Neuropathic pain after thoracotomy: tracking signs and symptoms before and at monthly intervals following surgery

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ORIGINAL ARTICLE

Neuropathic pain after thoracotomy: Tracking signs and symptoms before and at monthly intervals following surgery

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Abstract

Background: As the development of neuropathic symptoms contributes to pain severity and chronification after surgery, their early prediction is important to allow targeted treatment.

Objectives: We longitudinally investigated trajectories of signs and symptoms in patients undergoing thoracotomy and assessed whether and at which time they were related to the development of neuropathic pain symptoms 6 months after surgery.

Methods: Presurgical and 6 monthly postsurgical assessments included questionnaires for mental and physical well-being (e.g., depression/anxiety, pain catastrophizing, sleep quality, neuropathic pain symptoms), and quantitative sensory testing (QST).

Results: QST trajectories indicated nerve impairment of the surgery site with predominant loss of function. Signs of recovery towards the end of the assessment period were observed for some tests. Unsupervised cluster analysis with NPSI scores 6 months after surgery as clustering variable identified one group with no/low levels of neuropathic symptoms and one with moderate levels. The two groups differed w.r.t. several signs and symptoms already at early time points. Notably, neuropathic pain anywhere in the body differed already preoperatively and sleep impairment differentiated the two groups at all time points. Regression analysis revealed three factors that seemed particularly suited to predicted 6 months NPSI scores, namely preoperative neuropathic pain symptoms, with contributions from sleep impairment 1 month after surgery and the presence of dynamic mechanical allodynia 3 months after surgery.

Conclusions: Clinical routine should focus on the individual's physiological state, including pre-existing neuropathic pain and sleep quality to identify patients early who might be at risk to develop chronic post-surgical neuropathic pain.

Significance: Development of neuropathies contributes to pain severity and pain chronification after surgery. Here we demonstrate trajectories of quantitative sensory tests (assessed at monthly intervals for 6 months after surgery) that reveal accurate time courses of gain/loss of nerve function following thoracotomy. Independent of the degree of neuropathic signs after surgery, the main predictors for post-surgical neuropathic pain are self-reported neuropathic pain before surgery and sleep quality shortly after surgery.

1 | INTRODUCTION

Chronic post-surgical pain (CPSP) is increasingly recognized as major complication of many surgical procedures. Across surgery types, the prevalence of moderate CPSP is around 13% 12 months after surgery (Fletcher et al., 2015). Risk factors identified for CPSP include type of surgery (Fletcher et al., 2015), existence of preoperative pain (Abbott, Tyni-Lenne, & Hedlund, 2011; Fletcher et al., 2015), severity of acute postoperative pain (Bayman, Parekh, Keech, Selte, & Brennan, 2017; Fletcher et al., 2015), age (Pereira et al., 2017), psychological distress (in particular pain catastrophizing (Jackson, Tian, Wang, Iezzi, & Xie, 2016; Weinrib et al., 2017), anxiety (Jackson et al., 2016; Weinrib et al., 2017) and depression (Jackson et al., 2016; Weinrib et al., 2017)). As a neuropathic component appears to contribute to pain severity and chronification (Duale et al., 2014; Fletcher et al., 2015; P. M. Lavand'homme, Grosu, France, & Thienpont, 2014), it has been suggested that diagnosis of neuropathic symptoms, as early as possible, is important (Hayes, Browne, Lantry, & Burstal, 2002; P. Lavand'homme, 2017) to allow targeted treatment.

The prevalence of CPSP with a neuropathic component differs across surgical procedures (Duale et al., 2014; Haroutiunian, Nikolajsen, Finnerup, & Jensen, 2013), probably because of different likelihoods of surgery-related nerve injury. Besides breast surgery, thoracic surgery is associated with the highest rates of neuropathic CPSP (Duale et al., 2014; Haroutiunian et al., 2013). The 6-month prevalence of CPSP following thoracotomy is around 35%–60% (Bayman & Brennan, 2014; Montes et al., 2015) with 30%–40% of these patients displaying probable or definitive signs of neuropathy (Duale et al., 2014; Guastella et al., 2011; Haroutiunian et al., 2013). In addition to a history of a relevant neurological lesion and/or a neuroanatomically plausible pain distribution, the diagnosis of neuropathic pain requires the presence of sensory signs (Finnerup et al., 2016). Sensory signs can be negative (i.e., loss of function) or positive (i.e., gain of function) (Treede et al., 2008) and can be assessed using questionnaires such as the Neuropathic Pain Symptom Inventory (NPSI) (Bouhassira et al., 2004) or examinations such as quantitative sensory testing (QST) (Rolke et al., 2006). While both methods have been used to confirm probable neuropathic pain following thoracotomy (Duale et al., 2014; Guastella et al., 2011), no study has performed QST at multiple monthly time points after surgery to characterize trajectories of neuropathic signs. Consequently, important questions that remain unanswered concern the time courses of gain and loss of function following thoracotomy and whether the presence of these signs before or shortly after surgery can predict the degree of neuropathic CPSP.

Therefore, the main intention of this article was to describe QST trajectories after thoracotomy with a high density of testing time points to describe onset and recovery of neuropathic signs after thoracotomy. A second aim was to predict the chronification of neuropathic symptoms using QST performed at early post-surgical time points (up to 3 months after surgery). Lastly, questionnaires were used as additional measures to explain further variance.

2 | METHODS

To answer the research questions outlined above, we investigated patients undergoing posterolateral thoracotomy before (baseline) and at monthly intervals up to 6 months following surgery. Baseline assessment included questionnaires to assess pre-existing neuropathic pain anywhere in the body, anxiety, depression, pain catastrophizing and sleep impairment, and a brief QST protocol. Monthly post-surgical assessments included the same questionnaires and a more extensive QST assessment (applying the protocol of the German Research Network on Neuropathic Pain (Rolke et al., 2006), plus thermal wind-up). As outcome measure, we used NPSI scores 6 months after surgery.

2.1 | Study design

This study followed a prospective design investigating the development of neuropathic symptoms, using QST and questionnaires in patients before and up to 6 months after posterolateral thoracotomy. The study was approved by the local ethics boards of McGill University and the Montreal General Hospital. Patients gave written consent to partake in the study and all study procedures were in accordance with the declaration of World Medical Association (2013).

2.2 | Participants

We recruited 74 participants scheduled to undergo posterolateral thoracotomy, of which 37 were included in the final analysis. As depicted in the flow chart (Figure 1), the reduction in number was primarily due to the development of complications following surgery, and missing baseline data. Patients were initially approached by clinical staff at the Montreal General Hospital during their preoperative clinical assessment and, if they expressed an interest in the study and agreed to be contacted, received more information by a member of our research team. Of the final study sample of $N = 37$, 20 were men and 17 women. The majority of patients were diagnosed with lung cancer and underwent partial or full

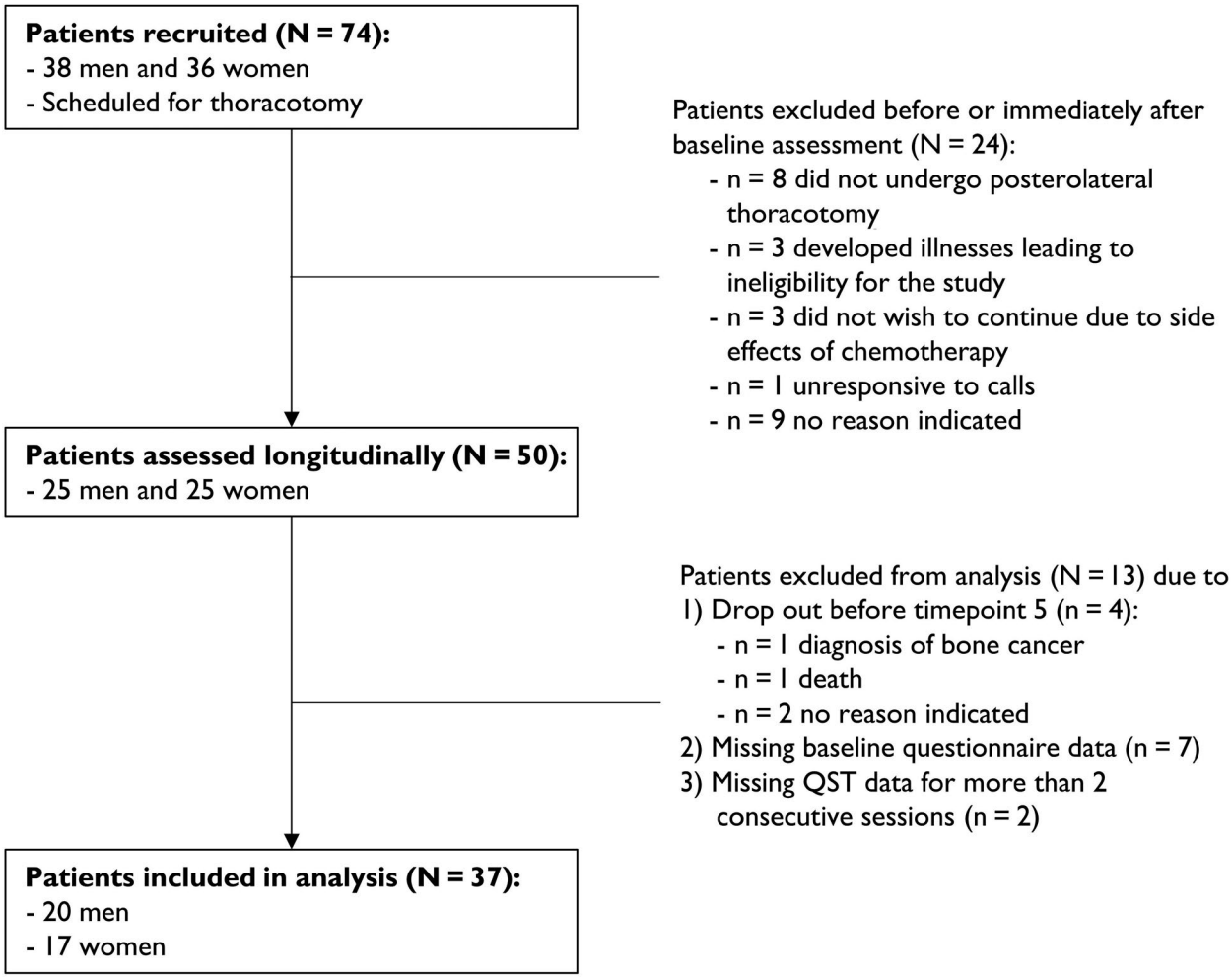

FIGURE 1 Flow chart of patient recruitment, drop outs and study population included in the final analysis

resection of one lung through a posterolateral thoracotomy (Table 1).

