BMC Cancer

RESEARCH Open Access

Sex-related differences in postoperative patient-reported outcomes among lung cancer patients: a multicenter cohort study

Jia Liao[1†], Xiaoqun Hu[1†], Xing Wei[1], Wei Dai[1], Hongfan Yu[2], Xin Tian[3], Yaqin Wang[1], Qin Qin[1], Na Xu[1], Yuanyuan Li[1], Qiang Li[1], Qiuling Shi[1,2,3*†] and Xiaoqin Liu[1*†]

Abstract

Background Studies on sex-related differences in post-lung cancer surgery symptoms are limited. Understanding these differences may provide insights into patient recovery. Therefore, we investigated sex-related differences in these symptoms and their underlying associated factors.

Methods We included patients aged ≥ 18 years undergoing surgery for lung cancer from a multicenter cohort study (CN-PRO-Lung 1) that focused on postoperative lung cancer symptoms trajectories. On a daily assessment schedule, we evaluated patients' symptoms and their impact on functioning from the day before surgery until discharge using the MD Anderson Symptom Inventory–Lung Cancer module. We evaluated sex-related differences in symptom scores over time and identified influencing factors using linear mixed models.

Results Of 372 eligible patients (196 men and 176 women;) symptoms were milder in men than in women for pain (estimate = 0.427, $P = 0.021$), fatigue (estimate = 1.071, $P < 0.001$), shortness of breath (estimate = 0.431, $P = 0.021$), lack of appetite (estimate = 0.728, $P < 0.001$), dry mouth (estimate = 0.438, $P = 0.015$), and constipation (estimate = 0.887, $P < 0.001$) during postoperative hospitalization (median: 7 days). Pain scores decreased over time in both sexes (estimate = -0.440 in men, $P < 0.001$; -0.510 in women, $P < 0.001$), while different factors were associated with increased pain in each group. In men, higher American Society of Anesthesiologists (ASA) classification (estimate = 0.430, $P = 0.035$), advanced pTNM stage (estimate = 0.550, $P = 0.007$), and having more than one chest drain (estimate = 0.690, $P = 0.001$) were associated with greater pain. In women, systematic lymph node dissection was associated with increased pain (estimate = 0.700, $P = 0.033$).

†Jia Liao and Xiaoqun Hu contributed equally to this work as co-first authors.

†Xiaoqin Liu and Qiuling Shi contributed equally to this work as corresponding authors.

*Correspondence:
Qiuling Shi
qshi@cqmu.edu.cn
Xiaoqin Liu
594922003@qq.com

Full list of author information is available at the end of the article

Conclusions Women reported a higher symptom burden than men in the early postoperative period after lung cancer surgery. Key factors associated with worse postoperative pain include higher ASA classification, advanced pTNM stage, and more than one chest tube in men and systematic lymph node dissection in women.

Trial registration number NCT03341377

Keywords Lung cancer, Postoperative symptom, Sex-related difference, Symptom severity

Introduction

Lung cancer is a significant global health concern, characterized by alarmingly high incidence and mortality rates [1]. Surgical intervention is widely recognized as the primary treatment for early-stage lung cancer [2]. However, individuals who have undergone lung cancer surgery frequently experience various postoperative symptoms that can profoundly impact their recovery processes and overall quality of life [3–5].

The symptom burden experienced by these patients has been extensively researched to identify strategies that improve symptom management and clinical outcomes [6–10]. However, these studies primarily focused on profiling and managing these symptoms within the patient group as a whole, without adequately considering sex-related differences in symptomatology [11–13]. Although previous studies have reported differences in the types and severity of postoperative symptoms between men and women with lung cancer [14–19], the precise causes underlying sex-specific differences in symptoms remains unclear [20].

Additionally, severe postoperative symptom burden interferes with daily functions and may affect postoperative recovery [21–23], increase the chance of readmission [24, 25], and even delay other postoperative treatments [26]. The monitoring and intervention of symptom burden can improve the postoperative symptom management of patients [7, 9, 26]; however, relevant supporting evidence for sex-related differences in symptoms and studies on its influencing factors are lacking.

To address this critical knowledge gap, this study aimed to investigate the differences in postoperative PROs, including symptoms and interference with daily functioning, between men and women who have undergone lung cancer surgery. Additionally, it sought to identify potential factors related to postoperative pain in men and women independently, to support the development of sex-specific postoperative care strategies.

Methods

Study design and patients

This study selected patients from a cohort study (CN-PRO-Lung 1, ClinicalTrials.gov identifier NCT03341377; trials registration first posted on 14 November, 2017) [27, 28] conducted in six tertiary hospitals from November 2017 to January 2020 that focused on the postoperative symptoms of primary lung cancer. The study protocol was approved by the Ethics Committee of Sichuan Cancer Hospital (No. SCCHEC-02-2017-042), and all patients provided written informed consent [27].

The inclusion criteria of this study were as follows: (1) age ≥ 18 years, (2) undergoing surgical treatment for primary lung cancer, and (3) pathologically confirmed primary lung cancer. Patients who met any one of the following criteria were excluded: (1) history of other cancers, (2) second surgery for lung cancer recurrence or double primary cancer, (3) metastatic lung cancer, or (4) preoperative neoadjuvant therapy.

General data collection

General patient information was extracted through the hospital's electronic medical record system, including demographic characteristics, preoperative characteristics, surgical data, postoperative pathological diagnosis [postoperative pathological staging was based on the 8th edition of the Tumor–Node–Metastasis (TNM) lung cancer classification], postoperative complications, and other clinical data. The above information was recorded on the REDCap platform of Sichuan Cancer Hospital by researchers trained in standard operating procedures to ensure the accuracy and traceability of data collection [29].

PRO measurement instruments and outcome measures

The MD Anderson Symptom Inventory–Lung Cancer module (MDASI-LC) was used to assess symptoms [4, 30]. Symptom severity and its impact on daily functioning were collected at baseline (3 days preoperatively) and subsequently daily postoperatively at the hospital for less than 14 days [27]. The patients independently completed the MDASI-LC. When assistance was needed, the investigator only read the questions aloud and recorded the patient's exact response without interpretation. All assessments were self-reported; no proxy responses were applicable or permitted in this study.

