CHARACTERIZING BREAST CANCER SURGERY PAIN TRAJECTORIES: PREOPERATIVE TO 2 YEARS POSTOPERATIVE

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ABSTRACT

This study characterized postoperative breast cancer surgery pain (BCSP) trajectory groups and explored pre- and postoperative factors associated with group membership. Numeric Rating Scale-Rest (NRS-R) scores at 2 years characterized 73 participants into two trajectory groups, then time to resolution and episodic pain pattern further characterized six trajectory subgroups, including: two subgroups whose pain had resolved (persistent resolved and episodic resolved); two subgroups whose pain had not resolved (persistent unresolved and episodic unresolved); a subgroup whose pain resolved by 6 months; and a subgroup who did not report pain at follow-up. Exploring individual trajectories revealed differences in average NRS-R and treatment-related adverse events. Backward binomial logistic regression found that mastectomy and parity were associated with group membership. Further exploration found preoperative pain interference associated with both group and subgroup membership. The results demonstrate a novel heuristic framework for examining BCSP trajectories to understand and modify risk factors.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
ABCSP	Acute breast cancer surgery pain
ALND	Axillary lymph node dissection
BCS	Breast cancer surgery
BCSP	Breast cancer surgery pain
BMI	Body Mass Index
BPI	Brief Pain Inventory
BPI-INT	Brief Pain Inventory - Interference
BPI-SEV	Brief Pain Inventory - Severity
CAM	Confusion Assessment Method
CBCSP	Chronic breast cancer surgery pain
CCI	Charlson Comorbidity Index
CES-D	Center for Epidemiologic Studies - Depression Scale
CIPN	Chemotherapy-induced peripheral neuropathy
CNS	Central nervous system
CPAQ	Chronic Pain Acceptance Questionnaire
DASH	Disabilities of the Arm Shoulder and Hands Questionnaire
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
ECR	Experiences in Close Relationships Inventory
ER+	Estrogen-receptor-positive (breast cancer)
ER+/PR+	Estrogen- and progesterone-receptor-positive (breast cancer)
ESAS	Edmonton Symptom Assessment System
FACIT-Sp-12	Functional Assessment of Chronic Illness Therapy - Spiritual Wellbeing 12
GBTM	Group-Based Trajectory Modelling
GCT	Gate Control Theory
GMM	Growth Mixture Modelling
IASP	International Association for the Study of Pain
IES-R	Impact of Event Scale - Revised
KPI	Karnofsky Performance Index
LBP	Low back pain
LCM	Latent Class Model
MCAR	Missing completely at random
MCID	Minimally clinically important difference
MICE	Multiple imputation by chained equations
MOS-SSS	Medical Outcomes Study - Social Support Survey
MPI	Multidimensional Pain Inventory & Caregiver Responses Scale
NRS	Numerical Rating Scale
NRS-M	Numerical Rating Scale - Movement
NRS-R	Numerical Rating Scale - Rest
PAQ-R	Pain Attitudes Questionnaire Revised

PASS	Pain Anxiety Symptom Scale
PASS-CA	Pain Anxiety Symptom Scale - Cognitive Anxiety
PASS-EA	Pain Anxiety Symptom Scale - Escape Avoidance
PASS-F	Pain Anxiety Symptom Scale - Fear
PASS-PA	Pain Anxiety Symptoms Scale - Physiological Anxiety
PCS	Pain Catastrophizing Scale
PCS-H	Pain Catastrophizing Scale - Helplessness
PCS-M	Pain Catastrophizing Scale - Magnification
PCS-R	Pain Catastrophizing Scale - Rumination
PMCC	Princess Margaret Cancer Centre
PMI	Pain Management Index
PR+	Progesterone-receptor-positive (breast cancer)
QST	Quantitative Sensory Testing
RA	Research assistant
RCT	Randomized controlled trial
RIBPN	Radiation-induced brachial plexus neuropathy
SAT	Satisfaction with pain control
SF-12	Medical Outcome Study Short-Form 12
SF12-MCS	Medical Outcome Study Short-Form 12 - Mental Health
SF12-PCS	Medical Outcome Study Short-Form 12 - Physical Health
SF-MPQ	Short Form McGill Pain Questionnaire
SF-NPQ	Short Form Neuropathic Pain Questionnaire
SOMC	Short Orientation-Memory-Concentration Test
STAI	State-Trait Anxiety Inventory
STAI-S	State-Trait Anxiety Inventory - State
STAI-T	State-Trait Anxiety Inventory -Trait
TGH	Toronto General Hospital
UHN	University Health Network
VAS	Visual Analogue Scale
VIF	Variable inflation factor
VRS	Verbal Rating Scale

INTRODUCTION

In Canada, breast cancer makes up 26% of all new cancer diagnoses in women.[1] As of 2026, 1 in 8 women will develop breast cancer in their lifetime. [1] Within a year of diagnosis, 88% will undergo at least one surgical treatment.[2] Due, in part, to advances in early detection and effective surgical interventions, breast cancer now has a 5-year survival rate of 89%.[3,4] However, as the mortality rate decreases, the consequences of treatment become increasingly apparent. Breast cancer surgery (BCS) is associated with symptoms ranging from short-term discomfort to long-term dysfunction across mental, physical, and social domains,[5,6] with the most common symptom being breast cancer surgery pain (BCSP).[7] Furthermore, chronic breast cancer surgery pain (CBCSP) has been identified as a prevalent and pressing issue, with some studies estimating that more than half of people undergoing surgery could develop CBCSP.[6,8–12] Yet, there have been no studies examining the course of BCSP sequentially from preoperative to postoperative beyond 6 months. As such, much remains unknown about pain experiences and the risk factors for chronic pain following BCS.

To address this gap, the current study presents the first, to my knowledge, examination of BCSP trajectories preoperative to 2 years postoperative. The characterization of BCSP trajectories and identification of preoperative risk factors may inform potential targets for intervention and reduce the burden of BCSP.

CURRENT STATE OF KNOWLEDGE AND RATIONALE

BCS and BCSP Prevalence

The most common surgical interventions for breast cancer in Canada are mastectomy (removal of the whole breast) and lumpectomy (removal of the tumour and a margin of surrounding tissue).[2,13] Surgery type may be determined by a range of factors, such as age, tumour characteristics, menopausal status, and participant preference.[14] In the current study, participants received one of two surgeries: modified radical mastectomy (unilateral or bilateral) or lumpectomy with axillary lymph node dissection (ALND), wherein both surgeries included the removal of 10-30 lymph nodes in the axilla (underarm) region.

Compared to other common surgeries in Canada, people undergoing BCS report a higher prevalence of postoperative pain immediately following surgery.[15–17] Some studies estimate that over 90% of people report pain within the first week, half of whom report moderate to severe intensity.[18–20] People undergoing BCS also report high rates of chronic pain, with some studies estimating that 20-60% of people may develop CBCSP.[6,8–12] Despite CBCSP being one of the most common symptoms after BCS, the prevalence varies greatly in the literature, with a recent systematic review (n= 297,612) reporting that prevalences ranged between 2-78%,[21] suggesting that there is little consensus and high heterogeneity in the existing CBCSP literature.

Pain Definition, Mechanisms, and Theories

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”.[22(p14)]

Prior to the current models of pain perception, the most influential theories included the Specificity, Intensity, and Pattern Theory.[23] According to Specificity Theory, non-noxious and noxious stimuli each have dedicated pathways with specific receptors and sensory fibres, wherein painful, or noxious, stimuli are encoded by nociceptors that project to pain centers in the brain through pain fibers.[24] According to Intensity Theory, the intensity of a stimulus is determined by the number of impulses in the neurons, where low levels of activity encode non-noxious stimuli and high levels, noxious stimuli.[23] According to Pattern Theory, sensations are associated with a specific and unique neural firing in which the spatial and temporal characteristics of peripheral nerve firing encodes the stimulus type and intensity.[25] Of these three theories, Specificity and Pattern theory were the most prominent. Despite some experimental support, they failed to account for more complex pain cases like hyperalgesia (increased sensitivity and extreme response to pain), allodynia (pain due to usually non-painful stimuli), spontaneous pain, injury without pain, delays between stimulus and pain, and the role of neurons in the central nervous system (CNS).[23,26]

Gate Control Theory

Gate Control Theory (GCT) was proposed in 1965 to incorporate the findings from Specificity and Pattern Theory while accounting for complex pain conditions.[26] GCT proposed that skin stimulation induces nerve impulses that are transferred by the peripheral nociceptors to the dorsal horn.[26] There, the impulse is integrated with signals from other afferent neurons, interneurons, and descending modulatory signals.[27] This modulation affects the membrane potential of afferent fiber terminals and determines the excitatory effect of incoming impulses.[26] The balance between nociceptive and facilitatory signals with non-nociceptive and

inhibitory signals in the dorsal horn determines if the gate will be “open” or “closed”, which then dictates whether the signal will travel to the brain.[26,28] Some factors, like psychological distress, “open” the gate, while others, like stress reduction, “close” the gate.[29] This theory proposes a possible mechanism for how higher cortical functions influence the subjective perception of pain.

Neuromatrix Theory of Pain

Even as theories of pain perception continued to develop, pain as a purely sensory and unidimensional experience persisted as the dominant assumption.[30] In 1968, Melzack and Casey[31] were the first to characterize pain as a multidimensional experience with affective and motivational qualities distinct from other sensory experiences. They outlined three major psychological components of pain: sensory-discriminative (e.g., location, intensity, or quality), motivational-affective (e.g., stress or fight-or-flight responses) and cognitive-evaluative (e.g., culture, personality, attention or depression).[23,31,32] Subsequently, the neuromatrix theory of pain was proposed and integrated into the GCT model.[33]

It proposes that a widely distributed neural network between the thalamus and cortex, and the cortex and limbic system creates the body-self. Initially, the spatial distribution and synaptic links of this network are genetically determined, but they are later influenced by sensory inputs.[34] Together, this network is called the neuromatrix. All inputs to the nervous system undergo a process to create signature patterns throughout the neuromatrix, resulting in a “neurosignature”. This neurosignature is projected into the sentient neural hub, where it is converted into a sense of awareness and movement.[32] The neurosignature undergoes a similar process to activate the spinal cord for complex actions.[34] Sensory-discriminative, motivational-

affective, and cognitive-evaluative factors contribute to the patterns of activity generated by the body-self neuromatrix, which is comprised of three neuromodules: sensory, cognitive and affective.[32]

These theories can be applied to both acute and chronic pain. Importantly, while acute pain is often comprised of brief and noxious signals, chronic pain often lacks a discernable causal stimulus.[35] Furthermore, the relationship between pathology and pain intensity is often unclear. [35] Rather, in chronic pain, it is the neurosignature rather than the direct sensory input from injury or other pathology, that produces the multiple dimensions of pain.[32] Furthermore, less input, whether noxious or non-noxious, is needed to trigger pain over time.[36]

The biopsychosocial model is a framework in which health can be understood as a product of biological, psychological, interpersonal, cultural and systemic dynamics.[37] Taken together with current theories of pain perception, pain can be understood as a multidimensional dynamic experience that is impacted by a range of variable biopsychosocial factors over time. As our conceptualization of pain has progressed, so too have the methods that may be required to adequately capture these pain experiences.

Trajectory Modelling

Trajectory modelling is a method used to examine the variability, development and resolution of different pain conditions over time.[38] First, individual trajectories are identified based on sequential measurement scores over multiple timepoints, then participants with similar trajectories are clustered together, creating trajectory groups.[38] Once the groups are identified, statistical testing can be used to describe longitudinal changes within and among

groups.[38,39] Through this process, the representative features of each trajectory group may emerge.

The most prominent statistical approaches to identifying trajectory groups and analysing differences are Latent Class Models (LCMs), such as Group-Based Trajectory Modelling (GBTM)[40,41] and Growth Mixture Modelling (GMM).[42–45] However, these methods are not recommended for small samples sizes (n<500) because they are likely to produce spurious results.[39,46–50] Techniques more suitable for smaller sample sizes will be discussed, given the sample size for the current project.

There are several advantages to using trajectory modelling in pain research. For self-limiting conditions, like some acute pain, trajectories provide insight into rate of resolution, which may otherwise be lost in cross-sectional, single-assessment designs.[51] In chronic, recurrent, conditions like low back pain (LBP)[43] or headache,[52] it becomes possible to discern whether a participant's pain is episodic, rather then multiple, unrelated, acute, events.[43,52] In both cases, trajectory modelling can be useful for examining risk factors and outcomes in groups where random assignment is not possible or there is high heterogeneity.[38] Furthermore, this method allows for the examination of both inter-individual changes, like predictors of trajectory group membership, and intra-individual changes, like a single participant's pain over time, which has not been possible with the existing methods. As such, this study chose to use trajectory modelling to examine CBCSP.

Trajectory Modelling in Chronic and Postoperative Pain Populations

Trajectory modelling is new and emerging in the CBCSP literature, so characteristic groups have yet to be established. However, trajectory modelling has been used widely in other

pain populations. Previous studies in the chronic and postoperative pain literature may provide insight into how CBCSP trajectory groups may be characterized and established.

In a study of adolescents with recurrent headache (n=2488), Stanford et al[52] used slope and variance in reported pain intensity to examine change over time, and intercepts to capture intensity at the beginning and end of participant trajectories. Then, they used regression analysis to determine that adolescents who reported higher baseline psychological distress were more likely than those who reported lower psychological distress to have more headaches over the course of adolescence.[52] In their review of LBP, Kongsted et al[53] were the first to propose a framework to characterize representative trajectories based on three characteristics: intensity (minor, mild, moderate and severe); variability (persistent, fluctuating, episodic, single episode); and change (rapid improvement, gradual improvement, progressing, no change).[53] Subsequent studies verified the prevalence of the representative trajectories,[54] determined factors associated with trajectory group membership,[55] and compared these findings to similar conditions, like neck pain.[56–58]

In the postoperative pain literature, trajectory modelling has been widely used to examine the rate of postoperative pain resolution and the effects of biopsychosocial factors over time.[10,42,59–64] In a study of people undergoing nonambulatory nonobstetric surgery (n= 7293), Tighe et al[64] examined the effects of age, sex and surgery type on pain intensity scores over the first 24 hours after surgery. They found that, while pain decreased significantly for all age groups, it decreased faster for younger participants compared to older participants and for digestive surgery compared to integumentary surgery.[64] In a study of elective surgery (n=502), Chapman et al[51] sought to characterize representative trajectories of postoperative pain using

intensity scores in the first 6 days after surgery. Rate of resolution (slope) and initial intensity (intercept) were used to cluster three groups: negative (n= 316, 63%), flat (n=126, 25%); and increasing (n=60, 12%).[51] In another study (n=199), Althaus et al[65] used acute postoperative trajectory to determine that groups with higher initial pain intensity and slower rate of resolution in the first 5 days after surgery were more likely than those with lower initial intensity and faster resolution to report chronic postoperative pain at 6 months.[65] Participants reporting higher levels anxiety reported more severe pain than participants with higher levels of depression immediately after surgery, but those with higher levels of depression reported lower rate of improvement in severity over the 5 days.[65]

Taken together, the findings and methods used in chronic and postoperative pain trajectory literature may guide this study's examination of BCSP trajectory, which may include time, rate of resolution and start- and end-point pain intensity. Once the common BCSP trajectories emerge, future studies may be able to expand on and refine the findings.

BCSP Trajectory Modelling

Expanding upon methodologies from other chronic conditions is particularly important as, to my knowledge, there are only five BCSP trajectory studies.[20,44,66–68] Of these studies, there was only one that considered intra-individual changes[68] and only one that examined a range of biopsychosocial predictors of group membership.[44]

In their study of acute breast cancer surgery pain (ABCSP) trajectory (n=123), Okamoto et al[69] used GBTM to form three groups based on pain intensity during the first week after surgery: mild (n=20, 16%), moderate (n=66, 54%) and severe (n=37, 30%). Using logistic regression, they found that participants in the severe group were nine times more likely than

participants in the mild group to report CBCSP at 6 months. Furthermore, the severe group reported significantly higher initial intensity and lower rate of resolution than the mild pain severity group. While this study was the first, to my knowledge, to examine ABCSP trajectory as a predictor of CBCSP, it only measured CBCSP as a dichotomous outcome.

Leblanc et al[66] examined ABCSP trajectories (n=608) as a risk factor for CBCSP at 2 years. They identified three trajectory groups based on pain intensity in the first 24 hours after surgery: low (n=388, 64%), resolved (n=182, 30%), and unresolved (n=38, 6%). Using logistic regression, they found that participants in the unresolved trajectory group were 16 times more likely than those in the low trajectory group to report CBCSP at 2 years. Similar to Okamoto et al[69], they only measured CBCSP as a dichotomous outcome.

To examine the relationship between ABCSP and pain expectations (n=563), Sipilä et al[67] used immediate postoperative pain intensity and slope over the first week after surgery to form three groups: flat slope (n=175, 31%), positive slope (n=107, 19%) and negative slope (n=281, 50%). They found that higher initial intensity was associated with faster resolution, and expecting severe pain, undergoing ALND and psychological distress were associated with higher intensity over the first 7 days after surgery. While this study was insightful into the relationship between ABCSP and pain expectations, it did not examine CBCSP trajectories or a wide range of biopsychosocial factors.

Voute et al[68] identified temporal patterns at pre-treatment baseline, immediately post-treatment, 6 months and 12 months (n=89). Using GBTM, they characterized two groups: transient pain trajectory (n=39, 44%) and persistent pain trajectory (n=50, 56%). They found that participants with transient pain did not have a linear trajectory, but rather, one that was

closer to a quadratic slope, characterized by minimal baseline pain, an increase in pain after intervention, and then a decrease until resolution at 12 months. Although participants with persistent pain had a similar increase in pain after intervention, their baseline pain was significantly higher, did not decrease as quickly, and did not resolve at 12 months, when compared to those with transient pain.[68] However, this study included participants who did not undergo surgery, limiting the interpretation of these results.

To examine a range of risk factors, Miaskowski et al[44] used worst, weekly, pain intensity and GMM to cluster participants (n=398) into three groups: mild pain class (n= 173, 43%), characterized by mild baseline intensity and mild average intensity over 6 months; moderate pain class (n=53, 13%), characterized by mild baseline intensity and moderate average intensity that increased from 2-5 months, then decreased slightly at 6 months; and severe pain class (n=46, 12%), characterized by severe baseline intensity and severe average intensity that decreased slightly over 6 months. They also identified a group of participants who did not report any pain (n=126, 32%) but excluded them from the initial group clustering. Compared to participants with moderate or severe pain, participants with no or low pain had lower preoperative pain, fewer comorbidities, fewer symptoms like swelling in the breast, increased quality of life, did not undergo ALND and reported fewer postoperative complications. However, this study excluded all intensity scores at 1 month from initial group clustering, did not extend beyond 6 months and did not consider intra-individual variability, limiting the generalization of these results.

The few longitudinal, non-trajectory, studies which examined BCSP over longer follow-up periods[70–72] found that younger age, surgery type, undergoing hormone therapy, higher

BMI, symptom burden, depression, stressful life events in the first year after study enrollment and low physical activity were associated with chronic pain. However, none of them included preoperative measurements, limiting the interpretation of these results.[70–72]

While these preliminary studies have examined ABCSP and CBCSP trajectory up to 6 months after surgery, they have not examined a wide range of biopsychosocial outcomes over a longer follow-up. Additionally, across the five BCSP trajectory studies, the most common pain characteristics studied were duration (acute or chronic) or intensity (mild, moderate or severe).[20,44,66–68] Outside BCSP, however, pain trajectory studies have also considered syndrome/diagnosis (e.g. cancer, surgical, radiation), type (e.g. nociceptive, neuropathic, inflammatory), temporal pattern (e.g. persistent, episodic) and quality (e.g. stabbing, burning, shooting).[30,35,73] These characteristics can overlap and change over time.[73,74] As the research advances, future studies should examine whether BCSP trajectories can be described using a wider range of characteristics.

The current study collected data at preoperative baseline and at 1 week, 6 months, 1 year and 2 years postoperative, offering the opportunity to extend the current available BCSP trajectory data well beyond 6 months. Given this study's sample size (n=73), methods like LCM cannot be used due to the risk of spurious results. Instead, forming trajectory groups based on slope and start- and end-point intercepts, followed by logistic regression to examine risk factors, was chosen as the most appropriate option. In on the existing literature, this method has been widely used to establish characteristic trajectories in other chronic and postoperative conditions.[42,51,64]

Measuring and Characterizing Pain Using Numerical Rating Scales (NRSs)

This study used NRS-R pain intensity ratings to plot trajectories. NRSs are a series of numbers from 0-10 (11-point) or 0-100 (101-point) with the zero-end labelled "no pain" and the highest-end labelled as "worst possible pain".[75,76] They can be administered verbally or by pencil-and-paper.[75] When scores are described categorically, they are most often, 0 = "no pain", 1-3 = "mild", 4-6= "moderate" and 7-10 = "severe",[77,78] with a minimally clinically important difference (MCID) of two points.[75,77–82] The NRS has been widely validated for use in a variety of pain conditions, including cancer and postoperative pain.[79,83–85]

NRSs have demonstrated sensitivity to treatments impacting pain intensity,[86] have significant correlation with other measures of intensity[76] and are easy to administer.[75] Similar pain assessments include the Verbal Rating Scale (VRS) where participants rate their pain using a list of adjectives describing different levels of intensity ("no pain", "mild pain", "moderate pain" or "severe pain") and the Visual Analogue Scale (VAS) which consists of a line (commonly 10cm long) whose ends are labelled "no pain" to "worst possible pain", and participants indicate which point on the line best captures their pain intensity.[75] While all three scales report strong psychometric properties,[75] several studies have reported that NRSs have the strongest psychometric properties of the three.[87–90] In particular, NRSs are suitable for both younger and older participants, as VASs and VRSs have greater error rates and lower face validity among older participants.[86,88,91] Given its strong psychometric properties, this study used the NRS as the primary measure of pain intensity. Specifically, it chose to use the NRS-R, rather than the NRS-M, as it more widely reported in the literature [92] and movement-evoked pain assessments often lack standardization.[93]

Risk Factors of BCSP

Given the current understanding of pain perception and pain as a multidimensional experience,[31] this study adopted a biopsychosocial model to examine risk factors and outcomes of CBCSP. According to this framework, CBCSP is likely to be predicted by a range of preoperative biopsychosocial factors.

Pain Factors

Preoperative Pain. Higher preoperative pain severity has been well-established as a predictor of higher postoperative severity.[94–97] Furthermore, recent systematic reviews have found that higher preoperative pain is a predictor of both acute [98] and chronic [99] postoperative pain.

While the examination of preoperative pain and CBCSP is emerging, recent studies are consistent with the wider postoperative pain literature.[8,67,100–102] For example, in a prospective cohort study of participants undergoing BCS (n=140), Chiang et al[103] identified moderate to severe preoperative pain as a risk factor for reporting CBCSP 6 months after surgery. Similarly, Schreiber et al[102] identified both breast-specific and general preoperative pain as risk factors for chronic breast pain at 12 months.

Acute Postoperative Pain. Acute pain refers to any pain that lasts less than 3 or 6 months, after which it is considered chronic.[104,105] However, this definition is not always consistent, for example, some studies label acute pain as “persistent” when it lasts longer than a week but less than 3 months.[104,105]

Generally, pain is expected after surgery.[105,106] However it has been well-established that higher acute postoperative pain is a risk factor for the development of chronic postoperative pain, and for that chronic pain to be more severe.[10,107–111] In an randomized

controlled trial (RCT) of the effect of gabapentin on postoperative pain trajectories (n=422), pain at postoperative day 10 was the strongest predictor of time to pain resolution and complete recovery after surgery in both the treatment and active placebo groups.[112] Furthermore, Danielsen et al[113] (n=85) found that participants with higher acute pain after lung cancer surgery were more likely than participants with lower acute pain to report protracted or incomplete recovery and more neuropathic pain symptoms.

These findings are consistent in the BCSP population.[19,20,114–123] For example, Habib et al[117] (n=124), found that participants with moderate to severe ABCSP were five times more likely that participants who reported mild ABCSP to report CBCSP at 6 and 12 months. There have also been two ABCSP trajectory studies that found participants in the severe group were more likely than those in the mild group to report chronic pain at 6 and 24 months.[20,66] However, these studies only examined CBCSP as a dichotomous outcome and did not consider chronic trajectory, limiting the interpretation of these results.

Neuropathic Pain. Neuropathic pain is associated with lesion or disease of the somatosensory nervous system.[73] Both the central and peripheral nervous systems play a role.[73] Neuropathy can be associated with negative symptoms, such as lack of sensation, or positive symptoms such as spontaneous pain, allodynia (pain from non-painful stimuli) or hyperalgesia (increased pain).[73]

Nerve damage, and subsequent neuropathic pain, after surgery is a concerning issue, with some studies estimating that 10-40% of people develop chronic, neuropathic, postoperative pain.[124,125] Furthermore, Vigotsky et al[126] found that preoperative neuropathic

pain symptoms following total knee replacement were associated with more severe pain trajectories 3, 6 and 12 months after surgery.

Similarly, 15-30% of people with CBSP report probable neuropathic pain.[8,127] This may be due to intra-operative ALND and damage to the intercostobrachial nerve.[114] Compared to people who do not report neuropathic pain symptoms immediately following surgery, those who do report symptoms may be at increased risk of developing CBCSP and for that pain to be more severe.[114,127,128] However, there are no studies, to my knowledge, that examined the role of preoperative neuropathic pain on CBCSP trajectory.

Pain Interference. Pain interference is an individual's perception of how much their pain limits daily life across physical, emotional, and social domains.[129] Higher preoperative pain interference is associated with higher postoperative severity.[130–133] For example, in a study of orthopedic surgery, Giordano et al[134] found that participants with higher preoperative interference were more likely than participants with lower preoperative interference to be in a persistently high, rather than a low or improving, trajectory.

Pain interference, to my knowledge, has only been examined as a postoperative outcome and there is no evidence on its role in BCSP trajectory. However, in people with CBCSP, interventions targeting interference have been associated with lower disability and higher quality of life in a range of domains, including physical and mental well-being.[135] These findings suggest that preoperative pain interference may play also significant role in BCSP trajectory group membership.

Pain Expectations. Preoperative expectations have been associated with acute and chronic postoperative outcomes.[131,136–139] Generally, higher preoperative expectations have

been associated with higher postoperative pain intensity.[140] Discrepancies between preoperative expectations and postoperative experience may be associated with higher pain intensity if participants' expectations were affected by anxiety, fear, helplessness or catastrophizing.[137,138] Positive expectations have also been associated with lower postoperative pain intensity.[138]

There are few studies examining pain expectations and BCSP, and especially CBCSP. However, one study found that higher preoperative expectations were associated with higher BCSP in the first week after surgery.[67] People who expected severe pain rather than moderate or low pain were more distressed, reported more preoperative pain, and consumed more analgesics.[67]

Surgical Factors

Surgery Type. The literature examining surgery type and BCSP is inconsistent and contradictory. Many studies have identified undergoing mastectomy, rather than lumpectomy, as a risk factor for CBCSP,[141–145] attributing it to mastectomy being more extensive, with longer recovery times and increased chances of complications.[141,146–148] However, some studies found lumpectomy to be more likely to be associated with CBCSP[149–151] or for surgery type to have no significant effect.[123,152,153] Heterogeneity within surgery types, and among participant characteristics,[123,145,150,154–156] may contribute to the mixed findings and inconsistencies in the literature. As such, this study included surgery type to elucidate its relationship with BCSP.

ALND. ALND is the removal of lymph nodes in the underarm area.[3] It is one of the most consistent predictors of CBCSP.[21,98,123,151,157,158] During this procedure, the intercostobrachial nerve may be damaged, with some studies estimating that it is only fully preserved in 34% of

surgeries. [159,160] This damages leads to an increased risk of neuropathic pain symptoms.[159,160] However, all of this study's participants underwent either modified radical mastectomy or lumpectomy with ALND wherein 10-30 lymph nodes in the axilla region were removed. Thus, future studies should investigate undergoing ALND and BCSP trajectories more closely, once characteristic trajectory groups have been established.

Physical Factors

Physical Symptoms and Comorbidities. Symptoms are subjective evidence of disease or physical disturbance observed by a participant.[161] The severity and impact of symptoms can accumulate, which is referred to as symptom burden.[162] Comorbidities are the presence of co-occurring conditions.[163–165]

People with advanced and chronic conditions often have multiple symptoms that increase in intensity over time.[166] In a study of people with cancer, Chang et al[167] found that those with moderate pain reported a median of 11 symptoms, whereas those with mild pain reported a median of eight. Not only was pain one of the most common symptoms, but compared to participants without pain, those with moderate pain had an increased risk of developing nausea, shortness of breath, lack of appetite, and fatigue.[167,168]

BCSP has been associated with high symptom burden,[168–170] and most people with BCSP report symptoms which interfere with their lives.[168] Higher symptom burden[167] and a greater number of comorbidities was associated with increased pain, complications and morbidity following BCS.[171,172] Thus, this study included measures of physical symptoms and comorbidities to further elucidate this relationship.

Demographic Factors

Age. The literature on age and postoperative pain is inconsistent, with studies finding acute and chronic pain to be associated with younger age, older age, or no effect of age at all.[173–175] The mechanisms behind any age-related patterns are unclear, but may span neurobiological changes and psychosocial factors.[176] The literature on age and BCSP is also inconsistent, with studies finding ABCSP and CBCSP associated with younger age, older age, or no effect of age at all.[119,157,177–183]

Many studies have found younger age to be a risk factor for BCSP,[102,177,184] including a recent meta-analysis and systematic review.[21] Younger age is also a risk factor for severe BCSP trajectory 6 months after surgery.[44] The reason for these findings remains unclear, but studies have suggested that younger participants were more likely to be diagnosed with more advanced cancer that needed more aggressive treatment; were more likely to undergo adjuvant treatment; or were more likely to report symptoms of psychological distress than older participants.[95,102,119,156,177,180,185] However, several recent studies have found that older age may be a risk for BCSP.[183,186–188] These studies suggested that older, rather than younger, participants were more likely to reported more advanced cancer or larger tumours,[183,187–189] to have more comorbidities, and to receive inadequate pain management.[183,187,188] Finally, there have also been studies that show no age effect on BCSP.[190,191] These studies suggest that the influence of age was a proxy for other risk factors, like health- and mental health-related quality of life, comorbidities and symptom burden.[157,190,191]

The extent to which age influences BCSP, if it influences it at all, requires further research. This study included age to further examine its influence on BCSP trajectories, especially beyond 6 months.

Treatment Factors

Treatment-related Pain. People may undergo additional treatment after BCS to destroy undetected cancer cells and reduce the rate of recurrence.[192,193] Treatment after surgery varies widely and can depend on factors like the number and timing of treatments; cancer and tumour characteristics; type of surgery; or age.[192,193] In the present study, additional treatments included chemotherapy, radiation therapy, hormone therapy, or a combination of the three.[192,193] Importantly, all three treatments have been associated with the development of BCSP and neuropathic pain symptoms.[100,144,194–199]

Chemotherapy uses drugs to target and destroy cancer cells.[200] Chemotherapy after BCS has been associated with acute and chronic pain.[201,202] One study estimated that participants undergoing adjuvant (additional treatment after surgery) chemotherapy were 40% more likely than those who did not to develop chronic pain. In addition, 40-60% of participants report chemotherapy-induced peripheral neuropathy (CIPN). In many cases, CIPN resolves shortly after finishing treatment, but in some cases, symptoms may persist for months or years.[203–205] In addition to neurotoxic damage, chemotherapy is also associated with side effects, such as muscle wasting, that may increase the likelihood of developing chronic pain after surgery.[206,207]

Radiation therapy uses high-energy particles to kill cancer cells.[208] It is commonly given after lumpectomy to reduce the risk of recurrence but may also be given after mastectomy.[193] While it can be given at the same time as hormone therapy, it is usually given after chemotherapy.[209] Adjuvant radiation therapy has been associated with both acute and chronic pain.[196,210,211] Commonly, pain may be a result of dermatitis, lymphedema or radiation-induced brachial plexus neuropathy (RIBPN).[210,212] While symptoms and side effects often resolve after

treatment is completed, RIBPN can occur and continue for months or years after radiation therapy is completed.[213]

Hormone therapy is used for breast cancer that is estrogen-receptor positive (ER+), progesterone-receptor positive (PR+), or both (ER+/PR+), in which drugs block or remove the hormones cancer cells need to grow.[214] The duration of treatment is usually 5-10 years, with common drugs including tamoxifen and aromatase inhibitors.[214] As with radiation therapy, it is most often given after chemotherapy.[209] Adjuvant hormone therapy has been associated with chronic pain, specifically, musculoskeletal symptoms like joint pain.[215–217] One meta-analysis estimated that 20-74% of people utilizing aromatase inhibitors report joint pain.[218]

Lymphedema. Lymphedema is a chronic and progressive condition where disruption of the lymphatic system causes the accumulation of fluid in the interstitial space of an affected body part.[219,220] In people with breast cancer, the swelling is commonly in the arm or hand, but can also be in the shoulder, breast, chest wall, or trunk.[221] After BCS, 20-40% of people may report lymphedema[222] and while most cases emerge within the first 2 years after surgery, there have been cases that occurred years or decades later.[219,222–224] Surgical factors and adjuvant treatment are strong predictors of lymphedema. For example, undergoing ALND, mastectomy, delaying reconstruction, chemotherapy, and radiation have all been associated with an increased risk of lymphedema.[219,222,223,225,226] Participants with lymphedema report long-term burdens, including chronic pain, disability to the affected limb, significant impacts to quality of life, and psychosocial challenges.[219,221,223,227] Not only is it directly associated with treatment-related pain, but recent studies have found that after BCS, people who developed lymphedema

were more likely than those who did not to report higher pain intensity, pain sensitivity, neuropathic symptoms, and kinesiophobia (fear of movement).[228,229]

Previous Treatment. Participants in this study may have undergone preoperative chemotherapy, radiation therapy and hormone therapy, including those continuing treatment for a previous tumour. The literature comparing pain after neoadjuvant (additional treatment before surgery) and adjuvant treatment is mixed, depending on the treatment. A recent meta-analysis suggested that people who underwent neoadjuvant chemotherapy were more likely than those who underwent adjuvant chemotherapy to report severe discomfort.[230] In a study of neoadjuvant radiation, Civil et al[231] found that participants who underwent radiation before surgery reported lower acute postoperative pain than those who underwent radiation after surgery. A recent RCT comparing preoperative hormone therapy to standard adjuvant care after surgery did not observe a difference in the rate of musculoskeletal pain at 9 months.[232] These mixed findings may reflect the heterogeneity of participants undergoing BCS. For example, while treatment-related pain from neoadjuvant treatment may increase the likelihood of developing postoperative pain, the reduction of tumour size through neoadjuvant treatment may be associated with a reduction in postoperative pain.[195,233]

Given that it is common for people undergoing BCS to undergo additional treatment after surgery, and the gaps in our knowledge about how treatment-related pain influences the development and maintenance of BCSP, this study tracked pre- and postoperative treatments to examine their influence on BCSP trajectories.

Psychological Factors

Anxiety. Anxiety is the tendency for intense worry and apprehension about adverse future events.[234,235] State anxiety is an acute, situation-driven reaction that reflects current subjective feelings.[235,236] It usually does not persist beyond the triggering situation and may include tension, nervousness, worry, and activation of the autonomic nervous system.[235–238] Trait anxiety is a stable personality feature, and reflects anxiety proneness, including states of security, calmness and confidence.[235,237,238] State anxiety may be more predictive of acute pain after surgery than trait anxiety[236,239] and some studies have suggested that the State Trait Anxiety Inventory – Trait (STAI-T) may be a measure of negative affect, rather than trait anxiety.[240,241]

State anxiety has been associated with higher levels of acute postoperative pain.[81,242–244] In a systematic review of 48 studies (n= 23,037), state anxiety was identified as one of the most significant predictors of postoperative pain intensity.[242] Furthermore, an RCT (n=90) found that lowering preoperatively state anxiety through education predicted lower acute postoperative pain.[245] Anxiety has also been associated with chronic postoperative pain.[11,140,246–248] Approximately 41-75% of people undergoing breast cancer surgery report moderate to high preoperative anxiety. [249,250]

Higher levels of preoperative state anxiety has consistently been associated with increased rates and severity of ABCSP[109,119,140,251–253] and CBCSP.[254] A study examining the differences between breast cancer survivors with and without chronic pain (n=417) found that those with pain reported significantly higher levels of anxiety and emotional distress than those without pain.[255] However, the effect of anxiety on CBCSP is not consistent. For example, a prospective study examining risk factors for CBCSP (n=1544) found that preoperative anxiety

was correlated with, but not predictive of, chronic pain.[256] A similar study (n=475) found that preoperative anxiety was not associated with pain at rest or with movement 1 year after surgery.[114]

A few studies have examined how anxiety impacts other pain trajectories,[109,251,256] but there is only one, to my knowledge, that examined the role of anxiety on CBCSP trajectories.[44] This study found that participants in the "no pain" (n=126) trajectory reported lower state anxiety scores than those with severe pain trajectories.[44]

Pain-related Anxiety. Pain-related anxiety is the tendency for an individual to respond with anxiety or fear to an actual or potential painful experience.[257] The fear-anxiety response can occur during non-painful activities.[258] It is usually measured across four components (cognitive anxiety, escape avoidance, fear, and physiological anxiety)[258] and is distinct from pain catastrophizing, state anxiety, and anxiety sensitivity.[258,259]

People with chronic pain report higher levels of pain-related anxiety than those without pain.[260,261] In a meta-analysis of a range of clinical pain samples (n=20,028), higher pain-related anxiety was moderately associated with higher pain severity.[262] Picavet et al[263] found that among people with LBP, pain-related anxiety was a significant predictor of severe pain and pain-related disability at 6 months.

A longitudinal study of thoracic surgery (n=104) found that higher pain-related anxiety 1-week after surgery was the strongest predictor of chronic postoperative pain intensity at 3 months.[264] However, results are inconsistent. For example, a longitudinal study of participants (n=259) undergoing general, gynecology and thoracic surgery found that pain-related anxiety did not predict acute or chronic postoperative pain.[265]

A study of participants undergoing BCS (n=1889) found that participants with preoperative breast pain had increased pain-related anxiety scores when compared to participants with no preoperative breast pain.[121]

Pain Catastrophizing. Pain catastrophizing is the tendency to magnify, ruminate and feel hopeless at the thought of, or in anticipation of, pain.[266] It can be a major component of fear avoidance, leading to depression, avoidance of daily activities and withdrawal from work, social life, and health maintenance activities.[266]

A meta-analysis of chronic musculoskeletal pain (n=13,628) found that, cross-sectionally, higher levels of catastrophizing were associated with increased pain intensity.[267] Five out of six longitudinal studies in the meta-analysis found that higher baseline catastrophizing was associated with higher pain intensity during subsequent assessments, even when controlling for other variables.[267]

In a study of postoperative pain trajectories (n=348), Giordano et al[268] found that pain catastrophizing changed over time. They characterized four catastrophizing groups: stable (consistently low scores over time), remitting (high baseline scores that decreased over time), worsening (low baseline scores that increased over time), and unremitting (consistently high scores over time). At baseline, participants in the stable trajectory, compared to all other groups, reported the lowest postoperative pain intensity. At 6 months, participants in the stable trajectory continued to report significantly lower postoperative pain than those in worsening or unremitting trajectories. Participants with worsening, rather than stable or remittent, catastrophizing reported worsening pain intensity over time.[268] Despite having significantly higher initial preoperative pain scores, participants in the remittent group reported

the largest overall reduction in postoperative pain intensity, similar to the stable group.[268] These interactions suggest that changes in catastrophizing may affect postoperative intensity over time, where worsening catastrophizing may also worsen pain intensity and complicate recovery.

In participants undergoing BCS, the effect of pain catastrophizing was similar. Bovbjerg et al[255] found that people with pain after BCS were more likely than people without pain after surgery to report higher psychological distress and catastrophizing.[255]

Mechanisms of Anxiety, Pain-related Anxiety and Catastrophizing. There are several theories of how anxiety can potentiate and maintain pain. Anxiety has been associated with several physiological responses that may potentiate pain, including an increase in inflammatory cytokines [269] and dysregulation of emotional and sensory processing.[270,271] However, the prominent theory is that psychological distress, including anxiety, pain-related anxiety, and catastrophizing, creates a positive feedback loop that maintains pain.[258,272] This distress can disrupt attention, which interferes with effective behaviours and successful problem solving; lead to extreme or persistent arousal in tissues, making them sensitive to other painful stimuli; and lead people to perceive more physical symptoms.[258] This may lead to subsequent avoidance, inactivity and physical deconditioning, which increases the likelihood of greater disability, proneness to injury and worsening pain.[258,272,273]

The present study assessed preoperative state anxiety; pain-related anxiety and pain catastrophizing to explore their influence on BCSP trajectories. A measure of trait anxiety was not included in the interests of reducing patient burden and because the STAI-T has been found

to be a strongly correlated with negative affect and depression, rather than anxiety, and may not reflect changes over time[274].

Depression. Depression is a state of low mood or anhedonia, and can encompass a wide range of psychological, physiological and behavioural symptoms.[275,276] The bidirectional relationships between depression and chronic postoperative or cancer pain have been well-established.[262,277–280] People with depression who are pain-free are more likely than those without depression to develop chronic pain, and people with chronic pain are more likely than those without to develop depression.[281] Furthermore, pain and depression can have overlapping symptoms such that symptoms of one condition worsen the other.[282]

Depression and CBCSP have been widely examined.[246,247,283] People with higher preoperative depression are more likely than those with lower preoperative depression to develop CBCSP and to report higher intensity.[246,247,284–286] For example, in a recent systematic review, Moloney et al[287] found that preoperative symptoms of depression were a predictor of acute and chronic pain after sugary at all time points up to 12 months. However, further research is needed to confirm this finding across BCSP trajectories.

Pain Attitudes, Acceptance and Coping. How participants perceive and manage their pain before surgery, including attitudes, acceptance, effective coping and traumatic stress can influence postoperative outcomes. For example, participants who received interventions targeting acceptance after surgery were less likely than those who did not receive intervention to report psychological distress and develop chronic postoperative pain.[288,289]

These trends are consistent in participants with BCSP. A recent systematic review found that psychological factors related to distress were associated with CBCSP immediately after

surgery and at 12 months.[290] This study also included measures of pain attitudes, pain acceptance, and traumatic stress to continue exploring their role across BCSP trajectories.

Spirituality. Spirituality is the meaning by which people understand their lives, which can exist separate from religious belief. In people with chronic and postoperative pain, spirituality has been associated with higher mental and physical well-being, through improved coping.[291–294] There were no studies, to my knowledge, that examined its role in BCSP trajectory. So, this study included a measure of spirituality to elucidate this relationship.

Social Factors

Social factors are strong predictors of wellbeing in cancer,[295,296] including breast cancer.[297] These factors may influence cancer pain directly or they may interact with other factors like stress, coping, anxiety, depression and catastrophizing to influence cancer pain. In studies of postoperative pain, the relationship between pain and social factors is less clear. Some studies have found an association[298,299], while others did not.[300] In participants undergoing BCS, social needs are among the most frequently reported.[301] Despite the literature examining the influence of social factors in breast cancer, the literature on breast cancer surgery and recovery, specifically, is more limited. The present study examined a range of social factors, including social support, marital satisfaction, perceived caregiver's responses to pain, and attachment style.

Social Support. Social support is the perception of being cared for, loved and esteemed in mutual replationships.[302] In this study, social support was measured by the amount of perceived functional support across emotional, tangible, affectionate, and positive domains,[303] like help getting to appointments or having someone to confide in.

In people with cancer, higher social support was associated with higher quality of life and lower pain severity.[304,305] Studies in postoperative pain, however, were more mixed.[298–300,306] A recent systematic review and meta-analysis of participants undergoing major surgery found that social support did not influence postoperative pain.[307] Conversely, recent studies in specific surgeries, like total knee replacement, found that higher social support may be associated with lower acute and chronic postoperative pain.[298,299,306] These findings suggest that the role of social support may change depending on surgery type.

In people with breast cancer, lower perceived social support has been associated with higher acute and chronic treatment pain.[308–310] This relationship may also be influenced by age. Some studies have found that younger adults tended to have worse social functioning and treatment-related pain than older adults.[311] Others have found that low social and emotional support has also been associated with pain and health-related quality of life after surgery in older adults as well. [312,313]

There was only one study, to my knowledge, that examined social support and breast cancer surgery pain specifically, in which Munk et al[314] found that higher perceived social support was associated with lower acute pain unpleasantness at 4 weeks after surgery. Given these findings, further research is needed to examine the relationship between social support and BCSP.

Marital satisfaction. To measure marital satisfaction, the present study collected scores on how satisfied participants were with their relationship, their partner as a partner, and their relationship with their partner.

In participants with cancer, marital quality and satisfaction have been associated with pain intensity.[315] Moreover, marital satisfaction may be an important mediator between pain and other factors, like pain interference, effective coping and psychological distress.[316–318] For example, Badr et al[319] found that higher pain severity was associated with greater relationship distress and that the provision of support may be contingent on the perception of this distress within the relationship.

In participants with breast cancer, a longitudinal study found that, compared to those dissatisfied with their marriages, women who were satisfied with their marriage reported fewer treatment-related symptoms, including pain, at baseline and over time.[320]

Caregiver's Responses to Pain. Support from caregivers is critical for patient adjustment, effective coping and wellbeing in cancer.[317] For people with cancer pain, caregiver's responses can be perceived as helpful (solicitous/distracting) or negative (punishing),[318] and the perception of these responses can reinforce or minimize pain behaviours.[316,318] For example, solicitous responses (e.g., asking how to help) may reinforce maladaptive behaviours, while distracting (e.g., encouraging to work on a hobby) or punishing (e.g., getting angry) responses may minimize them.[316]

While perceived solicitous responses have been associated with chronic postoperative pain[321,322] the data regarding the role of caregiver's responses in BCSP is lacking. In a study of women with metastatic breast cancer, only punishing responses were related to pain behaviours. [316] Specifically, in women with high levels of pain, reporting more perceived punishing responses was associated with engaging in more pain behaviours. On the other hand, in women with low levels of pain, reporting more perceived punishing responses was

associated with engaging in fewer pain behaviours, suggesting that caregivers' responses may be perceived differently, depending on pain severity.[316] These findings suggest that, while perception of caregivers' responses plays a role in breast cancer pain, further research is needed to extend the findings to participants undergoing BCS.

Attachment style. Attachment style is the way emotional connections are approached in relationships.[323,324] According to attachment theory, these cognitive schemas are developed during early life and continue into adulthood.[323] Attachment style may be characterized in three ways: secure, being comfortable getting close to others without being worried about being abandoned or others getting too close; anxious, being reluctant to get close to others in fear of being rejected or abandoned; and avoidant, being uncomfortable with being close and depending on others[325,326].

Attachment style is activated during stressful situations (e.g., breast cancer surgery) and has been strongly associated with the ability and extent to which one is able to elicit and respond to support.[327] For example, individuals with secure attachment may be more willing to depend on others.[328] While the association between pain and attachment style has been established in chronic pain populations,[329–331] the literature in cancer and non-obstetric postoperative pain is still emerging.[318,332] Similarly, the literature on its relationship with BCSP is lacking.

In a recent systematic review of attachment style and quality of life in participants with early-stage breast cancer, Karveli et al found[333] that avoidant, rather than anxious attachment, was associated with lower quality of life and higher distress.[333] There was only one study, to my knowledge, examining the role of attachment style on chronic pain after breast cancer

treatment, in which Smith et al[334] found that high attachment anxiety, but not avoidance, was associated with chronic pain. Further research is needed to examine the relationship between attachment style and breast cancer surgery pain.

Based on the current literature, a number of social factors play significant roles in cancer and postoperative pain. Few studies have examined the role of these factors in BCSP, the literature is broadly lacking. To address this gap in the literature, this study included a range of social factors to examine their relationship with pain.

Relevance and Importance

Despite emerging literature, BCSP trajectories remain understudied. Establishing characteristic trajectory groups allows for the closer examination of heterogenous groups that has not previously been done. Furthermore, considering a wide range of biopsychosocial risk factors for trajectory group membership allows for the identification of potential modifiable factors.

Objectives

1. To characterize postoperative BCSP trajectories across 2 years.
2. To explore factors associated with BCSP trajectory group membership.
3. To develop a model of preoperative factors associated with unresolved BCSP at 2 years.

METHODS

Study Design and Setting

This study was a sub-analysis of data collected in a previous, larger study on postoperative pain after BCS (Canadian Cancer Society Research Institute Grant no. 18367) carried out at Toronto General Hospital (TGH) and Princess Margaret Cancer Centre (PMCC) in Toronto, Ontario. Ethics approval was obtained from the University Health Network (UHN) and York University (#07-0553).

Study Sample, Inclusion and Exclusion Criteria

300 participants scheduled for unilateral or bilateral modified radical mastectomy or lumpectomy with ALND were recruited. *Inclusion criteria* included: sufficient ability to read and write English to provide informed consent and complete questionnaires and age >= 18. *Exclusion criteria* included: Significant CNS, respiratory, cardiac, hepatic, renal or endocrine dysfunction and/or any significant sequelae; contraindications to opioids, acetaminophen or Tylenol 3, documented DSM-IV Axis I disorder or cognitive dysfunction, documented substance abuse or dependence within 1 year, pregnancy or breastfeeding within 6 months or use of exogenous hormones in regularly menstruating participants (e.g. oral contraceptives or hormone replacement therapy) within 3 months, immunization within 30 days, blood donation within 60 days, acute or infectious illness, allergic reactions, herbal supplements, physical injuries or dental work within 2 weeks.

Procedure

Acronyms will be used to discuss the data collection measures in this section of the procedure. Explanations of the acronyms for measures relevant to the present study will be

included in the measures section and a full list of abbreviations is included in the beginning of this document (page xii).

Preadmission Assessments

Participants were recruited from BCS info sessions and at the preadmission clinic for their surgery. They were approached by a research assistant (RA) who explained the study. Once recruited, all participants were documented, and reasons for exclusion, drop-out and withdrawal were recorded. An RA obtained informed consent and administered the SOMC. More than 10 errors on the SOMC indicate cognitive impairment,[335] and these participants were removed from the study. Eligible participants provided demographic information and pain history. They completed measures of pain, physical function and wellbeing, psychological factors, and allodynia measures (Quantitative Sensory Testing; QST). Blood samples to assess cytokines, hormones, and other measures of comorbidities and physical functioning were also completed at this time. The SF-MPQ, SF-NPQ, NRS-R, NRS-M, arm function, menstrual status, ESAS, and QST were completed on-site. The BPI, SF-12, STAI, PASS, PCS, CES-D were completed at home and returned the day of their surgery. After the assessment, the RA conducted a chart review for additional disease information and completed measures of comorbidities.

Preoperative, Intraoperative and Postoperative Assessments

All pre-, intra-, and immediate postoperative assessments were completed on-site. Immediately before their surgery, participants completed the SF-MPQ, NRS and SF-NPQ, measures of menstrual status, ESAS, STAI-S QST, and analgesic consumption in-person. Blood samples to assess estradiol, progesterone and cytokines were completed. Analgesic consumption, surgical duration, and complications were recorded intraoperatively.

6-hours after surgery, participants completed the NRS and CAM. Participants with CAM scores indicating delirium that required nurse intervention were withdrawn from the study. 24-, 48- and 72-hours after surgery, blood samples to assess estradiol, progesterone, cytokines, and morphine (M3G, M6G) was collected alongside analgesic consumption and adverse events. Additionally, participants completed the SF-MPQ, NRS, satisfaction with pain control, SF-NPQ, arm function, ESAS, CAM, STAI-S, CES-D, and QST 24 hours .

Baseline and Follow-up Assessments

Baseline assessment was completed 1 week before surgery and follow-up assessments 1 week ±1 day, 6 months ±2 weeks and 1 year ±3 weeks and 2 year ±3 weeks after surgery. Participants were contacted for follow-up via email and telephone. The SOMC was completed at the beginning of each assessment. Following the SOMC, an RA completed demographics and updated medical information, including new treatment or intervention, repeated surgery, and analgesic use.

At the 1-week and 6-month follow-ups, participants completed the NRS-R, NRS-M, SAT, ESAS, and analgesic consumption with an RA, either on-site or at their home. If participants were on-site, blood samples to assess estradiol, progesterone, and cytokines and QST were completed. The SF-MPQ, SF-NPQ, BPI, STAI-S and CES-D were given to participants to complete at home and return by mail. The CCI and KPI were completed by an RA using their chart information.

At the 1-year follow-up, participants were asked to complete pain history and arm function with an RA on-site or at their home. The SF-MPQ, SF-NPQ, NRS-R, NRS-M, SAT, BPI, ESAS, SF-12, DASH, PASS, STAI-S, PCS, CES-D, CPAQ, FACIT-Sp-12, PAQ-R, IES-R, MOS-SS, MPI

caregiver response, ECR, KMS, R-DAS, analgesic use, and adverse effects were given to the participants to completed and return by mail. The CCI and KPI were completed by an RA after the assessment using the participant's chart information.

In cases where participants did not wish to travel or have an RA come to their home, questionnaires were completed with an RA over the phone. The completed questionnaire packages were returned by mail. Those who did not return the questionnaire package after 2 weeks were telephoned as a reminder.

