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Original Article

Risk factors for chronic postsurgical pain following thoracoscopic surgery for lung cancer

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Abstract: Objective: Chronic post-surgical pain (CPSP) following thoracoscopic lung cancer surgery is a common and challenging complication. Identifying risk factors and predictive markers is essential for improving patient outcome. Methods: In this retrospective case-control study, the clinical data from 106 patients with non-small cell lung cancer (NSCLC) who underwent thoracoscopic radical resection between January 2021 and December 2023 were comprehensively analyzed. Patients were divided into a CPSP group (n = 41) and a non-CPSP group (n = 65) based on CPSP status. An external validation cohort of 20 patients was also assessed. Demographic data, perioperative characteristics, psychological states, and pain scores were compared between the two groups. Logistic regression analysis was used to identify predictors of CPSP, and their predictive performance was validated using receiver operating characteristic (ROC) curve analysis. Results: Age and TNM stage were significantly higher in the CPSP group ($P < 0.001$). Significant differences were observed in pain scores on postoperative days 1-3 and Fear of Pain Questionnaire-III (FPQ-III) scores ($P = 0.003$ and $P < 0.001$, respectively) between the two groups. Multivariate logistic regression identified age (OR, 1.230; $P < 0.001$), TNM staging (OR, 5.106; $P < 0.001$), early postoperative pain score (OR, 1.868; $P = 0.012$), and FPQ-III score (OR, 1.135; $P < 0.001$) as independent predictors of CPSP. A nomogram based on these predictors demonstrated excellent discrimination ability, with an area under the curve (AUC) of 0.891. External validation yielded an AUC of 0.956, confirming high sensitivity (1.00) and specificity (0.923). Conclusion: Age, advanced TNM stage, early postoperative pain intensity, and higher fear of pain are significant predictors of chronic postoperative pain following thoracoscopic lung cancer surgery. Incorporating these factors into predictive models may improve postoperative management and reduce CPSP incidence.

Keywords: Chronic postsurgical pain, thoracoscopic surgery, lung cancer, risk factors, pain prediction, logistic regression

Introduction

Chronic post-surgical pain (CPSP) significantly affects the quality of life, mobility, and mental health of affected individuals [1]. Within the scope of post-surgical outcomes, thoracoscopic surgery - a minimally invasive procedure often employed in the treatment of lung cancer - has been associated with the development of chronic pain among survivors [2]. Lung cancer itself remains one of the leading causes of cancer mortality worldwide, causing approximately 18.0% of all cancer deaths [3]. Despite advancements in surgical technique and postoperative care, the burden of chronic pain persists as a major postoperative complication following thoracic surgery [4]. Addressing this issue is essential due to its association with long-term disability, increased healthcare use, and decreased patient satisfaction [5]. Thoracic surgery pain syndromes are complex, typically involving nociceptive, neuropathic, and psychogenic components, making effective management challenging and necessitating further investigation to improve patient outcome [6].

Current treatments for chronic pain in clinical practice include multimodal analgesia, physical therapy, psychological interventions, and pharmacologic therapies such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and adjuvant medications [7].

Existing literature [8] recognizes that various factors contribute to the risk of developing

chronic pain following surgery, including patient-related factors such as gender, age, psychological state, and genetics, as well as surgery-related factors like the extent of surgical trauma, duration of the procedure, and perioperative care [9]. Specifically, thoracoscopic surgery, although offering advantages over open surgery due to less tissue trauma and shorter recovery periods, presents unique challenges regarding chronic pain development [10]. While several potential risk factors have been proposed, the exact mechanisms leading to chronic pain after lung cancer surgery remain poorly understood [11]. However, a comprehensive model to identify at-risk patients accurately before surgery has yet to be developed.

Significant knowledge gaps persist in the field. For instance, it remains unclear which preventive strategies would most effectively mitigate these risks or how multidisciplinary approaches could be better coordinated during the perioperative period to reduce chronic pain [12]. While analgesic techniques and pharmacologic interventions represent most of the current pain management strategies, they often fall short in providing long-term resolution of chronic pain [13].

Addressing this gap in knowledge is essential to developing targeted interventions that can preemptively reduce the incidence of CPSP and improve patient outcomes [14]. Our study aims to explore these unidentified risk factors by analyzing substantial clinical data using a robust statistical approach. By employing comprehensive data analytics and interdisciplinary collaboration, we aim to unravel the complex interplay of factors contributing to CPSP and propose innovative approaches to manage or even prevent CPSP after surgery. Specifically, this study develops a predictive model that incorporates age, TNM stage, early postoperative pain intensity, and fear of pain to identify patients at high risk of CPSP. Additionally, we validated this predictive model in an external cohort, demonstrating its generalizability. Furthermore, we utilized a multidisciplinary approach involving surgeons, anesthesiologists, and psychologists to enhance the understanding and management of CPSP.

Materials and methods

Study design

In this retrospective case-control study, the clinical data from 106 patients with lung cancer treated at Jiangnan University Medical Center between January 2021 and December 2023 were meticulously reviewed. Patients were categorized into two groups based on the presence of chronic postsurgical pain: a CPSP group (n = 41) and a non-CPSP group (n = 65). CPSP is defined as pain that arises following acute postoperative pain and persists for more than two months. An external validation cohort of 20 patients was also included, including 7 cases with CPSP and 13 cases without.

Inclusion criteria: 1) Patients with a pathologic confirmation of non-small cell lung cancer (NSCLC), confirmed through imaging studies and biopsy; 2) Patients eligible for thoracoscopic surgery, specifically undergoing thoracoscopic radical lung cancer resection; 3) Patients with full cognitive awareness, free from cognitive impairment, and capable of understanding the Visual Analog Scale (VAS) for pain assessment; 4) No prior history of chronic pain disorders; 5) No history of long-term analgesic medication use; 6) Patients classified with a clinical malignant tumor staging (TNM) of stage I-IIIA; 7) Expected survival of more than three months.

Exclusion criteria: 1) Patients with pre-existing psychiatric disorders; 2) Patients with a history of chronic pain or those who had been on long-term analgesics prior to surgery; 3) Patients who underwent re-thoracotomy within six months of this study; 4) Patients with other intrathoracic tumors; 5) Patients with insufficient function of other organs; 6) Patients with comorbid thrombotic diseases, infectious diseases, or autoimmune disorders; 7) Patients with incomplete clinical data.

