



Uniportal video-assisted thoracic surgery versus open thoracotomy for chronic pain after surgery: a prospective cohort study

Yang Gu¹ · Xiang Li^{1,2} · Qing Zhou^{1,3} · Huimin Deng¹ · Faqiang Zhang¹ · Juan Wei¹ · Xin Lv¹

Received: 3 March 2024 / Accepted: 9 May 2024 / Published online: 20 May 2024
© The Author(s) under exclusive licence to Japanese Society of Anesthesiologists 2024

Abstract

Purpose The potential of uniportal video-assisted thoracic surgery (U-VATS) to reduce chronic pain after thoracic surgery (CPTS) compared to open thoracotomy (OT) remains unexplored. This prospective study aims to assess the incidence of CPTS following U-VATS or OT and identify associated risk factors.

Methods Patients undergoing thoracic surgery were recruited from March 2021 to March 2022, categorized by surgical approach (U-VATS vs. OT). Standard clinical protocols for surgery, anesthesia, and analgesia were followed. Pain symptoms were assessed using the Short-form McGill Pain Questionnaire, with follow-ups up to 6 months. Perioperative factors influencing CPTS at 3 months were analyzed through univariate and multivariate methods.

Results A total of 694 patients were analyzed. Acute pain after thoracic surgery (APTS) was significantly less severe in the U-VATS group ($p < 0.001$). U-VATS patients exhibited a lower incidence of CPTS at 3 months (63.4% vs. 80.1%, $p < 0.001$), with reduced severity among those experiencing CPTS ($p = 0.007$) and a decreased occurrence of neuropathic pain ($p = 0.014$). Multivariate analysis identified OT incision, moderate to severe APTS (excluding moderate static pain at 24 h postoperative), nocturnal surgery, and lung surgery as risk factors for CPTS.

Conclusion This study underscores the potential of U-VATS to reduce both the incidence and severity of CPTS at 3 months compared to OT. Furthermore, it highlights risk factors for CPTS, including OT incision, inadequately managed APTS, lung surgery, and nocturnal surgery. These findings emphasize the importance of considering surgical approach and perioperative pain management strategies to mitigate the burden of CPTS.

Keywords Acute pain after thoracic surgery · Chronic pain after thoracic surgery · Open thoracotomy · Uniportal video-assisted thoracic surgery

Introduction

Chronic pain after thoracic surgery (CPTS) has been affecting 30–80% of those surgical patients [1, 2]. Possible risk factors for CPTS include female sex, preoperative pain catastrophizing, severe acute pain after thoracic surgery, and postoperative radiation therapy [3–6]. The definition of CPTS did not reach consensus until 2019 when the WHO adopted the 11th edition of International Classification of Diseases (ICD-11) in which chronic pain with subgroups was recognized as a health condition. The current classification criteria for CPTS emphasized on persisting or recurring for at least 3 months, localization to surgical field, and post thoracic surgery etiology of the pain [7, 8]. Although modern treatments for CPTS can relieve the symptoms in many patients, identifying robust risk factors to prevent CPTS progression is crucial [9]. However, controversy surrounds the

Yang Gu and Xiang Li are co-first authors.

✉ Juan Wei
sudaweijuan@163.com.

✉ Xin Lv
xinlv@126.com

¹ Department of Anesthesiology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, 507 Zhengmin Rd, Yangpu, Shanghai, China

² Department of Anesthesiology, The First Affiliated Hospital of Anhui Medical University, Hefei, China

³ Department of Anesthesiology, The Second Affiliated Hospital of Nanchang University, Nanchang, China

impact of thoracoscopic surgery on the incidence of CPTS compared to lateral open thoracotomy (OT) [10, 11]. The evolution from multi-portal video-assisted thoracic surgery (M-VATS) to the more recent uniportal-VATS (U-VATS), characterized by minimized incision number and size, marks a significant development in thoracic surgical techniques. Building on this evolution, our study focuses on a research gap in the current literature by investigating whether U-VATS yields improved outcomes in CPTS compared to OT approach. We hypothesize that U-VATS is associated with a lower incidence and less severe CPTS compared to OT. For this purpose, we recruited patients based on 2 surgical approaches (U-VATS vs OT), and evaluated them for up to 6 months.

Methods

Study design and setting

This prospective cohort study used the Strength of Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. It was approved by our hospital's Institutional Research Board and Ethics Committee (L21-028) and registered at Chinese Clinical Trial Registry (ChiCTR2100044640; date: March 25, 2021; Principal investigator: Yang Gu). The study was conducted in accordance with the current Declaration of Helsinki. Patients were recruited from a tertiary hospital from March 2021 to March 2022. Written informed consent was obtained from each patient before enrollment.

Patient selection criteria

Trained clinical researchers screened patients on all weekdays, at all hours, to minimize selection bias.

Inclusion criteria

Adult patients (≥ 18 years) scheduled for U-VATS or OT on either side.

Procedures performed under general anesthesia with double-lumen endobronchial tube intubation.

American Society of Anesthesiologists (ASA) physical status I to III.

Exclusion criteria

Preoperative cognitive dysfunction.

Difficulty understanding the questionnaire or scale.

Bilateral thoracic surgery.

Preoperative history of chronic pain.

Previous thoracic surgery.

Substance abuse.

Severe psychiatric disorders.

Drop-out criteria

Scheduled operation approach changed to bilateral or M-VATS.

Severe cardiovascular or cerebral events.

Postoperative cognitive dysfunction or delirium.

Re-operation due to postoperative bleeding or other medical reasons.

Postoperative intubation.

Death.

Loss to follow-ups.

Surgical approach

Surgical approach was our primary exposure and determined by the surgeons based on preoperative evaluations, such as the size or the location of the tumor, the lymph nodes invasion, but it was adaptable, with the option to switch from U-VATS to OT or vice versa after a second risk–benefit analysis, depending on suitability. Patients were repositioned from supine to lateral decubitus after induction. Isolated ventilation of the dependent lung was established, allowing the operative lung to collapse. The incision size for U-VATS was kept at 4–5 cm to avoid rib spreading, while OT required at least a 10 cm incision based on surgical needs. In U-VATS, the approach was made on the 4th or 5th intercostal space perpendicular to the axillary line, with most of the incision anterior to the latissimus dorsi. On the other hand, OT might involve additional procedures, such as rib resection and muscle division, with a curvilinear incision extending from the base of pectoralis major anteriorly to latissimus dorsi posteriorly. The use of a retractor was consistently necessary to improve exposure.

