire sample was 41.7 years (SD: 14.7) and the majority of the subjects were male (54%), white (90%), and reported greater than high school education (59%). The majority of injuries were passengers in a motor vehicle accident (38%) and falls (29%), resulting most commonly in a tibia (51%) or femur (25%) fracture. The STarT-LE medium risk subgroup was the most common risk stratification level (52.5%) while the high risk subgroup was the smallest risk category (17.5%) (Table 4.6).

Bivariate Analysis

Each increase in STarT-LE risk category at six weeks post-surgical fixation was associated with higher rates of chronic pain development (Low: 14.7%, Medium: 48.3%, High: 85.0%), worse pain interference (Low: 48.6 ± 8.88, Medium: 56.33 ± 8.79, High: 61.65 ± 7.74), and worse physical function (Low: 50.77 ± 9.89, Medium: 42.52 ± 6.47, High: 37.44 ±7.46) at 12 months (Table 4.7). The STarT-LE low risk subgroup compared to medium and high risk subgroups demonstrated high sensitivity (range: 84.9%-93.9%) while the high risk subgroup compared to the medium and low risk subgroups demonstrated high specificity (range: 87.7%-95.2%) for each dichotomized 12-month outcome of chronic pain, pain interference, and physical function (Table 4.8).

Multivariable Regression Analyses

The results of the multivariable logistic regression analyses demonstrated that each increase in STarT-LE risk category at six weeks was strongly associated with increased odds of developing chronic pain at 12 months (Table 4.9). When compared to the STarT-LE low risk category, the medium risk subgroup had 4.24 greater odds (95% CI: 1.21 to 14.94) and the high risk subgroup had 13.51 greater odds (95% CI: 2.32 to 78.60) of reporting chronic pain, after adjusting for BMI, ISS, age, smoking status, and pain severity at baseline. Similarly the medium risk subgroup had 4.50 greater odds (95% CI: 1.21 to 16.69) and the high risk subgroup had 7.68 greater odds (95% CI: 1.42 to 41.40) to report a CPGS Grade >II when compared to the STarT-LE low risk category. Each one-point increase in pain severity was associated with 43% (95%CI: 8% to 89%) increase in odds of developing chronic pain, and a 44% (95%CI: 9% to 91%) increase in odds of a CPGS Grade >II.

The results of the multivariable linear regression analyses demonstrated that increasing STarT-LE risk category at six weeks was strongly associated with worse Pain Interference and Physical Function at 12 months when compared to the STarT-LE low risk category. When compared to the STarT-LE low risk category, the medium and high risk subgroups scored 4.38 (95%CI: 0.19 to 8.56) and 7.03 (95%CI: 1.27 to 12.80) points worse on the PROMIS Pain Interference, respectively, after adjusting for BMI, ISS, age, smoking status, and pain interference at baseline (Table 4.10). Similarly, when compared to the low risk subgroup the medium risk subgroup scored 3.77 (95%CI: -7.40 to -0.13) points worse and the high risk subgroup scored 7.51 (95%CI: -12.53 to -2.50) points worse on the PROMIS Physical Function. Finally, each 10 Kg/m^2 increase in BMI was associated with 2.2 points worse on the PROMIS Physical Function, while each 10-year increase in age was associated with 1.2 points worse on the PROMIS Physical Function (Table 4.10).

Discussion

The purpose of this study was to determine the predictive validity of the STarT-LE in patients with lower extremity fracture requiring surgical fixation. The results indicated that each increase in STarT-LE risk category at six weeks is associated with worse chronic pain, pain interference, and physical function at 12-month follow-up. These findings provide evidence that the STarT-LE Screening Tool is a valid tool for identifying patients at-risk for poor long-term pain and physical function outcomes following surgical fixation of a lower extremity fracture.