2.3 | Anaesthesia and post-operative analgesic regime

Two large-bore intravenous cannulas and an arterial line were placed before induction of anaesthesia.

An epidural catheter was inserted at the T4-T5 or T5-6 level and balanced General Anaesthesia was induced with a double-lumen endotracheal tube to isolate and deflate the non-dependent (operative) lung, maintaining one-lung ventilation throughout the surgery. Intraoperative anaesthesia/analgesia management was left to the attending anaesthesiologist, but always included opioids (fentanyl, sufentanyl and/or remifentanil), muscle relaxants and a gas (such as sevofluorane or desfluorane) or total intravenous anaesthesia. Once the surgery was completed and the chest tubes were in working mode, patients received ondansentron and ketorolac, were awakened and transferred to the Post Anesthesia Care Unit (PACU). The analgesia and respiratory function were optimized in the PACU before transfer to the ward with the epidural catheter and multimodal analgesia. Epidurals were kept for 4 days, until the chest tube was removed. The standard protocol of the Acute Pain Service at the Montreal General Hospital for epidural solutions is Bupivacaine 0.1% with Fentanyl 3ug/ml at rates between 7 and 10 ml per hour, with the possibility of a rescue bolus of 6–8 ml every 4 hr.

In addition to a functional continuous epidural block, postoperative standard multimodal analgesia involved celecoxib, acetaminophen and rescue oral opioids.

As per the standard Clinical Pathway for thoracotomies in our institution, patients get 975mg Acetaminophen orally, every 6 hr for 5 days then, every 6 hr only as needed, 100 mg Celecoxib orally, twice daily for 5 days, 5–7.5 mg Oxycodone orally, every 4 hr as needed, 15 mg Oxazepam orally, every night at bedtime as needed, 25–50 mg dimenhydrate intravenously/orally, every 8 hr as needed, 100 mg Docusate orally, twice daily, on top of the epidural analgesia daily optimized by the Acute Pain Service.

TABLE 1 Age, surgery-related data and baseline psychometrics for male and female patients

	Men	Women
Number	20	17
Age (years, mean ± *SD*)	61 ± 16	58 ± 14
Surgery side		
Left	10	7
Right	10	10
Diagnosis		
Carcinoma	14	13
Sarcoma	0	2
Granuloma	0	1
Anthracosis	0	1
Lymphoma	1	0
Sarcoidosis	1	0
Schwannoma	1	0
COPD	1	0
Hamartoma	1	0
Cyst	1	0
Adjunct treatment		
Chemotherapy	7	8
Radiotherapy	0	1
Psychometric baseline data		
Depressive symptoms (HADS)		
None (score of 0–7)	18	13
Mild (score of 8–10)	0	3
Moderate (score of 11–14)	2	1
Severe (score of 15–21)	0	0
Anxiety symptoms (HADS)		
None (score of 0–7)	18	4
Mild (score of 8–10)	1	5
Moderate (score of 11–14)	1	8
Severe (score of 15–21)	0	0
Pain Catastrophizing (PCS, mean ± *SD*)	13 ± 2	10 ± 3
Sleep Impairment (PSQI, mean ± *SD*)	5 ± 1	7 ± 1

Abbreviations: COPD, chronic obstructive pulmonary disease; HADS, Hospital Anxiety and Depression Scale (maximum score per scale = 21); PCS, Pain Catastrophizing Scale (maximum score = 52); PSQI, Pittsburgh Sleep Quality Index (maximum score = 21); *SD*, standard deviation.

2.4 | Surgery

Patients were positioned in the classic lateral decubitus position for posterolateral thoracotomy. A posterolateral access to the thoracic cavity was created by dividing the skin and the muscular planes (latissimus dorsi and intercostal muscles, saving the serratus and rhomboid muscles), typically at the intercostal space T4-5. No costal resections were performed, and the intercostal muscles division was created on the superior edge of the inferior rib in an attempt to preserve the intercostal nerve. A rib retractor was carefully positioned to separate the ribs and prevent rib fractures in the process.

2.5 | Measures

2.5.1 | Questionnaires

Neuropathic pain symptom inventory (NPSI)

Participants were asked to complete the NPSI at the beginning of every testing session. The NPSI is a validated self-report questionnaire evaluating different neuropathic symptoms, encompassing five sub-scales (burning spontaneous pain, pressing spontaneous pain, paroxysmal pain, evoked pain and dysesthesia/ paresthesia (Bouhassira et al., 2004)). The sub-scale 'burning spontaneous pain' includes one item; 'pressing spontaneous pain', 'paroxysmal pain' and 'dysesthesia/ paresthesia' include two items each; and 'evoked pain' includes three items. Each item is rated on an 11-point Likert scale (ranging from 0 to 10). Scores for each sub-scale are divided by its number of items, resulting in a maximum score of 10 (range 0–10) per sub-scale, and a maximum of 50 (range 0–50) for the total NPSI score. Before surgery, participants were instructed to relate the phenomena described in the NPSI to symptoms anywhere in their body. After surgery, they were specifically instructed to relate the NPSI to symptoms perceived at or around the operation site on their thorax. The NPSI score of the participant's final visit (6 months after surgery for $n = 35$, and 5 months after surgery for $n = 2$ due to missing data for their 6th session) was used as the main outcome measure, i.e., neuropathic CPSP. For simplicity, we refer to this measure as '6 months NPSI score' hereafter. The NPSI scores of the remaining time points served as predictor variable.

Hospital Anxiety and Depression Scale (HADS)

Participants were asked to complete the HADS (Zigmond & Snaith, 1983) at the beginning of every testing session. The HADS is a validated self-report questionnaire evaluating psychological distress, encompassing two sub-scales, i.e., anxiety and depression. Each subscale consists of seven items, with each item being scored on a 0–3 scale, resulting in a maximum score of 21 per subscale and 42 for the total score.

Pain Catastrophizing Scale (PCS)

Participants were asked to complete the PCS (Sullivan, Bishop, & Pivik, 1995) at the beginning of every testing session. The PCS is a validated self-report questionnaire evaluating catastrophic thinking related to pain. It consists of 13 items in total and encompasses three sub-scales, i.e.,

rumination (4 items), magnification (3 items) and helplessness (6 items). Each item is scored on a 0–4 scale, resulting in a maximum score of 52.

Pittsburg Sleep Quality Index (PSQI)

Participants were asked to complete the PSQI (Buysse et al., 1991) at the beginning of every testing session. The PSQI is a validated self-report questionnaire evaluating sleep quality of the previous month, with higher scores indicating greater sleep impairment. It encompasses seven subscales (i.e., subjective sleep quality, sleep latency, sleep duration habitual sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction), which can each range from 0 to 3, resulting in a maximum total score of 21.

2.5.2 | QST protocol

For QST assessments, participants lay on their back. Tests were performed on the control site first, followed by the surgery site (or eventual surgery site for the preoperative baseline assessment). To ascertain that the QST measures were indeed assessed within the area affected by the surgery the skin area around the scar was mapped for sensory alterations prior to testing. The skin was stroked using a SENSELab Brush-05 (Somedic, Sweden), approaching the scar from seven directions (sparing the direction along the scar). Each stroke was 2 cm long and was applied with a force of 20–40 mN and a speed of 2 cm/s. Strokes were first applied well outside the affected area and each subsequent brush stroke was applied slightly closer to the scar than the preceding one. The strokes were stopped as soon as the patient reported a change in sensation. The position of the last stroke was marked on the skin for each of the seven directions. The testing site of 2 by 4 cm was then determined within the mapped area, avoiding scar tissue and as distal to the scar tissue as possible. If participants did not report any changes in sensation during this mapping procedure, we chose a testing site 2 cm distal to the scar and following the fifth and sixth rib. The homologous contralateral site served as control site. During testing, the room temperature was kept at 23°C and the participant`s skin temperature (measured using an infrared thermometer) for each testing site was documented.

QST assessments followed the protocol of the German Research Network on Neuropathic Pain (DFNS, (Rolke et al., 2006)): assessment of cold and warm detection thresholds, and cold pain and heat pain thresholds was followed by assessments of mechanical detection and mechanical pain thresholds, mechanical pain sensitivity, presence of dynamic mechanical allodynia, vibration detection, PPT and mechanical temporal summation by calculating the mechanical wind-up ratio (WUR) (Rolke et al., 2006). In addition to the DFNS protocol, we tested thermal temporal summation (Staud, 2004; Staud, Vierck, Cannon, Mauderli, & Price, 2001). Details of the employed QST apparatus and methods are listed in Table 2.

One tester (L.N.) performed the QST in the participants (in 31 out of 37). Two further testers (W.G. and C.W.) tested the remaining six participants (2 and 4, respectively). Each participant was tested by only one tester, meaning that each tester always saw their participants through all seven testing sessions.

2.5.3 | Quality control—baseline QST

To ascertain that differences in the QST measures between control and surgery site indeed reflected the underlying thoracic nerve damage rather than general changes in sensitivity after surgery, we performed a shortened QST protocol before surgery (hereafter referred to as 'baseline QST') in 32 participants (the remaining participants, $N = 5$, were not available to undergo QST before surgery due to time constraints on their end). This additional baseline assessment allowed us to test (a) whether QST measures on the control site were stable across time by comparing baseline and post-surgical measures for the control site, and (b) whether the control and surgery site were comparable in their sensitivity before surgery by comparing control and surgery site measures for the baseline QST.

The baseline QST took place at the Montreal General Hospital at the day of the participant's pre-surgical clinical assessment. Baseline QST was performed on the skin of patients' anterolateral thorax on the midclavicular line between the fifth and sixth rib. The protocol comprised the assessment of mechanical detection threshold (MDT) and pressure pain threshold (PPT) (details on methods and employed apparatus are presented in Table 2). These quantitative tests were followed by two qualitative tests assessing sensation in response to brush strokes using a SENSELab Brush-05 (Somedic, Sweden) and to a pinprick stimulus (Neuropen®; Owen Mumford Ltd.). Each stimulus was applied to the control site first and immediately afterwards to the surgery site. Participants were asked to indicate whether the stimuli felt the same on the two sites, or stronger or weaker on the surgery compared to the control site.