The sample size calculation was based on the anticipated effect size and the desired power to detect significant differences between the groups. Using a power analysis with an alpha level of 0.05 and a power of 0.85, we estimated the required sample size to detect a significant difference in the primary outcome measure (chronic postoperative pain). The anticipated effect size was derived from previous studies reporting differences in chronic pain rates between similar groups [15]. Based on these calculations, the minimum sample size required per group was 37. A total of 106 patients were included in the study, with data obtained from the case search system.

This study was approved by the Ethics Committee of Jiangnan University Medical Center.

Surgical procedure

Routine disinfection and draping were applied before surgery. A small incision, measuring 1-2 cm, was created between the 7th and 8th intercostal spaces on the anterior chest to introduce the thoracoscope for observation. Subsequently, a 2-3 cm incision was made at the 4th intercostal space along the scapular line at the 7th/8th intercostal spaces to facilitate the resection of the affected lung lobe with thoracoscopic assistance. If the surgical procedure was more complex, the incision could be extended to 6-10 cm to provide additional access. Routine lymph node dissection was performed, and a drainage tube was placed as standard practice. Postoperatively, all patients received appropriate antimicrobial therapy.

Data collection

Data collection included a comprehensive assessment of patient demographics, encompassing age, gender, body mass index (BMI), smoking history, alcohol consumption, educational level, pathologic subtype, TNM staging, hypertension, diabetes, and genetic mutation characteristics. Additionally, perioperative features were documented, including surgical duration, resected portions, intraoperative blood loss, pain scores from postoperative days 1 to 3, duration of closed-chest drainage, postoperative complications, and length of hospital stay. Furthermore, the psychological states of patients were also evaluated, focusing on factors such as pain-related fear, anxiety, and depressive symptoms.

Genetic testing

All lung cancer tissue samples were obtained under sterile conditions during surgical procedures involving lobectomy or segmentectomy, along with systematic lymph node dissection. Tumor samples measuring approximately 0.5 × 0.5 cm were placed in centrifuge tubes containing formalin and sent to the laboratory for standard processing. The tumor specimens were fixed in 10% neutral formalin, stained with hematoxylin and eosin (H&E), and tumor tissue blocks were selected based on the presence of more than 10% tumor cell composition. After deparaffinization with xylene, DNA from the tumor tissue was extracted using a DNA extraction kit, achieving a photometric absorbance ratio of D260/D280 between 1.8 and 2.1. The DNA concentration was measured using a Qubit 4.0 nucleic acid quantifier (Thermo Fisher Scientific, Shanghai, China), and all procedures were conducted following the manufacturer's instructions and laboratory protocols. ARMS-PCR detection was performed using the SLAN fully automated medical PCR analysis system (SLAN96S). The Bio-Rad S1000 PCR instrument was utilized to determine the yield and final concentration of the pre-library, as well as to assess library fragmentation using the Agilent 2100 Bioanalyzer (Agilent Technologies Inc., California, USA). Sequencing of the constructed DNA library was carried out on the Illumina NextSeq 550Dx sequencer, adhering to the library preparation and sequencing protocols outlined in the system user manual, with sequencing reads averaging approximately 150 bp in length.

Pain assessment

The Visual Analogue Scale (VAS) was employed to evaluate the intensity of pain experienced by patients. Participants rated their pain on a numerical scale ranging from 0 to 10, where 0 indicated no pain, 1 to 3 represented mild pain typically considered tolerable, 4 to 6 denoted moderate pain that could interfere with sleep but remained manageable, and 7 to 10 signified severe pain that was challenging to tolerate and strongly impacted sleep quality and appetite. Higher scores corresponded to greater pain severity. The reliability of the VAS was determined to be 0.94 [16].

Pain fear assessment

The Fear of Pain Questionnaire-III (FPQ-III) was administered to assess patients' pain-related fears. This scale consists of 30 items related to various pain scenarios, with each item scored on a 1-5 point scale, with a total score ranging from 30 to 150, with higher scores indicating greater levels of pain fear. The reliability of this scale was found to be 0.938 [17].

Self-Rating Anxiety Scale

The Self-Rating Anxiety Scale (SAS) was utilized to evaluate the patients' levels of anxiety. This scale consists of 20 items, each addressing common anxiety symptoms. Responses to these items are scored on a four-point scale: 1

(none or very little time), 2 (a small part of the time), 3 (considerable time), and 4 (most of the time or all the time). The scores from the 20 items are totaled and multiplied by 1.25 to obtain an integer value that represents the standard score. Higher scores indicate more severe anxiety symptoms. The reliability of this scale was previously shown to be 0.770 [18].

Self-Rating Depression Scale (SDS)

The Self-Rating Depression Scale (SDS) was employed to assess patients' level of depression. This self-assessment tool comprises 20 sub-items, each scored on a four-point scale. Respondents rate each item according to frequency that best reflects their circumstances, selecting from 1 (none or occasionally), 2 (sometimes), 3 (often), or 4 (almost always). Higher scores signify more severe depressive symptoms. A score below 53 is considered normal, while scores of 53-62, 63-72, and 73 or above indicate mild, moderate, and severe depression, respectively. The reliability of this scale was determined to be 0.73 [19].

Statistical methods

Data analysis was conducted using the SPSS 29.0 statistical software (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as n (%). For sample sizes ≥ 40 with theoretical frequencies (T) ≥ 5, a chi-square test was applied using the basic formula; for sample sizes of ≥ 40 but with $1 \leq T < 5$, a chi-square test with a correction formula was employed; for sample sizes < 40 or when $T < 1$, Fisher's exact probability method was utilized for statistical analyses. The Shapiro-Wilk test was used to assess the normality of continuous variables. For continuous variables that followed a normal distribution, results were reported as mean ± SD, and the adjusted variance t-test was used for comparisons. A two-tailed *p*-value of < 0.05 was considered statistically significant. Indicators identified with significance in both difference analysis and correlation analysis, including age, TNM staging, pain scores on postoperative days 1-3, and pain fear scores, were included as covariates in logistic regression analysis. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated to evaluate the diagnostic efficacy of the combination of age, TNM stage, postoperative pain score, and pain fear score for predicting chronic postoperative pain.

Results

General data

Notable differences were observed between the two groups in terms of age and TNM staging. The CPSP group had a significantly higher mean age (62.48 ± 4.74 years) compared to the non-CPSP group (58.36 ± 4.94 years) (t = 4.252, P < 0.001) (**Table 1**). Additionally, the difference in TNM stage between the groups was significant (χ^2 = 27.415, P < 0.001), with a higher prevalence of Stage IIIA disease in the CPSP group (43.9% vs 3.08%). Images of NSCLC are shown in **Figure 1**. No significant differences were found in gender distribution, BMI, smoking, and drinking histories, hypertension, diabetes, education level, pathological classification, or genetic mutation profiles including EGFR, TP53, and KRAS mutations (all P > 0.05). These results highlight age and TNM stage as significant factors associated with chronic pain development post-surgery.

