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ORIGINAL ARTICLE

Pain trajectories and neuropathic pain symptoms following lung cancer surgery: A prospective cohort study

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Abstract

Background: Persistent postsurgical pain (PPSP) after lung cancer surgery is common and current definitions are based on evaluations at a single time point after surgery. Pain intensity and symptoms may however fluctuate and change over time, and be impacted by multiple and shifting factors. Studies of postoperative recovery patterns and transition from acute to chronic pain are needed for further investigation of preventive measures and treatments to modify unfavourable recovery paths.

Methods: In this explorative study, 85 patients undergoing surgery due to either presumptive or confirmed lung cancer reported pain intensities bi-monthly for 12 months. Pain trajectories during recovery were investigated, using group-based trajectory modelling. Associations with possible risk factors for PPSP, including clinical variables and anxiety and depression score (HADS), were also explored.

Results: A trajectory model containing three 12-month pain recovery groups was computed. One group without PPSP fully recovered (50%) within two to three months. Another group with mild-intensity PPSP followed a protracted recovery trajectory (37%), while incomplete recovery was observed in the last group (13%). Acute postoperative pain and younger age were associated with a less favourable recovery trajectory. More neuropathic pain symptoms were observed in patients with incomplete recovery.

Conclusions: Three clinically relevant recovery trajectories were identified, based on comprehensive pain tracking. Higher acute postoperative pain intensity was associated with an unfavourable pain recovery trajectory.

Significance Statement: Understanding the transition from acute to chronic postoperative pain and identifying preoperative risk factors is essential for the development of targeted treatments and the implementation of preventive measures. This study (1) identified distinct recovery trajectories based on frequent pain assessment follow-ups for 12 months after surgery and (2) evaluated risk factors for unfavourable postoperative pain recovery paths. Findings suggest that early higher postoperative pain intensity is associated with an unfavourable long-term recovery path.

1 | INTRODUCTION

Persistent postsurgical pain (PPSP) is common within most fields of surgery (Kehlet et al., 2006). Current consensus defines PPSP as any novel pain, occurring after a surgical procedure in relation to the surgery area, persisting beyond two to three months (Schug et al., 2019). The incidence of PPSP after lung cancer surgery remains high, regardless of the expanding use of minimally invasive techniques, with reported prevalences of 30 to 60% (Wang et al., 2023). The majority of previous studies evaluate chronic pain outcome at a single time point, typically three to 12 months after surgery (Bayman et al., 2017; Bayman & Brennan, 2014; Bendixen et al., 2016; Wildgaard et al., 2009, 2016). However, pain intensity and symptoms may fluctuate, and the perception and impact of chronic pain can be influenced by many factors not necessarily attributed to a specific surgical trauma or underlying condition (Bean et al., 2021; Galve Villa et al., 2020).

Optimal pain management is a key aspect in present and evolving Enhanced Recovery After Surgery (ERAS) protocols (Batchelor et al., 2019). Individualized pain risk assessment and identification of potential modifiable pre- and perioperative risk factors are considered central and pragmatic approaches for treatment interventions aimed at preventing the transition from acute to chronic pain (Amaya, 2018; Gupta et al., 2020; Humble et al., 2015). Several possible predictors of PPSP after thoracic surgery have been explored, e.g., quantitative sensory testing (QST), preoperative chronic pain, acute postoperative pain, psychological factors, sleep pattern and comorbidities (Bayman et al., 2017, 2019; Gandhi et al., 2020; Grosen et al., 2014; Liu et al., 2021; Wang et al., 2012; Yarnitsky et al., 2008) without consistent findings except from acute postoperative pain and possibly preexisting pain (Lim et al., 2021). Associations between possible predictors of PPSP and pain outcomes based on long-term pain trajectories after surgery have only been investigated in few studies (Bendixen et al., 2016; Ellyson et al., 2022; Gottschalk & Ochroch, 2008; Hovik et al., 2016; Liu et al., 2021; Müller et al., 2021). This approach is of particular interest, as it may enable preoperative PPSP risk profiling and provide information on when recovery trajectories diverge, hence indicating the timing for intervention to alleviate or prevent an unfavourable recovery path.

The aims of this exploratory study were to bi-weekly track the postoperative pain intensity over a 12-month period in a cohort of patients undergoing lung cancer surgery and to identify potential preoperative risk factors for PPSP. The hypotheses were (1) that distinct pain trajectories could be identified in patients who develop PPSP, with the option to detect the time interval when trajectories begin to diverge; (2) that these distinct pain trajectories were associated with preoperative risk factors for PPSP (acute postoperative pain, age, sex, surgical approach and psychological symptoms); and finally, (3) that neuropathic pain symptoms are common and more pronuonced in PPSP after lung cancer surgery.

2 | METHODS

2.1 | Study population and recruitment

Patients referred for elective surgery with confirmed or presumptive primary lung cancer were consecutively recruited during a three-year period from May 2014 until April 2018. Inclusion criteria were age ≥18 years, proficiency in reading and understanding Danish, and scheduled for thoracic surgery with pulmonary resection. Exclusion criteria were active or prior drug and/or substance abuse, preexisting pain conditions, cancellation of surgery or reoperation, inability to cooperate at the preoperative evaluation, and synchronous cancer diagnose other than primary lung cancer.

