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Original Article

Effects of preoperative current smoking on chronic postsurgical pain in thoracic surgery: a retrospective cohort study

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Abstract: Objective: This study aimed to investigate the effect of preoperative current smoking on chronic postsurgical pain in patients who underwent thoracic surgery. Methods: A total of 5,395 patients aged over 18 years old who underwent thoracic surgery from January 2016 to March 2020 in Henan Provincial People's Hospital were enrolled. Patients were divided into two groups: the smoking group (SG group) and the nonsmoking group (NSG group). Propensity score matching was utilized to eliminate the influence of confounding factors, and a multivariable logistic regression model was established to determine the effect of preoperative current smoking on chronic postsurgical pain. The dose-response relationship between the smoking index (SI) and chronic postsurgical pain at rest was analyzed using a restricted cubic spline curve. Results: In a matched cohort of 1028 patients, the incidence of chronic pain at rest was 13.2% in the smoking group and 19.0% in the nonsmoking group (P = 0.011). Three different models were used to verify the stability of the model between preoperative current smoking and chronic postsurgical pain. A regression model was established to determine the influence of different smoking indexes (SIs) on chronic postsurgical pain. The incidence of chronic pain at rest was lower in patients with SI ≥400 before thoracic surgery than in patients whose SI was less than 400. Conclusions: A relationship between the preoperative current smoking index and chronic postsurgical pain at rest was observed. The incidence of chronic postsurgical pain at rest was lower in patients whose SI was greater than 400.

Keywords: Chronic postsurgical pain, smoking, thoracic surgery, retrospective cohort, dose-response relationship

Introduction

The International Association for the Study of Pain (IASP) defines chronic postsurgical pain (CPSP) as pain that arises postoperatively and lasts for at least 3 months, which is longer than the normal healing time [1]. CPSP is a frequent and important complication in thoracic surgery. CPSP occurs in 25 to 60% of post-thoracic surgery patients, and it decreases the patient's quality of life and hampers their daily activities [2].

Many studies have discussed the relationship between smoking and postoperative pain, but the conclusions are inconsistent. Fan et al. found that cigarette smoking was associated with increased postoperative acute pain intensity and higher pain scores [3]. Yao et al. reported that acute severe pain was correlated with smoking history [4]. Oh et al. showed that patients who had never smoked had lower opioid analgesic consumption on the days immediately following surgery, but current smoking or the total amount of smoking in packs did not affect postoperative pain outcomes after video-assisted lung lobectomy [5]. Acute pain is a clinical risk factor for the development of chronic pain [6]. Other studies focused on the relationship between smoking and CPSP. Tian et al. showed that non-smoking was a factor associated with the presence of CPSP on movement [7]. Schug et al. showed that smoking was a sig-

nificant risk factor for CPSP [8]. Therefore, the effects of smoking on CPSP are not clear.

According to the enhanced recovery after surgery (ERAS) guideline recommendations, smoking should cease at least 4 weeks before thoracic surgery. However, many patients have poor compliance and do not follow this smoking cessation time [9]. These patients continued smoking within 4 weeks before surgery. Therefore, the effects of preoperative current smoking on CPSP need further investigation. Several aspects of the effects of preoperative smoking are not clear. (1) Is preoperative current smoking a protective factor or a risk factor for CPSP? (2) Is the effect of smoking on CPSP relating to different smoking indexes? (3) Is there a dose-response relationship between the smoking index and CPSP?

Preoperative smoking status may have a greater impact on CPSP in smokers who continue to smoke within 4 weeks before surgery than ex-smokers. Therefore, we hypothesized that there exists a dose-response relationship between the preoperative current smoking index and CPSP in thoracic surgery. We performed a retrospective cohort study to test this hypothesis and examine the effects of the smoking index on CPSP.

Materials and methods

Patient selection and ethics statement

This study was approved by the ethics committee of our hospital and adopted a retrospective cohort study design. 5395 patients who underwent thoracic surgery in our hospital from January 2016 to March 2020 through the electronic medical record system were selected according to the following inclusion criteria: (I) Patients undergoing thoracic surgery involving: lung cancer, lobectomy, esophageal cancer, mediastinal surgery and other thoracic surgery; (II) The surgical time takes more than 30 min, and the postoperative hospital stay is longer than 1 day; (III) Patients aged ≥18 years without substantial hearing impairment or loss, vision impairment or dementia before operation; (IV) Patients without history of operation and without history of analgesic drugs preoperatively; (V) Patients with complete and standard medical records including current and past medical history, preoperative laboratory and imaging examination results, as well as intraoperative data; (VI) Patients with correct postoperative pain evaluation and full records. The exclusion criteria were as follows: (I) acute pain data in the first 24 hours after surgery were not recorded; (II) patients who died within 3 months after thoracic surgery; (III) postoperative follow-up was refused; (IV) incomplete patient baseline data; (V) patients who underwent surgery within 3 months after thoracic surgery; and (VI) patients who smoked again within 3 months after thoracic surgery.