Measures

Given that this study is a sub-analysis of the previous, larger, study, only a subset of the collected measures will be used. Measures of menstrual status, cytokines and hormones, analgesic consumption, dyadic adjustment, marital status and QST were not included because they are beyond the scope of this study.

Primary Outcome Measures

Pain intensity at rest (NRS-R) and *with movement (NRS-M*)[76] are 11-point numerical rating scales (NRS). Horizontal lines are numbered from 0 (no pain) to 10 (worst possible pain). For the NRS-R, participants were asked to report their present pain. For the NRS-M participants were asked to sit up and take two maximal breaths before reporting their pain. The NRS has demonstrated good reliability and validity in participants with cancer,[89] older adults [91] and postoperative populations.[88]

Secondary Measures

The *Short Orientation-Memory-Concentration Test (SOMC)* [335] is a 6-item mental status exam for acute care settings. It has been shown to be valid and reliable for the identification of

significant impairment of memory and concentration for participants in early post-acute stages of illness and with progressive or severe illnesses.[336]

The *Confusion Assessment Method (CAM)*[337] is a 9-item questionnaire to identify delirium through ratings of observable behaviours. In this study, the CAM was scored by an RA. It has demonstrated strong psychometric properties in a variety of medical settings.[50,338]

Pain Measures

Brief Pain Inventory (BPI)[129] is an 11-item questionnaire that assesses a participant's pain severity and its interference in daily activities across physical, emotional, and social domains. It is rated on a 0 (does not interfere) to 10 (completely interferes) NRS. It has demonstrated strong psychometric properties for both chronic[339] and cancer pain.[340]

Pain Management Index (PMI) is constructed using the BPI. The PMI represents the relationship between the level of pain and type of analgesic prescribed. Scores ranged from –3 to +3, where a negative value represents inadequate pain management.[341] It is frequently used in cancer populations and compares the most potent analgesic used by a participant relative to their pain intensity.[342,343]

Satisfaction with pain control (SAT) is an NRS ranging from 0 (extremely dissatisfied) to 10 (extremely satisfied) with pain control. It is also part of the BPI. NRSs of satisfaction demonstrate good validity and reliability in surgical and BCS populations.[44,344,345]

Short Form McGill Pain Questionnaire (SF-MPQ)[346] is a multidimensional measure of pain qualities, both nociceptive and neuropathic, using 11 sensory and four affective descriptors rated from 0-3 (none, mild, moderate, or severe). It has been validated for a variety of pain conditions,[347,348] including cancer pain.[349]

Short Form Neuropathic Pain Questionnaire (SF-NPQ)[350] is a 3-item questionnaire that measures neuropathic pain qualities. Participants rate the intensity of tingling, numbness, and pain due to touch from 0 (no pain) to 100 (worst pain) to determine probable or non-probable neuropathic pain. It has demonstrated moderate internal consistency and satisfactory validity in a variety of pain conditions,[351] including chronic cancer pain.[352]

Physical Function

Edmonton Symptom Assessment System (ESAS)[353] is a measure of nine cancer-related symptoms and their severity scored from 0 (no symptom) to 10 (worst possible symptom). The ESAS has been shown to be reliable in a variety of populations[354] and is valid for use in individuals with advanced cancer.[355,356] In our study, the ESAS was modified to evaluate physical symptom severity that excludes pain, anxiety, and depression. This was done because the psychological symptom cluster may have poor validity[356] and to reduce shared variance for pain items.[357]

Medical Outcome Study Short-Form 12 (SF-12)[358] is a 12-item measure of functional status, including physical and mental health. It has good psychometric properties for a variety of pain conditions,[359] including breast cancer.[360]

Charlson Comorbidity Index (CCI)[165] measures the presence of 19 co-occurring conditions. It has been validated for participants with cancer, including breast cancer,[163,164] as well as surgical and older cancer populations.[361]

Karnofsky Performance Index (KPI)[362] is an observer rating of a participant's functional status in terms of observed ability to complete everyday activities. It is scored from 0 (dead) to

100 (normal activity). The KPI has demonstrated strong reliability and validity in individuals with cancer.[363]

Disabilities of the Arm Shoulder and Hands Questionnaire (DASH)[364] is a 30-item measure of upper-extremity function and symptoms. Each item is scored 0 (not difficult) to 5 (unable). The final score ranges from 0-100, with a higher score indicating greater disability. It has strong reliability and validity[365] and has been validated for longitudinal use among participants with musculoskeletal disorders.[366] In this study, two additional items were added: 14a) Touch your back on the same side as your surgery and 14b) Touch your back on the opposite side as your surgery, to better capture arm dysfunction associated with BCS.

Psychosocial Function

State-Trait Anxiety Inventory (STAI)[238] measures trait (STAI-T) and state (STAI-S) anxiety, each with 20 items. Participants rate how well each statement reflects how they feel on a 4-point Likert scale from "not at all" to "very much so". It has good reliability and validity[238] and has been validated for older participants[367,368] and participants with breast cancer.[369] For this study, only the state anxiety subscale was used.

Pain Anxiety Symptoms Scale (PASS)[370] is a 40-item questionnaire measuring pain-related anxiety and fear. Participants rate how often they engage in each of the thoughts or activities related to their pain from 0 (never) to 5 (always). It has demonstrated sound psychometric properties in participants with chronic pain.[371]

Pain Catastrophizing Scale (PCS)[372] is a 13-item scale which measures pain catastrophizing or excessive pain-related thoughts. Participants rate from 1 (not at all) to 5 (all the time), how often they have each thought about their pain. The PCS has demonstrated good

psychometric properties in adults and pain outpatient groups.[373,374] It has been preliminarily validated for participants with cancer.[375]

Center for Epidemiologic Studies – Depression Scale (CES-D)[376] *is* composed of 20-items measuring how often participants felt each depressive symptom in the past week, from 1 (rarely) to 5 (most of the time). The CES-D has been validated for use in the general population,[376] as well as in participants with cancer[377] and older adults.[378]

Functional Assessment of Chronic Illness Therapy – Spiritual Wellbeing 12 (FACIT-Sp-12)[379] is a 12-item scale measuring the extent to which spirituality and faith contribute to wellbeing. Each item is rated from 0 (not at all) to 4 (very much). The FACIT-Sp-12 has been shown to have sound psychometric properties in participants with cancer.[380]

Pain Attitudes Questionnaire Revised (PAQ-R)[381]is a 24-item questionnaire measuring stoicism and cautiousness attitudes in adults with chronic pain. Participants rate how much they agree with the statement from 1 (strongly disagree) to 5 (strongly agree). The PAQ-R has demonstrated sound psychometric properties for individuals with advanced cancer.[382]

Impact of Event Scale – Revised (IES-R)[383,384] is a 22-item questionnaire that measures traumatic stress, including the avoidance of thoughts and the presence of intrusive thoughts. Participants rate how distressed they were by each difficulty from 0 (not at all) to 4 (extremely). The IES-R has demonstrated good psychometric properties,[385,386] and has been validated in participants with cancer,[387] including participants with risk of hereditary breast cancer.[388]

Chronic Pain Acceptance Questionnaire (CPAQ)[389] is a 20-item measure of pain acceptance, where higher scores indicate greater acceptance of chronic pain through activity engagement or pain willingness. Participants rate their acceptance of each statement from 0

(never true) to 6 (always true). The CPAQ has demonstrated satisfactory psychometric properties[390] and has been validated for participants with chronic pain[389]and used in participants with advanced cancer pain.[391]

Medical Outcomes Study – Social Support Survey (MOS-SSS)[303] is a 19-item questionnaire measuring the number of close friends and relatives and the perceived amount of functional social support across emotional, tangible, affectionate and positive domains. Participants rate how available each type of support is from 1 (none of the time) to 5 (all the time). It has good psychometric properties for use in a variety of chronic disease populations.[303]

Experiences in Close Relationships Inventory (ECR)[392] is a 36-item questionnaire measuring adult attachment style in close relationships, whether in current relationships or generally. Participants rate how much they agree with each statement from 1 (disagree strongly) to 7 (agree strongly). The ECR has good psychometric properties and is suitable for medically ill, older adults.[393]

Multidimensional Pain Inventory & Caregiver Responses Scale (MPI)[394] is a two-part questionnaire. The first section is 20 items measuring the extent pain affects a participant's life and their relationship with their significant other. The second section is a 14-item scale that examines perceived responses of significant others to communications of pain (solicitous, distracting, punishing). For this study, significant other could mean a spouse, partner, housemate, friend, neighbor, relative, or other. It is rated from 0 (never) to 6 (very often). The MPI has been validated with participants with chronic pain and their significant others.[394]

DATA ANALYSES

Missing Data

All data were checked for entry errors prior to analysis. Missing data were assessed using Little's Missing Completely at Random test (MCAR). Missing data were imputed using multiple imputation by chained equations (MICE)[395] with five iterations. Demographic data and NRS-R scores were not imputed. All data were presented with imputed data and pooled when appropriate.

To characterize BCSP trajectories and to develop a model of unresolved BCSP, only participants with complete NRS-R scores at each follow-up were included in this study. Participants missing one or more NRS-R scores were excluded. Tests of the null hypotheses were completed to assess whether participants who were included (n=73) or excluded (n=111) were significantly different ($p<0.05$). The Mann-Whitney U test was used for continuous variables, to account for non-normally distributed variables, and a chi-squared test was used for categorical variables.

Descriptive Statistics

In order to determine normality**,** a skew cut-off of 3.29 was used to determine normality.[396] Scores on the NRS-R, NRS-M, PPI, SF-MPQ Sensory, SF-MPQ Affective, BPI-SEV, BPI-INT, SF-12-PCS, ESAS, STAIS-S and PCS-M were found to be non-normal (Appendix A). Tests robust against non-normality were chosen for analyses, therefore data were not transformed. Means and standard deviations are reported for normally distributed variables. Median and interquartile range (IQR) were calculated for non-normally distributed variables, and

frequencies for categorical variables. Independent sample t-tests, Mann-Whitney U tests and Fisher's Exact tests were used to assess group differences.

Trajectory Plotting

Initially, it was planned to characterize trajectory groups using slope, start-intercept (NRS-R score at 1-week) and end-intercept (NRS-R score at 2-years). Both linear and quadratic slopes were to be tested for best fit. Individual trajectory plots would then be used to cluster participants into flat slope (constant intensity), positive slope (worsening intensity) and negative slope (improving intensity). Then, participants were grouped based on end-intercept NRS-R score, where 0 = "no pain", 1-3 = "mild", 4-6= "moderate" and 7-10 = "severe".[75,77–8]

However, upon plotting individual trajectories, it emerged that these characteristics were not sufficient for capturing the heterogenous intra-individual patterns. Instead, visual inspection was used to cluster participants into six parsimonious trajectory subgroups based on NRS-R at 2 years and the timing of pain versus pain-free intervals. First, NRS-R scores were plotted over time (24 hours, 1 week, 6 months, 1 year and 2 years). Second, participants were categorized into larger trajectory groups based on NRS-R scores at 2 years, where the resolved group consisted of participants who reported NRS = 0 at 2 years and the unresolved group consisted of participants who reported NRS > 0 at 2 years. Finally, trajectory subgroups were formed based on time to resolution and episodic pain pattern. To account for the role of adequate pain management and analgesic use, reporting a pain-free interval at 24 hours and 1 week was not considered episodic.

Model Building

To develop a model of postoperative pain resolution, participants in the resolved group and the unresolved group were compared. Given considerations related to the small sample size and potential multicollinearity. These larger trajectory groups were used for the binomial logistic regression. Bivariate analysis was used to identify preliminary candidate correlates to be included in the analysis. Point-biserial correlation, chi-square tests, and Cramer's V were used. A priori, the significance cut-off for inclusion was $p<0.1$. In the case where predictors were highly correlated ($r>0.7$) the variable with the least missing data was included.[397] Variable inflation factor (VIF) and tolerance were also assessed to further identify issues with multicollinearity. Based on previous literature, surgical procedure, age and SF-NPQ were forced into the model.[197,398,399] Backward binomial logistic regression was used to determine significant preoperative predictors of unresolved pain with a critical significance of $p<0.05$. Assumptions of binomial logistic regression were assessed, where Box-Tidwell was used to assess linearity of the logit.[397]

Trajectory Group Differences

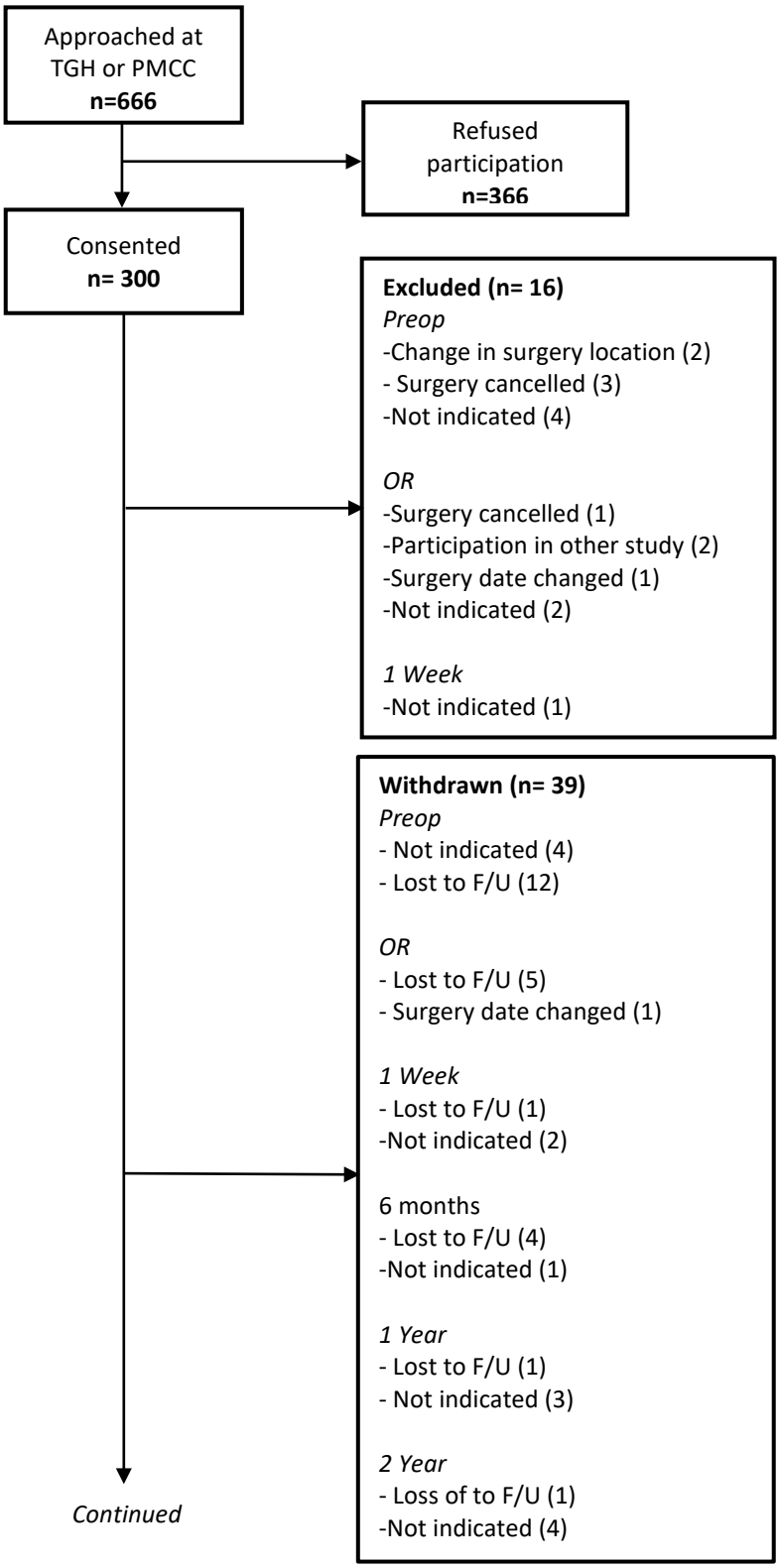
To explore predictors of trajectory subgroup membership, subgroups were compared to each other. Because of the small sample size and uneven groups, Fisher's Exact test and Kruskal-Wallis tests were used to assess the differences between subgroups. The candidate correlates identified in the previous resolution model were used.

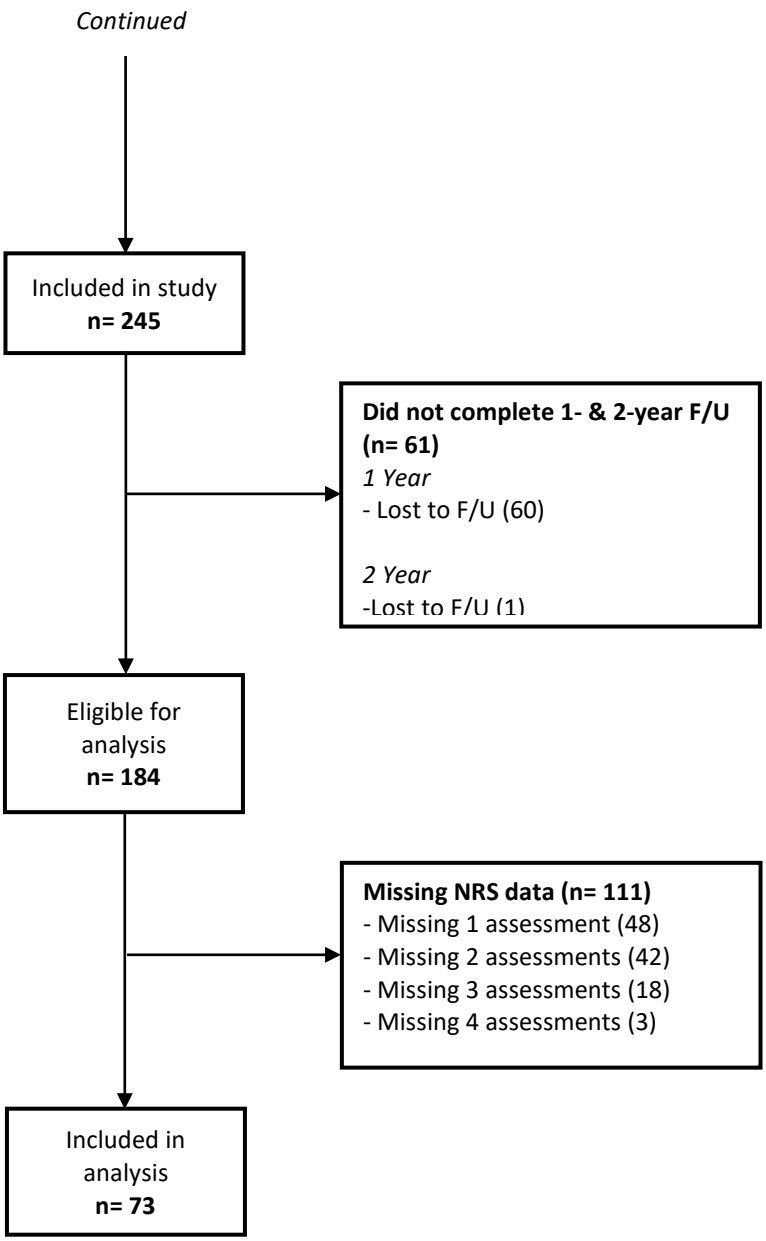
Analyses were done in RStudio v. 2023.03.1+446 and SPSS v.29.

RESULTS

A flowchart of study inclusion is presented in Figure 1. For this sub-study, only participants with complete NRS-R data were included. 73 participants had complete NRS-R data. Of the 111 that were excluded for having incomplete NRS data, 48 (43%) missed one follow-up assessment and four (4%) missed four assessments.

Figure 1. Study inclusion




Continued
Included in study
n= 245
Did not complete 1- & 2-year F/U (n= 61)
1 Year
- Lost to F/U (60)
2 Year
-Lost to F/U (1)
Eligible for analysis
n= 184
Missing NRS data (n= 111)
- Missing 1 assessment (48)
- Missing 2 assessments (42)
- Missing 3 assessments (18)
- Missing 4 assessments (3)
Included in analysis
n= 73

Missing Data

All data were found to be missing completely at random. When comparing participants with complete NRS-R data who were included versus those with incomplete NRS-R data who were excluded, results indicated that excluded participants were significantly younger (*Mdn* = 49.0, IQR = 43.0, 55.0) than those included (*Mdn* = 56.0, IQR = 50.0, 62.0, *U* = 2714.50, *z* = -3.79, *p*=<.001, *r*=-0.09) and had significantly higher pain expectations of surgical pain (*Mdn* = 4.0, IQR =2.7, 5.0) than those included (*Mdn* = 3.3, IQR = 1.7, 4.8, *U* = 4395.0, *z*=2.195, *p*=0.028, *r*=0.03). All other variables were not statistically different.

Participant Descriptives

Table 1, 2 and 3 show the participants and resolution group characteristics. Briefly, the participants included in this study were primarily English-speaking (86%, n=63), White (86%, n=63), and educated (96%, n=70). Most of them were married or in a common-law relationship (74%, n=54) and the majority had children (82%, n=60). Participant age ranged from 27-77, with the mean age being 56. Most of them were diagnosed with Stage 1 or 2 cancer (67%, n=48), with approximately 18% (n=13) undergoing treatment prophylactically. Before surgery, most did not have ongoing chronic pain (74%, n=54) or other comorbidities (CCI=0.56, sd=.88). In this sample, approximately half underwent lumpectomy (48%, n=35).

Table 1. Preoperative Participant Characteristics: Categorical Variables

	Total (n=73)		Resolved (n=39)		Unresolved (n=34)		P value
	Frequency (%)		Frequency (%)		Frequency (%)		
Demographic							
Religion							
Not religious	20	(27.4)	13	(33.3)	7	(20.6)	
Religious	52	(71.2)	25	(64.1)	27	(79.4)	0.628
Missing	1	(1.4)	1	(2.6)	0	(0.0)	
Highest level of education							
Elementary school	3	(4.1)	2	(5.1)	1	(2.9)	
High school or higher	70	(95.9)	37	(94.9)	33	(97.1)	0.852
Marital status							
Single	6	(8.2)	0	(0.0)	6	(17.6)	
Married & common law	54	(74.0)	31	(79.5)	23	(67.6)	0.037*
Separated, divorced or widowed	13	(17.8)	8	(20.5)	5	(14.7)	
Living arrangements							
Alone	10	(13.7)	3	(7.7)	7	(20.6)	0.110
With others	26	(35.6)	11	(28.2)	15	(44.1)	
Child and living situation							
No child	13	(17.8)	2	(5.1)	11	(32.4)	
Living with child, alone	5	(6.8)	3	(7.7)	2	(5.9)	0.013*
Living with child and partner	31	(42.5)	21	(53.8)	10	(29.4)	
Child not at home	24	(32.9)	13	(33.3)	11	(32.4)	
Primary language							
English	63	(86.3)	6	(15.4)	4	(11.8)	0.742
Non-English	10	(13.7)	33	(84.6)	30	(88.2)	
Ethnicity							
White	63	(86.3)	34	(87.2)	29	(85.3)	
Non-white	8	(11.0)	4	(10.3)	4	(11.8)	1.000
Missing	2	(2.7)	1	(2.6)	1	(2.9)	
Have children							
No	13	(17.8)	2	(5.1)	11	(32.4)	0.004**
Yes	60	(82.2)	37	(94.9)	23	(67.6)	
Surgical							
Procedure							
Lumpectomy	35	(47.9)	21	(53.8)	14	(41.2)	0.350
Mastectomy	38	(52.1)	18	(46.2)	20	(58.8)	

Table 1. (continued)

	Total (n=73)		Resolved (n=39)		Unresolved (n=34)		P value
	Frequency (%)		Frequency (%)		Frequency (%)		
ALND							
No	52	(71.2)	32	(82.1)	20	(58.8)	
Yes	17	(23.3)	7	(17.9)	10	(29.4)	0.167
Missing	4	(5.5)	0	(0.0)	4	(11.8)	
SLND							
No	19	(26.0)	9	(23.1)	10	(29.4)	
Yes	51	(69.9)	28	(71.8)	23	(67.6)	0.601
Missing	3	(4.1)	2	(5.1)	1	(2.9)	
Disease History							
Preop stage							
Stage 0	5	(6.8)	4	(10.3)	1	(2.9)	
Stage 1	27	(37.0)	16	(41.0)	11	(32.4)	
Stage 2	21	(28.8)	10	(25.6)	11	(32.4)	0.278
Stage 3	6	(8.2)	1	(2.6)	5	(14.7)	
Prophylactic	13	(13.0)	7	(17.9)	6	(17.6)	
Missing	1	(1.0)	1	(2.6)	0	(0.0)	
Metastatic							
Prophylactic	11	(15.1)	6	(15.4)	5	(14.7)	
Non-metastatic	37	(64.4)	28	(71.8)	19	(55.9)	0.840
Locally advanced	7	(9.6)	1	(2.6)	6	(17.6)	
Missing	8	(11.0)	4	(10.3)	4	(11.8)	
Recurrence							
Prophylactic	13	(17.8)	8	(20.5)	5	(14.7)	
Recurrence (same breast)	8	(11.0)	4	(10.3)	4	(55.9)	
Recurrence (opposite breast)	3	(4.1)	3	(7.7)	0	(0.0)	0.412
Non-recurrent	48	(65.8)	24	(61.5)	24	(79.6)	
Missing	1	(1.4)	0	(0.0)	1	(2.9)	
Previous chemotherapy							
No	53	(72.6)	29	(74.4)	24	(70.6)	0.795
Yes	20	(27.4)	10	(25.6)	10	(29.4)	
Previous trastuzumab							
No	70	(95.9)	37	(94.9)	33	(97.1)	1.000
Yes	3	(4.1)	2	(5.1)	1	(2.9)	
Previous radiation							
No	55	(75.3)	29	(74.4)	26	(76.5)	1.000
Yes	18	(24.7)	10	(25.6)	8	(23.5)	

Table 1. (continued)

	Total (n=73)		Resolved (n=39)		Unresolved (n=34)		P value
	Frequency (%)		Frequency (%)		Frequency (%)		
Previous aromatase inhibitor							
No	58	(79.5)	32	(82.1)	26	(76.5)	0.576
Yes	15	(20.5)	7	(17.9)	8	(23.5)	
Biopsy before surgery							
No	17	(23.3)	9	(23.1)	8	(23.5)	1.000
Yes	56	(76.7)	30	(76.9)	26	(76.5)	
Previous surgeries							
No	6	(8.2)	4	(10.3)	2	(5.9)	0.679
Yes	67	(91.8)	35	(89.7)	32	(94.1)	
Previous surgery related to breast							
No	42	(57.5)	21	(53.8)	21	(61.8)	0.636
Yes	31	(42.5)	18	(46.2)	13	(38.2)	
Pain Measures							
Chronic pain and/or analgesic intake							
No	54	(74.0)	34	(37.2)	20	(58.8)	0.008**
Yes	19	(26.0)	5	(12.8)	14	(41.2)	
Any ongoing (chronic) pain from past surgeries							
No	66	(90.4)	38	(97.4)	28	(82.4)	0.045*
Yes	7	(9.6)	1	(2.6)	6	(17.6)	
Ongoing pain problems							
No	41	(56.2)	23	(59.0)	18	(52.9)	0.478
Yes	30	(41.1)	14	(35.9)	16	(47.1)	
Missing	2	(2.7)	2	(5.1)	0	(0.0)	
SF-MPQ - PPI							
No pain	50	(68.5)	30	(76.9)	20	(58.8)	0.085
Mild	15	(20.5)	6	(15.4)	9	(26.5)	
Discomforting	6	(8.2)	1	(2.6)	5	(14.7)	
Distressing	1	(1.4)	1	(2.6)	0	(0.0)	
Missing	1	(1.4)	1	(2.6)	0	(0.0)	
SF-NPQ							
Non-probable	67	(91.8)	36	(92.3)	29	(85.3)	0.406
Probable	6	(8.2)	2	(5.1)	4	(11.8)	
Missing	2	(2.7)	1	(2.6)	1	(2.9)	

[a] **p<0.05, **p<0.01*

[b] *Abbreviation: all acronyms can be found in the abbreviation list (p.xii).*

Table 2. Preoperative Participant Characteristics: Continuous Normal Variables

	Total (n=73)		Resolved (n=39)		Unresolved (n=34)		P value
	Mean (SD)		Mean (SD)		Mean (SD)		
Demographic							
Age	55.7	(10.6)	55.6	(10.8)	55.7	(0.6)	0.941
Surgical							
Surgical duration	255.9	(234.4)					0.972
Biological and Health Status							
BMI	26.6	(4.5)	26.1	(4.4)	27.1	(4.7)	0.336
Psychological Measures							
SF-12 MCS	47.5	(10.0)	48.9	(9.5)	45.9	(10.6)	0.193
PASS-F	11.7	(7.7)	10.3	(7.1)	13.2	(8.1)	0.108
PASS-EA	20.3	(9.1)	18.5	(7.4)	22.3	(10.4)	0.078
PASS-PA	13.1	(9.3)	12.1	(7.9)	14.2	(10.7)	0.338
PASS-CA	20.0	(8.7)	18.3	(7.4)	21.9	(9.7)	0.076
CES-D	15.8	(11.1)	13.4	(10.0)	18.5	(11.9)	0.050*
Pain expectations	3.3	(1.9)	3.0	(1.8)	3.6	(2.0)	0.152
PCS-R	10.6	(4.4)	9.5	(3.5)	11.8	(5.0)	0.021*
PCS-H	11.8	(4.6)	10.4	(3.8)	13.4	(5.0)	0.004**
CCI	0.6	(0.9)	0.5	(0.8)	0.6	(0.9)	0.923

[a] **p<0.05, **p<0.01*

[b] *Abbreviation: all acronyms can be found in the abbreviation list (p.xii).*

Table 3. Preoperative Participant Characteristics: Continuous Non-normal Variables

	Total (n=73)		Resolved (n=39)		Unresolved (n=34)		P value
	Median (IQR)		Median (IQR)		Median (IQR)		
Pain Measures							
NRS-R	0.0	(0.0, 1.0)	0.0	(0.0, 0.0)	0.0	(0.0, 1.6)	0.013*
NRS-M	0.0	(0.0, 1.0)	0.0	(0.0, 1.0)	0.0	(0.0, 2.0)	0.327
SF-MPQ Sensory	0.0	(0.0, 2.0)	0.0	(0.0, 1.0)	0.0	(0.0, 1.0)	0.075
SF-MPQ Affective	0.0	(0.0, 0.0)	0.0	(0.0, 0.0)	0.0	(0.0, 2.0)	0.538
BPI-SEV	0.8	(0.0, 1.7)	0.3	(0.0, 1.5)	1.2	(0.5, 2.8)	0.006**
BPI-INT	0.2	(0.0, 1.5)	0.0	(0.0, 1.0)	0.8	(0.0, 3.0)	0.013*
SF12-PCS	53.1	(49.1, 58.4)	55.1	(55.1, 57.1)	52.6	(41.3, 58.0)	0.328
ESAS	1.3	(0.8, 2.2)	1.0	(0.3, 2.1)	1.5	(1.0, 2.2)	0.145
Psychological Measures							
STAI-S	43.0	(37.0, 49.5)	41.1	(33.0, 47.0)	43.5	(39.8, 58.3)	0.035*
PCS-M	5.0	(4.0, 6.0)	5.0	(4.0, 5.9)	5.0	(4.0, 9.0)	0.062

[a] **p<0.05, **p<0.01*

[b] *Abbreviation: all acronyms can be found in the abbreviation list (p.xii).*

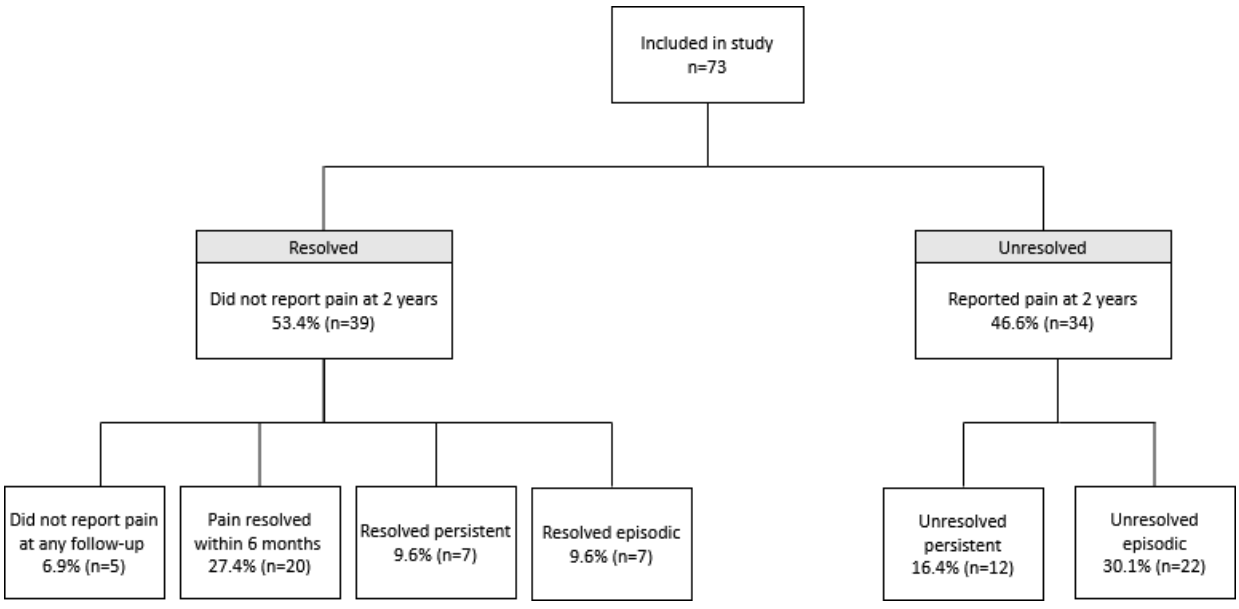
Trajectory Group and Subgroup Plots

After each participant's trajectory was plotted and inspected, two trajectory groups and six trajectory subgroups were formed. Figure 2 illustrates how these groups are categorized.

Participants' pain was characterized as resolved if they did not report pain at rest at their 2-year follow-up. If they did not report pain at an earlier follow-up, they had to continue reporting no pain at all subsequent follow-ups to be categorized as resolved.

If participants reported more than one period of pain after 6 months separated by a period of no pain, their trajectory was considered episodic. Approximately 40% of participants in this study reported episodic pain, with the majority (75%, n=29) being in the unresolved group. This pattern was labelled "episodic" to avoid confusion with intermittent, or breakthrough pain, that is commonly associated with cancer pain, which is a short-term exacerbation in a relatively stable baseline pain, that is spontaneous or triggered.[83,400–402]

Figure 2. Trajectory Group and Subgroup Distribution



Approximately half of all participants developed CBCSP that did not resolve by 2 years. Of the participants whose pain did resolve, approximately half had it resolve within the first 6 months. More participants had unresolved episodic pain than unresolved persistent pain. Participants with resolved pain (n=39, 53%) had significantly different marital status (p=.037) and child and living situations (p=.013) than those with unresolved pain (n=34, 47%). Participants with resolved pain were significantly more likely than those with unresolved pain to have children (p=.004), significantly less likely to have chronic pain and/or take analgesics (p=.008), have ongoing pain from past surgeries (p=.045), and have lower pain intensity (NRS-R; p=.013), severity (BPI-SEV; p=.006), interference (BPI-INT p=.013), as well as lower state anxiety (STAI-S; p=.035), ruminations about pain (PCS-R; p=.021), and hopelessness about pain (PCS-H; p=.004). Pain-related anxiety (PASS) did not differ. In our sample, an equal number of participants with resolved pain had persistent versus episodic pain (Figure 2).

Each participant's graph was inspected individually but they are presented clustered to simplify comparisons. Figure 3-4 show the resolved and unresolved groups and Figure 5-10 illustrate the subgroups. To maintain time as a continuous variable for the graphs, each follow-up period was converted to days rather than weeks, months and years (i.e. 1, 7, 183, 365, and 730 days).

Figure 3. Resolved Group: Pain Intensity Over Time

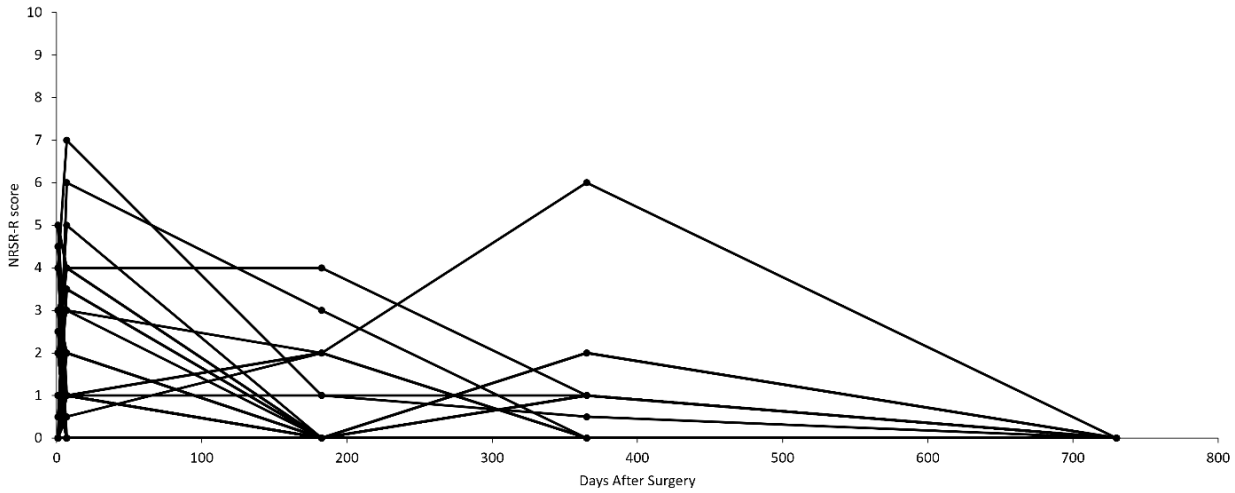


Figure 4. Unresolved Group: Pain Intensity Over Time

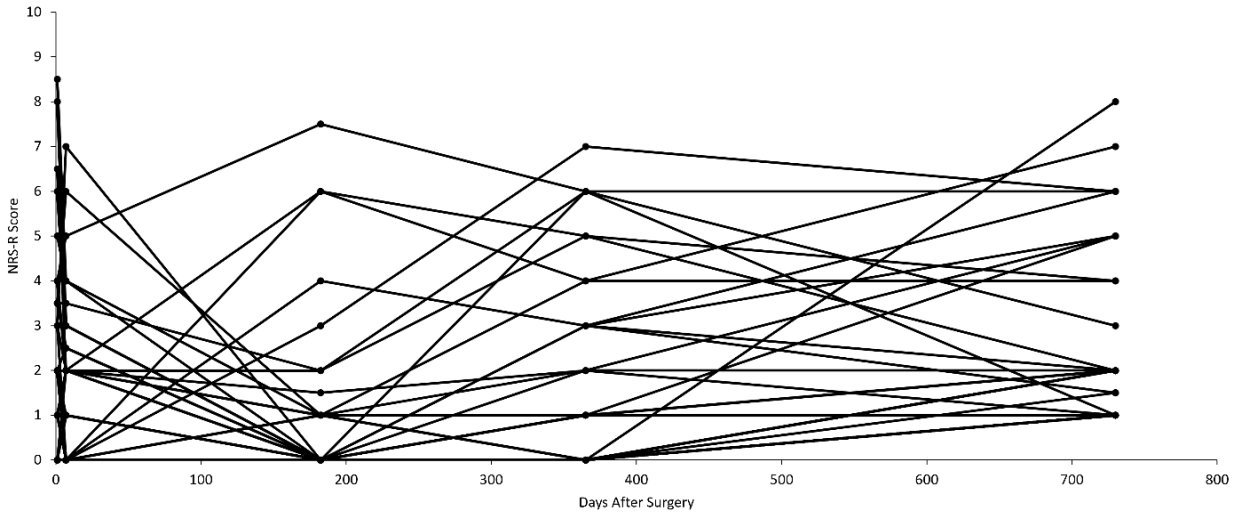


Figure 5. Subgroup Who Did Not Report Pain at Any Follow-up: Pain Intensity Over Time

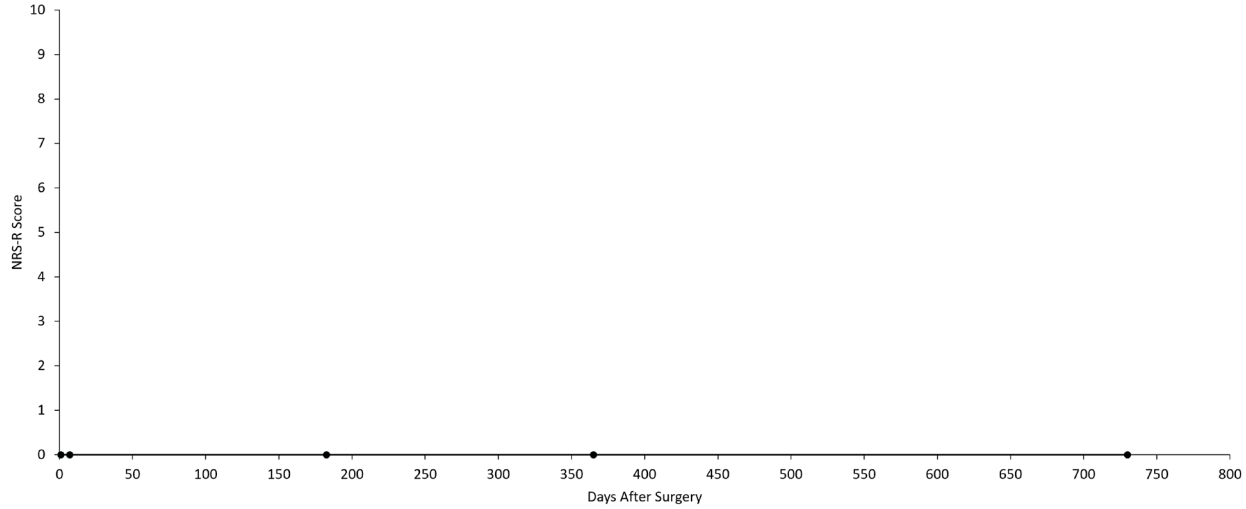


Figure 6. Subgroup Whose Pain Resolved Within 6 Months: Pain Intensity Over Time

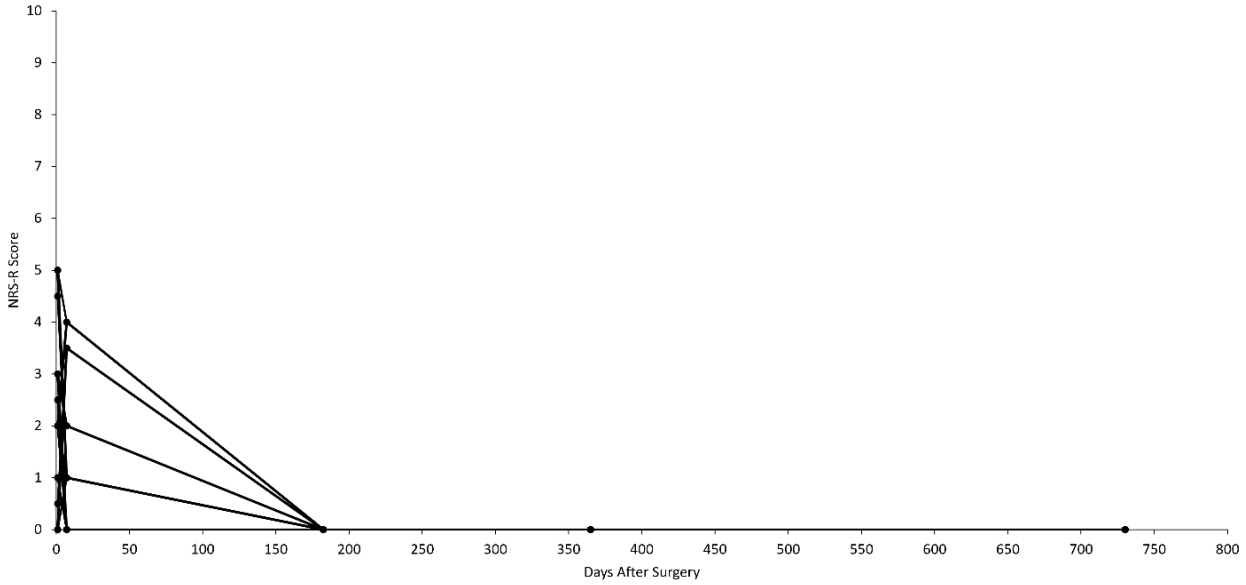


Figure 7. Resolved Persistent Subgroup: Pain Intensity Over Time

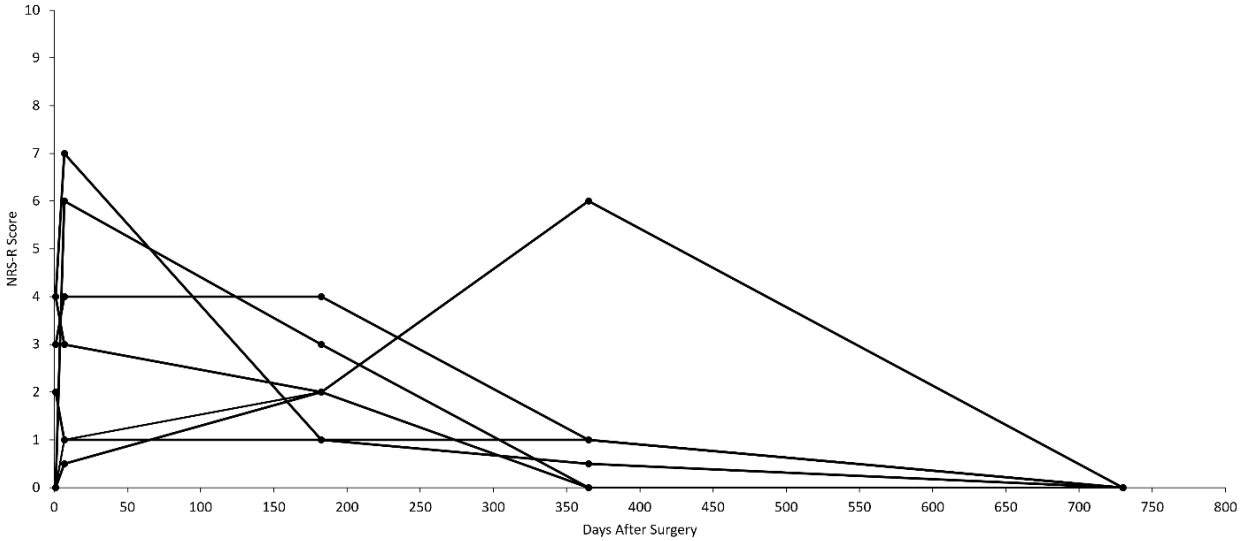


Figure 8. Resolved Episodic Subgroup: Pain Intensity Over Time

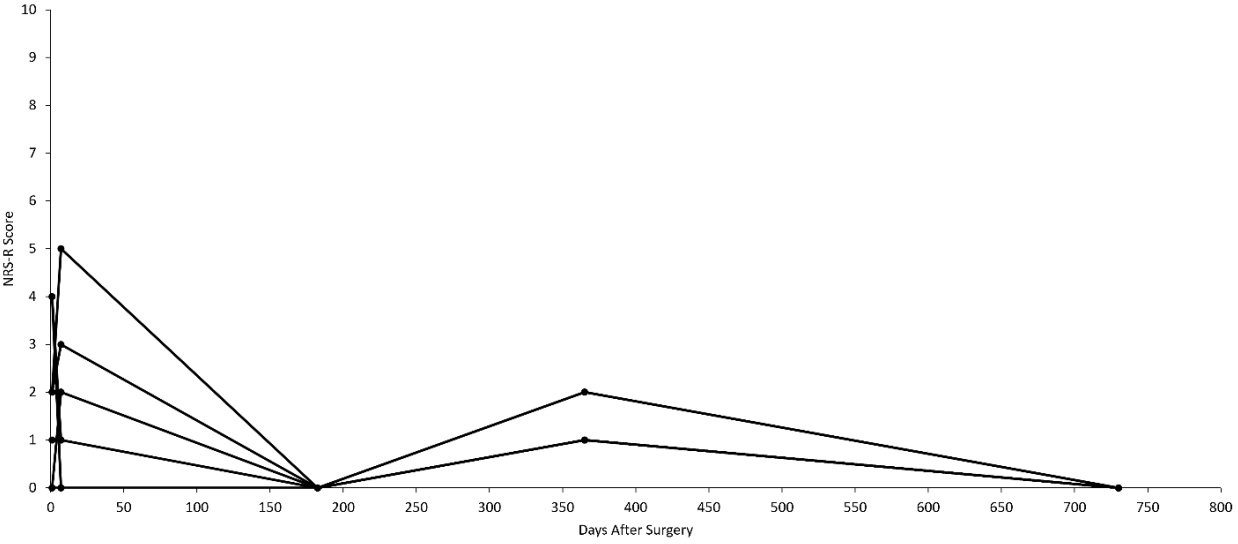


Figure 9. Unresolved Persistent Subgroup: Pain Intensity Over Time

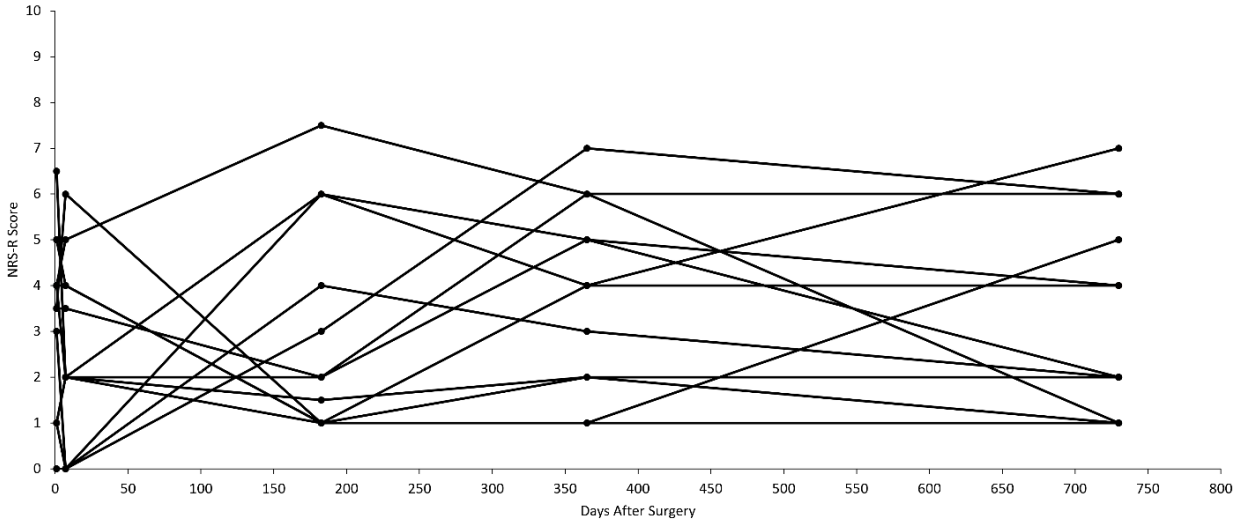


Figure 10. Unresolved Episodic Subgroup: Pain Intensity Over Time

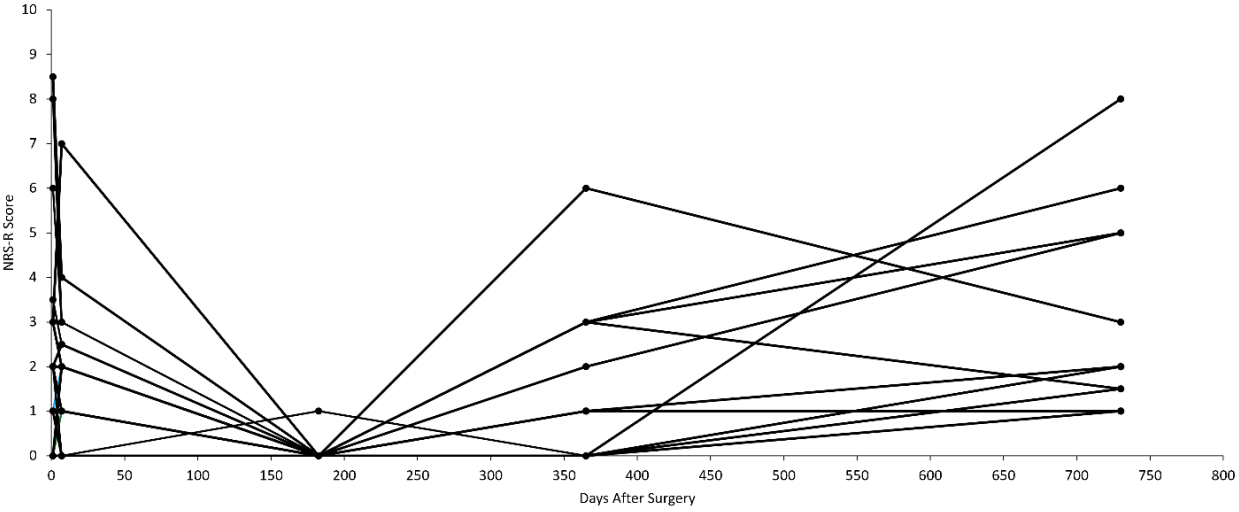
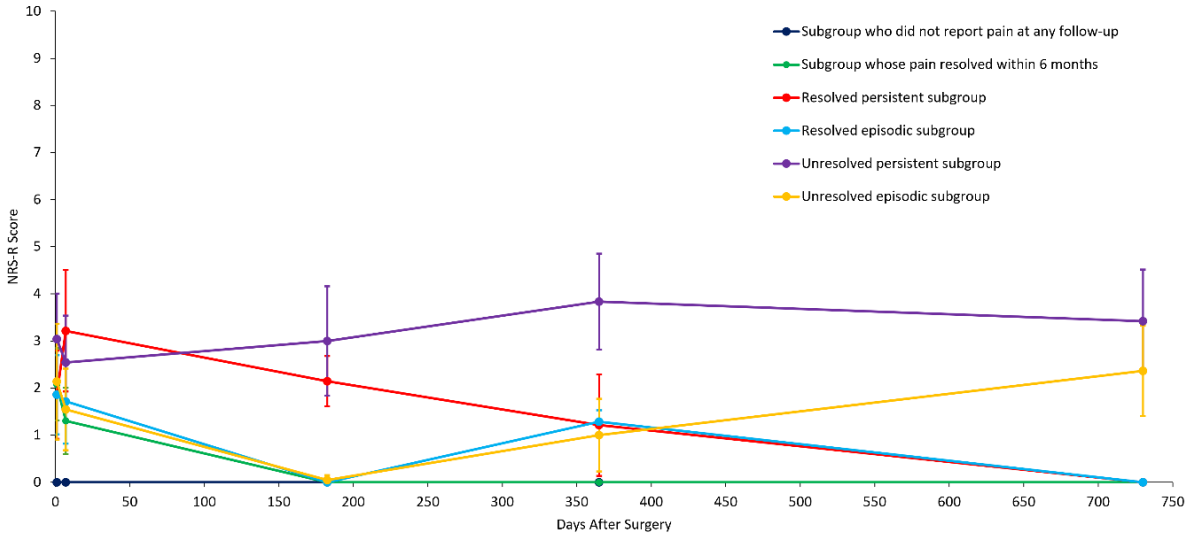


Figure 11 compares the average pain intensity of the trajectory subgroups over time. Participants with persistent pain that resolved within 2 years, had the highest mean NRS-R score at one week, before decreasing over time. Participants with persistent unresolved pain, had the highest average NRS-R score at all other follow-ups.