Perioperative characteristics

As shown in **Table 2**, patients in the CPSP group reported higher mean pain scores from postoperative days 1 to 3 (5.48 ± 1.64) compared to the non-CPSP group (4.62 ± 0.95) (t = 3.047, P = 0.003). No significant differences were found between the non-CPSP and CPSP groups for surgery duration, resection site, intraoperative blood loss, duration of closed thoracostomy drain, postoperative complications, or length of hospital stay (all P > 0.05). These findings suggest that early postoperative pain intensity may be a risk factor for chronic pain development post-thoracoscopic surgery for lung cancer. Other perioperative factors did not show a significant association with chronic pain occurrence.

Psychological states

As shown in **Table 3**, patients in the CPSP group reported significantly higher FPQ-III scores (78.55 ± 8.67) compared with the non-CPSP group (70.94 ± 7.02), indicating greater fear of pain (t = 4.957, P < 0.001). No significant differences were found between the groups regarding SAS and SDS scores (P = 0.418, 0.208,

Table 1. Comparison of general data between the two groups

	Non-CPSP group (n = 65)	CPSP group (n = 41)	t/χ^2	P
Age	58.36 ± 4.94	62.48 ± 4.74	4.252	< 0.001
Gender (Male/Female)	42 (64.62%)/23 (35.38%)	24 (58.54%)/17 (41.46%)	0.395	0.529
BMI	22.64 ± 2.56	23.48 ± 2.74	1.603	0.112
Smoking History	11 (16.92%)	6 (14.63%)	0.098	0.754
Drinking History	7 (10.77%)	6 (14.63%)	0.349	0.555
Education Level			1.500	0.472
Junior High School or Below	18 (27.69%)	10 (24.39%)		
High School or Vocational School	36 (55.38%)	20 (48.78%)		
College or University and Above	11 (16.92%)	11 (26.83%)		
Pathological Classification			0.316	0.574
Adenocarcinoma	51 (78.46%)	34 (82.93%)		
Squamous Cell Carcinoma	14 (21.54%)	7 (17.07%)		
TNM Stage			27.415	< 0.001
Stage I	23 (35.38%)	9 (21.95%)		
Stage II	40 (61.54%)	14 (34.15%)		
Stage IIIA	2 (3.08%)	18 (43.9%)		
Hypertension	18 (27.69%)	9 (21.95%)	0.437	0.509
Diabetes	11 (16.92%)	6 (14.63%)	0.098	0.754
Genetic Mutation Profile				
EGFR	45 (69.23%)	27 (65.85%)	0.132	0.717
TP53	23 (35.38%)	13 (31.71%)	0.152	0.697
KRAS	10 (15.38%)	8 (19.51%)	0.304	0.581

BMI, body mass index; TNM, tumor node metastasis; EGFR, epidermal growth factor receptor; TP53, tumor protein P53; KRAS, Kirsten rat sarcoma viral oncogene homolog.

respectively). These results suggest that a higher fear of pain is associated with the development of chronic pain following thoracoscopic surgery for lung cancer, while anxiety and depression levels were not significantly different between the groups.

Logistic regression analysis of chronic pain after thoracoscopic lung cancer surgery

Single-factor logistic regression analysis identified age, TNM stage, postoperative pain scores from days 1-3, and FPQ-III score as significant risk factors for the development of chronic pain following thoracoscopic lung cancer surgery (**Table 4**). Increasing age was associated with higher odds of chronic pain (OR, 1.189; 95% CI, 1.090-1.311; $P < 0.001$). Higher TNM stage also significantly increased the risk (OR, 3.551; 95% CI, 1.873-7.317; $P < 0.001$). Patients with higher pain scores in the first three postoperative days had greater odds of developing chronic pain (OR, 1.717; 95% CI, 1.238-2.485; $P = 0.002$). An elevated FPQ-III score was similarly associated with increased risk (OR, 1.131; 95% CI, 1.071-1.204; $P < 0.001$).

Multivariate logistic regression confirmed these factors as independent predictors of chronic pain (**Table 5**). Age remained a significant factor (OR, 1.230; 95% CI, 1.092-1.385; $P < 0.001$), as did TNM staging (OR, 5.106; 95% CI, 2.051-12.711; $P < 0.001$), pain scores (OR, 1.868; 95% CI, 1.150-3.033; $P = 0.012$), and FPQ-III scores (OR, 1.135; 95% CI, 1.058-1.218; $P < 0.001$). These findings underscore the importance of early postoperative pain management and psychological assessment for patients undergoing thoracoscopic lung cancer surgery.

Performance of the muti-factor logistic regression model

In this study, we performed multi-factor logistic regression analysis to identify the risk factors for chronic pain development after thoracoscopic surgery for lung cancer. The regression