The study sample in this exploratory trajectory-based study was derived from a larger cohort study that evaluated preoperative risk factors of chronic post-thoracotomy pain (Danielsen et al., 2023).

2.2 | Data collection

A baseline assessment was performed one to three days before surgery in connection to routine preoperative clinical evaluation.

2.2.1 | Preoperative hospital anxiety and depression scale (HADS)

Preoperative anxiety and depression symptoms were assessed by HADS which contains fourteen items on anxiety and depression with a score of 0 to 3 for each item with maximum anxiety and depression sub-scores of 21 and a total combined score of 42. HADS is widely used and validated, also in cancer patients (Annunziata et al., 2020).

2.2.2 | Neuropathic pain symptom inventory (NPSI)

Neuropathic pain symptoms were evaluated by NPSI at baseline, six and twelve months after surgery. NPSI

contains five dimensions (burning, pressing, paroxysmal, evoked and dysesthesia) evaluated by a Numerical rating scale (NRS) from 0 (no pain) to 10 (worst pain imaginable) in for each dimension up to a maximum NPSI-score of 50 (Bouhassira et al., 2004).

2.2.3 | Preoperative sensory testing

Allodynia in the operation area was assessed by standard sensory brush (Somedic production AB, Sweden) where participants were instructed to report sensation during stimulation as either a light touch or unpleasant/painful. Hyperalgesia was assessed by weighted pinprick stimulation with increasing force (3.2, 6,4, 12.8, 25.6, 50.1 and up to 60.0 mN) on both sides of the chest wall until the patient reported a pricking pain. Testing was commenced on the contralateral side opposite to the operation area (ipsilateral).

2.2.4 | Clinical characteristics

Demographic data, type of surgical procedure and approach by either anterolateral thoracotomy or VATS (Video-Assisted Thoracoscopic Surgery), regional anaesthesia and tumour histology were extracted from the electronic medical records.

2.2.5 | Continuous pain survey

During follow-up, questionnaires were issued every 2 weeks for 12 months following surgery. Participants reported intensity of movement evoked pain, pain at rest, and pain course described as either no pain, constant pain with light fluctuations, constant pain with pain attacks, pain attacks without pain in between, and frequent pain attacks. Pain intensity was reported by NRS.

2.3 | Statistical analyses

Continuous variables are presented as means with standard deviations (SD) or medians with interquartile range (IQR), as appropriate, after evaluation of normality by QQ plots. Comparisons of univariate analysis of possible predictors were performed by one-way ANOVA with Tukey's test to determine estimates of differences in multiple comparisons, and the Kruskal–Wallis and Wilcoxon signed rank tests, as appropriate. Categorical variables were compared using Pearson's Chi-square test.

Multi-trajectory modelling was used to calculate multiple data-driven trajectories rather than using prespecified groups (D. S. Nagin et al., 2016). Multi-trajectory modelling is a method for group-based trajectory modelling (GBTM) and was performed using STATA Version 16.1 (StataCorp) with the *traj* package (Jones & Nagin, 2013; Nagin et al., 2016). Three normal censored models were investigated, using two to four pain intensity trajectory plots with different terms from linear to cubic order. Models were evaluated by Bayesian information criterion (BIC) and Akaike information criterion (AIC) where lower values represent better model fit. Group classifications within each model were evaluated by three assesments; mean probability of group membership, graphical plot assesment of trajectory curves and entropy which denotes class/group separation, where values closer to 0 indicates poor separation and a value of 1 signifies optimal separation. The principle of parsimony in the model evaluation was applied favouring the simplest model without loss of clinically relevant information. Final model selection was based on statistical evaluation of model fit, median number of observations in each group, graphical evaluation, and clinical application with regard to pain intensities between groups (Nagin & Odgers, 2010).

Neuropathic symptoms were evaluated by NPSI at baseline, 6 and 12 months after surgery, and compared in relation to pain trajectory. Emergent or increased postoperative neuropathic pain symptoms were defined as any increase in NPSI compared to baseline.

Participants with incomplete data were excluded from individual analyses. Statistical analyses were conducted in the STATA Version 16.1 software package, StataCorp. College Station, Texas.

2.4 | Ethics

The study was approved by The North Denmark Region Committee on Health Research Ethics (N-20140062) and conducted by the Declaration of Helsinki.

3 | RESULTS

3.1 | Descriptive statistics and response rate

Two hundred and one patients were recruited and a total of 39 (19.4%) were excluded due to reported preoperative pain and 19 (9.5%) due to unknown preoperative pain status. A total of 85 patients (42%) remained responsive during follow-up and were included in final analyses. A flowchart of the study sample is presented in Figure 1.