2.6 | Study procedures

2.6.1 | Baseline session

During the baseline session, a brief clinical interview was performed to obtain demographic data and a brief medical history including medications. Questionnaires were administered to assess variables commonly reported to predict CPSP. Specifically, neuropathic pain symptoms anywhere in the body (NPSI; Bouhassira et al., 2004), depression and anxiety (HADS; Zigmond & Snaith, 1983), pain catastrophizing (PCS; Sullivan et al., 1995) and sleep impairments (PSQI;

TABLE 2 QST subtests, employed apparatus and their application

Subtest	Method	Apparatus
CDT CPT	Baseline temperature: 32°C Rate of decreasing temperature: 0.5°C/s (CDT); 1°C/s (CPT) Participant indicated: first cool sensation (CDT): first painfully cold sensation (CPT) CDT: average temperature across three repetitions that participant indicated as cool CPT: average temperature across three repetitions that participant indicated as just painfully cold	TSA-II-NeuroSensory Analyzer, Medoc Ltd. (Haifa, Israel); 16 x16 mm Peltier thermode
WDT HPT	Baseline temperature: 32°C Rate of increasing temperature: 0.5°C/s (WDT); 1°C/s (HPT) Participant indicated: warm sensation/painfully hot WDT: average temperature across three repetitions that participant indicated as warm HPT: average temperature across three repetitions that participant indicated as just painfully hot	
Thermal WUR	Applied temperature: 50°C Application rate: 0.5 Hz Stimulus: manually tapping the thermode onto the participant's skin for 700 ms (ISI 1,300 ms) Number of stimuli: 1 baseline stimulus and a series of 15 consecutive stimuli WUR_{th}: maximum pain rating for the series of 15 stimuli was divided by the pain rating for the single baseline stimulus	
MDT	Method: modified method of limits using alternatingly five series of ascending stimulus intensity and five series of descending stimulus intensity, crossing the mechanical detection threshold 10 times MDT: geometric mean across the five sub-threshold and five supra-threshold intensities	von Frey filaments, Opihair2-Set, MARSTOCKnervtest (Schriesheim, Germany)
MPT	Method: modified method of limits using alternatingly five series of ascending stimulus intensity and five series of descending stimulus intensity, crossing the mechanical pain threshold 10 times MPT: geometric mean across the five sub-threshold and five supra-threshold intensities	Weighted Pinprick probes, MRC Systems GmbH (Heidelberg, Germany)
MPS	To test pinprick hyperalgesia, weighted pinprick probes of various intensities (8mN, 16mN, 32mN, 64mN, 128mN, 256mN, 512mN) were applied across five blocks, with each block containing one repetition of each intensity, presented in a pseudo-randomized order that differed for each block. Patients rated each stimulus in its intensity on a 0 (no pain) to 10 (most intense pain tolerable) numeric rating scale MPS: geometric mean across all ratings	
Mechanical WUR	Applied intensity: 256 mN Application rate: 1 Hz Number of stimuli: 1 baseline stimulus and a series of 10 stimuli; three repetitions WUR_{mech}: maximum pain rating for the series of 10 stimuli was divided by the pain rating for the single baseline stimulus, calculating the arithmetic mean across the three repetitions	
DMA	The three tactile stimuli were each applied using a single stroke of approximately 2 cm across the skin, starting on the control site, followed by the surgery side. Patients were asked to compare the sensation on each side and indicate whether it felt less intense on the surgery compared to control side, the same on both sides, or more intense on the surgery side. Each stimulus pair (control and surgery side) was repeated three times DMA: If participants reported the stimulation to be more intense on the surgery versus control side for a minimum of 1 test, while the remaining tests felt similarly intense on both sides, the presence of DMA was coded as 1. If patients perceived the intensity for all three tests as similar on both sides, or less intense on the surgery side, the absence of DMA was coded as 0	Set of three non-noxious tactile stimuli: Cotton wisp (~3mN), Cotton wool tip fixed on an elastic strip (~100 mN, Standardized brush (~200−400mN, Somedic, Sweden)
VDT	Vibrating tuning fork was placed on participant's rib (within the identified testing area), where it was held in place until participant indicated to no longer perceive vibration VDT: arithmetic mean of the indicated disappearance threshold (as displayed by the 8/8 scale) across three repetitions	Rydel Seiffer Neurological Tuning Fork (64 Hz, with 8/8-scale)

(Continues)

TABLE 2 (Continued)

Subtest	Method	Apparatus
PPT	Pressure algometer was placed in between ribs (within the identified testing area) and pressure slowly increased until participant indicated the pressure to be just painful Increasing rate: ~0.5 kg/cm^2 s PPT: arithmetic mean of the indicated pain threshold across three repetitions	Pressure algometer FDN200 with rubber tip (probe area of 1 cm^2), Wagner Instruments (Greenwich, CT, USA)

Abbreviations: CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

Buysse et al., 1991) were assessed. A subset of participants further underwent the baseline QST assessment as described in section 2.5.3.

2.6.2 | Post-surgical assessments

In the first 24 hr after surgery, clinical staff recorded acute post-operative pain intensity three times, using a 0–10 numerical rating scale. After being discharged from the hospital, participants were contacted by a research team member to schedule an appointment for the first follow-up session 1 month after the date of surgery.

2.6.3 | Post-surgical experimental sessions

Post-surgical experimental sessions were performed monthly, up to 6 months after surgery. In each of the follow-up sessions participants were asked to complete pain drawings, indicating on a 2-dimensional manikin (pen-and-paper) where on their body they perceived pain and—if any pain was reported—how intense the pain was, using the above-described 0–10 numerical rating scale. Patients further underwent the QST assessment and completed the questionnaires at the end of the session.

2.7 | Data analysis

2.7.1 | Quality controls

Comparison of control and surgery sites before surgery

Baseline MDT and PPT values for control and surgery site were normally distributed in log space and therefore logarithmically transformed before comparing the two sites using paired *t*-tests. Brush stroke and pinprick sensations were coded in binary fashion with 0 indicating no difference between sites and 1 indicating a difference in perceived intensity between the sites. Sites were compared using a chi-square test.

Stability of QST measures on the control site over time

To differentiate whether any post-surgical changes on the surgery site are restricted to the surgical site or represent generalized phenomena after surgery, we tested whether sensitivity on the control site remained stable over time. We performed this assessment for the two quantitative subtests obtained during the baseline session, i.e., PPT ($n = 30$) and MDT ($n = 32$). As data were not normally distributed, Wilcoxon signed rank test for dependent samples was used to compare QST thresholds on the control side for each post-surgical time point to its respective baseline value.

2.7.2 | Post-surgical QST trajectories

Thresholds for all QST subtests were compared between surgery and control site for each of the post-surgical time points. Because data were not normally distributed (even after log-transformation), Wilcoxon signed rank test for dependent samples was used.

To further assess whether QST signs after surgery indicated recovery/worsening over time or remained stable across the study period, ordinary least squares regression was performed, using time (months after surgery) as the independent variable and the QST measures on the surgery site for each subtest as the dependent variable. Standardized betas are reported to describe the linear trend of each QST sign over time.

2.7.3 | Normalization of post-surgical QST data

For the remaining analysis patients' QST scores for the surgery site were normalized using the six time points of each individual's control site as reference—i.e., $z = (\text{value}_{\text{surgery site}} - \text{mean}_{\text{control site across all six time points}})/\text{SD}_{\text{control site across all six time points}}$. The aim of this approach was to control for any general alteration of an individual in sensitivity following surgery, thereby obtaining QST scores more directly associated with the underlying nerve damage.

Before transforming the data, it was assured that central sensitization following surgery or differences between the control and test site at baseline were not present in our patient population, as these factors would have jeopardized the approach taken (see methods for quality control checks above in section 2.7.1 and their results below in section 3.2.1).

Because some participants did not perceive the single stimulus of either or both of the temporal summation assessments ($WUR_{mechanical}$ and $WUR_{thermal}$) on the affected site following surgery but did perceive the series of repeated stimulation as painful, the resulting WUR mathematically approaches infinity. To give justice to the fact that these patients clearly showed temporal summation, while keeping the variance across the group at a reasonable level, we conservatively put the WUR values of these patients to `9' (i.e., as if the series was rated as a 9 and the single stimulus as a 1) before normalizing the WUR data. A score of 9 corresponded to 6.1SD and 6.2SD above the $mean_{surgery\ site}$ of the remaining participants' data for $WUR_{mechanical}$ and $WUR_{thermal}$, respectively (with a range of 0–7.5 for mechanical and 0–8 for thermal WURs).

2.7.4 | Linear Regression Analysis to identify early predictors of chronic postoperative neuropathic pain

A step-wise linear regression analysis was performed to assess the predictive values of QST and questionnaire data for the 6-months' NPSI score. For data reduction, we only entered variables that significantly correlated with 6-months NPSI scores using Pearson's correlation coefficient ($p < .05$). Dummy variables were defined for the two categorial measures (gender, male = 1 and female = 2; and DMA, 0 = absence of DMA and 1 = presence of DMA on the surgery site).

Because the aim was to predict neuropathic pain at the earliest time point possible, we used a step-wise regression, entering identified baseline variables only into the first model, followed by variables at 1 month after surgery (2nd model), 2 months after surgery as the final step (3rd model), and finally added variables at 3 months after surgery as the final step (4th model). Thus, the regression analysis provided us with the opportunity to examine the best combination of pre- and early post-operative factors to predict 6 months NPSI scores after surgery at the earliest time point(s) possible. Adjusted coefficients of determination (adjusted R^2) were calculated for each model to assess the variance of the dependent variable that was explained by each model. Standardized betas are reported for all variables that significantly predicted the dependent variable within the best suited model (based on significant changes in explained variance). Given the relatively large number of factors within the regression model and a sample size of 37 participants, there was a risk for the regression model of being underpowered, thereby limiting external validity of the findings. Therefore, we performed an additional linear regression enter model with the same dependent variable (6-months NPSI scores) but including only independent variables that were identified as predictors for 6-months NPSI scores by the previous step-wise regression model. A confirmation of the previous results by this additional analysis would be interpreted as supporting the external validity of the findings.