Figure 11. Average NRS-R Score by Trajectory Subgroup



Examination of Individual Subgroup Trajectories

This study used a quasi-qualitative and hypothesis-generating approach[403] to explore a subset of individual trajectories of interest. Using a purposeful sampling approach that emphasized maximum variability,[404,405] two participants were selected from each subgroup: (i) the participant with the highest 24-hour NRS-R and highest preoperative BPI-INT scores; (ii) the lowest 24-hour postoperative NRS-R and lowest preoperative BPI-INT scores. Specifically, participants were ranked on both NRS-R and BPI-INT scores, the ranks were summed, and participants with the highest and lowest total rank were selected. If multiple participants had the same rank, cases were chosen at random. Each of these selected participants is described below, ordered by descending subgroup prevalence: unresolved episodic subgroup, subgroup whose pain resolved within 6 months, unresolved persistent subgroup, resolved persistent subgroup, resolved episodic subgroup and subgroup who did not report pain at any follow-up. All initials were randomized. To better understand how timing of treatment-related adverse events influences postoperative pain experience, each trajectory plot included their expected pain after surgery; when participants underwent chemotherapy, radiation therapy or hormone therapy; reported lymphedema; any corrective surgery; and reconstruction.

This analysis was conducted after all other analyses in this study, but is presented here, alongside the subgroup trajectory graphs, for clarity.

Maintaining Participants' Privacy

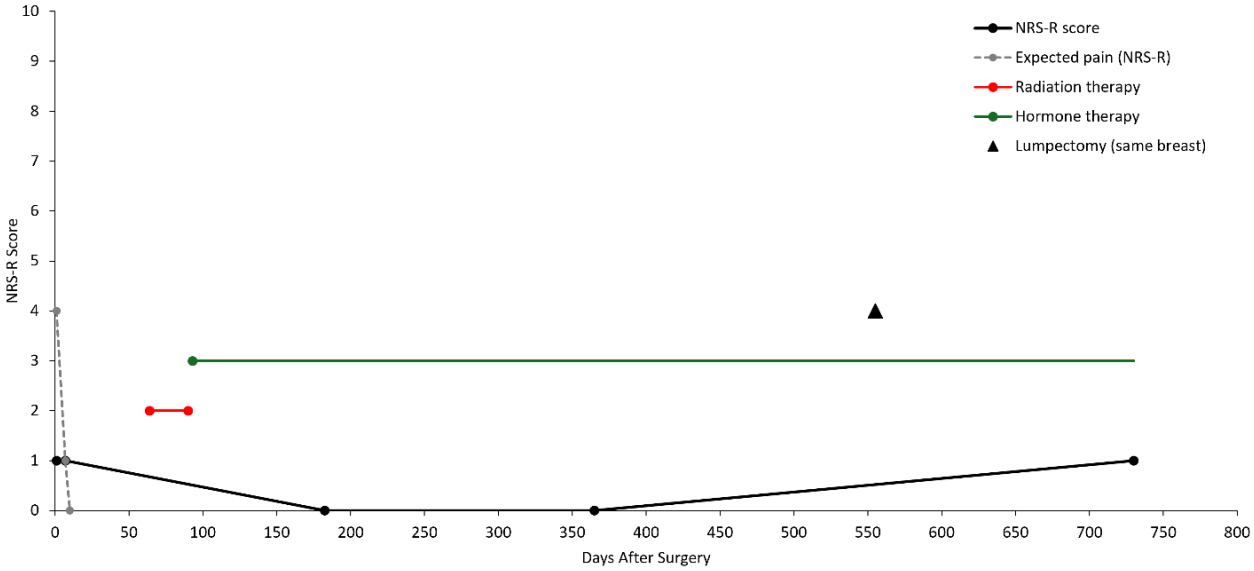
Based on the current standards and recommendations found in the literature, steps were taken in this study, and the larger study it is a sub-analysis of, to anonymize participants and protect participant privacy.[406–408] In the larger study, all physical records were anonymized

and stored in locked cabinets in locked rooms. Digital records were also anonymized and password-protected. In the digital database, participants were only referred to by participant number and randomized initials. Consent forms and records matching participants to participant IDs were all stored separately. Only the principal investigator of the larger study and the institution (UHN) had access to these documents. In the current study, participants selected for individual trajectory exploration were assigned new randomized initials. The demographic and medical data presented to characterize the following trajectories were generalized (e.g., using broad occupational categories rather than specific professions) to further de-identify participants. The nature of this study's findings was not impacted by these generalizations.

Unresolved Episodic Subgroup

The largest subgroup in this study was the unresolved episodic subgroup (30%, n=34). Half of this subgroup reported one pain-free interval (most often at 6 months) while the other half reported two pain-free intervals. Overall, two patterns emerged – participants who, after a pain-free interval, had CBCSP pain that was more severe than their ABCSP (33%, n=12) and participants who, after a pain-free interval, had CBCSP that was less severe than their ABCSP (66%, n=22).

Figure 12. Unresolved Episodic: Pain Trajectory for DY (Lowest 24hr Postoperative NRS-R and Preoperative Pain Interference)



DY was a legal professional in her late 40's with invasive ductal carcinoma who underwent lumpectomy in her right breast (Figure 12). She lived alone with her partner. She did not have any history of cancer or chronic pain but reported ongoing non-cancer pain affecting her legs. Prior to surgery, she had not undergone any previous treatment for her tumor. At her preoperative assessment, she reported no pain at rest but mild pain interference affecting

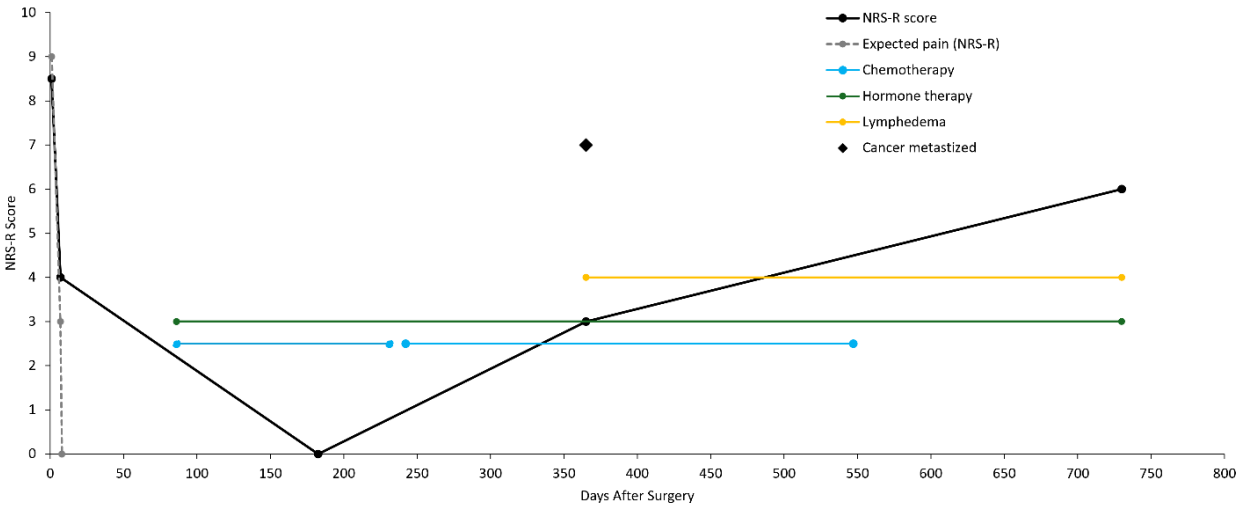
normal work. She expected moderate pain immediately following surgery, mild pain after 1 week, and recovery within 2 weeks. Prior to surgery, she did not report symptoms consistent with elevated catastrophizing, state anxiety, pain-related anxiety, or depression.

24 hours after surgery, DY reported mild pain at rest and did not report symptoms consistent with elevated state anxiety or depression. At her 1-week, 6-month, 1-year and 2-year follow-ups, DY did not report symptoms consistent with elevated state anxiety or depression. Furthermore, she did not report symptoms consistent with elevated pain-related anxiety or catastrophizing at 1 and 2 years.

By her 6-month follow-up, she had completed her radiation treatment and begun hormone therapy, she reported side effects from both treatments, including breast pain. While she did not report pain at rest, she reported mild interference of pain in her mood, normal work, relations with others, sleep, and ability to enjoy life.

At her 1-year follow-up, she did not report pain at rest or interference. Between her 1-year and 2-year follow-ups, DY underwent a second lumpectomy on the same breast. Then, at her 2-year follow-up, she reported pain at rest and mild interference of pain with her ability to walk, do normal work, have relations with others, sleep, and enjoy life.

Figure 13. Episodic Unresolved: Pain Trajectory for FZ (Highest Postoperative 24hr NRS-R and Preoperative Pain Interference)



FZ was a woman in her late 50's with invasive ductal carcinoma and ductal carcinoma in situ (DCIS) who underwent mastectomy on her left breast (Figure 13). She was married with two children and lived with her partner and at least one of her children. She did not have any family history of cancer but reported chronic and ongoing pain due to arthritis that prevented her from working. Prior to surgery, she had not undergone any previous treatment for her tumor. She reported moderate pain at rest that greatly interfered with her life, particularly in normal work, sleep, and enjoyment of life. She expected severe pain immediately following surgery, mild pain after 1 week and recovery within 1 week. She reported symptoms consistent with elevated state anxiety, pain-related anxiety, catastrophizing, and depression.

24 hours after surgery, FZ reported severe pain at rest. She reported symptoms consistent with elevated depression but not state anxiety. At her 1-week follow-up, she reported moderate pain at rest and symptoms consistent with elevated state anxiety and depression. By her 6-month follow-up, FZ had begun chemotherapy, from which she reported

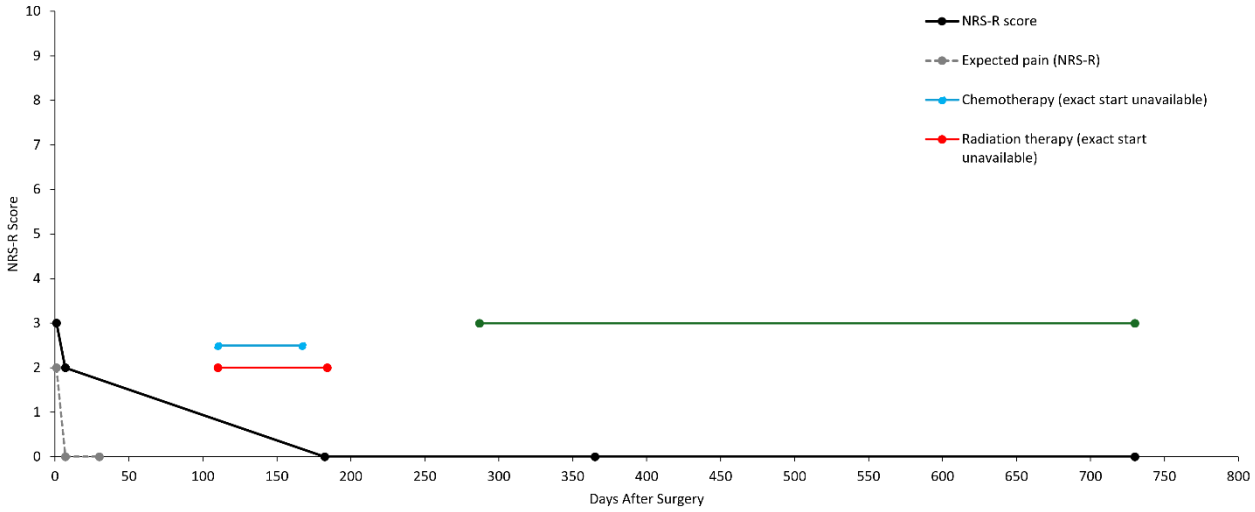
significant side effects. She also reported starting hormone therapy, including multiple medication changes due to side effects. While she did not report pain at rest or pain interference, she continued to report symptoms consistent with elevated state anxiety and depression.

By her 1-year follow-up, FZ's breast cancer had metastasized. She continued to report side effects from her surgery and had developed lymphedema that caused loss of grip strength in the affected arm. She reported mild pain at rest and interference that affected a range of domains, most severely her ability to walk and enjoy life. By her 2-year follow-up, FZ had undergone additional chemotherapy and stopped hormone therapy, possibly due to side effects. She reported moderate pain at rest, and that her interference had worsened, as it now moderately impacted multiple domains and severely impacted her ability to perform general activities, walk, do normal work, and sleep. Throughout her 1 and 2-year follow-ups, FZ reported symptoms consistent with elevated pain-related anxiety, depression, catastrophizing, and state anxiety.

Subgroup Whose Pain Resolved Within 6 Months

The second largest subgroup in this study was the subgroup whose pain resolved within 6 months (27%, n=20). Half of these participants reported pain at both acute follow-ups (24 hours, 1 week), and the other half only reported pain at one acute follow-up.

Figure 14. Subgroup Whose Pain Resolved Within 6 Months: Pain Trajectory for EJ (Lowest 24hr Postoperative NRS-R and Preoperative Pain Interference)

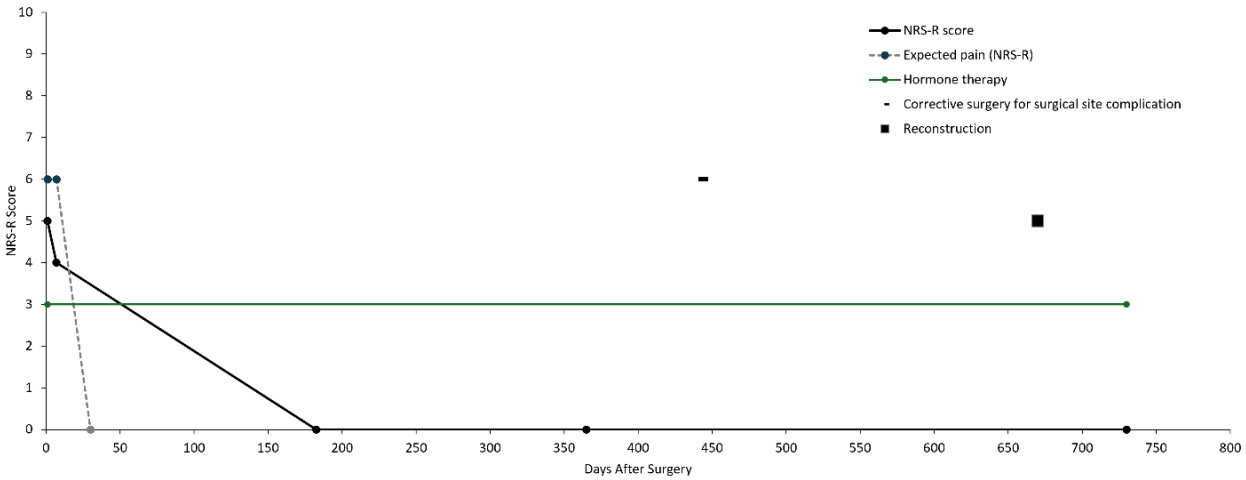


EJ was an educator in her late 50's with invasive ductal carcinoma who underwent lumpectomy on her right breast (Figure 14). She was separated from her partner, had one child, and lived alone. She did not have a family history of cancer but reported a history of non-cancer chronic pain. Prior to surgery, she had not undergone any previous treatment for her tumor. At her preoperative assessment, she did not report pain at rest or interference. She expected mild pain immediately following surgery, no pain after 1 week and recovery within a month. She reported symptoms consistent with elevated state anxiety, but not pain-related anxiety, catastrophizing, or depression.

At her 24-hour and 1-week follow-ups, EJ reported mild pain at rest and did not report symptoms consistent with elevated state anxiety or depression. At her 6-month, 1-year, and 2-year follow-ups, EJ did not report pain at rest, interference, or symptoms consistent with elevated state anxiety or depression. Similarly, at her 1 and 2-year follow-ups she did not report symptoms consistent with elevated pain-related anxiety or catastrophizing.

By the time of her 6-month follow-up, she had already completed her chemotherapy and radiation treatments. By her 1-year follow-up, she had begun hormone therapy, which she continued through her 2-year follow-up. During this time, EJ reported she had retired.

Figure 15. Subgroup Whose Pain Resolved Within 6 Months: Pain Trajectory for LD (Highest Postoperative 24hr NRS-R and Preoperative Pain Interference)



LD was a manager in her early 50's undergoing prophylactic mastectomy on her left breast (Figure 15). She was married with three children, and she lived with her partner and at least one of her children. She had a family history of cancer but no history of chronic pain. Several years prior, she had undergone lumpectomy and then mastectomy for a tumor on her right breast, followed by adjuvant chemotherapy, radiation, and hormone therapy. Her previous hormone therapy was ongoing during and after the current surgery. At her preoperative assessment, she reported no pain at rest, but mild interference, particularly with walking. She expected moderate pain immediately following surgery and after 1 week and recovery within a month. She reported symptoms consistent with elevated state anxiety, but not pain-related anxiety, catastrophizing, or depression.

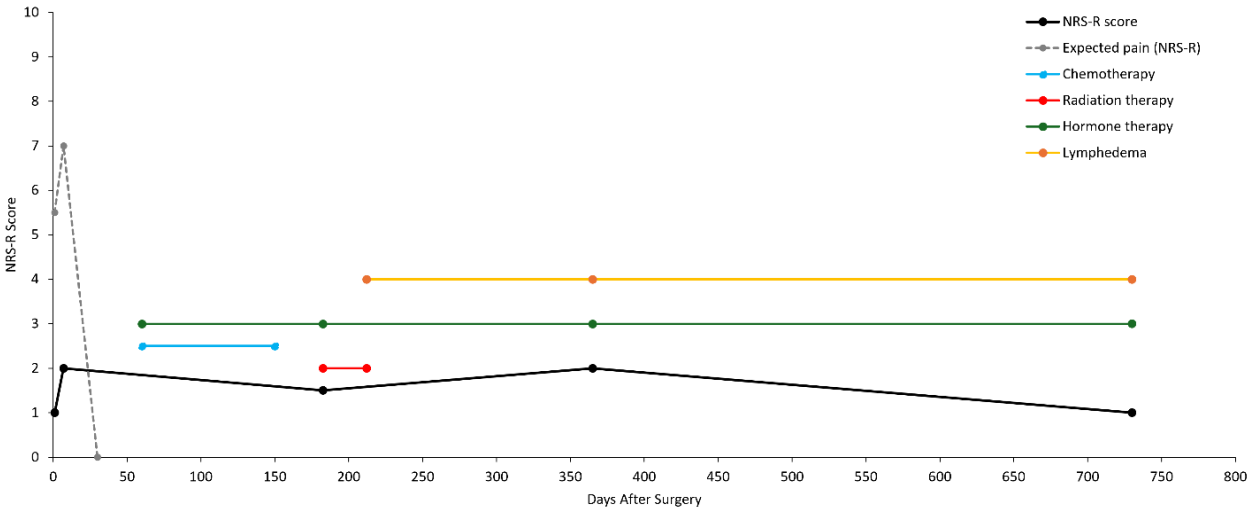
At her 24-hour and 1-week follow-ups, LD reported moderate pain at rest and did not report symptoms consistent with elevated state anxiety or depression. At her 6-month follow-up, she did not report pain at rest, interference, or symptoms consistent with elevated state anxiety or depression.

At her 1 year-follow-up, she reported a complication related to her mastectomy that required surgical treatment shortly after her. By 2 years, LD had undergone reconstruction. Despite this, at both her 1-year and 2-year follow-ups, LD did not report pain at rest, interference, or symptoms consistent with elevated state anxiety, depression, pain-related anxiety, or catastrophizing.

Unresolved Persistent Subgroup

The third largest group was participants who reported unresolved persistent pain (16%, n=12). These participants reported pain at rest at every follow-up. Most (75%, n=9) participants in this group reported at least one follow-up where their CBCSP was more severe than their ABCSP. The remaining (25%, n=3) reported CBCSP that was less severe than their ABCSP at every follow-up.

Figure 16. Unresolved Persistent: Pain Trajectory for PK (Lowest 24hr Postoperative NRS-R and Preoperative Pain Interference)



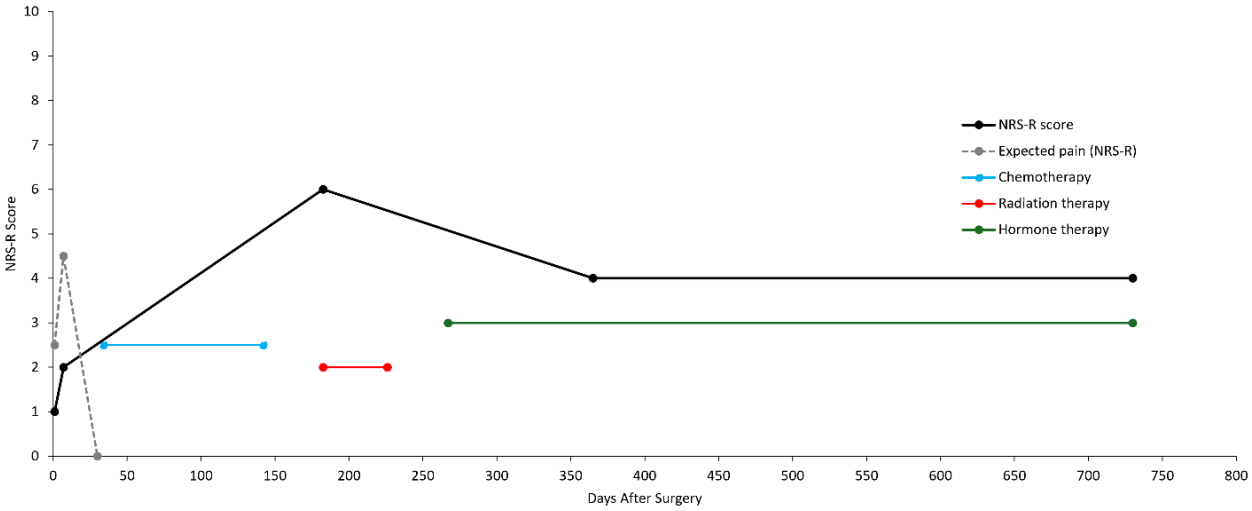
PK was an office worker in her late 60's with invasive ductal carcinoma and DCIS who underwent mastectomy on her left breast (Figure 16). She was married with three children and lived alone with her partner. She had a family history of breast cancer but reported no history of chronic pain. Several years prior, PK had undergone surgery in this breast due to a previous tumor that had metastasized to her axillary lymph nodes and subsequently underwent chemotherapy for 3 months. Prior to the current surgery, she reported mild pain at rest and mild pain interference with sleep. She expected moderate pain immediately following surgery,

mild pain after 1 week and recovery within 2 weeks. She reported symptoms consistent with high pain-related anxiety, catastrophizing, and state anxiety, but not depression.

24 hours after surgery, PK reported moderate pain at rest but no longer reported symptoms consistent with elevated state anxiety or depression. Throughout her 1-week, 6-month, 1-year and 2-year follow-up, PK continued to report mild pain at rest. While she did not report symptoms consistent with elevated state anxiety and depression, she continued to report symptoms of elevated catastrophizing at her 1 and 2-year follow-ups.

PK underwent hormone therapy and reported switching medications twice due to the side effects. By the time of her 1-year follow-up, PK had completed chemotherapy and radiation, from which she reported significant side effects. Also, at 1-year, she reported developing lymphedema prior to the follow-up, which affected her mood. By 2 years, she reported the lymphedema was causing painful swelling and affecting her ability to travel or perform manual tasks.

Figure 17. Unresolved Persistent: Pain Trajectory for RH (Highest Postoperative 24hr NRS-R and Preoperative Pain Interference)



RH was a manager in her late 50's with invasive ductal carcinoma and DCIS who underwent lumpectomy on her right breast (Figure 17). She was married with four children and lived with her partner and at least one of her children. She did not have a family history of cancer but did have a history of chronic pain and ongoing, non-cancer, pain affecting her knees. Prior to surgery, she did not undergo any previous treatment for her tumor, which had metastasized to her lymph nodes. She expected mild pain immediately following surgery, moderate pain after 1 week, and recovery within 2 months. Prior to surgery, she reported mild pain at rest and severe interference, particularly with work, relationships, and ability to enjoy life. She reported symptoms consistent with elevated catastrophizing, state anxiety, and depression.

24 hours after surgery, she reported mild pain at rest but did not report symptoms consistent with elevated state anxiety or depression. After reporting mild pain at rest during her 1-week follow-up, RH reported moderate pain at rest during her 6-month, 1-year and 2-

year follow-ups. By her 6-month follow-up, she had completed chemotherapy and had begun radiation. RH reported side effects for both. At the same follow-up, she reported moderate pain interference which affected her mood, ability to walk, normal work and sleep.

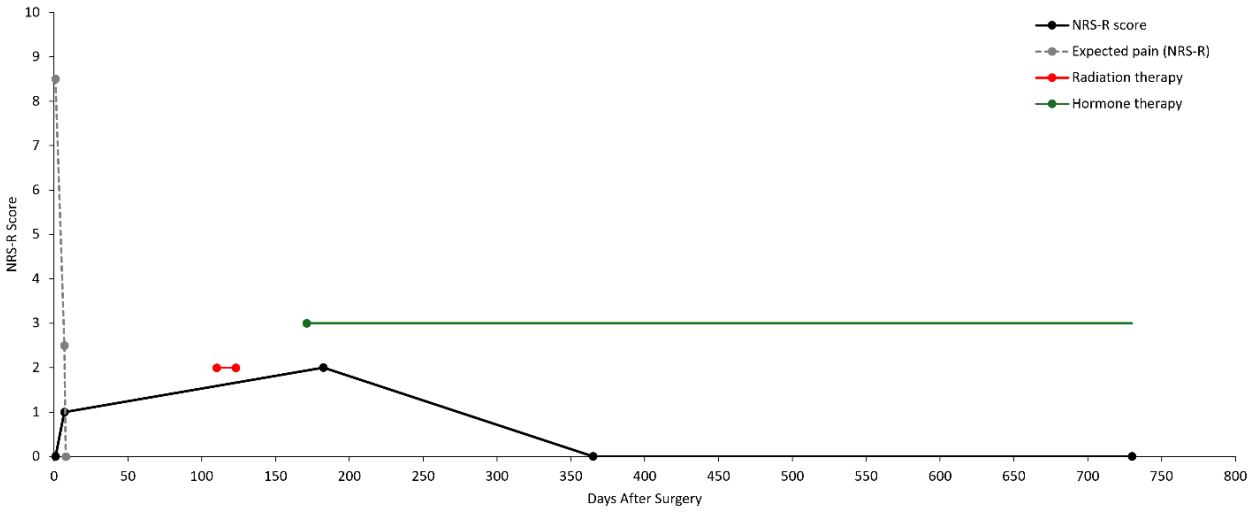
While RH did not report symptoms consistent with elevated catastrophizing or depression, she reported symptoms consistent with elevated state anxiety, at her 1-year and 2-year follow-ups.

By her 1-year follow-up, RH had begun hormone therapy. At the same follow-up she reported moderate pain at rest and interference, which affected a range of domains, but moderately impacted her relations with others and ability to enjoy life. At her 2-year follow-up, she reported worsened interference that severely impacted her relations with others and her ability to enjoy life, among other domains.

Resolved Persistent Subgroup

Tied for the fourth largest subgroup (10%, n=7) were the resolved persistent subgroup. (discussed first) and the resolved episodic subgroup. In the resolved persistent subgroup, there was only one participant who reported their highest pain intensity at 1 year. One (14%) reported the highest pain intensity at their 24-hour follow-up, and the remaining (86%, n=6) reported the highest pain intensity at their 6-months follow-up.

Figure 18. Resolved Persistent: Pain Trajectory for KM (Lowest 24hr Postoperative NRS-R and Preoperative Pain Interference)



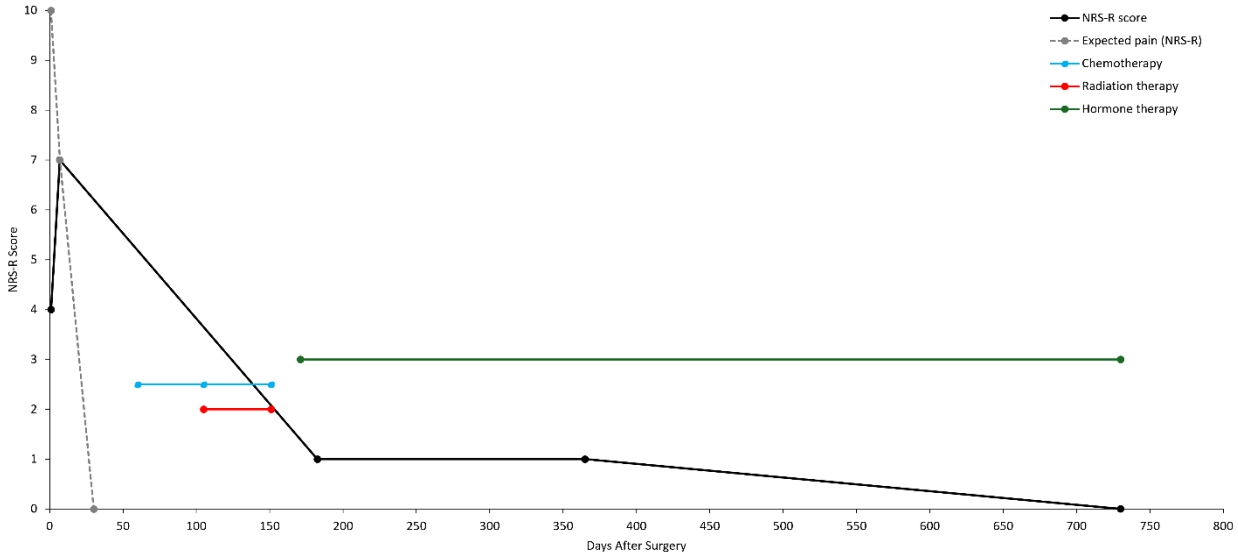
KM was a medical professional in her late 50's with DCIS who underwent lumpectomy on her left breast (Figure 18). She was married with three children and lived with her partner and at least one of her children. She had a family history of cancer and chronic pain, including shoulder pain. Prior to surgery, she had not undergone any previous treatment for her tumor and reported no pain at rest or pain interference. She expected severe pain immediately following surgery. mild pain after 1-week and recovery within a week. At her preoperative

assessment, KM did not report symptoms consistent with elevated state anxiety, pain-related anxiety, catastrophizing, or depression.

24 hours after surgery, she reported no pain at rest and did not report symptoms consistent with elevated state anxiety or depression. 1 week after surgery, she reported mild pain at rest but continued to report no symptoms consistent with elevated state anxiety or depression. By her 6-month follow-up, KM had completed her radiation treatment. She reported mild pain at rest and mild interference that impacted her mood but did not report symptoms consistent with elevated state anxiety or depression.

At her 1-year follow-up, KM reported that she had taken time off work for surgery and radiation but had returned by 1-year follow-up. At the same follow-up, she reported lymphedema but did not describe the symptoms. At both her 1 and 2-year follow-ups, KM did not report pain at rest, pain interference, or symptoms consistent with elevated state anxiety, depression, pain-related anxiety, or catastrophizing.

Figure 19. Resolved Persistent: Pain Trajectory for QW (Highest Postoperative 24hr NRS-R and Preoperative Pain Interference)



QW was a retail worker in her late 40's with invasive ductal carcinoma who underwent lumpectomy on her right breast (Figure 19). She was married and lived alone with her partner. She had a family history of cancer, but no history of chronic pain. At her preoperative assessment, she reported no pain at rest, but mild interference that affected her mood and sleep, as well as ongoing non-cancer pain affecting her arms. Prior to surgery, she had not undergone any previous treatment for her tumor. She expected severe pain immediately following surgery and after 1 week, and recovery within a month. She reported symptoms consistent with elevated state anxiety, pain-related anxiety, and depression.

24 hours after surgery, she reported moderate pain at rest and symptoms consistent with elevated state anxiety and depression. 1 week later, she reported severe pain at rest and continued to report symptoms consistent with elevated state anxiety and depression.

By her 6-month follow-up, she had completed her radiation and soon began hormone therapy. She reported mild pain at rest and pain interference that severely impacted her sleep

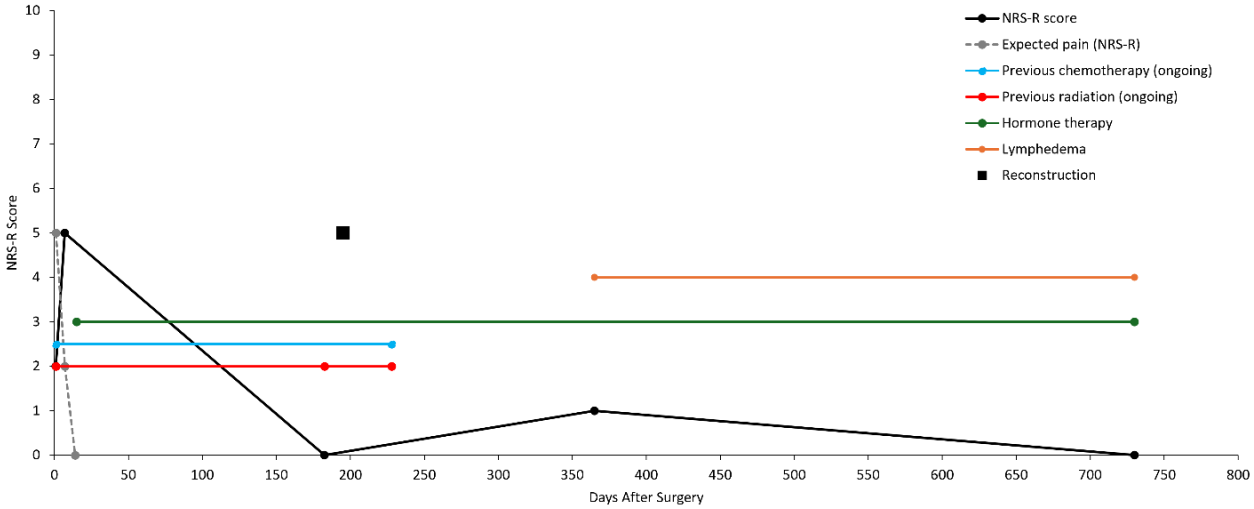
and mildly impacted her mood. She did not report symptoms consistent with elevated state anxiety or depression.

At her 1-year follow-up, she reported mild pain at rest, with interference that moderately impacted her sleep and mildly impacted her ability to do normal work. At her 2-year follow-up, she reported no pain at rest or pain interference. She did not report symptoms consistent with elevated state anxiety, depression, pain-related anxiety, or catastrophizing at her 1- and 2-year follow-ups.

Resolved Episodic Subgroup

Tied for the fourth largest group (10%, n=7) was the resolved episodic subgroup. All participants in this subgroup reported a pain-free interval at 6 months. None of the participants in this subgroup reported a pain-free interval at their 1-year follow-up.

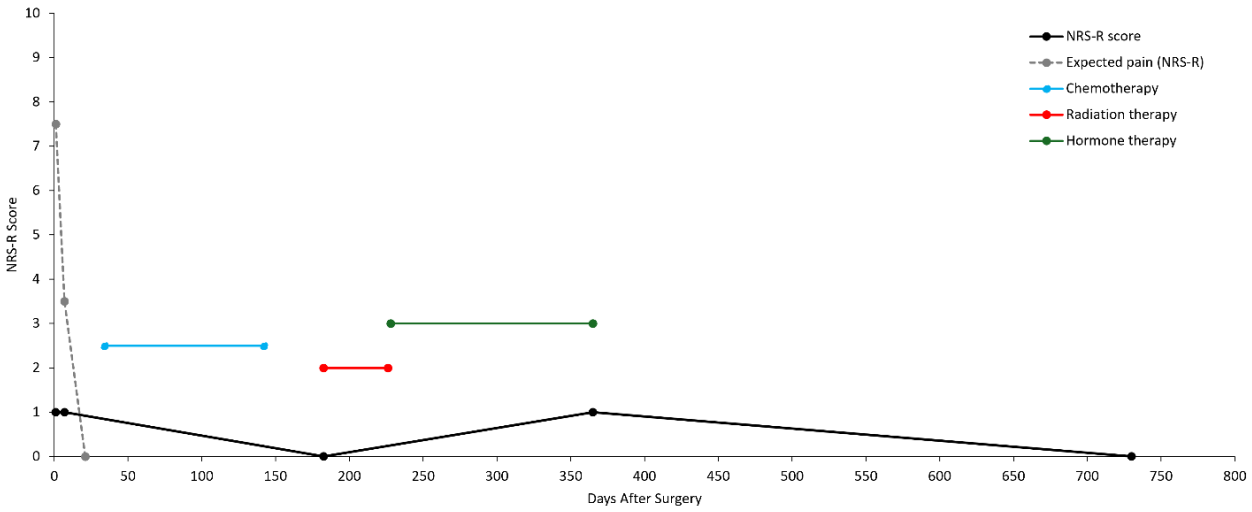
Figure 20. Resolved Episodic: Pain Trajectory for BT (Lowest 24hr Postoperative NRS-R and Preoperative Pain Interference)



BT was an executive in her late 40's who underwent prophylactic mastectomy on her left breast (Figure 20). She was married with two children and lived with her partner and at least one of her children. She had a family history of cancer but did not report a history of chronic pain. Several years prior, she had undergone mastectomy and reconstruction for a tumor in her right breast, along with adjuvant chemotherapy, radiation, and hormone therapy. Prior to the current surgery, she reported mild pain at rest but no interference. She expected moderate pain immediately following surgery, mild pain after 1 week, and recovery within 2 weeks. She did not report symptoms consistent with elevated state anxiety, pain-related anxiety, catastrophizing, or depression.

24 hours after surgery, she reported mild pain at rest. She did not report symptoms consistent with elevated state anxiety or depression. 1 week later, she reported moderate pain at rest and symptoms consistent with elevated state anxiety and depression. Throughout her 6-month, 1-year and 2-year follow-ups, BT reported mild pain. At 2 years, she also reported mild interference that affected her ability to enjoy life. While BT continued not to report symptoms consistent with elevated state anxiety or depression, she did report symptoms consistent with elevated pain-related anxiety and catastrophizing at her 1- and 2-year follow-ups. By her 1-year follow-up, BT had completed chemotherapy and radiation therapy for her previous tumor. At the same follow-up, she reported having undergone reconstructive surgery and beginning hormone therapy. At her 2-year follow-up, she reported lymphedema but did not describe the symptoms or severity.

Figure 21. Resolved Episodic: Pain Trajectory for CP (Highest Postoperative 24hr NRS-R and Preoperative Pain Interference)



CP was a woman in her early 60's who underwent prophylactic mastectomy on her right breast (Figure 21). She was married with three children and lived alone with her partner. She had family history of cancer but no history of chronic pain. Several years prior, she had undergone mastectomy for a tumor in left breast, along with adjuvant chemotherapy and radiation. At her preoperative assessment for the current surgery, she reported no pain at rest but mild interference with walking. She also reported lymphedema, which she reported did not affect her functioning, and a non-cancer health condition that affected word recall that prevented her from continuing to work. She expected severe pain immediately following surgery, moderate pain after 1 week, and recovery within 3 weeks. She did not report symptoms consistent with elevated state anxiety, pain-related anxiety, catastrophizing, or depression.

At her 24-hour and 1-week follow-ups, CP reported mild pain at rest. She did not report symptoms consistent with elevated state anxiety or depression. At her 6-month follow-up, CP

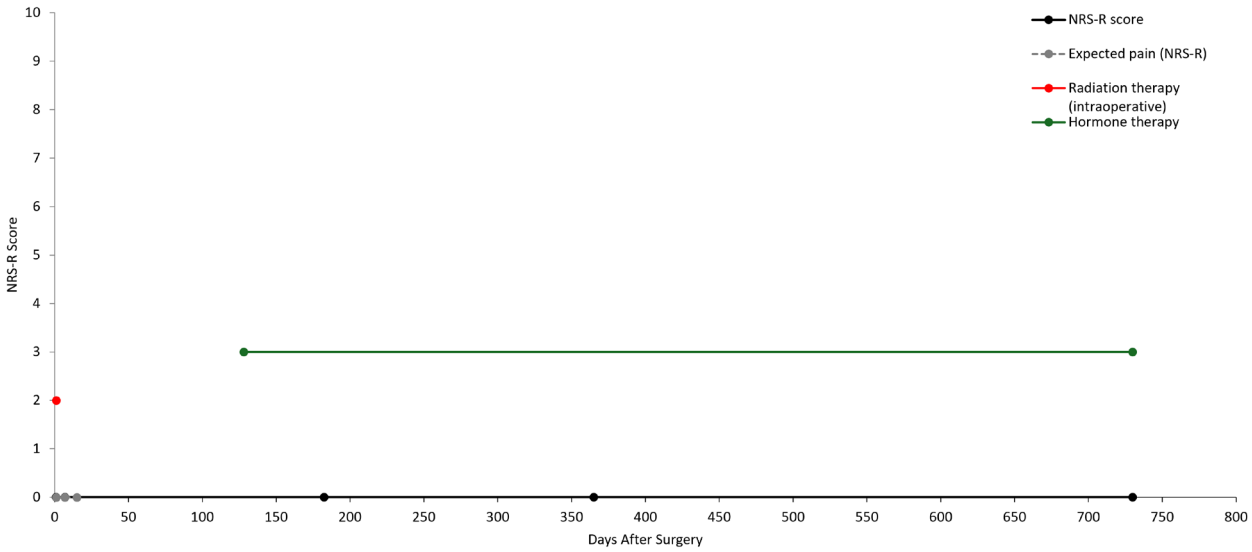
did not report pain at rest, interference, or symptoms consistent with elevated state anxiety or depression. At her 1-year and 2-year follow-ups, she did not report symptoms consistent with elevated state anxiety, depression, pain-related anxiety, or catastrophizing.

By her 1 year-follow-up, CP had undergone reconstructive surgery. At this follow-up, CP reported complications with her surgical wound. She reported mild pain at rest and mild interference that impacted a variety of domains, particularly her ability to enjoy life, but also doing general activities, her mood, and relations with others. At her 2-year follow-up, CP did not report pain at rest but reported mild interference affecting her sleep.

Subgroup Who Did Not Report Pain at Any Follow-up

Our smallest group (7%) were participants who did not report pain at any follow-up (NRS =0).

Figure 22. Subgroup Who Did Not Report Pain at Any Follow-up: Pain Trajectory for NU (Lowest 24hr Postoperative NRS-R and Preoperative Pain Interference)



NU was an executive in her late 60's with invasive ductal carcinoma undergoing lumpectomy on her left breast (Figure 22). She was widowed with one child and lived alone. She had a family history of cancer but did not report a history of chronic pain. Prior to surgery, she did not undergo any previous treatment for her tumor. At her preoperative follow-up, she reported ongoing shoulder pain but did not report pain at rest or interference. She expected no pain after surgery, mild pain after 1 week, and recovery by 2 weeks. She did not report symptoms consistent with elevated state anxiety, pain-related anxiety, catastrophizing, or depression.

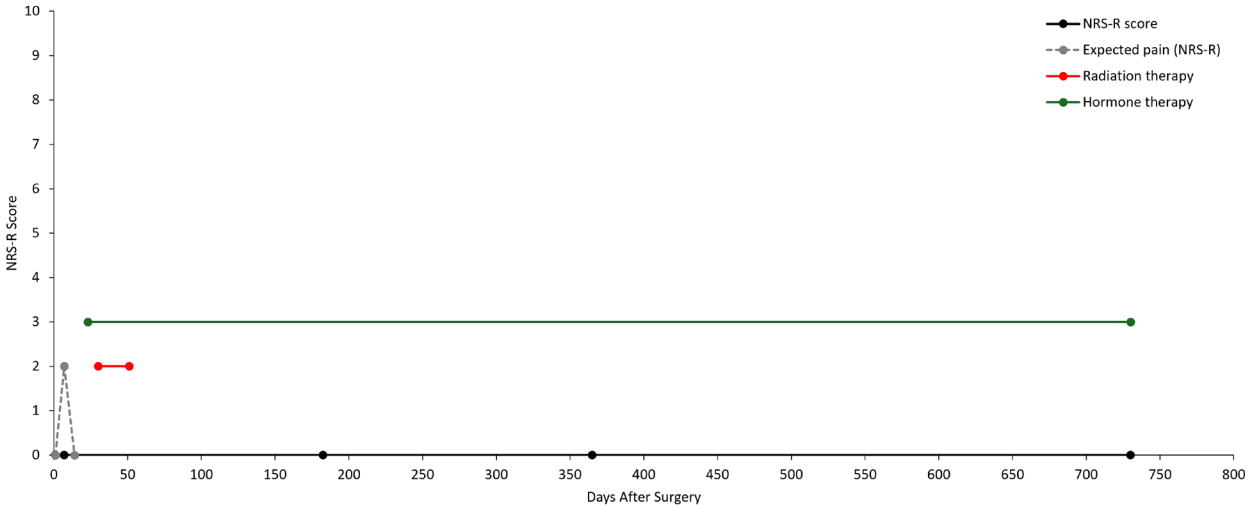
NU did not report pain at rest or symptoms consistent with elevated state anxiety or depression at her 24 hours, 1-week, 6-months, 1-year, or 2-year follow-ups.

NU was part of a different study examining intraoperative radiation outcomes. Instead of adjuvant radiation therapy, during her surgery, she received a single dose of radiation where the tumor was removed. By her 6-month follow-up, she had begun her hormone therapy. She changed medications, due to side effects.

While NU did not report pain at rest at her 1-year follow-up, she did report interference which mildly impacted her ability to do general activities. While she did not complete the catastrophizing questionnaire at her 1-year follow-up, she did not report symptoms consistent with elevated pain-related anxiety. At this follow-up, NU reported that she had retired from work.

She did not report pain interference at her 2-year follow-up. However, she did report symptoms consistent with elevated pain-related anxiety, but not catastrophizing.

Figure 23. Subgroup Who Did Not Report Pain at Any Follow-up: Pain Trajectory for TL (Highest Postoperative 24hr NRS-R and Preoperative Pain Interference)



TL was a consultant in her early 70's with invasive lobular carcinoma undergoing lumpectomy on her right breast (Figure 23). She was married with three children and lived alone with her partner. She had a family history of cancer but did not report a history of chronic pain. She had not undergone any previous treatment. At her preoperative assessment, she did not report pain at rest but did report severe pain interference, particularly with walking and general activity, and ongoing non-cancer pain affecting her feet. She expected no pain after surgery, mild pain after 1 week and recovery within 2 weeks. She did not report symptoms consistent with elevated state anxiety, pain-related anxiety, catastrophizing, or depression.

TL did not report pain at rest at 24 hours, 1-week, 6-months, 1-year, or 2-year follow-ups. Similarly, she did not report symptoms consistent with elevated state anxiety or depression at any follow-up, or symptoms consistent with pain-related anxiety or catastrophizing at 1-year and 2-year follow-ups. During this time, she completed her radiation treatment and began hormone treatment before her 6-month follow-up.

While she had not reported pain at rest during her follow-ups, TL did report pain interference that moderately affected her relations with others and severely affected her ability to do general activities and walk at her 1-year follow-up. Then, at her 2-year follow-up, she continued to report pain interference that moderately impacted her ability to walk and do normal work.

Exploratory Findings from Individual Trajectory Investigation

Complications, treatment-related side effects, additional or prolonged treatment, elevated scores of state anxiety, depression, pain-related anxiety, catastrophizing, or pain interference were present across all trajectory subgroups. However, compared to participants whose pain resolved within 6 months, participants with unresolved pain more often reported undergoing treatments like radiation, chemotherapy, and hormone therapy beyond 6 months following BCS, often with significant side effects that prolonged treatment. Three of the 12 women reported lymphedema. Two, FZ (Figure 13) and PK (Figure 16), were in the persistent unresolved subgroup and one, BT (Figure 21), was in the episodic resolved subgroup. An overview of when participants reported undergoing chemotherapy, radiation therapy, hormone therapy, and lymphedema is included in Appendix G.

Participants reporting symptoms consistent with elevated preoperative state anxiety, depression, pain-related anxiety, or catastrophizing were present across all trajectory groups. In most cases, these scores decreased after surgery, except for QW (Figure 19), whose scores increased after surgery. QW had the highest 24hr NRS-R score and preoperative pain interference of the persistent resolved trajectory group.

The subgroup who did not report pain at any follow-up had no participants who underwent ALND. Compared to the other subgroups, participants in this subgroup also reported fewer surgical and treatment complications, did not undergo chemotherapy, finished radiation therapy earlier, were older, and reported fewer symptoms of psychological distress.

Identifying Candidate Correlates of BCSP

Including the variables that were forced in, the bivariate analysis identified 21 potential candidate correlates. These included: marital status, child and living situation, having children, age, preoperative chronic pain or analgesic intake, preoperative ongoing pain from a past surgery, procedure, SF-MPQ PPI, BPI-SEV, BPI-INT, SF-NPQ, SF12-PCS, PASS-EA, PASS-CA, STAI-S, CES-D, PCS-R, PCS-M, and PCS-H. The complete results of the bivariate analyses can be found in Table 4.

Multicollinearity

Based on the tolerance and VIF, there were no issues with multicollinearity.[397,409] However, several variables were highly correlated ($r>0.7$).[409] Highly correlated scales included the SF-MPQ Sensory, NRS-R, PPI, BPI-SEV, BPI-INT, CES-D, STAI-S, SF12-PCS, PCS-R, PCS-H, PCS-M, PASS-F, PASS-EA, PASS-PA, and PASS-CA. Full correlation results for continuous variables can be found in Appendix B. For categorical variables, multicollinearity was assessed using Fisher's Exact test. Child and living situation was significantly correlated with marital status, having children, and living situation ($p<.001$), as well as the SF-NPQ and PPI ($p=0.004$).

To resolve potential multicollinearity, several steps were taken. First, variables with missing data were excluded. Then, a literature review was conducted to determine whether the

variables were capturing distinct constructs despite being highly correlated. Variables with sufficient support from previous literature were kept in the model. The BPI-SEV and BPI-INT were retained, as they measure distinct aspects of pain, including severity and pain interference, which were not captured by other scales.[410] Previous literature has established that, although measures of depression and state anxiety are correlated, they measure distinct constructs.[410] Similarly, inclusion of the PCS subscales, PASS subscales, and SF12-PCS were supported by previous literature.[411,412] For multicollinearity between categorical variables, child and living situation was based on having children, living situation, and living arrangement. As a result, the other variables were redundant and only child and living situation was retained. Given that BPI-SEV was already included, the SF-MPQ PPI was excluded. After resolving issues with multicollinearity, 17 variables were entered into the regression.

