Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Does Preoperative Hookwire Localization Influence Postoperative Acute and Chronic Pain After Video-Assisted Thoracoscopic Surgery: A Prospective Cohort Study

Lingchao Kong[1,2,*], Lingling Gao[1,2,*], Hong Zhang[1,2], Xin Wang[1,2], Jun Zhang[1,2]

[1]Department of Anesthesiology, Fudan University Shanghai Cancer Center, Shanghai Medical College, Fudan University, Shanghai, People's Republic of China; [2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jun Zhang, Department of Anesthesiology, Shanghai Cancer Center, Fudan University and Department of Oncology, Shanghai Medical College, Fudan University, No. 270 Dong'An Road, Xuhui District, Shanghai, 200032, People's Republic of China, Tel +86-21-64175590, Fax +86-21-64174774, Email snapzhang@aliyun.com

Purpose: This study aimed to investigate whether preoperative computerized tomography-guided hookwire localization-associated pain could affect acute and chronic postsurgical pain (CPSP) in patients undergoing video-assisted thoracoscopic surgery (VATS).

Methods: We enrolled 161 adult patients who underwent elective VATS; sixty-nine patients experienced hookwire localization (Group A) and 69 did not (Group B). Group A was further subdivided into the multiple localization group (n=35, Group $A_{multiple}$) and the single localization group (n=34, Group A_{single}) according to the number of hookwires. The numerical rating scale (NRS) was used preoperatively, during recovery at the post-anesthesia care unit (PACU), and the first two days, 3 and 6 months postoperatively. Furthermore, multivariate regression analysis was used to identify the risk factors associated with CPSP. The postoperative adverse events, length of hospital stay, and satisfaction in pain management were also recorded.

Results: The incidence and severity of acute postoperative pain were similar between Group A and Group B ($p > 0.05$). The incidence (56.5% vs 30.4%, $p = 0.002$) and the NRS scores (2.0 [2.0–3.0] vs 1.0 [1.0–2.0], $p = 0.011$) for CPSP were significantly higher in Group A than in Group B at 3 months postoperatively. On subgroup analysis, compared with Group A_{single}, the intensity of CPSP (2.0 [2.0–3.0] vs 2.0 [1.0–2.0], $p = 0.005$) in Group $A_{multiple}$ was slightly higher at 3 months postoperatively. Conversely, the CPSP incidence (60.0% vs 29.4%, $p = 0.011$) was significantly higher at 6 months postoperatively in Group $A_{multiple}$. The multivariate regression analysis further validated hookwire localization as a risk factor for CPSP (odds ratio: 6.199, 95% confidence interval 2.049–18.749, $p = 0.001$). Patient satisfaction relating to pain management at 3 months postoperatively was lower in Group A ($p = 0.034$).

Conclusion: The preoperative pain stress of hookwire localization increased the incidence and intensity of CPSP rather than acute pain at 3 months postoperatively, especially in patients with multiple hookwires.

Keywords: chronic postsurgical pain, postoperative acute pain, hookwire localization, video-assisted thoracoscopic surgery, lung cancer

Introduction

Postoperative pain after thoracic surgery affects the quality of a patient's recovery and its management remains a major clinical challenge. The suboptimal control of acute pain after thoracotomy or video-assisted thoracoscopic surgery (VATS) is associated with chronic postsurgical pain (CPSP). CPSP, defined by pain intensity and pain-related functional interferences, is a common post-thoracotomy complication. The incidence of CPSP in thoracic surgery varies from 14% to 83% depending on the type of surgery or the definition of CPSP.[1–4] CPSP can lead to increased postoperative complications, long-term disability, reduced quality of life, and increased healthcare spending.[5] The development of CPSP is considered a multifactorial

Received: 25 August 2022
Accepted: 24 December 2022
Published: 5 January 2023

© 2023 Kong et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

process. Numerous studies have investigated the risk factors associated with "pain chronification" after thoracic surgery. Moreover, pre-existing pain is one of these risk factors contributing to the development of CPSP.[6] A recent meta-analysis reported that the pooled unadjusted odds ratios (ORs) for the development of CPSP were 2.43 for preoperative pain at the surgical site, 1.75 for preoperative pain elsewhere, and 3.95 for preoperative pain at an unspecified site.[7] Considering this, pre-existing pain is not only associated with severe postoperative acute pain,[8] but also with CPSP.[9] Furthermore, pre-existing pain is usually of a chronic nature before surgery.[10–12] Importantly, whether preoperative acute pain stress influence the incidence and intensity of CPSP are unknown.

The excision of lung nodules during thoracoscopic surgery is popular under the concept of enhanced recovery after surgery. Lung nodules within lung parenchyma judged too small or too far from the pleural surface must be localized preoperatively. The percutaneous placement of spring hookwires is widely used to localize small pulmonary nodules under computerized tomography (CT) guidance before VATS.[11,12] This aims to assist thoracic surgeons to quickly identifying the targeted lesions during thoracoscopic resections. Although local anesthesia is used, hookwire localization-associated pain remains a concern in the clinical setting.[13] The extent and mechanism of preoperative pain stress caused by CT-guided hookwire localization and its effects on postoperative acute and chronic pain have not been previously reported.

In this prospective observational cohort study, we aimed to determine whether the acute pain stress from preoperative CT-guided hookwire localization influences the incidence and intensity of postoperative acute and chronic pain after VATS at a single cancer center.

Materials and Methods

Patients and Groups

Consecutive patients, aged 18–75 years, indicated for VATS for lung cancer under general anesthesia and assessed with the American Society of Anesthesiologists (ASA) physical status of I–II, were recruited from the Fudan University Shanghai Cancer Center (FUSCC) from August to December 2021. The study was completed in July 2022. Exclusion criteria included severe cardiac and lung diseases, history of chronic pain or painkillers or psychotropic drugs usage within 3 months before surgery, severe anxiety or depression, and preoperative chemotherapy and radiation therapy. This study was approved by the Institutional Review Board of FUSCC (Number: 2107238–15) and written informed consent was obtained from all trial participants. The trial was registered after patient enrollment at clinicaltrials.gov (NCT05478460, Principal investigator: Jun Zhang, link to trial registry: https://register.clinicaltrials.gov/, Date of registration: May 30, 2022).