Data collection

This study was a retrospective cohort study performed at Henan Provincial People's Hospital, China. The Reports of Observational Enhanced Epidemiology (STROBE) checklist for cohort studies was referenced in the preparation of the article. The study design, outcome variables, and analysis plan were determined before data analyses. The Information Center Department of Henan Provincial People's Hospital collected each inpatient's homepage, medical records and anesthesia record forms using a unified data collection system. The data for our study were obtained from electronic medical records and collected retrospectively. Anonymized data on basic patient information, clinical diagnosis codes of the International Statistical Classification of Diseases and Related Health Problems (10th edition), surgery-related information, and preoperative current smoking history were transferred to specific data management agencies. A trained anesthesiology nurse who was blinded to the study parameters obtained CPSP data at 3 months postoperatively via telephone follow-up. Patients and their families are required to truthfully inform about smoking status and pain. The specific follow-up protocol was described in Lu et al. [10]. At the 3-month follow-up, the diagnosis of CPSP was made by asking patients about the presence of pain localized to their surgical incision that was not present before surgery or caused by any other known cause, such as infection or malignancy. Patients were asked to report the intensity of pain at rest and at activity (when coughing) via a telephone review. CPSP was defined when the pain intensity measured by an 11-point numeric rating scale (NRS) was higher than 1 point for at least 3 months after surgery.

Baseline data were stratified by dividing the study population into a preoperative current smoking group and nonsmoking group according to the following definitions [11]: 1) nonsmoking group, patients who had never smoked a cigarette or who had smoked fewer than 100 cigarettes in their whole lifetime; and 2) preoperative current smoking group, patients who had smoked more than 100 cigarettes in their lifetime and currently smoked before surgery (within 4 weeks preoperatively) [9].

Variables

Variables that may be associated with postoperative chronic pain were selected based on a literature review. Patients with complete data for age, sex, body mass index (BMI), smoking history, drinking history, American Society of Anesthesiologists (ASA) physical status, medical history (hypertension, diabetes, previous nonthoracic surgery, cerebrovascular and cardiac disease, and immune system disease), coagulopathy, thoracic nerve block, intraoperative dosage of sufentanil, surgical features (surgical methods, type and time), vasoactive drugs, total fluid volume, blood loss, urine volume, length of stay (LOS) in the postanesthesia care unit (PACU), patient-controlled intravenous analgesia (PCIA), length of hospital stay, postoperative analgesic drug use, postoperative pulmonary complications, acute pain at rest (24 h postoperative), acute pain with activity (24 h postoperative), chronic pain at rest (3 months postoperative), chronic pain with activity (3 months postoperative) and Quality of Recovery-15 (QoR-15) (3 months postoperative). The smoking index (SI, defined as the number of cigarettes smoked per day multiplied by the number of years of smoking) [12] was calculated from the detailed smoking history recorded in electronic medical records.

Endpoints and confounders

The primary endpoint of our study was the incidence of chronic pain 3 months after surgery. The following secondary endpoints were included: the incidence of acute postoperative pain 24 hours after surgery, the relationship between the duration from smoking cessation to surgery and postoperative chronic pain, dose-response relationship between the smoking index and CPSP, postoperative length of hospital stay, postoperative pulmonary complications and QoR-15. CPSP was divided into chronic pain at rest and chronic pain with activity (cough).

Baseline factors related to postoperative pain were considered potential confounders for the analysis. Based on clinical experience and previous studies, we adjusted for potential confounding effects of age, sex, BMI, drinking history, surgical method, intraoperative sufentanil consumption, regional anesthesia, dexmedetomidine and patient-controlled intravenous analgesia (PCIA). All information on potential confounders was retrieved from medical records.

Statistical analysis

Continuous variables for each group are expressed as the means ± standard deviations (when the data were normally distributed) or quartiles, and categorical variables are expressed as percentages. Continuous variables that were not normally distributed were analyzed using the rank sum test. Categorical variables were analyzed using the chi-squared test. A 2-tailed $P<0.05$ was established as the threshold of statistical significance. Data analyses were performed using SPSS 26.0 and R version 4.2.0.