Table 4. Results Of The Bivariate Analysed: Unresolved Group

Variable Name	r	Chi-square	Cramer's V	p value
Demographic				
Religion			1.660	.292
Education		0.220		1.00
Marital status		0.322		.022*
Living arrangements			2.555	.172
Child and living situation		0.374		.014*
Age	-0.009			.942*
Primary language			0.201	.742
Ethnicity			0.045	1.00
Have children			9.198	.004*
Disease History				
Diagnosis		0.096		.776
Preoperative stage		0.272		.268
Metastatic			0.278	.405
Recurrence			0.211	.405
Previous chemotherapy			0.130	.795
Previous trastuzumab			0.220	1.00
Previous radiation			0.044	1.00
Previous aromatase inhibitor			0.347	.576
Biopsy before surgery			0.002	1.00
Chronic Pain and/or analgesic intake			7.586	.008*
Previous surgeries			0.461	.6479
Previous surgery related to breast			0.466	.636
Ongoing pain from past surgeries			4.766	.045*
Ongoing pain problems			0.617	.478
Pain Measures				
NRS-R	0.348			.002*
NRS-M	0.156			.189
SF-MPQ - PPI		0.109		.078*
CCI		0.238		.225
SF-MPQ Sensory	0.157			.185
SF-MPQ Affective	0.026			.832
BPI Severity	0.344			.003*
BPI-INT	0.354			.002*
SF-NPQ			1.074	.406*

Table 4. (continued)

Variable Name	r	Chi-square	Cramer's V	p value
Biological and Health Status				
BMI	0.113			.341
SF12-PCS	-0.206			.087*
ESAS	-0.145			.222
Psychological Measures				
SF12-MCS	-0.153			.198
PASS-F	0.189			.113
PASS-EA	0.212			.076*
PASS-PA	0.116			.332
PASS-CA	0.208			.081*
STAI-S	0.276			.020*
CES-D	0.229			.054*
Pain expectation	0.168			.157
PCS-R	0.272			.021*
PCS-M	0.278			.017*
PCS-H	0.328			.005*
Surgical Factors				
Mastectomy			1.168	.350*
Surgical duration	0.004			.972
ALND			2.162	.167
SLND			0.315	.315

[a]* Included in analysis. SF-NPQ and Procedure were forced in.
[b]Abbreviation: All acronyms can be found in the abbreviation list (p.xii).

Analysis of Trajectory Group Differences

Binary logistic regression modelling was performed with the candidate correlates: marital status, child and living situation, having children, age, preoperative chronic pain or analgesic intake, preoperative ongoing pain from a past surgery, SF-MPQ, BPI-SEV, BPI-INT, SF-NPQ, SF12-PCS, PASS-EA, PASS-CA, STAI-S, CES-D, PCS-R, PCS-M, and PCS-H to determine risk factors for unresolved pain at 2 years. The new model was not significantly different from the baseline model, indicating that it was more parsimonious (F-=0.914, p=0.504). This test confimed that even when candidate correlates were removed, there was no significant reduction in how much variance this model predicted (R^2= .45). As shown in Table 5, procedure and child and living situation contributed significantly to the model. Two other non-significant predictors, the presence of preoperative chronic pain and pain interference, were retained in the model.

Table 5. Binomial Logistic Regression Results For Unresolved Pain Group

	B	**SE**	**Wald**	**df**	**p**	**OR**	**95% CI OR**	
							LL	**UL**
Continuous	0.660	0.846	0.780	63.993	0.438	1.935	0.357	10.490
Procedure (Mastectomy)	**1.553**	**0.730**	**2.126**	**63.644**	**0.037**	**4.724**	**1.098**	**20.330**
Preoperative Chronic Pain	1.562	0.818	1.909	63.951	0.061	4.769	0.930	24.450
Pain Interference	0.509	0.263	1.935	61.136	0.058	1.664	0.983	2.815
Living with child alone	**-3.184**	**1.568**	**-2.030**	**64.056**	**0.047**	**0.041**	**0.002**	**0.951**
Living with child and partner	**-3.518**	**1.100**	**-3.199**	**63.804**	**0.002**	**0.030**	**0.003**	**0.267**
Child not at home	**-2.325**	**0.998**	**-2.328**	**63.893**	**0.023**	**0.098**	**0.013**	**0.719**

[a]Child and living situation was entered in the model as a categorical variable 0= "did not have children" as the reference group

The model showed that participants undergoing a mastectomy, rather than a lumpectomy, were significantly more likely to have unresolved postoperative pain at 2 years. Participants with children, whether living alone, with a partner, or where the child was not living with the parent, were significantly less likely to have unresolved pain than participants who did not have children. Specifically, living with a child and partner was the most significant contributor to the model.

Trajectory Subgroup Differences

Given the small and uneven sample size among each trajectory subgroup, multiple logistic regression was not used to investigate predictors of trajectory subgroup membership. Instead, Fisher's Exact test and Kruskal-Wallis tests were used to examine the differences between trajectory subgroups. The same predictors included through the bivariate analysis were used.

Table 6 shows that only the BPI-SEV and BPI-INT were significantly different between trajectory groups. Post-hoc tests (Dunn-Bonferroni) were used to compare group differences (Appendix C). Given the familywise error rate (0.54), there were no significant pairwise comparisons for BPI-SEV (Table 3.1). For pairwise comparisons of BPI-INT (Table 3.2), participants with persistent resolved pain had lower preoperative pain interference than those with persistent unresolved pain (-2.99, adjusted p=0.04).

Table 6. Results of Kruskal-Wallis and Fisher's Exact Tests

	Kruskal-Wallis H	**Fisher's Z**	**df**	**p-value**
Age	7.42		5	0.191
SF-MPQ	8.42		5	0.135
BPI-SEV	12.78		5	0.026*
BPI-INT	11.24		5	0.047*
STAI-S	9.71		5	0.084
CES-D	7.49		5	0.187
PCS-R	5.07		5	0.408
PCS-M	0.21		5	0.256
PCS-H	8.77		5	0.118
SF12-PCS	1.12		5	0.952
PASS-EA	4.70		5	0.454
PASS-CA	4.64		5	0.462
SF-NPQ		1.71	-	0.957
Procedure		14.45	-	0.403
Chronic pain or analgesic intake		8.04	-	0.125
Previous Surgery pain		4.22	-	0.431

[a]*p<0.05 ** degrees of freedom are not available for binary outcomes.
[b]Abbreviation: All acronyms can be found in the abbreviation list (p.xii).

Exploratory Analyses of Pain Interference

Given the results of the trajectory group and subgroup differences, several post-hoc tests were used to explored preoperative pain interference and interference over time in the larger trajectory groups. Specifically, the analyses compared pain interference at baseline to 2 years postoperative. Participants who were missing preoperative or 2-year BPI-INT scores were excluded (n=11). Compared to participants who were included (n=62), participants who were excluded (n=11) reported significantly shorter surgeries (p=.028).

Descriptives. On the BPI-INT, 0-4 is "mild interference", 5-6 is "moderate interference" and 7-10 is "severe interference". [413] Based on total BPI-INT scores, preoperatively 57 (92%) participants had mild interference and five (8%) had moderate interference. At 2 years, 60 (97%), participants had mild interference, one (2%) had moderate interference, and one (2%) had severe interference.

Internal Consistency and Inter-item Correlation. First, to investigate and verify how the BPI-INT items capture pain interference, internal consistency and inter-item correlation were assessed using Chronbach's alpha and Pearson's correlation, respectively.

As Table 7 shows, all the BPI-INT items were positively associated with one another. The highest correlation was between relations with other and enjoyment of life (r=.896). While interference with walking had the lowest overall correlation values with other items, it nonetheless was correlated at .814 with general activity, and >.6 with mood, normal work and enjoyment of life. Consistent with the inter-item correlations, the BPI-INT had a high Chronbach's alpha (α=.949), based on its preoperative scores.[414,415]

Table 7. Inter-item Correlations for Preoperative BPI-INT Scores

	9a. General activity	9b. Mood	9c. Walking	9d. Normal Work	9e. Relations with Others	9f. Sleep	9g. Enjoyment of life
9a. General activity	-						
9b. Mood	.682	-					
9c. Walking	**.814**	.689	-				
9d. Normal work	**.841**	.692	.612	-			
9e. Relations with others	**.761**	**.830**	.590	**.841**	-		
9f. Sleep	**.745**	**.822**	.579	**.732**	**.756**	-	
9g. Enjoyment of life	**.787**	**.824**	.658	**.882**	**.896**	**.707**	-
M	1.258	0.887	1.081	1.121	0.710	1.194	1.194
SD	2.032	1.611	2.190	2.204	1.430	2.172	2.032

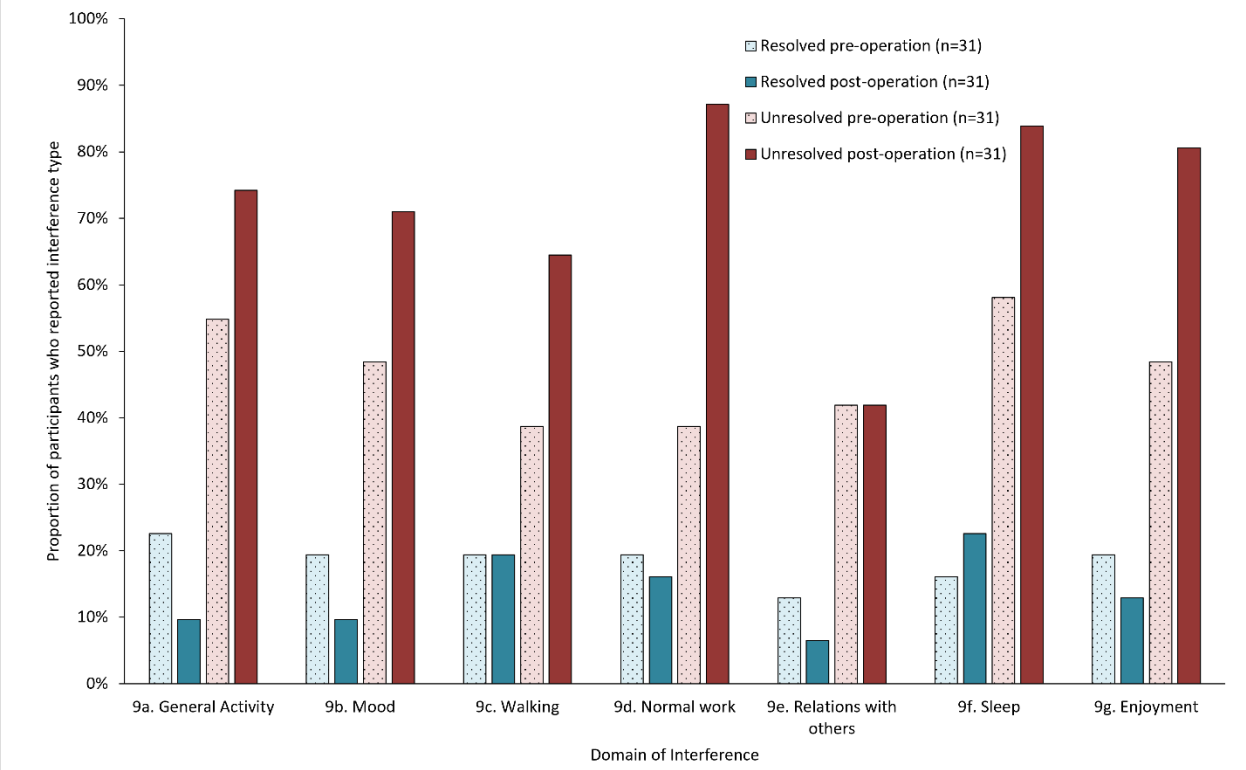
Frequency of Pain Interference Items by Trajectory Group

To explore the relationship between pain interference and resolution, the number of participants who reported a score > 0 on each BPI-INT domain at baseline and 2 years were assessed. Overall, as shown in Figure 24, participants with unresolved pain reported a higher frequency of interference than participants with resolved pain, regardless of domain. Among those with unresolved pain at 2 years, the frequency of reporting each interference item was greater at 2 years than preoperatively. This occurred for all domains of interference except for relations with others, which stayed the same. Conversely, when compared to participants with unresolved pain, participants with resolved pain reported a lower frequency of pain interference for all domains after surgery except for walking, which stayed the same, and sleep, which increased. Preoperatively, approximately half of participants with unresolved pain

reported interference with general activity (55%, n=34), sleep (58%, n=36), mood (48%, n=30), and enjoyment of life (48%, n=30). 2 years after surgery, most reported some kind of pain interference, with normal work (87%, n=54), sleep (84%, n=54) and enjoyment of life (81%, n=50) being the most prevalent. In participants with resolved pain, interference with general activity (23%, n=14) was most common preoperatively. At 2 years, interference with sleep (23%, n=14) was the most common.

Given these observations, and with limitations in sample size, a combination of tests were used to explore the change in pain interference before and after surgery. First, participants with resolved and unresolved pain were compared on total BPI-INT scores to assess the change in overall interference over time. Then, these groups were compared on individual BPI-INT items to assess changes in each domain.

Figure 24. Proportion of Participants Reporting Pre- and Postoperative Interference Items by Trajectory Group



Total Score Repeated Measures ANOVA. To follow-up the observations in Figure 24, repeated measures ANOVA was used to assess the overall change in baseline and 2-year pain interference scores between participants with resolved and unresolved pain. As shown in Table 8, total pain interference scores did not change significantly pre- to postoperatively.

However, as Table 9 shows, tests of between-subjects confirmed that participants with unresolved pain had significantly higher total pain interference scores than those with resolved pain at both timepoints. This result is illustrated in Figure 25.

Table 8. Repeated Measures ANOVA Test of Within-subjects Variables (BPI-INT Total)

	SS	*df*	*MS*	*F*	*p*
Time	0.124	1	0.124	0.163	0.688
Time*Resolved	1.597	1	1.597	2.096	0.153
Error(Time)	45.710	60	0.762		

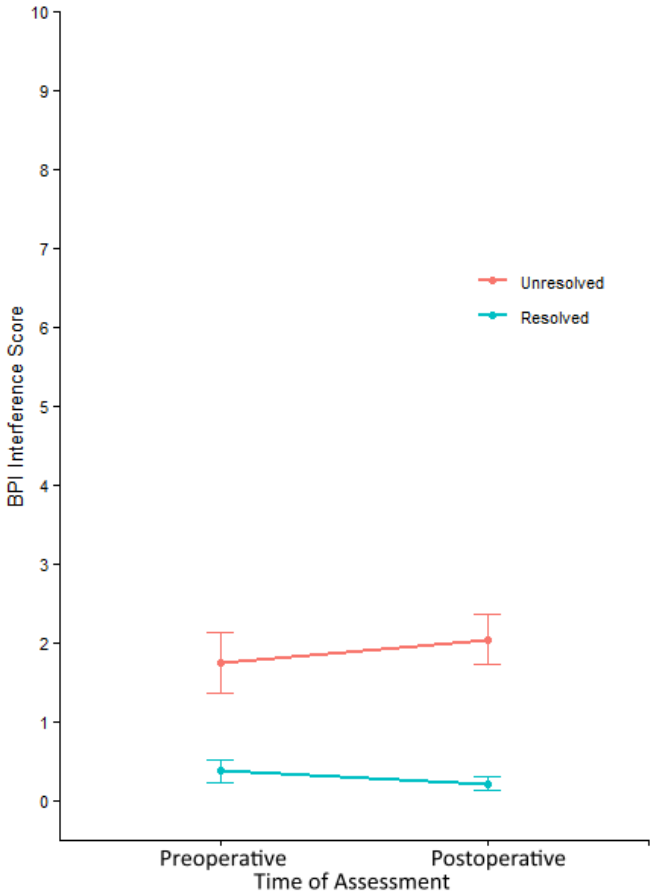
[a]*p<0.05, **p<0.01

Table 9. Repeated Measures ANOVA Test of Between-subjects Variables (BPI-INT Total)

	SS	*df*	*MS*	*F*	*p*
Resolved	79.61	1	79.61	22.527	<.001***
Error	212.04	60	3.53		

[a]*p<0.05, **p<0.01

Figure 25. Average Total Pain Interference Scores by Trajectory Group Over Time



Item Score Repeated Measures ANOVA. Repeated measures ANOVA was used to assess the overall change in baseline and 2-year pain interference item scores between resolved and unresolved trajectory groups (Appendix D). The seven items included: interference with general activity (9a), mood (9b), walking (9c), normal work (9d), relations with others (9e), sleep (9f) and enjoyment of life (9g).

As shown in Table 11, there was a significant interaction between resolution group and interference with walking ($F(1, 60) = 4.074$, $p=0.048$) such that participants with unresolved pain had an increase in walking interference at 2 years and participants with resolved pain had a decrease in walking interference at 2 years. Furthermore, as show in Table 10, tests of within-subjects effects confirmed that interference with walking (9c) scores changed significantly from pre- to postoperatively. Furthermore, As seen in Figure 26, participants with resolved and resolved pain did not have significantly different preoperative scores of interference with walking.

Table 10. Repeated Measures ANOVA Test of Within-subjects Variables (BPI-INT 9c: Walking)

	SS	***df***	***MS***	***F***	***p***
Time	1.36	1	1.363	0.632	0.430
Time*Resolved	8.78	1	8.782	4.074	0.048*
Error(Time)	129.35	60	2.156		

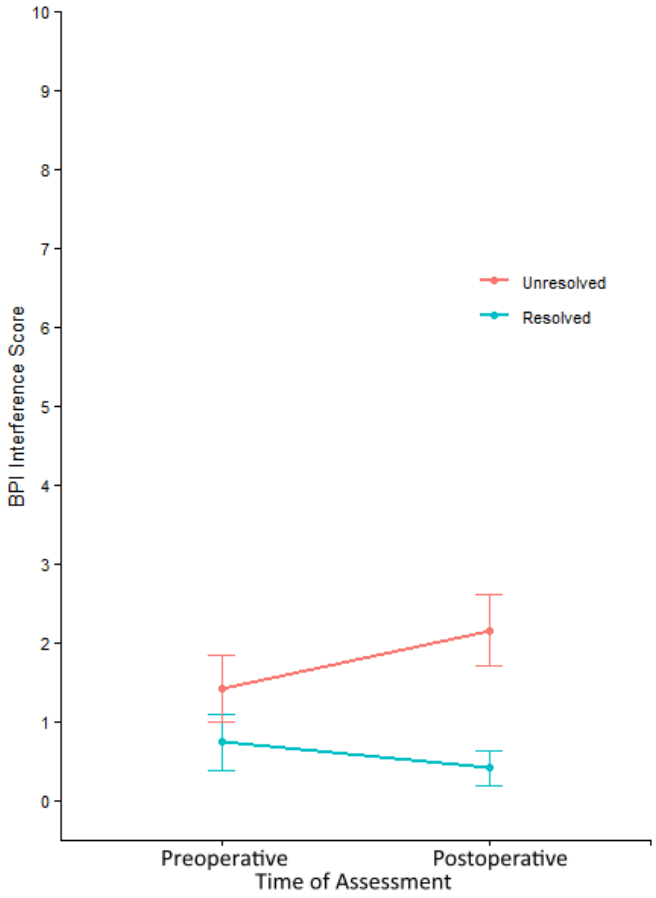
[a] **p<0.05, **p<0.01*

Table 11. Repeated Measures ANOVA test of between-subjects variables (BPI-INT 9c: Walking)

	SS	***df***	***MS***	***F***	***p***
Resolved	45.40	1	45.36	7.017	.010**
Error	387.90	60	6.46		

[a] **p<0.05, **p<0.01*

Figure 26. Average Pain Interference with Walking (9c) Score by Trajectory Group Over Time



Other Domains of Interference. While not significant, the interaction between resolution group and interference was also observed in mood (Table D.3; p=.065), general activity (Table D.1; p=.13), and normal work (Table D.5; p=.16). Compared to participants with resolved pain, whose interference stayed the same or decreased, participants with unresolved pain reported an increase in pain interference.

On all seven items, between-subjects tests confirmed that participants with unresolved pain had significantly higher pain interference than those with resolved pain at baseline and 2

years. Tables for the repeated measures ANOVA tests (Table D.1-4.12), as well as accompanying figures (Figure D.1-D.6), for all the items are included in Appendix D.

Pain Resolution and Mood. Repeated measures ANOVA were conducted to further investigate how pre- and postoperative total depression scores (CES-D) changed between resolution groups. Six participants were excluded due to missing data at the preoperative follow-up. Compared to participants who were included (n=56), those who were excluded (n=5) had significantly higher preoperative PASS-F (p=.008), PASS-PA (p=.014), STAI-S (p=.022), PCS-R (p=.012), PCS-H (p<.001), and PCS-M (p=.006) scores.

As seen in Table 12, there was a significant main effect between depression and time of follow-up, such that participants with both resolved and unresolved pain saw a significant decrease in pre- to postoperative total depression scores ($F(1,54) = 33.227$, $p<.0001$). Furthermore, shown in Table 13, between-subjects tests found that participants with unresolved pain had significantly higher depression scores than participants with resolved pain at both timepoints. These effects were illustrated in Figure 27.

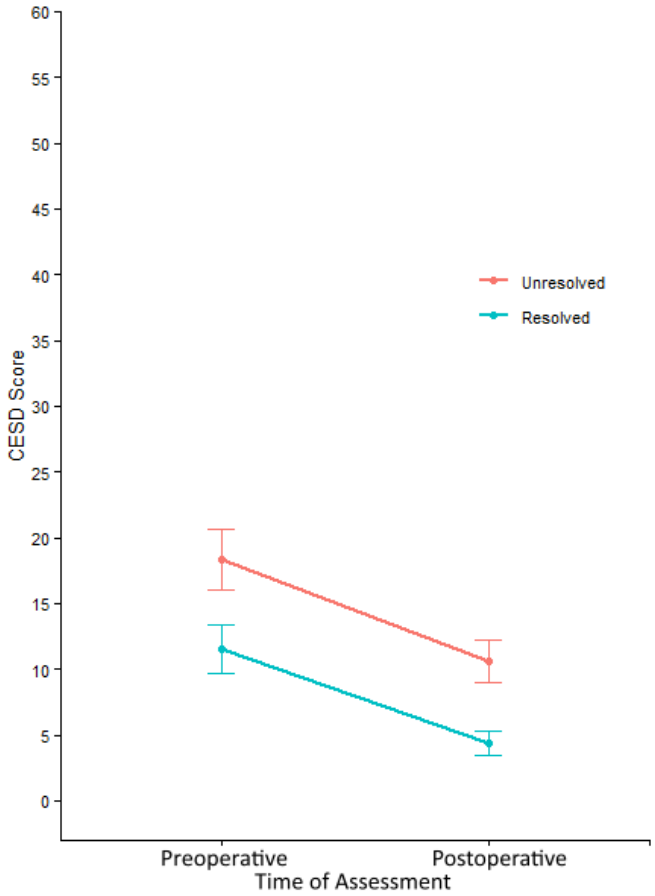
Table 12. Repeated Measures ANOVA Test of Within-subjects Variables (CES-D Total)

	SS	*df*	*MS*	*F*	*p*
Time	1541.4	1	1541.4	33.227	<.0001***
Time*Resolved	2.1	1	2.1	.045	.832
Error(Time)	2505.1	54			

Table 13. Repeated Measures ANOVA Test of Between-subjects Variables (CES-D Total)

	SS	*df*	*MS*	*F*	*p*
Resolved	1178	1	1177.9	9.931	<.00265**
Error	6505	54	118.6		

Figure 27. Average depression (CES-D) scores by trajectory group over time



DISCUSSION

This was the first longitudinal study of breast cancer surgery pain (BCSP) trajectory with longer than 6-month follow-up. It was also the first study to examine trajectory group and subgroup membership using a wide range of preoperative demographic, biological, psychological, social, and pain characteristics. Six distinct trajectory subgroups were identified, based on time to resolution and episodic pain pattern, including: two subgroups whose pain had resolved by 2 years (persistent resolved and episodic resolved); two subgroups whose pain had not resolved by 2 years (persistent unresolved and episodic unresolved; a subgroup whose pain resolved by 6 months; and a subgroup who did not report pain at any follow-up. The only preoperative biopsychosocial factor that was associated with subgroup membership was pain interference. Upon further exploration of resolution groups, this study found that participants in the unresolved group had significantly higher preoperative pain interference than those in the resolved group. From preoperative to 2 years postoperative, participants with unresolved pain reported worsening interference, whereas participants with resolved pain reported improving interference.

The Importance of Trajectory in Characterizing BCSP

In this study, 27% of participants reported acute breast cancer surgery pain (ABCSP) within the first 24 hours after surgery and 34% continued to report pain within the first week. This is consistent with other studies of ABCSP,[18,120,416] as well as other surgical populations.[15,417,418] Importantly, almost half (47%) of participants reported unresolved pain 2 years after surgery. This is also consistent with prevalence rates of chronic breast cancer surgery pain (CBCSP), which ranged from 37 – 50% 2 years after surgery in a recent systematic

review and meta-analysis,[21] as well as in cross-sectional studies.[419,420] These findings suggest that our sample was representative of the larger ABCSP and CBCSP populations.

Many studies have found that CBCSP is a highly prevalent outcome. While previous research has been instrumental, intra-individual variability of pain has not received the attention it deserves. Currently, studies examining CBCSP prioritize inter-individual differences, where it is described as a binary outcome (did report pain/did not report pain) or, at most, categorically by severity (mild, moderate, severe) at discrete time points.[21] This approach reflects the general belief that pain after breast cancer surgery (BCS) decreases as the wound heals or else remains at a fixed intensity and becomes chronic, with very little variability.[117] Under the most conservative version of this approach, it is assumed that individuals who do not report pain at a specific time point will not report pain at any subsequent time;[421] similar consistency of intensity is also assumed.[44] That is, individuals who report "mild" pain will always experience mild pain.

However, it has become increasingly recognized that the course of pain following BCS–its trajectory–is not always linear but can fluctuate, [106,108,422,423] and the lack of recognition of these fluctuations may contribute to inappropriate care that may lead to, or maintain, chronic pain.[424] In other pain populations, trajectory studies, which sequentially examine more than two timepoints, have been used to address the gaps and limitations in the literature.

There are few studies using this methodology with the BCSP population. There is only one, to my knowledge, that considered intra-individual variations in pain.[68] However, the study did not differentiate between episodic and persistent pain and included participants who did not have surgery. The remaining BCSP trajectory studies used varying methodologies where a

small number of trajectory groups were formed based on average pain severity[20,44,67,68] or resolution.[66,68] This approach is useful for assessing outcomes, but the formation of a small number of groups without examining intra-individual variability may obscure highly heterogenous patterns. Many of these BCSP trajectory studies only followed participants 6 months after surgery, [44,425] included participants who did not have surgery,[68] employed simple dichotomous outcomes, [20,66,67] and varied widely in methodology, further limiting interpretation. With limited consensus regarding the definition and nature of CBCSP trajectories, these studies do not overcome the limitations present in the literature. Ultimately, the literature's inability to form consensus is a major obstacle to the understanding, recognition, and adequate treatment of pain in the post-treatment period.

As there was no adequate framework within the cancer pain literature to meet our objectives, our study adapted a more heuristic framework from research in participants with low back pain (LBP), another chronic pain condition that has different pain patterns and trajectory subgroups.[53,54] This framework simultaneously considered several key characteristics, including intensity, variability (persistent/fluctuating/episodic/single episode), and change (rapid improvement/gradual improvement/progressing), which are more consistent with the current conceptualization of pain.[53] Using this method, researchers characterized common trajectories across ten cohorts of participants with LBP in different settings and countries and have identified trajectory groups at increased risk of functional impairment, disability, psychosocial distress, and severe pain over time.[54,56–58] Furthermore, studies have emerged examining the stability of trajectory group membership.[57] These findings suggest that trajectory

patterns may be used as a prognostic factor for pain chronicity and to inform the development of targeted interventions.

Employing this adapted comprehensive approach, our study was able to contribute to our understanding of recovery in the first 2 years after surgery. Specifically, our study used visual inspection to cluster participants into six parsimonious trajectory groups based on pain intensity at 6 months coupled with its persistence over time: first, NRS-R scores were plotted over time; second, participants were categorized into resolution groups; and finally, trajectory subgroup membership was determined using time to resolution and episodic pain pattern. This careful, stepwise analysis revealed two subgroups whose pain had resolved by 2 years (persistent resolved and episodic resolved), two subgroups whose pain had not resolved by 2 years (persistent unresolved and episodic unresolved), a subgroup whose pain resolved by 6 months and a subgroup who did not report pain at any follow-up.

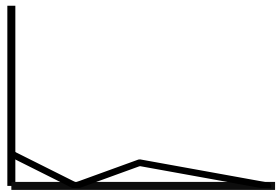
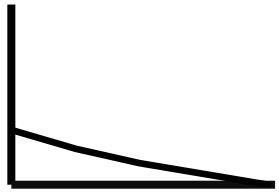
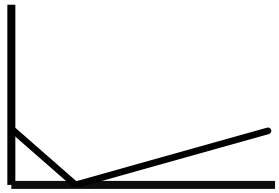
Initially, this study sought to characterize trajectory groups based on slope and start- and end-point intercepts. But, upon inspection of individual plots, it became clear that this more comprehensive approach was necessary. Yet, had this study not employed visual inspection and undergone this development, it would not have been possible to observe the trends that allowed us to discern intra-individual variability within participants trajectories.

BCSP Trajectory Groups

Consistent with the literature, there were two major groups: resolved and unresolved pain at 2 years.[21] Subgroups within each of these major groups were then identified. In the following section, I will consider the resolved group first, including the two subgroups whose pain resolved by 2 years (persistent resolved and episodic resolved), the subgroup whose pain

resolved by 6 months and the subgroup who did not report pain at any follow-up. Then, I will turn to the unresolved group and its subgroups, unresolved episodic and unresolved persistent. To visualize the features of each trajectory subgroup, Figure 28 presents stylized graphs of the principal patterns. For individual trajectories, Figure 12-23 are included alongside a close examination of a subset of participants from each subgroup and all individual trajectory graphs are included in Appendix H-M.

Figure 28. Characteristics of BCSP Trajectory Subgroups

Characteristic pattern	Terminology for labelling	Suggested definition	N (%)
Resolved			
	Did not report pain at follow-ups	- Reported NRS-R = 0 at all follow-ups	5 (7)
	Pain resolved within 6 months	- Reported pain immediately following surgery - Reported NRS-R = 0 at 6-month, 1 year and 2-year follow-ups	20 (27)
	Resolved episodic pain	- Reported NRS-R = 0 at 2 years - Reported periods of pain separated by period with no pain	7 (10)
	Resolved persistent pain	- Reported NRS-R = 0 at 2 years - Reported pain at 6-month and 1 year follow ups.	7 (10)
Unresolved			
	Unresolved episodic pain	- Reported NRS-R > 0 at 2 years - Reported periods of pain separated by period with no pain	22 (30)
	Unresolved persistent pain	- Reported NRS-R > 0 at 2 years - Reported pain at 6 month and 1-year follow-ups	12 (16)

[a]Stylized representation of BCSP principal patterns based on average NRS-R. This figure was adapted from Kongsted et al who developed this method when the principal trajectories of LBP were first outlined. [426]

[b]Abbreviations: NRS-R (Numerical Rating Scale – Rest)

Resolved Trajectory Subgroups

The four subgroups within the resolved group were, in order of prevalence, subgroup with pain that resolved within 6 months (27%, n=20), resolved episodic (10%, n=7), resolved persistent (10%, n=7) and subgroup who did not report pain at any follow-up (7%, n =5).

Subgroup Whose Pain Resolved Within 6 Months. In this study, the largest resolved subgroup – the second largest overall – was participants whose pain resolved within 6 months (27%, n=20). It consisted of participants who reported pain immediately after surgery but did not report pain at 6 months, 1 year and 2 years. Several studies of people with BCSP reported similar prevalence of chronic pain, including a recent systematic review and meta-analysis, where 50-70% of people did not report pain at a 6 months follow-up.[6,184,194] Unlike our study, these studies did not consider trajectory, meaning they did not examine individual follow-ups sequentially. Our finding was also consistent with recent longitudinal studies examining postoperative recovery in people undergoing breast and chest surgery, which found that pain resolution most commonly occurred within the first 6 months after surgery.[69,427] Along with our findings, these data suggest that if a participant's BCSP resolved, it was most likely in the first 6 months after surgery. Given that treatment-related adverse effects may play a role in time to resolution[69,427] and that adjuvant treatment, like radiation therapy, often take place months after surgery, these data reflect a growing understanding that a longer follow-up period immediately after surgery may be necessary for capturing recovery.[69,427]

Using our adapted framework, this study was able to investigate the course of CBCSP in the same people and discern intra-individual variability. Doing so reflected the heterogenous experiences in people with BCSP, which the current literature has difficulty capturing. For

example, people who report no pain 6 months but then report pain at the next follow-up may be mischaracterized as having resolved pain. Through a conservative and stringent approach, this study's findings were able to provide important context into the existing literature on time to resolution and the prevalence of pain resolution at 6 months.

Resolved Episodic Subgroup. The resolved episodic trajectory subgroup accounted for 10% (n=7) of participants in this study. It consisted of participants whose pain resolved by 2 years but, before resolution, reported periods of pain separated by periods of no pain. Given that resolved episodic BCSP has not, to my knowledge, been documented previously, these findings capture a novel subset of participants with BCSP. These findings demonstrate that people may not experience constant pain during recovery, even when they report BCSP, and people whose pain does not resolve within 6 months may still go on to experience pain resolution over time. Ultimately, more consistent and precise measurements may be required to avoid mischaracterization of participants in the resolved episodic subgroup, such as when a pain-free follow-up is assumed to be resolution. It was beyond the scope of the present study, but given these novel findings, future research should continue exploring factors that affect time to resolution and the differences between participants whose pain resolved within 6 months versus those that resolve at 1 or 2 years.

Resolved Persistent Subgroup. The resolved persistent trajectory subgroup accounted for 10% (n=7) of participants in this study. It consisted of participants who did not report pain at 2 years but reported pain at their 6-month and 1-year follow-ups. The prevalence of this subgroup is lower than what is reported in much of the literature,[68,428] however, there were studies that found a similar prevalence of pain resolution at 2 years.[429] This discrepancy may be

because in other CBCSP studies, participants' pain is always assumed to be persistent.[68,428] Combining, rather than differentiating, persistent and episodic subgroups may contribute to a higher prevalence of the resolved persistent subgroup reported in the literature.[68,287,428,430] These findings demonstrate that when trajectory is considered, the prevalence of participants with resolved persistent pain may be much lower than what the literature suggests. Participants in this subgroup may experience increases or decreases in pain severity throughout recovery, even when their pain is persistent, which may be overlooked when only average subgroup pain severity is considered. Given this new context, future studies should examine the prevalence of resolved persistent versus resolved episodic pain.

Subgroup Who Did Not Report Pain at Any Follow-up. The smallest subgroup in this study (7%) was participants who did not report pain at any follow-up. To date, there is limited consensus regarding how to manage data from participants who do not report pain at any follow-up. Most often, participants who do not report pain are grouped together with participants who report mild pain.[66,101,421,431,432] In contrast, this study adopted a conservative and stringent definition for participants in this subgroup. This was done for several reasons: first, cut-off scores for mild pain can vary in the literature, with the upper limit ranging from 2-4 on the NRS-R[101,421,433]; second, combining these participants together assumes that reporting no pain and reporting mild pain are not distinct outcomes and can be treated the same; third, it limits the interpretability of results, such as when average pain severity scores are greatly decreased because of the participants who are not reporting pain. In one study, participants who reported any NRS-R score <4 were grouped together, which encompassed 80% of study participants.[433]

There was one other BCSP trajectory study which reported on participants who did not report pain at any follow-up. In that study, this subgroup accounted for 30% (n=126) of participants,[44] but they were excluded from the analyses conducted for subgroup formation. The remaining participants were placed into trajectory groups based on their baseline and worst pain scores at 2-6 months, with no consideration for intra-individual variability. Combining or excluding participants, especially for the sake of statistical and methodological considerations, rather than patients' experiences, limits the validity of study findings while also potentially obscuring relevant clinical outcomes.

Our findings demonstrate that participants may be likely to be mischaracterized because their pain was not examined over multiple timepoints or combined with those who reported mild pain. Future studies should be conservative when distinguishing between no and mild pain, as well as re-examine the prevalence of CBCSP when intra-individual variability is considered.

Unresolved Trajectory Subgroups

The two unresolved subgroups included participants who reported unresolved episodic (30%, n=22) and unresolved persistent (16%, n=12) pain.

Unresolved Episodic Subgroup. The unresolved episodic subgroup accounted for 30% of participants in this study. It consisted of participants whose pain did not resolve within 2 years, and who reported periods of pain separated by period of no pain. It was the largest subgroup in this study. Not only was this the first study, to my knowledge, to document unresolved episodic BCSP, but it also suggests that episodic pain may be the most prevalent subgroup for participants with BCSP.

There was only one other study, to my knowledge, that specifically examined non-linear BCSP, but it did not differentiate between episodic and persistent pain and included participants who did not undergo surgery.[68] Often, participants with non-persistent pain are excluded[428] or inconsistently labelled, like transient, recurrent, or fluctuating,[68,428] making it hard to compare the prevalence of episodic pain in this study to other BCSP studies. However, in studies of participants with neck pain and LBP, from which our framework was adapted, it was reported that 26-35% of participants had unresolved episodic pain.[56,57,434] These data suggest that participants with unresolved episodic CBCSP have been overlooked in the literature. If future studies do not adopt a more heuristic framework, the principal patterns and prevalent subgroups of participants with CBCSP will continue to go unrecognized.

Unresolved persistent subgroup. The unresolved persistent trajectory subgroup accounted for 16% of our participants. It consisted of participants who reported pain at their 6-month, 1-year and 2-year follow-ups. This prevalence was inconsistent with other studies of CBCSP, which reported a higher prevalence of unresolved persistent CBCSP at 1- and 2-year follow-ups.[68,428,430,435] As discussed with the resolved subgroups, these other studies did not differentiate between persistent and episodic pain. By examining the course of CBCSP in the same participant, our study was able to differentiate between persistent and episodic pain. Unlike other studies, our data demonstrate that unresolved persistent pain may be less prevalent than unresolved episodic pain. Given these novel findings, future studies should verify and explore the prevalence of episodic pain in participants with CBCSP.

Comparing Trajectory Subgroups

In this study, people with resolved pain reported, on average, lower pain severity scores than those with unresolved pain. These findings are supported by the literature, where it has been well-documented that participants with resolved CBCSP reported lower average pain severity than those with unresolved CBCSP.[21,436] Broadly, these findings were expected, as average NRS-R scores of participants in resolved subgroups included a larger proportion of follow-ups where participants did not report pain, such as when their pain resolved.

Surprisingly, however, our study found that participants with unresolved episodic pain reported, on average, lower pain severity than participants with unresolved persistent pain at every follow-up. This was also observed in resolved subgroups, but not at every follow-up. While there are not, to my knowledge, any CBCSP studies examining the relationship between subgroup membership and average pain severity, there are findings from studies in other chronic pain populations where the trajectory framework is more robust, like headache, neck and back pain.[54,58,437] Concerning participants in the unresolved episodic and unresolved persistent subgroups, participants with episodic headache and neck pain reported lower average pain severity compared to participants with persistent pain.[57,437] Furthermore, participants in episodic subgroups reported lower psychological distress and disability and higher quality of life compared to those in persistent subgroups.[57,437] Concerning participants in the resolved episodic and resolved persistent subgroups, a recent study found that participants with episodic pain were more likely than those with persistent pain to recover after 1 year.[57] Furthermore, for participants whose chronic neck pain resolved, their subgroup membership most often transitioned from persistent to episodic before resolution rather than transitioning

directly from persistent to resolution.[57] These findings suggest that CBCSP subgroups may have different postoperative outcomes. Previously, the differences between persistent and episodic CBCSP have been unreported, but these finding suggest that participants with persistent pain may be at risk of reporting higher psychosocial distress, disability, and lower quality of life compared to those with episodic pain. While data is needed to confirm these findings, it may be possible that participants from different subgroups require individualized pre- or postoperative care to reduce outcomes like severe CBCSP.

Ultimately, this was the first study, to my knowledge, to document episodic pain in participants undergoing breast cancer surgery, as well as the only study to examine CBCSP trajectory subgroups beyond 6 months. Given the novelty of these findings, future studies should verify trajectory subgroups observed in this study, especially beyond 2 years and should explore the role of subgroup membership on postoperative outcomes to inform potential interventions.

Exploring Individual Trajectories

Given that my study was interested in individual trajectories, a quasi-qualitative and hypothesis-generating approach was used to examine a subset of individual trajectories in-depth.[403] All individual trajectories plots, ordered by subgroup prevalence, are included in Appendix H-M.

This analysis (Figure 12-23) showed that the timing of treatment-related adverse events may be important to BCSP and recovery. Specifically, participants in unresolved trajectories reported beginning or continuing adjuvant treatments 6-months after surgery more frequently than those in resolved trajectories. This was most prominent when comparing unresolved trajectories to the subgroup whose pain resolved in 6 months, where all adjuvant treatments were started and completed within 6 months of undergoing surgery. Lymphedema was also more frequently reported in unresolved trajectories than resolved trajectories. Specifically, seven of the 12 women with persistent unresolved pain reported lymphedema, but none of the women in the subgroup who did not report pain at any follow-up reported lymphedema.

This finding is consistent with the existing literature, where adjuvant treatment (chemotherapy, radiation therapy and hormone therapy) and treatment-related side effects (lymphedema) have been well-established as predictors of postoperative pain[100,144,194–199,219] and with BCSP trajectory studies that found participants who did not report pain were less likely than those with mild, moderate or severe trajectories to undergo radiation.[44,69]

It may be possible that adjuvant treatment, particularly chemotherapy and radiation, beyond 6 months, or the accumulation of multiple overlapping treatments or side effects, may be associated with chronic postoperative pain. For example, 66-year old PK (Figure 16), who

reported lymphedema after completing chemotherapy and radiation and continuing hormone therapy. It may also be possible that there are key timepoints where treatment-related adverse events contribute to pain chronicity. For example, 48-year old RH (Figure 20), who reported a pain-free interval near the end of her chemotherapy and radiation therapy for a previous tumour but then reported treatment-related and lymphedema 6 months.

Timing of adjuvant treatment has been examined in the literature, but only its relationship with breast cancer survival. While delayed chemotherapy, radiation therapy and hormone therapy have been associated with lower rate of breast cancer survival,[438–447] this association has yet to be examined in relation to treatment-related pain after surgery. Similarly, while risk factors associated with time of lymphedema development have been widely studied,[448–454] there are no studies, to my knowledge, that examined how time of lymphedema development influences postoperative pain.

Given that adjuvant treatment and lymphedema are well-established as predictors of treatment-related pain,[100,144,194–199,219] this study suggests that timing of adjuvant treatment may also be an important factor for treatment-related pain and recovery. Using individual trajectories to examine treatment-related adverse events may serve as a valuable heuristic. This may be especially important to consider for people with breast cancer, as participants with chronic treatment-related pain may find it difficult to seek support as their pain changes or if it is perceived as non BCS-related,[301,455,456] thereby reducing opportunity for targeted intervention. Future studies should explore how timing of adjuvant treatment and treatment-related adverse events impact postoperative pain. Furthermore, as this study did not

differentiate the extent to which participants' pain was surgical, future studies should elucidate to what extent pain after breast cancer surgery is surgical versus treatment-related.

Predictors of Trajectory Subgroup Membership

In this study, participants in the unresolved persistent subgroup reported higher preoperative pain interference than those in the resolved persistent subgroup. These findings motivated further exploratory examination of the relationship between pain interference and BCSP resolution, which will be discussed after the predictors of trajectory subgroup and group membership.

Data regarding BCSP and preoperative interference are very limited, as most studies focus on postoperative interference as an outcome.[8,44,153,436,457–461] There was only one study of participants undergoing lumbar decompression which found that higher preoperative interference was associated with higher postoperative pain and disability at 6 months after surgery.[96] The present study was the first, to my knowledge, to document the role of preoperative interference on postoperative BCSP subgroup membership. Importantly, it suggests that participants' perception of their pain before surgery, and to what degree it impedes their daily living, may play an important role in the development of CBCSP. There were no other preoperative biopsychosocial differences associated with trajectory subgroup membership, which suggests that the preoperative differences in pain interference could, potentially, affect which postoperative factors go on to affect subgroup membership.

Predictors of Pain Resolution (Trajectory Group Membership)

Mastectomy

This study found that the development of chronic pain was more likely in participants who underwent mastectomy, rather than lumpectomy. This finding was consistent with the literature [141–145] and is most often attributed to the longer recovery times and increased chances of complication.[141,146–148] Thus, it is possible that the participants undergoing mastectomy in our study reported a higher frequency of unresolved pain because it is longer and more invasive than lumpectomy.

However, there have also been studies that found lumpectomy, rather than mastectomy, to be associated with CBCSP[149–151] or for surgery type to have no significant effect.[123,152,153] These inconsistencies may reflect the heterogeneity of patients undergoing BCS. Different outcomes after the same surgery depend on a range of factors which can vary widely between participants, such as tumour characteristics, age, duration of surgery, psychological resilience, reconstruction, ALND, radiation, additional treatment, complications, perceived risk and surgical satisfaction.[123,145,150,154–156] Taken together and given the widespread effect of surgery, it remains important for future studies to continue investigating the relationship between surgery type and trajectory group membership.

Parity

This study found that the development of chronic pain after BCS was more likely among participants who did not have children. While there are not, to my knowledge, any studies designed a priori to examine parity and CBCSP, studies that included it among their

demographic variables did not identify it as a predictor of CBCSP.[158,432,462,463] Given this limited evidence, the interpretation of the role of parity is not immediately apparent.

However, pregnancy is associated with widespread hormonal and physiological changes in the body,[464] some of which may have long-term or permanent impacts, like increased risk for ischemic stroke or chronic disease.[464–472] Recent research has also found that participants who had never given birth (nulliparous) may be at higher risk of developing chronic diseases, like multiple sclerosis (MS),[465] while parity was associated with decreased risk of progression to moderate disability in participants with relapsing-remitting MS.[473] It is possible that the widespread, and as yet poorly understood, changes associated with pregnancy may impact recovery from BCS and development of chronic postoperative pain. One explanation is changes in estrogen, which may influence inflammation and pain sensitization.[474,475] Nulliparous women tend to have higher estrogen levels than multiparous women, even after menopause.[476,477] A recent study demonstrated this in mice, where higher levels of circulating estrogen in nulliparous mice increased their inflammatory and nociceptive responses to noxious stimuli, when compared to multiparous mice.[478,479] As such, it may be possible that differences and changes in estrogen and parity played a role recovery from BCS.

In this study, most participants were peri- or post-menopausal. During this time, there are significant hormonal fluctuations and changes, many of which have been associated with chronic pain and inflammation.[480,481] Given the impact estrogen has on regulatory systems, like the immune system, this may have further contributed to BCSP resolution. There are studies examining parity, menopausal status and pain[482–484] but none, to my knowledge, examining parity, menopausal status and CBCSP resolution or trajectory group membership. Taking these

findings together, it is possible that widespread changes to hormonal systems, whether through pregnancy or peri- and post-menopause, may play a significant role in the development of chronic pain following BCS, particularly among people who have not had children. Future studies should this hypothesis.

Exploration of Pre- and Postoperative Pain Interference

People who developed CBCSP had increasing interference of pain in activities over time while those who did not develop chronic pain had decreasing interference over time. Specifically, people who developed chronic pain reported worsening interference with walking and, while not statistically significant, with mood, general activity, and performing normal work. For other domains of interference, participants with chronic pain still reported greater interference than those without pain, but both groups reported decreased interference over time.

Higher preoperative pain interference was significantly correlated with higher pain-related fear and cognitive anxiety, state anxiety, rumination, magnification, helplessness, and depression. In addition, higher postoperative pain interference was significantly correlated with higher disability of the arm and shoulder, avoidance, intrusion, hyperarousal, rumination, magnification, helplessness, depression, state anxiety and lower activity engagement and pain willingness.

Other studies have found that preoperative interference was associated with higher psychological distress and postoperative complications[485,486] and that lowering postoperative pain interference also lowered disability and increased quality of life in a range of domains, including physical, psychological and social well-being.[135] However, there were no studies

examining how preoperative pain interference changes over time with BCSP trajectory group membership.

Interestingly, a recent study of pain self-management in breast cancer survivors found that pain interference, not severity, was associated with engaging in pain management behaviours.[487] Specifically, participants used behaviours like walking, distraction, stretching, and strengthening with the goal of reducing pain interference, not severity.[487] Taken together with this study's findings, it may be possible that participants with low or decreasing interference perceived this as a return to daily life, whether before or after surgery. Conversely, participants with high or worsening interference may have perceived it as the inability to return to their usual activities. This possible explanation also complements the fear-avoidance model of pain, where participants reporting pain catastrophizing, fear of pain, fear of recurrence, or kinesiophobia engage in behaviours like avoidance, negative cognitions, and attention to pain that contribute to emotional and psychological distress.[488,489] This distress then amplifies the subjective intensity of pain experiences.[488,489] In the wider breast cancer literature, kinesiophobia and fear of recurrence are well-documented,[490–495] as well as a subsequent decrease in health maintenance behaviours that exacerbate chronic pain and disability.[491,495] While further exploration is outside the scope of this study, treatment-related adverse events, which were previously discussed, have also been found to contribute to fear of recurrence and disruption of daily life.[301,456] Ultimately, it may be possible that participants with chronic pain perceived their pain as high impact, and experienced a reduction in effective coping and increase in catastrophizing and distress which inhibited their ability to perform health maintenance behaviours, contributing to worsening pain [424]. Future prospective studies should

test this hypothesis, as well as the role of subgroup membership and episodic pain, as it could be crucial in the development of targeted interventions to decrease pain interference and CBCSP.

Addressing Methodological Considerations

Given the novelty of this study, it was important to consider which methodologies were most suitable for group formation. All recent studies on BCSP and postoperative pain trajectory used latent class modelling (LCM) for group formation and risk factor identification.[20,44,66,496] However, like most trajectory studies, our study was limited by small sample size, lack of established BCSP trajectory groups and high heterogeneity in postoperative pain scores.

LCM has been shown to produce spurious results in small sample sizes[48]; it assumes that there is no variance between individuals in the same class[38] which makes it unsuitable for samples with high heterogeneity; and it is iterative and a priori, making it impossible to discern any unknown trajectories in a sample.

As such, LCM was not suitable, and a different methodology, visual inspection, was adapted and used instead. Visual inspection can be implemented in small sample sizes, allows for the formation of parsimonious groups without restriction to the number of groups, does not require a priori assumptions, and relies on observable and verifiable qualities of the data, making trajectories easy to form and observe. Visual inspection's main limitation is that it is time-consuming,[497] especially in larger samples. However, even in large sample sizes, visual inspection has been recommended for hypothesis generation and verification of trajectory groups.[48] Ultimately, it was straightforward to implement and an effective methodology to use in this study.

Limitations

There were several limitations that should be considered when interpreting the results of this study. First, because complete NRS-R data were required to plot the trajectories without imputation, the sample size was small. However, several other trajectory studies of shorter follow-up length have similar sample sizes[68] and conservative levels of statistical significance were adopted in this study,[397] even for exploratory analyses. Secondly, the sample was predominantly White, well-educated, and English-speaking. Future research should examine this study's wide range of biopsychosocial factors in a larger, more diverse sample. Finally, given the extended period between 1- and 2-year follow-ups, this study cannot definitively determine which participants may have experienced episodic pain or pain resolution. For example, participants experiencing episodic pain may have been misclassified as having persistent pain if they reported pain at every follow-up. While this study examined a range of timepoints to capture participants' expected transition to chronicity or resolution, they were not chosen a priori to examine BCSP trajectory. As such, to further elucidate the prevalence of episodic pain and subgroup membership, future studies could use methods like weekly SMS follow-ups[58] or daily diaries[55] to more closely examine participants in episodic subgroups.

Implications and Future Direction

This study examined BCSP from preoperative to 2-years postoperative because there were few studies bridging the gap between the acute and chronic breast cancer surgery literature. However, future research should continue examining longer follow-ups, not only to verify the principal patterns of BCSP subgroups, but also to discern the stability of subgroups over time. Studies in other conditions, like neck pain, have found that trajectory groups are

relatively stable, with transitions being mostly towards resolution,[57] but this may not be the case for participants with BCSP. While a few longitudinal studies examining breast cancer pain[70–72] none of them included preoperative assessments. As the literature expands, the stability of BCSP may become clearer.

In this study's examination of individual trajectories, the timing and accumulation of treatment-related adverse effects may be associated with BCSP and recovery. To extend this study's findings, pain sensitization may be a possible mechanism for how the accumulation of treatment-related stressors contribute to the development and maintenance of chronic pain. Pain sensitization reduces the threshold for nociceptors in the central nervous system, which can lead to allodynia (pain from non-painful stimuli) or hyperalgesia (increased pain).[498] Symptoms of pain sensitization have been identified as a prominent issue for people with BCSP, and were associated with the development and maintenance of CBCSP.[153] Importantly, lymphedema, hormone therapy, undergoing multiple adjuvant treatments, negative side effects and psychological distress also have been associated with pain sensitization.[158,499–502] Participants with symptoms of pain sensitization may be more likely to report kinesiophobia, higher pain interference, pain catastrophizing and psychological distress.[503,504] Similar to this study's findings on pain interference, this cycle may decrease health maintenance behaviours and exacerbate chronic pain. Examining this relationship was outside the scope of the current study, but future studies should explore this hypothesis.