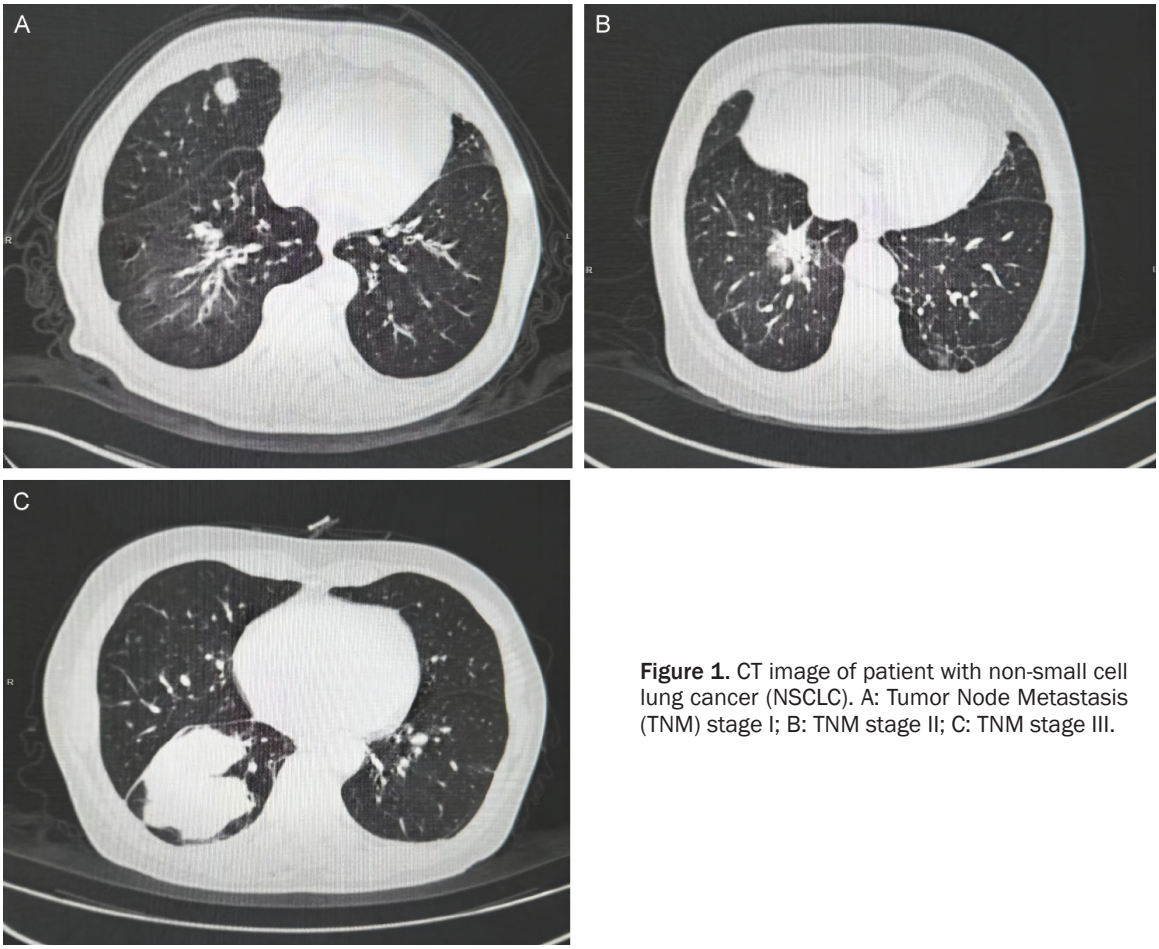

Figure 1. CT image of patient with non-small cell lung cancer (NSCLC). A: Tumor Node Metastasis (TNM) stage I; B: TNM stage II; C: TNM stage III.

model was visualized using a nomogram (**Figure 2A**). The nomogram revealed the predictive effect for the probability of chronic pain occurrence, which included FPQ-III, age, TNM staging, and postoperative pain score from days 1-3 as significant predictors. The parameter importance score (**Figure 2B**) showed that FPQ-III was the most important predictor. The calibration plot (**Figure 2C**) demonstrated good agreement between the predicted and actual probabilities of chronic pain occurrence. Decision curve analysis (**Figure 2D**) revealed that the nomogram had higher net benefits than the "treat-all-patients" and "treat-none-patients" strategies across a wide range of threshold probabilities. The AUC was 0.891 (**Figure 2E**), indicating excellent discrimination ability. Finally, the clinical impact curve (**Figure 2F**) showed that using the nomogram could substantially reduce the number of high-risk patients with chronic pain events compared to the treat-all-patients strategy. Overall, these findings suggest that our nomogram can effectively identify patients at high risk of developing chronic pain after thoracoscopic surgery for lung cancer.

General data of external validation set

In the external validation cohort, comprising 20 patients (13 in the non-CPSP group and 7 in the CPSP group), significant differences were observed in age and TNM stage. The CPSP group had a significantly higher mean age (63.88 ± 4.11 years) compared to the non-CPSP group (57.87 ± 5.38 years) (t = 2.564, P = 0.020). Regarding TNM stage, the CPSP group demonstrated a significantly higher frequency of Stage IIIA disease that the non-CPSP group (57.14% vs 0.00%; P = 0.012). Other baseline characteristics, such as gender distribution, BMI, smoking and drinking history, education level, pathological classification, hypertension, diabetes, and genetic mutation profiles (EGFR, TP53, and KRAS), showed no significant differences between the groups (all P >

Table 2. Comparison of perioperative characteristics between the two groups

	Non-CPSP group (n = 65)	CPSP group (n = 41)	t/χ^2	P
Surgery Duration (min)	143.21 ± 28.66	142.09 ± 24.89	0.205	0.838
Resection Site			4.060	0.541
Right Upper Lobe	6 (9.23%)	8 (19.51%)		
Right Middle Lobe	5 (7.69%)	5 (12.2%)		
Right Lower Lobe	27 (41.54%)	13 (31.71%)		
Left Upper Lobe	18 (27.69%)	8 (19.51%)		
Left Lower Lobe	4 (6.15%)	3 (7.32%)		
Combined Lobectomy	5 (7.69%)	4 (9.76%)		
Intraoperative Blood Loss (ml)	175.14 ± 31.31	181.26 ± 29.65	1.000	0.319
Postoperative Pain Score of days 1-3	4.62 ± 0.95	5.48 ± 1.64	3.047	0.003
Duration of Closed Thoracostomy Drain Postoperatively (d)	9.19 ± 1.65	9.44 ± 1.74	0.746	0.457
Postoperative Complications	5 (7.69%)	4 (9.76%)	0	0.989
Length of Hospital Stay After Surgery	7.28 ± 1.49	7.31 ± 1.56	0.103	0.918

Table 3. Comparison of psychological states between the two groups

	Non-CPSP group (n = 65)	CPSP group (n = 41)	t/χ^2	P
FPQ-III	70.94 ± 7.02	78.55 ± 8.67	4.957	< 0.001
SAS	32.57 ± 6.29	33.64 ± 7.01	0.812	0.418
SDS	28.34 ± 5.79	29.73 ± 5.12	1.266	0.208

FPQ-III, Fear of Pain Questionnaire-III; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale.

0.05) (**Table 6**). These findings reinforce the association of advanced age and higher TNM stage with the development of chronic pain following thoracoscopic surgery for lung cancer.

Postoperative pain scores from days 1-3 in external validation set

In the external validation patient cohort, analysis of postoperative pain scores from days 1-3 and FPQ-III scores revealed significant differences between the non-CPSP and CPSP groups (**Table 7**). The CPSP group reported significantly higher pain scores in the first three postoperative days (5.71 ± 1.37) compared to the non-CPSP group (4.26 ± 1.14) (t = 2.538, P = 0.021). Furthermore, the CPSP group exhibited greater fear of pain, as indicated by their FPQ-III scores (75.15 ± 7.02 versus 67.14 ± 6.55; t = 2.548, P = 0.020). These findings suggest that both postoperative pain intensity and heightened fear of pain are associated with the development of chronic pain following thoracoscopic surgery for lung cancer.