Because this study was a retrospective database study, the number of eligible patients was fixed. Therefore, we estimated statistical power rather than calculating a sample size. We used propensity score matching (PSM) to exclude systematic bias. Patients were matched on the propensity score scale using 1:1 nearest neighbor matching with a size of 0.02 calipers. Patients were matched on the following covariates: sex, age, BMI, ASA physical status, drinking history, surgery time, surgery type, surgery method, dosage of intraoperative sufentanil, PCIA, and regional anesthesia. The covariate balance was estimated by calculating the standardized mean differences (SMD). A good balance was considered for SMD <0.1. An SMD of 0.1-0.3 was considered a small difference; a value above 0.3 was suggested as moderate to considerable. Matched baseline data were included in a multivariate logistic regression equation to analyze the association between exposure and outcome. Univariate logistic regression was used to test the relationship between smoking cessation duration and postoperative chronic pain. To test the stability of

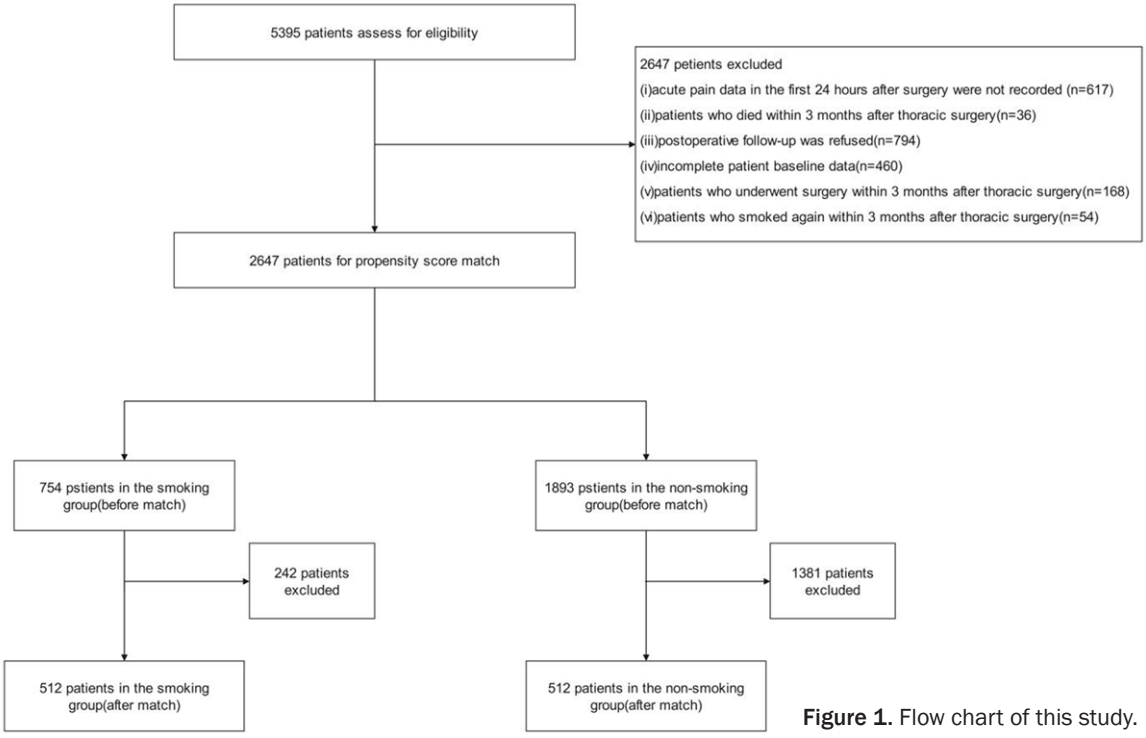

Figure 1. Flow chart of this study.

our main findings, we used the step-wise variable-entering method and constructed 3 analytical models: "Model 1" was a rough model; "Model 2" was adjusted for age and sex; and "Model 3" included age, sex, surgical method, regional anesthesia, PCIA, drinking history, and intraoperative sufentanil as adjusted variables. Continuous variables are converted into classified variables as the sample size is limited.

The dose-response relationship between the smoking index and postoperative chronic pain was analyzed. A univariate dose-response relationship model was used to analyze the effect of different smoking indexes on postoperative chronic pain, and the 95% confidence interval (CI) was calculated.