Approximately 45% of all the subjects in this study developed chronic pain at 12 months, which is consistent with other research indicating a high prevalence of chronic

pain in the long-term after lower extremity fracture.[1, 3, 39] Our results also suggest that patients in the low risk category were less likely to develop chronic pain (14.7%) and were likely to have Pain Interference and Physical Function scores at 12 months consistent with the mean of the U.S. population.[36] Individuals in the high risk category had a higher incidence of chronic pain (85%) when compared to other studies evaluating long-term pain outcomes after lower extremity trauma,[38, 39] and were on average greater than one standard deviation worse than the U.S. population on both Pain Interference and Physical Function.[36] The poor pain and physical function outcomes of the entire cohort at 12 months are consistent with recent literature that has indicated the adverse long-term outcomes patients have after lower extremity fracture.[3, 17, 47-49]

The high sensitivity of the low risk subgroup and specificity of the high risk subgroup for the outcomes of chronic pain, pain interference, and physical function is consistent with what Hill et al. reported in the original validation study of the STarT Back Tool for patients with low back pain.[12] In-fact, both Hill et al. and our results show that the specificity of the high risk group is better than the sensitivity of the low risk group for most outcomes.[12] This makes sense given that many patients with a traumatic lower extremity injury do very poorly in the long run; therefore, an individual that screens into a high risk subgroup increases our confidence that the patient will indeed have poor long-term outcomes.

In the multivariable models predicting the development of chronic pain, each increase in risk category was associated with greater odds of reporting chronic pain at 12 months with large odds ratios. To our knowledge, this is the first study that has evaluated the transition from acute injury to chronic pain after lower extremity fracture in patients

without a history of chronic pain. Therefore, it is important to note that both the NIH definition of chronic pain[20] and the CPGS[28] outcomes resulted in very similar multivariable regression results thereby validating that the STarT-LE consistently predicts chronic pain development. The small differences in odds ratio between the two chronic pain outcomes is likely driven by the fact that perceived disability plays a significant role in determining the CPGS Grade,[28-31] whereas the NIH definition focuses more on pain duration and bothersomeness.[20]

Our models predicting the development of chronic pain are consistent with that of the Lower Extremity Assessment Project (LEAP) group, which reported that worse psychosocial symptoms were associated with increased CPGS scores after severe limb threatening trauma.[1, 39] Additionally, other research has indicated that catastrophizing[50] and psychological distress[51] strongly predict long-term persistent pain after traumatic injury. Consistent with past studies conducted in patients with lower extremity trauma, pain intensity at baseline is an important factor to consider for chronic pain development.[1, 38, 39] Therefore, it is important to consider both the patient's pain intensity and STarT-LE risk category at baseline when assessing risk for the outcome of chronic pain after lower extremity injury requiring surgical fixation.

The STarT-LE was independently associated with pain interference at 12 months in the multivariable linear regression model. Moving from a lower to higher risk category on the STarT-LE is associated with an increase in the psychosocial contribution to the patient's symptoms. Therefore, our results are consistent with what Archer et al. reported, which indicated the important association catastrophizing and depression four weeks after lower extremity fracture carries with 12-month pain interference.[17]

Additionally, the LEAP Group found that depression and anxiety are strongly associated with long-term pain outcomes after limb-threatening lower extremity trauma.[1] In light of these prior findings, our results indicate that this short screening instrument accurately represents multiple psychosocial domains simultaneously, and is an efficient means to determine which patients early after surgery will have long-term pain-related disability.

The final regression model indicated that multiple factors are associated with long-term physical function. The STarT-LE carried a strong association with physical function, which is consistent with a large body of literature indicating the important role disability and psychosocial variables carry with long-term physical function after injury. O'Donnell et al. reported that depression played the strongest role in predicting disability after traumatic injury.[5] A recent study reported that psychosocial distress mediated the relationship between pain severity and disability after lower extremity trauma, indicating that psychosocial variables are driving long-term patient function.[52] Systematic reviews also show that psychosocial symptoms carry important associations with long-term disability after traumatic injury.[3, 53] In addition to the STarT-LE, BMI and age were significant predictors of physical function. These results are consistent with prior work reporting the strong association increased BMI[37] and age[54, 55] carry with reduced levels of physical function. Our results indicated that even when controlling for BMI and age, individuals in medium and high risk categories on the STarT-LE at six weeks are at substantially greater risk of reduced self-reported physical function at 12 months.