The patients were assigned into two groups (Group A: preoperative hookwire localization and Group B: without preoperative hookwire localization). Patients in Group A underwent CT-guided hookwire localization 1 hour before VATS on the day of surgery. In brief, the patient was placed on a CT table in a suitable position (supine, prone, lateral) according to the location of the pulmonary nodule(s) to obtain the shortest needle insertion route for their initial CT scan. Local anesthesia of the skin and planned puncture tract was performed by a radiologist using 1% lidocaine. Then, a needle was advanced using a technique identical to that for CT-guided biopsies, and a hookwire or multiple hookwires (20 G ×120 mm, PAJUNK®, Geisingen, Germany) were inserted into or close to the pulmonary nodule(s). The localizations were deemed successful in all patients who were able to hold his/her breath. Patients who did not undergo preoperative hookwire localization (Group B) had the same preoperative preparation as patients in Group A other than the localization.

Anesthetic Management

Anesthesia and perioperative management were identical for both groups. Standard monitoring was performed including electrocardiogram (ECG), invasive blood pressure, pulse oxygen saturation (SpO_2), and end-tidal carbon dioxide partial pressure ($PetCO_2$) during the surgical procedures. Bispect ral index (BIS) monitoring (Version XP, Covidien plc, Dublin, Ireland) was used intraoperatively to maintain the appropriate depth of anesthesia. Specifically, 1 mg midazolam, propofol targeted controlled infusion (TCI) at 3–4 μg/mL (Marsh mode), 0.03 μg/kg sufentanil, and 0.6 mg/kg rocuronium, were used for anesthetic induction, and endotracheal intubation. The correct placement of a double-lumen tube was confirmed by fiber bronchoscopy. Propofol TCI at 2–4 μg/mL, and remifentanil TCI 1–2 ng/mL (Minto mode) were used intraoperatively to maintain the loss of consciousness and analgesia. Intermit rocuronium was administered for immobility. The intraoperative

hemodynamics was kept stable Changes in blood pressure and heart rate generally were kept within 20% of the preoperative levels. One-lung ventilation was performed before VATS to secure the collapse of the independent lung. The patients were delivered to PACU for further monitoring and postoperative management following surgery. Subsequently, patients were transferred to the ward when the Steward score was >4.

Surgical Procedure

VATS procedure for lung cancer was performed in the lateral position. The types of surgical procedures included lobectomy, segmentectomy, and wedge resection. The single-port, two-port, or three-port VATS and location of the chest wall incision were selected to remove lung cancer by an experienced thoracic surgeon group according to the clinical features of the patient's lesion. Lymph node excision was performed as necessary. The length of incisions was identical and the resected tissues were extracted from a disposable incision protector placed at the port. At the end of the surgery, a chest tube was placed for postoperative thoracic drainage. During the insertion of the chest drain, injury to the intercostal nerves was cautiously avoided. The draining chest tube was removed once significant air leakage was not detected for more than 24 hours and the total amount of pleural effusion was less than 200 mL per day.

Postoperative Pain Control

A patient-controlled intravenous analgesic (PCIA) pump was used by all patients after surgery. The analgesia formula included 100 ug sufentanil and 200 mg flurbiprofen diluted in 200 mL with normal saline. The settings of the PCIA pump were managed by a dedicated Acute Pain Service team. The pump settings included a background infusion at 4 mL/h and a patient-controlled bolus at 4 mL/time, with a lockout interval of 20 min. In patients with a persistent numerical rating scale (NRS) score of >5 for 1 hour, intravenous oxycodone (30 mg) was provided as rescue analgesia.

Pre- and Postoperative Pain Evaluations

Acute Pain Evaluation

The NRS was used for evaluating pre- and postoperative pain. The pain intensity was classified as no pain (NRS = 0), mild pain (NRS = 1–3), moderate pain (NRS = 4–6), and severe pain (NRS = 7–10). The preoperative pain was assessed following the hookwire localization procedure when the patient was in the waiting area, whereas acute postoperative pain was assessed in the PACU, 24 and 48 hours postoperatively in the ward. Patients were requested to report their pain scores both at rest and on coughing.

CPSP Evaluation

Telephone follow-up interviews were performed to assess chronic pain 3 and 6 months after VATS. The incidence and intensity of pain were assessed based on the following questions:

1. Have you experienced any pain along the scar after surgery, and was the pain different from what you experienced one day before the surgery?
2. Is there any other cause for the pain (eg, recurrence of a malignant tumor or chronic wound infection)?
3. Has the pain persisted for at least 3 (or 6) months?
4. Please breathe deeply and cough twice. Then, rate your chest pain on the NRS from 0–10 (0: no pain and 10: worst possible pain).

We defined CPSP in the same way as Macrae.[14] Pain score of ≥1 at surgical sites measured by an 11-point NRS was diagnosed as CPSP.[15] In particular, the following were considered: 1) pain that developed after surgery; 2) other etiologies have been excluded; 3) the exacerbation of pre-existing chronic pain has been ruled out; and 4) pain that persisted for at least 3 (or 6) months after VATS.

Demographic characteristics and clinical data including preoperative anxiety and depression status, intraoperative opioids consumption, surgical duration, and postoperative nausea (PON) and vomiting (POV), shoulder-back pain, the length of hospital stay, satisfaction of pain management, were collected. The patient's satisfaction for pain management

was rated with a 5-point Likert scale (1 = very unsatisfied, 5 = very satisfied). The status of anxiety and depression were evaluated by the Hamilton anxiety scale (HAMA-14)[16] and the Hamilton depression scale (HAMD-17),[17] respectively.

Statistical Analysis

Sample Size Calculation

From our preliminary results, the NRS score at 3 months postoperatively (POM3) was 2.5±1.2 in patients with preoperative hookwire localization, and 1.8±0.8 in those without preoperative hookwire localization, respectively. There was a 0.7 difference between the two groups, with a variance of 1.2. Considering a statistical power of 90% and a two-sided α significance level of 0.05, a sample size of 62 patients in each arm was required to test our hypothesis. A dropout rate of 10% was included. In total, 69 patients were required for each group and a total of 138 patients were needed for our study.

Data normality was tested using the Kolmogorov–Smirnov test. Categorical variables were presented as numbers (percentage) or proportions, and continuous variables were presented as mean ± standard deviation (SD), or median (interquartile ranges, IQR), depending on the data distribution (normal distribution or not). The continuous variables were analyzed using the independent *t*-test for variables with a normal distribution and the Mann–Whitney *U*-test for variables that did not demonstrate a normal distribution. Pearson χ^2 test or Fisher exact test for categorical variables was used to compare between two groups. Multivariate logistic regression analysis was used to identify the risk factors that were predictive of CPSP after VATS. Statistical significance was defined as $p<0.05$. Statistical analyses were performed using SPSS 19.0 (SPSS, Inc., Chicago, IL, USA).