Another important finding in our study was that pre- and postoperative pain interference may be a major contributor to severe, and worsening, CBCSP. However, to extend this study's hypothesis on the fear-avoidance model of pain, it may also be a contributor to the

high heterogeneity in participants with CBCSP. As a subjective measure, pain interference can reflect how participants interpret their pain. Mischaracterization of pain, dismissal of symptoms, unmet needs, or delays in receiving or accessing care can all contribute to worsening catastrophizing or fear.[455,505,506] Further exploration into pain interference may provide insight into how participants reporting the same pain severity or risk factors may have significantly different outcomes.

Finally, this study established that examining pain over time is crucial as a next step in developing a nuanced understanding of participants with CBCSP. As more participants live with the effects of cancer treatment, the cumulative and lifetime effects of CBCSP cannot be ignored. The gaps in the current literature may be due to methodological traditions that do not accommodate the close examination of individual participants over time. Not considering temporal pain patterns, or other overlooked characteristics in the assessment of people with CBCSP, may obscure critical elements of their pain experiences. It is key that future studies continue prioritizing the understanding and characterization of CBCSP over time to address gaps in the literature with the goal of improving the lies of people with breast cancer.

CONCLUSION

In conclusion, the exploratory findings of this study support the continued exploration of CBCSP trajectories through a framework that considers heterogenous inter- and intra-individual changes. Episodic pain pattern has not previously been studied in participants with CBCSP but may be very common. As such, the six subgroups outlined in this study require further research to examine the prevalence and stability of group membership over time. Trajectory modelling is an indispensable tool to examine BCSP. Furthermore, the consideration

of individual trajectories should be taken, especially in conditions with a highly heterogenous population, like people with breast cancer. This study also supports the biopsychosocial model of pain, as it demonstrated that CBCSP may be affected by a range of factors, which may also have different effects depending on trajectory subgroup. The modifiable nature of the predictors of group and subgroup membership provide insight into targets to prevent or treat CBCSP. Ultimately, these findings provide a foundation for future research to verify the role of these principal patterns and potentially modifiable risk factors.

APPENDICES

Appendix A. Skew and Kurtosis of Non-normal Variables

	Z Skew	Z Kurtosis
NRS-R	7.52	6.27
NRS-M	7.38	7.01
PPI	5.85	3.77
SF-MPQ Sensory	8.98	11.42
SF-MPQ Affective	18.04	53.39
BPI-SEV	4.07	1.47
BPI-INT	5.70	5.70
SF12-PCS	-3.66	1.11
ESAS	3.73	2.06
STAI-S	0.47	-1.02
PCS-M	5.01	3.60

[a]Abbreviation: all acronyms can be found in the abbreviation list (p.xii)

Appendix B. Correlation Results for Continuous Variables

		Resolved pain	Age	BPI-SEV	BPI-INT	SF-NPQ	SF12 PCS	PASS-EA	PASS-CA	STAI-S	CES-D	PCS-R	PCS-M	PCS-H
Age														
	Pearson's *r*	0.009												
	p	0.942												
BPI-SEV														
	Pearson's *r*	-.344**	-0.035											
	p	0.003	0.771											
BPI-INT														
	Pearson's *r*	-.354**	-0.052	.688**										
	p	0.002	0.662	0.000										
SF-NPQ														
	Pearson's *r*	-0.121	-0.141	0.221	.443**									
	p	0.311	0.234	0.062	0.000									
SF12 PCS														
	Pearson's *r*	0.206	-0.086	-.312**	-.627**	-.416**								
	p	0.087	0.478	0.007	0.000	0.000								
PASS-EA														
	Pearson's *r*	-0.212	0.036	-0.014	0.111	0.174	-0.013							
	p	0.076	0.771	0.906	0.354	0.142	0.915							
PASS-CA														
	Pearson's *r*	-0.208	-0.048	0.130	.302**	.348**	0.011	.702**						
	p	0.081	0.690	0.274	0.009	0.002	0.929	0.000						
STAI-S														
	Pearson's *r*	-.276*	-0.217	.297*	.294*	0.221	-0.052	0.134	.390**					
	p	0.020	0.071	0.012	0.011	0.061	0.665	0.262	0.001					

Appendix B. (continued)

		Resolved pain	Age	BPI-SEV	BPI-INT	SF-NPQ	SF12 PCS	PASS-EA	PASS-CA	STAI-S	CES-D	PCS-R	PCS-M	PCS-H
CESD														
	Pearson's *r*	-0.229	-0.156	.333**	.267*	0.196	-0.051	0.178	.440**	.802**				
	p	0.054	0.196	0.004	0.022	0.096	0.669	0.134	0.000	0.000				
PCS-R														
	Pearson's *r*	-.272*	-0.124	0.119	.291*	.324**	0.032	.543**	.650**	.422**	.412**			
	p	0.021	0.298	0.322	0.012	0.005	0.793	0.000	0.000	0.000	0.000			
PSC-M														
	Pearson's *r*	-.278*	-0.100	0.098	.324**	.325**	-0.151	.526**	.624**	.366**	.417**	.649**		
	P	0.017	0.407	0.413	0.005	0.005	0.207	0.000	0.000	0.001	0.000	0.000		
PCS-H														
	Pearson's *r*	-.328**	0.009	0.145	.309**	.406**	-0.165	.517**	.691**	.410**	.471**	.754**	.777**	
	p	0.005	0.941	0.225	0.008	0.000	0.167	0.000	0.000	0.000	0.000	0.000	0.000	

[a] **p<0.05, **p<0.01*

[b] *Abbreviation: all acronyms can be found in the abbreviation list (p.xii).*

Appendix C. Pairwise Comparisons (Pain Severity and Pain Interference)

Figure C.1. Pairwise Comparisons of Pain Severity Scores (NRS-R) Between Subgroups

	Test statistic	**Std. error**	**Std. test stat**	**Sig.**	**Adjusted Sig.**
Did not report pain - Resolved persistent	-2.27	12.17	-0.19	0.85	1.00
Did not report pain - Pain resolved by 6mos	-9.05	10.39	-0.87	0.38	1.00
Did not report pain - Resolved episodic	-16.23	12.17	-1.33	0.18	1.00
Did not report pain - Unresolved episodic	-17.65	10.29	-1.72	0.09	1.00
Did not report pain - Unresolved persistent	-27.71	11.06	-2.51	0.01	0.18
Resolved persistent - Pain resolved by 6mos	6.86	9.12	0.75	0.41	1.00
Resolved persistent - Resolved episodic	-12.93	11.11	-1.16	0.24	1.00
Resolved persistent - Unresolved episodic	-15.38	9.02	-1.71	0.09	1.00
Resolved persistent - Unresolved persistent	-26.49	9.88	-2.68	0.01	0.11
Pain resolved by 6mos- Resolved episodic	-5.49	9.12	-0.60	0.55	1.00
Pain resolved by 6mos - Unresolved episodic	-8.33	6.42	-1.30	0.19	1.00
Pain resolved by 6mos - Unresolved persistent	-18.66	7.59	-2.46	0.01	0.21
Resolved episodic - Unresolved episodic	-3.18	9.02	-0.35	0.72	1.00
Resolved episodic - Unresolved persistent	-12.71	9.88	-1.44	0.15	1.00
Unresolved episodic - Unresolved persistent	-9.65	7.46	-1.29	0.20	1.00

[a] **p<0.05, **p<0.01*

[b] Abbreviation: 6mos: 6 months

Figure C.2. Pairwise Comparisons of Pain Interference Scores (BPI-INT) Between Subgroups

	Test statistic	**Std. error**	**Std. test stat**	**Sig**	**Adjusted Sig**
Resolved persistent - Did not report pain	9.43	11.94	0.79	0.43	1.00
Resolved persistent - Pain resolved by 6mos	10.39	8.95	1.16	0.25	1.00
Resolved persistent - Resolved episodic	-9.21	10.90	-0.85	0.40	1.00
Resolved persistent - Unresolved episodic	-15.70	8.85	-1.77	0.08	1.00
Resolved persistent - Unresolved persistent	-29.03	9.70	-2.99	0.00	0.04*
Did not report pain - Unresolved episodic	-1.53	10.19	-0.15	0.88	1.00
Did not report pain - Unresolved persistent	-6.27	10.10	-0.62	0.53	1.00
Pain resolved by 6mos - Unresolved episodic	-18.78	10.85	-1.73	0.08	1.00
Pain resolved by 6mos - Unresolved persistent	-5.31	6.30	-0.84	0.40	1.00
Resolved episodic - Unresolved episodic	-17.35	7.44	-2.33	0.02	0.30
Resolved episodic - Unresolved persistent	-6.34	8.85	-0.72	0.47	1.00
Unresolved episodic - Unresolved persistent	-18.95	9.70	-1.95	0.05	0.76
Resolved episodic - Did not report pain	-12.60	7.32	-1.72	0.08	1.00
Resolved episodic - Pain resolved by 6mos	0.56	11.94	0.05	0.96	1.00
Pain resolved by 6mos - Did not report pain	1.03	8.95	0.10	0.92	1.00

[a] **p<0.05, **p<0.01*

[b] Abbreviation: 6mos: 6 months

Appendix D. Comparison of Pre- and Postoperative BPI-INT Item Scores

Figure D.1. Average Pain Interference with General Activity (9a) Over Time

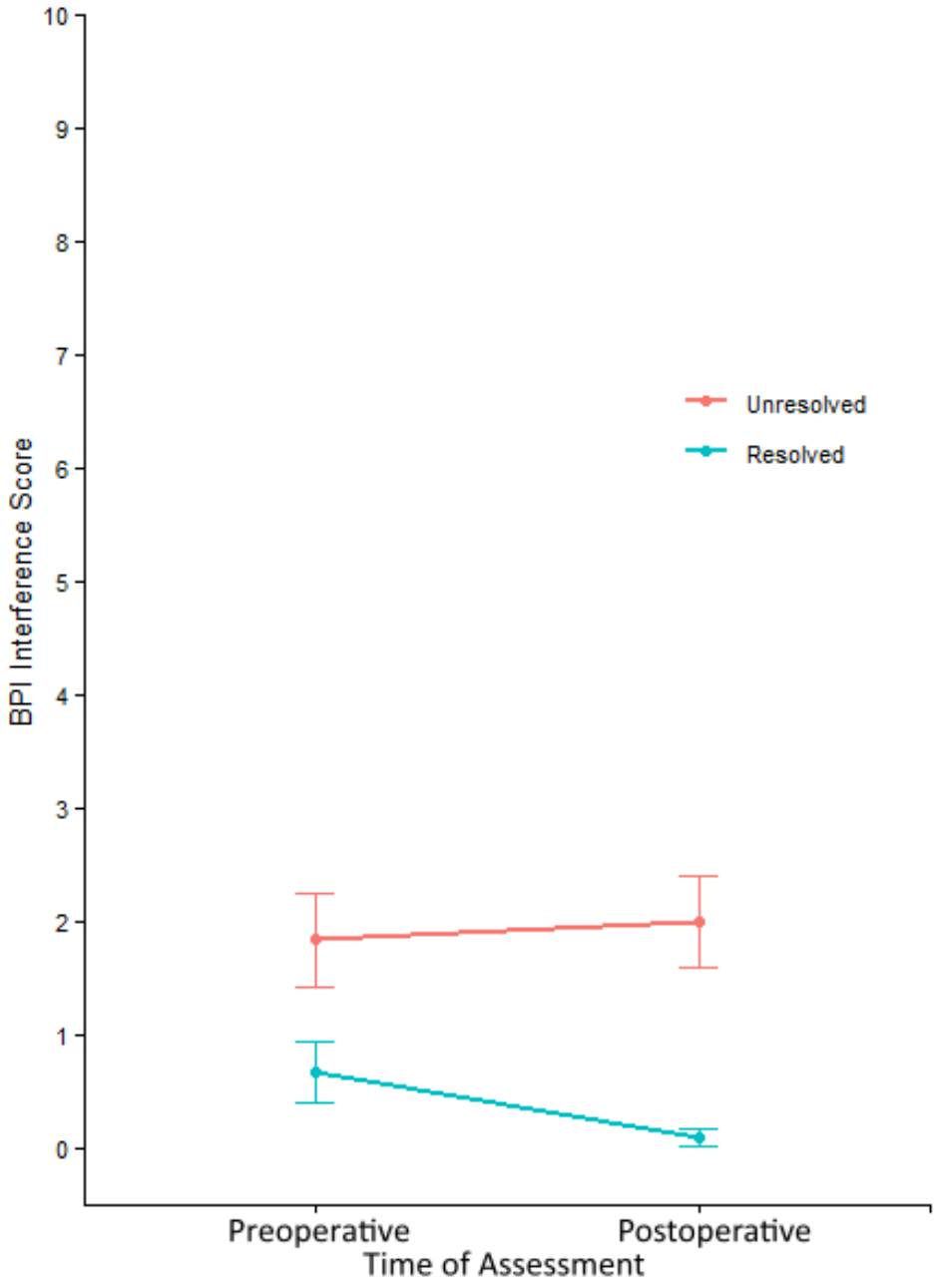


Table D.1. Repeated Measures ANOVA Test of Within-subjects Variables (9a: General Activity)

	SS	df	MS	F	p
Time	1.36	1	1.363	0.758	0.387
Time*Resolved	4.27	1	4.266	2.373	0.129
Error(Time)	107.87	60	1.798		

[a] **p<0.05, **p<0.01*

Table D.2. Repeated Measures ANOVA Test of Between-subjects Variables (9a: General Activity)

	SS	df	MS	F	p
Resolved	72.78	1	72.78	15.61	.0002**
Error	279.81	60	4.66		

[a] **p<0.05, **p<0.01*

Figure D.2. Average Pain Interference with Mood (9b) Over Time

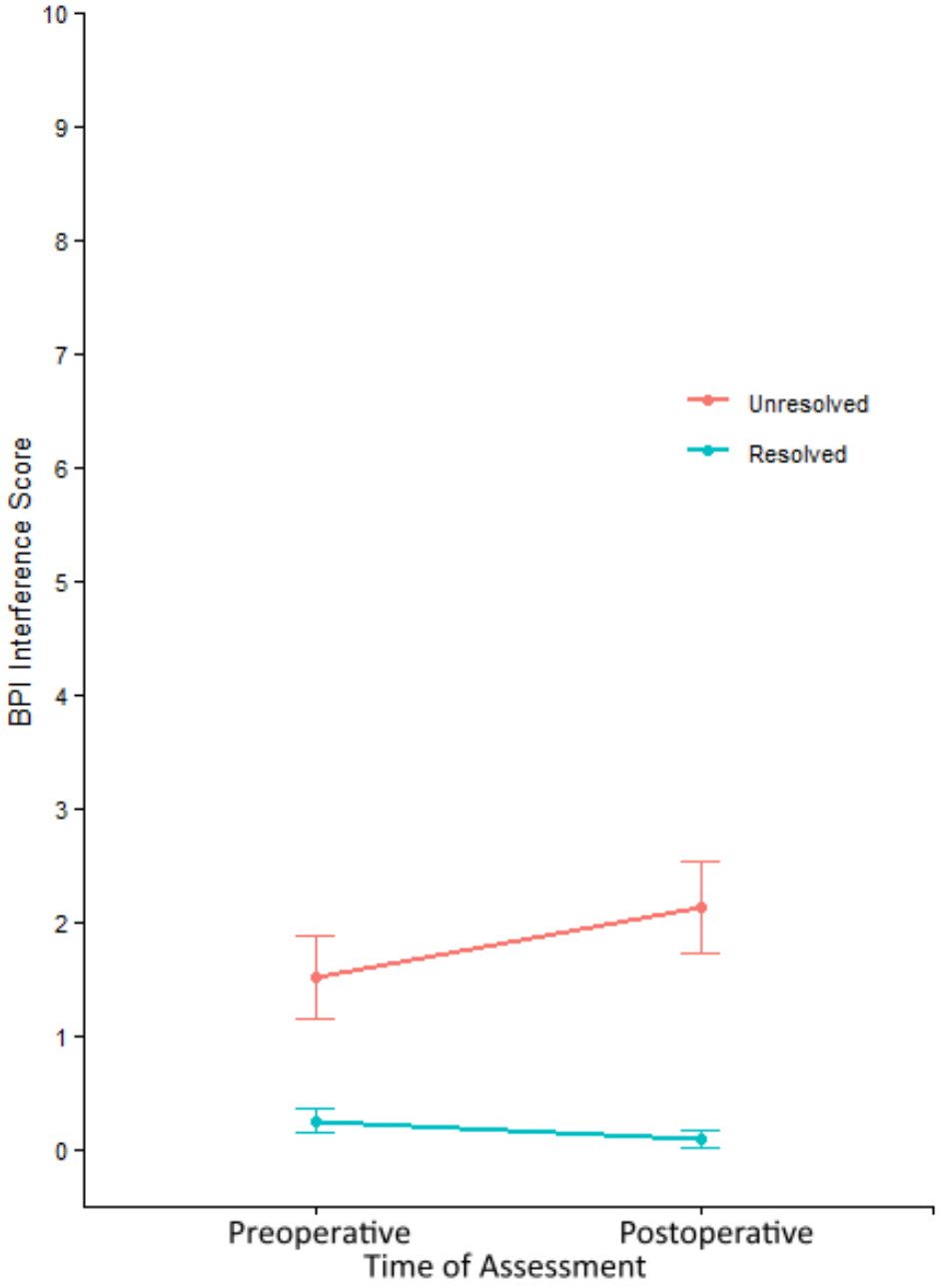


Table D.3. Repeated Measures ANOVA Test of Within-subjects Variables (9b: Mood)

	SS	df	MS	F	p
Time	1.58	1	1.581	1.204	0.277
Time*Resolved	4.65	1	4.645	3.538	0.065
Error(Time)	78.77	60	1.313		

[a]**p<0.05, **p<0.01*

Table D.4. Repeated Measures ANOVA Test of Between-subjects Variables (9b: Mood)

	SS	df	MS	F	p
Resolved	83.90	1	83.90	23.85	<.0001***
Error	211.10	60	3.52		

[a]**p<0.05, **p<0.01*

Figure D.3. Average Pain Interference with Normal Work (9d) Over Time

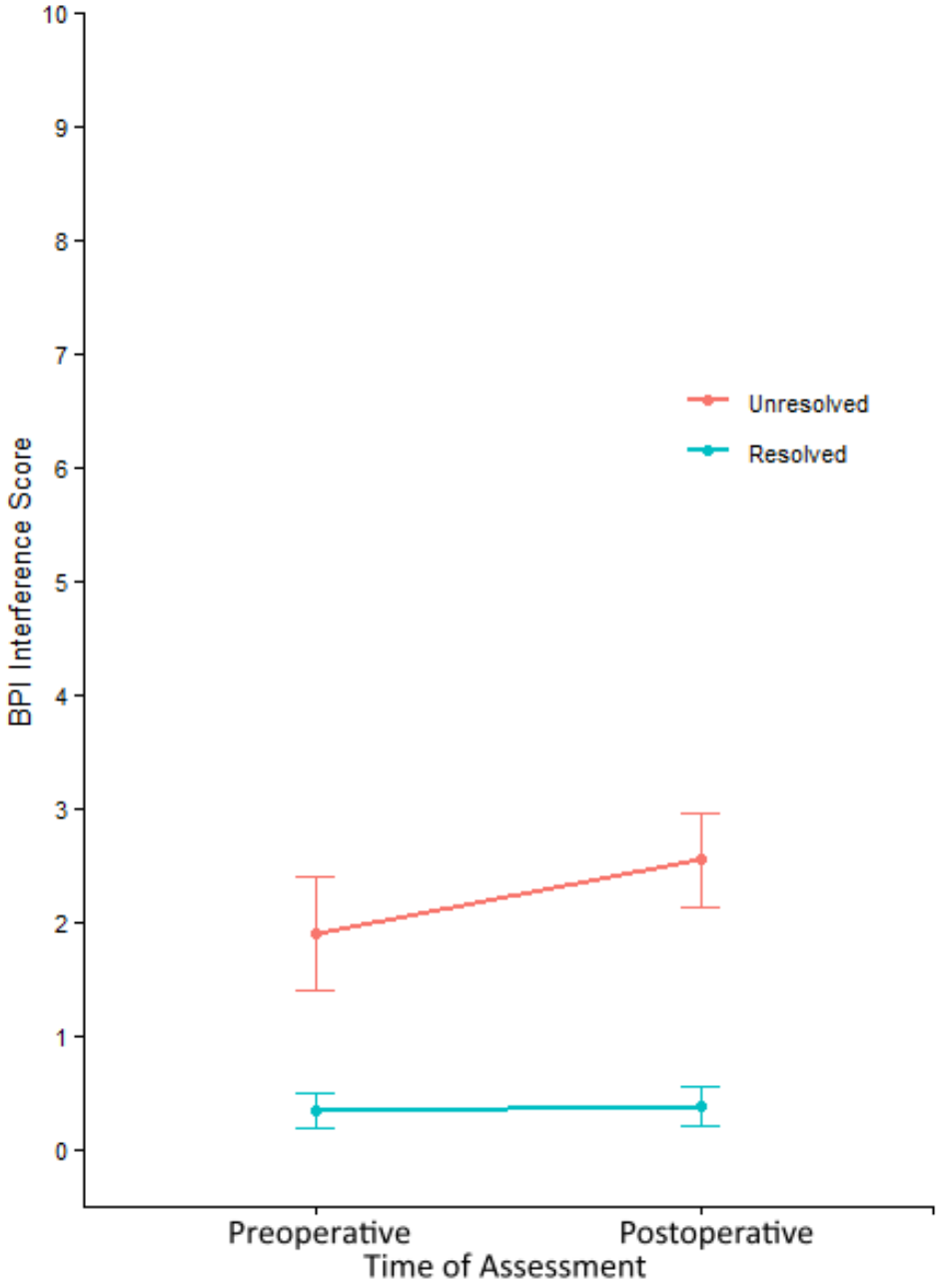


Table D.5. Repeated Measures ANOVA Test of Within-subjects Variables (9d: Normal Work)

	SS	df	MS	F	p
Time	3.73	1	3.728	2.757	0.102
Time*Resolved	2.76	1	2.760	2.041	0.158
Error(Time)	81.14	60	1.352		

[a] **p<0.05, **p<0.01*

Table D.6. Repeated Measures ANOVA Test of Between-subjects Variables (9d: Normal Work)

	SS	df	MS	F	p
Resolved	107.60	1	107.58	17.53	<.0001***
Error	368.30	60	6.14		

[a] **p<0.05, **p<0.01*

Figure D.4. Average Pain Interference with Relations with Others (9e) Over Time

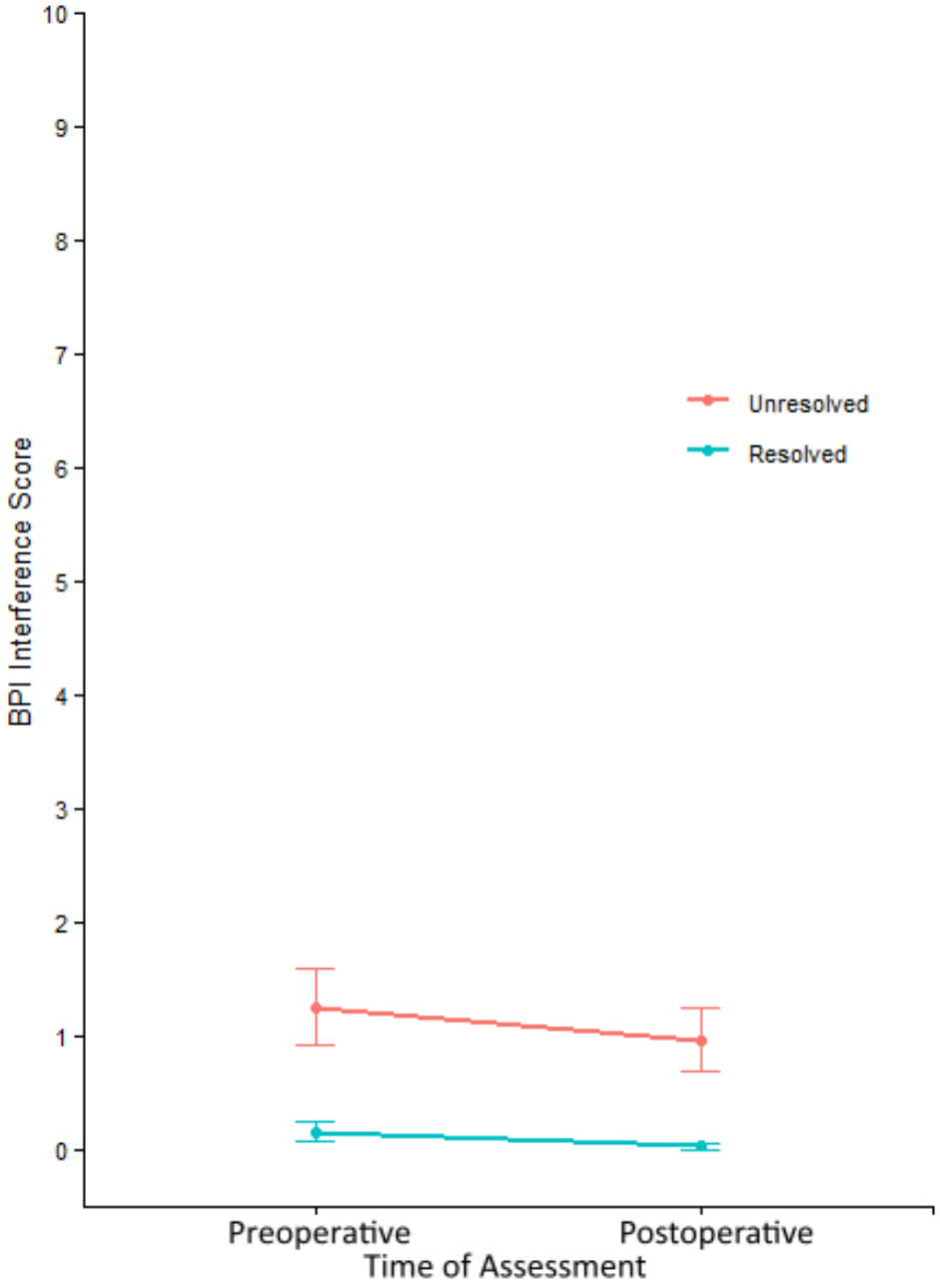


Table D.7. Repeated Measures ANOVA Test of Within-subjects Variables (9e: Relations With Others)

	SS	**df**	**MS**	**F**	**p**
Time	1.36	1	1.363	2.826	.0979
Time*Resolved	.202	1	.2016	.418	.5204
Error(Time)	28.94	60	.4823		

[a] **p<0.05, **p<0.0*

Table D.8. Repeated Measures ANOVA Test of Between-subjects Variables (9e: Relations With Others)

	SS	**df**	**MS**	**F**	**p**
Resolved	32.91	1	32.01	12.71	.0007***
Error	151.13	60	2.52		

[a] **p<0.05, **p<0.01*

Figure D.5. Average Pain Interference with Sleep (9f) Over Time

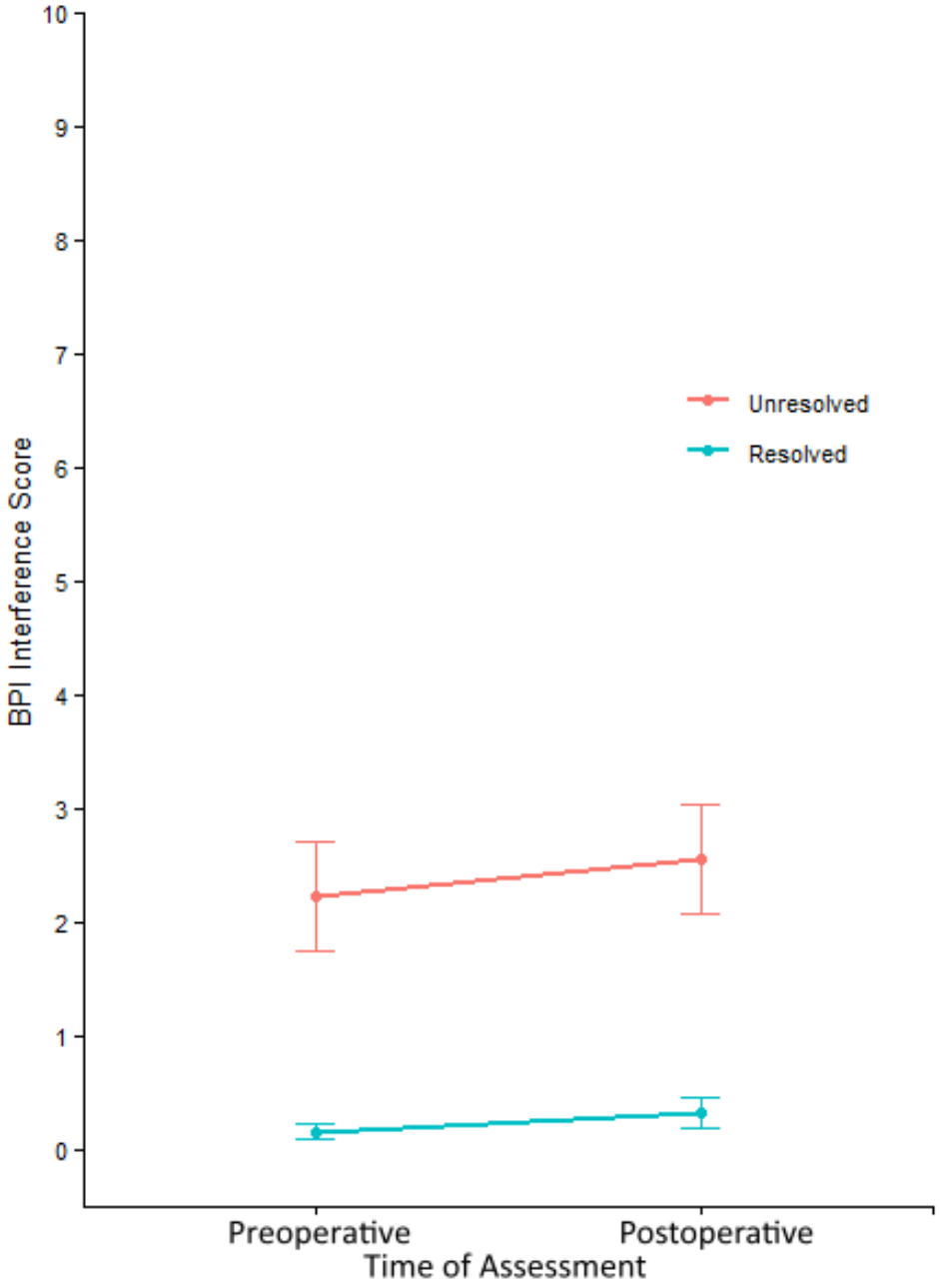


Table D.9. Repeated Measures ANOVA test of Within-Subjects Variables (9f: Sleep)

	SS	df	MS	F	p
Time	1.81	1	1.8145	1.259	.266
Time*Resolved	.20	1	.2016	.140	.710
Error(Time)	86.48	60	.4414		

[a] **p<0.05, **p<0.01*

Table D.10. Repeated Measures ANOVA Test of Between-subjects Variables (9f: Sleep)

	SS	df	MS	F	p
Resolved	142.7	1	142.65	23.29	<.0001***
Error	367.6	60	6.13		

[a] **p<0.05, **p<0.01*

Figure D.6. Average Interference with Enjoyment of Life (9g) Over Time

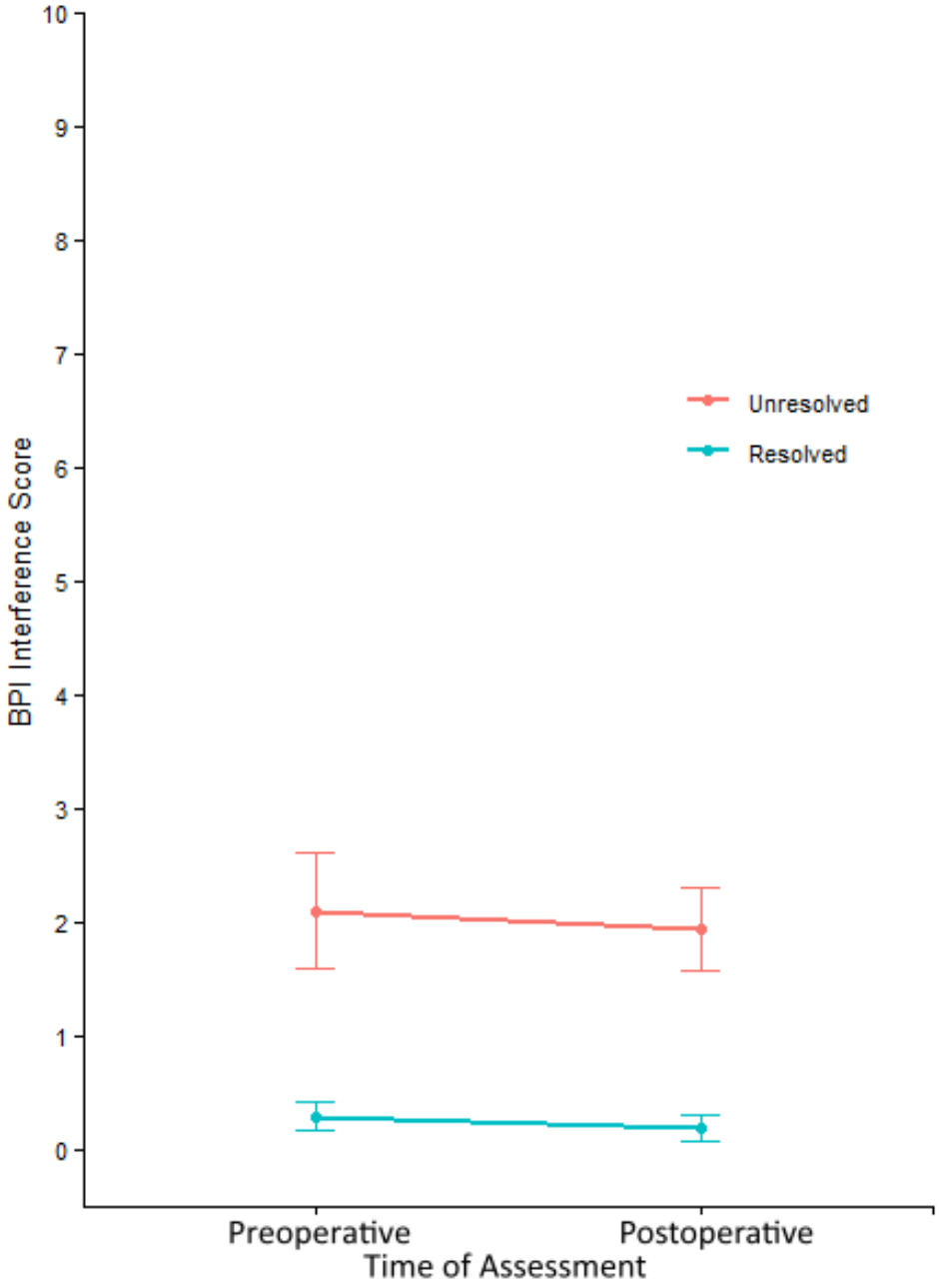


Table D.11. Repeated Measures ANOVA test of Within-subjects Variables (9g: Enjoyment of Life)

	SS	df	MS	F	p
Time	.52	1	.5161	.286	.595
Time*Resolved	.03	1	.0323	.894	.894
Error(Time)	108.45	60	1.8075		

[a]*p<0.05, **p<0.01

Table D.12. Repeated Measures ANOVA Test of Between-subjects Variables (9g: Enjoyment of Life)

	SS	df	MS	F	p
Resolved	97.58	1	97.58	20.52	<.0001***
Error	4.76	60	4.76		

[a]*p<0.05, **p<0.01

Appendix E. Correlates for Having Children

Table E.1. Preoperative Correlates for Having Children

		Have children	PASS-F	PASS-EA	PASS-PA	PASS-CA	PASS Total	PCS-R	PCS-M	PCS-H	PCS Total	STAI-S	CES-D
PASS-F	Pearson's *r*	-.109											
	p	.360											
PASS-EA	Pearson's *r*	-.043	.594**										
	p	.721	<.001										
PASS-PA	Pearson's *r*	-0.52	.630**	.588**									
	p	.666	<.001	<.001									
PASS-CA	Pearson's *r*	-.063	.692**	702**	.777**								
	p	.597	<.001	<.001	<.001								
PASS Total	Pearson's *r*	-.075	.829**	.839**	.872**	.918**							
	p	.530	<.001	<.001	<.001	<.001							
PCS-R	Pearson's *r*	-.108	.516**	.543**	.445**	.650**	.621**						
	p	.365	<.001	<.001	<.001	<.001	<.001						
PCS-M	Pearson's *r*	-.071	.632**	.526**	.584**	.624**	.681**	.649**					
	p	.552	<.001	<.001	<.001	<.001	<.001	<.001					
PCS-H	Pearson's *r*	-.137	.675**	.517**	.640**	.691**	.726**	.754**	.777**				
	p	.250	<.001	<.001	<.001	<.001	<.001	<.001	<.001				
PCS Total	Pearson's *r*	-.124	.663**	.581**	.606	.726**	.742**	.911**	.846**	.943**			
	p	.299	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001			
STAI-S	Pearson's *r*	-.261*	.505**	.134	.288	.390**	.370**	.422**	.366**	.410**	.446**		
	p	.026	<.001	.262	.014	<.001	.001	<.001	.001	<.001	<.001		

Appendix E. (continued)

		Have children	PASS-F	PASS-EA	PASS-PA	PASS-CA	PASS Total	PCS-R	PCS-M	PCS-H	PCS Total	STAI-S	CES-D
CES-D	Pearson's *r*	-.224	.605**	.178	.425**	.440**	.467**	.412**	.417**	.471**	.480**	.802**	
	p	.057	<.001	.134	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	
BPI-INT	Pearson's *r*	-.083	.260*	.111	.098	.302**	.218	.291*	.324**	.309**	.445**	.294*	.267*
	p	.490	.027	.354	.411	.009	.065	.012	.005	.008	.004	.011	.022

**p<0.05, **p<0.01*

Table E.2. 2-Year Postoperative Correlates for Having Children

		Have children	KMS Total	MOS Total	MOS-EI	MOS-T	MOS-A	MOS-PSI	IES-R-A	IES-R-I	IES-R-H	PASS EA	PASS PA	PASS CA	PASS Total	CESD
KMS Total	Pearson's *r*	.066														
	p	.608														
MOS Total	Pearson's *r*	.226	.514**													
	p	.064	<.001													
MOS-EI	Pearson's *r*	.218	.351**	.910**												
	p	.068	.006	<.001												
MOS-T	Pearson's *r*	.139	.502**	.826**	.680**											
	p	.251	<.001	<.001	<.001											
MOS-A	Pearson's *r*	.120	.588**	.824**	.755**	.670**										
	p	.319	<.001	<.001	<.001	<.001										
MOS-PSI	Pearson's *r*	.083	.424**	.834**	.761**	.687**	.767**									
	p	.489	<.001	<.001	<.001	<.001	<.001									
IES-R-A	Pearson's *r*	-.049	-.022	-.250*	-.216	-.221	-.269*	-.102								
	p	.681	.867	.041	.072	.068	.024	.398								
IES-R-I	Pearson's *r*	-.223	-.221	-.431**	-.377**	-.408**	-.289*	-.211	.679**							
	p	.060	.084	<.001	.001	<.001	.015	.077	<.001							
IES-R-H	Pearson's *r*	-.141	-.255*	-.429**	-.451**	-.364**	-.344**	-.245*	568**	.806**						
	p	.237	.045	<.001	<.001	.002	.004	.039	<.001	<.001						
PASS-F	Pearson's *r*	-.095	-.183	-.458**	-.449**	-.392**	-.337**	-.264*	.455**	.591**	.698**					
	p	.442	.166	<.001	<.001	.001	.005	.031	<.001	<.001	<.001					
PASS-EA	Pearson's *r*	-.045	-.253	-.156	-.128	-.056	-.178	-.132	.178	.234	.326**	.337**				
	p	.713	.052	.214	.302	.651	.150	.282	.142	.053	.006	.006				
PASS-PA	Pearson's *r*	-.092	-.168	-.330**	-.316**	-.220	-.181	-.139	.312**	.515**	.537**	.603**	.531**			
	p	.449	200	.007	.009	.074	.140	.256	.009	<.001	<.001	<.001	<.001			

Table E.2. (continued)

		Have children	KMS Total	MOS Total	MOS-EI	MOS-T	MOS-A	MOS-PSI	IES-R-A	IES-R-I	IES-R-H	PASS EA	PASS PA	PASS CA	PASS Total	CESD
PASS CA	Pearson's *r*	-.109	.021	-.296*	-.296*	-.163	-.209	-.093	.369**	.532	.574**	.728**	.503**	.818*		
	p	.369	.873	.017	.014	.187	.087	.445	.002	<.001	<.001	<.001	<.001	<.001		
PASS Total	Pearson's *r*	-.098	-.134	-.340**	-.321**	-.205	-.236	-.152	.387**	.544**	.630**	.814**	.696**	.867**	.920**	
	p	.420	.308	.006	.008	.095	0.53	.211	<.001	<.001	<.001	<.001	<.001	<.001	<.001	
CESD	Pearson's *r*	-.154	-.354**	-.590**	-.527**	-.497**	-.538**	-.412**	.513**	.744**	.786**	.713**	.295*	.491**	.599**	.616**
	p	.197	.004	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	.014	<.001	<.001	<.001

**p<0.05, **p<0.01*

Appendix F. Pre- and Postoperative Correlates for Pain Interference (BPI-INT)

Table F.1. Correlates for Pain Interference (BPI-INT) at Postoperative 2 Years

		BPI-INT	DASH Total	CPAQ Activity Engagement	CPAQ Pain Willingness	IES-R Avoidance	IES-R Intrusion	IES-R Hyperarousal	PCS-R	PCS-M	PCS-H	Total ECR Avoidance	Total ECR Anxiety	CES-D
DASH Total	Pearson's *r*	.778**												
	p	<.001												
CPAQ Activity Engagement	Pearson's *r*	-.252	.104											
	p	.188	.638											
CPAQ Pain Willingness	Pearson's *r*	-.219	-.420	-.056										
	p	.265	.052	.779										
IES-R Avoidance	Pearson's *r*	.484**	.400**	-.321	-.108									
	p	<.001	.001	.096	.591									
IES-R Intrusion	Pearson's *r*	.599**	.551**	-.120	-.219	.679**								
	p	<.001	<.001	.544	.272	<.001								
IES-R Hyperarousal	Pearson's *r*	.666**	.689**	-.291	-.234	.568**	.806**							
	p	<.001	<.001	.133	.241	<.001	<.001							
PCS-R	Pearson's *r*	.399**	.223	-.384*	-.290	.222	.311**	.389**						
	p	<.001	.079	.044	.143	.061	.008	<.001						
PCS-M	Pearson's *r*	.587**	.586**	-.239	-.242	.362**	.546**	.662**	.689**					
	p	<.001	<.001	.220	.223	.002	<.001	<.001	<.001					
PCS-H	Pearson's *r*	.538**	.273**	-.387*	-.453*	.359**	.444**	.580**	.734**	.782**				
	p	<.001	<.001	.042	.018	.002	<.001	<.001	<.001	<.001				
Total ECR Avoidance	Pearson's *r*	.289*	.214	-.033	-.129	.355**	.456**	.444**	.177	.277*	.246*			
	p	.015	.095	.867	.514	.002	<.001	<.001	.139	.020	.039			
Total ECR Anxiety	Pearson's *r*	.153	.196	-.119	-.409*	.098	.326**	.330**	.323**	.297*	.259*	.464**		
	p	,203	.127	.538	.031	.418	.006	.005	.006	.012	.029	<.001		

Table F.1. (continued)

		BPI-INT	DASH Total	CPAQ Activity Engagement	CPAQ Pain Willingness	IES-R Avoidance	IES-R Intrusion	IES-R Hyperarousal	PCS-R	PCS-M	PCS-H	Total ECR Avoidance	Total ECR Anxiety	CES-D
CES-D	Pearson's *r*	.663**	.542**	-.361	-.156	.513**	.744**	.786**	.428**	.601**	.461**	.505**	.438**	
	p	<.001	<.001	.055	.427	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	
STAI-S	Pearson's *r*	.553**	.398**	-.241	-.180	.499**	.700**	.709**	.381**	.510**	.448**	.475**	.540**	.804**
	p	<.001	.001	.235	.388	<.001	<.001	<.001	.001	<.001	<.001	<.001	<.001	<.001

**p<0.05, **p<0.01*

Table F.2. Preoperative Correlates for Pain Interference (BPI-INT)

		BPI-INT	PASS-F	PASS-EA	PASS-PA	PASS-CA	STAI-S	PCS R	PCS M	PCS H
PASS F	Pearson's *r*	.260*								
	p	.027								
PASS EA	Pearson's *r*	.111	.594**							
	p	.354	<.001							
PASS PA	Pearson's *r*	.098	.630**	.588**						
	p	.411	<.001	<.001						
PASS CA	Pearson's *r*	.302**	.692**	.702**	.777**					
	p	.009	<.001	<.001	<.001					
STAI S	Pearson's *r*	.294	.505**	.134	.288*	.390**				
	p	.011	<.001	.262	.014	<.001				
PCS R	Pearson's *r*	.291*	.516**	.543**	.445**	.650**	.422**			
	p	.012	<.001	<.001	<.001	<.001	<.001			
PCS M	Pearson's *r*	.324**	.632**	.526**	.583**	.624**	.366**	.649**		
	p	.005	<.001	<.001	<.001	<.001	.001	<.001		
PCS H	Pearson's *r*	.309**	.675**	.517**	.640**	.691**	.410**	.754**	.777*	
	p	.008	<.001	<.001	<.001	<.001	<.001	<.001	<.001	
CESD	Pearson's *r*	.267*	.605**	.178	.425**	.440**	.802**	.412**	.417**	.471**
	p	.022	<.001	.134	<.001	<.001	<.001	<.001	<.001	<.001

**p<0.05, **p<0.01*

Appendix G. Description and Timing of Postoperative Treatment

Timeframe undergoing Chemotherapy	Timeframe undergoing Radiation	Timeframe undergoing hormone therapy	Other surgery	Initial timeframe reporting lymphedema	Trajectory subgroup
		Exact date unclear (reported at 2 years post-op)	Reconstruction (intra-op); removed at 2 months post-op (infection)		Did not report pain at any follow-up
	Pre-op-2 months post-op	Exact date unclear (reported at 2 years post-op)			Did not report pain at any follow-up
	1 session (intra-op)				Did not report pain at any follow-up
	1-2 months post-op	Exact date unclear (reported at 2 years post-op)			Did not report pain at any follow-up
	1-2 months post-op				Did not report pain at any follow-up
1-3 months post-op (on medication change)	4-5 months post-op	4 months post-op – ongoing			Resolved within 6 months
			Reconstruction (2 years post-op)		Resolved within 6 months
			BCS complication requiring surgical treatment (2 weeks post-op)		Resolved within 6 months
Exact date unclear (reported at 2 years post-op; one medication change)	4-5 months post-op	4-6 months post-op			Resolved within 6 months

Appendix G. (continued)

Timeframe undergoing Chemotherapy	Timeframe undergoing Radiation	Timeframe undergoing hormone therapy	Other surgery	Initial timeframe reporting lymphedema	Trajectory subgroup
			Reconstruction (2 years post-op)		
		Exact date unclear	BCS complication requiring surgical treatment (13 months post-op)		Resolved within 6 months
1-4 month post-op	1 month post-op	BCS complication requiring surgical treatment (2 weeks post-op)		10-15 month post-op	Resolved within 6 months
	3 months post-op	2 months post-op - ongoing			Resolved within 6 months
	2-3 months post-op				Resolved within 6 months
	1-2 months post-op	1 month post-op-ongoing	Surgery related to previous tumor (exact date unclear)		Resolved within 6 months
			Reconstruction related treatment (10 and 17 months post-op)		Resolved within 6 months
		Exact date unclear	Reconstruction related treatment (20 months post-op)		Resolved within 6 months
3-5 months post-op		10-11 months post-op		10 months post-op	Resolved within 6 months
	3-4 months post-op				Resolved within 6 months

Appendix G. (continued)

Timeframe undergoing Chemotherapy	Timeframe undergoing Radiation	Timeframe undergoing hormone therapy	Other surgery	Initial timeframe reporting lymphedema	Trajectory subgroup
Pre-op (previous tumor)		Exact date unclear (ongoing)	Surgical intervention related to reconstruction (11 months post-op)		Resolved within 6 months
		2 months-ongoing			Resolved within 6 months
			Reconstruction treatment (10-11 month)		Resolved within 6 months
Pre-op chemo	1 month post-op	Exact date unclear	Reconstruction (13 month post-op)	4 months post-op	Resolved within 6 months
	1 month post-op				Resolved within 6 months
		Date missing			Resolved persistent
		Date missing	BCS complication (exact date unclear, reported at 2 years post-op)		Resolved persistent

Appendix G. (continued)

	Timeframe undergoing Chemotherapy	Timeframe undergoing Radiation	Timeframe undergoing hormone therapy	Other surgery	Initial timeframe reporting lymphedema	Trajectory subgroup
		3-4 months post-op			Exact date unclear (reported at 2 years)	Resolved persistent
		3-5 months post-op	6 month-ongoing			Resolved persistent
			1 month post-op-ongoing			Resolved persistent
		Post-op-1 month post-op				Resolved persistent
	1-2 months post-op	1-2 months post-op	1 year pre-op-ongoing (previous tumor)	Implants (6 months post-op)		Resolved episodic
				Reconstruction (intraoperation) Reconstruction related treatment (2 years post-op)	Exact date unclear (reported at 2 years post-op)	Resolved episodic
		Start date unclear- 3 months post-op	Exact date unclear			Resolved episodic
	2-4 months post-op	6-7 months post-op	Exact date unclear	Reconstruction (14 month post-op)		Resolved episodic

Appendix G. (continued)

Timeframe undergoing Chemotherapy	Timeframe undergoing Radiation	Timeframe undergoing hormone therapy	Other surgery	Initial timeframe reporting lymphedema	Trajectory subgroup
	1-2 months post-op				Resolved episodic
post-op-4 months post-op		Pre-op (previous tumour) 5 month post-op-ongoing (current surgery)		18 months post-op	Resolved episodic
1-4 months post-op	5-6 months post-op	2 months post-op-ongoing			Unresolved episodic
	3 months post-op				Unresolved episodic
		1 year post-op - ongoing			Unresolved episodic
					Unresolved episodic
7 months post-op-ongoing (one medication change)		Start date unclear-18 months post-op		8 months post-op	Unresolved episodic
	5-6 months post-op	Exact date unclear			Unresolved episodic
2-5 month post-op		2 months post-op	Reconstruction (2 years post-op)		Unresolved episodic
	3 months post-op	Tamoxifen (date unclear)			Unresolved episodic

Appendix G. (continued)

Timeframe undergoing Chemotherapy	Timeframe undergoing Radiation	Timeframe undergoing hormone therapy	Other surgery	Initial timeframe reporting lymphedema	Trajectory subgroup
Start date unclear- 19 months post-op	13-18 month post-op	8 months-ongoing		13-18 months post-op	Unresolved episodic
				After radiation (5-7 months postop) exact date unclear	Unresolved episodic
1-4 months postop	5-7 months postop	19 months postop			Unresolved episodic
		1 year postop - ongoing, switched medication once		9 months post-op, low impact; weight loss helped recovery	Unresolved episodic
	1-2 months postop	7 months pre-op - ongoing			Unresolved episodic
	2 months post-op	3 months post-op			Unresolved episodic
		Start date unclear-2 years post-op (two medication changes)			Unresolved episodic
	2 months post-op	Tamoxifen			Unresolved episodic
1-4 months post-op	1-2 months post-op				Unresolved episodic
1-6 months post-op	7 months post-op	4 -12 months post-op			Unresolved episodic

Appendix G. (continued)

Timeframe undergoing Chemotherapy	Timeframe undergoing Radiation	Timeframe undergoing hormone therapy	Other surgery	Initial timeframe reporting lymphedema	Trajectory subgroup
3-5 months post-op					Unresolved episodic
2 months post-op	8-10 months post-op				Unresolved episodic
	4 months post-op	3 months -ongoing			Unresolved persistent
3 months to 1 year post-op		8 month post-op - ongoing			Unresolved persistent
1-4 months post-op	6-7 months post-op	1 year post-op - ongoing			Unresolved persistent
1-3 months post-op	5-7 months post-op	Exact date unclear	Additional prophylactic BCS and reconstruction (2 years post-op)	2 years post-op	Unresolved persistent
			Reconstruction related surgery (19 months post-op)		Unresolved persistent
				Date unclear (reported at 2 years post-op)	Unresolved persistent
2-3 months post-op	6-8 months post-op	6 months post-op-ongoing		Date unclear (reported at 2 years post-op)	Unresolved persistent

Appendix G. (continued)

Timeframe undergoing Chemotherapy	Timeframe undergoing Radiation	Timeframe undergoing hormone therapy	Other surgery	Initial timeframe reporting lymphedema	Trajectory subgroup
2-5 months post-op	6-7 months post-op	Exact date unclear (two medication changes)		1 year post-op	Unresolved persistent
		3 months post-op-ongoing (one medication change)		Date unclear (reported at 2 years post-op)	Unresolved persistent
1-5 months post-op	6-7 months post-op			19 months post-op	Unresolved persistent
		Start date unclear-ongoing		21 months post-op	Unresolved persistent