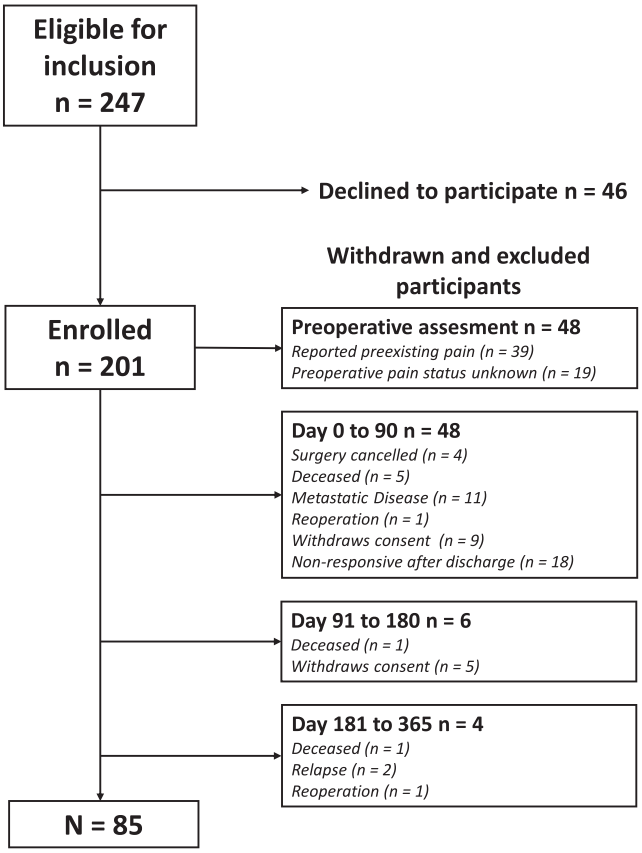

FIGURE 1 Flowchart of study inclusion and follow-up. Withdrawn and excluded participants by time points with reasons indicated.

Cohort baseline characteristics and missing data are presented in Table 1. Missing baseline variables >10% occurred in maximum acute postoperative pain (16.5%), with no reasons recorded.

Overall response rates during the continuous pain survey were high with a median (IQR) of 25 (20; 26) reported pain scores of 27 possible from baseline until the end of follow-up after 12 months. Seven participants (8.2%) reported less than ten pain scores for movement-evoked pain.

TABLE 1 Baseline demographics and clinical characteristics.

N **= 85**	
Age (years) *mean (SD)*	68.1 (9.9)
Sex (female) *n* (%)	49 (57.7)
Body mass index (kilograms/meter^2) *mean (SD)*	26.0 (5.0)
Surgery	
Surgical procedure *n* (%)	
VATS lobectomy	24 (28.2)
Open lobectomy	22 (25.9)
VATS wedge resection	26 (30.6)
Open wedge resection	3 (3.5)
Pneumonectomy	3 (3.5)
Other open resection	3 (3.5)
Other VATS resection	4 (4.7)
Postoperative regional anaesthesia *n* (%)	
Peroperative intercostal blockade	40 (47.1)
Epidural catheter	30 (35.3)
Intercostal blockade + epidural catheter	5 (5.9)
No regional anaesthesia recorded	10 (11.7)
Length of hospital stay (days) *median (IQR)*	4 (2; 8)
Maximum acute pain POD 0 (NRS)[a] *median (IQR)*	4 (0; 6)
Histology	
Primary lung cancer *n* (%)	62 (72.9)
Benign histology *n* (%)	23 (27.1)
Hospital Anxiety and Depression Scale (HADS)	
Anxiety score[b] *mean (SD)*	5.8 (2.8)
Depression score[c] *mean (SD)*	5.1 (2.1)
Combined HADS score[d] *mean (SD)*	11.0 (4.1)

Note: Missing, *n* (%).

Abbreviations: HADS; Hospital Anxiety and Depression Scale; NRS, numeric rating scale; POD, postoperative day; VATS, video-assisted thoracoscopic surgery.

[a]Maximum acute pain POD 0; 14 (16.5).

[b]HADS anxiety score; 5 (5.9).

[c]HADS depression score; 5 (5.9).

[d]Combined HADS score; 7 (8.2).

3.2 | Recovery trajectories

Evaluations of investigated models are presented in Table 2. All models exhibited high entropy above 0.8, with high mean probabilities of trajectory group membership >90% between classes. The two-class model displayed the best fit according to AIC and BIC, but contained only two trajectory groups, resulting in the loss of clinically relevant information on recovery trajectories for patients consistently reporting pain throughout the entire follow-up. The four-class model displayed the poorest fit and clinical relevance of trajectories.

The three-class model was chosen because it exhibited good fit (mean probability of group membership >0.9 in all groups with an entropy value of 0.94), and identified three clinically relevant recovery trajectories related to PPSP outcomes after 12 months, corresponding to three distinct recovery paths: (1) Complete recovery where pain resolved within two to three months ($n = 43$), (2) Protracted recovery where pain was mild and declined more slowly ($n = 31$), and (3) Incomplete recovery, where pain remained mild to moderate without any significant decline ($n = 11$). The median (IQR) number of reported NRS scores within trajectory groups were 25 (23; 26) in

TABLE 2 Fit statistics of group-based trajectory modelling.

	2-group model	3-group model	4-group model
Fit statistics			
AIC	−1979.28	−1820.21	−1777.18
BIC	−1987.82	−1833.65	−1795.50
Entropy	0.935	0.943	0.865
Number of participants in classes	50/35	43/31/11	24/19/32/10
Probability of group class membership among members *mean (SD)*			
Class 1 (linear)	0.98 (0.1)	0.96 (0.13)	0.97 (0.05)
Class 2 (Quadratic)	0.98 (0.1)	0.98 (0.08)	0.93 (0.14)
Class 3 (Quadratic)		0.94 (0.15)	0.95 (0.13)
Class 4 (Quadratic)			0.92 (0.17)
Number of observations per participant *median (IQR)*			
Class 1	25 (24; 27)	25 (17; 27)	25 (23; 26)
Class 2	26 (22; 27)	25 (23; 26)	25 (22; 26)
Class 3		23 (16; 26)	25 (19; 27)
Class 4			23 (16; 26)

Note: Lower Akaike information criterion (AIC) and Bayesian information criterion (BIC) values and higher entropy (values closer to 1.00) indicate better model fit.