Results

This study recruited 161 patients. All cases of one or multiple hookwires were successful. Of the 161 patients, 23 patients withdrew from the study due to various reasons: 11 cases were changed to thoracotomy, two required re-operation during the first 3 months postoperatively, five required repeat thoracic catheter insertion during hospitalization, two experienced chest infection, and three were lost to follow-up. Hence, 138 patients were included in the final analysis (Figure 1). Of the 138 patients, 69 underwent hookwire localization (Group A) and 69 did not (Group B). None of the patients required a preoperative drain for pneumothorax. Small pulmonary nodules (SPNs) in both groups of patients were successfully removed thoracoscopically. The demographic characteristics and clinical data are summarized in Table 1. The two groups were comparable in terms of age, gender, body mass index (BMI), ASA classification, age-adjusted Charlson Comorbidity Index (aCCI), previous surgical history, preoperative Hamilton anxiety scale and Hamilton depression scale (HAMA/MAMD) scores, type of lung surgery, duration of chest drainage, and postoperative length of stay. Notably, the SPNs were located more in the left lung in Group A than in Group B ($p = 0.013$), and there were more ports for VATS in Group B than in Group A ($p = 0.025$). Moreover, the duration of surgery and anesthesia was longer in Group B than in Group A (91.5±40.8 vs 73.8±38.1, $p = 0.009$; 125.5±41.6 vs 109.3±38.1, $p = 0.019$, respectively). Furthermore, there was no significant difference in the intraoperative consumption of sufentanil and remifentanil between the two groups (Supplementary Table 1).

Acute Pre- and Postoperative Pain

In Group A, the incidence of acute pain after hookwire localization was 95.65% (66/69). These patients generally experienced mild-moderate pain. The NRS score was 2.0 (1.0, 2.0) at rest, and 3.5 (2.0, 5.0) on coughing (Table 2). Half of the patients (33/66) reported mild pain and the other half (33/66) indicated moderate pain.

The Intensity of acute postoperative pain both at rest (PACU: $p = 0.239$, postoperative day (POD)1: $p = 0.531$, POD2: $p = 0.797$) and on coughing (PACU: $p = 0.250$, POD1: $p = 0.066$, POD2: $p = 0.157$) were comparable in the PACU and at POD1 and POD2 between two groups (Table 2). Correspondingly, the sufentanil consumption was similar for both the groups at POD1 and POD2. However, at POD1, the patients in Group A (2.0 [1.0–6.0]) utilized the PCIA more times than the patients in Group B (1.0 [1.0–4.0], $p = 0.045$, Supplementary Table 1). This suggests that patients who underwent preoperative hookwire localization may have more severe acute postoperative pain shortly after VATS.

CPSP

The incidence of CPSP 3 months after surgery in Group A (56.5%, 95% confidence interval (CI): 44.5–68.5%) was higher than in Group B (30.4%, 95% CI: 19.3%–41.6%, $p = 0.002$) (Figure 2). Furthermore, the NRS score 3 months

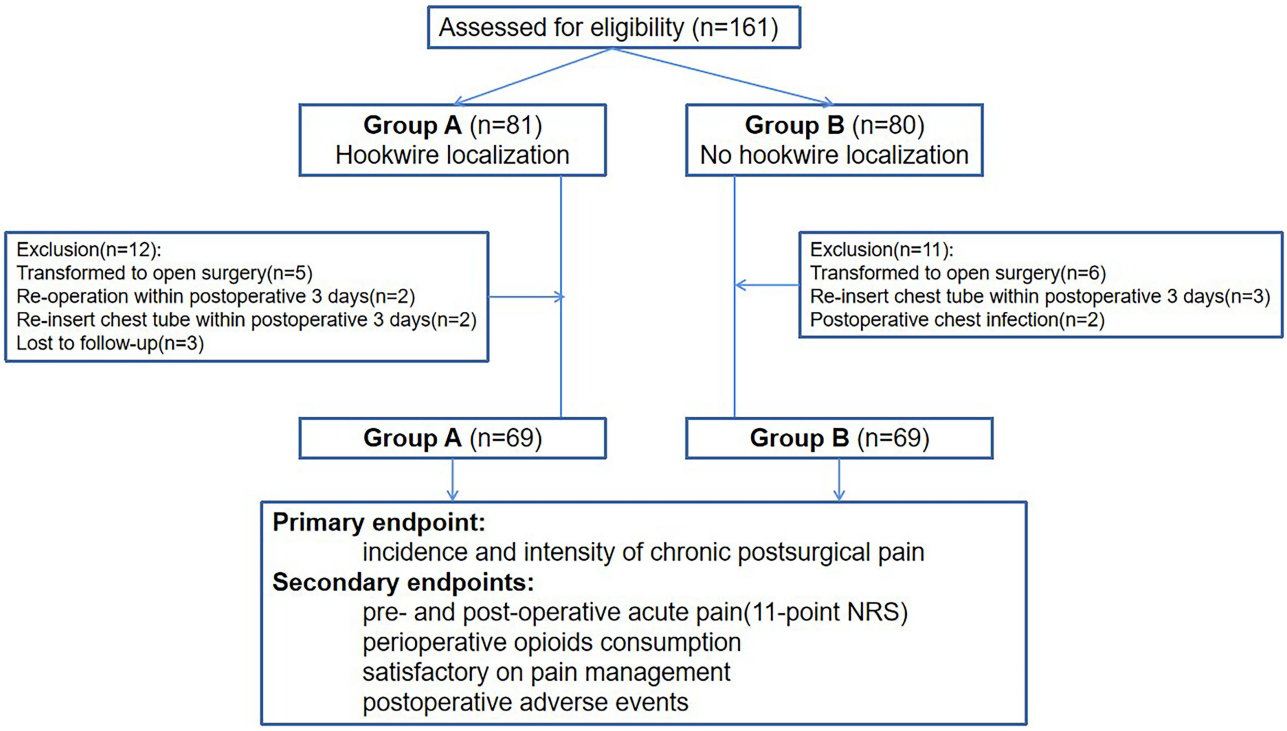

Figure 1 The study flowchart.
Abbreviation: NRS, Numeric Rating Scale.