Pain management strategy

Postoperative pain management followed the World Health Organization three-step analgesic ladder and was consistently applied across all patients. None of the patients received local pain management strategies such as paravertebral blocks or epidurals, nor was

patient-controlled analgesia (PCA) standard practice in this cohort. The attending physician adjusted the analgesic regimen based on the patient's reported pain intensity, response to treatment, and potential side effects. Oral analgesics included NSAIDs (e.g., loxoprofen, aspirin), compound preparations (e.g., sustained-release codeine tablets), and weak opioids (e.g., compound codeine oral solutions, tramadol). Intravenous options comprised NSAIDs (e.g., trometamol ketorolac, parecoxib) and strong opioids (e.g., butorphanol, buprenorphine, dezocine, morphine, sufentanil). This individualized approach ensured that each patient's pain management needs were met while maintaining a consistent overall protocol.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Sichuan Cancer Hospital (Approval number: SCCHEC-02-2017-042). Informed consent was obtained from all participants included in the study.

Statistical analysis

We analyzed the longitudinal PRO data of the patients from the preoperative day until discharge or the 7th day after surgery., given that the median length of postoperative hospital stay was 7 days. Normally and non-normally distributed continuous variables are presented as mean ± standard deviation and median and interquartile range, respectively. Categorical variables are expressed as numbers (percentages). To assess differences, the *t*-test and Mann–Whitney U test were used for the normally and non-normally distributed continuous variables, respectively, and the chi-squared or Fisher's exact test was used for the categorical variables. Additionally, we calculated the completion rate at each time point to describe data availability.

A linear mixed-effect (LME) model was used to assess sex-related differences in symptom scores over time. The dependent variable was the score for each item, and the independent variables were sex, time, and adjustments for sex, adjusted age, education level, Charlson Comorbidity Index (CCI) score, smoking history, surgical approach (video-assisted thoracoscopic surgery [VATS] or open surgery), type of resection (lobectomy or extended resection), pathological TNM (pTNM) stage, histological type, and lymphadenectomy. Models were assessed using the maximum likelihood estimation method to evaluate the random effects of intercept and time and the fixed effects of independent variables (such as sex). Different covariance structures (unstructured, simple, first-order autoregressive, and compound symmetric) were compared during model building using the Bayesian information criterion (BIC). The first-order autoregressive model with the lowest BIC was selected to fit the models.

A LME model was usedto identify the risk factors for pain in men and women independently since pain was the most common and significantly different symptom between sexes in this study. The potential risk factors included the postoperative time and all patient characteristic variables. A two-tailed P-value of < 0.05 was considered statistically significant, and statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Sample demographic characteristics

Overall, 372 patients who met the inclusion criteria were included. Table 1 presents the demographic and disease characteristics of the patients. This study included 196 men and 176 women with mean ages of 58.18 ± 10.16 and 53.73 ± 9.80 years, respectively. More women had no smoking history (men = 32.14% vs. women = 96.59%,$P < 0.001$), whereas more men than women had a CCI score of ≥ 1 (men = 78.57% vs. women = 60.80%, $P < 0.001$). The proportion of men who underwent VATS was lower than that of women (men = 71.43% vs. women = 91.48%, $P < 0.001$). More women than men had a pTNM stage of ≤ I (men = 51.02% vs. women = 81.25%, $P < 0.001$). Adenocarcinoma was the most common histology in both sexes, although it was more common in women than in men (men = 71.43% vs. women = 94.32%, $P < 0.001$). More women underwent non-systematic lymph node dissection than men (men = 54.59% vs. women = 64.77%, $P = 0.046$). The median postoperative hospital stay was 7 days for men and 6 days for women ($P < 0.001$). Although the highest level of education ($P = 0.019$) and access ($P = 0.014$) differed between the sexes, the number of chest tubes placed, complications, and other demographic and disease characteristics were not significantly different (Table 1).

Top five symptoms

Regarding PRO data availability, the preoperative completion rate in both men and women was 100%, whereas the postoperative completion rate during hospitalization was 91.08–98.43% and 88.24–97.16%, respectively. The lowest compliance rate within the first 7 days postoperatively was 91.08% for men on the sixth day and 88.24% for women on the seventh day. At discharge, the compliance rates were 76.02% and 84.66% for men and women, respectively.

The top five symptoms, identified based on the highest mean scores during hospitalization, were pain, coughing, fatigue, disturb sleep, shortness of breath. (Table 2). The mean scores of the top 5 symptoms for male and female