There are a number of inherent strengths to this study. First, the follow-up rate was excellent (93.4%), which reduces the likelihood that selection bias influenced the results. Additionally, patients with a history of chronic pain were excluded from the

study. This allows our results to show how likely an individual will transition from an acute injury to the development of chronic pain. Third, we screened patients early in the recovery process which will allow for targeted interventions to be tested in at-risk subgroups. Having the capability to apply early interventions has many important financial, health care utilization, and patient suffering implications. Finally, our regression models controlled for important baseline variables and the STarT-LE was strongly associated with each outcome of interest in this study demonstrating the importance of the STarT-LE to a broad range of pain-related outcomes.

There are a number of important limitations that must be considered when interpreting the results of this study. First, the PROMIS Physical Function was not measured at baseline. Even though other research has indicated that Pain Interference can be used as a surrogate measure of Physical Function due to the strong correlation between the two measures,[42] the strength of the findings would have been improved if Physical Function was collected and controlled for at baseline. Second, the generalizability of these findings may be limited in that this study was conducted at a single center with narrow inclusion/exclusion criteria. For example, a patient with a long-standing history of drug use that subsequently sustains a traumatic fracture will likely respond differently than the patients that were included in this study. Future studies may consider evaluating how the STarT-LE predicts long-term outcomes with a multicenter design and less strict eligibility criteria.

Future research should determine whether improved long-term clinical outcomes can be achieved in this population by applying targeted treatment strategies by individual risk category. Given that the high risk group is determined by the patient's psychosocial

component score on the STarT-LE, this agrees with prior literature indicating the important role psychosocial beliefs contribute to the development of chronic pain and poor function in patients with lower extremity trauma.[17, 38, 49, 52, 56] The medium risk subgroup is determined by combined perceived disability and psychosocial beliefs while the low risk group has healthy psychosocial beliefs and less perceived levels of disability. Therefore, low risk patient subgroups may benefit from standard of care (physical therapy referral and periodic follow-up assessments with the surgeon) while the medium and high risk subgroups would likely benefit from additional referral to improve outcomes. Cognitive behavioral strategies have proven effective in patient populations with chronic pain[57-59] and might prove useful in improving the outcomes of high risk patients, while the medium risk group may improve with graded exercise treatment programs that build patient confidence and improve function. Further research is needed before these can be recommended for implementation into clinical practice. Additionally, the majority (52.5%) of the patients in this study screened into the medium risk subgroup at six weeks post definitive surgical fixation. While the multivariable models demonstrated that the medium risk subgroup was associated with worse outcomes than that of the low risk patient subgroup, there was substantial heterogeneity in the outcomes of this risk group. This may indicate an opportunity to further stratify the risk of the medium risk subgroup into a medium-low and medium-high risk category in order to better direct treatment efforts toward this patient subgroup.

Conclusion

We have prospectively validated a simple, concise screening tool to stratify patients with lower extremity fracture requiring surgical fixation. Specifically, each

increase in STarT-LE risk category at six weeks was associated with a greater frequency of chronic pain development, worse pain interference, and worse physical function at 12 months. Our results indicate that the STarT-LE Screening Tool has the potential to inform the post-surgical management of patients with lower extremity fracture requiring surgical fixation.

Table 4.6 Characteristics of study population 6 weeks after definitive surgical fixation for lower extremity fracture (N=122).