2.7.5 | Subgroups of patients with different levels of chronic neuropathic pain symptoms

Taking an exploratory approach, we performed a two-step unsupervised cluster analysis to distinguish between patients with different levels of neuropathic symptoms 6 months after surgery, with the intend to identify variables (using QST and questionnaire data) that distinguished between these groups. In a first step of the unsupervised cluster analysis, two clusters were identified within the present sample with good cluster quality (silhouette measure of cohesion and separation >0.5). In a second step, a k-mean cluster analysis with $k = 2$ clusters was performed. Convergence criterion was set at 0, with a maximum number of iterations of 50. Cluster membership and Euclidian distance to the cluster centre were inspected, and distances to the cluster centre were compared between the two subgroups (as defined by cluster membership) using a Mann–Whitney *U* test for independent samples. The two identified groups were further compared in the specific self-reported neuropathic pain symptoms across time (based on the NPSI sub-scales) using a Mann–Whitney *U* test, their demographic data—i.e., age using a Mann–Whitney *U* test for independent samples, and gender distribution using a chi-square test—pre-existing neuropathic pain symptoms, acute post-OP pain and all questionnaire data (i.e., HADS, PCS, and PSQI) using Mann–Whitney *U* tests for independent samples. To compare post-surgical QST data between patients with no/low and moderate 6-months NPSI scores DMA was coded in binary fashion with 0 indicating the absence of DMA and 1 indicating the presence of DMA on the surgery site. Groups with no/low versus moderate 6-months NPSI scores were compared using a chi-square test. For the QST subtests with quantitative data, normalized post-surgical QST data were compared for all time points between the group with no/low versus moderate 6-months' NPSI scores using Mann–Whitney *U* tests for independent samples. Non-parametric test statistics were chosen because of the relatively small group sizes (i.e., 7 versus. 30).

All analysis was performed using IBM SPSS Statistics, version 24 (IBM Corp.). Data are presented in mean ± *SD* for parametrically analysed data and as median and 95% confidence interval (CI) for non-parametrically analysed data. The significance level was set to $p < .05$.

3 | RESULTS

3.1 | Neuropathic pain symptoms 6 months after surgery

The median of the 6-months NPSI score was 2.00(95% CI [1.67; 4.87], range 0–23). Of the 37 patients, 24 reported a score higher than zero and, thus, indicating the presence of some neuropathic symptoms.

3.2 | QST analysis

3.2.1 | Quality Controls

Testing site corresponds to self-reported pain after surgery

All patients reported pain at their first post-surgical visit. Inspecting the respective pain drawings revealed that 36/37 patients indicated their pain to be located on the surgery side of the anterolateral thorax, including the area that we used as testing site for the QST measures. A majority of these patients (33/37) reported additional pain sites (mostly on their backs, along the scar tissue that had resulted from the thoracic surgery). Only 1/37 patients reported their pain to be at a site different to the one used as testing site for the QST (i.e., on his back along the scar tissue but not on the anterolateral thorax). Based on these findings, we conclude that functional abnormalities identified via QST measures were located within the same area as the pain that was perceived following surgery, i.e., the innervation area of the affected intercostal nerve.

Comparison of control and surgery sites before surgery

Baseline data of MDT ($n = 32$), PPT ($n = 30$), and differences in brush stroke ($n = 28$) and pinprick sensation ($n = 29$) were compared between control and surgery sites. Analysis revealed no differences for any of the performed tests (Table 3), indicating that the sensitivity of the control and surgery sites was comparable before surgery.

Stability of QST measures on the control site over time

For the two quantitative tests of the baseline assessment (i.e., MDT and PPT), we further tested whether the sensitivity of the control site changed over time following surgery (Figure 2). For both tests, none of the post-surgical thresholds differed significantly from the pre-surgical baseline measurements (Table 4).

The performed quality checks thus indicated that differences in the QST measures between control and surgery site (described hereafter) do reflect changes in sensitivity within the innervation area of the affected intercostal nerve rather than general changes in sensitivity after surgery.

3.2.2 | QST trajectories for the surgery site

Comparison of post-surgical and baseline data for MDT and PPT for the surgery site

In contrast with the control site, all time points for MDT and most time points for PPT (time point 1 through 5) after surgery differed significantly compared to baseline on the surgery site (Table 4). Results showed an increase in mechanical detection thresholds following surgery (indicating a loss of function) and decreased thresholds for pressure pain (indicating a gain of function).

TABLE 3 Control and surgery sites before surgery

	Control site (mean ± *SD*)	Future surgery site (mean ± *SD*)	*N*	*t*	*p*
MDT (mN)	5.41 ± 9.05	7.40 ± 12.01	32	0.78	.441
PPT (kg/cm^2)	2.60 ± 0.90	2.63 ± 0.86	30	0.32	.749

	Number of participants who found stimulations between control and future surgery site				
	Comparable	Different	*N*	X^2	*p*
Brush stroke	26	3	28	0.07	.782
Pin prick	24	5	29	0.17	.684

Note: MDT and PPT, data were log-transformed for the analysis.

Abbreviations: MDT, mechanical detection threshold; PPT, pressure pain threshold.

Comparison of post-surgical QST data between control and surgery site

Comparing surgery and control sites for all post-surgical time points (Table 4), it was found that the surgery site exhibited predominant signs of a loss of nerve function (Figures 2a and 3). CDT, WDT, HPT, MDT, MPT, MPS and VDT showed significant differences between surgery and control site for all time points following surgery (all z's ≤ -2.79, all p's $\leq .005$). CPT results showed reduced sensitivity to cold pain on the surgery site for the first three months after surgery and 5 months after surgery (all z's ≤ -2.09, all p's $\leq .037$), but no difference at 4 months (z=−0.85, $p = .394$) and 6 months (z=−1.31, $p = .192$)—with a positive linear trend of CPT signs on the surgery site over time (standardized beta = 0.13, $p = .049$), indicating recovery of nerve function towards the end of the study period. Further linear trends indicating recovery from loss of function following surgery were found for CDT (standardized beta = 0.15, $p = .023$) and MDT (standardized beta = −0.13, $p = .046$, Figure 2a). For all remaining tests that had shown loss of nerve function (WDT, HPT, MPT, MPS and VDT) sings remained stable after surgery with linear trends over time that were not differed from zero (all standardized beta's $< |0.10|$, all p's $\geq .160$).

PPT was the only test showing a gain of function on the surgery site (Figure 2b), with all time points after surgery showing significant differences between surgery and control site (all z's ≤ 2.81, all p's $\leq .005$, Table 4). The slope of PPT over time revealed no linear trend of recovery within the 6 months following surgery (standardized beta = 0.11, $p = .115$).

Neither of the temporal summation measures ($WUR_{mechanical}$ and $WUR_{thermal}$) was affected by surgery: none of the post-surgical time points differed significantly between surgery and control site for either test (all Z's ≤ -1.74, all p's $\geq .081$).

3.3 | Early predictors of neuropathic pain symptoms 6 months after surgery

For clinical practice, tests are needed to identify patients at risk to develop chronic neuropathic pain following surgery as early as possible, ideally before symptoms are chronic. We thus entered all variables assessed at an early time point (from baseline to 3 months following surgery)—QST and questionnaire data—that correlated significantly with 6-months NPSI scores into a step-wise regression (Table S1 depicts all correlation coefficients). Within this regression model, we entered identified baseline variables first (i.e., baseline NPSI and PSQI scores), followed successively by variables assessed 1 month (i.e., PSQI scores, PCS scores, HADS depression score), 2 months (i.e., PSQI scores, PCS scores, HADS depression and anxiety scores), and 3 months (i.e., PSQI scores, PCS scores, HADS depression and anxiety scores, HPT z-score, MPS z-score, presence of DMA) after surgery, to identify the earliest time point to predict the outcome measure. All test assumptions for linear regression were met (i.e., no outliers, all variables were multivariate normal, no auto-correlations, i.e., independence of observations, as assessed by a Durbin-Watson statistic of 2.27, and the presence of homoscedasticity).

The four models tested within the step-wise procedure explained significant variance of neuropathic pain symptoms 6 months after surgery. While model 2 and 3 (each $p > .10$) did not explain significantly more variance than model 1 (adjusted $R^2 = 0.61$, change in $F_{3,33} = 19.71$, $p < .001$), model 4 explained more variance compared

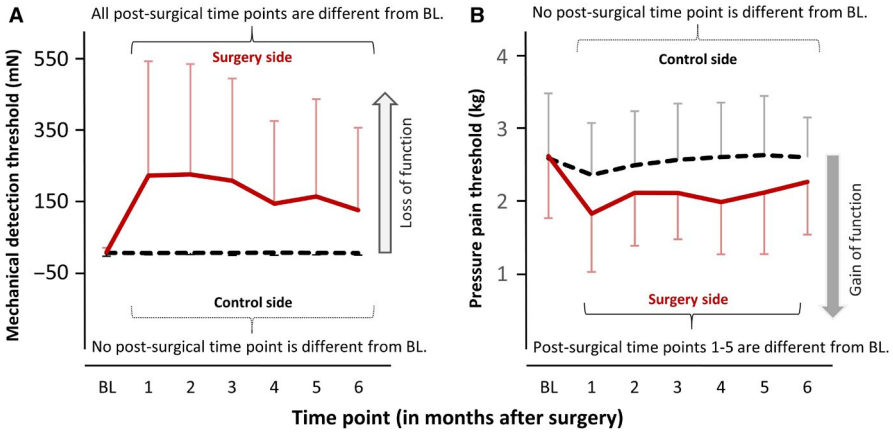

FIGURE 2 (a) MDT and (b) PPT illustrate that sensitivity of the control site (in black, dashed line) was stable across the seven time points of the experiment (no differences were found between any of the post-surgical time points and baseline). In contrast, the surgery site (in red, solid line) showed impairments in sensitivity after surgery across the whole patient sample, with all (MDT) or the first five time points (PPT) after surgery being significantly different from baseline. Comparing control and surgery site to each other revealed no differences at baseline but significant differences for all post-surgical time points (MDT and PPT). Depicted are means and *SD*. BL, baseline