Table 1 Baseline demographic and patient characteristics

Variables	Total (*n* = 372)	Men (*n* = 196)	Women (*n* = 176)	*P*-value
Age (years), mean (SD)	56.07 ± 10.22	58.18 ± 10.16	53.73 ± 9.80	
Age group (years)				**< 0.001**[a]
≤ 60	237 (63.71%)	104 (53.06%)	133 (75.57%)	
> 60	135 (36.29%)	92 (46.94%)	43 (24.43%)	
BMI, mean (SD)	22.93 ± 2.79	23.33 ± 2.68	22.50 ± 2.85	
Education level				**0.019**[c]
Middle school graduate or below	176 (47.31%)	104 (53.06%)	72 (40.91%)	
Above middle school graduate	196 (52.69%)	92 (46.94%)	104 (59.09%)	
Smoking history				**<0.001**[c]
No	233 (62.63%)	63 (32.14%)	170 (96.59%)	
Yes	139 (37.37%)	133 (67.86%)	6 (3.41%)	
CCI score				**<0.001**[c]
0	111 (29.84%)	42 (21.43%)	69 (39.2%)	
≥ 1	261 (70.16%)	154 (78.57%)	107 (60.80%)	
ASA classification				0.388[c]
1	173 (46.51%)	87 (44.39%)	86 (48.86%)	
> 1	199 (53.49%)	109 (55.61%)	90 (51.14%)	
Surgical approach				**<0.001**[c]
Video-assisted thoracoscopic surgery	301 (80.91%)	140 (71.43%)	161 (91.48%)	
Open surgery	71 (19.09%)	56 (28.57%)	15 (8.52%)	
Operative time (min), mean (SD)	139.05 ± 51.79	135.94 ± 53.12	142.51 ± 50.19	
Resection type				**0.003**[c]
*Sublobectomy	78 (20.97%)	30 (15.31%)	48 (27.27%)	
Lobectomy	238 (63.98%)	128 (65.31%)	110 (62.50%)	
Other	56 (15.05%)	38 (19.39%)	18 (10.23%)	
pTNM stage				**<0.001**[c]
≤I	243 (65.32%)	100 (51.02%)	143 (81.25%)	
> I	129 (34.68%)	96 (48.98%)	33 (18.75%)	
Tumor pathological type				**<0.001**[c]
Adenocarcinoma	306 (82.26%)	140 (71.43%)	166 (94.32%)	
Non-adenocarcinoma	66 (17.74%)	56 (28.57%)	10 (5.68%)	
#Number of chest tubes				0.696[c]
One	235 (63.16%)	122 (62.24%)	113 (64.20%)	
Two	137 (36.82%)	74 (37.76%)	63 (35.80%)	
Lymphadenectomy				**0.046**[c]
Systematic lymph node dissection	151 (40.59%)	89 (45.41%)	62 (35.23%)	
Non-systematic lymph node dissection	221 (59.41%)	107 (54.59%)	114 (64.77%)	
Perioperative complication				0.144[c]
No	281 (75.54%)	142 (72.45%)	139 (78.98%)	
Yes	91 (24.46%)	54 (27.55%)	37 (21.02%)	
PHS (days), median (IQR)	7 (3)	7 (4)	6 (2)	**<0.001**[b]

Statistically significant values are given in bold ($P < 0.05$)

Data are expressed as median (IQR) or n (%)

ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson Comorbidity Index; IQR, interquartile range; PHS, postoperative hospital stay; pTNM, pathological Tumor–Node–Metastasis; SD, standard deviation

*Sublobectomy includes wedge resection and segmentectomy

#Chest tube sizes ranged from 20 to 28 French and were made of flexible silicone-based materials

[a] t-test; [b] Mann–Whitney U test; [c] chi-squared tests; [d] Fisher's exact test

Table 2 Comparison top five symptoms between male and female patients

Time point	Men ($n=196$)			Women ($n=176$)			*P*-value
	n	Mean ± SD	95% CI	*n*	Mean ± SD	95% CI	
Baseline	196	1.18 ± 1.25	1.25–1.36	176	1.13 ± 1.2	1.2–1.31	0.688
POD 1	184	4.29 ± 2.08	2.08–4.59	169	4.21 ± 1.94	1.94–4.51	0.706
POD 2	190	3.62 ± 1.97	1.97–3.9	171	3.81 ± 2.09	2.09–4.12	0.385
POD 3	191	3.13 ± 1.96	1.96–3.41	170	3.61 ± 1.89	1.89–3.9	**0.018**
POD 4	188	3.16 ± 1.98	1.98–3.45	163	3.19 ± 1.83	1.83–3.47	0.902
POD 5	164	3.07 ± 1.91	1.91–3.37	141	3.1 ± 1.86	1.86–3.4	0.916
POD 6	143	2.98 ± 1.79	1.79–3.28	99	3 ± 1.81	1.81–3.36	0.946
POD 7	114	3.03 ± 1.92	1.92–3.39	60	3.07 ± 1.89	1.89–3.55	0.917
At discharge	149	2.59 ± 1.9	1.9–2.9	149	2.62 ± 1.71	1.71–2.89	0.89

CI, confidence interval; POD, postoperative day; SD, standard deviation

The top five symptoms during hospitalization, based on highest mean scores, were pain, coughing, fatigue, disturbed sleep, and shortness of breath

patients showed statistically significant differences on the third day post-surgery.(Table 2).

Comparison of pros longitudinally between men and women patients

As shown in Fig. 1; Table 3, the following symptoms were less severe in men than in women: pain (estimate = 0.427, $P=0.021$), fatigue (estimate = 1.071, $P<0.001$), shortness of breath (estimate = 0.431, $P=0.021$), lack of appetite (estimate = 0.728, $P<0.001$), dry mouth (estimate = 0.438, $P=0.015$), and constipation (estimate = 0.887, $P<0.001$).

In-hospital pain severity and its influencing factors

The pain score in patients (both sexes) was the lowest preoperatively (men vs. women, 0.56 ± 1.24 vs. 0.59 ± 1.31) and the highest on the first day postoperatively (men vs. women, 5.58 ± 2.61, 5.47 ± 2.53). On the day of discharge, the average scores were similar between both sexes. In men, postoperative time (Time, POD) was closely associated with a significant decrease in pain scores (estimate = -0.440, $P<0.001$) (Table 4). Additionally, the American Society of Anesthesiologists (ASA) classification had a significant associated with postoperative pain (estimate = 0.430, $P=0.035$), indicating that pain was more pronounced in men with an ASA classification of 1 or higher. Men with a pTNM stage higher than I also showed a significant increase in pain (estimate = 0.550, $P=0.007$). The placement of two chest tubes was significantly associated with greater postoperative pain (estimate = 0.690, $P=0.001$). In women, postoperative time (Time, POD) was similarly associated with a significant decrease in pain scores (estimate = -0.510, $P<0.001$). Additionally, systematic lymph node dissection was associated with postoperative pain in women (estimate = 0.700, $P=0.033$).

Discussion

This study revealed sex-based disparities in symptoms following lung cancer surgery, with men reporting lower postoperative scores for pain, fatigue, shortness of breath, lack of appetite, dry mouth, and constipation. These differences were statistically significant and aligned with previous findings [31–36]. To the best of our knowledge, no prior longitudinal study has explored the differences in postoperative symptoms between men and women with lung cancer from the patient's perspective. Additionally, the observed differences in the factors associated with pain trajectories in men and women indicate the necessity for tailored perioperative care strategies.