ROC curve analysis of performance of the logistic regression model in external validation set

An ROC curve was applied to validate the predictive performance of the multi-factor logistic regression model in the validation set. The area under the receiver operating characteristic curve (**Figure 3**) was 0.956, with a specificity of 0.923 and a sensitivity of 1.00, indicating excellent discrimination ability.

Discussion

In this retrospective case-control study, we investigated the risk factors associated with the development of chronic postsurgical pain (CPSP) following thoracoscopic surgery for lung cancer. Our findings revealed several significant predictors, including age, TNM stage, early postoperative pain intensity, and fear of pain scores, which contributed to the likelihood of CPSP development. The results underscore the multifactorial nature of CPSP and suggest potential interventions to mitigate its occurrence.

Age emerged as a significant predictor of CPSP in our cohort, corroborating prior research linking advanced age to an increased risk of chronic pain development following surgery [20]. This relationship could be attributed to multiple factors. Aging is often accompanied by physiologi-

Table 4. Single factor logistic regression analysis of chronic pain after thoracoscopic lung cancer surgery

	Coefficient	Std error	Wald	OR	CI lower	CI upper	*P* Value
Age	0.173	0.047	3.715	1.189	1.090	1.311	< 0.001
TNM Stage	1.267	0.344	3.683	3.551	1.873	7.317	< 0.001
Postoperative Pain Score from Days 1-3	0.541	0.176	3.066	1.717	1.238	2.485	0.002
FPQ-III	0.123	0.030	4.150	1.131	1.071	1.204	< 0.001

TNM, Tumor Node Metastasis; FPQ-III, Fear of Pain Questionnaire-III.

Table 5. Muti-factor logistic regression analysis of chronic pain after thoracoscopic lung cancer surgery

	Coefficient	Std Error	Wald Stat	OR	OR CI Lower	OR CI Upper	*P* Value
Age	0.207	0.061	3.418	1.230	1.092	1.385	< 0.001
TNM Stage	1.630	0.465	3.504	5.106	2.051	12.711	< 0.001
Postoperative Pain Score from Days 1-3	0.625	0.247	2.526	1.868	1.150	3.033	0.012
FPQ-III	0.126	0.036	3.516	1.135	1.058	1.218	< 0.001

TNM, Tumor Node Metastasis; FPQ-III, Fear of Pain Questionnaire-III.

cal changes, such as altered pain processing and decreased regenerative capacity, which can impact pain perception and healing [21]. Additionally, older patients may have a higher prevalence of comorbid conditions that can complicate recovery and contribute to prolonged pain experiences [22]. Older individuals may also experience diminished neural plasticity, hindering the ability of their nervous systems to adapt and reorganize after acute injuries, thereby increasing susceptibility to chronic pain syndromes [23]. For instance, a study by Walker et al. [24] found that older adults exhibited increased nociceptive sensitivity, which could contribute to higher rates of CPSP. Similarly, Mills et al. [25] noted that older individuals had reduced pain tolerance thresholds, possibly explaining the higher incidence of chronic pain in this demographic.

TNM stage also played a crucial role in predicting CPSP. Patients with advanced-stage cancer (Stage IIIA) had a higher prevalence of CPSP compared to those with earlier stages. This could be partly due to the greater extent of surgical intervention required for advanced-stage tumors, leading to more extensive tissue damage and subsequent pain [26]. Furthermore, the psychological burden of a more advanced cancer diagnosis might influence pain perception and reporting [27]. Chronic stress and anxiety, often associated with severe illness, can heighten pain sensitivity, a phenomenon well-documented in the literature [28]. The body's stress response may exacerbate inflammatory processes, further propagating pain pathways [29]. In alignment with these findings, a meta-analysis by Cheville et al. [30] demonstrated that patients with more advanced cancer stages experience higher rates of CPSP, likely due to the increased surgical complexity and associated tissue damage. Similarly, a study by Koo et al. [31] found that patients with higher TNM stages had a higher prevalence of chronic pain, supporting our observations.

The intensity of pain experienced in the early postoperative period significantly correlated with chronic pain development, supporting the pain memory hypothesis, which posits that severe acute pain can lead to sensitization of the central nervous system [32]. Such sensitization can manifest as hyperalgesia or allodynia, persisting long after the initial tissue damage has healed [33]. Inadequate postoperative pain management may induce plastic changes in the spinal cord and brain, perpetuating a chronic pain state [33]. This highlights the importance of aggressive and proactive pain management strategies immediately after surgery to prevent these maladaptive changes. Research by Admiraal et al. [34] supports this notion, showing that inadequate pain control in the immediate postoperative period increases the risk of transitioning to chronic pain.

Psychological factors, especially fear of pain, were also significant contributors to CPSP. High FPQ-III score was associated with a greater likelihood of chronic pain. This association aligns with the fear-avoidance model of chronic pain,