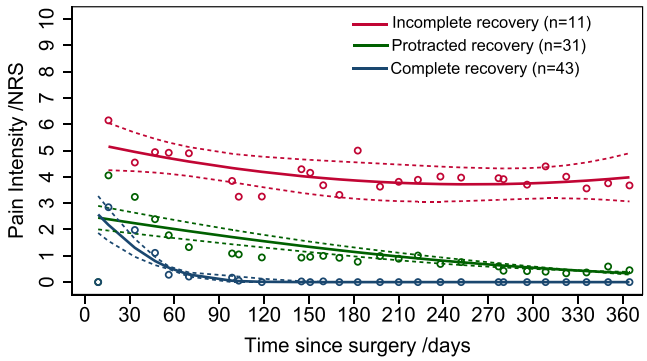

FIGURE 2 Twelve-month postoperative recovery trajectories after lung cancer surgery. Individual data points show mean pain intensity for movement-evoked pain. Solid lines show trajectories for each group. Dashed lines indicate upper and lower bounds of 95% confidence intervals.

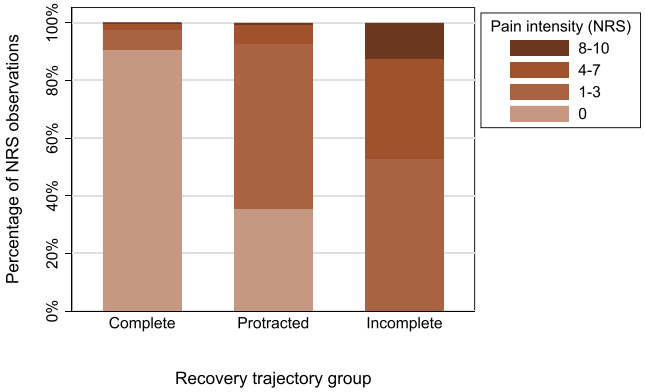

FIGURE 3 Distributions of NRS scores in recovery trajectory groups.

the complete recovery group, 25 (17; 27) in the protracted recovery group, and 23 (16; 26) in the incomplete recovery group. There were no significant differences in response rates between trajectory groups ($p = 0.47$).

The final model is presented in Figure 2. Distributions of reported NRS scores are presented in Figure 3. Underlying individual NRS observations within trajectory groups are reported in the supplemental material (Figure S1 and Table S1), together with Individual probabilities of membership within trajectory groups (Table S2).

Throughout follow-up, trajectories remained significantly different, without overlapping confidence intervals beyond the first month, where an overlap between the complete and protracted recovery groups was observed (Figure 2). A total of 43 participants (50.1%) did not develop PPSP and followed a declining trajectory with complete recovery (NRS = 0) after 60–90 days. Participants following the protracted recovery trajectory ($n = 31$, 36.7%) also exhibited a decline in pain and eventually reached recovery towards the end of follow-up, with a final reported mean NRS (95% CI) of 0.34 (0.28; 0.39) after 12 months. Participants following the incomplete recovery trajectory ($n = 11$, 13.2%) did not experience any significant decline in pain intensity during follow-up, and their pain remained constant, with a mean NRS (95% CI) of 4.0 (3.1; 4.9) at the end of follow-up.

3.3 | Neuropathic pain

No participants suffered from preoperative allodynia in relation to the planned surgical area, evaluated by brush stimulation. Differences in pin-prick pain thresholds when comparing the surgical side (ipsilateral) to the control (contralateral) side were present in two participants (2.4%) belonging to the complete recovery group; one participant reported a decreased threshold (3.2 g vs. 12.8 g), and one reported increased threshold (no pain versus 60.0 g).

A significant relationship was found between emergent and increased postoperative neuropathic pain symptoms and PPSP, as participants following the incomplete recovery trajectory were more likely to report neuropathic pain symptoms after 6 months ($\chi^2 = 11.9$, $p < 0.01$) and 12 months ($\chi^2 = 16.7$, $p < 0.01$) (Table 3). When comparing ΔNPSI, participants following the incomplete recovery trajectory reported higher NPSI compared to the protracted and complete recovery groups. However, only a clinically modest difference was observed in ΔNPSI (median ΔNPSI 1.5 IQR (1.0; 4.3), $p < 0.01$). Neuropathic pain symptoms were more frequently reported after 12 months in the protracted and incomplete trajectory groups compared to participants with complete recovery. A comparison of NPSI scores and neuropathic pain symptoms between trajectory groups is presented in Table 3. All recovery groups experienced a

TABLE 3 Neuropathic pain symptoms at baseline, 6 and 12 months after surgery in relation to recovery trajectory.