Previous studies have indicated significant sex-specific differences in postoperative symptom presentation in the context of various surgical procedures, and symptoms such as pain, fatigue, postoperative nausea, and vomiting have been typically found to be more pronounced in women than in men [31–34]. In our study, we found that pain incidence in both sexes was the lowest before lung cancer surgery but peaked on POD1. Notably, women reported higher pain scores than did men. The influence of sex on pain perception has been the subject of extensive research. Studies have suggested that women may have a lower pain threshold than men [37], which could explain why they experience more frequent and intense postoperative pain compared to their men counterparts [33]. These sex-related disparities may be partially explained by underlying biological and psychosocial mechanisms. Biologically, hormonal differences—particularly the role of estrogen—have been associated with increased pain sensitivity and inflammatory responses, potentially intensifying postoperative symptoms in women [38]. Psychosocial factors, such as greater emotional expressiveness and different pain coping strategies, may also influence symptom perception and reporting [39]. Women may be more likely to report symptoms, while men may underreport due to sociocultural expectations around stoicism. Understanding

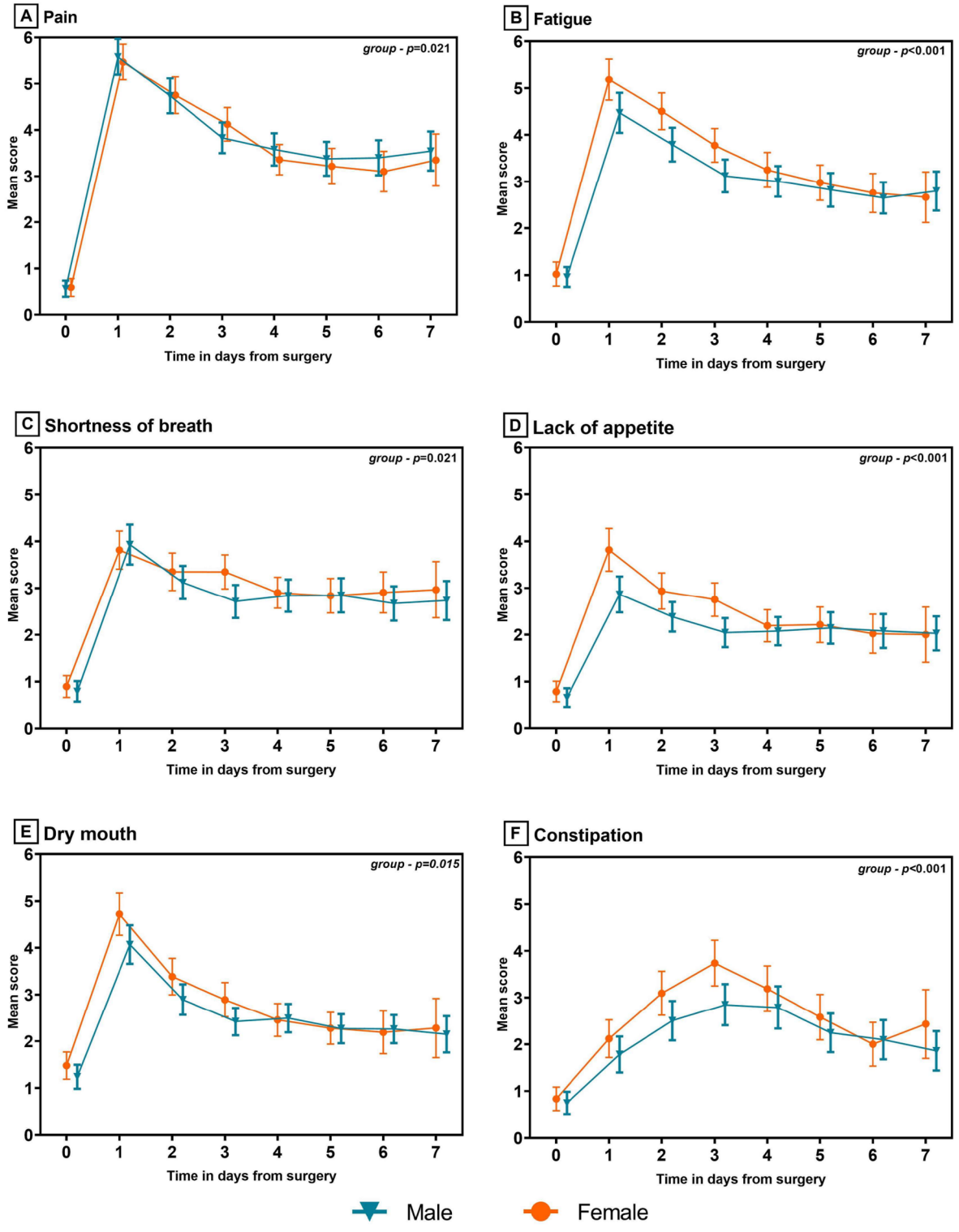

Fig. 1 Comparison of postoperative in-hospital patient-reported outcomes between men and women

these complex interactions is essential for designing sex-specific approaches to symptom monitoring and management [40]. Pain is not only a physical and psychological challenge for patients but also interacts with various factors that can considerably affect postoperative recovery [3, 41, 42]. Therefore, developing targeted and individualized pain management strategies is essential. By effectively mitigating postoperative pain, quicker

Table 3 Comparison of patient-reported outcomes during postoperative hospitalization between men and women