Primary outcomes

CPTS incidence and severity were assessed using the Short-form McGill Pain Questionnaire (SF-MPQ), a tool validated in multiple languages, including Chinese, Greek, and Japanese, demonstrating convincing sensitivity and specificity [12–14]. The Chinese version comprises sensory and affective sub-scales, with each item rated on an intensity scale (0-none, 1-mild, 2-moderate, 3-severe), explained to patients preoperatively. If a patient scored ≥ 1 , it indicated the occurrence of CPTS; scoring between 1 and 3 denoted mild CPTS, 4–6 indicated moderate CPTS, and scoring ≥ 7 signified severe CPTS. To minimize dropouts, preoperatively, at least two phone numbers

each from patients and family members were documented, and researchers attempted contact three times both in the morning and afternoon during weekends before confirming loss to follow-ups. Telephone interviews evaluated patients based on SF-MPQ over the past week. Cause-specific morbidity in our study is favorable based on ICD-11. The study's sensitivity is influenced by the drop-out rate, which varies between the two groups.

Secondary outcomes

Acute pain assessment after thoracic surgery involved the Numeric Rating Scale (NRS-11) to quantify static pain (SP) or dynamic pain (DP) at 24 h and 48 h, a well-validated self-report scale for adults. Criteria for its application included direct bedside communication, separate evaluation of SP or DP, anchor descriptors (ranging from “no pain” at 0 to “worst experienced pain” or “worst bearable pain” at 10), patient cognitive and literacy levels, and a recall time frame of the most severe pain intensity in the past 24 h. The pain level was graded into 4 ranks: no pain (0), mild pain (1–3), moderate (4–6) and severe pain (7–10). Acute ipsilateral shoulder pain (ISP) was identified 24 h after the operation with answers of “yes” or “no”. Postoperative nausea and vomiting (PONV) within 48 h were also identified with “yes” or “no” responses. Chronic neuropathic pain (NPP) was evaluated with the Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS). A total score of 12 or more suggests NPP. However, potential information bias could occur due to the scale involving not only sensory appraisal but also patient examination involving rubbing and pressing on painful and non-painful areas.

Anesthesia and analgesia management

Routine perioperative care was administered by anesthesiologists and surgeons. Intravenous fast induction commenced with midazolam, sufentanil, propofol, and rocuronium. Maintenance was regulated with a continuous infusion of propofol and remifentanil, supplemented by intermittent injections of rocuronium and sufentanil as needed. All patients received the same patient-controlled intravenous analgesia via an infusion pump, containing 120 ml suspension with sufentanil (100 µg), flurbiprofen (100 mg), and ondansetron (8 mg). While other analgesic interventions, such as nerve blocks, non-steroidal anti-inflammatory drugs, and opioids, were not mandatory, their utilization, if any, was documented in the medical records. All patients were strictly monitored throughout the perioperative period.

Statistical analysis

To minimize the risk of confounders, we conducted a properly sized sample mimicking an RCT, with the aim of comparing surgical approaches on CPTS after 3 months and possible risk factors for CPTS 3 months. The sample size was calculated using PASS 15.0 (Power and Sample Size, © 2012, Kaysville, Utah). The primary focus was on detecting the incidence difference of CPTS between the two surgical approaches. We employed tests for two proportions in a two-sided test, with a significance level of 0.05, statistical power of 90%, and an expected 3 month CPTS incidence after OT based on previous literature (53%) [11]. The anticipated proportion difference was set at 13.34%. Accounting for an expected 20% loss to follow-up, a total of 694 patients were deemed necessary for the study. The data analysis utilized SAS version 9.4 (SAS Institute Inc., Cary, NC), employing per-protocol analysis for all datasets. A significance level of two-sided $p < 0.05$ was considered statistically significant for all analyses. Normality testing was performed using the Shapiro–Wilk test or Kolmogorov–Smirnov Test. Quantitative data were presented as mean (standard deviation, SD) if normally distributed, otherwise as median with interquartile range (IQR). Two independent-sample t tests were employed for normally distributed data, while the Wilcoxon rank-sum test was used for skewed distributed variables. Categorical variables are presented as frequencies and proportions, and compared between groups with χ^2 test or Fisher's exact test based on their expected counts. Ranked data like the level of acute or chronic postoperative pain within the group were analyzed using Trend test. To explore associations between perioperative variables and the risk of CPTS, univariate analysis with a generalized estimating equation model was conducted, providing relative risk (RR) and 95% confidence interval (CI). Significant factors identified during univariate analysis were further investigated using multivariate analysis with maximum likelihood estimation, presenting RR and 95%CI.

Results

Baseline characteristics, recruitment, and follow-ups

Recruitment and follow-up timeline is presented in Fig. 1. From the initial 744 patients, 694 were included, but 80 were lost to follow-ups within 3 months post-operation. Of those retained, 281 in the OT group and 333 in the U-VATS group completed the primary outcome