[a]BCS: breast cancer surgery, pre-op: preoperative, post-op: postoperative

Appendix H. Unresolved Episodic Subgroup Trajectory Plots

Figure H.1. Individual Trajectory Plot (H1)

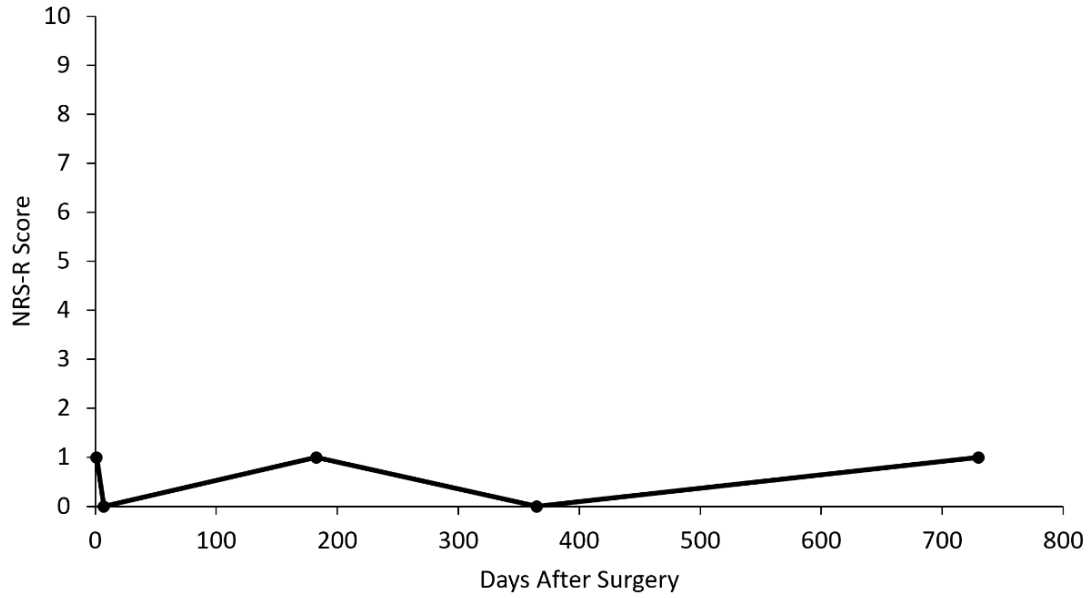


Figure H.2. Individual Trajectory Plot (H2)

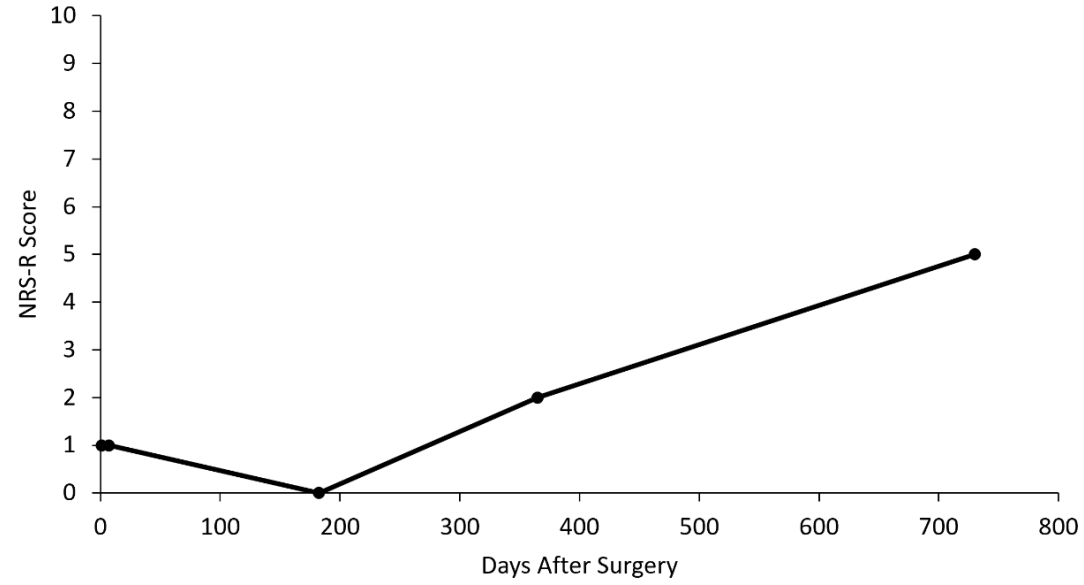


Figure H.3. Individual Trajectory Plot (H3)

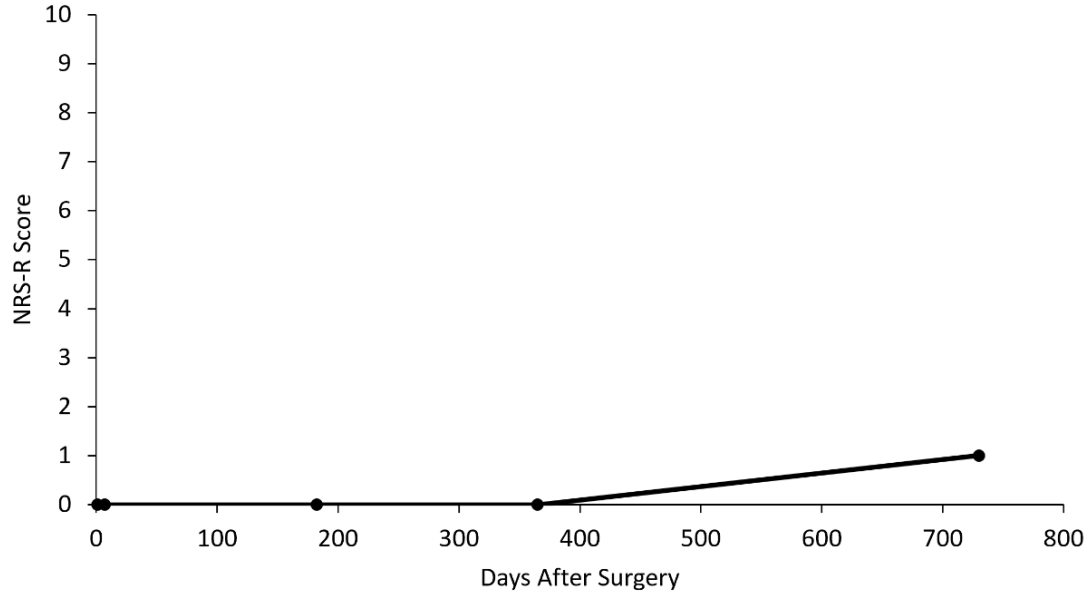


Figure H.4. Individual Trajectory Plot (H4)

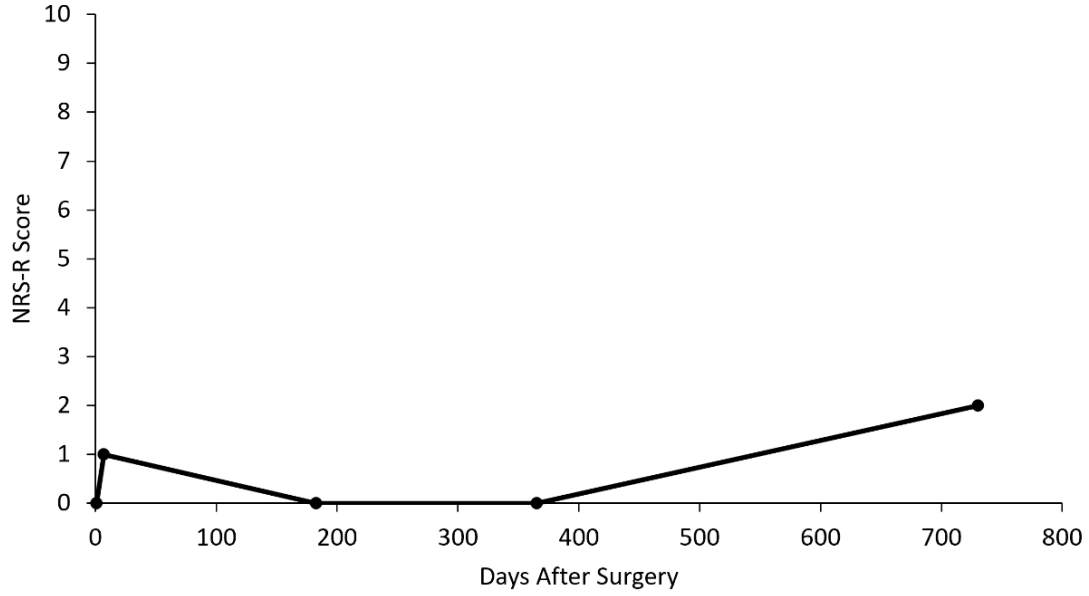


Figure H.5. Individual Trajectory Plot (H5)

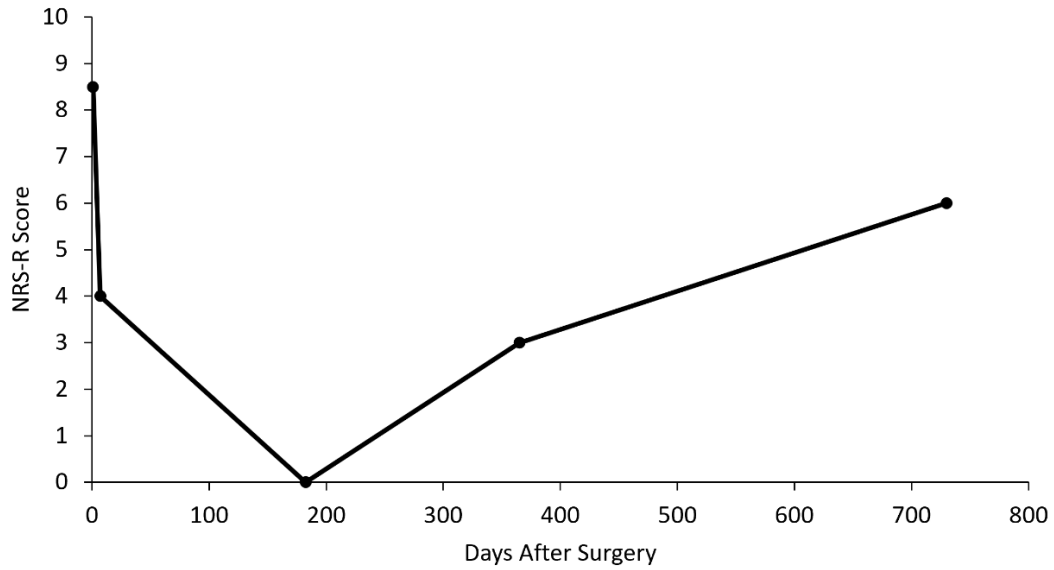


Figure H.6. Individual Trajectory Plot (H6)

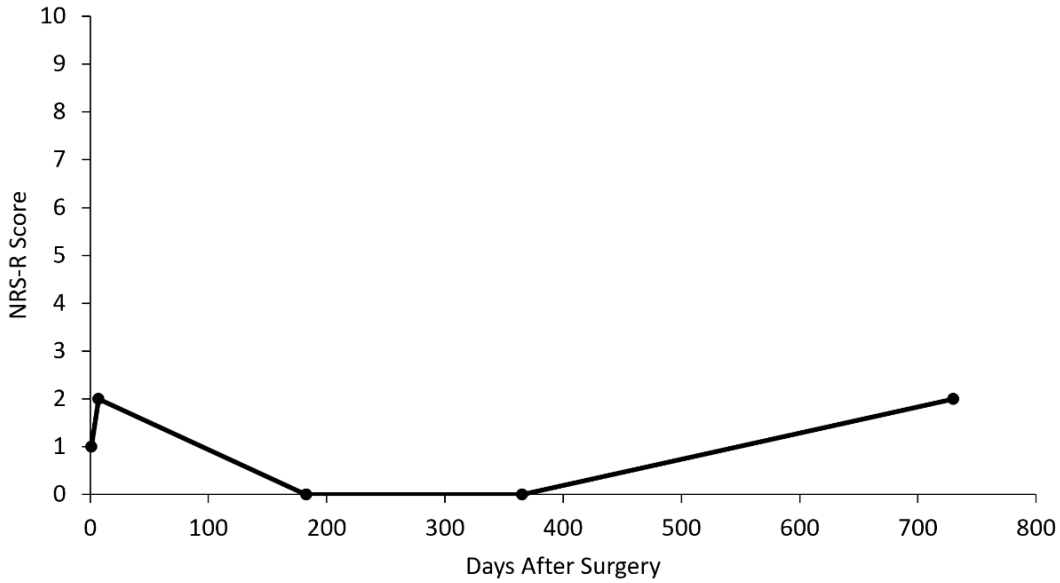


Figure H.7. Individual Trajectory Plot (H7)

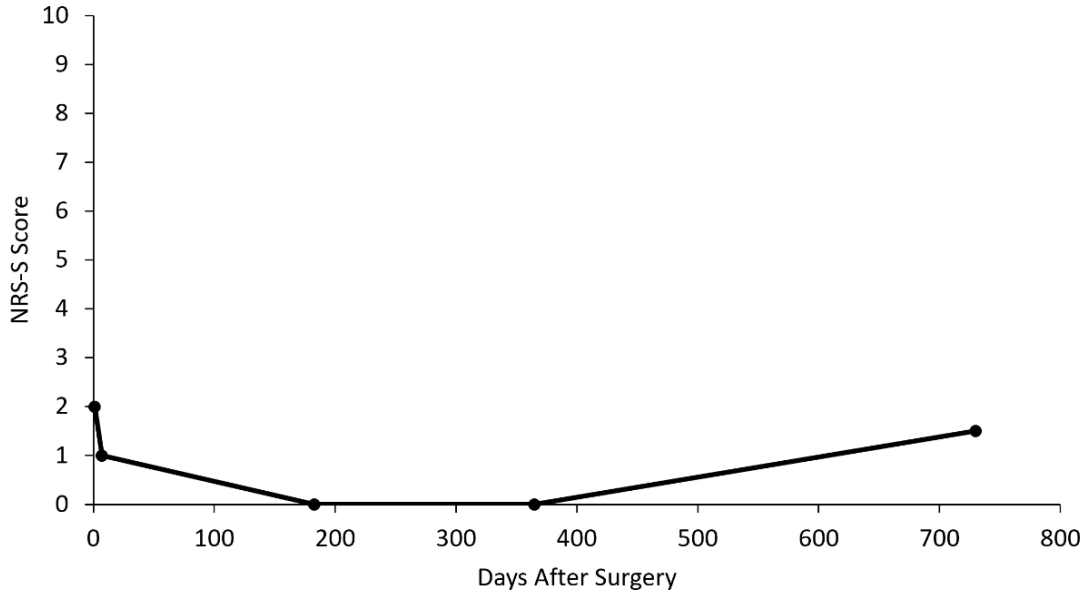


Figure H.8. Individual Trajectory Plot (H8)

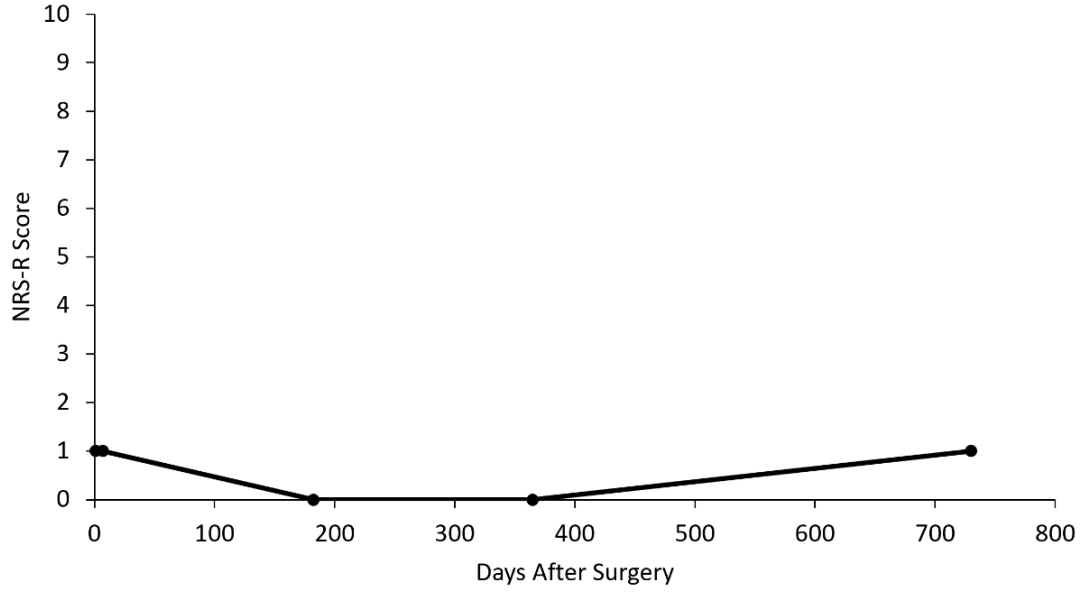


Figure H.9. Individual Trajectory Plot (H9)

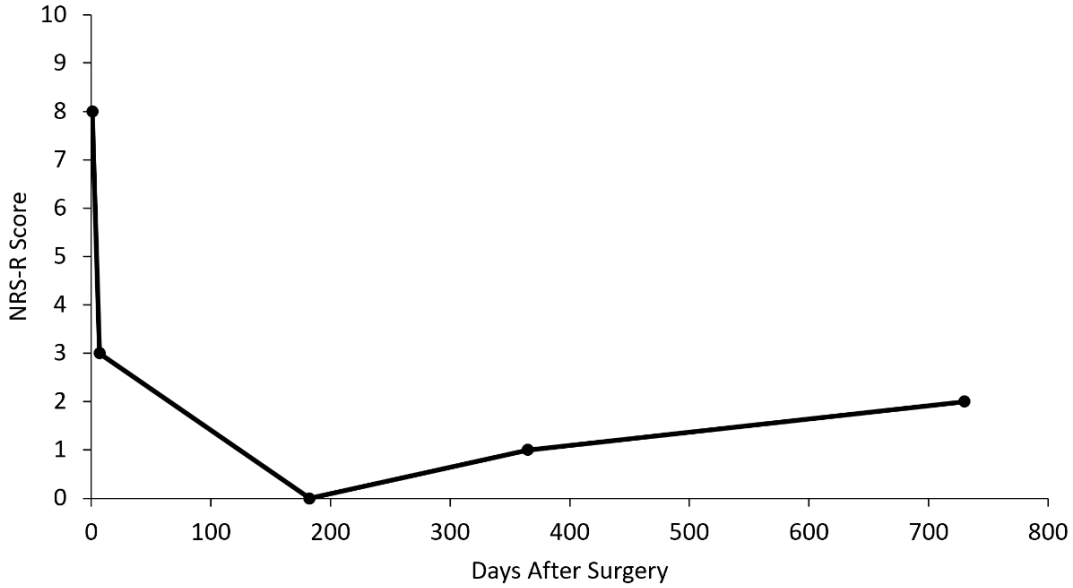


Figure H.10. Individual Trajectory Plot (H10)

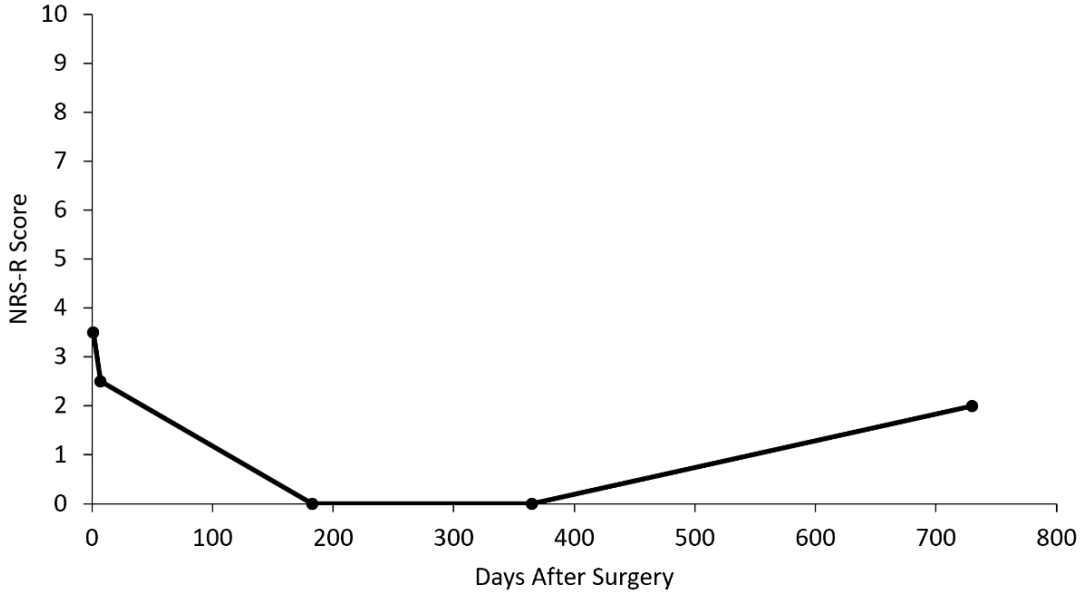


Figure H.11. Individual Trajectory Plot (H11)

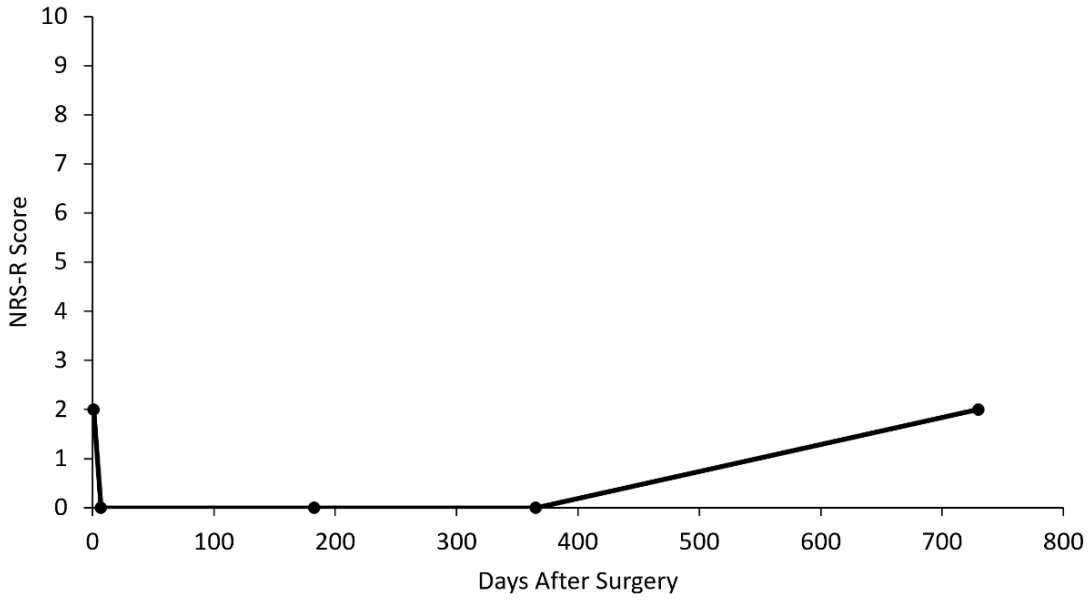


Figure H.12. Individual Trajectory Plot (H12)

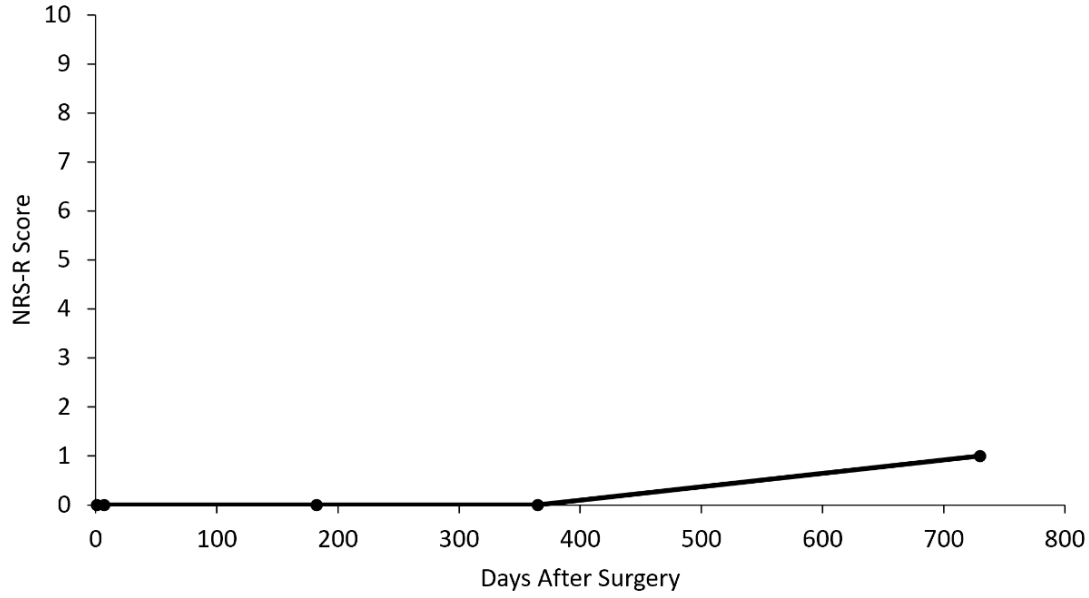


Figure H.13. Individual Trajectory Plot (H13)

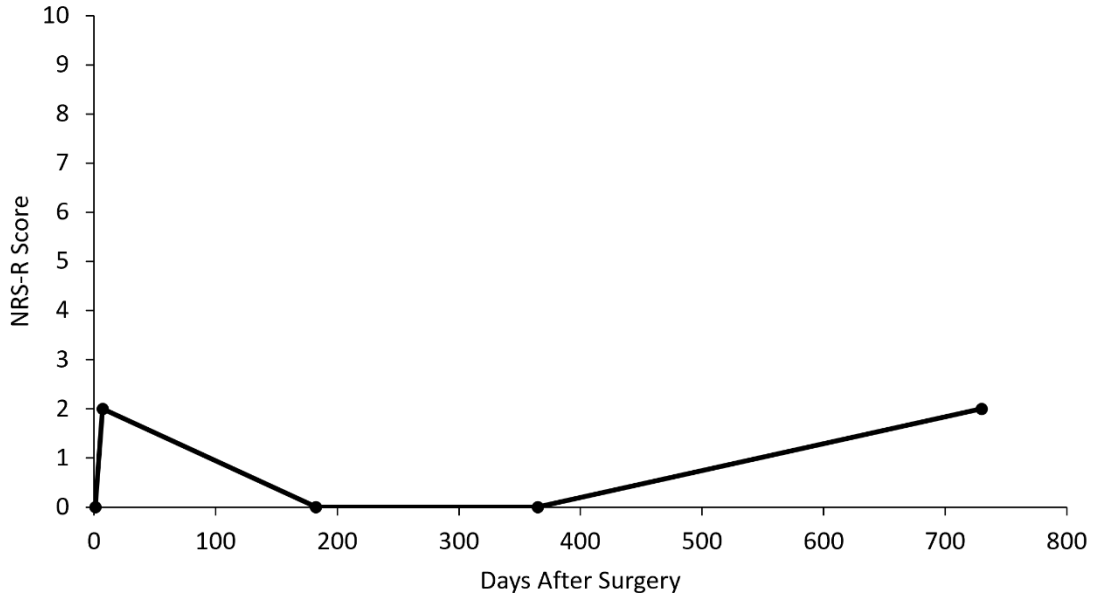


Figure H.14. Individual Trajectory Plot (H14)

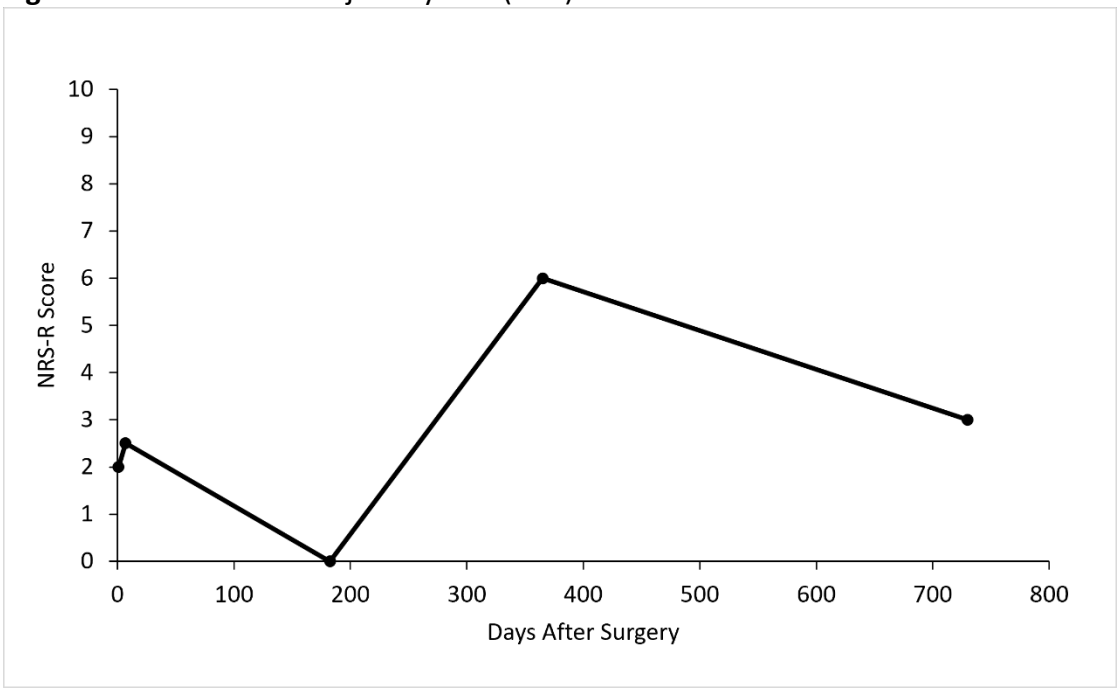


Figure H.15. Individual Trajectory Plot (H15)

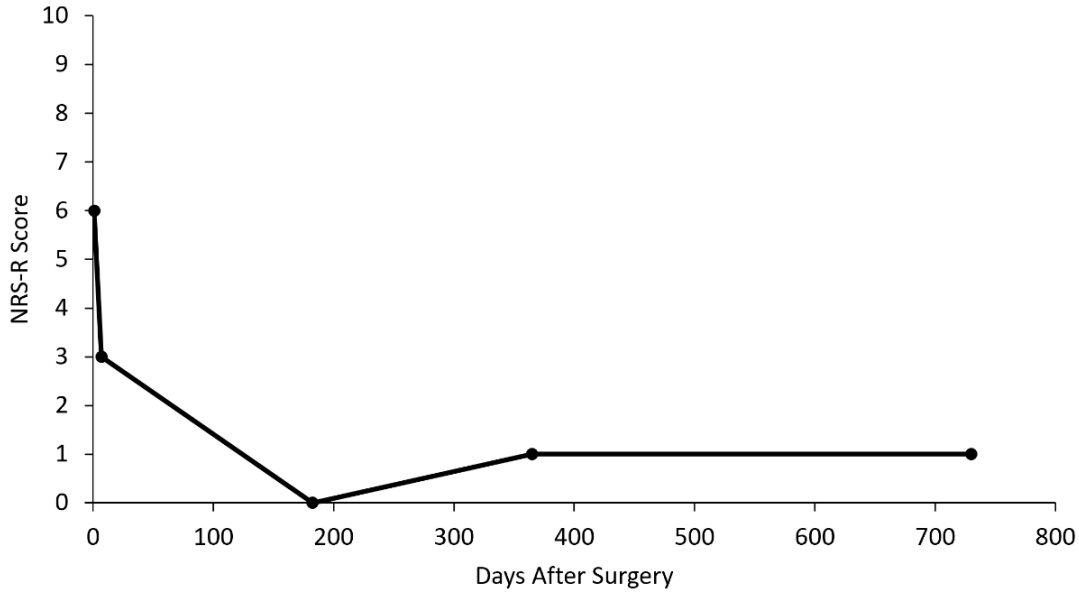


Figure H.16. Individual Trajectory Plot (H16)

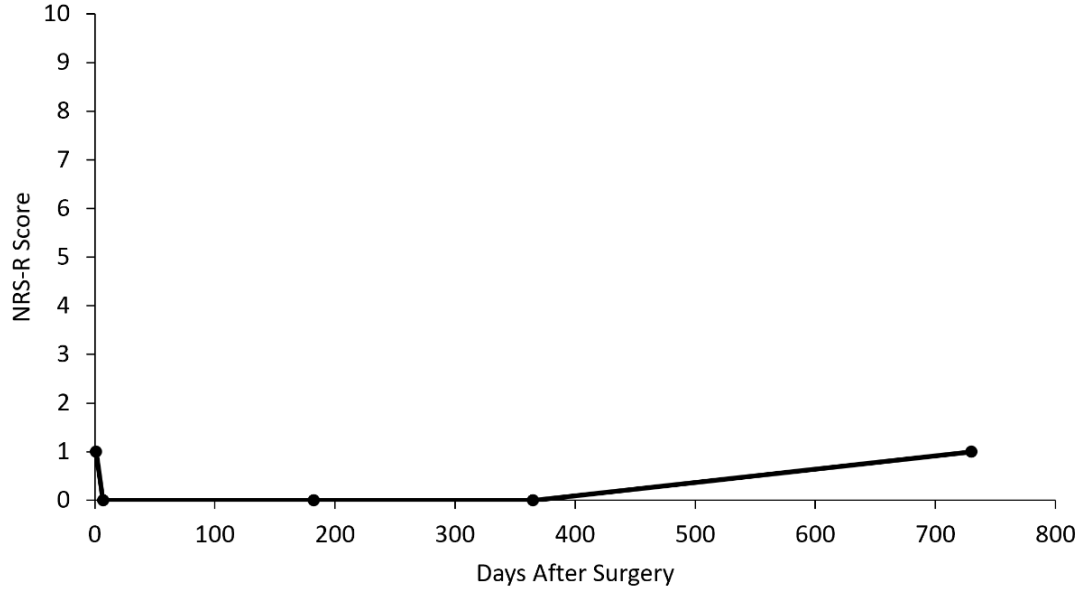


Figure H.17. Individual Trajectory Plot (H17)

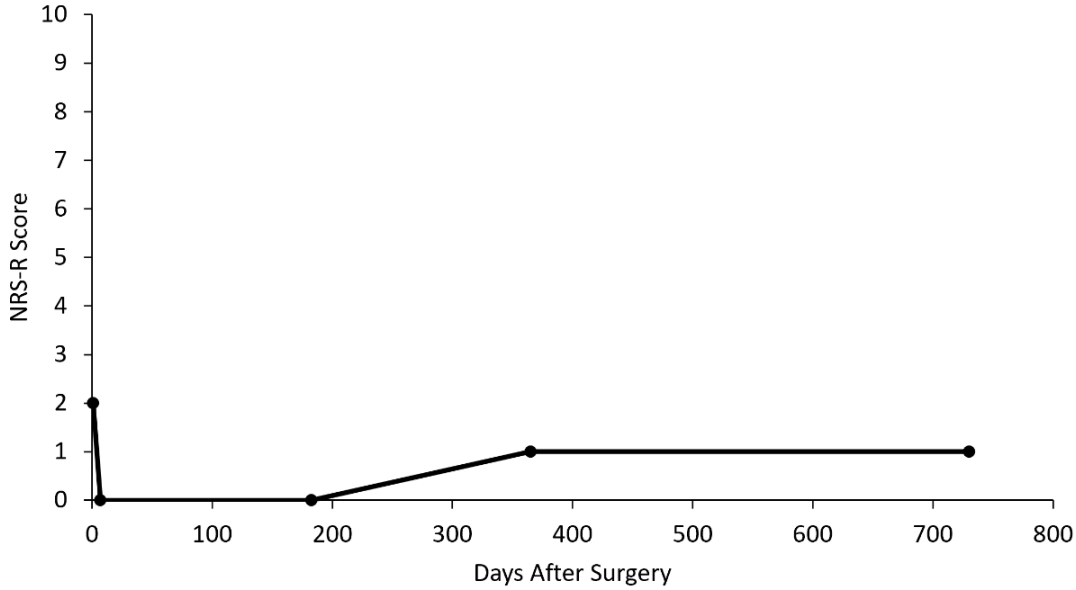


Figure H.18. Individual Trajectory Plot (H18)

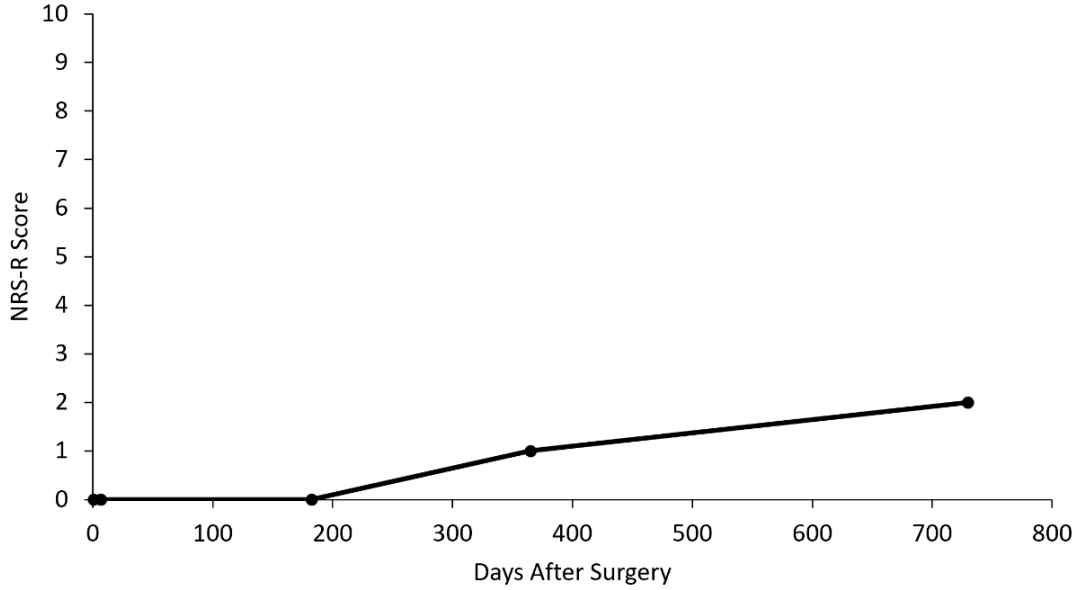


Figure H.19. Individual Trajectory Plot (H19)

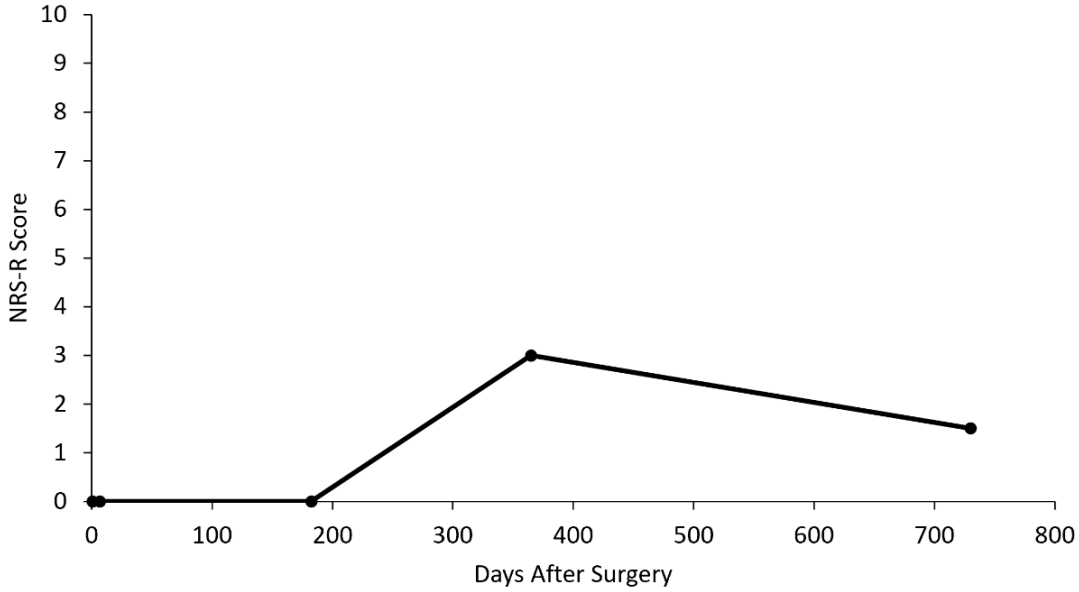


Figure H.20. Individual Trajectory Plot (H20)

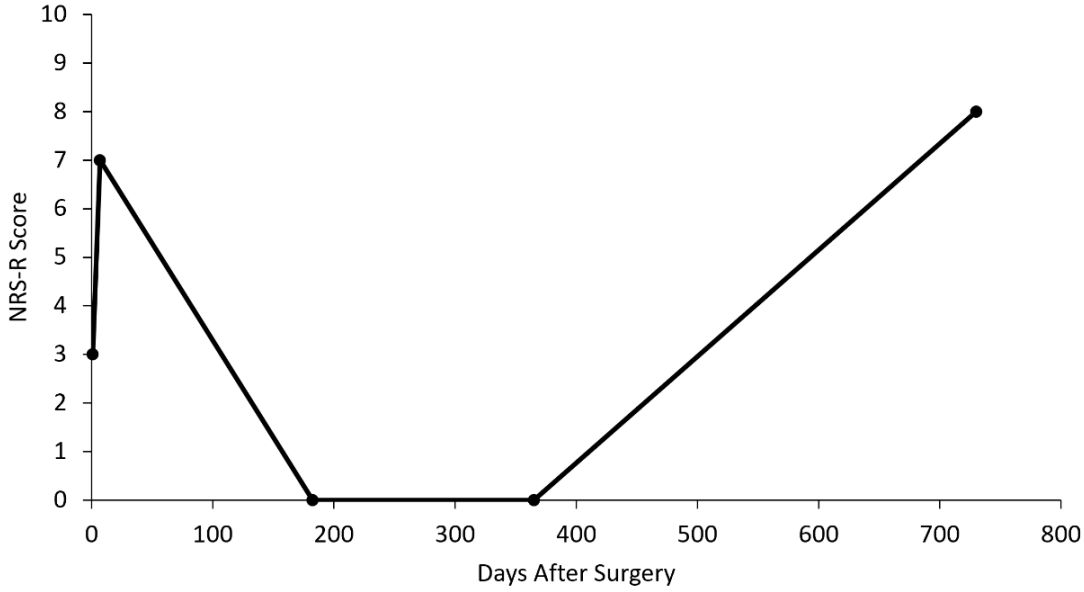


Figure H.21. Individual Trajectory Plot (H21)

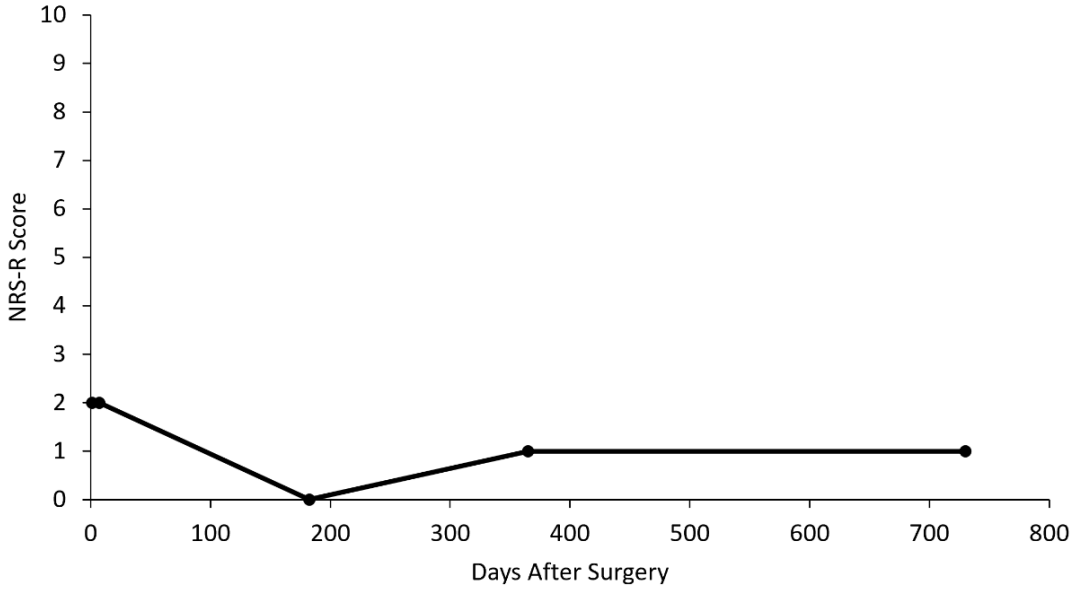
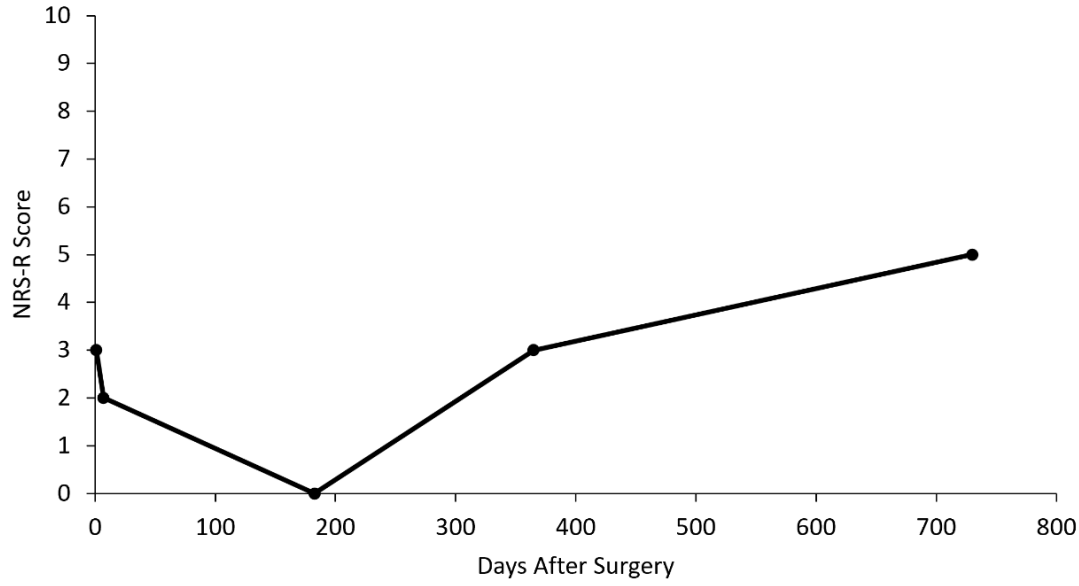


Figure H.22. Individual Trajectory Plot (H22)



Appendix I. Subgroup Whose Pain Resolved In 6 Months Individual Trajectory Plots

Figure I.1. Individual Trajectory Plot (I1)

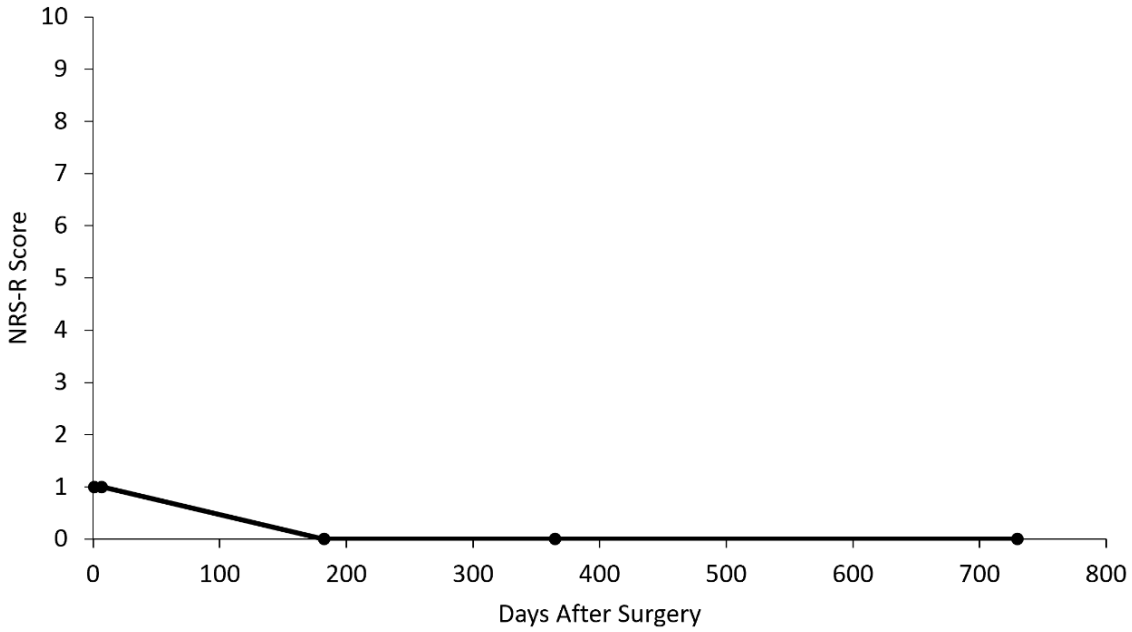


Figure I.2. Individual Trajectory Plot (I2)

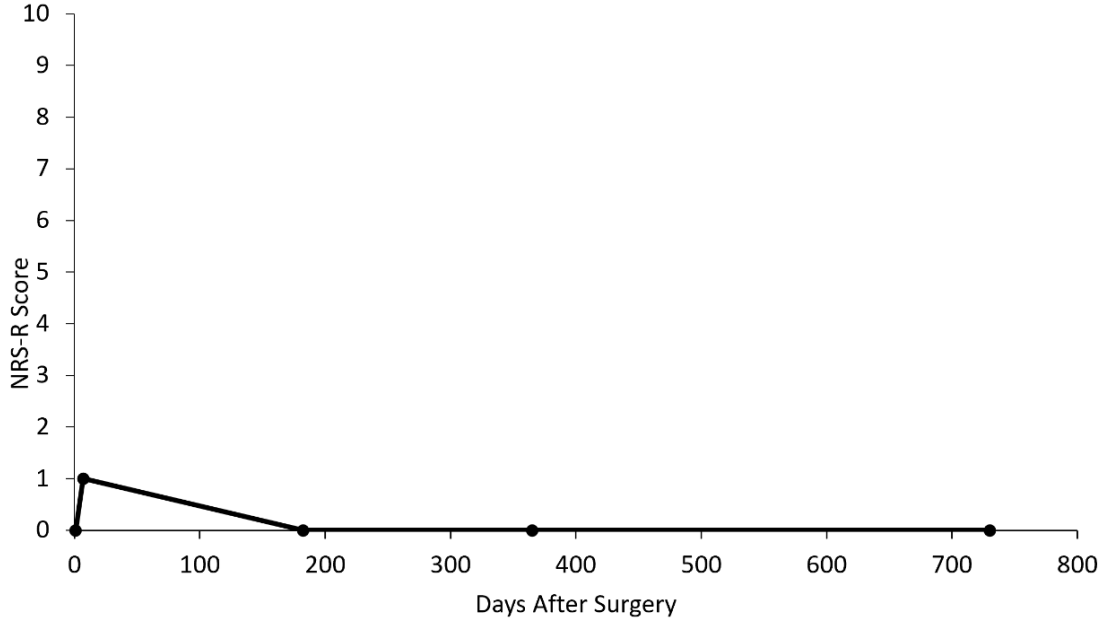


Figure I.3. Individual Trajectory Plot (I3)

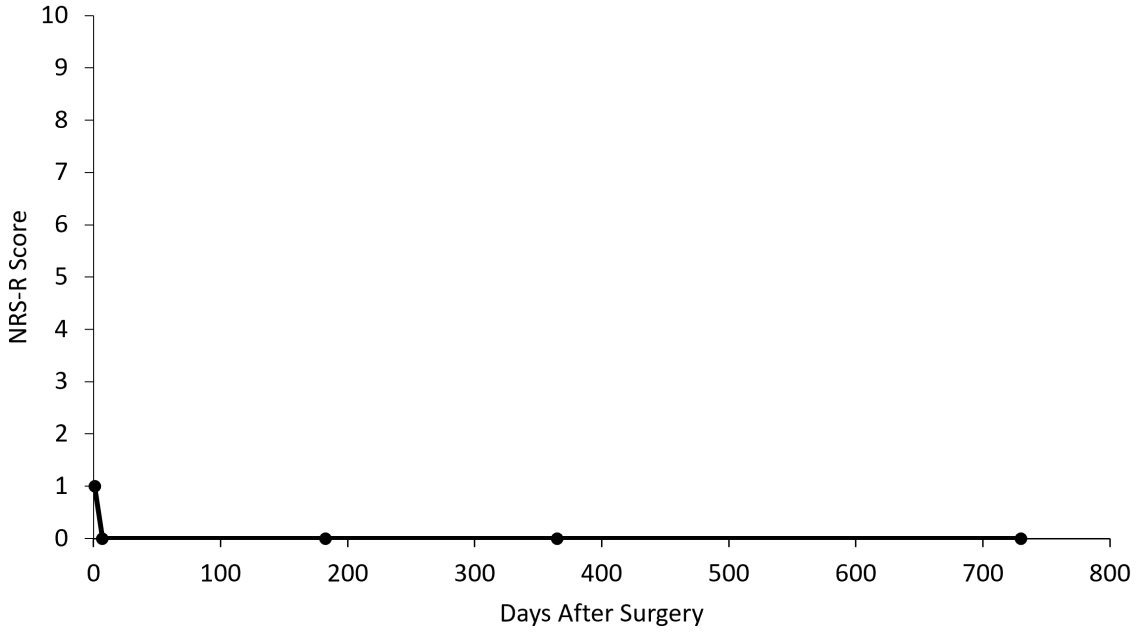


Figure I.4. Individual Trajectory Plot (I4)