Items	Men (as reference) versus Women					
	Group			Time		
	Estimate	SE	P-value	Estimate	SE	P-value
Pain	0.427	0.184	**0.021**	-0.492	0.032	**< 0.001**
Fatigue (tiredness)	1.071	0.187	**< 0.001**	-0.436	0.032	**< 0.001**
Nausea	0.001	0.143	0.993	-0.146	0.024	**< 0.001**
Disturbed sleep	0.189	0.203	0.352	-0.194	0.035	**< 0.001**
Distressed (upset)	-0.112	0.195	0.568	-0.198	0.033	**< 0.001**
Shortness of breath	0.431	0.186	**0.021**	-0.214	0.032	**< 0.001**
Problems remembering things	0.306	0.247	0.215	-0.043	0.015	**0.004**
Lack of appetite	0.728	0.177	**< 0.001**	-0.227	0.03	**< 0.001**
Drowsy (sleepy)	0.271	0.186	0.145	-0.347	0.031	**< 0.001**
Dry mouth	0.438	0.181	**0.015**	-0.376	0.03	**< 0.001**
Sadness	0.037	0.264	0.888	-0.085	0.019	**< 0.001**
Vomiting	0.131	0.118	0.267	-0.06	0.02	**0.0029**
Numbness or tingling	-0.024	0.142	0.863	-0.085	0.024	**< 0.001**
Coughing	-0.218	0.181	0.228	0.015	0.031	0.632
Constipation	0.887	0.221	**< 0.001**	-0.012	0.037	0.742
Sore throat	0.071	0.256	0.782	-0.138	0.019	**< 0.001**
Activity	0.227	0.218	0.298	-0.378	0.037	**< 0.001**
Mood	-0.052	0.195	0.791	-0.145	0.033	**< 0.001**
Work	0.481	0.277	0.082	-0.435	0.047	**< 0.001**
Relations with other people	-0.089	0.198	0.654	-0.008	0.034	0.822
Walking	0.125	0.221	0.571	-0.598	0.037	**< 0.001**
Enjoyment of life	-0.148	0.224	0.509	-0.254	0.038	**< 0.001**

Statistically significant values are given in bold ($P < 0.05$)

Adjusted variables: age, education level, Charlson Comorbidity Index score, smoking history, surgical approach, surgical resection type, pathological Tumor–Node–Metastasis stage, pathological types, and lymphadenectomy

Estimate: Coefficients from our linear mixed-effects (LME) model

Group Estimate represents the fixed effect of sex (with men as the reference), indicating the estimated difference in symptom scores between women and men

Time Estimate represents the fixed effect of postoperative day, reflecting changes in symptom scores over time

SE, standard error

patient recovery and reduced risk of complications can be achieved.

For men, ASA classification, pTNM stage, and the number of chest tubes were particularly prominent factors influencing postoperative pain. First, the significant impact of ASA classification in men suggests that a higher ASA classification (≥ 1) may be associated with more complex postoperative management needs, which aligns with previous findings linking poorer ASA classification to adverse outcomes. Therefore, ASA classification should be considered when assessing postoperative pain in men. Second, men with a pTNM stage higher than I exhibited significantly increased pain, indicating that tumor staging may be associated with postoperative pain, especially in patients with more advanced disease. This finding underscores the importance of individualized pain management strategies. Additionally, the placement of two chest tubes was significantly associated with greater postoperative pain in men, likely reflecting the association between more invasive surgical procedures and increased pain levels, suggesting that clinicians should consider the additional burden of pain in postoperative chest tube management. In contrast, postoperative pain in women was more significantly influenced by systematic lymph node dissection. This finding is consistent with studies indicating that systematic lymph node dissection has been associated with greater tissue damage and postoperative complications in women. Therefore, pain management interventions in women may need to focus specifically on the extent of lymph node dissection and the speed of postoperative recovery.

Furthermore, while many of the observed differences were statistically significant, it is important to assess whether these differences hold clinical relevance. Based on existing literature, a change of approximately 0.8–1.0 on a 0–10 scale is generally considered the minimal clinically important difference (MCID) for patient-reported symptom scores [30, 43]. Interpreting our findings through the lens of MCID helps to distinguish statistically significant changes that likely have genuine clinical relevance from those with limited practical implications. This approach enables clinicians to better prioritize

Table 4 Factors associated with postoperative pain in men and women with lung cancer

Men					Women				
Variables		**Estimate**	**SE**	***P*-value**	**Variables**		**Estimate**	**SE**	***P*-value**
Time, POD		-0.440	0.040	**< 0.001**	**Time, POD**		-0.510	0.030	**< 0.001**
Age group	≥ 60 vs. < 60 (as reference)	0.220	0.220	0.322	Age group	≥ 60 vs. < 60	0.040	0.380	0.911
Education level	Middle school graduate or below vs. Above middle school graduate	-0.280	0.200	0.165	Education level	Middle school graduate or below vs. Above middle school graduate	-0.110	0.300	0.704
Smoking history	Yes vs. No	0.150	0.210	0.459	Smoking history	Yes vs. No	-0.070	0.820	0.923
CCI score	≥ 1 vs. 0	-0.390	0.270	0.157	CCI score	≥ 1 vs. 0	-0.190	0.310	0.538
ASA classification	≥ 1 vs. 0	0.430	0.200	**0.035**	ASA classification	≥ 1 vs. 0	0.440	0.290	0.136
Surgical approach	Open surgery vs. Video-assisted thoracoscopic surgery	-0.270	0.250	0.279	Surgical approach	Open surgery vs. Video-assisted thoracoscopic surgery	0.960	0.550	0.082
Resection type	Extended resection vs. Lobectomy	0.230	0.260	0.378	Resection type	Extended resection vs. Lobectomy	0.350	0.470	0.455
	Other vs. Lobectomy	-0.290	0.280	0.310		Other vs. Lobectomy	0.220	0.360	0.539
pTNM stage	> I vs. ≤ I	0.550	0.200	**0.007**	pTNM stage	> I vs. ≤ I	-0.190	0.410	0.636
Tumor pathology	Non-adenocarcinoma vs. Adenocarcinoma	0.070	0.240	0.774	Tumor pathology	Non-adenocarcinoma vs. Adenocarcinoma	0.620	0.710	0.380
Number of chest tubes	Two vs. One	0.690	0.210	**0.001**	Number of chest tubes	Two vs. One	0.430	0.300	0.147
Lymphadenectomy	Systematic lymph node dissection vs. Non-systematic lymph node dissection	-0.270	0.210	0.200	**Lymphadenectomy**	Systematic lymph node dissection vs. Non-systematic lymph node dissection	0.700	0.330	**0.033**

ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; POD, postoperative day; pTNM, pathological Tumor–Node–Metastasis; Estimate, The coefficients derived from our linear mixed-effects model, which quantify the relationship between the specified variable and postoperative pain. Positive values indicate a higher pain score associated with that variable, while negative values indicate a lower pain score; SE, standard error

symptoms that may meaningfully affect patient care and informs the development of more targeted and effective postoperative interventions.