	Complete recovery $n = 43$		Protracted recovery $n = 31$		Incomplete recovery $n = 11$		
***N* = 85**	***n****		***n****		***n****		***p*-value**
Emergent or increased neuropathic pain symptoms after surgery *n* (%)							
6 months							
Increased	36	11 (30.6)	22	15 (68.2)	7	6 (85.7)	<0.01[a]
No change	36	25 (69.4)	22	7 (31.8)	7	1 (14.3)	
12 months							
Increased	34	5 (14.7)	19	10 (52.6)	7	6 (85.7)	<0.01[a]
No change	34	29 (85.3)	19	9 (47.4)	7	1 (14.3)	
Neuropathic pain symptoms after 12 months *n* (%)							
Burning	40	2 (5.0)	27	7 (24.9)	8	2 (25.0)	0.24[a]
Squeezing	40	2 (5.0)	26	6 (23.1)	8	3 (37.5)	0.08[a]
Pressure	40	3 (7.5)	26	10 (48.5)	8	5 (72.5)	<0.01[a]
Electric shocks	38	0 (0.0)	26	4 (15.4)	8	2 (25.0)	<0.01[a]
Stabbing	38	0 (0.0)	26	9 (44.6)	8	7 (87.5)	<0.01[a]
Pain evoked by light touch/brushing	38	3 (7.9)	26	7 (76.9)	8	3 (38.5)	0.07[a]
Pain evoked by pressure	38	3 (7.9)	26	12 (54.1)	8	5 (62.5)	<0.01[a]
Pain evoked by cold	38	2 (5.3)	26	7 (26.9)	8	2 (25.0)	0.01[a]
Pins and needles	38	6 (15.8)	26	6 (23.1)	8	5 (62.5)	0.03[a]
Tingling	38	3 (7.9)	26	12 (54.1)	8	4 (50.0)	<0.01[a]
NPSI-score *median (IQR)*							
Baseline	41	0 (0; 0)	26	0 (0; 0.3)	10	0 (0; 0)	0.09[b]
6 months	38	0 (0; 0.5)	25	1.2 (0.5; 4.3)	8	6.3 (3.5; 8.5)	<0.01[b]
12 months	35	0 (0; 0.5)	21	0.7 (0; 2.0)	7	2.0 (1.0; 4.3)	<0.01[b]
ΔNPSI-score *median (IQR)*							
0–6 months	36	0 (0; 0.8)	22	1.1 (0; 4.0)	7	5.5 (1.5; 9.0)	<0.01[b]
6–12 months	33	0 (−0.2; 0)	20	−0.25 (−2.8; 0.17)	6	−5.1 (−6.0; −0.5)	0.07[b]
0–12 months	34	0 (0;0)	19	0.3 (0; 2.3)	7	1.5 (1.0; 4.3)	0.01[b]

Note: Emergent or increased neuropathic pain is defined as any increase in NPSI compared to baseline. Number of participants with complete NPSI-data available for analysis denoted by '*n**'. Results from univariate analyses with *p*-values.

Abbreviations: NPSI, Neuropathic pain symptom inventory; NRS, Numeric rating scale; ΔNPSI, change in NPSI.

[a]Chi-square test.

[b]Kruskal–Wallis test.

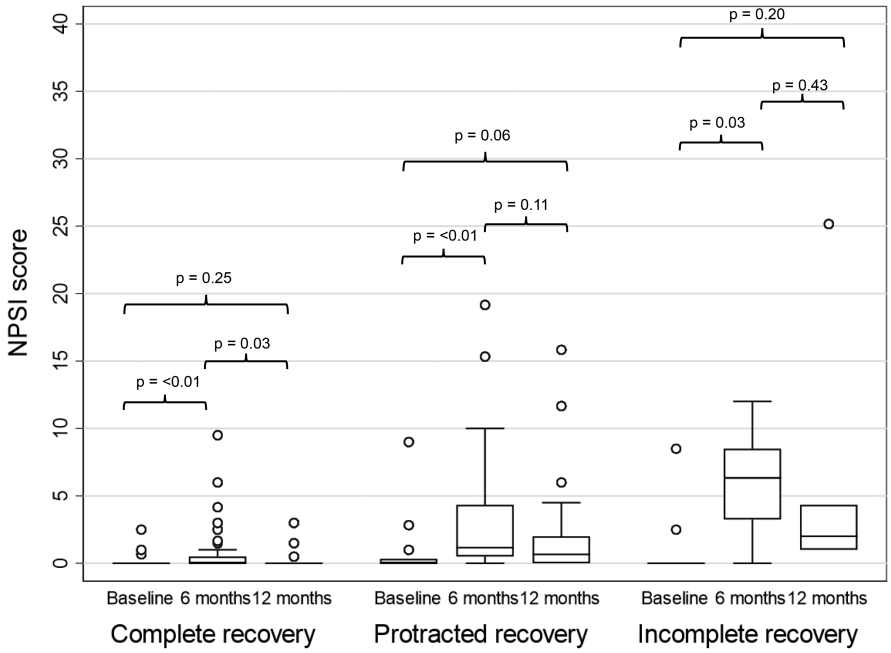

FIGURE 4 Neuropathic pain symptom inventory (NPSI) scores before surgery (baseline) and after six and 12 months in relation to recovery trajectory. Boxes show upper and lower quartiles with median indicated (line). Whiskers indicate maximum and minimum. Dots show individual outliers. *p*-values from analyses of intragroup changes in NPSI scores between assessments.

significant increase in NPSI from baseline to 6 months after surgery, but no significant increases were observed between baseline and end of follow-up (Figure 4).