Injury Characteristics	Mean ± SD or N (%)
Age	41.7 ± 14.7
Body Mass Index (BMI)	31.2 ± 9.4
Gender	
Female	56 (46%)
Male	66 (54%)
Race	
White	110 (90%)
Nonwhite	12 (10%)
Education	
High School or less	50 (41%)
Greater than High School	72 (59%)
Current Smoker	33 (27%)
Mechanism of Injury	
Motor Vehicle Accident	46 (38%)
Motorcycle Accident	13 (11%)
Pedestrian/cyclist hit by vehicle	9 (7%)
Fall	36 (29%)
Blunt Trauma	13 (11%)
Other	5 (4%)
Primary Injury Location	
Pelvis/Acetabulum	21 (17%)
Femur	30 (25%)
Tibia	63 (51%)
Patella	2 (2%)
Ankle/Foot	6 (5%)
Articular Injury	
Yes	55 (45%)
No	67 (55%)
Injury Severity Score	9.1 ± 6.6
Length of Hospital Stay	3.5 ± 3.4
STarT-LE Risk Category*	
Low Risk	34 (27.8%)
Medium Risk	60 (49.2%)
High Risk	20 (16.4%)
Failed to Complete	8 (6.6%)

*STarT-LE=STarT Lower Extremity Screening Tool. Low risk is defined as STarT-Trauma total score ≤ 3, Medium risk as STarT-Trauma total score ≥ 4 and psychosocial subscale score ≤ 3, and High risk as STarT-Trauma psychosocial subscale score ≥ 4.

Table 4.7 STarT-LE risk category at six weeks by outcomes at 12 months.

	Low Risk	Medium Risk	High Risk	Entire Cohort
N	34 (30%)	60 (52.5%)	20 (17.5%)	114 (100%)
Chronic Pain*	5 (14.7%)	29 (48.3%)	17 (85.0%)	51 (44.7%)
Chronic Pain Grade Scale*	5 (14.7%)	29 (48.3%)	15 (75.0%)	49 (43.0%)
Pain Interference*	48.63 ± 8.88	56.33 ± 8.79	61.65 ± 7.74	54.96 ± 9.72
Physical Function*	50.77 ± 9.89	42.52 ± 6.47	37.44 ± 7.46	44.09 ± 9.08

Displayed as Mean ± Standard Deviation or N (%). See Table 1 for STarT-LE Low, Medium, and High risk definitions.

*indicates significant difference between each risk category

Table 4.8 Sensitivity, specificity, positive likelihood ratio (LR) and negative LR of the STarT-LE Screening Tool Risk categories at six weeks by 12-month outcomes.

Outcome*	STarT-LE Risk Cutoff†	Sensitivity: (95% CI)	Specificity: (95% CI)	Pos. LR (95% CI)	Neg. LR (95% CI)
Chronic Pain Development	L v M/H	84.9% (68.1-94.9)	57.5% (45.9-68.5)	0.26 (0.12-0.60)	2.0 (1.49-2.68)
	H v M/L	33.3% (20.8-47.9)	95.2% (86.5-99.0)	0.70 (0.57-0.86)	6.89 (2.14-2.20)
CPGS	L v M/H	84.9% (68.1-94.9)	55.0% (43.5-66.2)	0.28 (0.12-0.63)	1.89 (1.42-2.50)
	H v M/L	30.6% (18.3-45.4)	92.2% (82.7-97.4)	0.75 (0.62-0.92)	3.92 (1.53-10.04)
Pain Interference	L v M/H	93.9% (79.8-99.3)	47.5% (36.2-60.0)	0.13 (0.03-0.50)	1.79 (1.43-2.24)
	H v M/L	27.5% (14.6-43.9)	87.7% (77.9-94.2)	0.83 (0.67-1.02)	2.23 (1.01-4.93)
Physical Function	L v M/H	84.9% (68.1-94.9)	41.3% (30.4-52.8)	0.37 (0.16-0.86)	1.44 (1.14-1.82)
	H v M/L	31.6% (17.5-48.7)	89.3% (80.1-95.3)	0.77 (0.61-0.96)	2.96 (1.32-6.62)

*Outcome Definitions: Chronic Pain Development = Yes;[20] CPGS = Chronic Pain Grade Scale, Grade >2; Pain Interference ≥1SD above the mean; Physical Function ≥1SD below the mean.

†L=Low Risk, M=Medium Risk, H=High Risk.

Table 4.9 Multivariable logistic regression of STarT-LE risk categories six weeks post surgical fixation and the development of chronic pain at 12 months (N=114).