after surgery in Group A (2.0 [2.0–3.0]) was higher than that in Group B (1.0 [1.0–2.0], p = 0.011), indicating that more patients who underwent preoperative hookwire localization experienced serious CPSP 3 months postoperatively. In contrast, at 6 months postoperatively, these differences in the incidence (44.9%, 95% CI: 37.9–57.0% vs 30.4% 95% CI:

Table 1 Demographic Data and Clinical Characteristics

Variables	Group A (n=69)	Group B (n=69)	P value
Age (years)	53.1±11.8	54.9±11.3	0.347
Gender (male/female)	21/48	32/37	0.054
BMI (kg/m^2)	23.3±2.8	23.9±2.8	0.207
ASA physical status (I/II)	15/54	11/58	0.384
aCCI	3.4±1.2	3.4±1.2	0.944
Previous surgical history	27 (39.1%)	23 (33.3%)	0.595
Preoperative HAMA score	3.4±1.2	3.7±1.3	0.197
Preoperative HAMD score	2.1±1.4	1.8±0.9	0.165
Type of lung surgery			0.275
Wedge resection	40 (58.0%)	23 (33.3%)	
Segmentectomy	20 (29.0%)	24 (34.8%)	
Lobectomy	9(13.0%)	22 (31.9%)	
Number of port (single/two/three)	30/7/32	15/12/42	0.025*
Lung location of tumor (Left/Right)	51/18	36/33	0.013*
Duration of Surgery (min)	73.8±38.1	91.5±40.8	0.009**
Duration of anesthesia (min)	109.3±38.1	125.5±41.6	0.019*
Duration of drainage (days)	3.1±1.1	3.1±0.8	0.867
Postoperative length of stay (days)	4.0±1.2	4.0±1.0	0.908

Notes: Date were presented as mean±standard deviation and number or number (%). *p<0.05, **p<0.01.
Abbreviations: BMI, Body mass index; ASA, American Society of Anesthesiologists; aCCI, Age-adjusted Charlson Comorbidity Index; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale.

Table 2 The Incidence and Intensity (NRS) of Perioperative Acute Pain

Variables	Group A	Group B	P value
Hookwire localization-induced pain			
Incidence (%)	66/69 (95.65%)	/	/
NRS at rest	2.0 (1.0, 2.0)	/	/
NRS on cough	3.5 (2.0, 5.0)	/	/
Postoperative acute pain			
PACU			
NRS at rest	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.239
NRS on coughing	1.0 (0.0, 2.0)	2.0 (0.0, 2.0)	0.250
POD1			
NRS at rest	2.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.531
NRS on coughing	4.0 (3.0, 5.0)	3.0 (2.0, 4.0)	0.066
POD2			
NRS at rest	0.0 (0.0, 1.0)	0.0 (0.0, 2.0)	0.797
NRS on coughing	3.0 (2.0, 5.0)	3.0 (1.0, 3.5)	0.157

Note: Data were presented as median (interquartile range, IQR) or number (%).
Abbreviations: NRS, Numerical rating scale; PACU, Post-anesthesia care unit; POD1, postoperative 1st day; POD2, postoperative 2nd day.

19.3%–41.6%, p = 0.079) and intensity (2.0 [2.0–2.0] vs 2.0 [1.0, 2.0], p = 0.214) of CPSP between two groups were no longer statistically significant (Table 3). Furthermore, the dosages and durations of oral analgesic drugs at 3 months postoperatively (Supplementary Table 3) and 6 months postoperatively (Supplementary Table 4) were similar between the two groups.

To identify whether the number of hookwire influenced acute and chronic postoperative pain, we further subdivided the patients in Group A into Group A_{single} (n = 34) and Group $A_{multiple}$(n = 35). After hookwire localization, 32/34 (94.1%) of patients in Group A_{single} 32/34 (94.1%) and 34/35 (97.1%) of patients in Group $A_{multiple}$ reported pain. When the patients were in the waiting area, the NRS score at rest was similar between the two subgroups, whereas the NRS score on coughing was significantly higher in Group $A_{multiple}$ (4.0 [3.0–6.0]) than in Group A_{single} (3.0 [2.0–4.0], p = 0.037). In contrast, there was no difference in pain intensity at the PACU, and at POD1 and POD2 between the two subgroups (Table 4). Moreover, the incidence of CPSP at POM3 was 62.9% (95% CI: 46.0–79.7%) in Group $A_{multiple}$, and 50.0% (95% CI: 32.3–67.7%) in Group A_{single}, whereas the incidence of CPSP at POM6 was 60.0% (95% CI: 42.9–77.6%) in Group $A_{multiple}$, and 29.4% (95% CI:13.3–45.5%) in Group A_{single} (Figure 2). The results demonstrated that the CPSP incidence in Group $A_{multiple}$ was significantly higher at POM6 (p = 0.011) but not at POM3 (p = 0.281) than Group A_{single}. On the contrary, the intensity of

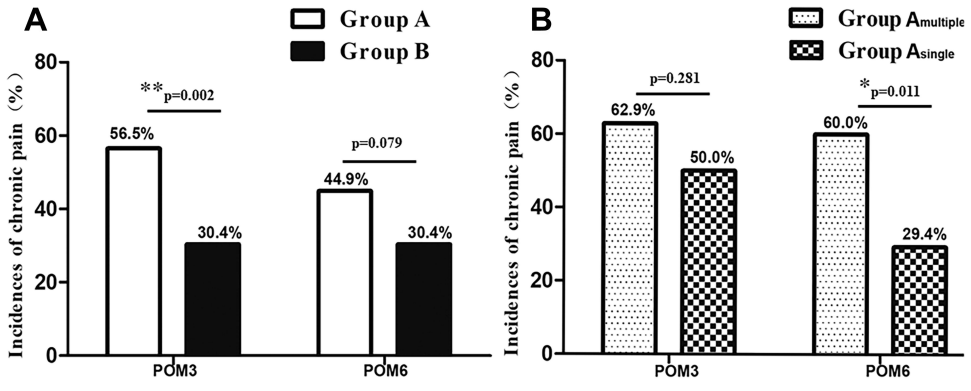

Figure 2 The incidences of chronic postsurgical pain (CPSP). (**A**) The comparison of CPSP between patients with preoperative hookwire localization (Group A) and those without hookwire localization (Group B); (**B**) The comparison of CPSP between multiple hookwires localization (Group $A_{multiple}$) and single hookwire localization (Group A_{single}). *p<0.05, **p<0.01.