Data on emergent or increased neuropathic pain in relation to surgical approach were available from 60 participants (70.6%). Thirty-six participants (60.0%) underwent VATS, and 9 (25.0%) of these reported new or increased neuropathic pain, compared to 12 of 24 participants (50.0%) undergoing open thoracotomy ($\chi^2 = 4.0$, $p = 0.05$).

3.4 | Predictors of pain trajectories

Univariate analyses of pain trajectory predictors are presented in Table 4. There was a significant effect of age (one-way ANOVA: $F(2,82) = 5.84$, $p < 0.01$). A Tukey post-hoc test revealed that participants following the protracted recovery trajectory were younger compared to the complete recovery group (mean difference −7.1 years 95%CI (−12.4; −1.8), $p < 0.01$), with a similar tendency observed when compared to the incomplete recovery group (mean difference − 7.6 years 95%CI (−15.6; −0.2), $p = 0.06$). No difference was observed when comparing the complete to the incomplete recovery trajectory group (mean difference 0.5 years 95%CI (−0.2; 15.6), $p = 0.99$).

Maximum acute postoperative pain was also significantly associated with a less favourable 12-month pain recovery trajectory ($\chi^2 = 12.47$, $p < 0.01$) (Table 4). More than half of the incomplete recovery group (54.6%) received an epidural catheter, but there were no significant differences in regional anaesthesia ($p = 0.73$) and surgical approach ($p = 0.74$) between and within groups (Table S3 in supplemental material).

Preoperative HADS score showed an overall significant effect on recovery trajectory (one-way ANOVA: $F(2,77) = 3.29$, $p = 0.04$). A Tukey post-hoc test did not reveal any significant differences when comparing the protracted recovery group to complete recovery group (mean difference 2.0 95%CI (-0.36; 4.4), $p = 0.11$), and when comparing the incomplete recovery group to the protracted (mean difference 0.8 95%CI (−2.6; 4.3), $p = 0.83$) and complete recovery groups (mean difference 2.9 95%CI (−0.4; 6.1), $p = 0.10$).

HADS anxiety and depression sub-scores did not exhibit a significant effect on pain recovery trajectory (one-way ANOVA: $F(2,77) = 2.24$, $p < 0.11$ and $F(2,77) = 2.20$, $p < 0.12$, respectively). When comparing the protracted recovery group to the complete recovery group, no differences were observed in anxiety (mean difference 1.1 95%CI (-0.5; 2.7), $p = 0.21$) and depression (mean difference 0.8 95%CI (-0.5; 2.0), $p = 0.29$) sub-scores. Similary, when comparing anxiety sub-scores in the incomplete recovery group to the protracted (mean difference 0.4 95%CI (−1.9; 2.7), $p = 0.89$) and complete recovery groups (mean difference 1.6 95%CI (-1.9; 3.8), $p = 0.21$), no differences were observed. The same was true for depression sub-scores; incomplete versus complete recovery (mean difference 1.3 95%CI (−0.4; 3.0), $p = 0.17$), and incomplete versus protracted recovery (mean difference 0.5 95%CI (−1.3; 2.3), $p = 0.76$).

TABLE 4 Results from univariate analysis of clinical characteristics and 12 months recovery trajectory groups.

	Complete recovery *n* = 43, 50.1%		Protracted recovery *n* = 31, 36.7%		Incomplete recovery *n* = 11, 13.2%		
***N* = 85**	***n****		***n****		***n****		***p*-value**
Demographics							
Age (years) *mean (SD)*	43	70.6 (8.9)	31	63.5 (10.6)	11	71.2 (7.8)	<0.01[a]
Sex (female) *n* (%)	43	23 (50.5)	31	21 (67.7)	11	5 (45.5)	0.32[b]
Body mass index (kg/m^2) *mean (SD)*	43	25.9 (4.9)	31	25.1 (4.2)	11	28.9 (6.3)	0.07[a]
Surgery							
Surgical approach *n* (%)							
VATS	43	29 (67.4)	31	18 (58.0)	11	7 (63.6)	0.71[b]
Open	43	14 (67.3)	31	27 (65.8)	11	4 (57.1)	
Surgical procedure *n* (%)							
VATS lobectomy	43	14 (32.6)	31	8 (25.8)	11	2 (18.2)	0.74[b]
Open lobectomy	43	9 (20.1)	31	10 (32.3)	11	3 (25.9)	
VATS wedge resection	43	14 (32.6)	31	8 (25.8)	11	4 (36.4)	
Open wedge resection	43	1 (2.3)	31	2 (6.5)	11	0 (0.0)	
Pneumonectomy	43	3 (7.0)	31	0 (0.0)	11	0 (0.0)	
Other open resection	43	1 (2.3)	31	1 (3.2)	11	1 (9.1)	
Other VATS resection	43	1 (2.3)	31	2 (6.5)	11	1 (9.1)	
Postoperative regional anaesthesia *n* (%)							
Peroperative intercostal blockade	43	20 (46.5)	31	15 (48.4)	11	5 (45.5)	0.73[b]
Epidural catheter	43	14 (32.6)	31	10 (32.3)	11	6 (54.5)	
Intercostal blockade + epidural catheter	43	3 (7.0)	31	2 (6.5)	11	0 (0.0)	
No regional anaesthesia	43	6 (14.0)	31	4 (12.9)	11	0 (0.0)	
Maximum acute pain POD 0 (NRS) *median (IQR)*	36	2 (0; 5)	25	5 (2; 7)	10	7 (4; 8)	<0.01[c]
Length of hospital stay (days) *median (IQR)*	43	4 (2; 9)	31	5 (3; 8)	11	5 (4; 7)	0.89[c]
Histology							
Primary lung cancer *n* (%)	43	32 (74.4)	31	22 (71.0)	11	8 (72.7)	0.95[b]
Benign histology *n* (%)	43	11 (25.6)	31	9 (29.0)	11	3 (27.3)	
Preoperative Hospital Anxiety and Depression Scale							
Anxiety score *mean (SD)*	41	4.2 (2.9)	28	6.3 (2.6)	11	6.7 (2.6)	0.11[a]
Depression *score mean (SD)*	41	4.7 (2.2)	28	5.5 (1.9)	11	6.0 (2.4)	0.12[a]
Combined HADS score *mean (SD)*	40	9.9 (4.2)	27	11.9 (3.6)	11	12.7 (4.4)	0.04[a]