TABLE 4 Comparison of QST data on surgery and control sites

	Timepoint (in months after surgery)													
	BL		1 ($N = 35$)		2 ($N = 33$)		3 ($N = 34$)		4 ($N = 36$)		5 ($N = 36$)		6 ($N = 35$)	
	Z	*p*	*Z*	*p*	*Z*	*p*	*Z*	*p*	*Z*	*p*	*Z*	*p*	*Z*	*p*
MDT (mN)														
Con (versus BL)			−0.26	.799	−0.88	.799	−0.74	.460	−0.95	.342	−0.63	.531	−0.07	.948
Sur (versus BL)			**−4.02**	**<.001**	**−4.00**	**<.001**	**−4.14**	**<.001**	**−3.93**	**<.001**	**−3.78**	**<.001**	**−3.85**	**<.001**
Sur versus con	−0.37	.710	**−4.30**	**<.001**	**−4.21**	**<.001**	**−4.71**	**<.001**	**−4.21**	**<.001**	**−4.69**	**<.001**	**−4.55**	**<.001**
PPT (kg)														
Con (versus BL)			−1.62	.106	−0.40	−689	−0.07	.946	−0.31	.755	−0.44	.657	−0.34	−737
Sur (versus BL)			**−3.65**	**<.001**	**−2.95**	**.003**	**−3.15**	**.002**	**−2.97**	**.003**	**−2.96**	**.003**	−1.74	.081
Sur versus con	−0.71	.478	**−3.12**	**.002**	**−3.31**	**.001**	**−2.94**	**.003**	**−3.60**	**<.001**	**−3.74**	**<.001**	**−2.81**	**.005**
CDT (°C)														
Sur versus con			**−4.99**	**<.001**	**−4.96**	**<.001**	**−4.82**	**<.001**	**−4.41**	**<.001**	**−4.47**	**<.001**	**−3.86**	**.001**
WDT (°C)														
Sur versus con			**−4.87**	**<.001**	**−4.76**	**<.001**	**−4.61**	**<.001**	**−4.59**	**<.001**	**−5.03**	**<.001**	**−4.90**	**<.001**
CPT (°C)														
Sur versus con			**−2.09**	**.037**	**−2.88**	**.004**	**−2.17**	**.030**	−0.85	.394	**−2.58**	**.010**	−1.31	.192
HPT (°C)														
Sur versus con			**−3.58**	**<.001**	**−3.84**	**<.001**	**−3.87**	**<.001**	**−2.80**	**.005**	**−4.10**	**<.001**	**−4.60**	**<.001**
MPT (mN)														
Sur versus con			**−4.09**	**<.001**	**−4.68**	**<.001**	**−4.64**	**<.001**	**−4.82**	**<.001**	**−4.73**	**<.001**	**−3.86**	**<.001**
MPS (NRS)														
Sur versus con			**−4.06**	**<.001**	**−4.49**	**<.001**	**−4.38**	**<.001**	**−3.95**	**<.001**	**−4.58**	**<.001**	**−3.82**	**<.001**
VDT (x/8)														
Sur versus con			**−3.29**	**.001**	**−3.67**	**<.001**	**−4.26**	**<.001**	**−2.99**	**.003**	**−3.71**	**<.001**	**−3.46**	**.001**
WUR_{mech}														
Sur versus con			−1.42	.155	−0.75	.455	−1.18	.238	−1.36	.174	−0.63	.526	−1.74	.081
WUR_{therm}														
Sur versus con			−1.00	.320	−0.89	.374	−0.12	.903	−0.27	.786	−1.72	.086	−1.70	.090

Note: Significant differences are highlighted using bold font.

Abbreviations: BL, baseline; CDT, cold detection threshold; Con, control side; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; NRS, 0–10 numerical rating scale; PPT, pressure pain threshold; Sur, surgery side; VDT, vibration detection threshold; WDT, warm detection threshold; WUR_{mech}, mechanical wind-up ratio; WUR_{therm}, thermal wind-up ratio.

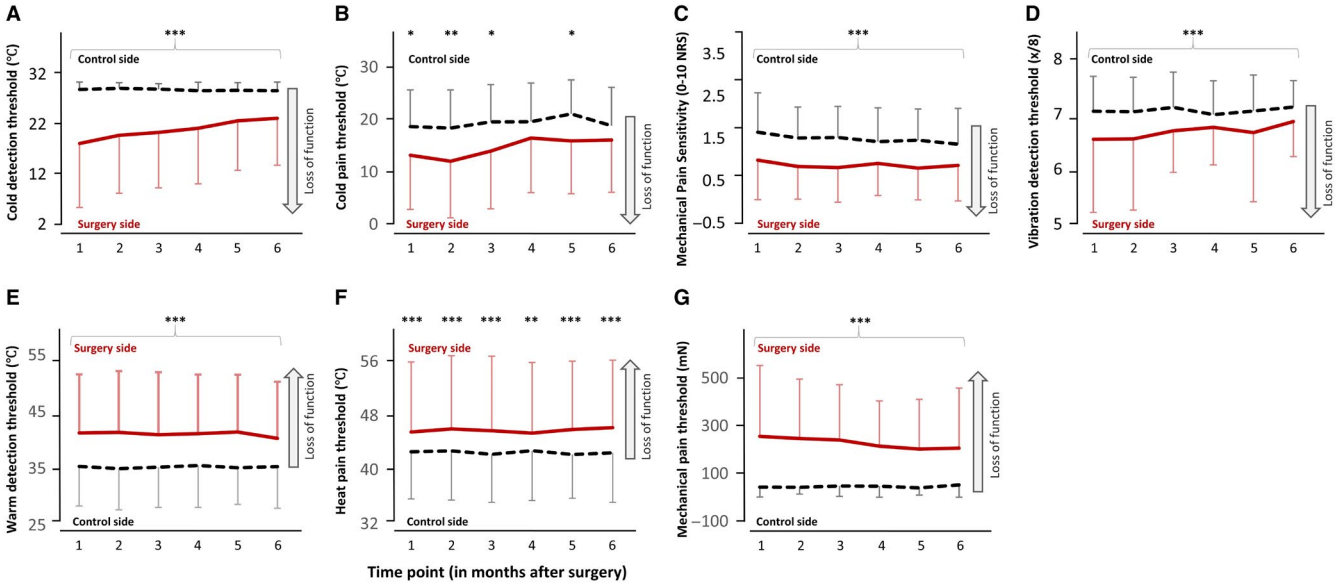

FIGURE 3 For most QST subtests, i.e., (a) CDT, (b) CPT, (c) MPS, (d) VDT, (e) WDT, (f) HPT, and (g) MPT, comparing control site (in black, dashed line) and surgery site (in red, solid line) revealed loss of function on the surgery site, i.e., surgery-induced loss of function. Depicted are means and *SD*. *$p < .05$, **$p < .01$, ***$p < .001$

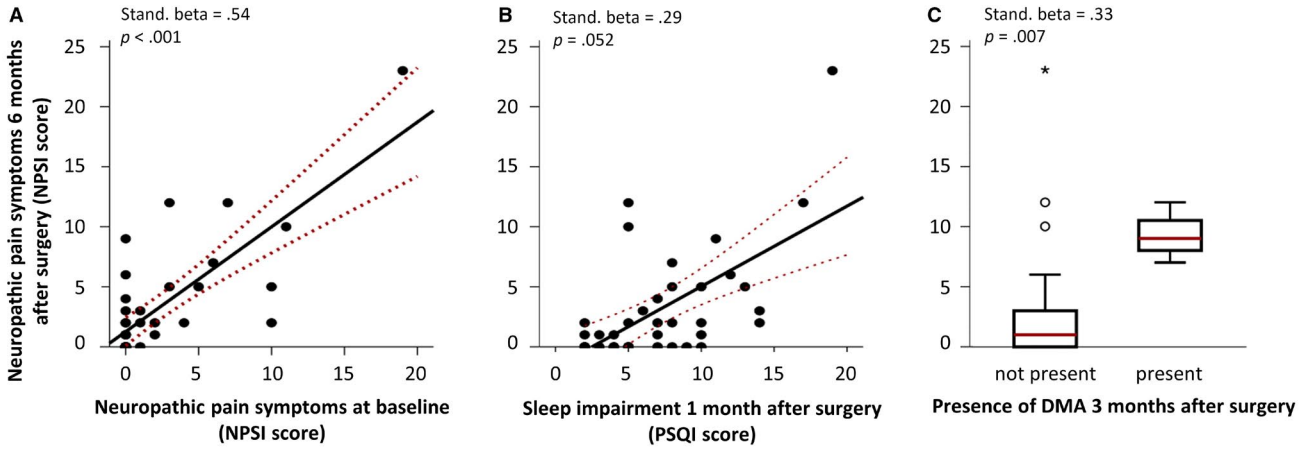

FIGURE 4 Neuropathic pain symptoms (with a maximum score of 50) anywhere in the body before surgery (a), sleep impairment (with a maximum score of 21) 1 month after surgery (b), and presence of dynamic mechanical allodynia (c) predicted the level of neuropathic pain symptoms that patients reported six months after surgery. Stand, beta standardized beta; NPSI, neuropathic pain symptom inventory; PSQI, Pittsburgh Sleep Quality Index; DMA, dynamic mechanical allodynia

to the previous models (change in $F_{7,19} = 3.69$, $p = .011$, Table S2a). Of the variables included in model 4 (adjusted $R^2 = 0.80$, $p < .001$), neuropathic pain symptoms before surgery (standardized ß = 0.54, $p < .001$), sleep impairment 1 month after surgery (standardized ß = 0.29, $p = .052$), and presence of dynamic mechanical allodynia at 3 months (standardized ß = 0.33, $p = .007$) predicted NPSI scores 6 months after surgery (Figure 4). This result indicates that neuropathic pain symptoms anywhere in the body before surgery, in combination with sleep impairments and the presence of dynamic allodynia shortly after surgery should be taken into consideration as early measures when predicting the level of neuropathic pain symptoms 6 months after surgery. It should, however, be noted that the *p*-value for sleep impairment 1 month after surgery was just above the pre-defined significance level of $p = .05$ and that dynamic mechanical allodynia as a predictor should also be taken with caution because of the very low number of patients with DMA (three at 3 months after surgery).

To support external validity of our data, we performed a multivariate linear regression. This analysis confirmed that all three factors (neuropathic pain symptoms before surgery, sleep quality 1 month after surgery and the presence of dynamic mechanical allodynia 3 months after surgery)

significantly predicted neuropathic pain symptoms 6 months after surgery (adjusted $R^2 = 0.74$, $p < .001$, Table S2b).