Table 3 The Incidence and Intensity (NRS) of Chronic Postsurgical Pain (CPSP)

Variables	Group A (n=69)	Group B (n=69)	P value
POM3			
Incidence (%)	39/69 (56.5%)	21/69 (30.4%)	0.002**
NRS	2.0 (2.0, 3.0) (n=39)	1.0 (1.0, 2.0) (n=21)	0.011*
POM6			
Incidence (%)	31/69 (44.9%)	21/69 (30.4%)	0.079
NRS	2.0 (2.0, 2.0) (n=31)	2.0 (1.0, 2.0) (n=21)	0.214

Notes: Data were presented as median (interquartile range, IQR) or number (%). *p<0.05, **p<0.01.
Abbreviations: NRS, Numerical rating scale; POM3, postoperative 3rd month; POM6, postoperative 6th month.

Table 4 The Incidence and Intensity (NRS) of Postoperative Acute and Chronic Pain in Subgroups

Variables	Group $A_{Multiple}$ (n=35)	Group A_{Single} (n=34)	P value
Hookwire localization-induced pain			
Incidence (%)	34/35 (97.1%)	32/34 (94.1%)	0.980
NRS at rest	2.0 (1.0, 2.0) (n=34)	1.0 (0.8, 2.0) (n=32)	0.067
NRS on cough	4.0 (3.0, 6.0) (n=34)	3.0 (2.0, 4.0) (n=32)	0.037*
Port number (single/two/three)	15/6/14	15/1/18	0.600
Postoperative acute pain			
PACU			
NRS at rest	0.0 (0.0,1.0)	0.0 (1.0,1.0)	0.638
NRS on cough	1.0 (0.0,3.0)	1.0 (0.0,2.0)	0.341
POD1			
NRS at rest	2.0 (0.0, 2.0)	2.0 (0.0, 2.0)	0.533
NRS on cough	4.0 (3.0, 5.0)	4.0 (2.0, 5.3)	0.985
POD2			
NRS at rest	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.978
NRS on cough	3.0 (2.0, 5.0)	3.0 (1.8, 4.0)	0.229
Chronic postsurgical pain (CPSP)			
POM3			
Incidence (%)	22/35 (62.9%)	17/34 (50.0%)	0.281
NRS	2.0 (2.0, 3.0) (n=22)	2.0 (1.0, 2.0) (n=17)	0.005**
POM6			
Incidence (%)	21/35 (60.0%)	10/34 (29.4%)	0.011*
NRS	2.0 (1.0, 2.0) (n=21)	2.0 (2.0, 2.0) (n=10)	0.330

Notes: Data were presented as median (interquartile range, IQR) or number (%). *p<0.05, **p<0.01.
Abbreviations: NRS, Numerical rating scale; PACU, Post-anesthesia care unit; POD1, postoperative 1st day; POD2, postoperative 2nd day; POM3, postoperative 3rd month; POM6, postoperative 6th month.

CPSP at POM3 (2.0 [2.0–3.0] vs 2.0 [1.0–2.0], p = 0.005) was higher in Group $A_{multiple}$ than in Group A_{single} but not at POM6 (2.0 [1.0–2.0] vs 2.0 [2.0–2.0], p = 0.330) (Table 4).

Postoperative Adverse Events and Satisfaction Rating

The study also evaluated the incidence of postoperative adverse events including postoperative nausea and vomiting (PONV), and shoulder-back pain, and the patient's satisfaction rating for pain management (Supplementary Table 2). The occurrences of PON (46.4% vs 30.4%, p = 0.081), POV (27.5% vs 20.3%, p = 0.318), shoulder-back pain (20.3% vs 18.8%, p = 0.830), and the satisfaction rating for pain management (4.3±0.7 vs 4.4±0.7, p = 0.336) on discharge were not different between Group A and Group B. However, the satisfaction rating for pain management 3 months after surgery

Table 5 Multivariate Logistic Regression Analysis of Factors Affecting Incidence of CPSP at Postoperative Third Month

Variables	Wals	*P* value	Odd Ratio	95% CI
Age (years)	0.425	0.514	1.513	0.436–5.247
Gender (male / female)	0.461	0.497	0.726	0.288–1.829
ASA physical status (I/II)	0.204	0.651	1.285	0.433–3.815
aCCI	1.745	0.186	1.365	0.860–2.164
Previous surgical history	4.115	0.042*	0.383	0.151–0.698
Preoperative HAMA score	0.993	0.319	1.311	0.770–2.232
Preoperative HAMD score	1.293	0.256	0.786	0.519–1.190
Number of port (single/two/three)	0.043	0.835	0.835	0.535–1.657
Lung location of tumor (Left/Right)	0.037	0.848	0.923	0.406–2.097
Duration of Surgery (min)	0.000	0.994	1.000	0.963–1.039
Duration of anesthesia (min)	0.275	0.600	1.010	0.973–1.049
Postoperative length of stay (days)	0239	0.625	0.939	0.729–1.209
Pain score in PACU on coughing	0.121	0.727	1.057	0.774–1.443
Pain score at POD1 on coughing	1.914	0.167	1.182	0.933–1.498
Pain score at POD2 on coughing	0.003	0.957	1.007	0.784–1.294
Hookwire localization	10.437	0.001**	6.199	2.049–18.749

Note: *p<0.05, **p<0.01.

Abbreviations: CPSP, chronic postsurgical pain; ASA, American Society of Anesthesiologists; aCCI, Age-adjusted Charlson Comorbidity Index; POD1, postoperative first day; POD2, postoperative second day; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale.

was lower in Group A (4.6±0.5) than in Group B (4.8±0.3, p = 0.034). At 6 months postoperatively, the satisfaction rating for pain management was similar between Group A (4.8±0.4) and Group B (4.9±0.3, p = 0.106).

Risk Factors Associated with CPSP

The multivariate regression analysis showed that preoperative hookwire localization (OR: 6.199, 95% CI: 2.049–18.749, p = 0.001) and surgical history (OR: 0.383, 95% CI: 0.151–0.698, p = 0.042) were associated with the development of CPSP (Table 5), whereas the lung tumor location, number of ports, and VATS surgery duration and anesthesia duration, were not associated with CPSP. The results further suggest that hookwire localization-associated acute pain can lead to CPSP following VATS. Interestingly, preoperative surgical history without chronic pain may be a protective factor for CPSP after VATS.