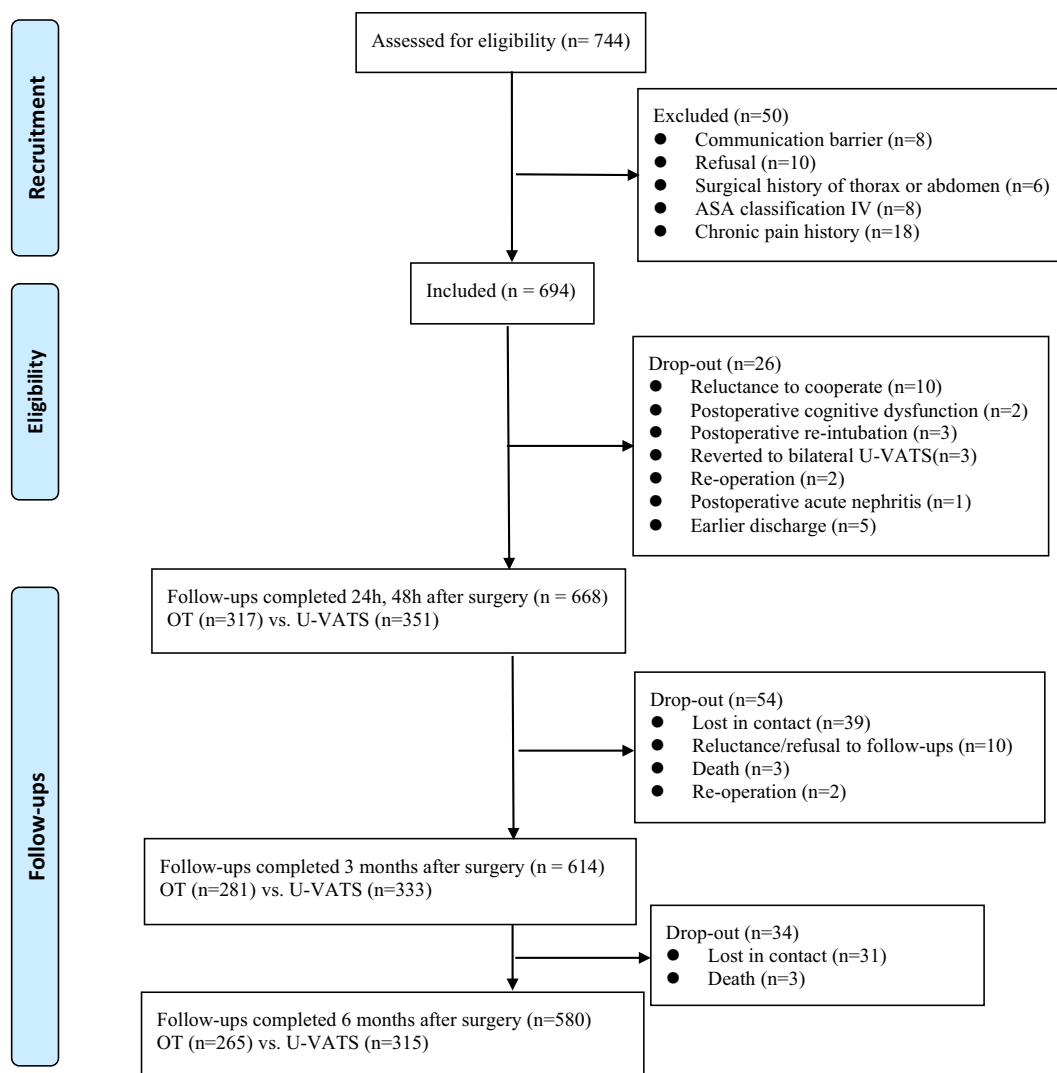


Fig. 1 Recruitment and follow-up diagram. ASA American Society of Anesthesiologists, OT open thoracotomy, U-VATS uniportal video-assisted thoracoscopy

evaluations. Preoperative data and intraoperative events are given in Table 1. Notably, significant differences exist in demographic and clinical characteristics between groups, spanning sex, age, body mass index (BMI), ASA classification, tobacco dependence, neoadjuvant therapy, operation side, target organ, operation duration, and blood loss.

Postoperative acute phase follow-ups

With the same patient-controlled intravenous analgesia regimen, though, on a broader scale, the use of rescue analgesia was less frequent in the U-VATS group. Table 2 reveals a higher severity of acute pain after thoracic surgery (APTS) in the OT group, regardless of SP or DP, when compared to the U-VATS group. Additionally, the incidence of ISP was

greater in the OT group than in the U-VATS group. Further, the incidence of PONV did not show a significant difference between the two groups.

Chronic phase evaluations (postoperative 3 months and 6 months)

Table 3 illustrates notable differences in the incidences of CPTS at 3 and 6 months between the U-VATS and OT groups. Specifically, at 3 months, the U-VATS group exhibited lower incidences (80.1% vs. 63.4%), with CPTS severity being significantly more pronounced in the OT group ($p = 0.007$). However, by 6 months, while the trend persisted favoring the U-VATS group (75.8% vs. 51.7%), the difference in severity became less pronounced ($p = 0.057$). Additionally, the occurrence of highly suspected NPP at 3 months

Table 1 Preoperative and intraoperative baseline characteristics

Variables	Sum (n = 694)	Surgical approach		p
		U-VATS (n = 357)	OT (n = 337)	
Sex				<0.001
Female	268 (38.6)	196 (54.9)	72 (21.4)	
Male	426 (61.4)	161 (45.1)	265 (78.6)	
Age (years)	57.3 ± 11.8	55.5 ± 12.0	59.4 ± 11.2	<0.001
Stratification				<0.001
≤ 50	166 (23.9)	121 (33.9)	45 (13.4)	
51–70	449 (64.7)	203 (56.9)	246 (73.0)	
> 70	79 (11.4)	33 (9.2)	46 (13.6)	
Height (cm)	163.9 ± 8.5	162.6 ± 9.5	165.1 ± 7.1	<0.001
Weight (kg)	65.1 ± 10.7	64.9 ± 11.4	65.3 ± 9.8	0.303
BMI (kg/m ²)				0.322
< 28	609 (87.8)	309 (86.6)	300 (89.0)	
≥ 28	85 (12.2)	48 (13.4)	37 (11.0)	
ASA classification				<0.001
I	238 (34.3)	155 (43.4)	83 (24.6)	
II	376 (54.2)	161 (45.1)	215 (63.8)	
III	80 (11.5)	41 (11.5)	39 (11.6)	
Tobacco dependence				0.021
Yes	130 (18.7)	55 (15.4)	75 (22.3)	
No	564 (81.3)	302 (84.6)	262 (77.7)	
Neo-adjuvant therapy				<0.001
No	619 (89.2)	347 (97.2)	272 (80.7)	
Yes	75 (10.8)	10 (2.8)	65 (19.3)	
Common residence				0.713
Eastern China	635 (91.5)	328 (91.9)	307 (91.1)	
Non-eastern China	59 (8.5)	29 (8.1)	30 (8.9)	
Operation starts				0.111
Before 17:00	523 (75.4)	260 (72.8)	263 (78.0)	
After 17:00	171 (24.6)	97 (27.2)	74 (22.0)	
Side				0.005
Left	308 (44.4)	140 (39.2)	168 (49.9)	
Right	386 (55.6)	217 (60.8)	169 (50.1)	
Organs				<0.001
Lung	589 (84.9)	274 (76.8)	315 (93.5)	
Mediastinum	69 (9.9)	57 (16.0)	12 (3.6)	
Lung & mediastinum	36 (5.2)	26 (7.2)	10 (2.9)	
Duration				<0.001
< 3 h	487 (70.2)	313 (87.7)	174 (51.6)	
≥ 3 h	207 (29.8)	44 (12.3)	163 (48.4)	
Blood loss				<0.001
< 500 ml	639 (92.1)	351 (98.3)	288 (85.5)	
≥ 500 ml	55 (7.9)	6 (1.7)	49 (14.5)	