Results

Characteristics of patients

Of the 5,395 patients who underwent thoracic surgery identified in our database, 617 patients did not have pain scores within 24 hours after surgery, 36 patients died within 3 months after surgery, 460 patients were lost to follow-up, 794 patients did not have complete baseline data, 168 patients underwent a second surgery within three months, and 54 patients smoked again without following the doctor's advice and were excluded (**Figure 1**). A total of 2647 patients were eligible for inclusion.

Of the 2647 patients enrolled, 754 patients were in the smoking group, and 1893 patients were in the nonsmoking group. There was no statistically significant difference in baseline data between the two groups after matching (**Tables 1** and **2**).

Primary endpoint

We used a propensity score paired analysis of the cohort to assess the association between preoperative current smoking and CPSP at rest. Before matching, the incidence of CPSP at rest was 12.2% in the smoking group and 17.7% in the nonsmoking group (P = 0.001). CPSP with activity did not differ significantly between the two groups. For the matched cohort of 1028 patients, the incidence of CPSP at rest was 13.2% in the smoking group and 19.0% in the nonsmoking group (P = 0.011) (**Table 3**). There was a significant difference between the two groups in the incidence of CPSP at rest (**Figure 2**). Among patients after PSM, the NRS of CPSP at rest was 0.0 (0 to 0) in the smoking group and 0.0 (0 to 0) in the nonsmoking group (P =

Table 1. Patient characteristics

Items	Before matched			After matched			SMD
	Smoker n = 754	Non-smoker n = 1893	*P*	Smoker n = 514	Non-smoker n = 514	*P*	
BMI (kg/m^2)	21.67 (19.33 to 25.14)	21.67 (19.33 to 25.14)	0.786	21.33 (19.33 to 25.00)	21.67 (19.33 to 24.86)	0.877	0.022
Age (year)	57 (50 to 65)	55 (47 to 64)	0.000	56 (47 to 63)	55 (47 to 64)	0.943	0.011
Sex			0.000			1	<0.001
Male	750 (99.5)	1323 (69.9)		510 (99.2)	510 (99.2)		
Female	4 (0.5)	670 (30.1)		4 (0.8)	4 (0.8)		
ASA physical status			0.277			0.615	0.074
I	29 (3.8)	98 (5.2)		27 (5.3)	23 (4.5)		
II	642 (85.1)	1619 (85.5)		436 (84.8)	438 (85.2)		
III	81 (10.7)	170 (9.0)		50 (9.7)	53 (10.3)		
IV	2 (0.3)	6 (0.3)		1 (0.2)			
Drinking history (yes)	418 (55.4)	426 (22.5)	0.000	229 (44.6)	211 (41.1)	0.615	0.071
History of nonthoracic surgery (yes)	254 (33.7)	820 (43.3)	0.000	164 (31.9)	194 (37.7)	0.05	0.123
Cerebral vascular disease (yes)	56 (7.4)	105 (5.5)	0.068	36 (7.0)	39 (7.6)	0.719	0.022
History of hypertension (yes)	162 (21.5)	411 (21.7)	0.899	111 (21.6)	129 (25.1)	0.184	0.083
Diabetes History (yes)	93 (12.3)	196 (10.4)	0.140	64 (12.5)	68 (13.2)	0.709	0.023
History of cardiac disease (yes)	62 (8.2)	133 (7.0)	0.287	42 (8.2)	38 (7.4)	0.641	0.029
History of immune system disease (yes)	3 (0.4)	14 (0.7)	0.321	3 (0.6)	3 (0.6)	1	<0.001
History of coagulation dysfunction (yes)	16 (2.1)	64 (3.4)	0.088	10 (1.9)	9 (1.8)	0.817	0.014

Data are presented as the mean (SD) or n (%) or median. Abbreviations: SD, Standard Deviation; BMI: Body Mass Index; ASA, American Society of Anesthesiologists.