Discussion

Chronic postsurgical pain severely impairs patients' health and their quality of life. The risk factors for CPSP include intraoperative nerve injury, surgery duration, pre-existing pain, younger age, female sex, genetic predisposition, psychological vulnerability, and severity of acute postoperative pain.[6] Although chronic preoperative pain enhanced the susceptibility to surgically induced pain,[12] the effects of preoperative hookwire localization-related pain on chronic postoperative pain after VATS have not been reported previously. In this study, we found that hookwire localization caused mild-moderate pain before surgery in most patients undergoing VATS, and that this pain seemed to have limited influence on acute postoperative pain. However, a higher incidence and intensity of CPSP were noted in patients with hookwire localization when compared with those without hookwire localization at 3 months postoperatively but not at 6 months postoperatively. The subgroup analysis showed that multiple hookwires localization induced a higher intensity of CPSP at 3 months postoperatively and a higher incidence of CPSP at 6 months postoperatively than single hookwire localization. These findings suggest that acute preoperative pain at the surgical site may influence chronic postoperative pain, thereby posing a challenge for optimal perioperative pain management in this surgical population.

CPSP, also known as persistent postsurgical pain, is defined as chronic pain that develops or increases in intensity after a surgical procedure or tissue injury, and persists at least 3 months after the surgery or tissue trauma in the International

Classification of Diseases-11 (ICD-11).[18] CPSP after thoracic surgery is relatively common, and the incidence rate is as high as 65%.[19] A meta-analysis of prospective studies reported that the incidence of CPSP at 3 and 6 months after thoracotomy was 57% and 47%, respectively,[20] whereas the incidence of CPSP after VATS varied greatly from 7.7% to 44.0%,[1,18,21–23] depending on the perioperative pain control and the number of ports. Notably, the definition of CPSP also influences the incidence. Previous studies reported that pain cut-offs of NRS >0, ≥3, or ≥4, used to define CPSP, produced rates of 37.5%, 9.7%, and 5.7%, respectively, in non-cardiac surgery.[24] The incidence of CPSP in the present study is relatively high. This may be because we used pain cut-offs of NRS ≥1. A large retrospective study on thoracic surgery reported that around 1/3 of patients suffering from CPSP reported moderate or severe chronic pain, but only 3% of patients with CPSP sought active analgesic therapy.[1] In the present study, the incidence of CPSP in patients with and without hookwire localization was 56.5% and 30.4%, respectively, and the incidence was higher (62.9%) in patients undergoing multiple hookwires localization. Nevertheless, most of the patients in our study reported mild-to-moderate pain intensities. Similar to previous studies, the incidence of CPSP after VATS also decreased over time in our study. These findings suggest that preoperative hookwire localization can influence the incidence of CPSP after VATS.

The removal of lung nodules by means of VATS is often helpful. Nevertheless, it is impossible to locate these lesions intraoperatively without the aid of preoperative localization techniques. The CT-guided hookwire localization prior to surgical resection is one of these techniques. Its complications include pain, pneumothorax (most are insignificant), hemorrhage, and hemoptysis. Other methods for preoperative localization of lung nodules include coil positioning, dye injection, and radionuclide location. These localization techniques yield similarly successful targeting rates and may have fewer complications.[25,26] However, they may lead to a higher localization-associated pain score when compared with that of hookwire localization.[27,28] The patients undergoing hookwire localization usually report moderate to severe postoperative chest pain,[29,30] which results from the irritation or injury of the pleural tissues caused by the retained hookwires. In our study, most of the patients with hookwire localization reported mild-moderate pain before VATS, which restricted their activities (reduced activities to reduce pain and prevent dislodgement or migration of hookwire(s)). Simultaneous preoperative multiple hookwires localization may induce a higher incidence and a higher intensity of preoperative pain stress compared with single hookwire localization.[31] Our result also revealed that patients with multiple hookwires localization experienced a higher pain intensity on coughing than those with single hookwire localization preoperatively. Nevertheless, the incidence of hookwire localization-associated pain between the two subgroups did not demonstrate a statistically significant difference. Furthermore, the number of hookwire also did not influence the incidence and intensity of early acute postoperative pain. Chronic preoperative pain is associated with an increased incidence of CPSP and prolonged opioid use,[10–12] Interestingly, we found, for the first time, that not only hookwire localization but also the number of hookwires may influence the development of CPSP more than acute postoperative pain. Our finding suggests that preoperative pain stress from hookwire localization may trigger a mechanism underlying acute preoperative pain transition to CPSP.

There are numerous treatment options for CPSP prevention. However, none of them is optimal as the mechanisms underlying the transition from acute pain to CPSP remain unclear.[32] Limited studies have reported on how preoperative pain, especially acute pain, increases the incidence of CPSP at the surgical site. Recent studies have indicated that preoperative inflammatory markers may be associated with the development of CPSP. Preoperative dysregulation of circulating microRNAs and long non-coding RNA (lncRNA) related to the inflammatory processes may serve as predictive biomarkers of pain outcome after surgery.[33,34] The hookwire localization may trigger releases of inflammatory mediators. In this study, we did not measure preoperative serum levels of inflammatory cytokines. The hookwire localization and related pain are preoperative stress which may cause prolongation of postsurgical pain.[35] The latest experimental studies showed that preoperative stress-induced expression of the transcription factor CCAAT/enhancer-binding protein β in spinal microglia may contribute to CPSP.[36] Conversely, perioperative activation of spinal α7 nAChR in microglia-alleviated preoperative stress-induced prolongation of postsurgical pain.[37] These preclinical data suggest that priming the proinflammatory activation of microglia may play a key role in the preoperative stress-induced prolongation of postsurgical pain. Since local anesthesia at puncture sites does not abolish pleuritic pain, preoperative control of hookwire localization-related pain with preoperative use of nonsteroidal anti-inflammatory drugs may improve CPSP after VATS. In the future, this hypothesis needs further clinical validation.

There are several confounders to our findings. In this study, the duration of surgery and anesthesia and the number of ports influenced the incidence of CPSP. The longer surgery duration is recognized as a predictor of CPSP.[5] However, in our study,

the patients without hookwire localization (Group B) had longer surgical and anesthetic times than those with hookwire localization (Group A). Meanwhile, the patients in Group B had fewer ports for the VATS procedures than those in Group A. Previous studies demonstrated that the use of multiple ports can lead to a higher acute postoperative pain intensity and a higher incidence of CPSP than the use of a single port.[23,38,39] However, there is no difference in the early acute postoperative pain scores between patients with multiple ports and those with a single port.[40] Overall, uniport VATS may have a small clinical benefit in reducing postoperative pain, considering the majority of studies reported on the first 72 h following surgery. In our study, the patients with hookwire localization utilized the patient-controlled analgesic pump more frequently on POD1, indicating a higher opioid use. Conversely, the patients with hookwire localization had a shorter surgical time and fewer numbers of port, but at 3 months postoperatively, they reported a higher incidence and intensity of CPSP. The multivariate linear regression analysis also confirmed that preoperative hookwire localization was associated with an increased risk of CPSP after VATS. Combined with an increased risk of CPSP in patients with multiple hookwire localization, these results further support that preoperative hookwire localization-related pain may promote the development of CPSP.