U-VATS uniportal video-assisted thoracic surgery, OT open thoracotomy, BMI body mass index, ASA American Society of Anesthesiologists. Data are presented as frequency (proportion) or mean ± standard deviation (SD)

Table 2 Acute postoperative follow-ups

Variables	Sum (N = 668)	Surgical approach		p
		U-VATS (n = 351)	OT (n = 317)	
SP 24 h		3.9 ± 2.6	5.3 ± 2.8	<0.001
DP 24 h		6.9 ± 2.2	8.2 ± 2.0	<0.001
SP 48 h		2.4 ± 2.0	3.6 ± 2.3	<0.001
DP 48 h		5.0 ± 2.1	6.6 ± 2.2	<0.001
ISP ⁵				<0.001
No	559 (83.7)	317 (90.3)	242 (76.3)	
Yes	109 (16.4)	34 (9.7)	75 (23.7)	
PONV				0.129
No	617 (92.4)	319 (90.9)	298 (94.0)	
Yes	51 (7.6)	32 (9.1)	19 (6.0)	
Rescue analgesia				<0.001
None	412 (61.7)	261 (74.4)	151 (47.6)	
Non-opioids	196 (29.3)	79 (22.5)	117 (36.9)	
Opioids	60 (9.0)	11 (3.1)	49 (15.5)	

U-VATS uniportal video-assisted thoracic surgery, OT open thoracotomy, SP static pain, DP dynamic pain, ISP ipsilateral shoulder pain, PONV postoperative nausea and vomiting. Data are presented as mean ± std or frequency (proportion)

Table 3 Chronic postoperative follow-ups

Variables	Surgical approach		p	
	U-VATS (n = 333)	OT (n = 281)		
CPTS (3 months)			<0.001	
No	178 (29.0)	122 (36.6)	56 (19.9)	
Yes	436 (71.0)	211 (63.4)	225 (80.1)	
Formation			0.004	
Mild	303 (69.5)	162 (76.9)	141 (62.6)	
Moderate	103 (23.6)	36 (17.0)	67 (29.8)	
Severe	30 (6.9)	13 (6.1)	17 (7.6)	
Severity			0.007	
NPP (3 months)			0.014	
No	588 (95.8)	325 (97.6)	263 (93.6)	
Highly susceptible	26 (4.2)	8 (2.4)	18 (6.4)	
CPTS (6 months)			<0.001	
No	216 (37.2)	152 (48.3)	64 (24.2)	
Yes	364 (62.8)	163 (51.7)	201 (75.8)	
Formation			0.152	
Mild	285 (78.3)	135 (82.8)	150 (74.6)	
Moderate	69 (19.0)	25 (15.3)	44 (21.9)	
Severe	10 (2.7)	3 (1.8)	7 (3.5)	
Severity			0.057	

U-VATS uniportal video-assisted thoracic surgery, OT open thoracotomy, CPTS chronic pain after thoracic surgery, NPP neuropathic pain. Data are presented as frequency (proportion)

was 4.2% overall, yet it was higher in the OT group (6.4% vs. 2.4%, $p=0.014$).

Univariate analysis of the perioperative factors on CPTS (3 months)

In Table 4, patients were categorized into two groups based on the occurrence of CPTS (436 vs. 178). Notably, the OT approach presented a significantly higher risk of CPTS compared to U-VATS ($p<0.001$, RR 95%CI 2.323 [1.608, 3.356]). Age between 51 and 70 also showed an elevated risk (RR 95%CI 1.634 [1.095, 2.439]) compared to those under 50 years old in preoperative factors. In intraoperative factors, CPTS was more likely when surgery started after 17:00 (RR 95%CI 1.534 [1.002, 2.347]) or lasted longer than 3 h (RR 95%CI 1.688 [1.119, 2.548]), but less likely when the target organ was mediastinum compared to lung surgery (RR 95%CI 0.352 [0.208, 0.598]). Acute postoperative evaluations revealed patients with ISP were more prone to CPTS (RR 95%CI 1.561 [1.147, 2.572]) although the p value was contradictory ($p=0.081$). For ranked pain severity, moderate to severe pain (excluding moderate SP 24 h postoperatively) significantly increased the likelihood of CPTS compared to no or mild pain (trend test, $p<0.001$).

Multi-variate analysis of the occurrence of CPTS (3 months)

Following the identification of significant indicators in the univariate analysis of CPTS occurrence, a multivariate analysis was conducted with maximum likelihood estimation to assess these factors (Table 5). After adjustment, the risk of developing CPTS was found to be 2.044 times higher in the OT group than in the U-VATS group ($p=0.001$; RR 95%CI 2.044 [1.350, 3.095]). Surgical procedures commencing after 17:00 still exhibited a higher risk of CPTS (RR 95%CI 1.555 [1.009, 2.397]). Also, mediastinum surgery demonstrated a lower likelihood of developing CPTS compared to lung surgery ($p=0.011$; RR 95%CI 0.483 [0.276, 0.846]). Aside from moderate SP 24 h postoperatively, an overall significant increased risk of CPTS with pain severity went from moderate to severe, compared to no pain or mild pain ($p<0.001$).

Discussion

To the best of our knowledge, this study represents the first prospective investigation comparing U-VATS to OT in the context of CPTS, incorporating a comprehensive analysis of perioperative factors with the largest sample size. Our findings reveal that U-VATS is significantly associated with a lower incidence and reduced severity of CPTS at

the 3-month mark in comparison to OT. Notably, U-VATS demonstrates a favorable impact on APTS severity, while heightened APTS severity correlates positively with CPTS incidence. Additionally, U-VATS is linked to a decreased incidence of highly suspected NPP. Exploring further, patients aged 51–70 years, surgeries exceeding 3 h, nocturnal surgeries, and lung surgeries emerge as potential risk factors for CPTS. However, our analysis indicates a lack of robust association between CPTS and factors, such as female sex, BMI, ASA classification, preoperative neoadjuvant therapy, tobacco dependence, operation side, blood loss, ISP, PONV, or the need for rescue analgesia.

CPTS etiology

Its elusive and distinct mechanisms may originate from incision induced injury, though, the ongoing and lasting inflammations, modulations, amplifications, pain threshold reduction, synaptic plasticity, and central sensitization have neurons, glial cells, peripheral and central circuits involved [15, 16]. CPTS has gone far beyond the temporal continuum of APTS. Aside from surgery trauma, CPTS could even be more related to demographic factors, such as age, sex, psychological features, and perioperative analgesia [17–19].