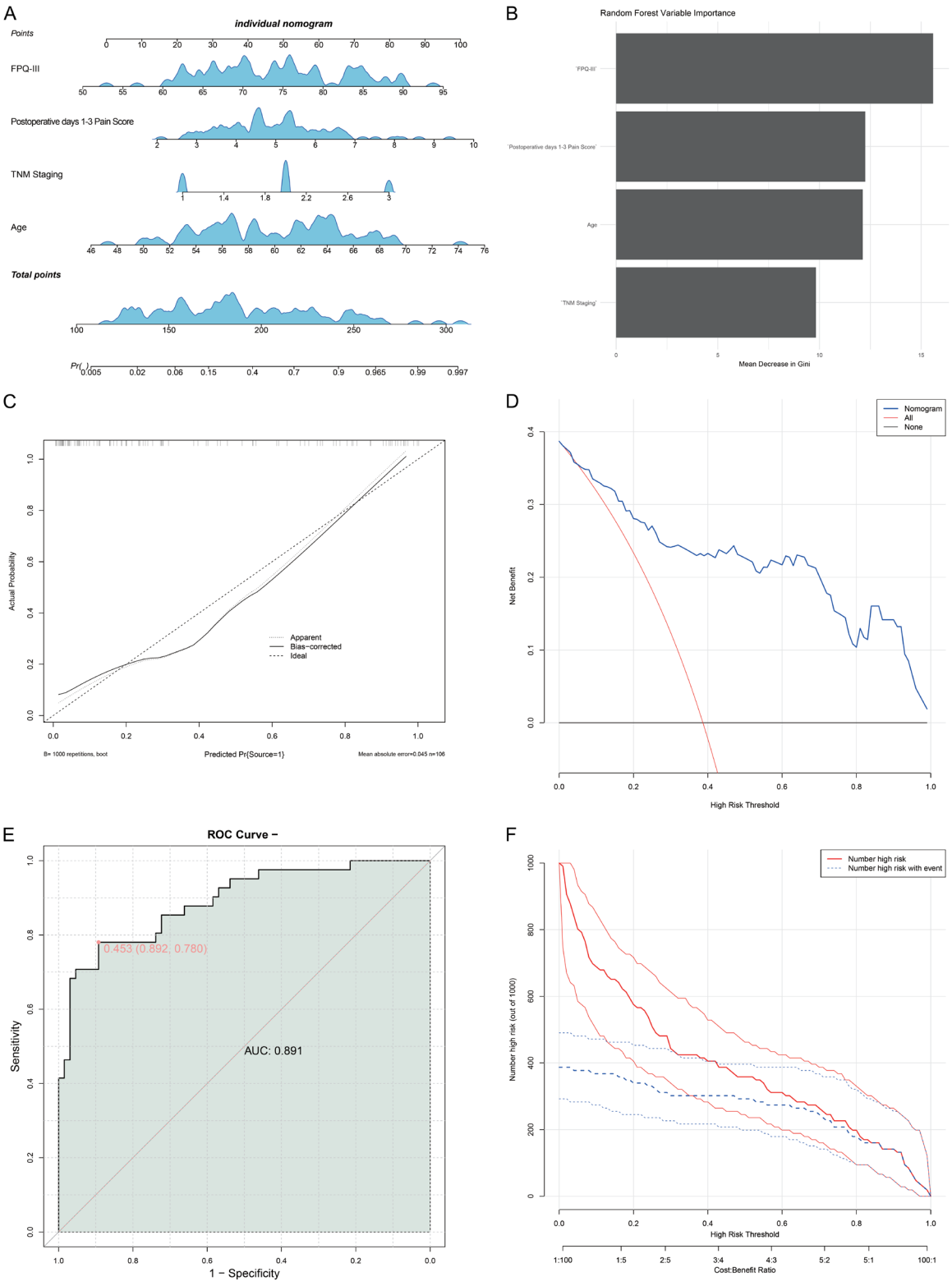

Figure 2. Muti-factor logistic regression assessment. A: Nomogram; B: Parameter importance score; C: Calibrate plot; D: Decision Curve Analysis curve (DCA); E: Receiver operating characteristic (ROC) curve; F: Clinical impact curve.

Table 6. Comparison of general data of between the two groups in the external validation cohort

	Non-CPSP group (n = 13)	CPSP group (n = 7)	t/χ^2	P
Age	57.87 ± 5.38	63.88 ± 4.11	2.564	0.020
Gender (Male/Female)	9 (69.23%)/4 (30.77%)	4 (57.14%)/3 (42.86%)	None	0.651
BMI	21.94 ± 1.97	22.36 ± 2.48	0.412	0.685
Smoking History	3 (23.08%)	1 (14.29%)	None	1.000
Drinking History	2 (15.38%)	0 (0.00%)	None	0.521
Education Level			None	0.845
Junior High School or Below	3 (23.08%)	2 (28.57%)		
High School or Vocational School	6 (46.15%)	4 (57.14%)		
College or University and Above	4 (30.77%)	1 (14.29%)		
Pathological Classification			None	0.587
Adenocarcinoma	11 (84.62%)	5 (71.43%)		
Squamous Cell Carcinoma	2 (15.38%)	2 (28.57%)		
TNM Stage			None	0.012
Stage I	6 (46.15%)	1 (14.29%)		
Stage II	7 (53.85%)	2 (28.57%)		
Stage IIIA	0 (0.00%)	4 (57.14%)		
Hypertension	3 (23.08%)/10 (76.92%)	3 (42.86%)/4 (57.14%)	None	0.613
Diabetes	3 (23.08%)/10 (76.92%)	1 (14.29%)/6 (85.71%)	None	1.000
Genetic Mutation Profile				
EGFR	8 (61.54%)	6 (85.71%)	None	0.354
TP53	5 (38.46%)	2 (28.57%)	None	1.000
KRAS	3 (23.08%)	1 (14.29%)	None	1.000

BMI, body mass index; TNM, tumor node metastasis; EGFR, epidermal growth factor receptor; TP53, tumor protein P53; KRAS, Kirsten rat sarcoma viral oncogene homolog.

Table 7. Comparison of postoperative pain scores from days 1-3 between the two groups in external validation cohort

	Non-CPSP group (n = 13)	CPSP group (n = 7)	t/χ^2	P
Postoperative Pain Score from days 1-3	4.26 ± 1.14	5.71 ± 1.37	2.538	0.021
FPQ-III	67.14 ± 6.55	75.15 ± 7.02	2.548	0.020

FPQ-III, Fear of Pain Questionnaire-III.

which suggests that individuals who perceive pain as threatening are more likely to avoid activities, leading to disuse, deconditioning, and exacerbation of pain [35]. This cycle of avoidance and pain can also heighten emotional responses, intensifying pain perception and prolonging its duration [36]. Psychological interventions, such as cognitive-behavioral therapy, might be beneficial in breaking this cycle by addressing maladaptive thought patterns and promoting adaptive coping strategies [23].

Interestingly, anxiety and depression, while prevalent in our surgical cohort, did not significantly differentiate between those who developed CPSP and those did not. This finding, which contrasts with some prior studies [20, 21], may suggest that while psychological distress is common among cancer patients, fear specifically related to pain has a more direct effect on chronic pain outcome. Further exploration is needed to better understand how different psychological constructs interact and influence pain chronicity. Studies [37, 38] have shown that fear of pain is a stronger predictor of chronic pain than general anxiety and depression, aligning with our findings. These studies suggest that targeted interventions aimed at reducing fear of pain may be more effective in preventing CPSP than those targeting general psychological distress.