This study has several limitations. First, this is an observational cohort study but not a randomized control study. Whether hookwire localization was performed or not was determined by thoracic surgeons according to the surgical indications. Therefore, the baseline clinical characteristics between the two groups demonstrated some differences. For example, the patients with hookwire localization had a higher proportion of lung edge resection and fewer ports for VATS. The results remained valid after controlling for confounders in the multivariate linear regression analysis. Second, the subgroup analysis compared the effects between preoperative single hookwire and multiple hookwire localization-related pain on the incidence and intensity of CPSP but these were not the primary endpoints of this study. Furthermore, the sample size may be not large enough for the desired statistical power. Finally, background infusion of PCIA was used during postoperative pain management. This is considered unsafe and may result in oversedation and ventilatory impairment due to opioid overdose. Our rationale for providing a background infusion was because the intensity of acute postoperative pain after VATS is commonly severe. Nevertheless, this may overestimate opioid consumption.

Conclusion

Hookwire localization induces mild-moderate preoperative pain, and importantly, this pain stress increases the risk of CPSP after VATS. Moreover, multiple hookwire localization may lead to worse CPSP. Greater attention should be paid to hookwire localization-associated pain. Management of the prior pain state may be helpful for the prevention and management of pain and the transition from acute to chronic pain.[33] Since the mechanism underlying hookwire localization-associated CPSP is unknown, clinically effective therapy that provides an overall improved outcome for the patients should be investigated.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. Files can be emailed to anyone that concerned.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the Fudan University Shanghai Cancer Center, with the ethics number:2107238-15. The trial was registered after patient enrollment at clinicaltrials.gov (NCT05478460). Patients provided written consent. All methods were carried out in accordance with Declaration of Helsinki.

Acknowledgments

This study was supported by Shanghai Municipal Natural Science Foundation (to Jun Zhang, No.22Y11904200). Thanks are also given to surgeons in Department of thoracic surgery for their help on data collection.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Funding

This work was funded by a grant from the Shanghai Science and Technology Committee (No.20Y11906200). The funder was not involved in the design, conduct, or publication of this work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Zhang Y, Zhou R, Hou B, et al. Incidence and risk factors for chronic postsurgical pain following video-assisted thoracoscopic surgery: a retrospective study. *BMC Surg*. 2022;22(1):76.
2. Peng Z, Li H, Zhang C, et al. A retrospective study of chronic post-surgical pain following thoracic surgery: prevalence, risk factors, incidence of neuropathic component, and impact on qualify of life. *PLoS One*. 2014;9(2):e90014. doi:10.1371/journal.pone.0090014
3. Yoon S, Hong WP, Joo H, et al. Long-term incidence of chronic postsurgical pain after thoracic surgery for lung cancer: a 10-year single-center retrospective study. *Reg Anesth Pain Med*. 2020;45(5):331–336. doi:10.1136/rapm-2020-101292
4. Bayman EO, Parekh KR, Keech J, et al. A prospective study of chronic pain after thoracic surgery. *Anesthesiology*. 2017;126(5):938–951. doi:10.1097/ALN.0000000000001576
5. Hanley C, Ladha KS, Clarke HA, et al. Association of postoperative complications with persistent post-surgical pain: a multicentre prospective cohort study. *Br J Anaesth*. 2022;128(2):311–320. doi:10.1016/j.bja.2021.10.027
6. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367(9522):1618–1625. doi:10.1016/S0140-6736(06)68700-X
7. Andreoletti H, Dereu D, Combescure C, et al. A systematic review and meta-analysis of three risk factors for chronic postsurgical pain: age, sex and preoperative pain. *Minerva Anestesiol*. 2022;88(10). doi:10.23736/S0375-9393.22.16489-8
8. Qian MP, Dong MR, Li J, et al. The duration of chronic low back pain is associated with acute postoperative pain intensity in lumbar fusion surgery: a prospective observational study. *BMC Anesthesiol*. 2022;22(1):129. doi:10.1186/s12871-022-01674-w
9. Khan JS, Sessler DI, Chan M, et al. Persistent incisional pain after noncardiac surgery: an international prospective cohort study. *Anesthesiology*. 2021;135(4):711–723. doi:10.1097/ALN.0000000000003951
10. Tian M, Li Z, Chen X, et al. Prevalence and predictors of chronic pain with two-year follow-up after knee arthroplasty. *J Pain Res*. 2022;15:1091–1105. doi:10.2147/JPR.S345496
11. Bruce J, Thornton AJ, Scott NW, et al. Chronic preoperative pain and psychological robustness predict acute postoperative pain outcomes after surgery for breast cancer. *Br J Cancer*. 2012;107(6):937–946. doi:10.1038/bjc.2012.341
12. Gerbershagen HJ, Ozgür E, Dagtekin O, et al. Preoperative pain as a risk factor for chronic post-surgical pain - six month follow-up after radical prostatectomy. *Eur J Pain*. 2009;13(10):1054–1061. doi:10.1016/j.ejpain.2008.11.020
13. Lenglinger FX, Schwarz CD, Artmann W. Localization of pulmonary nodules before thoracoscopic surgery: value of percutaneous staining with methylene blue. *AJR Am J Roentgenol*. 1994;163(2):297–300. doi:10.2214/ajr.163.2.7518642
14. Macrae WA. Chronic pain after surgery. *Br J Anaesth*. 2001;87(1):88–98. doi:10.1093/bja/87.1.88
15. Bendixen M, Jørgensen OD, Kronborg C, et al. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. *Lancet Oncol*. 2016;17(6):836–844. doi:10.1016/S1470-2045(16)00173-X
16. Zimmerman M, Martin J, Clark H, et al. Measuring anxiety in depressed patients: a comparison of the Hamilton anxiety rating scale and the DSM-5 anxious distress specifier interview. *J Psychiatr Res*. 2017;93:59–63. doi:10.1016/j.jpsychires.2017.05.014
17. Zhang A, Li G, Yang C, et al. Alterations of amplitude of low-frequency fluctuation in treatment-resistant versus non-treatment-resistant depression patients. *Neuropsychiatr Dis Treat*. 2019;15:2119–2128. doi:10.2147/NDT.S199456
18. Tong Y, Wei P, Wang S, et al. Characteristics of postoperative pain after VATS and pain-related factors: the experience in national cancer center of China. *J Pain Res*. 2020;13:1861–1867. doi:10.2147/JPR.S249134
19. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *Lancet*. 2019;393(10180):1537–1546. doi:10.1016/S0140-6736(19)30352-6
20. Bayman EO, Brennan TJ. Incidence and severity of chronic pain at 3 and 6 months after thoracotomy: meta-analysis. *J Pain*. 2014;15(9):887–897. doi:10.1016/j.jpain.2014.06.005
21. Zhao H, Wu Y, Zhang X, et al. The effect of preoperative serratus anterior muscle plane block on persistent postsurgical pain after video-assisted thoracic surgery: a retrospective cohort study. *Clin J Pain*. 2021;37(10):759–765. doi:10.1097/AJP.0000000000000969
22. Wang G, He M, Ji XL, et al. Identifying patients at high risk of chronic pain after video-assisted thoracoscopic surgery using thermal quantitative sensory testing. *J Cardiothorac Vasc Anesth*. 2022;36(8 Pt A):2406–2411. doi:10.1053/j.jvca.2022.03.015
23. Jin J, Du X, Min S, et al. Comparison of chronic postsurgical pain between single-port and multi-port video-assisted thoracoscopic pulmonary resection: a prospective study. *Thorac Cardiovasc Surg*. 2022;70(5):430–438. doi:10.1055/s-0042-1744546