Table 2. Intraoperative baseline data

Items	Before matched			After matched			SMD
	Smoker n = 754	Non-smoker n = 1893	*P*	Smoker n = 514	Non-smoker n = 514	*P*	
DEX (yes)	291 (38.6)	710 (37.5)	0.603	203 (39.5)	193 (37.5)	0.522	0.04
Regional anesthesia			0.000			1	<0.001
Yes	634 (84.1)	1467 (77.5)		421 (81.9)	421 (81.9)		
None	120 (15.9)	426 (22.5)		93 (18.1)	93 (18.1)		
Intraoperative Sufentanil (μg)	30 (25 to 31.25)	30 (25 to 30)	0.788	30 (25 to 30)	30 (25 to 30)	0.977	0.014
Surgical method			0.000			0.770	0.018
Open surgery	100 (13.3)	128 (6.8)		61 (11.9)	58 (11.3)		
Endoscopic surgery	654 (86.7)	1765 (93.2)		453 (88.1)	456 (88.7)		
Surgery type			0.000			0.632	0.100
Lung cancer	301 (39.9)	805 (42.5)		203 (39.5)	186 (36.2)		
Lobectomy	190 (25.2)	544 (28.7)		135 (26.3)	138 (26.8)		
Esophageal cancer	157 (20.8)	234 (12.4)		91 (17.7)	100 (19.5)		
Mediastinal surgery	51 (6.8)	202 (10.7)		42 (8.2)	52 (10.1)		
Other types	55 (7.3)	108 (5.7)		43 (8.4)	38 (7.4)		
Surgery time (min)	207 (155 to 275)	185 (140 to 240)	0.000	200 (148 to 266.25)	201 (150 to 260)	0.896	0.030
Vascular drugs (yes)	323 (42.8)	751 (39.7)	0.134	223 (43.4)	196 (38.1)	0.087	0.107
Total infusion volume (ml)	1500 (1150 to 2000)	1500 (1000 to 2000)	0.000	1500 (1100 to 2000)	1600 (1200 to 2000)	0.324	0.032
Amount of bleeding (ml)	100 (50 to 150)	100 (50 to 100)	0.000	100 (50 to 127.5)	100 (50 to 100)	0.299	0.039
Urine volume (ml)	400 (200 to 662.5)	350 (200 to 600)	0.012	400 (200 to 600)	400 (200 to 600)	0.741	0.032

Data are presented as the mean (SD) or n (%) or median. Abbreviations: SD, Standard Deviation; DEX, Dexmedetomidine.

Table 3. Patient data after surgery

Items	Before matched			After matched		
	Smoker n = 754	Non-smoker n = 1893	*P*	Smoker n = 514	Non-smoker n = 514	*P*
LOS in PACU (min)	65 (50 to 90)	70 (50 to 90)	0.446	67 (55 to 90)	65 (50 to 85)	0.114
PCIA (yes)	697 (92.4)	1720 (90.9)	0.193	465 (90.5)	471 (91.6)	0.512
length of hospital stay (day)	8 (6 to 10)	7 (6 to 10)	0.000	8 (6 to 10)	8 (6 to 10)	0.952
Postoperative analgesia drug (yes)	3 (0.4)	17 (0.9)	0.180	3 (0.6)	9 (1.8)	0.081
PPCS (yes)	211 (28)	524 (27.7)	0.875	142 (27.6)	139 (27.0)	0.834
Pneumonia (yes)	49 (6.5)	118 (6.2)	0.800	31 (6.0)	34 (6.6)	0.701
Atelectasis (yes)	38 (5.0)	98 (5.2)	0.885	21 (4.1)	32 (6.2)	0.121
Respiratory distress (yes)	2 (0.3)	5 (0.3)	0.996	1 (0.2)	0 (0)	1
Empyema (yes)	13 (1.7)	27 (1.4)	0.571	10 (1.9)	8 (1.6)	0.634
Pleural effusion (yes)	64 (8.5)	175 (9.2)	0.540	44 (8.6)	44 (8.6)	1
Chylothorax (yes)	11 (1.5)	25 (1.3)	0.782	9 (1.7)	8 (1.6)	0.807
Pneumothorax (yes)	30 (4.0)	88 (4.6)	0.451	22 (4.3)	22 (4.3)	1
Hemothorax (yes)	108 (14.3)	275 (14.5)	0.893	69 (13.4)	65 (12.6)	0.711
Respiratory failure (yes)	25 (3.3)	73 (3.9)	0.506	18 (3.5)	16 (3.1)	0.727
Bronchopleural fistula (yes)	7 (0.9)	18 (1.0)	0.957	5 (1.0)	6 (1.2)	0.762
Subcutaneous emphysema (yes)	16 (2.1)	47 (2.5)	0.583	12 (2.3)	18 (3.5)	0.266
Acute pain at rest (yes)	359 (47.6)	909 (48)	0.850	252 (49.0)	269 (52.3)	0.289
Acute pain with activity (yes)	558 (74)	1373 (72.5)	0.000	378 (73.5)	371 (72.2)	0.623
Chronic pain at rest (yes)	92 (12.2)	335 (17.7)	0.001	68 (13.2)	98 (19.0)	0.011
NRS of chronic pain at rest	0 (0 to 0)	0 (0 to 0)	0.000	0 (0 to 0)	0 (0 to 0)	0.010
Chronic pain with activity (yes)	195 (15.9)	601 (31.7)	0.003	131 (25.5)	159 (30.9)	0.052
QoR-15	150 (142.75 to 150)	150 (140 to 150)	0.016	150 (141.5 to 150)	150 (140 to 150)	0.079