This research highlights the importance of sex differences in postoperative pain management. Men and women exhibit significant differences in the risk factors for postoperative pain, which may reflect physiological, psychological, and sociocultural factors. These findings suggest that clinical practice should involve the development of more individualized pain management strategies based on the patient's sex, disease characteristics, and surgical approach to improve postoperative recovery outcomes.

Limitations

This study has several limitations. First, as an observational study, even though we used mixed-effect models to adjust for potential confounding factors, residual confounding is inevitable. For instance, psychosocial factors and hormonal differences were not measured and may have influenced the results, potentially limiting our ability to fully explain the observed sex differences in postoperative symptoms. Second, this study focused only on PROs during the postoperative hospital stay and did not include long-term follow-up data after discharge. As such, our findings are limited to early postoperative outcomes, and do not capture the trajectory of symptom resolution or persistence after discharge. Future studies should incorporate longitudinal follow-up to better understand recovery patterns and long-term sex differences in PROs. Third, the lack of formal adjustment for multiple comparisons may increase the risk of Type I errors. However, most key findings remained statistically significant under a conservative Bonferroni-corrected threshold ($P < 0.0023$), supporting the robustness of our results. Fourth, since our study population was exclusively Chinese, cultural norms around pain reporting and gender roles may have influenced the results, limiting the generalizability of our findings to non-Chinese populations. Lastly, while we adjusted for surgical approach (VATS vs. open) as a covariate, we did not perform subgroup analyses due to the limited sample size in the open surgery group. Further stratification by sex and surgical approach would reduce statistical power and reliability.

Future research should further explore long-term postoperative symptoms and functional outcomes to comprehensively understand the influence of sex differences on the recovery process after lung cancer surgery. Moreover, future studies should include diverse cultural settings and consider adjustments for previously unmeasured factors, such as psychosocial and hormonal influences, to enhance the robustness and generalizability of the results.

Conclusion

This study revealed that women's symptom burden was more severe in the initial days following lung cancer surgery. For men, particular attention should be given to higher ASA classification, pTNM stage, and use of two chest tubes. Meanwhile, systematic lymph node dissection may be an important factor associated with higher pain levels in women, requiring close clinical attention. These findings highlight the importance of targeted postoperative interventions, particularly early in the recovery period, to address sex-specific symptom patterns and enhance overall quality of life for both men and women.

Acknowledgements
We express our gratitude to all patients who willingly participated in this study, dedicating their time and providing invaluable assistance with data collection.

Author contributions
Conceptualization: Jia Liao, Wei Dai, Qiuling Shi and Xiaoqin Liu.Data curation: Jia Liao, Xiaoqun Hu, Xing Wei, Wei Dai, Hongfan Yu, Xin Tian, Yaqin Wang, Qin Qin, Na Xu and Yuanyuan Li.Formal analysis: Jia Liao, Xing Wei, Hongfan Yu, Xin Tian and Xiaoqin Liu.Funding acquisition: Xing Wei and Qiuling Shi. Investigation: Jia Liao, Xiaoqun Hu, Xing Wei, Wei Dai, Hongfan Yu, Xin Tian, Yaqin Wang, Qin Qin, Na Xu, Yuanyuan Li, Qiang Li, Qiuling Shi, and Xiaoqin Liu.Methodology: Hongfan Yu, Xin Tian and Qiuling Shi.Project administration: Qiang Li, Qiuling Shi, and Xiaoqin Liu.Resources: Jia Liao, Xiaoqun Hu, Xing Wei, Wei Dai, Hongfan Yu, Xin Tian, Yaqin Wang, Qin Qin, Na Xu, Yuanyuan Li, Qiang Li, Qiuling Shi, and Xiaoqin Liu.Software: Jia Liao, Xing Wei, Hongfan Yu, Xin Tian and Qiuling Shi.Supervision: Xing Wei, Wei Dai, Qiang Li, Qiuling Shi, and Xiaoqin Liu.Validation: Jia Liao, Xing Wei, Wei Dai, Hongfan Yu, Qiuling Shi, and Xiaoqin Liu.Visualization: Hongfan Yu.Writing - original draft and Writing - review & editing: Jia Liao, Xiaoqun Hu, Xing Wei, Wei Dai, Hongfan Yu, Xin Tian, Yaqin Wang, Qin Qin, Na Xu, Yuanyuan Li, Qiang Li, Qiuling Shi, and Xiaoqin Liu.

Funding
This work was supported by the National Key R&D Plan for Intergovernmental Cooperation, the Ministry of Science and Technology of China (grant number 2022YFE0133100) and the Natural Science Foundation of Sichuan Province (grant number 2023NSFSC1047). The funders played no part in the data collection, management, or analysis, nor did they have a role in the manuscript's preparation, the decision to submit the manuscript for publication, or in the choice of the journal to which the manuscript was submitted.

Data availability
The authors are willing to share data, analytic methods, and study materials related to this article with other researchers, provided that they will not be used for commercial or profit purposes. The corresponding author of this article can be contacted by e-mail regarding the research materials needed, with reasons for their use. The authors will be glad to provide relevant materials after approval and discussion.