Note: Percentages calculated from available data (*n**).

Abbreviations: HADS; Hospital Anxiety and Depression Scale; NRS, numeric rating scale; POD, postoperative day; VATS, video-assisted thoracoscopic surgery.

[a]One-way ANOVA.

[b]Chi-square test.

[c]Kruskal-Wallis test.

4 | DISCUSSION

Using bi-weekly pain assessments for 12 months after lung cancer surgery, this study identified three distinct and clinically relevant postoperative recovery trajectories. Higher acute pain during the first 24 h after surgery was associated with PPSP and a less favorable recovery trajectory. More neuropathic pain symptoms, but only a minimal increase in neuropathic pain symptom inventory score, were observed in the incomplete recovery trajectory group.

4.1 | Recovery trajectory modelling

Most evaluations of PPSP are based on observations at a single time point and do not provide information on mean pain intensity and fluctuations over time (Bayman

et al., 2017; Katz et al., 1996; Rizk et al., 2014; Wildgaard et al., 2016). According to the current IASP definition, any novel or intensified pain occurring in relation to the operation site persisting for more than two to three months should be considered as PPSP (Schug et al., 2019). When considering the prevalence of PPSP in relation to the presented recovery trajectories in our study, findings correspond to previous reports, as the prevalence of any pain (NRS≥1) at this time point was approximately 50%, and 12% when using NRS≥3 as cut-off. However, this static definition does not account for dynamic temporal fluctuations in pain intensity and offers no information on recovery paths.

Several recent studies on acute postoperative pain trajectories have also investigated the transition from acute to chronic pain (Awadalla et al., 2022; Bendixen et al., 2016; Ellyson et al., 2022; Gjeilo et al., 2020; Gottschalk & Ochroch, 2008; Liu et al., 2021; Müller et al., 2021; Saito et al., 2023). These studies primarily calculate trajectories based on frequent observations during hospitalization, while the observation frequency is considerably reduced after discharge. To our knowledge, the most detailed existing long-term study employing the method of GBTM in thoracic surgery was based on four assessments after discharge, without distinguishing between preexisting pain conditions and PPSP (Gjeilo et al., 2020). Other studies have also reported long-term recovery trajectories in thoracotomy patients, where patients were classified in relation to recovery status based on the final NRS score (Bayman et al., 2019; Gottschalk & Ochroch, 2008). Recovery to NRS <1 in the designated no-pain groups first occurred beyond 12–24 weeks, and NRS = 0 was, for obvious reasons, first reached at the end of follow-up. The presented trajectory model in our study possibly conveys a more clinically precise and relevant picture.

Our underlying hypothesis was that a specific time interval could be identified during recovery where trajectories started to diverge into either complete recovery or PPSP. The identified trajectories did not reveal a specific time interval for differentiation of recovery paths, but did demonstrate that the pain intensity differed significantly between trajectory groups during the 12-month follow-up period. The presented trajectory model supports the current definition of PPSP since full recovery was achieved within the first 3 months in the complete recovery group (Schug et al., 2019). The protracted recovery trajectory group did obtain near complete remission, with a mean NRS <1 after approximately nine to 12 months, indicating the possibility of recovery from PPSP. The model indicated only modest recovery at best in case of higher pain during the first weeks after surgery, as observed in the incomplete recovery group. This corresponds to findings from a similar trajectory study (Liu et al., 2021), implying that particular attention to early pain relief and control, including the first weeks after discharge, could be a potential target for prevention of PPSP, since current literature indicates acute pain as a substantial risk factor for PPSP (Awadalla et al., 2022; Bayman et al., 2017; Gottschalk & Ochroch, 2008; Katz et al., 1996; Niraj et al., 2017; Pluijms et al., 2006).