Data are presented as the mean (SD) or n (%) or median. Abbreviations: SD, Standard Deviation; LOS, Length Of Stay; PACU, Post-Anesthesia Care Unit; PCIA, Patient Controlled Intravenous Analgesia; PPCS, Postoperative Pulmonary Complications; QoR, Quality of Recovery.

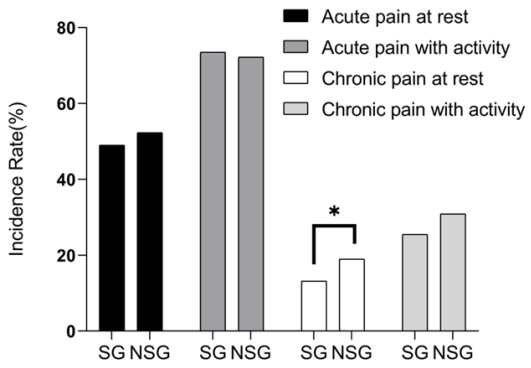

Figure 2. Incidence of postoperative pain between the two groups. The ordinate is the incidence rate. Categorical variables were analyzed using the chi-squared test. There was a statistically significant difference in chronic pain at rest between the two groups. The incidence of chronic pain at rest in the smoking group was significantly lower than that in the nonsmoking group. *P<0.05. SG: Smoking Group; NSG: Non Smoking Group.

0.010) (**Table 3**). NRS of nonsmoking group is significantly higher than that of smoking group.

Secondary endpoints

There was no significant difference between the two groups in the incidence of acute postoperative pain 24 hours after surgery, postoperative length of hospital stay, postoperative pulmonary complications or QoR-15 (**Table 3**). There was no statistical significance between the duration from the beginning of smoking cessation to the surgery and CPSP at rest (**Table 4**).

Models of multivariable logistic regression analyses

We analyzed three different models after propensity matching, including Model 1 (odds ratio (OR) = 0.647, 95% CI, 0.462-0.907; P = 0.011), Model 2 (adjusted OR = 0.645, 95% CI, 0.457-0.911; P = 0.013) and Model 3 (adjusted OR = 0.645, 95% CI, 0.457-0.911; P = 0.013), to verify the stability of the prediction model between preoperative current smoking and CPSP at rest (**Table 5**). Using the data from the regression equation, we constructed a forest plot (**Figure 3**). Preoperative current smoking (adjusted OR = 0.643, 95% CI, 0.455-0.909; P = 0.012) and older age (adjusted OR = 0.417, 95% CI, 0.294-0.593; P<0.0001) were protective factors for CPSP at rest. Females were more likely to experience CPSP at rest than males (adjusted OR = 15.763, 95% CI, 3.079-80.699; P = 0.0001).

Dose-response relationship between smoking index and CPSP at rest

A dose-response relationship between SI and CPSP at rest was observed (**Figure 4**). The ordinate of **Figure 4** is the odds ratio (0-1), and the abscissa is the SI. We observed that the incidence of CPSP at rest decreased with increasing SI. When the SI was greater than 400, the OR decreased very little, and the curve slope was gentle (**Figure 4**). Larger SIs correlated with a lower incidence of CPSP at rest. We constructed a univariate dose-response relationship model of different smoking indexes on CPSP at rest (**Table 6**). Three different ranges of SI on CPSP at rest were selected, including 1-200 (OR = 0.917, 95% CI, 0.533-1.518; *P = 0.744*), 201-399 (OR = 0.814, 95% CI, 0.47-1.354; *P = 0.445*), and ≥400 (OR = 0.465, 95% CI, 0.29-0.722; *P = 0.001*) (**Table 6**). Compared to the nonsmoking group, there was a significant difference between the two groups only when the SI was larger than 400. When the SI was greater than 400, the incidence of CPSP at rest was significantly lower than that in the nonsmoking group.