Declarations

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Thoracic Surgery, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Center, Sichuan Cancer Hospital & Institute, University of Electronic Science and Technology of China, No. 55, Section 4, South Renmin Road, Chengdu 610041, China
[2]State Key Laboratory of Ultrasound in Medicine and Engineering, College of Biomedical Engineering, Chongqing Medical University, Chongqing, China
[3]School of Public Health, Chongqing Medical University, Chongqing, China

Received: 27 January 2025 / Accepted: 21 April 2025
Published online: 29 April 2025

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7–33.
2. National Comprehensive Cancer Network. (NCCN) Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer, Version 10.2024
3. Wei X, Yu H, Dai W, Xu W, Yu Q, Pu Y, Wang Y, Liao J, Li Q, Shi Q. Discrepancy in the perception of symptoms among patients and healthcare providers after lung cancer surgery. Support Care Cancer. 2022;30(2):1169–79.
4. Tang L, Yu H, Dai W, Yang X, Wei X, Wang XS, Cleeland CS, Li Q, Shi Q. Symptom trajectories informing patient care after lung Cancer surgery: A longitudinal patient-Reported outcome study. Ann Surg Oncol. 2023;30(5):2607–17.
5. Merlo A, Carlson R, Espey J 3rd, Williams BM, Balakrishnan P, Chen S, Dawson L, Johnson D, Brickey J, Pompili C, et al. Postoperative symptom burden in patients undergoing lung Cancer surgery. J Pain Symptom Manage. 2022;64(3):254–67.
6. Yang D, Wei X, Hong Q, Zhao C, Mu J. Patient-Reported Outcome-Based prediction for postdischarge complications after lung surgery. Thorac Cardiovasc Surg; 2023;71(8):671–679
7. Dai W, Feng W, Zhang Y, Wang XS, Liu Y, Pompili C, Xu W, Xie S, Wang Y, Liao J, et al. Patient-Reported Outcome-Based symptom management versus usual care after lung Cancer surgery: A multicenter randomized controlled trial. J Clin Oncol. 2022;40(9):988–96.
8. Wei X, Yu H, Dai W, Mu Y, Wang Y, Liao J, Peng L, Han Y, Li Q, Shi Q. Patient-Reported outcomes of Video-Assisted thoracoscopic surgery versus thoracotomy for locally advanced lung cancer: A longitudinal cohort study. Ann Surg Oncol. 2021;28(13):8358–71.
9. Dai W, Zhang Y, Feng W, Liao X, Mu Y, Zhang R, Wei X, Wu C, Xie S, Li Q, et al. Using patient-reported outcomes to manage postoperative symptoms in patients with lung cancer: protocol for a multicentre, randomised controlled trial. BMJ Open. 2019;9(8):e030041.
10. Cheung YT, Chan A, Charalambous A, Darling HS, Eng L, Grech L, van den Hurk CJG, Kirk D, Mitchell SA, Poprawski D, et al. The use of patient-reported outcomes in routine cancer care: preliminary insights from a multinational scoping survey of oncology practitioners. Support Care Cancer. 2022;30(2):1427–39.
11. Liu J, Li D, Ma H, Li Y, Wei X, Dai W, Shi Q, Li Q, Zhou P, Wang X et al. Early postoperative Patient-Reported outcomes of sarcopenia versus nonsarcopenia in patients undergoing Video-Assisted thoracoscopic surgery for lung Cancer. Ann Surg Oncol 2025;32(2):801–810
12. Yu H, Lei C, Wei X, Wang Y, Xu W, Tang L, Dai W, Liao J, Pu Y, Gong R et al. Electronic symptom monitoring after lung cancer surgery: Establishing a core set of patient-reported outcomes for surgical oncology care in a longitudinal cohort study. Int J Surg 2024;110(10):6591–6600
13. Zhang K, Liu W, Zhao Y, Gao X, Dai W, Zhou X, Yu H, Shi Q, Li Q, Wei X. Comparison of early postoperative patient-reported outcomes after multiportal robotic-assisted thoracoscopic surgery and uniportal video-assisted thoracoscopic surgery for non-small cell lung cancer. Eur J Surg Oncol. 2024;50(9):108481.
14. Miaskowski C. Gender differences in pain, fatigue, and depression in patients with cancer. J Natl Cancer Inst Monogr. 2004;32:139–43.