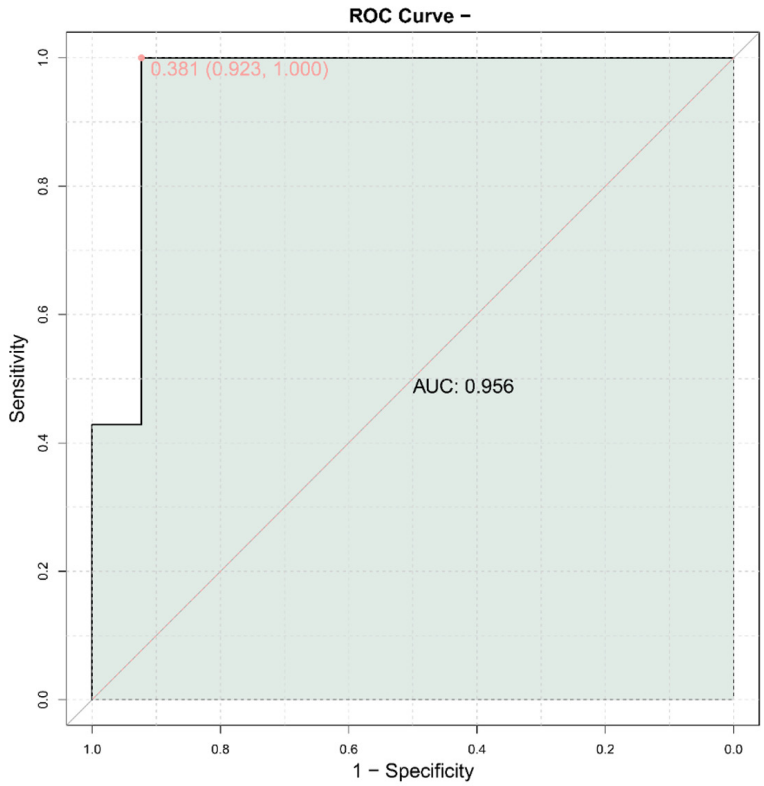

Figure 3. Receiver operating characteristic (ROC) curve for the predictive model in external validation cohort.

Our findings highlight several potential avenues for intervention. Targeting high-risk patients with tailored perioperative pain management and psychological support may reduce the incidence of CPSP. Pharmacological strategies, such as multimodal analgesia, could address different pain pathways, while non-pharmacologic interventions might include psychological therapy and physical rehabilitation. Early identification of patients with high levels of pain-related fear, combined with education on pain management techniques and gradual re-engagement in daily activities, may prevent fear-conditioned avoidance behaviors and reduce the risk of CPSP.

Despite these insights, our study has limitations. As a retrospective analysis, causality cannot be definitively established, and confounding variables, such as socioeconomic factors and individual pain threshold variations, may influence outcomes. The reliance on self-reported measures also introduces subjectivity in assessing psychological and pain-related parameters. Future research should consider longitudinal designs to track pain trajectories over time, ideally incorporating objective physiological measures alongside subjective reports to gain a more comprehensive understanding of CPSP mechanisms.

In conclusion, our study underscores the importance of a multifaceted approach in managing postoperative pain following thoracoscopic surgery for lung cancer. By addressing both physiological and psychological dimensions, healthcare providers can better tailor postoperative care to prevent the transition from acute to chronic pain. This approach has the ability to improve patients' quality of life and functional outcome. Enhancing surgical techniques to minimize tissue trauma, optimizing pain management protocols, and incorporating psychological assessments into standard care are strategies that may significantly reduce CPSP incidence and severity. The ongoing challenge lies in integrating these insights effectively into clinical practice, ensuring all patients receive holistic, personalized care during their cancer journey.

Disclosure of conflict of interest

None.

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References

[1] Millard SK, Furman AJ, Kerr A, Seminowicz DA, Gao F, Naidu BV and Mazaheri A. Predicting postoperative pain in lung cancer patients using preoperative peak alpha frequency. Br J Anaesth 2022; 128: e346-e348.

[2] Yao J, Novosel M, Bellampalli S, Kapo J, Joseph J and Prsic E. Lung cancer supportive care and symptom management. Hematol Oncol Clin North Am 2023; 37: 609-622.