Surgical approach, APTS severity, design feature, and CPTS outcome

The outcome of CPTS was controversial previously in the comparison of M-VATS vs. OT studies [11, 20–26], with most showing no significance between the 2 surgical techniques [11, 20, 21, 24–26]. Despite the theoretical advantage of reduced trauma with U-VATS due to its single incision, this was not confirmed in a limited previous study [27]. Our current investigation contributes to this discourse by providing evidence that the reduced surgical trauma associated with U-VATS results in attenuated APTS, subsequently leading to an improvement in CPTS. Notably, few studies investigating APTS related to CPTS employed a prospective design, ever since Katz J found that APTS could predict the long-term CPTS with only 23 effective sample size in OT lung surgeries [5]. APTS is correlated with perioperative analgesia, and similar APTS could be achieved with unbalanced analgesia management for different surgical approaches, and thus CPTS outcomes [11]. With similar analgesia for different incisions as in our study, the outcomes of APTS and CPTS are built on the incision choices. Our prospective feature also favors of decreasing the drop-out rates than retrospective studies [3, 24], less than 15% loss of follow-ups when primary outcome was achieved. Our continuous recruitment and balanced assignment for the 2 groups were possible with reasonable statistical power calculation, which was lack in previous studies [20, 21, 25, 26].

Table 4 Univariate analysis of perioperative variables on CPTS at 3 months

	CPTS (3 m)		<i>p</i>	RR (95%CI)
	No (<i>n</i> = 178)	Yes (<i>n</i> = 436)		
Surgical approach				< 0.001
U-VATS	122 (68.5)	211 (48.4)		REF
OT	56 (31.5)	225 (51.6)		2.323 (1.608, 3.356)
Sex				0.654
Female	70 (39.3)	180 (41.3)		REF
Male	108 (60.7)	256 (58.7)		0.922 (0.646, 1.316)
Age (years)				0.049
≤ 50	55 (30.9)	97 (22.2)		REF
51–70	102 (57.3)	294 (67.4)		1.634 (1.095, 2.439)
> 70	21 (11.8)	45 (10.3)		1.215 (0.657, 2.246)
BMI (kg/m ²)				0.540
< 28	154 (86.5)	385 (88.3)		REF
≥ 28	24 (13.5)	51 (11.7)		0.850 (0.505, 1.430)
ASA classification				0.190
I	59 (33.1)	161 (36.9)		REF
II	95 (53.4)	237 (54.4)		0.914 (0.624, 1.339)
III	24 (13.5)	38 (8.7)		0.580 (0.321, 1.049)
Tobacco dependence				0.560
Yes	35 (19.7)	77 (17.7)		REF
No	143 (80.3)	359 (82.3)		0.876 (0.562, 1.366)
Neo-adjuvant therapy				0.081
No	166 (93.3)	386 (88.5)		REF
Yes	12 (6.7)	50 (11.5)		1.792 (0.930, 3.452)
Common residence				0.762
Eastern China	165 (92.7)	401 (92.0)		REF
Non-eastern China	13 (7.3)	35 (8.0)		1.108 (0.571, 2.147)
Side				0.845
Left	74 (41.6)	185 (42.4)		REF
Right	104 (58.4)	251 (57.6)		0.965 (0.678, 1.375)
17:00				0.049
Before	143 (80.3)	317 (72.7)		REF
After	35 (19.7)	119 (27.3)		1.534 (1.002, 2.347)
Targeted organs				0.001
Lung	135 (75.8)	383 (87.8)		REF
Mediastinum	32 (18.0)	32 (7.3)		0.352 (0.208, 0.598)
Lung & mediastinum	11 (6.2)	21 (4.9)		0.846 (0.293, 2.446)
Duration				0.013
< 3 h	140 (78.7)	299 (68.6)		REF
≥ 3 h	38 (21.3)	137 (31.4)		1.688 (1.119, 2.548)
Blood loss				0.871
< 500 ml	166 (93.3)	405 (92.9)		REF
≥ 500 ml	12 (6.7)	31 (7.1)		1.059 (0.531, 2.112)
ISP				0.081
No	155 (87.1)	354 (81.2)		REF
Yes	23 (12.9)	82 (18.8)		1.561 (1.147, 2.572)
PONV				0.171
No	168 (94.4)	397 (91.1)		REF
Yes	10 (5.6)	39 (8.9)		1.650 (0.805, 3.383)
Rescue analgesia				

Table 4 (continued)

	CPTS (3 m)		<i>p</i>	RR (95%CI)
	No (<i>n</i> = 178)	Yes (<i>n</i> = 436)		
None	120 (67.4)	264 (60.6)		0.132 REF
Non-opioid	49 (27.5)	131 (30.0)		1.215 (0.820,1.800)
Opioid	9 (5.1)	41 (9.4)		2.071 (0.975,4.397)
SP 24 h				<0.001
None	24 (13.5)	26 (6.0)		REF
Mild	67 (37.6)	134 (30.7)		1.846 (0.986,3.458)
Moderate	58 (32.6)	143 (32.8)		2.276 (1.208, 4.287)
Severe	29 (16.3)	133 (30.5)		4.233 (2.134, 8.398)
			P for trend <i>p</i> < 0.001	
DP 24 h				<0.001
None	0 (0)	1 (0.2)		/
Mild	18 (10.1)	10 (2.3)		REF
Moderate	54 (30.3)	106 (24.3)		3.533 (1.526,8.181)
Severe	106 (59.6)	319 (73.2)		5.417 (2.425,12.100)
			P for trend <i>p</i> < 0.001	
SP 48 h				<0.001
None	45 (25.3)	58 (13.3)		REF
Mild	99 (55.6)	200 (45.9)		1.567 (0.992,2.477)
Moderate	31 (17.4)	132 (30.3)		3.304 (1.902, 5.737)
Severe	3 (1.7)	46 (10.6)		11.897 (3.473, 40.745)
			P for trend <i>p</i> < 0.001	
DP 48 h				<0.001
None	3 (1.7)	2 (0.5)		REF
Mild	46 (25.8)	57 (13.1)		1.859 (0.298,11.597)
Moderate	94 (52.8)	192 (44.0)		3.064 (1.503, 18.649)
Severe	35 (19.7)	185 (42.4)		7.929 (1.278, 49.194)
			P for trend <i>p</i> < 0.001	

CPTS chronic pain after thoracic surgery, RR relative risk, CI confidence interval, U-VATS uniportal video-assisted thoracic surgery, OT open thoracotomy, BMI body mass index, ASA American Society of Anesthesiologists, ISP ipsilateral shoulder pain, PONV postoperative nausea and vomiting, SP static pain, DP dynamic pain. Data are presented as frequency (percentage)

Additionally, the evaluation method matters, too, employing proper telephone interviews, resulted in a higher response rate compared to mail methods used in previous studies [20, 26]. Recognizing the complexity of CPTS, characterized by ambiguity, lower pain intensity, and multiple domains, our study employed a multi-dimensional SF-MPQ for a more comprehensive understanding of pain characteristics compared to single-dimension scales.