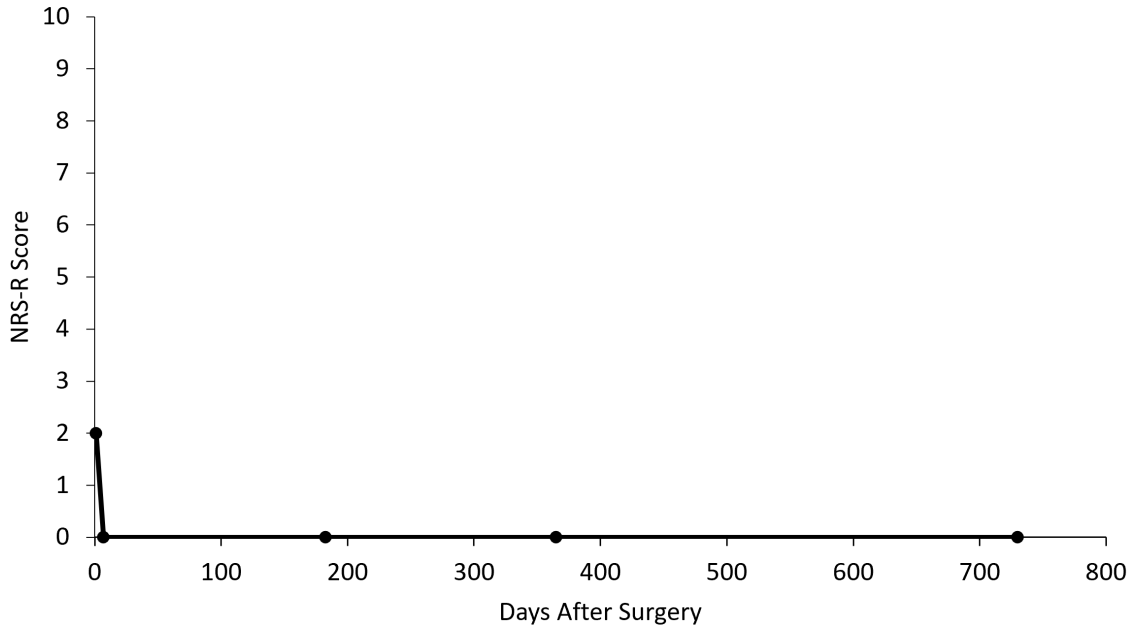


Figure I.5. Individual Trajectory Plot (I5)

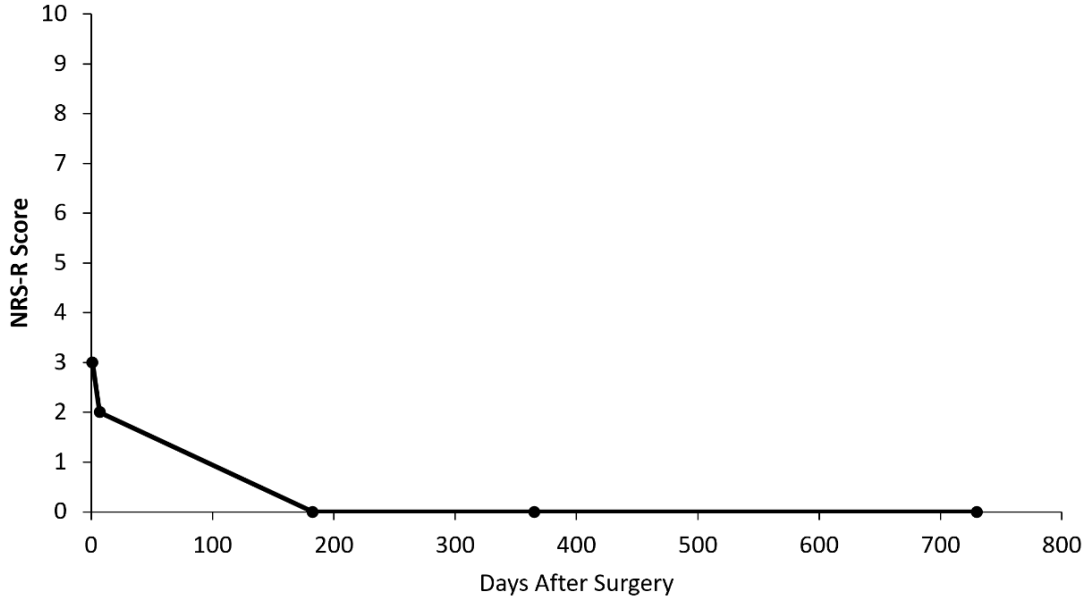


Figure I.6. Individual Trajectory Plot (I6)

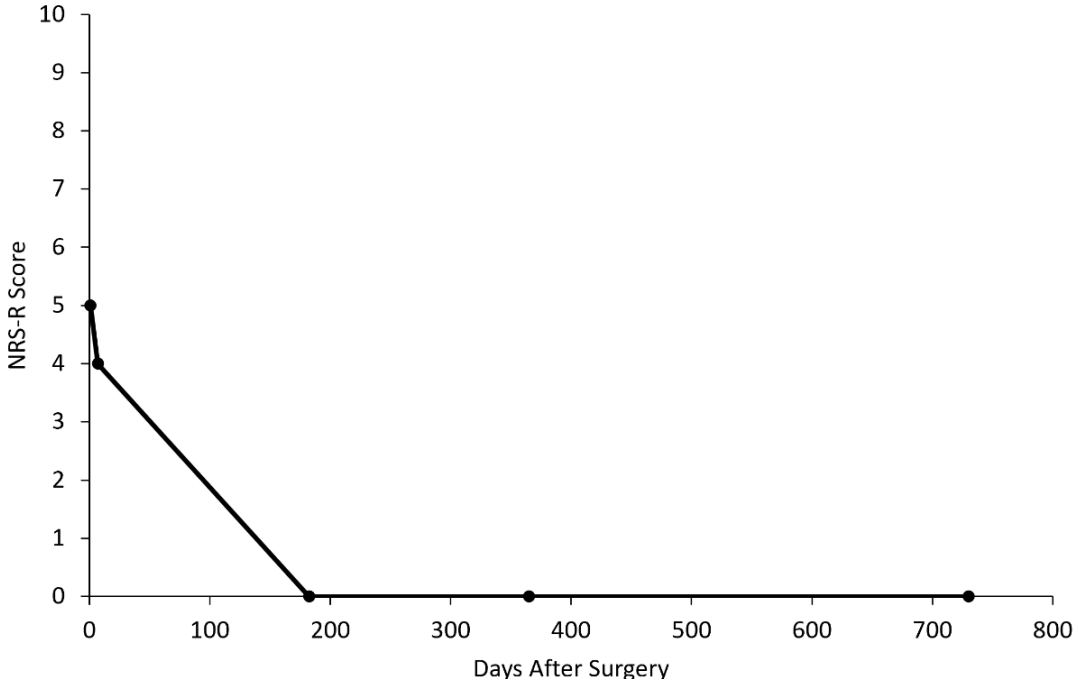


Figure I.7. Individual Trajectory Plot (I7)

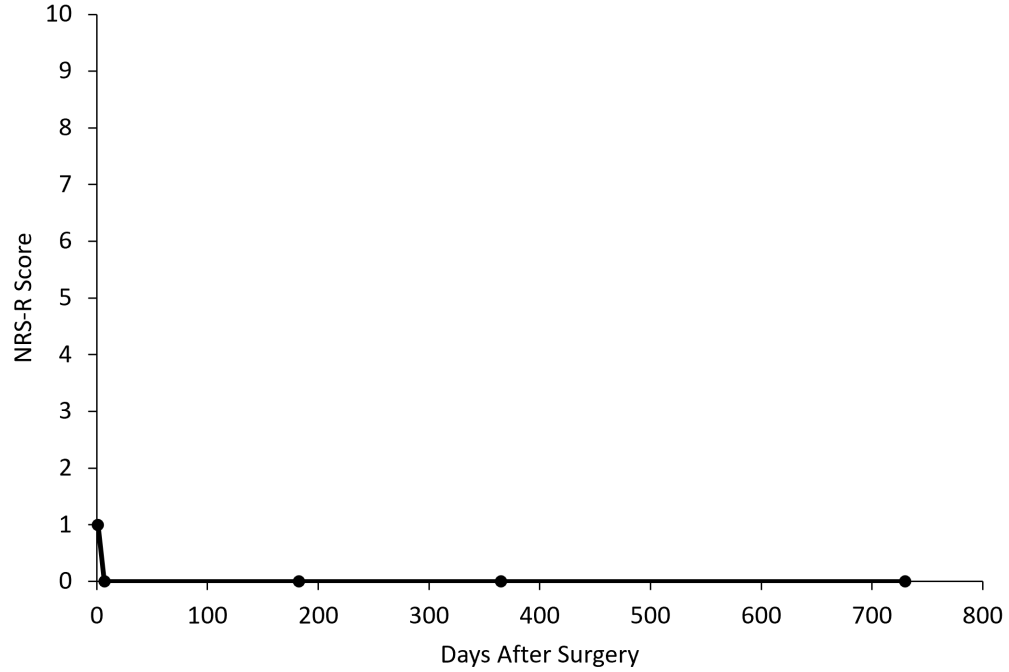


Figure I.8. Individual Trajectory Plot (I8)

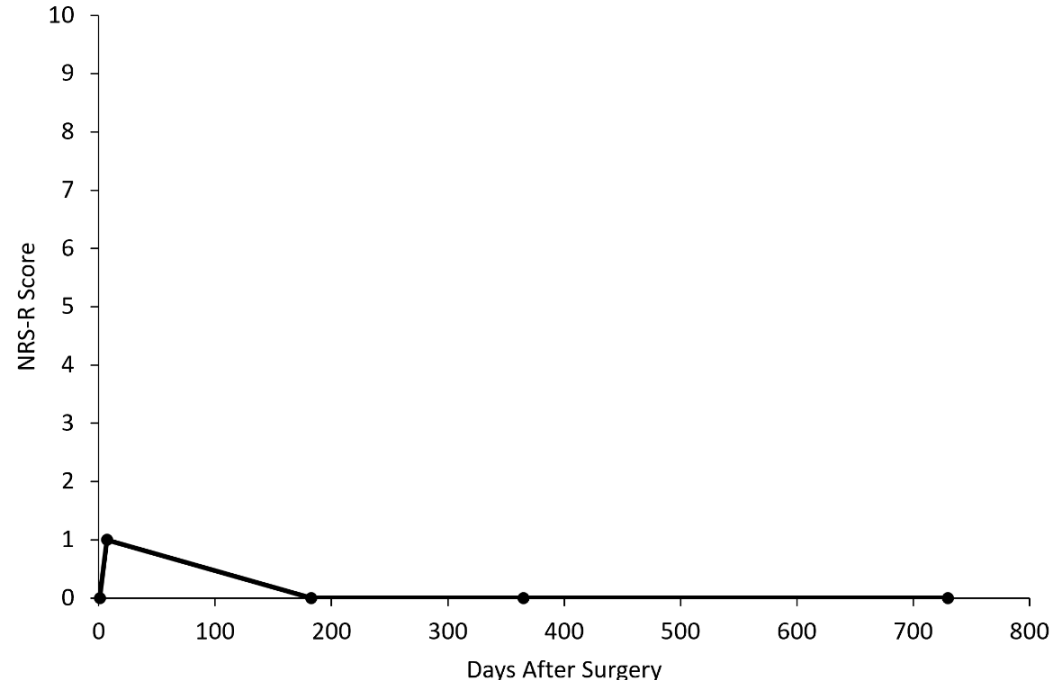


Figure I.9. Individual Trajectory Plot (I9)

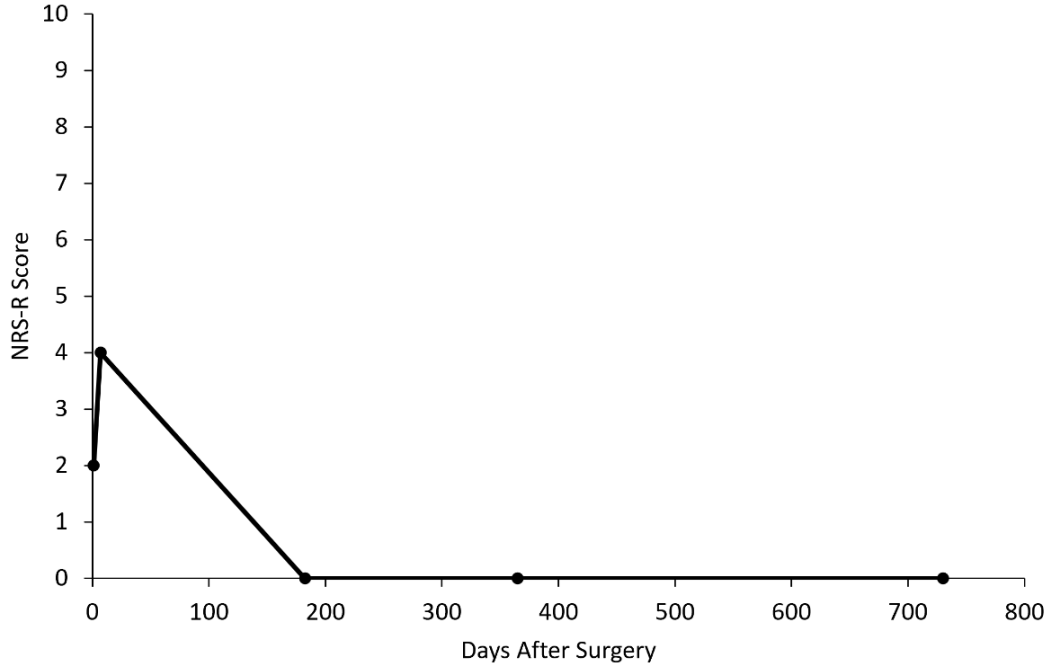


Figure I.10. Individual Trajectory Plot (I10)

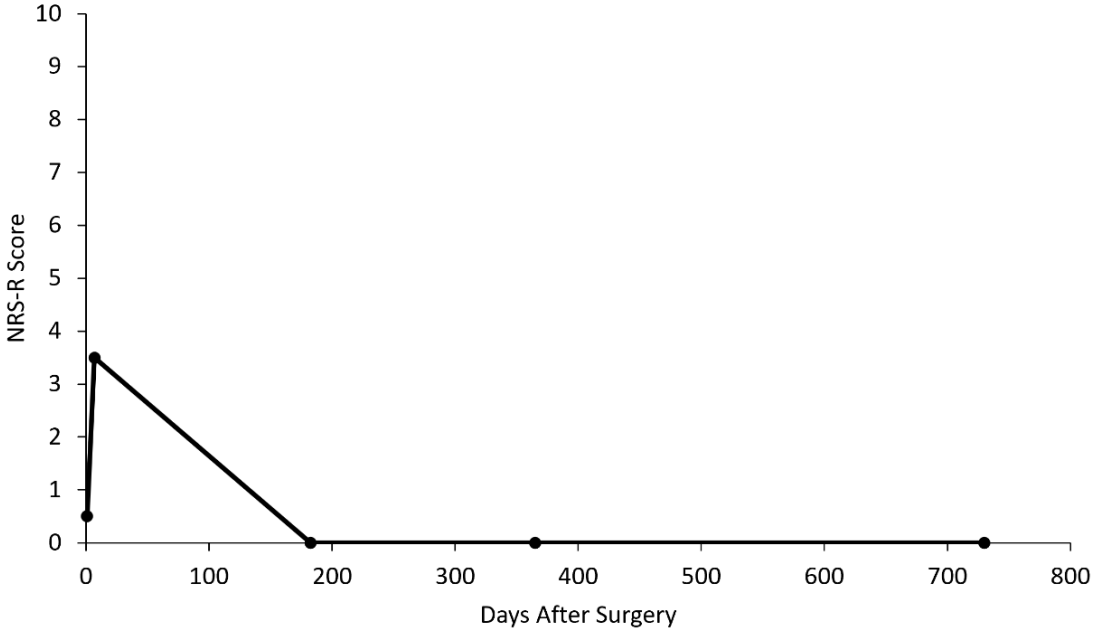


Figure I.11. Individual Trajectory Plot (I11)

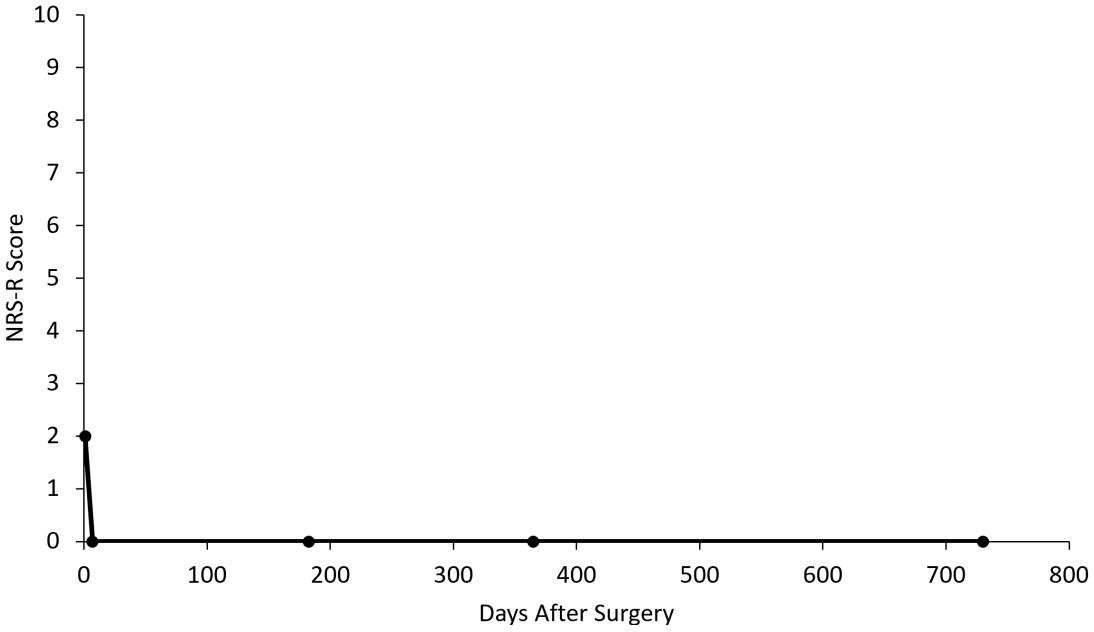


Figure I.12. Individual Trajectory Plot (I12)

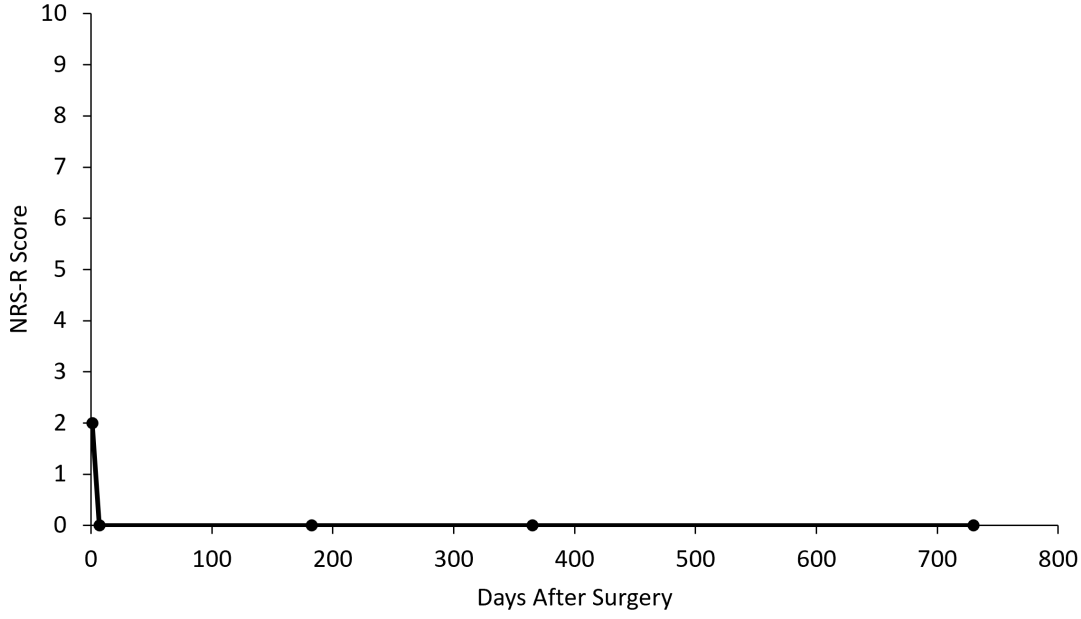


Figure I.13. Individual Trajectory Plot (I13)

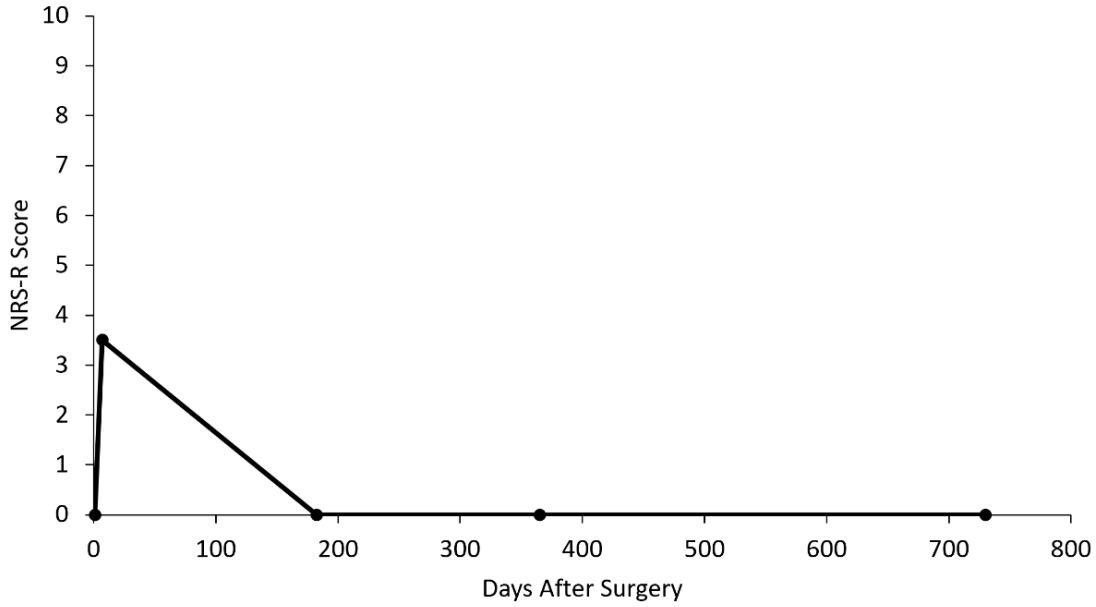


Figure I.14. Individual Trajectory Plot (I14)

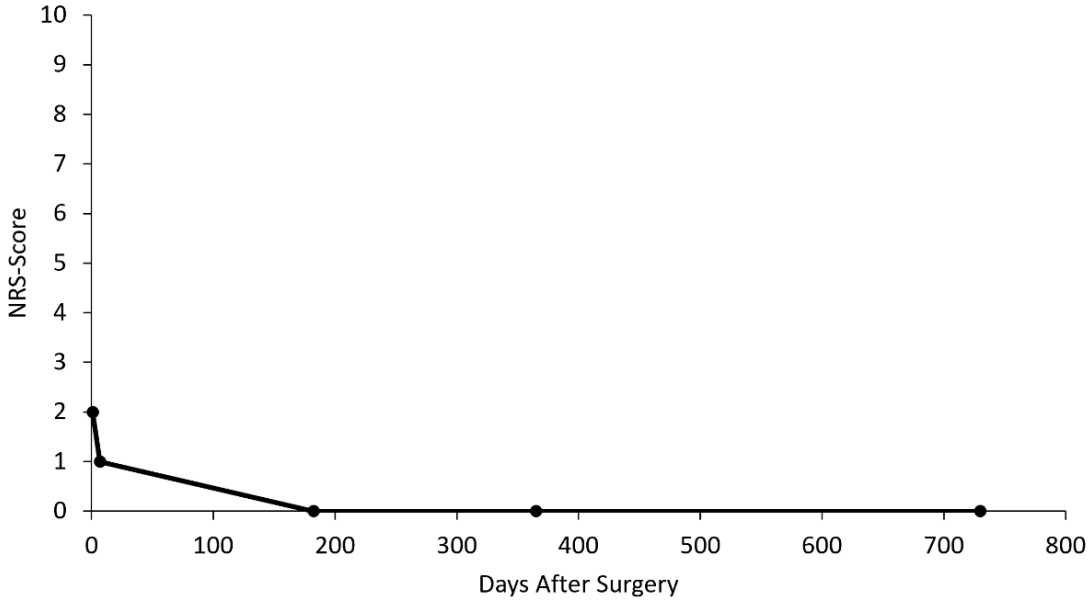


Figure I.15. Individual Trajectory Plot (I15)

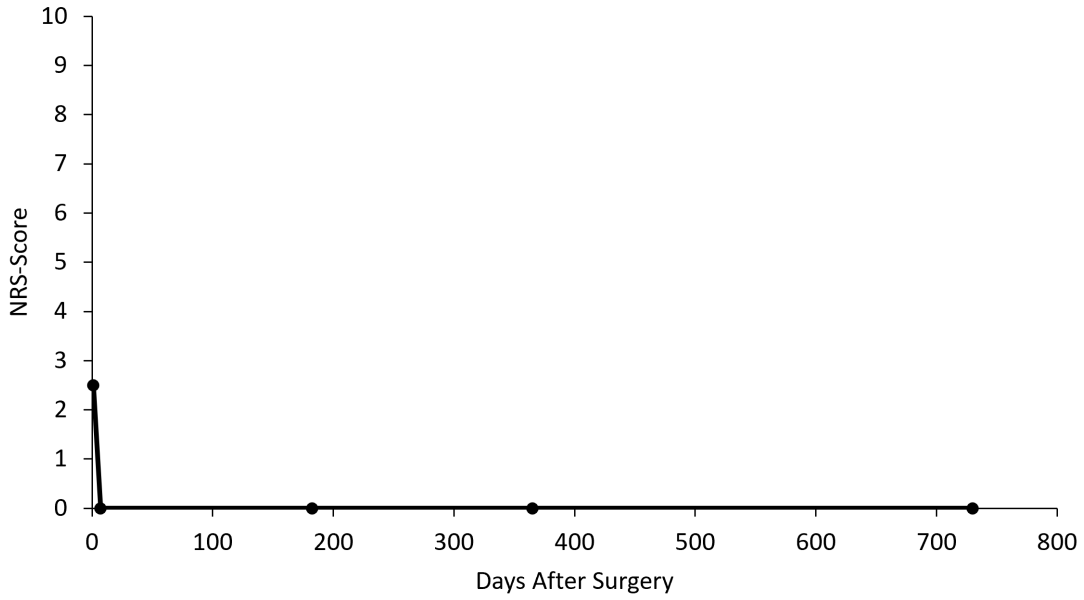


Figure I.16. Individual Trajectory Plot (I16)

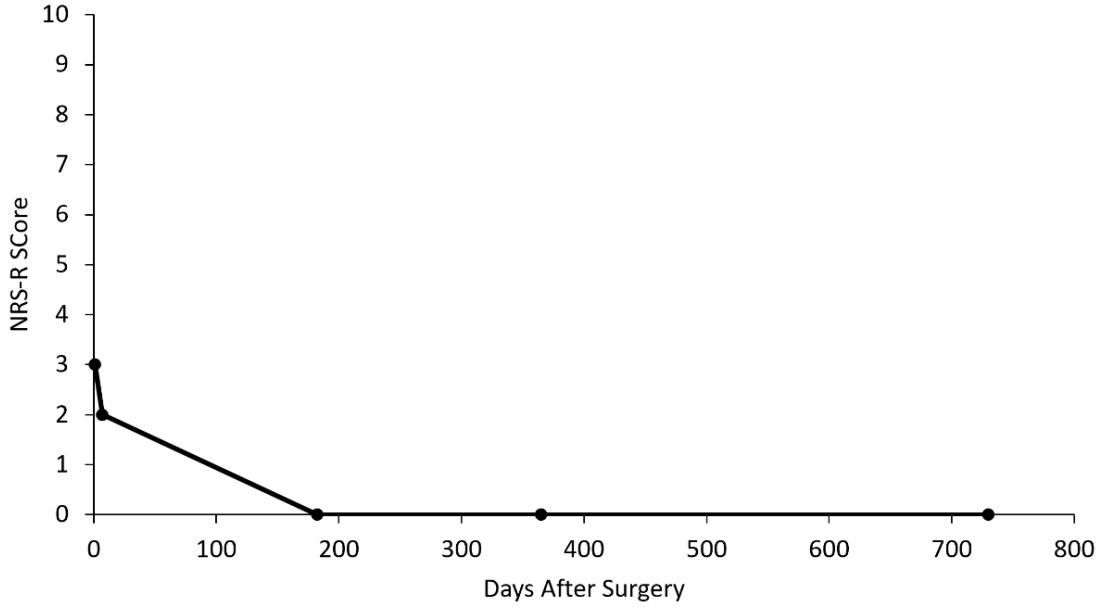


Figure I.17. Individual Trajectory Plot (I17)

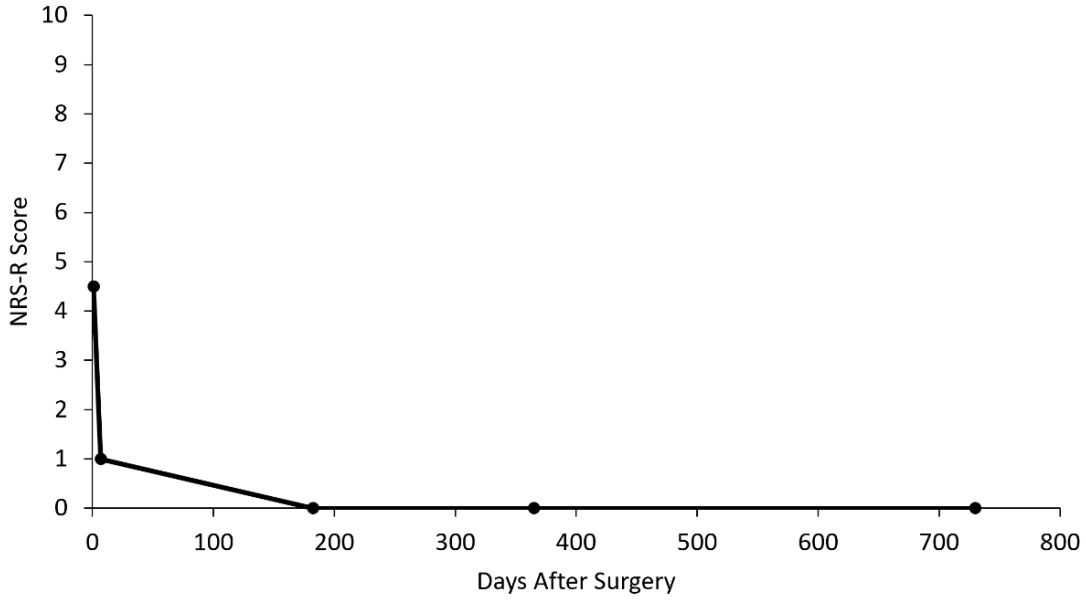


Figure I.18. Individual Trajectory Plot (I18)

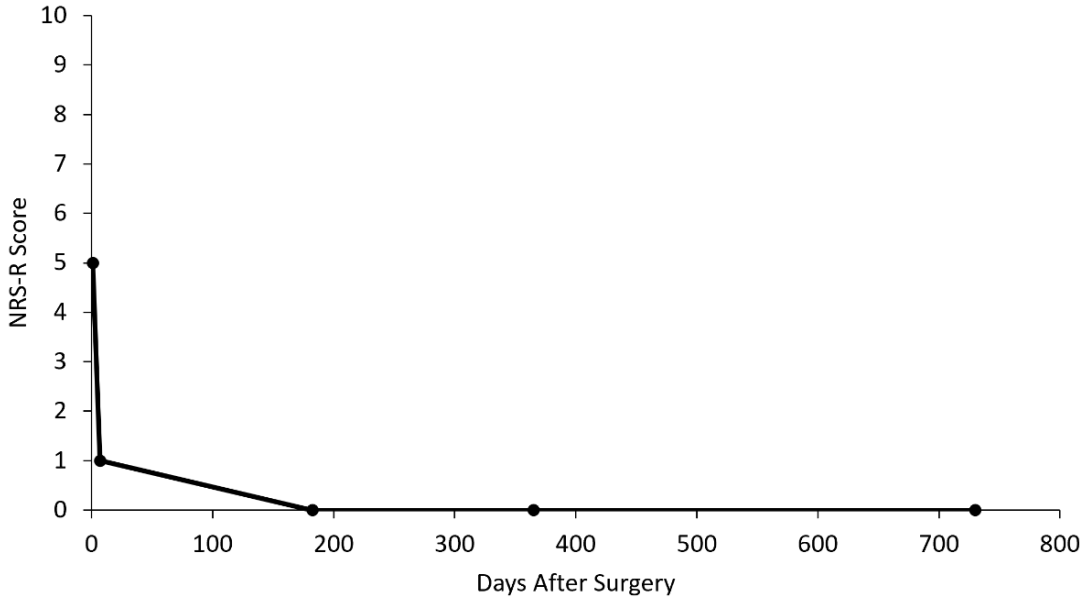


Figure I.19. Individual Trajectory Plot (I19)

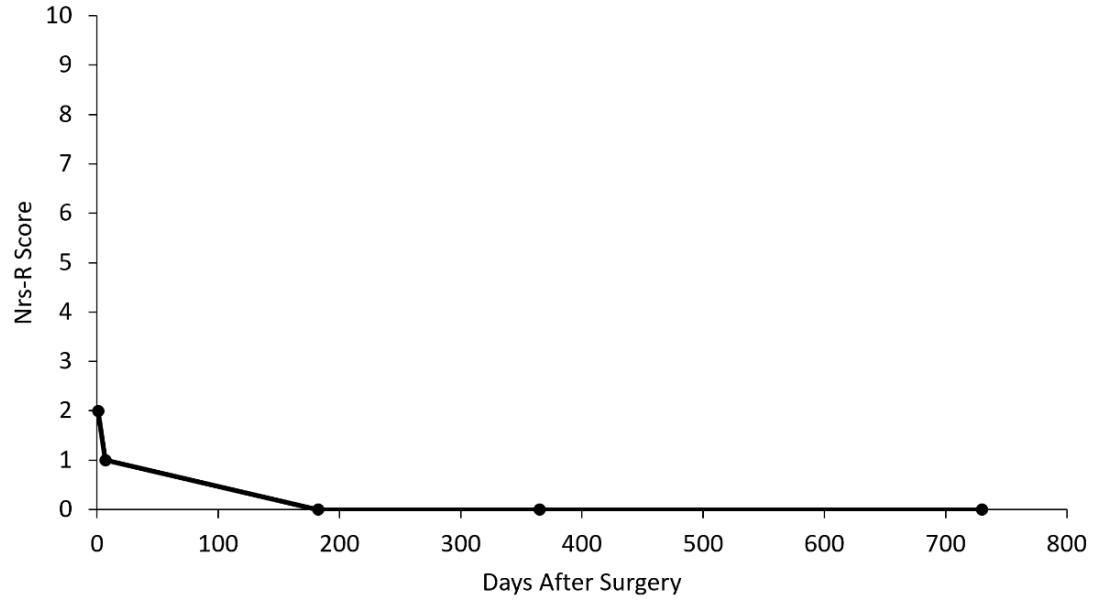
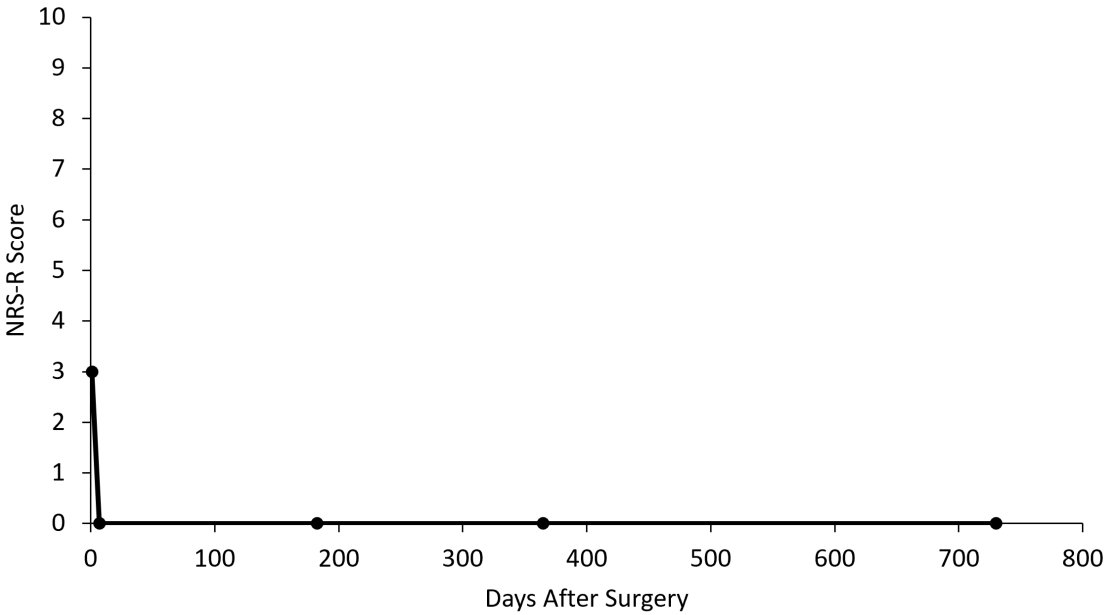


Figure I.20. Individual Trajectory Plot (I20)



Appendix J. Unresolved Persistent Subgroup Individual Trajectory Plots

Figure J.1. Individual Trajectory Plot (J1)

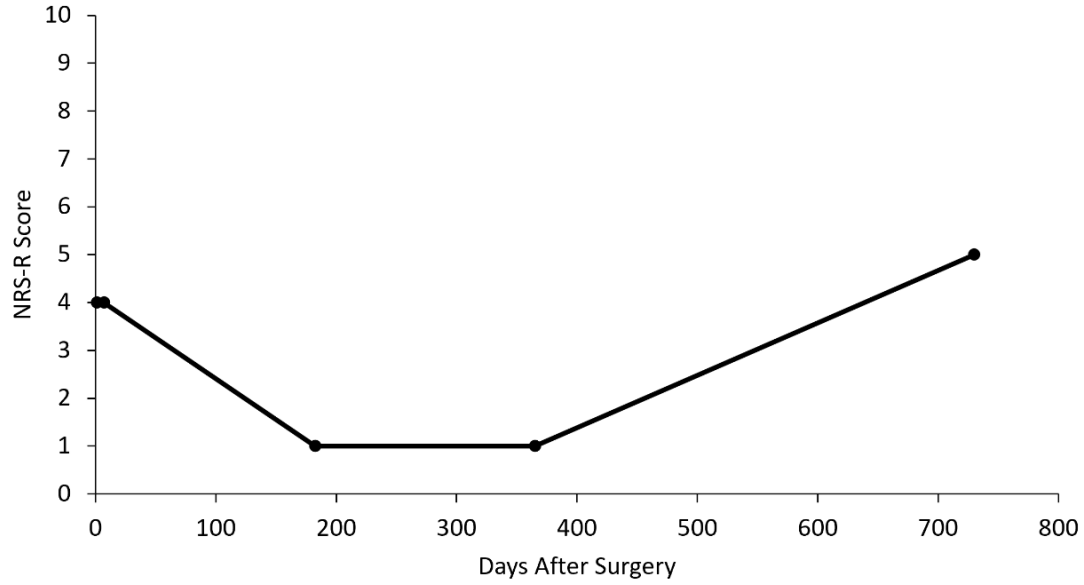


Figure J.2. Individual Trajectory Plot (J2)

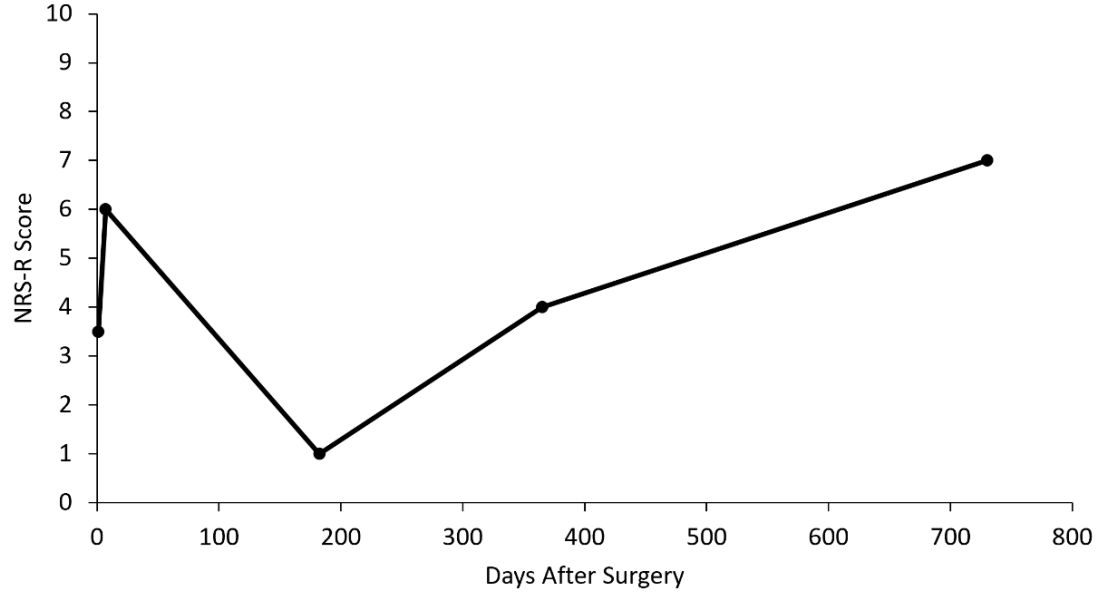


Figure J.3. Individual Trajectory Plot (J3)

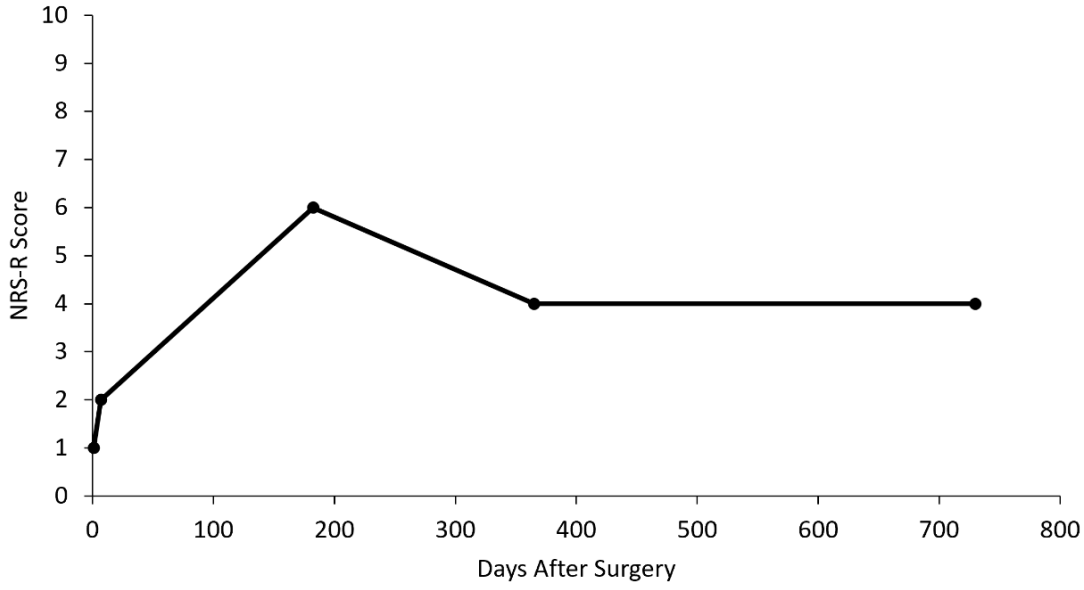


Figure J.4. Individual Trajectory Plot (J4)

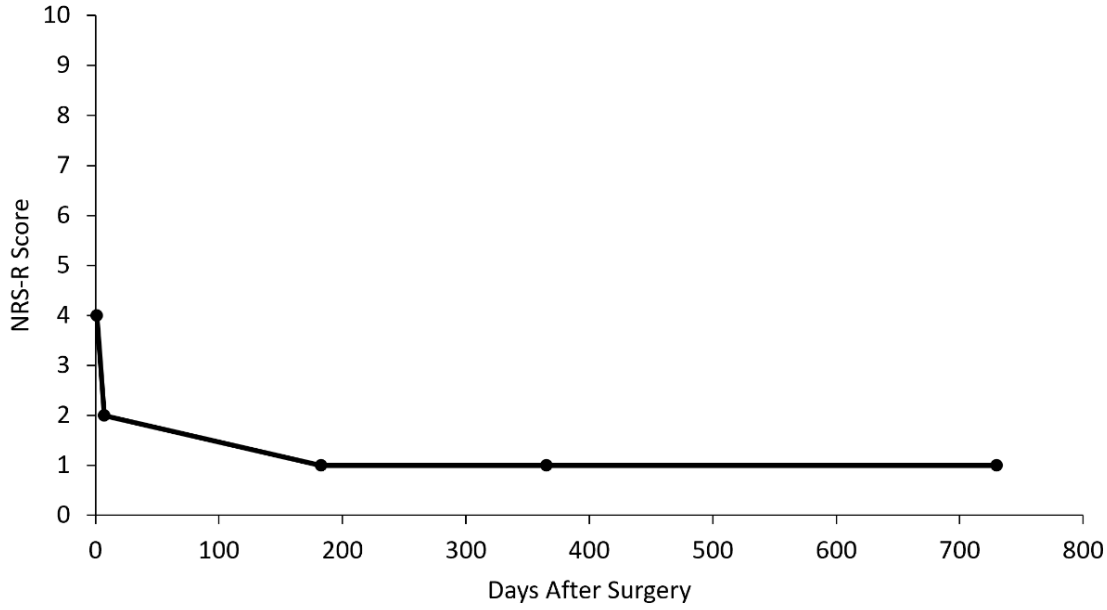


Figure J.5. Individual Trajectory Plot (J5)

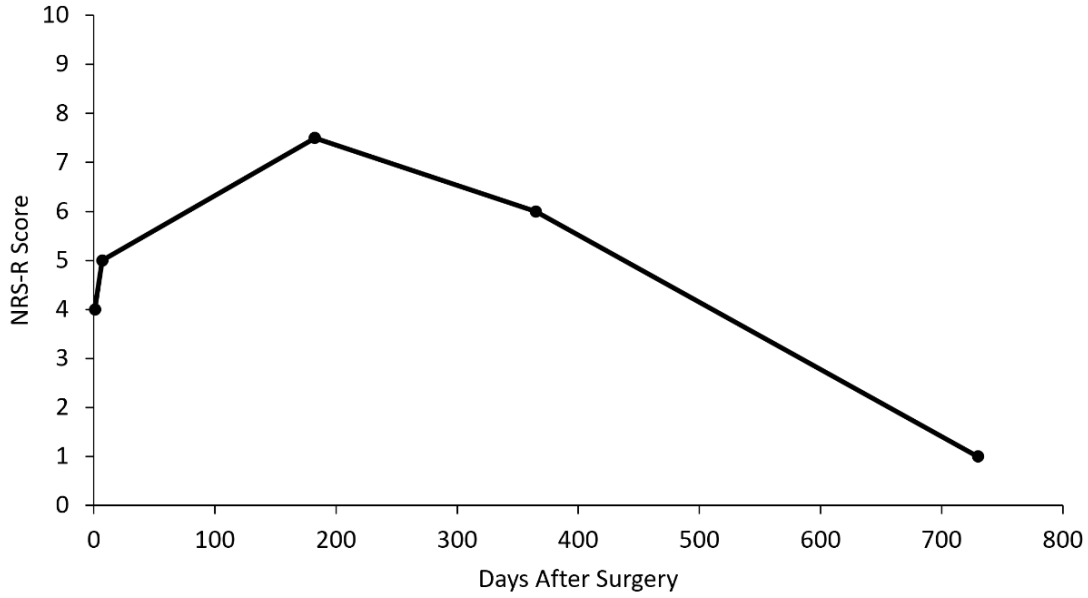


Figure J.6. Individual Trajectory Plot (J6)

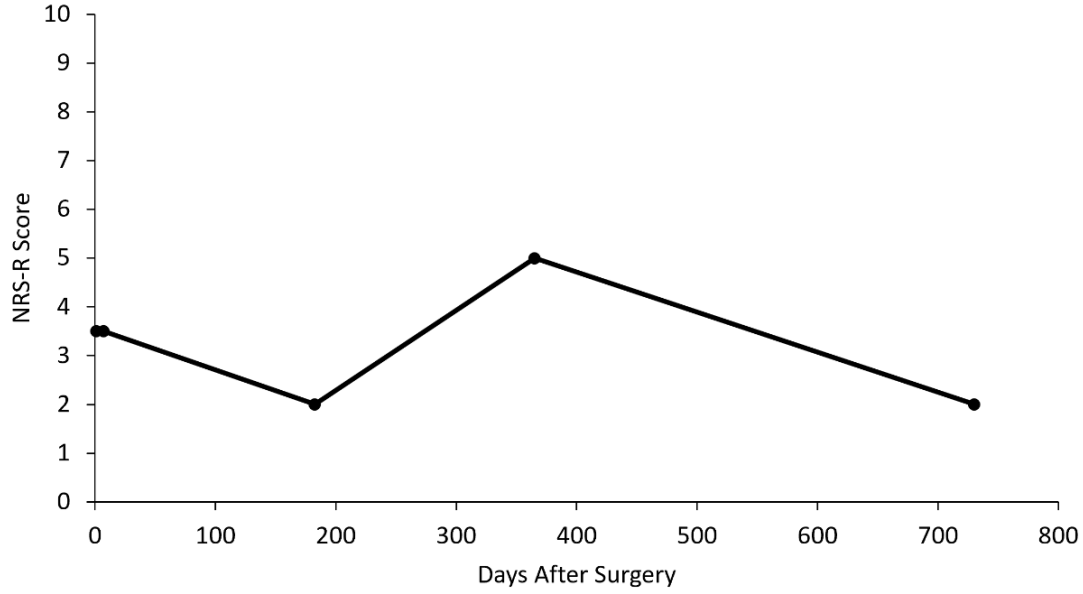


Figure J.7. Individual Trajectory Plot (J7)

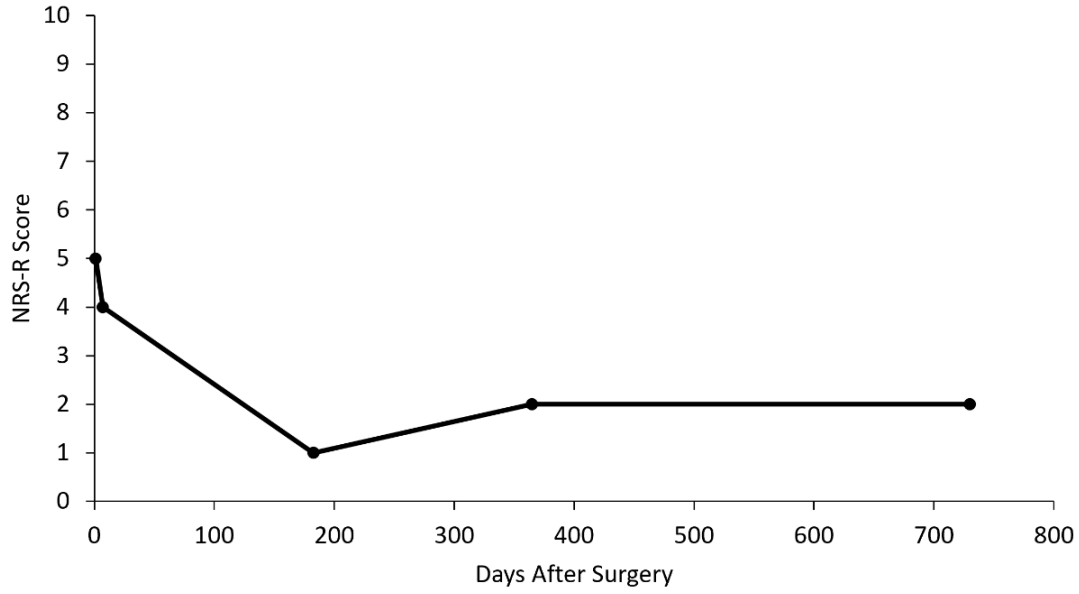


Figure J.8. Individual Trajectory Plot (J8)