3.4 | Comparing patients with low versus moderate 6 months NPSI scores

Un-supervised cluster analysis of the 6 months NPSI scores identified two sub-groups of uneven numbers, but with similar mean distances to the respective cluster centres ($p = .128$): $n = 30$ participants with no or low neuropathic pain symptoms 6 months after surgery (median pain = 1.00, 95% CI = 0.78–2.02), and a small group of $n = 7$ with moderate neuropathic pain symptoms (median pain = 10.00, 95% CI = 6.06–16.51, $U = 0$, $p < .001$, Figure 5). The cut-off score that distinguished between the two groups was 5. The distribution of group classification (low versus. moderate 6 months NPSI scores) was equal across the three different testers (as tested by Kruskal–Wallis test for independent samples, $p = .759$).

Comparing the two groups for their specific neuropathic symptoms based on the NPSI sub-scales revealed that patients with moderate 6-months NPSI total scores reported significantly higher levels of burning spontaneous pain sensations and paroxysmal pain than patients with no/low 6-months NPSI scores for all post-surgical testing time points, and significantly higher levels of pressing spontaneous pain sensations and dysesthesia/paresthesia for most post-surgical testing time points. Evoked pain, in contrast, was reported to be similarly low for both groups (for more details see Table S3 and Figure S1 of the supplementary material).

Both groups were similar in age and did not differ in their gender distribution (Table 5). Furthermore, the two groups did not differ w.r.t. pain and sleep quality ratings immediately after surgery (assessed within 24 hr after surgery) (Table 5). In contrast, neuropathic pain symptoms anywhere in the body before surgery, sleep impairment at all time points after surgery (1–6 months after surgery) and anxiety levels 2 months following surgery differed significantly between the two groups. For all of these variables, patients with moderate 6-months NPSI scores showed higher scores—i.e., more impairment—than the group who reported no/low 6 months NPSI levels (Table 5).

Next, we examined the QST trajectories for the two groups of patients, i.e., those who reported no/low neuropathic pain symptoms, compared to those with moderate levels of neuropathic pain symptoms 6 months after surgery in an explorative fashion due to the small size of one cluster. Interestingly, the trajectories for many QST subtests were similar for the two groups: no significant differences between groups were found for MPT, PPT, VDT, mechanical and thermal wind-up at any time point (Table 6). In contrast, CDT (2, 3, 4 and 6 months after surgery) and MPS (2, 3, 4 and 5 months after surgery) differed between the two groups at several time points, WDT at 4 and 6 months, CPT at 4 months, HPT at 4 and 6 months (Table 6a–c), MDT at 4 months and DMA at 3 months after surgery (Table 6b). For all QST measures that differed between the groups, we found that loss of function was associated with no/low levels of neuropathic pain symptoms 6 months after surgery. The group who reported moderate levels of neuropathic pain symptoms 6 months after surgery, in contrast, showed z-scores around zero in most instances (95% confidence intervals include zero) and were thus less affected in their sensitivity than the no/low 6-months NPSI group. Furthermore, among the variables that did differ between the two groups, only for CDT and MPS we detected differences at an early time point after

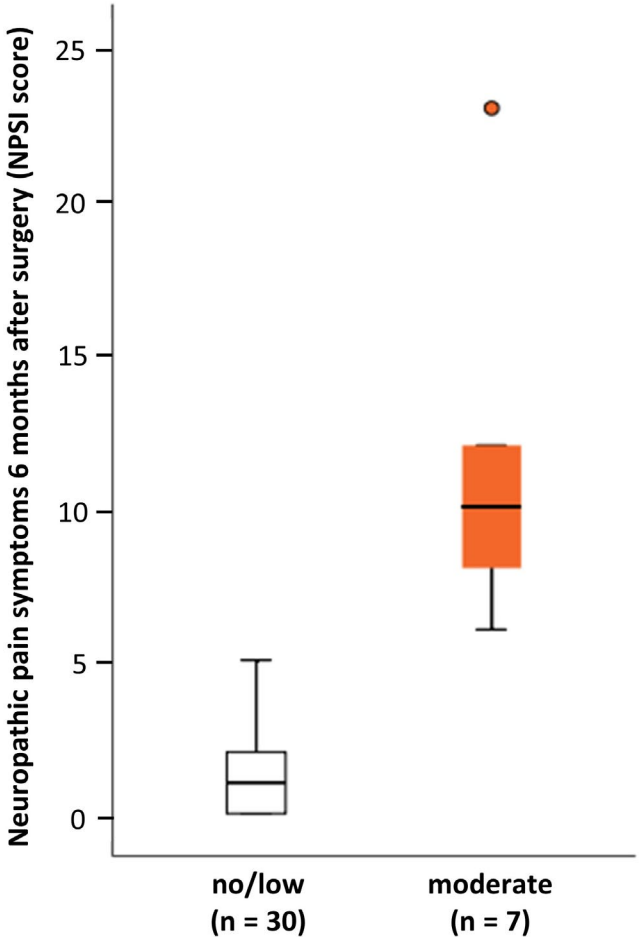

FIGURE 5 Neuropathic pain symptoms 6 months after surgery. While 30 participants (81%) reported no or low levels of neuropathic pain symptoms 6 months after surgery, seven (19%) reported moderate levels of neuropathic pain symptoms. Depicted is a box plot, illustrating for each group the minimum to maximum range (whiskers), the second and third quartile (lower and upper site of the box), the median (black horizontal line within the box), and one outlier (orange dot)

TABLE 5 Comparison of patients with no/low versus moderate 6-months NPSI scores—age, gender, pain, sleep and psychological variables

	No/low 6-months' NPSI	Moderate 6-months' NPSI	*p*-value
Number (*n*)	30	7	
Age (years; median and 95% CI)	62 (59–70)	54 (43–76)	.330
Gender (*n*)			
Women	12	5	
Men	18	2	.133[a]
Post-operative data (first 24 hr) (0–10 rating scale)			
Pain	2.67 (1.33–3.33)	2.67 (0.67–4.33)	.845
Sleep quality	2 (2–3)	2 (1–3)	.696
Questionnaire data (scores; median and 95% CI)			
NPSI at BL	0 (0–1)	6 (0–19)	.026
Sleep Impairment at BL	4 (3–6)	7 (2–14)	.071
Sleep Impairment at 1 month	6.5 (4–8)	11 (5–19)	.036
Sleep Impairment at 2 months	5.5 (4–8)	9 (3–11)	.032
Sleep Impairment at 3 months	5 (3–7)	11 (3–13)	.013
Sleep Impairment at 4 months	4 (2–5)	9 (2–17)	.010
Sleep Impairment at 5 months	4.8 (3–6)	10 (4–15)	.007
Sleep Impairment at 6 months	4 (3–7)	10 (4–15)	0.006
Anxiety at BL	6 (4–8)	9 (0–12)	.482
Anxiety at 1 month	4.5 (3–6)	5 (2–11)	.506
Anxiety at 2 months	3 (2–5)	7 (3–11)	.032
Anxiety at 3 months	3.5 (2–5)	5 (2.71–9.29)	.785
Anxiety at 4 months	3 (2–5)	9 (0–10)	.100
Anxiety at 5 months	4 (3–5)	8 (1–10)	.065
Anxiety at 6 months	3 (2–4)	8 (1–13)	.100
Depression at BL	2 (2–5)	3 (0–11)	.776
Depression at 1 month	4 (3–5)	7 (1–12)	.128
Depression at 2 months	3 (1–5)	4 (1–11.5)	.350
Depression at 3 months	3 (1–5)	4 (1–11.5)	.582
Depression at 4 months	2.5 (1–6)	6 (1–11)	.160
Depression at 5 months	3 (1–6)	8 (1–12)	.054
Depression at 6 months	2.5 (1–4)	5 (1–12)	.172
Catastrophizing at BL	7.5 (4–15)	9 (0–33)	.805
Catastrophizing at 1 month	7.5 (6–16)	18 (7–32)	.084
Catastrophizing at 2 months	4.5 (1–13)	7 (4–27)	.185
Catastrophizing at 3 months	3 (1–12)	13 (1–29)	.160
Catastrophizing at 4 months	2.5 (0–8)	13 (0–30)	.213
Catastrophizing at 5 months	3.5 (1–6)	14 (0–32)	.149
Catastrophizing at 6 months	3 (0–6)	10 (0–31)	.185

Abbreviations: BL, baseline; NPSI, neuropathic pain symptoms inventory.

[a]Based on Chi square test; all other comparisons are based on Mann–Whitney *U* test for independent samples.

surgery (i.e., from 2 months onward, Figure 6a,b). The ratio of DMA presence to DMA absence was higher in the 'moderate' compared to 'no/low' group 3 months after surgery and the other variables differed between the two groups only at 4 months after surgery or later, i.e., at a time when neuropathic symptoms can already be considered chronic.