	Chronic Pain Development		**CPGS***	
Predictor Variables	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
BMI	0.99 (0.95 to 1.05)	0.80	1.05 (1.0 to 1.1)	0.052
ISS	0.97 (0.90 to 1.10)	0.47	1.01 (0.94 to 1.09)	0.80
Age	0.97 (0.94 to 1.0)	0.09	0.97 (0.94 to 1.0)	0.07
Smoking Status	1.57 (0.53 to 4.62)	0.42	2.76 (0.94 to 8.08)	0.07
Pain Severity at Baseline	1.43 (1.08 to 1.89)	0.01	1.44 (1.09 to 1.91)	0.01
Medium Risk compared to Low Risk	4.24 (1.21 to 14.94)	0.02	4.50 (1.21 to 16.69)	0.025
High Risk compared to Low Risk	13.51 (2.32 to 78.60)	0.004	7.68 (1.42 to 41.40)	0.018

* Chronic Pain Grade Scale dichotomized (Grade >II)

Table 4.10 Multivariate linear regression of STarT-LE risk categories six weeks post surgical fixation and the outcomes of self-reported pain interference and physical function at 12 months (N=114).*

	Pain Interference		**Physical Function**	
Predictor Variables	**Final β Coefficient (95%CI)**	**p-value**	**Final β Coefficient (95%CI)**	**p-value**
BMI	0.16 (-0.01 to 0.32)	0.06	-0.22 (-0.36 to -0.08)	0.003
ISS	0.06 (-0.18 to 0.30)	0.64	-0.14 (-0.35 to 0.07)	0.20
Age	-0.03 (-0.14 to 0.08)	0.57	-0.12 (-0.22 to -0.03)	0.01
Smoking Status	1.77 (-1.93 to 5.46)	0.35	-0.87 (-4.08 to 2.35)	0.59
Outcome at Baseline	0.45 (0.20 to 0.69)	0.001	-0.37 (-0.58 to -0.15)	0.001
Medium Risk compared to Low Risk	4.38 (0.19 to 8.56)	0.04	-3.77 (-7.40 to -0.13)	0.04
High Risk compared to Low Risk	7.03 (1.27 to 12.80)	0.02	-7.51 (-12.53 to -2.50)	0.004

*Total adjusted variance accounted for in each regression model. Pain Interference: Adj. R^2=0.3, Physical Function: Adj. R^2=0.39.

CHAPTER FIVE:

Dissertation Summary

Dissertation Summary

Purposes, Aims, and Hypotheses

The purposes of this dissertation were to determine the earliest timeframe pain catastrophizing, pain self-efficacy, fear of movement, depression, and pain intensity can be screened to assess risk for chronic pain after lower extremity fracture; determine the most salient psychosocial factors at six weeks associated with chronic pain development, pain interference, and physical function 12 months after surgical fixation; and determine the reliability and validity of the STarT-LE at six weeks for the 12-month outcomes of chronic pain, pain interference, and physical function. These studies were developed to address the following specific aims and hypotheses in patients with lower extremity fracture requiring surgical fixation:

1. To evaluate when the psychosocial profile stabilizes throughout the first 12 months of recovery.

   Hypothesis: Patients will have a significant change in level of pain catastrophizing, pain self-efficacy, fear of movement, depression, and pain intensity between baseline and six weeks and remain stable thereafter.

2. To identify the earliest time of divergence in psychosocial profile between those individuals that do and do not develop chronic pain at 12 months.

   Hypothesis: Six weeks after definitive surgical fixation will be the earliest point in recovery that pain catastrophizing, pain self-efficacy, fear of movement, depression, and pain intensity will demonstrate divergence between the two groups with moderate effect sizes.

3. To determine which psychosocial factors six weeks after definitive surgical fixation predict the transition to chronic pain, pain interference, and physical function at 12 months.

    Hypothesis: Pain self-efficacy will carry the strongest association with all outcomes when controlling for depression at six weeks and other important baseline patient characteristics.

4. To assess the reliability and concurrent validity of the STarT-LE Screening Tool six weeks after definitive surgical fixation.