Chronic NPP

In our study, patients with highly suspected NPP were less in U-VATS group than in OT group (2.4% vs. 6.4%, *p* = 0.014), but in general, NPP incidence in the present study was lower than previous findings with rates between 8.8 and 29% [20, 25, 28–31]. Several factors may account for this disparity: first, patients with chronic pain or on

pain medicine were excluded preoperatively in our study; additionally, advancements in surgical techniques over the years may have contributed to reduced injury to the intercostal nerves and neurovascular bundles [32]; further, it has been suggested that the original cutoff value of 12 for the S-LANSS scale may be less sensitive for Asian patients, advocating for a lower cutoff value of 11 or 10 could be more practical [33].

CPTS risk factors analysis

With a large sample size in our study, we conducted univariate and multivariate analysis which identified OT surgical approach and APTS severity as 2 independent risk factors of CPTS at 3 months. Other perioperative factors are also analyzed.

Table 5 Multivariate analysis of perioperative factors on CPTS at 3 months

	MLE				RR (95%CI)
	Estimation	SD	Wald χ^2	<i>p</i>	
Approach					
U-VATS	REF				
OT	0.715	0.212	11.398	0.001	2.044 (1.350, 3.095)
Age (years)					
≤ 50	REF				
51–70	0.173	0.221	0.612	0.434	1.189 (0.771, 1.835)
> 70	– 0.153	0.327	0.219	0.640	0.858 (0.452, 1.629)
17:00					
Before	REF				
After	0.442	0.221	4.000	0.046	1.555 (1.009, 2.397)
Organs					
Lung	REF				
Mediastinum	– 0.727	0.286	6.480	0.011	0.483 (0.276, 0.846)
Lung & mediastinum	– 0.010	0.573	0.000	0.987	0.990 (0.323, 3.042)
Duration					
< 3 h	REF				
≥ 3 h	0.140	0.238	0.346	0.556	1.15 (0.722, 1.832)
SP 24 h					
None	REF				
Mild	0.215	0.392	0.300	0.584	1.240 (0.575, 2.674)
Moderate	0.119	0.423	0.079	0.778	1.126 (0.491, 2.582)
Severe	0.370	0.453	0.668	0.041	1.448 (1.196, 3.520)
DP 24 h					
Mild	REF				
Moderate	1.053	0.425	5.436	0.020	2.866 (1.183, 6.947)
Severe	0.955	0.473	4.080	0.043	2.599 (1.029, 6.565)
SP 48 h					
None	REF				
Mild	0.307	0.303	1.029	0.310	1.360 (0.751, 2.463)
Moderate	0.680	0.372	3.349	0.047	1.974 (1.053, 4.088)
Severe	1.727	0.732	5.560	0.018	5.621 (1.338, 23.608)
DP 48 h					
None	REF				
Mild	0.304	0.880	0.119	0.730	1.356 (0.241, 7.612)
Moderate	0.526	0.887	0.352	0.033	1.692 (1.097, 9.63)
Severe	0.818	0.905	0.816	0.016	2.265 (1.184, 13.342)

CPTS chronic pain after thoracic surgery, MLE maximum likelihood estimation, SD standard deviation, RR relative risk, CI confidence interval, U-VATS uniportal video-assisted thoracic surgery, OT open thoracotomy, SP static pain, DP dynamic pain

Age and sex

Univariate analysis shows that patients aged between 51 and 70 years old had a higher risk of CPTS compared to those under 50 years old, while multivariate analysis showed no difference. It's possible that age linked a spurious association with CPTS. Different from previous studies that female patients were at higher risk of CPTS

[3, 34], no difference was found in our study. Reports indicated that male, older patients were less likely to report chronic pain than female, younger patients due to cognitive decline and dementia [35–37], since we have excluded those patients with possible cognitive problems, the reporting bias could be lessened. Additionally, their willingness to report could be encouraged by proper telephone-based interviews.

Surgery duration

Consistent with previous studies [3, 38, 39] that longer surgery duration resulted in higher incidence of CPTS in univariate analysis, we set the cutoff point at 3 h based on the experience in our institution. Longer duration requires more opioid consumption intraoperatively, which increases the likelihood of developing opioid tolerance and hyperalgesia [40, 41] that would deteriorate APTS and CPTS consequently. However, the weak existent associations might be decreased when potential confounders were controlled by multivariate analysis.

Organ difference

Operating on the lung was more likely to induce CPTS than mediastinum, indicating that organ-based mechanisms were also involved aside from the incision. Since the injury to the periarterial nerve plexus, the peri-bronchial nerve plexus and the visceral pleura is unavoidable during the dissection of the bronchopulmonary segment, more noxious stimuli would be enforced for lung surgery compared to mediastinum surgery [42].

Nocturnal surgery

Surgery after 17:00 is associated with elevated risk of developing CPTS in our study. The circadian effect of CPTS has been discussed in many studies. It was proved that nocturnal surgery was associated with more intraoperative adverse events due to decreased alertness, teamwork and performance, compared to daytime surgery [43], subsequently leading to suboptimal postoperative pain care. Moreover, variations in pain perception may be attributed to the differential secretion of beta-endorphin, with higher levels during the day providing endogenous analgesic effects as ligands of mu-opioid receptors [44, 45].

Acute ISP

Previous descriptive study found acute ISP was not a predictor of CPTS [46], we find that ISP is positively associated with CPTS at 3 months [RR(95%CI), 1.561 (1.147, 2.572)]. However, the lack of statistical significance ($p=0.081$) suggests potential limitations in statistical power, attributable to a constrained sample size and a scarcity of patients with ISP in our study. Since our inquiry was “whether you are having shoulder pain on the surgical side?”, which would have included those ISP at rest only but potentially excluding those experiencing dynamic ISP.