4.2 | Neuropathic pain

Chronic neuropathic pain symptoms after thoracic surgery are common with reported incidences of 20%–30% after 6 to 12 months (Dualé et al., 2014; Homma et al., 2018; Maguire, Ravenscroft, et al., 2006; Shanthanna et al., 2016). The extent of intercostal nerve damage may be a key component in postoperative neuropathic pain, since less chronic neuropathic pain has been reported after minimally invasive VATS compared with open thoracotomy (Homma et al., 2018; Shanthanna et al., 2016), while others did not find any association with surgical approach (Maguire, Latter, et al., 2006; Searle et al., 2009). Our results indicate that emergent neuropathic pain in relation to the operation area was associated with open thoracotomy and a less favourable recovery trajectory.

Neuropathic pain intensity, evaluated by NPSI, increased from baseline to 6 months in all trajectory groups. However, all trajectory groups returned to preoperative baseline NPSI levels after 12 months. It has been suggested that surgical trauma and nerve damage are not necessarily associated with a long-term increase in neuropathic pain with a return to preoperative levels during recovery (Gandhi et al., 2020; Takenaka et al., 2020). Our study supports these findings, although the results should be interpreted with care due to small sample sizes and missing data.

4.3 | Pain trajectory predictors

The exploratory analysis identified acute pain intensity as a predictor of a less favourable recovery trajectory as previously reported in similar trajectory studies (Bayman et al., 2017; Gottschalk & Ochroch, 2008; Liu et al., 2021).

Younger age was associated with a protracted recovery trajectory. However, no significant associations were found when comparing the complete and incomplete recovery groups, which might be a result of the limited sample size in the latter. In thoracic surgery, current evidence suggests a small but significant association between PPSP and younger age (Lim et al., 2021). No effects of HADS in relation to recovery trajectory were observed in our study,

as previously been reported in a comparable study (Liu et al., 2021). Current evidence regarding the significance of psychological factors as predictors of PPSP risk in thoracic surgery is mixed (Lim et al., 2021), but compiled existing evidence across several surgical fields indicates an association between preoperative psychological factors and PPSP risk (Giusti et al., 2021).

4.4 | Limitations

Employing data-driven GBTM inherently carries a risk of irrelevant classification and misclassification, particularly when considering a complex clinical perspective. However, the identified trajectory model exhibited clinically relevant recovery paths, based on numerous observations within each trajectory group. While the probabilities of group membership were generally high, classification using GBTM is vulnerable to limited observations within smaller groups. The incomplete recovery group was relatively small, with two participants exhibiting a probability of membership lower than the mean probability of >90%, which was also observed for three and two patients in the protracted and complete recovery groups, respectively.

Our data did not contain information on the use of analgesics which constitutes a potential confounder although standard analgesics will only have minimal effect in those with neuropathic like pain. However, results from previous studies show that patients with higher pain trajectories use more analgesics (Gjeilo et al., 2020; Müller et al., 2021), implying that lower pain cannot be attributed to the use of analgesics, but rather the opposite.

Our study presents a detailed recovery trajectory model describing the gap between the earliest postoperative weeks and the transition to either PPSP or complete remission. However, it only contains limited information on early acute postoperative pain during admission. Previous reports indicate that an early high pain trajectory seems associated with postoperative pain beyond discharge, implying that a detailed picture of both acute and early short-term pain trajectories is also of interest in relation to PPSP (Awadalla et al., 2022; Bayman et al., 2017; Gottschalk & Ochroch, 2008).

Because all patients with preoperative pain were excluded, the impact of preexisting chronic pain was not investigated, which would be of interest, since existing studies have reported an increased risk of PPSP in lung cancer patients with preoperative pain conditions (Bayman et al., 2017; Gjeilo et al., 2020; Hetmann et al., 2015; Kampe et al., 2016; Liu et al., 2021). Chronic pain is common in any patient population and a broader clinical applicability of our results is restricted by excluding patients with preexisting pain. Nonetheless, this study presents a detailed picture of pain recovery trajectories in surgical lung cancer patients without preexisting pain, with an exclusive description of surgery-related pain only.

Our findings are based on a comprehensive follow-up, but the sample size remains relatively small, and the analysis of PPSP predictors should be interpreted accordingly.

5 | CONCLUSION

The bi-weekly pain assessments for 12 months provided a unique option to follow and describe 12-month postoperative recovery trajectories. Each trajectory represented a specific recovery path from early postsurgical pain to either complete recovery, protracted recovery, or incomplete recovery. Exploratory analyses of risk factors showed a significant association with acute postoperative pain and protracted or incomplete recovery. Patients following the incomplete recovery trajectory reported significantly more neuropathic pain symptoms, while only a small increase in neuropathic pain intensity was observed. Preoperative pain risk profiling and research into the transition from acute to chronic postsurgical pain is critical for further investigation of interventions to prevent and alleviate PPSP.

AUTHOR CONTRIBUTIONS

AVD contributed to the acquisition, validation, analysis and interpretation of the data together with drafting, revision and submission of the published version of this article. BD and JH contributed with expertise in electronic data acquisition and provided the platform and design of the database. Furthermore, JH contributed to data collection. CS included patients, performed preoperative assessments and contributed to data collection and interpretation. KD and JB contributed to data analysis and interpretation, together with critical inputs in the writing of the article. JJA, LAN and KKP contributed to the conception and design of the study, data analysis and interpretation, provided critical inputs in the writing of the article. All authors contributed to critical revision and final approval of the published article.

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CONFLICT OF INTEREST STATEMENT

The authors have no present or potential conflicts of interest to declare in relation to the current study.

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