24. Stamer UM, Ehrler M, Lehmann T, et al. Pain-related functional interference in patients with chronic neuropathic postsurgical pain: an analysis of registry data. *Pain*. 2019;160(8):1856–1865. doi:10.1097/j.pain.0000000000001560
25. Park CH, Han K, Hur J, et al. Comparative effectiveness and safety of preoperative lung localization for pulmonary nodules: a systematic review and meta-analysis. *Chest*. 2017;151(2):316–328. doi:10.1016/j.chest.2016.09.017
26. Kleedehn M, Kim DH, Lee FT, et al. Preoperative pulmonary nodule localization: a comparison of methylene blue and hookwire techniques. *AJR Am J Roentgenol*. 2016;207(6):1334–1339. doi:10.2214/AJR.16.16272
27. Yang F, Zhao H, Sui X, et al. Comparative study on preoperative localization techniques using microcoil and hookwire by propensity score matching. *Thorac Cancer*. 2020;11(6):1386–1395. doi:10.1111/1759-7714.13365
28. Hu L, Gao J, Chen C, et al. Comparison between the application of microcoil and hookwire for localizing pulmonary nodules. *Eur Radiol*. 2019;29 (8):4036–4043. doi:10.1007/s00330-018-5939-4
29. Sartoris F, Cittadini G, Saitta S, et al. CT-guided needle localization of lung nodules for thoracoscopic resection. *Eur Radiol*. 1996;6(4):420–424. doi:10.1007/BF00182455
30. Thaete FL, Peterson MS, Plunkett MB, et al. Computed tomography-guided wire localization of pulmonary lesions before thoracoscopic resection: results in 101 cases. *J Thorac Imaging*. 1999;14(2):90–98. doi:10.1097/00005382-199904000-00004
31. Hu L, Gao J, Hong N, et al. Simultaneous preoperative computed tomography-guided microcoil localizations of multiple pulmonary nodules. *Eur Radiol*. 2021;31(9):6539–6546. doi:10.1007/s00330-021-07772-6
32. Pozek JP, Beausang D, Baratta JL, et al. The acute to chronic pain transition: can chronic pain be prevented? *Med Clin North Am*. 2016;100 (1):17–30. doi:10.1016/j.mcna.2015.08.005
33. Giordano R, Petersen KK, Andersen HH, et al. Preoperative serum circulating microRNAs as potential biomarkers for chronic postoperative pain after total knee replacement. *Mol Pain*. 2020;16:2068200595. doi:10.1177/1744806920962925
34. Giordano R, Petersen KK, Santoro M, et al. Circulating long non-coding RNA signature in knee osteoarthritis patients with postoperative pain one-year after total knee replacement. *Scand J Pain*. 2021;21(4):823–830. doi:10.1515/sjpain-2021-0069
35. Schug SA, Lavand'Homme P, Barke A, et al. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. *Pain*. 2019;160(1):45–52. doi:10.1097/j.pain.0000000000001413
36. Jiang M, Huang Y, Hu L, et al. The transcription factor CCAAT/enhancer-binding protein β in spinal microglia contributes to pre-operative stress-induced prolongation of postsurgical pain. *Mol Pain*. 2022;18:804300640. doi:10.1177/17448069221099360
37. Sun R, Liu Y, Hou B, et al. Perioperative activation of spinal α7 nAChR promotes recovery from preoperative stress-induced prolongation of postsurgical pain. *Brain Behav Immun*. 2019;79:294–308. doi:10.1016/j.bbi.2019.02.017
38. Ji C, Xiang Y, Pagliarulo V, et al. A multi-center retrospective study of single-port versus multi-port video-assisted thoracoscopic lobectomy and anatomic segmentectomy. *J Thorac Dis*. 2017;9(10):3711–3718. doi:10.21037/jtd.2017.09.39
39. Hu CG, Zheng K, Liu GH, et al. Effectiveness and postoperative pain level of single-port versus two-port thoracoscopic lobectomy for lung cancer: a retrospective cohort study. *Gen Thorac Cardiovasc Surg*. 2021;69(2):318–325. doi:10.1007/s11748-020-01479-z
40. Young R, McElnay P, Leslie R, et al. Is uniport thoracoscopic surgery less painful than multiple port approaches? *Interact Cardiovasc Thorac Surg*. 2015;20(3):409–414. doi:10.1093/icvts/ivu391

Journal of Pain Research Dovepress

Publish your work in this journal

The Journal of Pain Research is an international, peer reviewed, open access, online journal that welcomes laboratory and clinical findings in the fields of pain research and the prevention and management of pain. Original research, reviews, symposium reports, hypothesis formation and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/journal-of-pain-research-journal