[3] Gjeilo KH, Oksholm T, Follestad T, Wahba A and Rustøen T. Trajectories of pain in patients undergoing lung cancer surgery: a longitudinal prospective study. J Pain Symptom Manage 2020; 59: 818-828, e811.
[4] Argo J. Estimation of chronic postsurgical pain after thoracic surgery: case closed? J Pain Symptom Manage 2020; 59: e3-e4.
[5] Costa AR, Lunet N, Martins-Branco D, Gomes B and Lopes S. Hospitalizations at the end of life among chronic obstructive pulmonary disease and lung cancer patients: a nationwide study. J Pain Symptom Manage 2021; 62: 48-57.
[6] Evenepoel M, Haenen V, De Baerdemaecker T, Meeus M, Devoogdt N, Dams L, Van Dijck S, Van der Gucht E and De Groef A. Pain prevalence during cancer treatment: a systematic review and meta-analysis. J Pain Symptom Manage 2022; 63: e317-e335.
[7] Schlaeger JM, Weng LC, Huang HL, Tsai HH, Takayama M, Ngamkham S, Yao Y and Wilkie DJ. Pain quality by location in outpatients with cancer. Pain Manag Nurs 2019; 20: 425-431.
[8] Zhong S, Sun Q, Wen J, Zhang Z, Chen Y, Ye H, Huang W, Zheng J, Liu H, Fan X, Jin J, Lyu Z, Li B, Ma D and Liao X. Dexmedetomidine attenuates inflammatory response and chronic pain following video-assisted thoracoscopic surgery for lung cancer. Surgery 2024; 176: 1263-1272.
[9] Tsuzuki Y, Nishiyama T, Ishida Y, Maeda R, Tomino M and Ohseto K. A case of nerve root radiofrequency thermocoagulation for pain due to pleural metastasis of lung cancer leading to improvement in the patient's quality of life. Palliat Med Rep 2023; 4: 288-291.
[10] Li G, Zhang C, Wang C and Xiao L. Acupuncture against chronic postsurgical pain in non-small cell lung cancer patients: a protocol of randomized controlled trial. Medicine (Baltimore) 2021; 100: e27461.
[11] Leuppi-Taegtmeyer AB, Reinau D, Yilmaz S, Rüegg S, Krähenbühl S, Jick SS, Leuppi JD and Meier CR. Antiseizure drugs and risk of developing smoking-related chronic obstructive pulmonary disease or lung cancer: a population-based case-control study. Br J Clin Pharmacol 2021; 87: 1253-1263.
[12] Yu YM, Long YZ and Zhu ZQ. Chitosan, a Natural Polymer, is an excellent sustained-release carrier for Amide Local Anesthetics. J Pain Res 2024; 17: 3539-3551.
[13] El-Tallawy SN, Nalamasu R, Salem GI, LeQuang JAK, Pergolizzi JV and Christo PJ. Management of musculoskeletal pain: an update with emphasis on chronic musculoskeletal pain. Pain Ther 2021; 10: 181-209.
[14] Yoon S, Hong WP, Joo H, Kim H, Park S, Bahk JH and 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: 331-336.
[15] Glette M, Stiles TC, Borchgrevink PC and Landmark T. The natural course of chronic pain in a general population: stability and change in an eight-wave longitudinal study over four years (the HUNT pain study). J Pain 2020; 21: 689-699.
[16] Naunheim MR, Dai JB, Rubinstein BJ, Goldberg L, Weinberg A and Courey MS. A visual analog scale for patient-reported voice outcomes: the VAS voice. Laryngoscope Investig Otolaryngol 2019; 5: 90-95.
[17] Ünver S and Turan FN. Turkish validity and reliability study of fear of pain questionnaire-III. Agri 2018; 30: 18-27.
[18] Ward CL, Flisher AJ, Zissis C, Muller M and Lombard C. Reliability of the beck depression inventory and the self-rating anxiety scale in a sample of South African adolescents. J Child Adolesc Ment Health 2003; 15: 73-75.
[19] Chagas MH, Tumas V, Loureiro SR, Hallak JE, Trzesniak C, de Sousa JP, Rodrigues GG, Santos Filho A and Crippa JA. Validity of a Brazilian version of the Zung self-rating depression scale for screening of depression in patients with Parkinson's disease. Parkinsonism Relat Disord 2010; 16: 42-45.
[20] Peng J, Wang Z, Ma L, Ma W, Liu G, Zhang H, Wang Q, Zhu B and Zhao L. Incidence and influencing factors of chronic postthoracotomy pain in lung tumor patients. J Healthc Eng 2022; 2022: 7584481.
[21] Ran W, Luo H, Wang Z, Hao Y, Liang N, Li P, Yin X and Gao J. Can ultrasound-guided continuous paravertebral block reduce the incidence of chronic postsurgical pain in patients with thoracoscopic lung cancer surgery? A randomized controlled trial. Pain Res Manag 2023; 2023: 6433494.
[22] O'Regan A, Fish LJ, Makarushka C, Somers T, Fitzgerald Jones K, Merlin JS, Dinan M, Oeffinger K and Check D. Managing chronic pain in cancer survivorship: communication challenges and opportunities as described by cancer survivors. Am J Hosp Palliat Care 2024; 41: 78-86.
[23] de Munter J, Dodlek N, Khmaladze A, Parreira ST, Ullgren H, de Man R, de Jong FA and Oldenmenger WH. The role of cancer nurses in cancer-related pain management in Europe. Palliat Care Soc Pract 2023; 17: 26323524-231216996.
[24] Walker SM. Developmental mechanisms of CPSP: clinical observations and translational laboratory evaluations. Can J Pain 2021; 6: 49-60.

[25] Mills SEE, Nicolson KP and Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth 2019; 123: e273-e283.
[26] Tanaka K, Kondo T, Narita M, Muta T, Yoshida S, Sato D, Suda Y, Hamada Y, Shimizu T, Kuzumaki N and Narita M. Cancer aggravation due to persistent pain signals with the increased expression of pain-related mediators in sensory neurons of tumor-bearing mice. Mol Brain 2023; 16: 19.
[27] Danielsen AV, Andreasen JJ, Dinesen B, Hansen J, Kjær-Staal Petersen K, Simonsen C and Arendt-Nielsen L. Chronic post-thoracotomy pain after lung cancer surgery: a prospective study of preoperative risk factors. Scand J Pain 2023; 23: 501-510.
[28] Danielsen AV, Andreasen JJ, Dinesen B, Hansen J, Petersen KK, Simonsen C and Arendt-Nielsen L. Corrigendum to "Chronic post-thoracotomy pain after lung cancer surgery: a prospective study of preoperative risk factors". Scand J Pain 2024; 24.
[29] Li X, Chen Y, Wang J, Jiang C and Huang Y. Lung cancer cell-derived exosomal let-7d-5p downregulates OPRM1 to promote cancer-induced bone pain. Front Cell Dev Biol 2021; 9: 666857.
[30] Cheville A, Smith S, Barksdale T and Asher A. Cancer rehabilitation. Braddom's Physical Medicine and Rehabilitation (Sixth Edition) 2021; 568-593.e567.
[31] Koo MM, Swann R, McPhail S, Abel GA, Elliss-Brookes L, Rubin GP and Lyratzopoulos G. Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. Lancet Oncol 2020; 21: 73-79.
[32] Zajączkowska R, Kocot-Kępska M, Leppert W and Wordliczek J. Bone pain in cancer patients: mechanisms and current treatment. Int J Mol Sci 2019; 20: 6047.
[33] Han P, Zhou J, Xiang J, Liu Q and Sun K. Research progress on the therapeutic effect and mechanism of metformin for lung cancer (Review). Oncol Rep 2023; 49: 3.
[34] Admiraal M, Hermanides J, Meinsma SL, Wartenberg HCH, Rutten MVH, Ward-van der Stam VMC, Hollmann MW and Hermanns H. Current multidisciplinary approaches to preventing chronic postoperative pain. Br J Anaesth 2021; 127: 331-335.
[35] Afriyie-Mensah JS, Kwarteng E, Tetteh J, Gbadamosi H, Dadzie MA, Mensah YB and Entsua-Mensah E. A three-year review of lung cancer patient characteristics in a tertiary hospital. Ghana Med J 2023; 57: 167-174.
[36] Ohashi K, Suzuki H, Sata Y, Tanaka K, Yamamoto T, Sakairi Y, Wada H, Nakajima T, Nozaki-Taguchi N, Isono S, Shiko Y, Kawasaki Y and Yoshino I. Postoperative pain and quality of life after lung cancer surgery: a prospective observational study. Ann Palliat Med 2023; 12: 346-355.
[37] Giusti EM, Lacerenza M, Manzoni GM and Castelnuovo G. Psychological and psychosocial predictors of chronic postsurgical pain: a systematic review and meta-analysis. Pain 2021; 162: 10-30.
[38] Angst F, Benz T, Lehmann S, Wagner S, Simmen BR, Sandòr PS, Gengenbacher M and Angst J. Extended overview of the longitudinal pain-depression association: a comparison of six cohorts treated for specific chronic pain conditions. J Affect Disord 2020; 273: 508-516.