TABLE 6 Comparison of patients with no/low versus moderate 6-months NPSI scores

	(a) Thermal QST subtests		
	No/low 6-months' NPSI	**Moderate 6-months' NPSI**	***p*-value**
Number (*n*)	30	7	
QST z values (median and 95% CI)			
CDT at 1 month	−7.67 (−16.94 to −2.49)	−2.94 (−91.76 to 0.75)	.312
CDT at 2 months	−8.24 (−14.75 to −2.24)	0.13 (−91.76 to 1.88)	.036
CDT at 3 months	−6.87 (−12.00 to −1.73)	0.02 (−91.76 to 2.15)	.026
CDT at 4 months	−2.39 (−10.82 to −1.55)	−0.06 (−91.76 to 2.30)	.015
CDT at 5 months	−3.67 (−7.21 to −1.14)	−0.71 (−68.12 to 1.77)	.199
CDT at 6 months	−3.73 (−7.69 to −0.87)	0.19 (−20.55 to 1.99)	.036
WDT at 1 month	−4.82 (−15.76 to −1.77)	−5.70 (−27.24 to −0.32)	1.000
WDT at 2 months	−6.58 (−14.88 to −2.18)	−4.03 (−27.24 to 1.56)	.458
WDT at 3 months	−5.22 (−13.96 to −1.68)	−2.35 (−27.24 to 1.33)	.276
WDT at 4 months	−6.46 (−9.99 to −2.49)	−1.08 (−27.24 to 1.22)	.049
WDT at 5 months	−8.15 (−11.79 to −2.16)	−0.50 (−26.51 to 0.10)	.054
WDT at 6 months	−4.69 (−11.13 to −1.96)	0.07 (−26.51 to 0.91)	.032
CPT at 1 month	−1.12 (−3.19 to −0.12)	0.37 (−13.68 to 1.37)	.350
CPT at 2 months	−2.17 (−3.91 to −0.27)	−0.75 (−13.68 to 1.54)	.350
CPT at 3 months	−0.53 (−2.71–0.59)	0.91 (−13.68 to 1.92)	.531
CPT at 4 months	0.05 (−1.67–0.64)	1.37 (−13.68 to 1.61)	.015
CPT at 5 months	−0.73 (−1.73–0.59)	0.44 (−10.47 to 1.61)	.413
CPT at 6 months	−0.23 (−1.87–0.38)	1.11 (−10.47 to 1.61)	.160
HPT at 1 month	−2.27 (−3.15 to −0.70)	0.56 (−2.94 to 1.43)	.138
HPT at 2 months	−2.24 (−3.15 to −1.24)	−1.71 (−2.94 to 1.26)	.243
HPT at 3 months	−1.77 (−2.88 to −0.87)	−0.38 (−2.94 to 0.69)	.138
HPT at 4 months	−1.54 (−2.83 to −0.52)	0.52 (−2.94 to 2.82)	.010
HPT at 5 months	−1.88 (−3.55 to −0.94)	−0.12 (−2.94 to 1.00)	.276
HPT at 6 months	−1.84 (−2.65 to −1.03)	−0.17 (−2.94 to 0.62)	.036
Therm. WU at 1 month	−0.58 (−1.24 to −0.17)	−0.96 (−1.27 to 1.82)	.747
Therm. WU at 2 months	−0.51 (−0.79–0.42)	−0.39 (−1.27 to 1.31)	.747
Therm. WU at 3 months	−0.53 (−0.73–0.50)	−0.39 (−1.78 to 0.55)	.482
Therm. WU at 4 months	−0.31 (−0.83–0.85)	−0.82 (−1.26 to 5.71)	.925
Therm. WU at 5 months	−0.53 (−0.83 to −0.12)	0.05 (−1.04 to 2.00)	.231
Therm. WU at 6 months	−0.68 (−0.85 to −0.12)	0.16 (−0.96 to 3.30)	.118
	(b) Mechanical, vibration and pressure QST subtests		
	No/low 6-months' NPSI	**Moderate 6-months' NPSI**	***p*-value**
Number (*n*)	30	7	
QST data (median and 95% CI)			
MDT at 1 month	−15.56 (−71 to −3)	−5.99 (−605 to 0)	.350
MDT at 2 months	−15.05 (−216 to −2)	−4.56 (−605 to 0)	.556
MDT at 3 months	−37.99 (−136 to −3)	−1.29 (−605 to 0)	.172
MDT at 4 months	−18.73 (−72 to −3)	−0.19 (−605 to 1)	.026
MDT at 5 months	−11.12 (−61 to −4)	−2.19 (−605 to 1)	.092
MDT at 6 months	−7.18 (−43 to −2)	−4.95 (−605 to 0)	.608

(Continues)

TABLE 6 (Continued)

	(b) Mechanical, vibration and pressure QST subtests		
	No/low 6-months' NPSI	**Moderate 6-months' NPSI**	***p*-value**
MPT at 1 months	−7.19 (−13 to −1)	−0.51 (−32 to 1)	.243
MPT at 2 months	−7.75 (−12 to −3)	−1.43 (−32 to 0)	.172
MPT at 3 months	−8.49 (−22 to −3)	−0.70 (−32 to 1)	.059
MPT at 4 months	−6.42 (−13 to −3)	−0.51 (−32 to 1)	.071
MPT at 5 months	−3.45 (−10 to −1)	−0.51 (−21 to 1)	.185
MPT at 6 months	−2.55 (−9 to −1)	0.50 (−15 to 1)	.149
MPS at 1 month	−1.45 (−2.73 to −0.72)	−0.11 (−1.82 to 1.60)	.084
MPS at 2 months	−1.86 (−2.88 to −1.29)	−0.03 (−2.70 to 0.21)	.023
MPS at 3 months	−2.16 (−2.83 to −1.46)	0.30 (−1.82 to 1.56)	<.001
MPS at 4 months	−1.84 (−2.65 to −0.86)	−0.16 (−2.11 to 0.83)	.009
MPS at 5 months	−1.94 (−2.91 to −1.45)	−0.32 (−1.75 to 1.15)	.001
MPS at 6 months	−1.73 (−2.75 to −0.92)	−0.56 (−1.75 to 1.55)	.036
VDT at 1 month	−1.01 (−2.18 to −0.50)	−0.71 (−12.60 to 0.60)	.747
VDT at 2 months	−1.59 (−2.61 to −0.95)	−0.71 (−2.14 to 1.27)	.118
VDT at 3 months	−1.64 (−2.18 to −0.65)	−0.60 (−2.26 to 3.24)	.149
VDT at 4 months	−0.84 (−1.96 to −0.29)	−0.52 (−2.71 to 0.90)	.413
VDT at 5 months	−1.20 (−1.96 to −0.33)	0.29 (−3.32 to 0.98)	.160
VDT at 6 months	−0.51 (−1.38 –0.12)	0.27 (−3.32 to 1.38)	.719
PPT at 1 month	1.59 (0.65 to 2.79)	2.35 (−0.38 to 4.50)	.227
PPT at 2 months	1.07 (0.54 to 1.58)	0.64 (−0.96 to 2.77)	.531
PPT at 3 months	1.23 (0.52 to 2.40)	0.44 (−1.73 to 3.09)	.391
PPT at 4 months	1.51 (0.53 to 2.11)	1.19 (−0.54 to 1.91)	.293
PPT at 5 months	1.31 (0.15 to 1.61)	0.38 (−0.70 to 2.09)	.635
PPT at 6 months	0.89 (0.47 to 1.33)	−0.69 (−1.50 to 1.91)	.118
Mech. WU at 1 month	0.03 (−0.53 to 1.40)	−0.08 (−1.94 to 2.55)	.925
Mech. WU at 2 months	−0.23 (−0.42 to 0.21)	0.70 (−1.94 to 2.23)	.608
Mech. WU at 3 months	0.25 (−0.91 to 1.44)	0.45 (−2.44 to 3.12)	.776
Mech. WU at 4 months	0.61 (0.03 to 1.52)	−0.35 (−1.94 to 3.28)	.391
Mech. WU at 5 months	−0.02 (−0.66 to 0.67)	0.29 (−1.23 to 12.87)	.435
Mech. WU at 6 months	0.14 (−0.23 to 1.27)	0.02 (−0.96 to 12.87)	.865

	(c) Qualitatively assessed presence of dynamic mechanical allodynia				
	No/low 6-months' NPSI		**moderate 6-months' NPSI**		***p*-value**
Number (*n*)	30		7		
Number of patients with/without DMA (*n*)	With DMA	Without DMA	With DMA	Without DMA	
DMA at 1 month	2	28	3	4	.037
DMA at 2 months	0	30	1	6	.189
DMA at 3 months	0	30	3	4	.005
DMA at 4 months	1	29	2	5	.086

(Continues)

TABLE 6 (Continued)

	(c) Qualitatively assessed presence of dynamic mechanical allodynia				
	No/low 6-months' NPSI		moderate 6-months' NPSI		*p*-value
DMA at 5 months	1	29	1	6	.347
months	0	30	1	6	.189

Note: (a and b) All comparisons are based on Mann–Whitney *U* test for independent samples. Negative *z* values indicate loss of function, positive ones indicate gain of function. (c) All comparisons are based on Chi-Square test.

Abbreviations: CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; Mech. WU, mechanical wind-up. DMA, dynamic mechanical allodynia; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; QST, quantitative sensory testing; Therm, WU thermal wind-up; VDT, vibration detection threshold; WDT, warm detection threshold.

4 | DISCUSSION

We investigated post-surgical QST trajectories over 6 months after thoracotomy, revealing an impairment of the affected intercostal nerve with a predominant loss of function. This study further revealed preoperative neuropathic pain symptoms, possibly in conjunction with sleep impairment within the first month after surgery and the presence of DMA 3 months after surgery, as key factor for an early prediction of 6-months NPSI scores.

In line with existing findings of incidence rates between 10%–33% (Duale et al., 2014; Guastella et al., 2011; Hopkins et al., 2015; Searle, Simpson, Simpson, Milton, & Bennett, 2009; Steegers, Snik, Verhagen, Drift, & Wilder-Smith, 2008), seven of 37 (19%) patients in the present study reported moderate neuropathic pain 6 months after thoracotomy. While the moderate group reported higher neuropathic pain anywhere in the body before surgery, more anxiety and sleep impairment after surgery, and showed an increased likelihood for DMA 3 months after surgery, it was the no/low group who showed overall more abnormal QST signs—all of which indicated functional loss. Due to relatively small group sizes, these comparisons should be interpreted with caution and future research is needed to confirm the findings.