    Hypothesis: The STarT-LE Screening Tool would demonstrate: (1) good test-retest reliability (Intraclass Correlation Coefficient ≥0.75), (2) adequate internal consistency (Cronbach's alpha >0.7), (3) no floor/ceiling effects (minimum and maximum score achieved in <15% of total responses), (4) moderate to strong convergent validity (spearman rho >0.4), (5) acceptable criterion validity (Area Under the Curve >0.7), and excellent discriminant validity.

5. To establish the predictive validity of STarT-LE risk category at six weeks for chronic pain development, pain interference, and physical function at 12 months.

    Hypothesis: Each increase in the STarT-LE risk category six weeks after surgical fixation would be associated with higher rates of chronic pain development, worse pain interference, and worse physical function at 12 months when controlling for important baseline variables.

Summary of Findings

The summary of findings for each specific aim are as follows:

1. To evaluate when the psychosocial profile stabilizes throughout the first 12 months of recovery.

   Findings: The hypothesis was partially supported given that pain self-efficacy, pain catastrophizing, fear of movement, and pain intensity changed significantly between baseline and six weeks. However, only pain catastrophizing and pain intensity remained stable thereafter. Depression, pain self-efficacy, and fear of movement demonstrated statistically significant changes between six weeks and three months and remained stable thereafter.

2. To identify the earliest time of divergence in psychosocial profile between those individuals that do and do not develop chronic pain at 12 months.

   Findings: The hypothesis was fully supported in that there were no differences in any of the psychosocial measures at baseline but significant differences on all measures at six-week, three-month, six-month, and 12-month follow-up with large to very large effect sizes (Cohen's d range: 0.79 to 1.96, $p<0.01$).

3. To determine which psychosocial factors six weeks after definitive surgical fixation predict the transition to chronic pain, pain interference, and physical function at 12 months.

   Findings: The hypothesis was partially supported given that self-efficacy at six weeks was the sole psychosocial variable associated with chronic pain development (odds ratio: 0.95; 95% CI: 0.91-0.99; $p=0.02$) and physical function (β:0.134; $p=0.048$) at 12 months when controlling for

depression and other important baseline variables. However, pain catastrophizing at six weeks was the sole psychosocial variable associated with pain interference (β:0.217; p=0.045) at 12 months when controlling for depression at six weeks and other important baseline variables.

4. To assess the reliability and concurrent validity of the STarT-LE six weeks after definitive surgical fixation.

   Findings: The specific hypotheses were supported overall. The results of this study indicate that the STarT-LE had good test-retest reliability (total: ICC=0.85, 95% CI: 0.78-0.91; psychosocial subscale: ICC=0.79, 95% CI: 0.68–0.87) and acceptable internal consistency (α=0.74). Additionally, the STarT-LE did not demonstrate floor/ceiling effects (<15%), moderate to strong convergent validity (r=0.48-0.75, p<0.001), acceptable to excellent criterion validity (AUC=0.75-0.89), and excellent discriminant validity.

5. To establish the predictive validity of STarT-LE risk category at six weeks for chronic pain development, pain interference, and physical function at 12 months.

   Findings: The hypothesis was supported in that each increase in STarT-LE risk subgroup was associated with higher frequency of developing chronic pain, worse pain interference, and worse physical function at 12 months (p<0.05). The multivariable results showed that medium and high-risk STarT-LE risk categories at six weeks were associated with chronic pain development (OR: 4.24, 95% CI: 1.21-14.94; and 13.51, 95% CI: 2.32-78.60), increased pain interference (β: 4.38 and β: 7.03), and worse physical function (β: -3.77 and β: -7.51) at 12 months, respectively.

Synthesis of Results and Future Research Implications

There are a number of important clinical conclusions and implications for future research that can be made based on the results of these studies.