15. Sartipy U. Influence of gender on quality of life after lung surgery. Eur J Cardiothorac Surg. 2010;37(4):802–6.
16. Zirafa CC, Romano G, Sicolo E, Castaldi A, Davini F, Melfi F. Lung cancer surgery in women: focus on gender-related outcomes—a narrative review. Precision Cancer Med. 2023;6:5–5.
17. Tong BC, Kosinski AS, Burfeind WR Jr., Onaitis MW, Berry MF, Harpole DH Jr., D'Amico TA. Sex differences in early outcomes after lung cancer resection: analysis of the society of thoracic surgeons general thoracic database. J Thorac Cardiovasc Surg. 2014;148(1):13–8.
18. Stabellini N, Bruno DS, Dmukauskas M, Barda AJ, Cao L, Shanahan J, Waite K, Montero AJ, Barnholtz-Sloan JS. Sex differences in lung Cancer treatment and outcomes at a large hybrid Academic-Community practice. JTO Clin Res Rep. 2022;3(4):100307.
19. Ragavan M, Patel MI. The evolving landscape of sex-based differences in lung cancer: a distinct disease in women. Eur Respir Rev 2022, 31(163).
20. Nelson DB, Lapid DJ, Mitchell KG, Correa AM, Hofstetter WL, Mehran RJ, Rice DC, Sepesi B, Walsh GL, Vaporciyan AA, et al. Perioperative outcomes for stage I Non-Small cell lung cancer: differences between men and women. Ann Thorac Surg. 2018;106(5):1499–503.
21. Hugoy T, Lerdal A, Rustoen T, Oksholm T. Predicting postoperative fatigue in surgically treated lung cancer patients in Norway: a longitudinal 5-month follow-up study. BMJ Open. 2019;9(9):e028192.
22. Yu Q, Yu H, Xu W, Pu Y, Nie Y, Dai W, Wei X, Wang XS, Cleeland CS, Li Q, et al. Shortness of breath on day 1 after surgery alerting the presence of early respiratory complications after surgery in lung Cancer patients. Patient Prefer Adherence. 2022;16:709–22.
23. Zhang J, Su X, Xu W, Yu Q, Dai W, Wang Y, Zhuang X, Li Q, Wang XS, Shi Q. Identifying patients who suffered from post-discharge cough after lung cancer surgery. Support Care Cancer. 2022;30(9):7705–13.
24. Johnson PC, Xiao Y, Wong RL, D'Arpino S, Moran SMC, Lage DE, Temel B, Ruddy M, Traeger LN, Greer JA, et al. Potentially avoidable hospital readmissions in patients with advanced Cancer. J Oncol Pract. 2019;15(5):e420–7.
25. Nipp RD, El-Jawahri A, Ruddy M, Fuh C, Temel B, D'Arpino SM, Cashavelly BJ, Jackson VA, Ryan DP, Hochberg EP, et al. Pilot randomized trial of an electronic symptom monitoring intervention for hospitalized patients with cancer. Ann Oncol. 2019;30(2):274–80.
26. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, Rogak L, Bennett AV, Dueck AC, Atkinson TM, et al. Symptom monitoring with Patient-Reported outcomes during routine Cancer treatment: A randomized controlled trial. J Clin Oncol. 2016;34(6):557–65.
27. Dai W, Xie S, Zhang R, Wei X, Wu C, Zhang Y, Feng W, Liao X, Mu Y, Zhou H, et al. Developing and validating utility parameters to Establish patient-reported outcome-based perioperative symptom management in patients with lung cancer: a multicentre, prospective, observational cohort study protocol. BMJ Open. 2019;9(10):e030726.
28. Wei X, Yu H, King-Kallimanis B, Liu Y, Huang L, Dai W, Yang D, Zhou X, Li Q, Shi Q. Long-Term function recovery following upper versus lower lobectomy for lung cancer: A multicenter longitudinal cohort study. Thorac Cancer. 2025;16(1):e15505.
29. Yu H, Yu Q, Nie Y, Xu W, Pu Y, Dai W, Wei X, Shi Q. Data quality of longitudinally collected Patient-Reported outcomes after thoracic surgery: comparison of Paper- and Web-Based assessments. J Med Internet Res. 2021;23(11):e28915.
30. Mendoza TR, Wang XS, Lu C, Palos GR, Liao Z, Mobley GM, Kapoor S, Cleeland CS. Measuring the symptom burden of lung cancer: the validity and utility of the lung cancer module of the M. D. Anderson symptom inventory. Oncologist. 2011;16(2):217–27.
31. Salazar-Parra M, Guzman-Ramirez BG, Pintor-Belmontes KJ, Barbosa-Camacho FJ, Bernal-Hernandez A, Cruz-Neri RU, Fuentes-Orozco C, Aguirre LLR, Rodriguez-Navarro D, Brancaccio-Perez IV, et al. Gender differences in postoperative pain, nausea and vomiting after elective laparoscopic cholecystectomy. World J Surg. 2020;44(12):4070–6.
32. Koch M, Hjermstad MJ, Tomaszewski K, Tomaszewska I, Hornslien K, Harle A, Arraras J, Morag O, Pompili C, Ioannidis G, et al. Gender effects on quality of life and symptom burden in patients with lung cancer: results from a prospective, cross-cultural, multi-center study. J Thorac Dis. 2020;12(8):4253–61.
33. Auinger D, Sandner-Kiesling A, Striessnig A, Lindenmann J, Smolle J, Friedl H, Smolle-Juttner FM. Is there an impact of sex on acute postthoracotomy pain?? A retrospective analysis. Ann Thorac Surg. 2020;109(4):1104–11.
34. Schmidt CE, Bestmann B, Kuchler T, Longo WE, Rohde V, Kremer B. Gender differences in quality of life of patients with rectal cancer. A five-year prospective study. World J Surg. 2005;29(12):1630–41.
35. Hanna EY, Mendoza TR, Rosenthal DI, Gunn GB, Sehra P, Yucel E, Cleeland CS. The symptom burden of treatment-naive patients with head and neck cancer. Cancer. 2015;121(5):766–73.
36. Wagner MK, Christensen AV, Hassager C, Stenbaek DS, Ekholm O, Borregaard B, Thrysoee L, Rasmussen TB, Thorup CB, Mols RE et al. Sex differences in Patient-Reported outcomes in the immediate recovery period after resuscitation: findings from the Cross-sectional DenHeart survey. J Cardiovasc Nurs 2023;38(3):279–287
37. Meyer-Friessem CH, Attal N, Baron R, Bouhassira D, Finnerup NB, Freynhagen R, Gierthmuhlen J, Haanpaa M, Hansson P, Jensen TS, et al. Pain thresholds and intensities of CRPS type I and neuropathic pain in respect to sex. Eur J Pain. 2020;24(6):1058–71.
38. Lenert ME, Avona A, Garner KM, Barron LR, Burton MD. Sensory neurons, neuroimmunity, and pain modulation by sex hormones. Endocrinology 2021, 162(8).
39. Le LHL, Brown VAV, Mol S, Azijli K, Kuijper MM, Becker L, Koopman S. Sex differences in pain catastrophizing and its relation to the transition from acute pain to chronic pain. BMC Anesthesiol. 2024;24(1):127.
40. Samulowitz A, Gremyr I, Eriksson E, Hensing G. Brave men and emotional women: A Theory-Guided literature review on gender Bias in health care and gendered norms towards patients with chronic pain. Pain Res Manag. 2018;2018:6358624.
41. Dai W, Dai Z, Wei X, Pompili C, Shi QL, Xie TP, He JT, Li Q. Early Patient-Reported outcomes after uniportal vs multiportal thoracoscopic lobectomy. Ann Thorac Surg 2022;114(4):1229–1237
42. Wei X, Yu H, Shi Q. ASO author reflections: using Patient-Reported outcomes to evaluate surgical approaches for locally advanced lung Cancer. Ann Surg Oncol. 2021;28(13):8372–3.
43. Sloan JA, Vargas-Chanes D, Kamath CC. Detecting worms, ducks and elephants: A simple approach for defining clinically relevant effects in quality-of-life measures. 2003.

Publisher's note