A central element of the present study was the monthly QST profiles, revealing trajectories of functional loss and gain as a consequence of intercostal nerve damage. Across patients, we

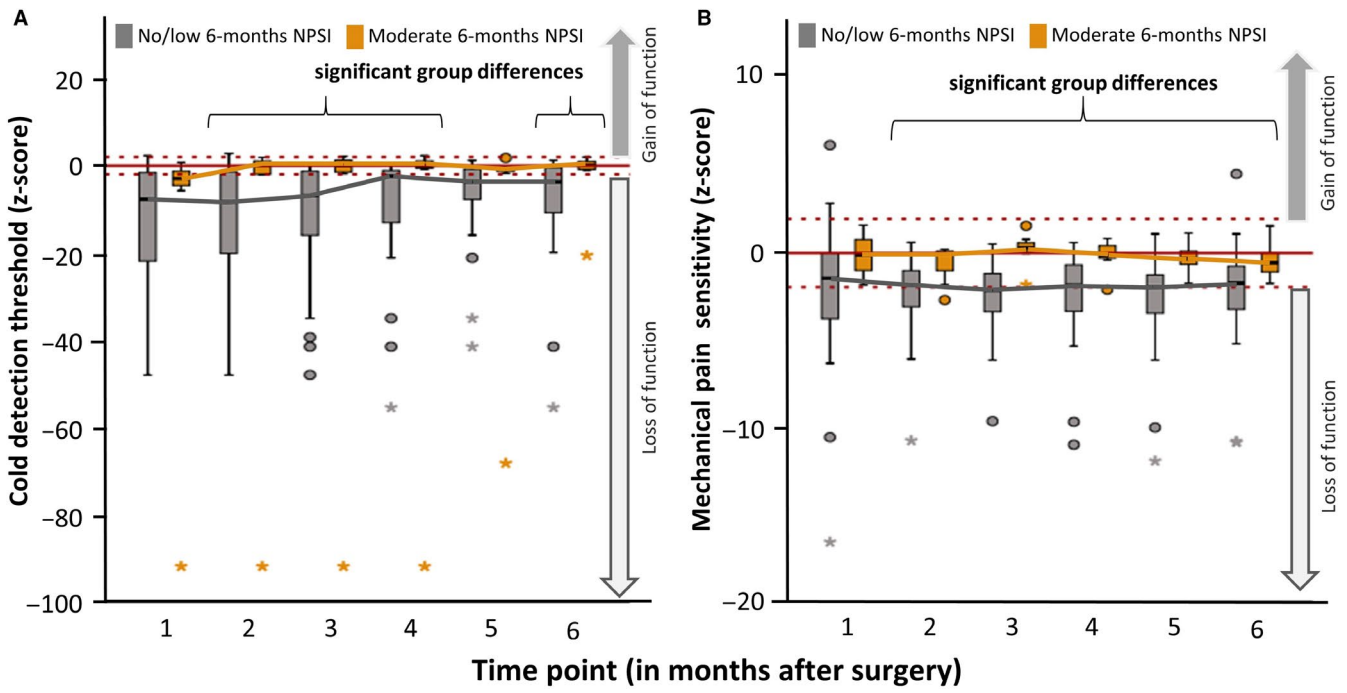

FIGURE 6 QST trajectories for (a) CDT and (b) MPS comparing patients who report no/low and moderate neuropathic pain symptoms 6 months after surgery. Negative symptoms are represented by z-scores below zero. CDT and MPS are the only QST subtests that differed between the two groups already at an early time point (2 months following surgery) and across several assessment time points. Loss of function was generally associated with low 6-months' NPSI scores. Depicted are box plots for each group and time point, with circles indicating outliers and stars indicating extreme outliers

observed predominantly functional loss, including increased thresholds for mechanical detection, mechanical pain, thermal detection thermal pain, and vibration. The only observed gain of function was increased sensitivity to pressure pain. The presence of functional loss following thoracotomy—at least immediately after surgery—is unsurprising, given that a total or partial conduction block in the affected nerve around incision has been reported, using intercostal nerve stimulation and measurements of motor evoked potentials, after removal of rib retractors (Rogers, Henderson, Mahajan, & Duffy, 2002). The QST trajectories in the present sample suggest that most negative signs—possibly representing a conduction block—remain stable for several months. This is comparable to previous results observed in patients with various peripheral nerve lesions, typically reporting loss of function that is still present months to even years after the initial onset of nerve damage (A. Hartmann et al., 2017; Wildgaard et al., 2012) or a combination of loss and gain of function (Gierthmuhlen et al., 2012; Pfau et al., 2014; Vollert et al., 2016). Across studies, the most commonly reported types of functional loss include decreased sensitivity to warmth, cold, mechanical detection and vibration (Gierthmuhlen et al., 2012; A. Hartmann et al., 2017; Pfau et al., 2014; Vollert et al., 2016). The most commonly reported gain of function is increased pressure pain (Gierthmuhlen et al., 2012; Pfau et al., 2014; Vollert et al., 2016), as observed here.

In the present study, various QST tests (including sensitivity to thermal and mechanical stimuli) differed between patients with no/low versus moderate 6-months NPSI scores. Interestingly, though, the findings imply greater impairment of the affected intercostal nerve in the group with no/low 6-months NPSI scores. Thus, the degree of self-reported neuropathic pain 6 months after surgery seems to be dissociated from the QST profiles. Examining the existing literature reveals mixed results for the association between neuropathic symptoms and nerve function assessed by QST. Across patients with different neuropathies, concordance rates between self-reported data and various QST subtests were generally weak (Gierthmuhlen, Binder, Forster, & Baron, 2018). When correlations were found between the measures, they were mainly reported for positive neuropathic pain symptoms, for instance allodynia, hyperalgesia (Attal et al., 2008; Freeman, Baron, Bouhassira, Cabrera, & Emir, 2014) and increased temporal summation of pain (Schreiber, Zinboonyahgoon, Vasudevan, Cornelius, & Edwards, 2017). In contrast, QST profiles of the present study revealed a clear predominance of negative signs, especially for the group that reported no/low 6-months NPSI scores. Therefore, we conclude that loss of nerve function is not a crucial factor for the development of neuropathic pain following thoracotomy.

Early factors that did predict chronic neuropathic pain symptoms included preoperative neuropathic pain symptoms anywhere in the body, and sleep impairment. Preoperative pain is consistently found to predict the development of chronic neuropathic pain (Duale et al., 2014; Martinez et al., 2015; Masselin-Dubois et al., 2013; Mustonen et al., 2018; Noiseux et al., 2014; Pereira et al., 2017). Like Dualé et al. (2014), we specifically assessed symptoms of neuropathic pain prior to surgery and found that a history of neuropathic pain was the strongest predictor of chronic neuropathic pain symptoms resulting from thoracotomy. This might indicate a genetic vulnerability for the development of neuropathies (Zorina-Lichtenwalter, Meloto, Khoury, & Diatchenko, 2016).

In addition to preoperative neuropathic pain symptoms, sleep impairment seemed to play a role in the chronification of neuropathic pain symptoms—sleep impairment differentiated the groups of low versus moderate 6-months NPSI scores at all post-surgical time points. When sleep impairment scores from baseline to 3 months after surgery were entered in the regression, there was a trend for sleep impairment 1 month after thoracotomy to predict 6-months NPSI scores. In line with recent research, proposing a causal link—rather than a reciprocal association –between sleep impartment and the manifestation of chronic pain (Gasperi, Herbert, Schur, Buchwald, & Afari, 2017; Harrison, Wilson, Munafò, & r., & management., 2014; Stocks et al., 2018), *reviewed in* (Finan, Goodin, & Smith, 2013), our findings suggest an influence of sleep impairment on the development of chronic neuropathic pain symptoms.

In contrast with physical preoperative predictors, findings for psychological predictors of neuropathic pain are less consistent across studies. While some studies report a predictive value of affective states for the development of neuropathic symptoms (Masselin-Dubois et al., 2013; Mustonen et al., 2018; Noiseux et al., 2014), Masselin-Dubois et al. (2013) reported that none of the preoperative psychological factors measured (depressive symptoms, anxiety, catastrophizing) distinguished the group of pain patients with and without neuropathic components after surgery. In line with this study, none of the psychological variables included in the present study differed at baseline between the groups of patients with no/low versus moderate 6-months NPSI scores. The fact, however, that none of the patients in the present study showed severe and only a few patients moderate anxiety or depression symptoms before surgery (6/37 and 3/37, respectively) (Stern, 2014), may explain why no influence of baseline anxiety and depression on the development of chronic neuropathic pain symptoms was detected. The earliest time point at which a difference in anxiety between the groups was observed was 2 months after surgery. However, anxiety levels did not add to the prediction of 6-months NPSI scores and may therefore be a consequence of experiencing neuropathic symptoms rather than a contributing factor to their development.

The emerging picture indicates an important role for physical well-being (including pre-existing pain and sleep quality) before and immediately after surgery in the development of chronic neuropathic pain. While the development

of neuropathic post-surgical pain may seem less dependent on pre-existing psychological components than described for predictors of any type of CPSP (e.g. (Abbott et al., 2011; Brandsborg, Nikolajsen, Kehlet, & Jensen, 2008; Fletcher et al., 2015; K. E. Hartmann et al., 2004; Jackson et al., 2016; Vandyk, Brenner, Tranmer, & Kerkhof, 2011; Weinrib et al., 2017)), it may be linked to physical/genetic factors [1; 10] and appears to be independent of the magnitude of nerve damage.

4.1 | Limitations

The sample size of this study is relatively small and the list of included risk factors was not exhaustive. Nevertheless, the strength of the study is the high density of QST measurements in a patient population with a high risk of neuropathic pain development. There are no comparable previous studies that assessed thoracotomy patients longitudinally for as many time points as we did, running comprehensive QST protocols and affective assessments in each session. Given the complexity and length of the testing, it was expected that a considerable number of patients would prematurely terminate the study or would have incomplete data sets. We consider it a success to obtain complete or nearly complete QST and NPSI trajectories of 5 to 7 testing time points for 37 patients.

To keep each testing session to a tolerable length we restricted the number of test variables. Variables that were included in addition to the QST data, such as measures of psychological distress (Jackson et al., 2016; Weinrib et al., 2017), and sleep impairment (Finan et al., 2013), were chosen because of strong evidence for their role in pain chronification. In fact, many of the included variables successfully distinguished between the groups with no/low and moderate 6-months NPSI scores. Finally, other factors that have been suggested previously to possibly have an influence on neuropathic pain development after surgery were standardized across patients, including surgery technique, the same surgeon for all patients, and a standardized anaesthesia/analgesia regime. Overall, this study describes trajectories of neuropathic signs and symptoms in addition to carefully chosen affective and physical factors in patients before and for 6 months following thoracotomy.

5 | CONCLUSIONS

Independent of the degree of nerve damage, the main predictors for post-surgical neuropathic pain were related to physical well-being before and shortly after surgery. Clinical routine should focus on the individual's physiological state for example by using easy-to-use self-report questionnaires, to identify patients early who are likely to develop chronic post-surgical neuropathic pain.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

WG contributed to conception and design, acquisition of data, analysis and interpretation of the data; she further drafted and revised the article and gave final approval of the version to be published. FBP contributed to the acquisition of data, analysis and interpretation of the data; she further helped revising the manuscript by her critical intellectual input and gave approval of the final version to be published. LN contributed to the design and acquisition of the data; she further helped revising the manuscript by her critical intellectual input and gave approval of the final version to be published. JFA contributed to the conception and design, acquisition and interpretation of data; he further helped revising the manuscript by his critical intellectual input and gave approval of the final version to be published. PS contributed to conception and design, and analysis and interpretation of the data; she further revised the article and gave final approval of the version to be published. All authors discussed the results and commented on the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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