1. Screening patient's psychosocial profile to assess risk of adverse long-term outcomes after lower extremity fracture can be completed as early as six weeks after surgical fixation. While our results demonstrate that screening at baseline is ineffective, our results are inconclusive regarding the effectiveness of screening between baseline and six-week follow-up. Future research may consider if screening psychosocial variables at two weeks and four weeks after surgical fixation is able to provide any further resolution for determining risk of chronic pain.
2. Future studies may consider developing more sensitive cut off scores on each psychosocial measure for the earlier stages of recovery. Current validated cut-off scores are based on patient populations with current chronic pain, but our results are clear that patients without chronic pain have entirely different psychosocial component scores in the earlier stages of recovery.
3. Incorporating the pain self-efficacy questionnaire at six-week follow-up appointments may help with informing clinical decision making. Future research may consider using the pain self-efficacy questionnaire to inform treatment efforts to improve patient pain and physical function outcomes, suffering, and health care utilization. This could be tested by providing patients with low self-efficacy with early pain management treatment (transcutaneous electrical nerve stimulation, interferential current therapy, manual therapy), additional skilled physical therapy intervention focused on building confidence with a functional exercise

progression, and cognitive behavioral treatment efforts to improve the patient's optimism and expectations. Psychological interventions have had inconsistent effects on patients with current chronic pain, but treating patients early may decrease the effect maladaptive psychosocial beliefs have on the central nervous system's processing of pain, thereby improving patient outcomes.

4. The STarT-LE at six weeks carried statistically and clinically important associations with chronic pain development, pain interference, and physical function at 12 months. Using this tool may help inform clinical decision making in the earlier stages of recovery to improve patient outcomes. Similar to that noted in the prior point, the STarT-LE may be used to guide treatment efforts to improve patient pain and physical function outcomes, suffering, and health care utilization. This could also be tested by providing the medium and high risk subgroups with early pain management treatment (transcutaneous electrical nerve stimulation, interferential current therapy, manual therapy), additional skilled physical therapy intervention focused on building confidence with a functional exercise progression, and cognitive behavioral treatment efforts to improve the patient's optimism and expectations. Our results indicate that the low risk subgroup does well with current standard of care treatment.
5. Future research may consider how the STarT-LE compares to other multidimensional screening tools, such as the Orebro. This will aid in determining the most clinically relevant tool to better inform clinical decision-making.

6. The STarT-LE low risk and high risk categories demonstrate fairly homogenous long-term outcomes. However, approximately 50% of the subjects scored in the medium risk category of the STarT-LE and the outcomes of this patient population demonstrated substantial heterogeneity. Future work may consider using an additional measure, such as the pain self-efficacy questionnaire, to further stratify the medium risk subgroup in the early stages of recovery for long-term outcomes. This would potentially allow for the placement of individuals into medium-low and medium-high risk categories, and result in a more effective delivery of care to this medium risk cohort.
7. Brain activation changes in the emotional regulatory centers are likely to have occurred in the acute stages of recovery from a lower extremity fracture. Quantifying these changes in locations such as the mediodorsal thalamus, inferior parietal lobule, and default mode network over time and associating these neuroplastic changes with psychosocial assessments may allow for a more mechanistic understanding of the issues involved in the transition from acute injury to chronic pain. This would be most easily accomplished by implementing a prospective study design with multiple follow-ups in patients without a history of chronic pain. Functional MRI scans of the brain and survey-based psychosocial assessments could be performed two weeks, six weeks, three months, six months, and 12 months after injury. Evaluating how the brain changes over time between those individuals with chronic pain at 12 months compared to those without chronic pain could further guide how to best direct treatment efforts to this patient population in the early stages of recovery.

Conclusion

This dissertation evaluated how self-reported psychosocial measures were associated with the development of adverse pain and disability outcomes. The results clearly demonstrate that patients with heightened psychosocial profiles in early stages of recovery have the worst long-term outcomes. These data support screening the psychosocial profile of patients early in recovery in order to assess patient risk for worse pain and disability. This may help direct treatment efforts, reduce health care utilization, and improve patient suffering after lower extremity fracture requiring surgical fixation.