Discussion

This retrospective cohort study focused on the effect of smoking index and CPSP after thoracic surgery. To the best of our knowledge, this is the first study on this topic and three main findings were presented: First, the preoperative current smoking status reduced the incidence of CPSP at rest 3 months postoperatively in patients undergoing elective thoracic surgery. Second, a dose-response relationship between SI and CPSP at rest was observed. Third, the range of preoperative SI for antalgic effects on CPSP at rest was ≥400.

We investigated the relationship between preoperative current smoking and CPSP by reviewing data from patients who received elective thoracic surgery, including esophageal surgery, lung surgery, and mediastinal surgery over a four-year period. We analyzed three different models after propensity score matching and found that preoperative current smoking reduced the incidence of CPSP at rest, which fur-

Table 4. Univariate logistic regression analysis of duration from the beginning of smoking cessation to the surgery on CPSP at rest

Variable	OR (95% CI)	*P*
duration from the beginning of smoking cessation to the surgery	0.889 (0.607 to 1.301)	0.544

OR, Odds Ratio; CI, Confidence Interval.

Table 5. Multivariable logistic regression analysis of smoking on CPSP at rest

Variable	Adjusted OR (95% CI)	*P*
Model 1	0.647 (0.462 to 0.907)	0.011
Model 2	0.645 (0.457 to 0.911)	0.013
Model 3	0.645 (0.457to 0.911)	0.013

Model 1 was a rough model. Model 2 was adjusted for age and sex using multivariable logistic regression. Model 3 was adjusted for age, sex, surgical method, regional anesthesia, PCIA, BMI, drinking history and intraoperative sufentanil using multivariable logistic regression. OR, Odds Ratio; CI, Confidence Interval; PCIA, Patient Controlled Intravenous Analgesia; BMI, Body Mass Index.

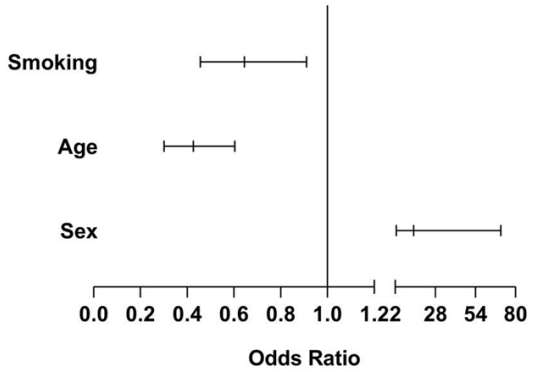

Figure 3. Forest plot for multivariable logistic regression analysis. The forest plot was drawn from the data obtained from the multiple logistic regression equation. Current smoking (adjusted OR = 0.645, 95% CI, 0.457-0.911; P = 0.013) and older age (adjusted OR = 0.427, 95% CI, 0.301-0.604; P<0.0001) were protective factors for CPSP at rest. Females were more likely to experience CPSP at rest than males (adjusted OR = 13.895, 95% CI, 2.741-70.445; P = 0.0001).

ther supports that this result was very stable. The incidence of CPSP in our study was lower than that in Bayman EO's study [2], and this difference may be due to different inclusion and exclusion criteria and different follow-up times. Previous small-sample prospective studies showed that smoking history increased the incidence and severity of postoperative pain [13, 14]. Several meta-analyses suggest that smoking (and the associated long-term nicotine exposure) is a definite risk factor for acute postoperative and chronic pain [15, 16]. Some retrospective studies have suggested that preoperative current smoking history is a risk factor for chronic postoperative pain [17, 18].

Our study showed that the preoperative current smoking state reduced the incidence of CPSP at rest. This result is obviously different from some previous studies. It should be noticed that our study only enrolled smokers who continued smoking within 4 weeks before surgery. To emphasize the recent preoperative smoking status to maximize the impact of current smoking status on postoperative outcome, we excluded patients who had a smoking history but did not currently smoke before surgery. We believe this exclusion would serve to better reveal the effect of smoking on CPSP. The definition of smoking history differed in previous studies. Most previous studies only considered a history of smoking, not recent smoking. Smokers who continued smoking before surgery were clearly different from smokers who had quit smoking. This difference may explain why our results are different from those of previous studies.

Nicotine is the most important pain-related substance in tobacco. The concentration of nicotine fluctuates with smoking status. Preoperative current smoking may have reduced CPSP at rest based on the relationship between nicotine and pain. Nicotine has a significant analgesic effect [19], which has been confirmed in animal experiments [20]. Nicotine produces analgesic effects by acting on the $\alpha_4\beta_2$ and α_7 nicotinic acetylcholine receptors [21]. The association of preoperative current smoking with a decreased incidence of CPSP may be due to the higher preoperative concentration of nicotine.