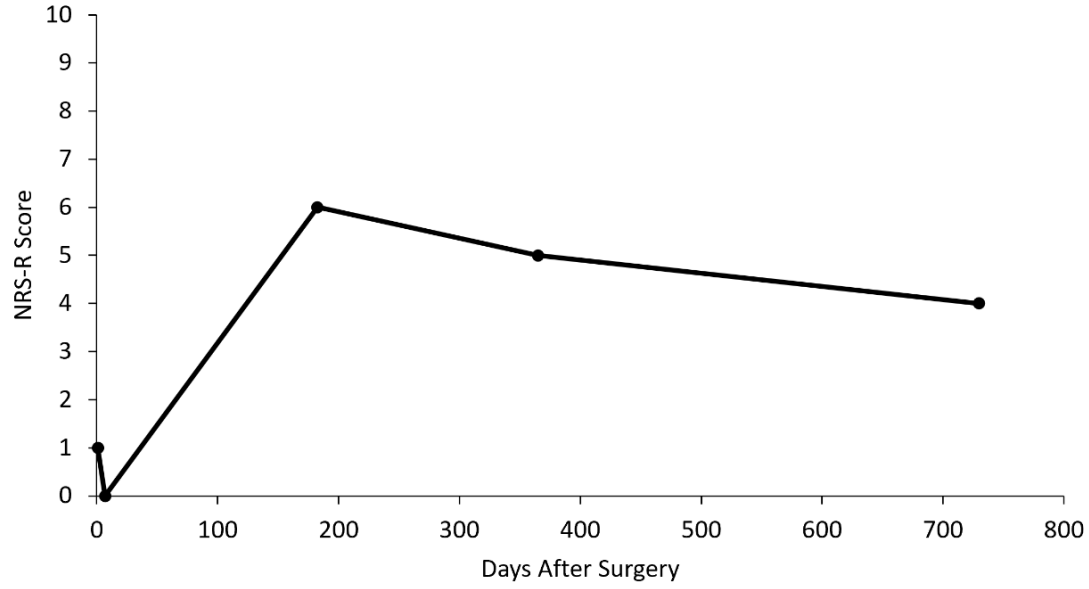


Figure J.9. Individual Trajectory Plot (J9)

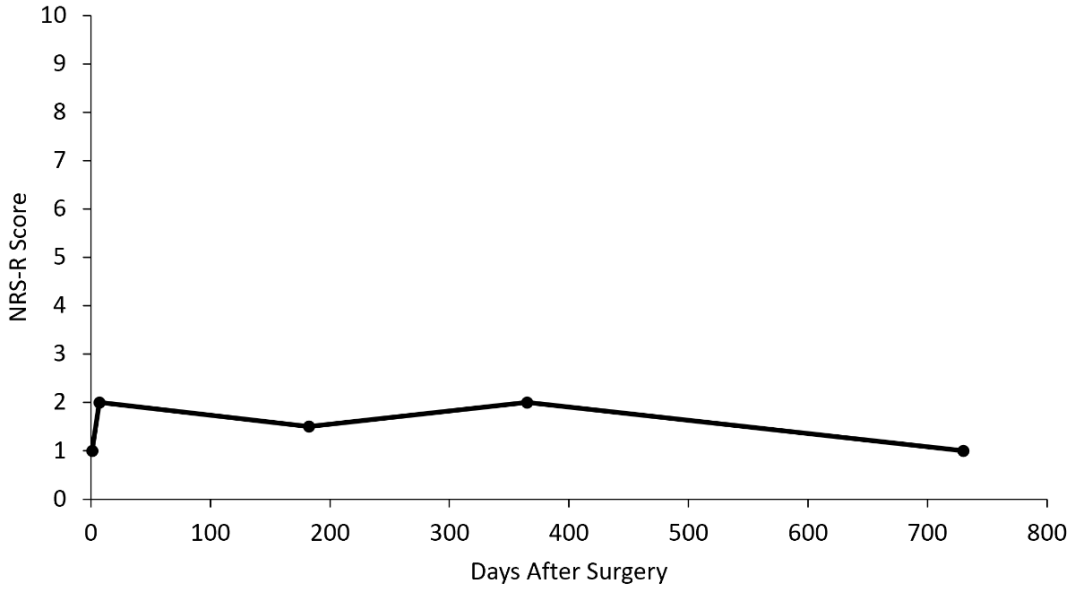


Figure J.10. Individual Trajectory Plot (J10)

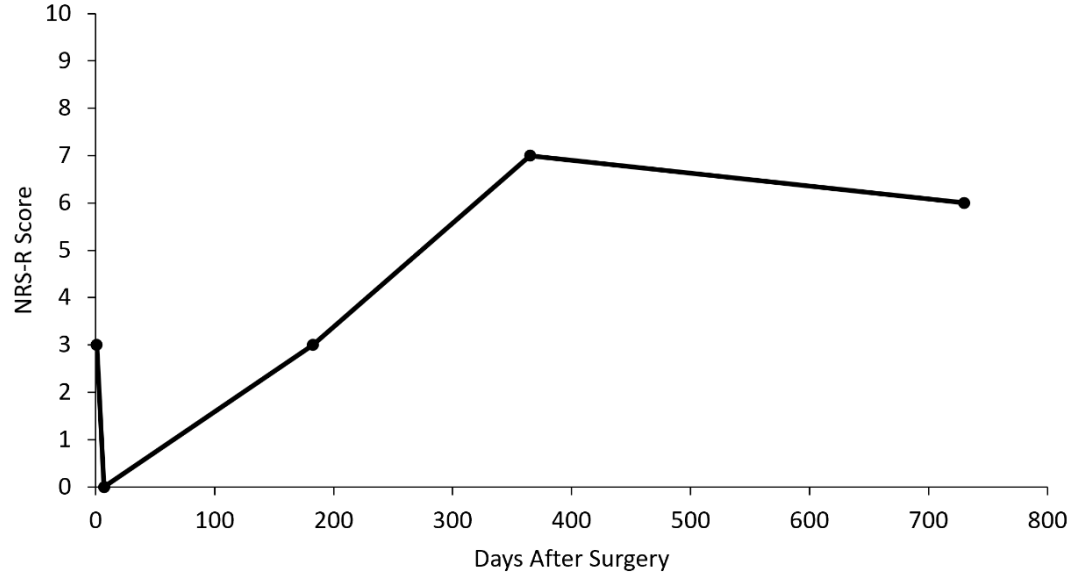


Figure J.11. Individual Trajectory Plot (J11)

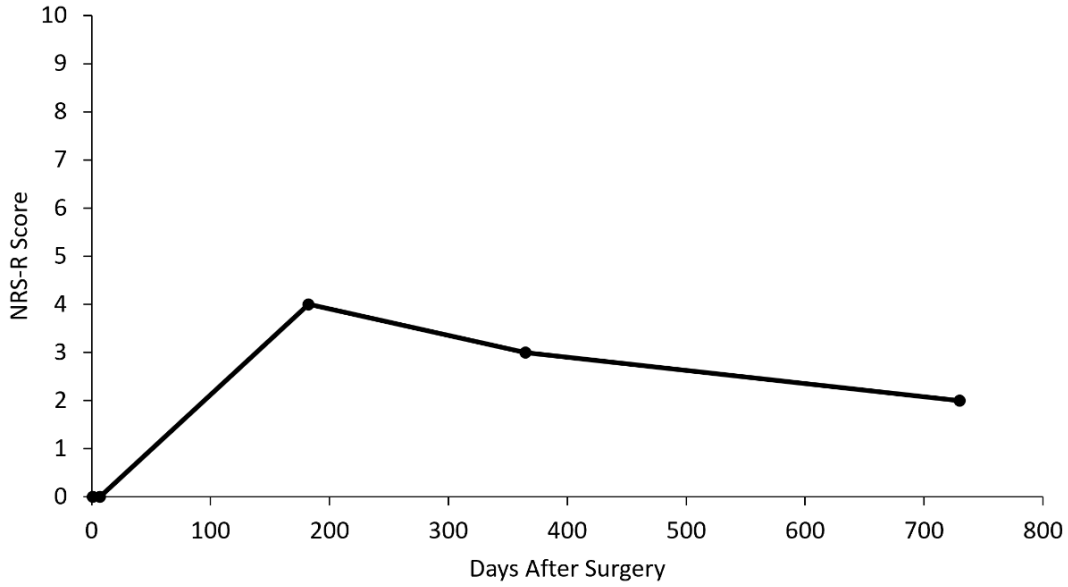
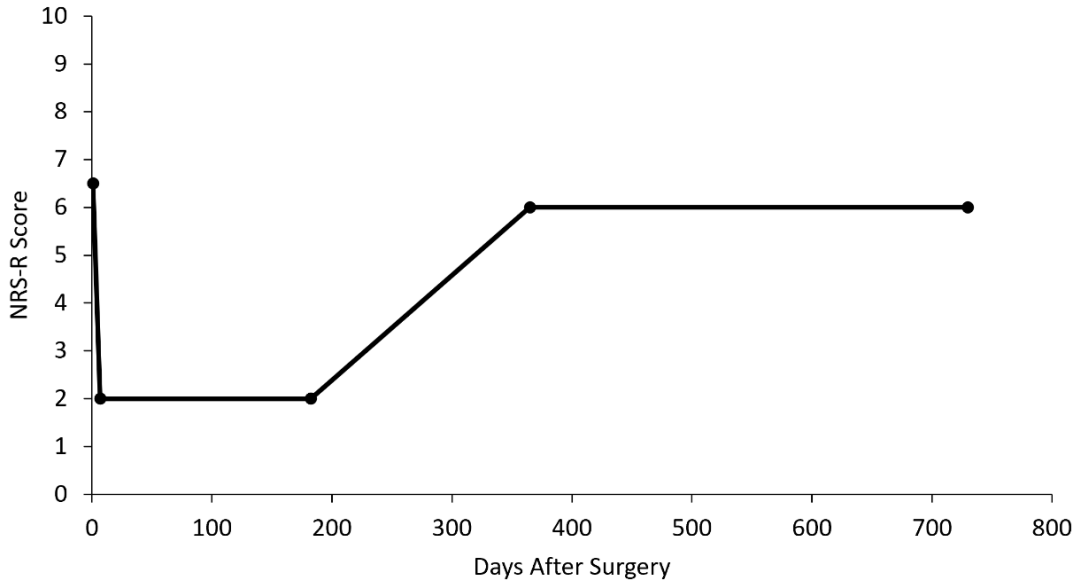


Figure J.12. Individual Trajectory Plot (J12)



Appendix K. Resolved Episodic Subgroup Individual Trajectory Plots

Figure K.1. Individual Trajectory Plot (K1)

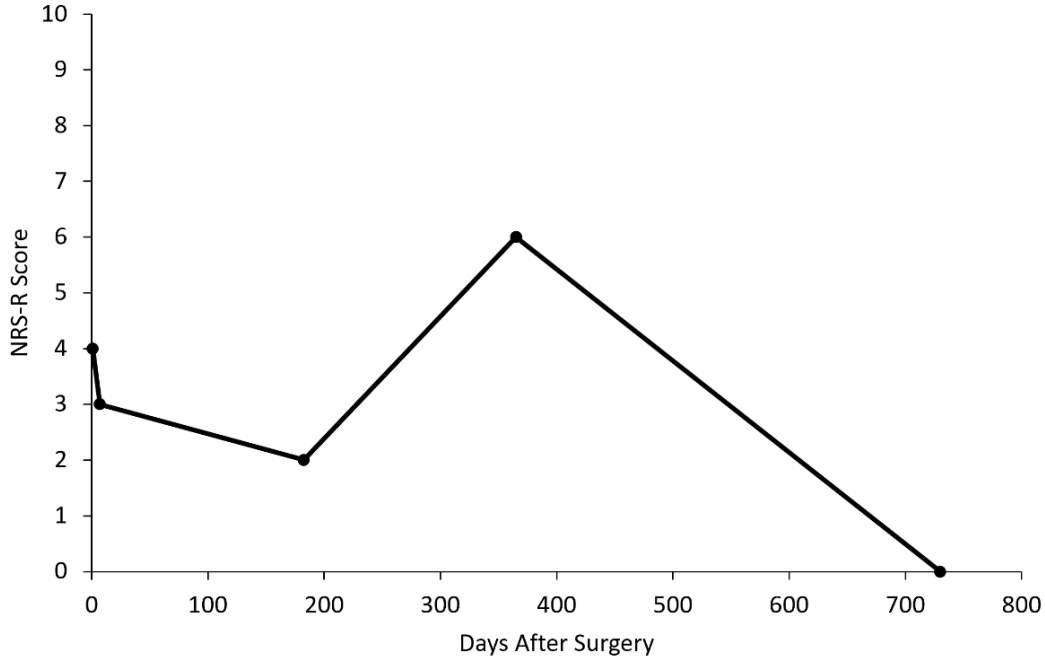


Figure K.2. Individual Trajectory Plot (K2)

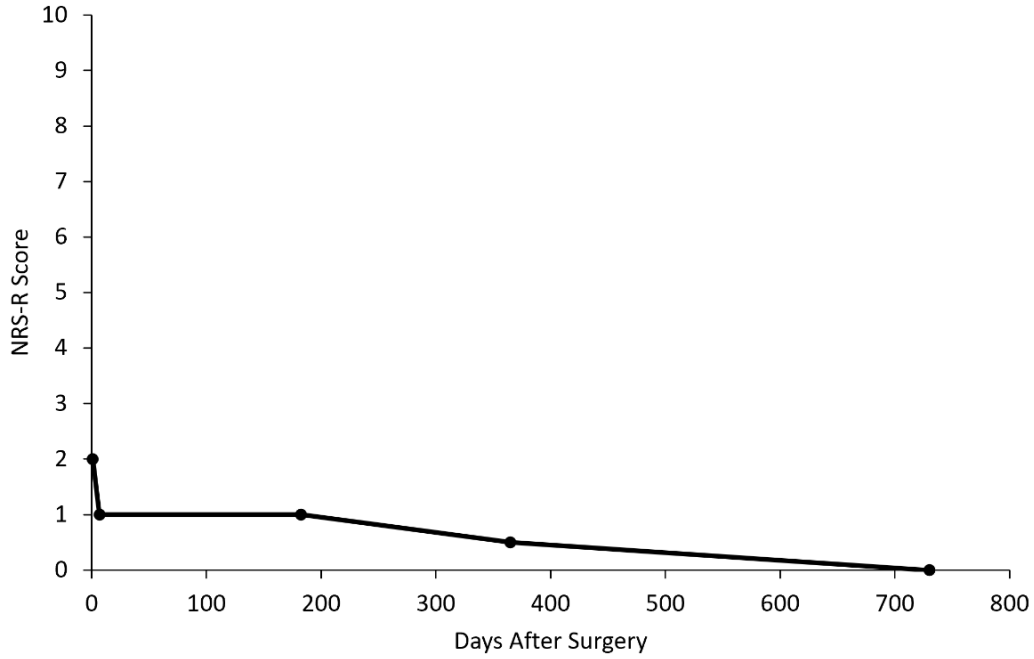


Figure K.3. Individual Trajectory Plot (K3)

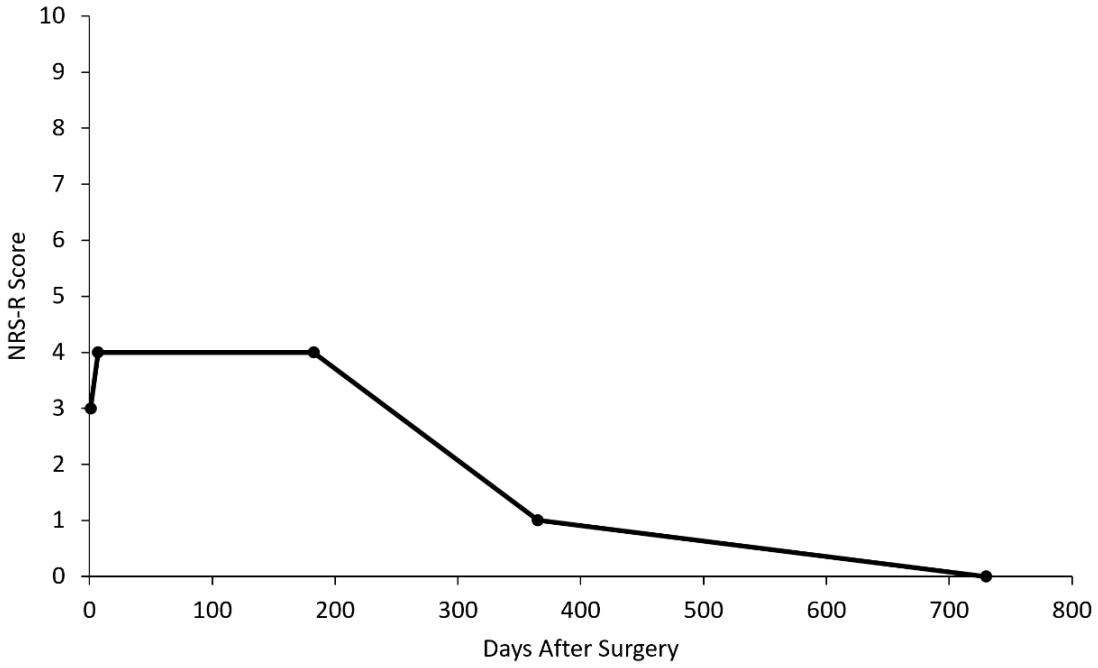


Figure K.4. Individual Trajectory Plot (K4)

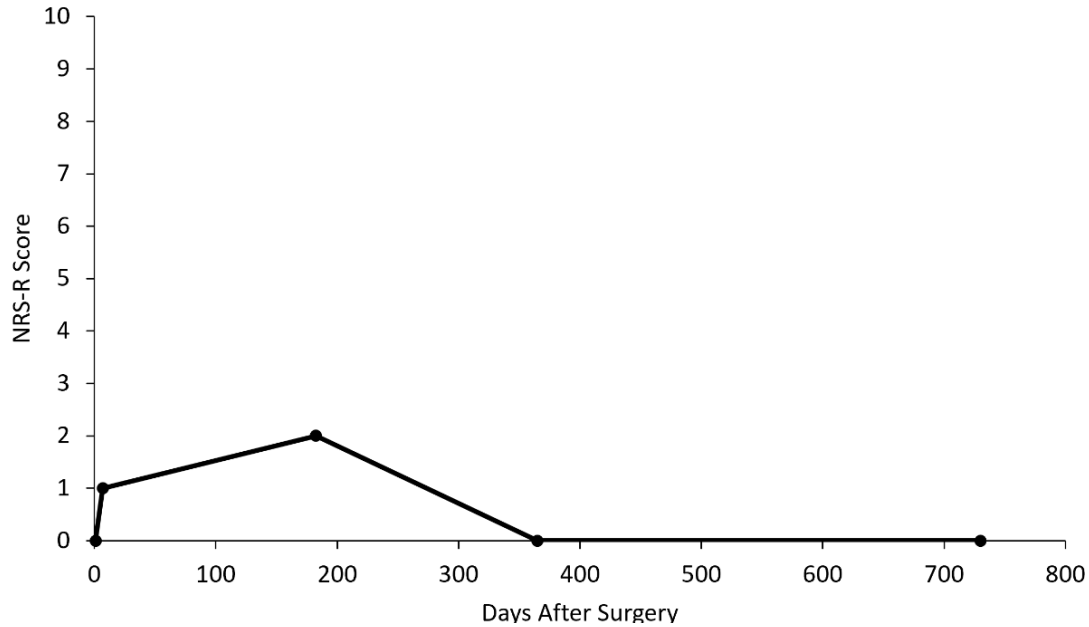


Figure K.5. Individual Trajectory Plot (K5)

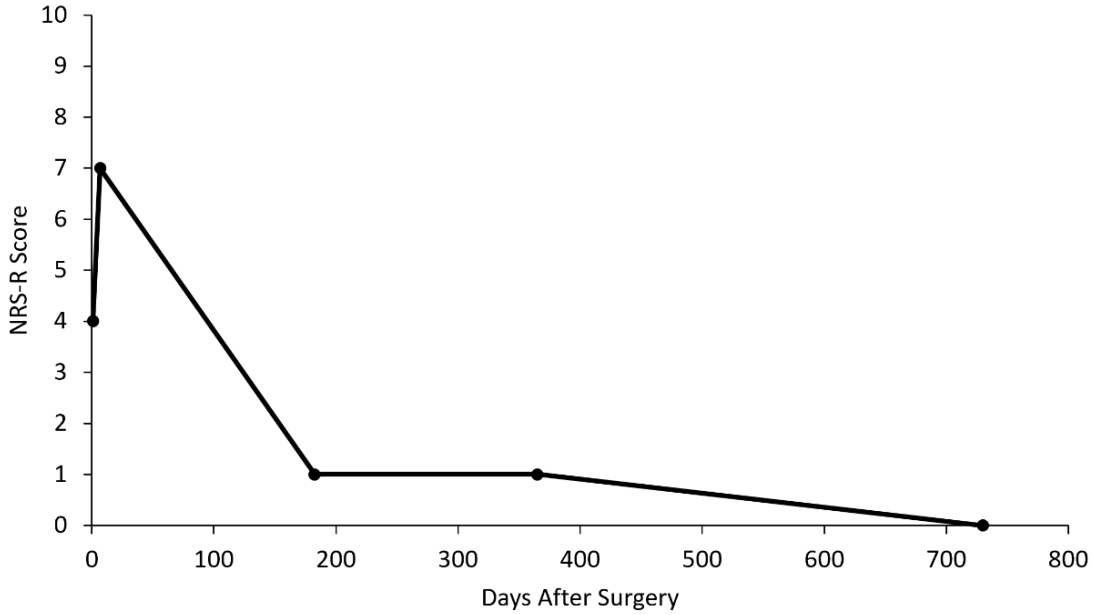


Figure K.6. Individual Trajectory Plot (K6)

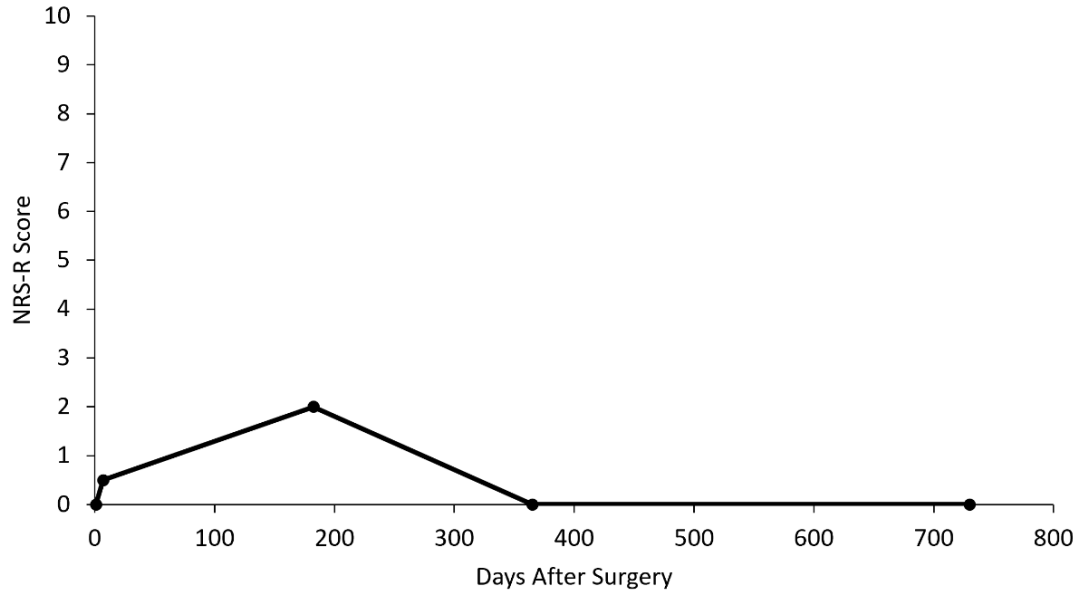
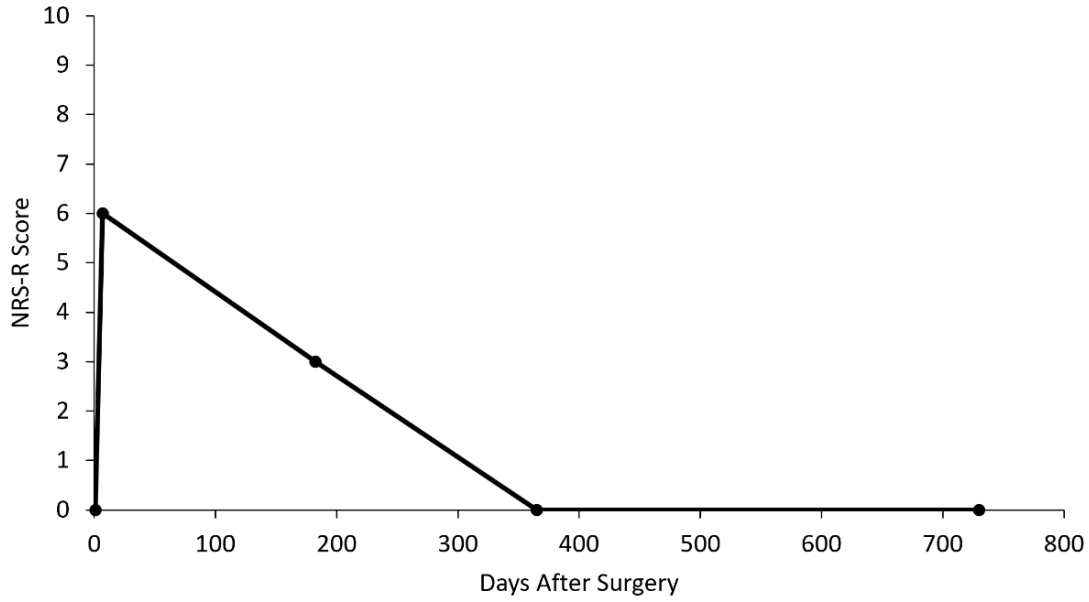


Figure K.7. Individual Trajectory Plot (K7)



Appendix L. Resolved Persistent Subgroup Individual Trajectory Plots

Figure L.1 Individual Trajectory Plot (L1)

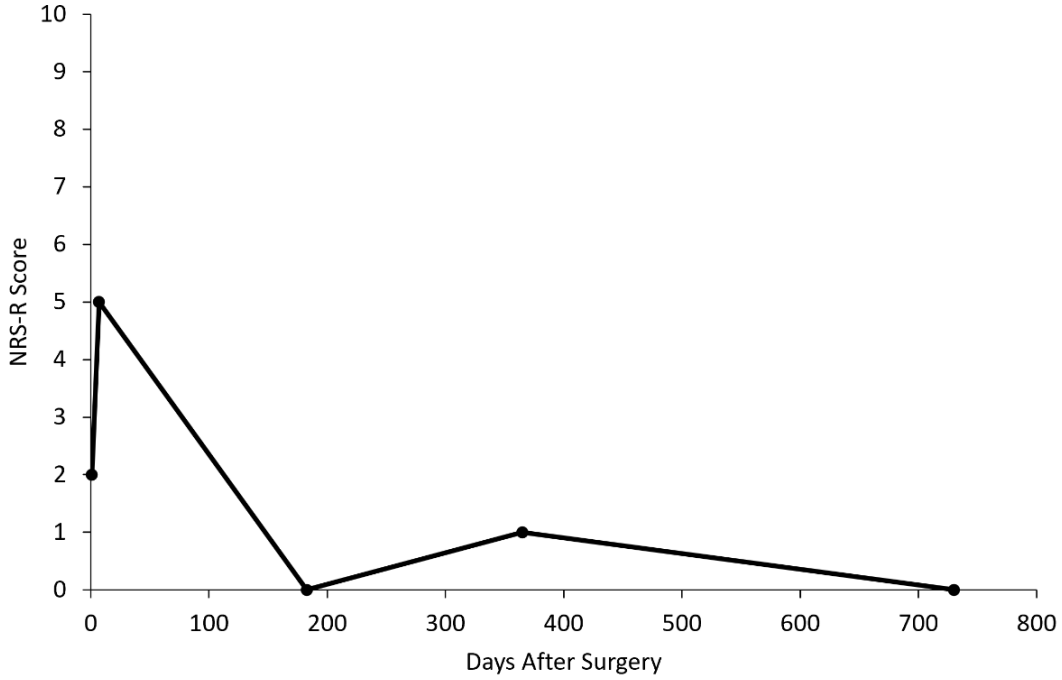
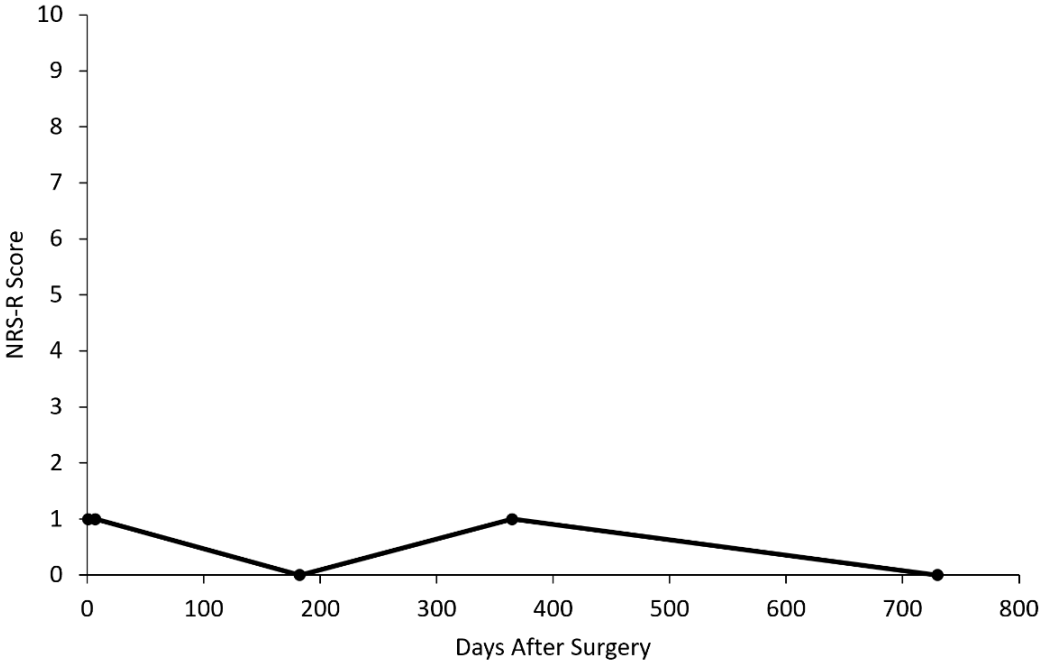


Figure L.2. Individual Trajectory Plot (L2)



L.3. Individual Trajectory Plot (L3)

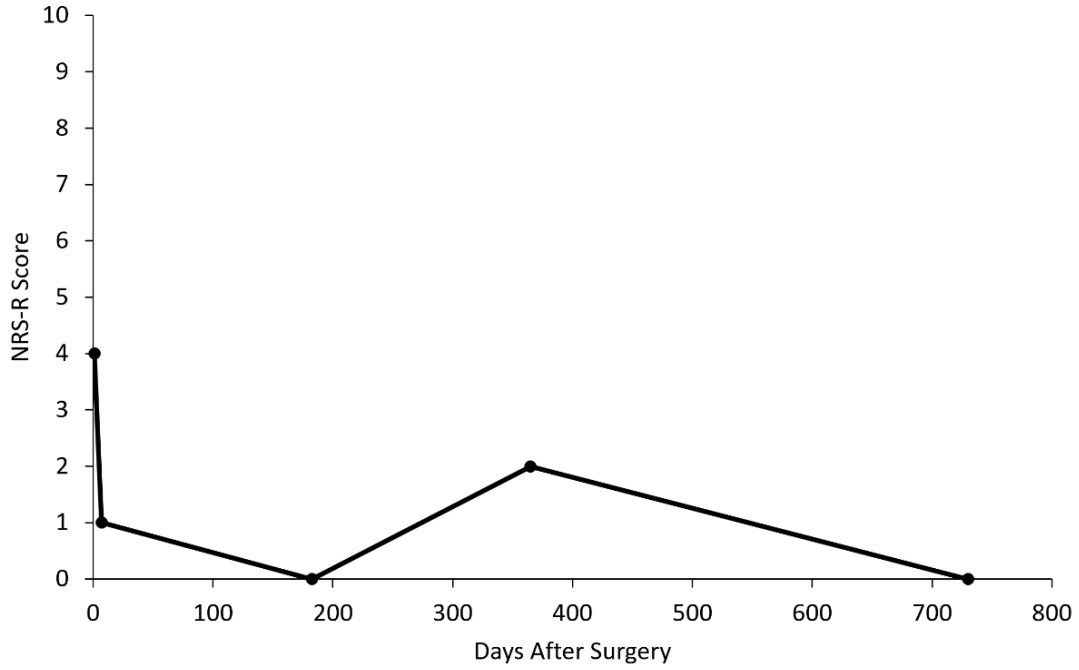


Figure L.4. Individual Trajectory Plot (L4)

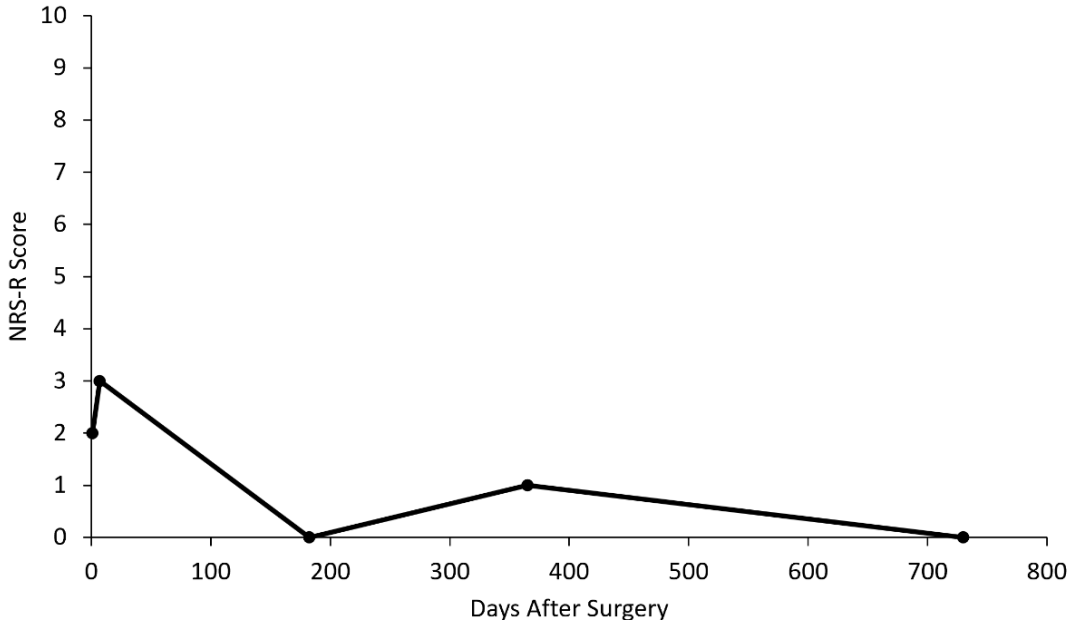


Figure L.5. Individual Trajectory Plot (L5)

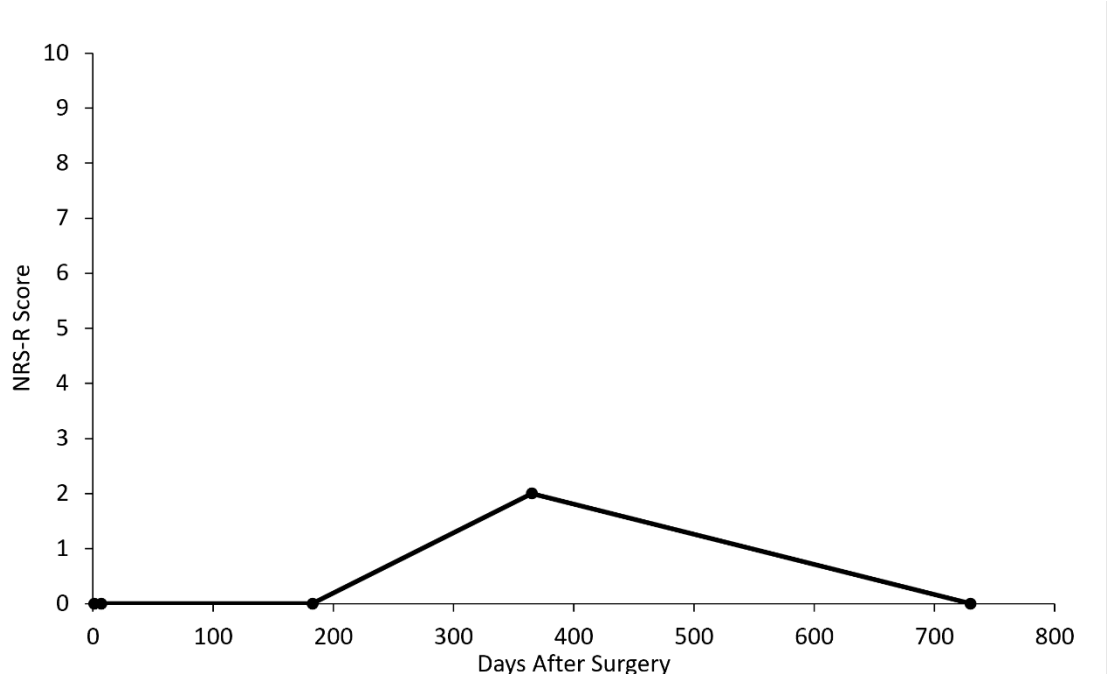


Figure L.6. Individual Trajectory Plot (L6)

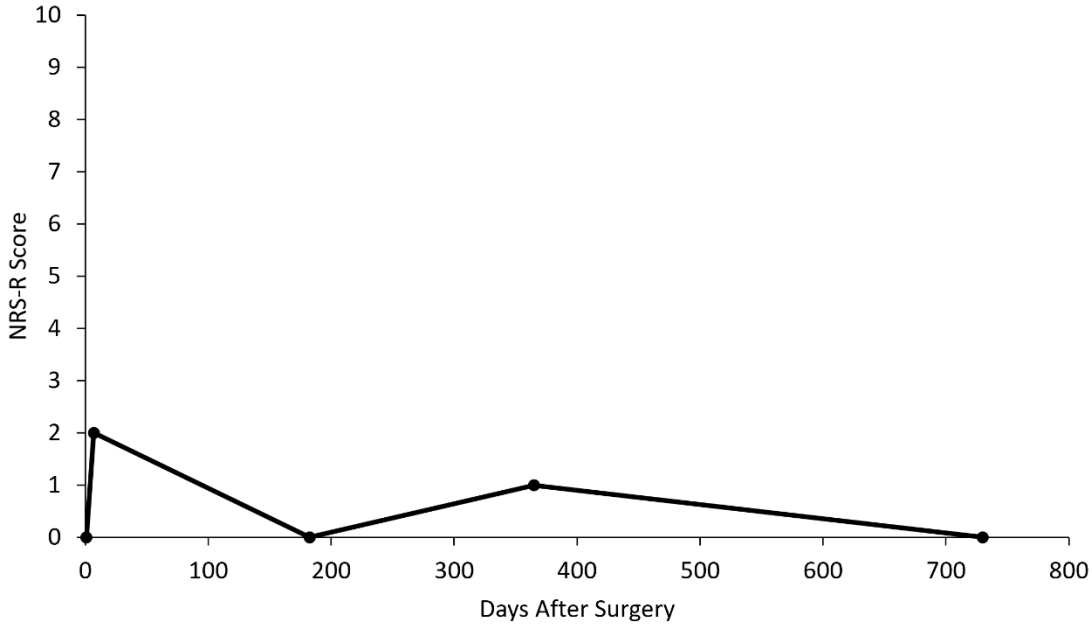
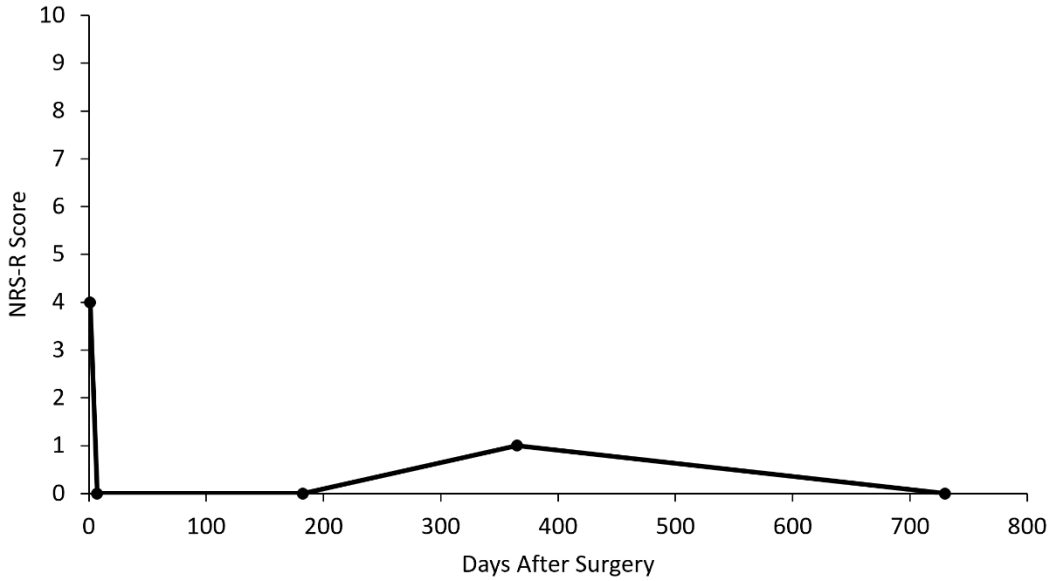


Figure L.7. Individual Trajectory Plot (L7)



Appendix M. Subgroup Who Did Not Report Pain at Any Follow-up Individual Plots

Figure M.1. Individual Trajectory Plot (M1)

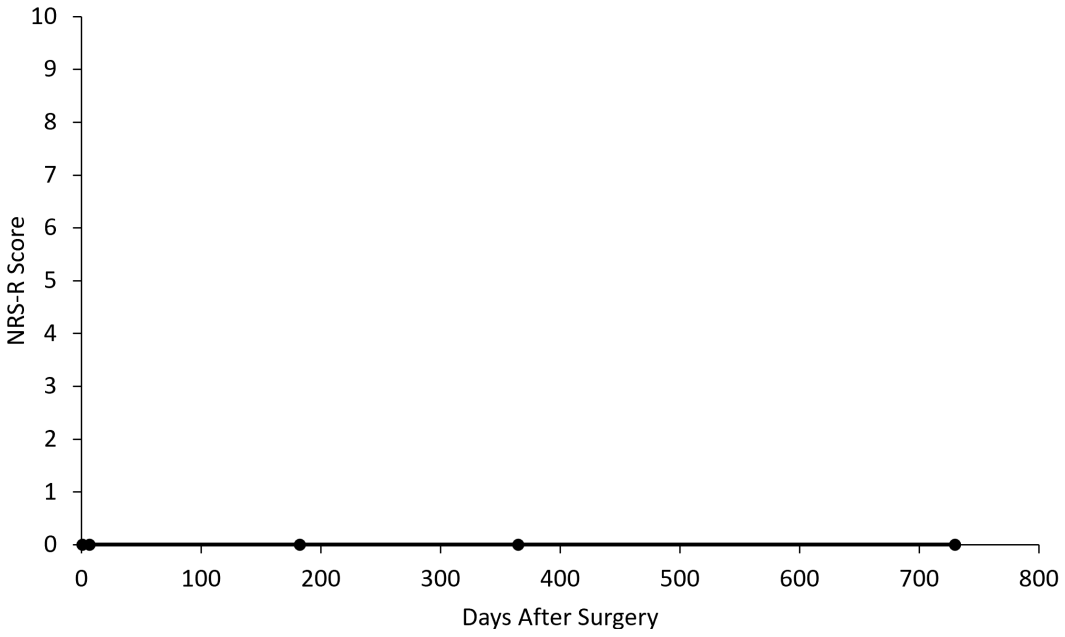


Figure M.2. Individual Trajectory Plot (M2)

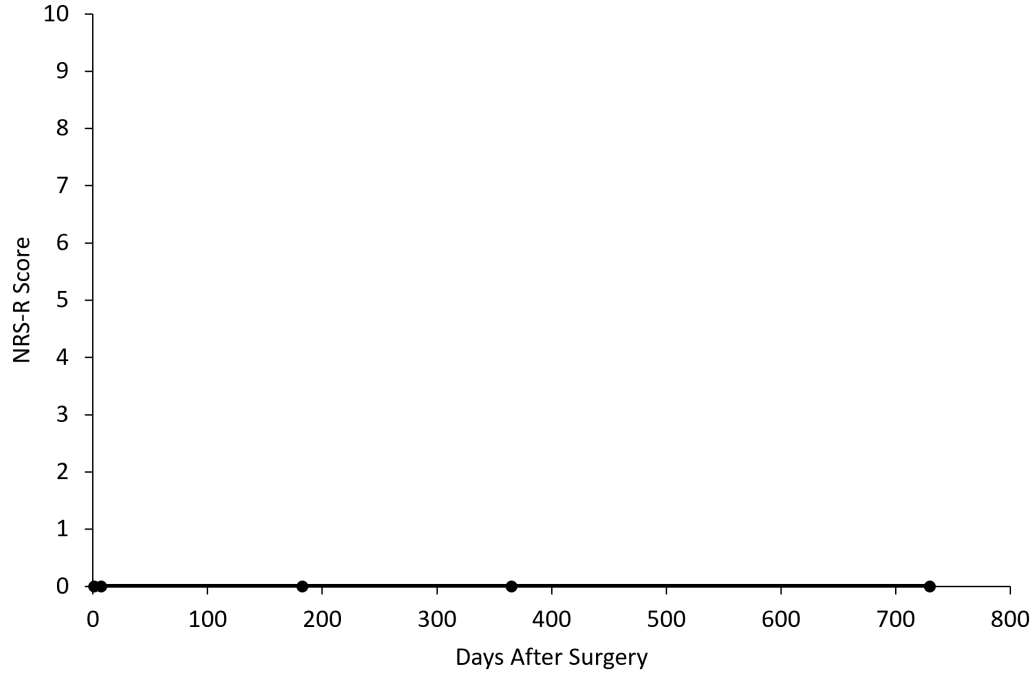


Figure M.3. Individual Trajectory Plot (M3)

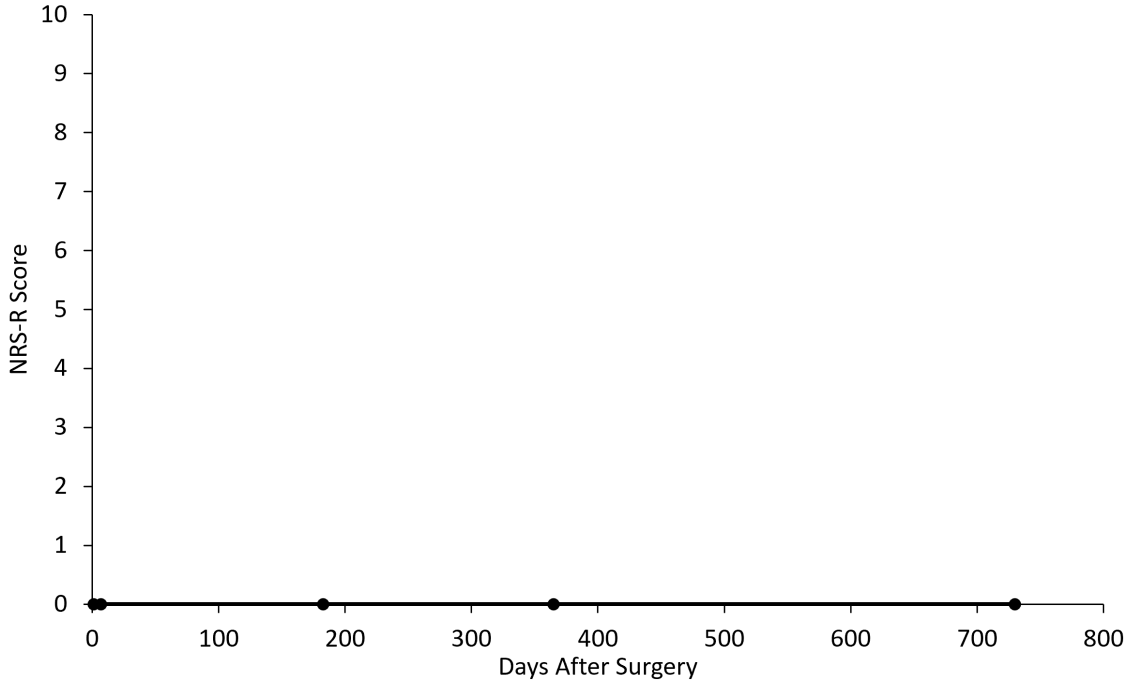


Figure M.4. Individual Trajectory Plot (M4)

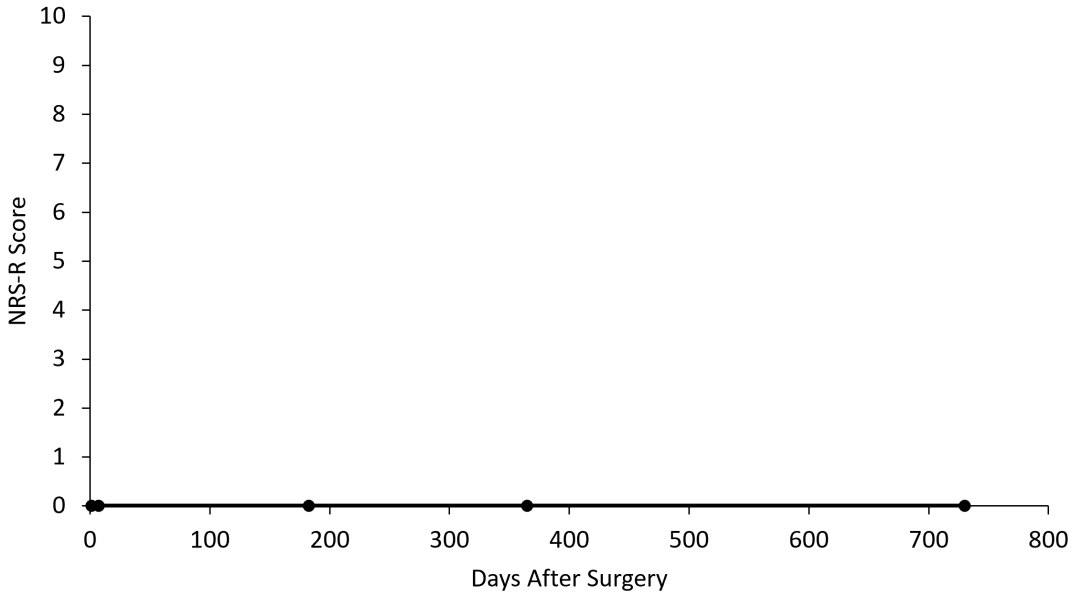
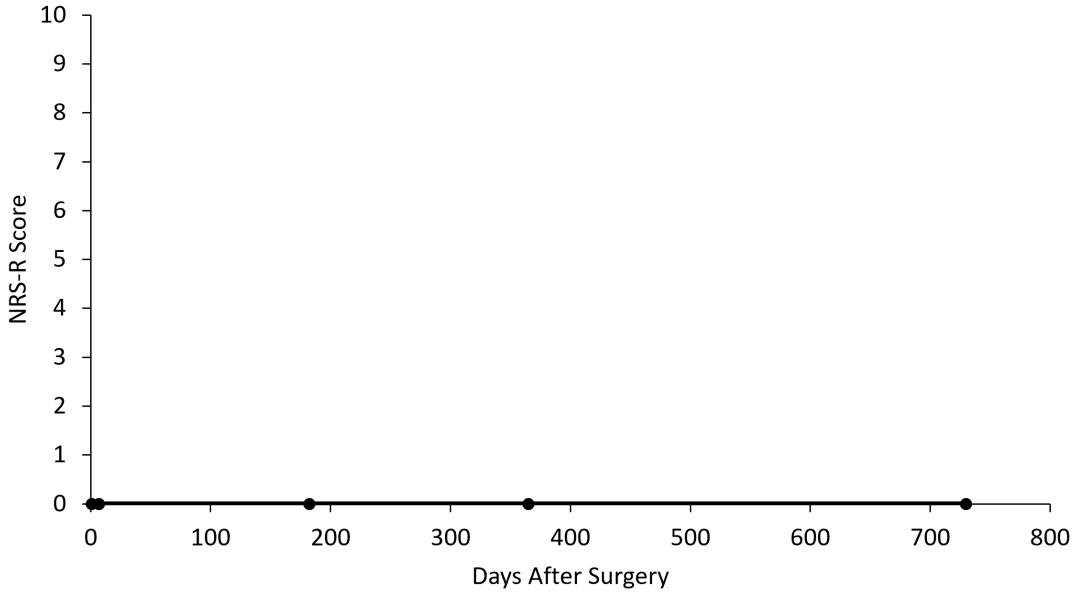


Figure M.5. Individual Trajectory Plot (M5)



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