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Chapter One

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Vita

Education

Institution	Degree	Date Conferred	Field of Study
U.S. Army-Baylor University	D.P.T	2011	Physical Therapy
U.S. Air Force Academy	B.S.	2008	Biology

Professional Experience

Year	Employer	Title
2016-2017	Kunsan Air Base, Kunsan, Republic of Korea	Director, Dept of Physical Therapy, Health Promotion, and Human Performance Optimization
2014-2016	Charleston Air Force Base, Charleston, SC	Director, Department of Physical Therapy
2011-2014	Wright-Patterson Air Force Base, Dayton, OH	Director, Department of Physical Therapy

Honors and Awards:

2020 Marilyn Gossman Graduate Student Finalist, Combined Sections Meeting, American Physical Therapy Association

2017 Meritorious Service Medal, 8th Medical Group, Kunsan AB, ROK

2016 Flight Commander of the Year, 8th Medical Group, 8th Medical Operations Squadron, Kunsan AB, ROK

2016 Professional Team of the Year, 8th Medical Group, 8th Medical Operations Squadron, Kunsan AB, ROK

2016 Professional Team of the Quarter (Jul-Sept), 8th Medical Group, 8th Medical Operations Squadron, Kunan AB, ROK

2016 Meritorious Service Medal, 628th Medical Group, Joint Base Charleston, SC

2016 Company Grade Officer of the Quarter, (Jan-Mar), 628th Medical Group, 628th Medical Operations Squadron, Joint Base Charleston, SC

2014 Air Force Commendation Medal, 88th Medical Group, Wright-Patterson AFB, OH

2014 Company Grade Officer of the Quarter, (April-June), 628th Air Base Wing, 628th Medical Group, 628th Medical Operations Squadron, Joint Base Charleston, SC

2014 Company Grade Officer of the Year, 628th Air Base Wing, 628th Medical Group, 628th Medical Operations Squadron, Joint Base Charleston, SC

2013 Company Grade Officer of the Quarter, (April-June), 88th Air Base Wing, 88th Medical Group, 88th Medical Operations Squadron, Wright-Patterson AFB, OH

2013 Small Team of the Quarter, (July-September), 88th Medical Operations Squadron, Wright-Patterson AFB, OH

2013 Air Force Material Command Biomedical Clinician Category II Company Grade Officer of the Year

2013 Pennsylvania Physical Therapy Association Best Case Report of the Year Award

2013 Company Grade Officer of the Year, 88th Air Base Wing, 88th Medical Group, 88th Medical Operations Squadron, Wright-Patterson AFB, OH

2012 Air Force Achievement Medal, 88th Medical Group, Wright-Patterson AFB, OH

2012 Large Team of the Quarter (July-Sept), 88th Air Base Wing, Medical Group, and Medical Operations Squadron, Wright-Patterson AFB, OH

2008 Distinguished Graduate, (Ranked #78 of 1027 graduates with academic and athletic distinction), U.S. Air Force Academy, Colorado Springs, CO

2008 Brett Hyde Award for Drive and Determination, U.S. Air Force Academy, Colorado Springs, CO

2008 Team Captain Award for Exemplary Leadership on and off the athletic field, U.S. Air Force Academy, Colorado Springs, CO

Peer Reviewed Publications:

1. Van Wyngaarden JJ, Archer KR, Jacobs C, Matuszewski P, Noehren B. Reliability and Concurrent Validity of the STarT-Lower Extremity Screening Tool for Patients with Lower Extremity Fracture: A Cross-Sectional Study. Arch Phys Med Rehabil, *In Review.*

2. Van Wyngaarden JJ, Noehren B, Archer KR. Assessing psychosocial profile in the physical therapy setting. Journal of Applied Biobehavioral Research, Mar 2019; 24(2): 12165. Article Link

3. Van Wyngaarden JJ, Ross MD, Hando BR. Abdominal Aortic Aneurysm in a patient with low back pain. J Orthop Sports Phys Ther. 2014 July; 44(7):500-7. Article Link

4. Childs JD, Teyhen DS, Van Wyngaarden JJ, et al. Predictors of web-based follow-up response in the Prevention of Low Back Pain in the Military Trial (POLM). BMC Musculoskeletal Disorders 2011, 12:132. Article Link

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