Limitations

First, this study did not conduct a thorough analysis of disease severity, which could affect CPTS, as well as perioperative variables like surgical approach, operation duration, opioid consumption, and perioperative neoadjuvant therapy. Second, the observational study’s inherent nature introduces potential selection bias, given surgeons’ varied approaches and pain management providers’ diverse analgesia strategies within the same condition. These complexities may impact study outcomes. Third, the higher drop-out rate in the OT group raises concerns about study representativeness, potentially introducing bias. Lastly, while our findings provide insights into adult patients, caution is needed when extrapolating to the pediatric population. A comprehensive understanding of disease severity’s role in various outcomes could enhance the study’s applicability and robustness.

Conclusions

Our study underscores the potential of U-VATS to reduce both incidence and severity of CPTS at 3 months compared to OT. We also identified several risk factors for CPTS, including OT incision, inadequately managed APTS, lung surgery, and nocturnal surgery.

Acknowledgements None

Author contributions All authors contributed to the study conception, design, material preparation, data collection, data analysis, draft of manuscript. All authors read and approved the final manuscript.

Funding This work was supported by Development Fund for the Department of Anesthesiology by Shanghai Pulmonary Hospital (2022); Grant of Key Supported Disciplines by Shanghai Municipal Health Commission (grant number: 2023ZDFC0204).

Data availability The datasets generated and analyzed during the current study are available from the authors on reasonable request.

Declarations

Conflict of interest All authors have no conflicts of interest to disclose.

References

1. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery: a review of predictive factors. *Anesthesiol.* 2000;93(4):1123–33.
2. Perttunen K, Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow-up study. *Acta Anaesthesiol Scand.* 1999;43(5):563–7.
3. Yoon S, Hong WP, Joo H, Kim H, Park S, Bahk JH, Lee HJ. 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):331–6.
4. Liu CW, Page MG, Weinrib A, Wong D, Huang A, McRae K, Fiorellino J, Tamir D, Kahn M, Katznelson R, Ladha K, Abdallah F, Cypel M, Yasufuku K, Chan V, Parry M, Khan J, Katz J, Clarke H. Predictors of one year chronic post-surgical pain trajectories following thoracic surgery. *J Anesth.* 2021;35(4):505–14.
 5. Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. *Clin J Pain.* 1996;12(1):50–5.
 6. Fiorelli S, Cioffi L, Menna C, Ibrahim M, De Blasi RA, Rendina EA, Rocco M, Massullo D. Chronic pain after lung resection: risk factors, neuropathic pain, and quality of life. *J Pain Symptom Manage.* 2020;60(2):326–35.
 7. Steingrimsdóttir ÓA, Landmark T, Macfarlane GJ, Nielsen CS. Defining chronic pain in epidemiological studies: a systematic review and meta-analysis. *Pain.* 2017;158(11):2092–107.
 8. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the international classification of diseases (ICD-11). *Pain.* 2019;160(1):19–27.
 9. Gottschalk A, Cohen SP, Yang S, Ochroch EA. Preventing and treating pain after thoracic surgery. *Anesthesiology.* 2006;104(3):594–600.
 10. Landreneau RJ, Mack MJ, Hazelrigg SR, Naunheim K, Dowling RD, Ritter P, Magee MJ, Nunchuck S, Keenan RJ, Ferson PF. Prevalence of chronic pain after pulmonary resection by thoracotomy or video-assisted thoracic surgery. *J Thorac Cardiovasc Surg.* 1994;107(4):1079–85.
 11. Bayman EO, Parekh KR, Keech J, Selte A, Brennan TJ. A prospective study of chronic pain after thoracic surgery. *Anesthesiology.* 2017;126(5):938–51.
 12. Wang JL, Zhang WJ, Gao M, Zhang S, Tian DH, Chen J. A cross-cultural adaptation and validation of the short-form McGill pain questionnaire-2: chinese version in patients with chronic visceral pain. *J Pain Res.* 2017;10:121–8.
 13. Georgoudis G, Watson PJ, Oldham JA. The development and validation of a greek version of the short-form McGill pain questionnaire. *Eur J Pain.* 2000;4(3):275–81.
 14. Arimura T, Hosoi M, Tsukiyama Y, Yoshida T, Fujiwara D, Tanaka M, Tamura R, Nakashima Y, Sudo N, Kubo C. Pain questionnaire development focusing on cross-cultural equivalence to the original questionnaire: the Japanese version of the short-form McGill Pain questionnaire. *Pain Med.* 2012;13(4):541–51.
 15. Bliss TV, Collingridge GL, Kaang BK, Zhuo M. Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. *Nat Rev Neurosci.* 2016;17(8):485–96.
 16. Boroujerdi A, Kim HK, Lyu YS, Kim DS, Figueroa KW, Chung JM, Luo ZD. Injury discharges regulate calcium channel alpha-2-delta-1 subunit upregulation in the dorsal horn that contributes to initiation of neuropathic pain. *Pain.* 2008;139(2):358–66.
 17. Vasilopoulos T, Wardhan R, Rashidi P, Fillingim RB, Wallace MR, Crispin PL, Parvataneni HK, Prieto HA, Machuca TN, Hughes SJ, Murad GJA, Tighe PJ. Patient and procedural determinants of postoperative pain trajectories. *Anesthesiology.* 2021;134(3):421–34.
 18. Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. *Clin J Pain.* 2012;28(9):819–41.
 19. Bouman EA, Theunissen M, Bons SA, van Mook WN, Gramke HF, van Kleef M, Marcus MA. Reduced incidence of chronic postsurgical pain after epidural analgesia for abdominal surgery. *Pain Pract.* 2014;14(2):E76–84.
 20. Steegers MA, Snik DM, Verhagen AF, van der Drift MA, Wilder-Smith OH. Only half of the chronic pain after thoracic surgery shows a neuropathic component. *J Pain.* 2008;9(10):955–61.
 21. Rizk NP, Ghanie A, Hsu M, Bains MS, Downey RJ, Sarkaria IS, Finley DJ, Adusumilli PS, Huang J, Sima CS, Burkhalter JE, Park BJ, Rusch VW. A prospective trial comparing pain and quality of life measures after anatomic lung resection using thoracoscopy or thoracotomy. *Ann Thorac Surg.* 2014;98(4):1160–6.
 22. Shanthanna H, Aboutouk D, Poon E, Cheng J, Finley C, Paul J, Thabane L. A retrospective study of open thoracotomies versus thoracoscopic surgeries for persistent postthoracotomy pain. *J Clin Anesth.* 2016;35:215–20.
 23. Miyazaki T, Sakai T, Tsuchiya T, Yamasaki N, Tagawa T, Mine M, Shibata Y, Nagayasu T. Assessment and follow-up of intercostal nerve damage after video-assisted thoracic surgery. *Eur J Cardiothorac Surg.* 2011;39(6):1033–9.
 24. Sugiyama Y, Iida H, Amaya F, Matsuo K, Matsuoka Y, Kojima K, Matsuno F, Hamaguchi T, Iseki M, Yamaguchi K, Takahashi Y, Hara A, Sugasawa Y, Kawamata M, Tanaka S, Inagaki Y, Otsuki A, Yamazaki M, Ito H. Prevalence of chronic postsurgical pain after thoracotomy and total knee arthroplasty: a retrospective multicenter study in Japan (Japanese study group of subacute postoperative pain). *J Anesth.* 2018;32(3):434–8.
 25. Kampe S, Geismann B, Weinreich G, Stamatis G, Ebmeyer U, Gerbershagen HJ. The influence of type of anesthesia, perioperative pain, and preoperative health status on chronic pain six months after thoracotomy—a prospective cohort study. *Pain Med.* 2017;18(11):2208–13.
 26. Hopkins KG, Ferson PF, Shende MR, Christie NA, Schuchert MJ, Pennathur A. Prospective study of quality of life after lung cancer resection. *Ann Transl Med.* 2017;5(10):204.
 27. McElnay PJ, Molyneux M, Krishnadas R, Batchelor TJ, West D, Casali G. Pain and recovery are comparable after either uniportal or multiport video-assisted thoracoscopic lobectomy: an observation study. *Eur J Cardiothorac Surg.* 2015;47(5):912–5.
 28. Gandhi W, Pomares FB, Naso L, Asenjo JF, Schweinhardt P. Neuropathic pain after thoracotomy: Tracking signs and symptoms before and at monthly intervals following surgery. *Eur J Pain.* 2020;24(7):1269–89.
 29. Guastella V, Mick G, Soriano C, Vallet L, Escande G, Dubray C, Eschalié A. A prospective study of neuropathic pain induced by thoracotomy: incidence, clinical description, and diagnosis. *Pain.* 2011;152(1):74–81.
 30. Dualé C, Ouchchane L, Schoeffler P, Dubray C. Neuropathic aspects of persistent postsurgical pain: a French multicenter survey with a 6-month prospective follow-up. *J Pain.* 2014;15(1):24e1–e0.
 31. Searle RD, Simpson MP, Simpson KH, Milton R, Bennett MI. Can chronic neuropathic pain following thoracic surgery be predicted during the postoperative period? *Interact Cardiovasc Thorac Surg.* 2009;9(6):999–1002.
 32. Ranganathan P, Jiwnani S, Pramesh CS. Intercostal nerve protection to prevent post-thoracotomy pain. *J Thorac Dis.* 2019;11(Suppl 9):S1434–5.
 33. Isomura T, Sumitani M, Matsudaira K, Kawaguchi M, Inoue R, Hozumi J, Tanaka T, Oshima H, Mori K, Taketomi S, Inui H, Tahara K, Yamagami R, Hayakawa K. Development of the Japanese version of the leeds assessment of the neuropathic symptoms and signs pain scale: diagnostic utility in a clinical setting. *Pain Pract.* 2017;17(6):800–7.
 34. Chen WC, Bai YY, Zhang LH, Liu YB, Liu CY, Liang JW, He HF. Prevalence and predictors of chronic postsurgical pain after video assisted thoracoscopic surgery a systematic review and meta-analysis. *Pain Ther.* 2022;12(1):117–39.

35. Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. *Br J Anaesth*. 2019;123(2):e273–83.
36. Schofield P. The assessment of pain in older people: UK national guidelines. *Age Ageing*. 2018;47(suppl_1):i1–22.
37. Greenspan JD, Craft RM, LeResche L, Arendt-Nielsen L, Berkeley KJ, Fillingim RB, Gold MS, Holdcroft A, Lautenbacher S, Mayer EA, Mogil JS, Murphy AZ, Traub RJ. Studying sex and gender differences in pain and analgesia: a consensus report. *Pain*. 2007;132(Suppl 1):S26–s45.
38. Loriga B, Di Filippo A, Tofani L, Signorini P, Caporossi T, Barca F, De Gaudio AR, Rizzo S, Adembri C. Postoperative pain after vitreo-retinal surgery is influenced by surgery duration and anesthesia conduction. *Minerva Anesthesiol*. 2019;85(7):731–7.
39. Chung F, Ritchie E, Su J. Postoperative pain in ambulatory surgery. *Anesth Analg*. 1997;85(4):808–16.
40. Yu EH, Tran DH, Lam SW, Irwin MG. Remifentanyl tolerance and hyperalgesia: short-term gain, long-term pain? *Anaesthesia*. 2016;71(11):1347–62.
41. Higgins C, Smith BH, Matthews K. Evidence of opioid-induced hyperalgesia in clinical populations after chronic opioid exposure: a systematic review and meta-analysis. *Br J Anaesth*. 2019;122(6):e114–26.
42. Dail DH, Liebow AA, Gmelich JT, Friedman PJ, Miyai K, Myer W, Patterson SD, Hammar SP. Intravascular, bronchiolar, and alveolar tumor of the lung (IVBAT) An analysis of twenty cases of a peculiar sclerosing endothelial tumor. *Cancer*. 1983;51(3):452–64.
43. Cortegiani A, Gregoretti C, Neto AS, Hemmes SNT, Ball L, Canet J, Hiesmayr M, Hollmann MW, Mills GH, Melo MFV, Putensen C, Schmid W, Severgnini P, Wrigge H, de GamaAbreu M, Schultz MJ, Pelosi P. Association between night-time surgery and occurrence of intraoperative adverse events and postoperative pulmonary complications. *Br J Anaesth*. 2019. <https://doi.org/10.1016/j.bja.2018.10.063>.
44. Gil-Ad I, Dickerman Z, Amdursky S, Laron Z. Diurnal rhythm of plasma beta endorphin, cortisol and growth hormone in schizophrenics as compared to control subjects. *Psychopharmacology*. 1986;88(4):496–9.
45. Argueta DA, Aich A, Lei J, Kiven S, Nguyen A, Wang Y, Gu J, Zhao W, Gupta K. β -endorphin at the intersection of pain and cancer progression: preclinical evidence. *Neurosci Lett*. 2021;744:135601.
46. Blichfeldt-Eckhardt MR, Andersen C, Ørding H, Licht PB, Toft P. From acute to chronic pain after thoracic surgery: the significance of different components of the acute pain response. *J Pain Res*. 2018;11:1541–8.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.