Previous studies examined the dose-response relationship between smoking and pain. There is a significant dose-response relationship between exposure to environmental tobacco

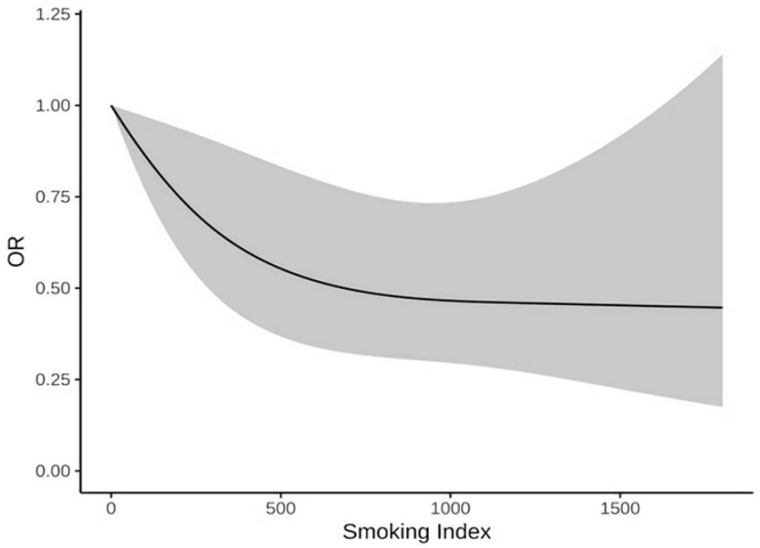

Figure 4. Dose-response relationship between smoking index and CPSP. The ordinate is the OR (0-1), and the abscissa is the SI (≥0). Larger SI values are associated with a lower incidence of CPSP at rest. OR: Odds Ratio; SI: Smoking Index.

Table 6. Univariate dose-response relationship model of different smoking index on CPSP at rest

Variable	OR (95% CI)	*P*
0	reference	reference
1-200	0.917 (0.533 to 1.518)	0.744
201-399	0.814 (0.470 to 1.354)	0.445
≥400	0.465 (0.290 to 0.722)	0.001

OR, Odds Ratio; CI, Confidence Interval.

smoke and an increased incidence of dysmenorrhea in young women [22]. Another study showed that preoperative smoking was dose-dependently associated with a higher incidence of narcotic pain medication prescriptions in older women who had surgical spine disease [23]. Nicotine mediates the relationship between smoking and pain, and intrathecal nicotine produces a dose-dependent analgesic effect [24]. The intensity of smoking varies greatly in patients with a history of smoking. However, a dose-dependent effect of smoking on CPSP was not established. Therefore, we examined the dose-response relationship of the smoking index and CPSP at rest. Our study showed that the incidence of CPSP at rest decreased with increasing SI. We found a significant dose-response relationship between SI and CPSP at rest, but the range of SI was too extensive. When SI ≥400, the protective effect of preoperative current smoking on CPSP at rest tended to be stable, which suggests that the benefit of SI on CPSP decreases. We analyzed three different ranges of SI for the analgesic effects of smoking on CPSP at rest and showed a significant difference only when the SI was ≥400. Based on our results, the range of SI for analgesic effects on CPSP at rest is ≥400.

According to our results, preoperative current smoking reduced the incidence of CPSP at rest. However, we acknowledge that this result must be interpreted with caution. According to the ERAS guidelines [9], smoking cessation is recommended for at least 4 weeks before surgery. Our study only found a relationship between preoperative current smoking and CPSP at rest. However, many other measures may be taken to reduce chronic pain after surgery, and smoking should not be encouraged only to reduce chronic pain.

There are several limitations to this observational study, including its retrospective nature, which prevented us from obtaining clinical details from decision-makers. First, despite the rigorous training of our researchers and accurate blinding, retrospective cohort studies are biased. Fortunately, our sample size was large enough to reduce this bias. Second, the follow-up time was up to the set three-month follow-up date, and there were no long-term follow-up data. Third, specific drug use for postoperative PCIA was not recorded, and the analgesic effects of different drugs were not considered.

In conclusion, preoperative current smoking was significantly associated with a decreased incidence of CPSP in a dose-dependent manner. A higher smoking index was associated with a lower incidence of CPSP. The smoking index range for reducing CPSP in elective thoracic surgery was ≥400.

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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