



Research article

Gender differences in postoperative pain, sleep quality, and recovery outcomes in patients undergoing visual thoracoscopic surgery

Hongyu Wang^a, Man Luo^{a,1}, Yanping Yang^a, Shiyi Li^a, Song Liang^b, Ran Xu^b, Junchao Zhu^{a,**}, Bijia Song^{a,*}

^a Department of Anesthesiology, Beijing Friendship Hospital, Capital Medical University, Beijing, China

^b Department of Thoracic Surgery, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China

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ABSTRACT

Objective: The purpose of our study was to investigate the effect of gender on postoperative pain, sleep quality, and recovery outcomes in patients undergoing VATS surgery under general anesthesia.

Method: Perioperative peripheral blood inflammatory markers system inflammation Index (SII) was recorded for perioperative inflammatory response. The visual analog scale (VAS) was used to evaluate pain level. And the Athens Insomnia Scale (AIS) was evaluated on the night before surgery (sleep preop 1), the first night after surgery (sleep POD 1), and the third night after surgery (sleep POD 3) for postoperative sleep.

Result: In this prospective cohort study, 79 males and 79 females were consecutively included. Females had significantly higher pain score (both rest and cough pain) compared to the males at 3 h after the surgery (3.85 ± 1.2 vs. 3.16 ± 1.1) (rest) ($p < 0.001$) and 5.10 ± 1.3 vs. 4.46 ± 1.6 (coughing) ($p = 0.006$). Patients in the male group had significantly lower AIS scores than those in the female group at Sleep POD 1 and Sleep POD 3 ($p = 0.024$ and $p = 0.045$). And in both groups, postoperative SII was increased and statistically significant compared to preoperative SII ($p < 0.001$, respectively). Women presented higher levels of SII on the first day after surgery, and the increase of postoperative SII in females groups was significantly higher than that in male group when compared to preoperative SII (1806.33 ± 1314.8 vs 1430.55 ± 958.4) ($p = 0.042$).

Conclusion: These findings highlight the complex multidimensional nature of postoperative pain, nausea and vomiting, sleep quality and the potential contributory role of sex in shaping these outcomes. Women had worse sleep quality, higher postoperative inflammatory response level and pain level than men.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality for both men and women all over the world. Annually, approximately

* Corresponding author.

** Corresponding author.

E-mail addresses: zhujunchao1@hotmail.com (J. Zhu), songbijia@163.com (B. Song).

¹ contribute equally to the work.

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631 000 deaths were reported because of lung cancer according to Chinese national statistics [1,2]. According to the determination report of the global cancer survival trend published by the World Health Organization (WHO) in 2018, the 5-year survival rate of lung cancer patients with clear diagnosis is only 10 %–20 %. Once the symptoms appear, it has reached the middle and late stage, and the prognosis is very poor [3]. Different from the extremely low survival rate of patients with intermediate and advanced lung cancer, surgery is currently the standard treatment for patients with stage I non-small cell lung cancer (NSCLC), whose 5-year survival rate of patients with early lung cancer can reach 80 %–95 % after aggressive treatment such as surgical resection after detection [4]. However, surgery in whatever form constitutes an injury process. Various physiological and immune stress responses result from this. Post-operative systemic inflammatory responses may exacerbate neuroinflammation, leading to deleterious neurological sequelae in some patients (eg, delirium, cognitive impairment, and dementia), which are associated with sleep disturbance and negative mood [5,6]. Compared with thoracotomy, video-assisted thoracoscopic surgery (VATS) is increasingly used as an alternative to thoracotomy lobectomy in the treatment of early-stage NSCLC, which is characterized by less trauma and less perioperative bleeding, shorter hospital stay and earlier return to normal activities [7,8]. Although potentially less postoperative pain was generally expected as one of the benefits of VATS, many patients still suffer moderate to severe pain postoperatively [9]. Previously, several factors such as preoperative pain, negative mood and type of surgery have been identified contributing to the development of severe postoperative pain. However, most of them are focused on the social psychological and clinical factors that contributing to the development of severe postoperative pain, individual sex difference is not fully discussed. Many epidemiological studies demonstrated that due to differences in hormone levels between men and women, there are approximately three times as many females suffering from thyroid cancer as males, however, male gender is reported to be a poor prognostic factor in papillary thyroid carcinoma, with male gender was significantly associated with central lymph node metastasis. Moreover, healthy women may have significantly lower pain threshold and tolerance for electrical, pressure and thermal stimuli [10–13]. Previous studies evaluating postoperative pain have demonstrated that female gender is a risk factor for intense postoperative pain compared with male gender after open cholecystectomy and pacemaker implant, but the findings are inconsistent [14,15]. Detailed data on gender differences after VATS are lacking. The purpose of our study was to investigate the effect of gender on postoperative pain, sleep quality, and recovery outcomes in patients undergoing VATS surgery under general anesthesia. Early identification of patients at risk may help to allow early application of effective treatment strategies to prevent unexpected suffering in these patients.

2. Materials and methods

The prospective observational study enrolled patients received VATS between May 2021 and February 2022. Written informed consent was obtained from all the patients. The study was registered on [Clinicaltrials.gov](https://clinicaltrials.gov) (NCT04608435) before the patients were enrolled. Participants who received elective VATS at Shengjing Hospital of China Medical University were consecutively included in this study. The inclusion criteria were as follows: (1) patients with American Society of Anesthesiologists grades I–II; (2) patients aged 18–75 years. (3) No neoadjuvant or adjuvant chemotherapy was performed before surgery; (4) No drugs affecting hematological data were taken before surgery. (5) No acute or chronic inflammatory diseases, anti-inflammatory or immunosuppressive drugs were used within 3 months before surgery; (6) Normal liver function. The exclusion criteria are as follows: (1) Patients with central nervous system and psychiatric diseases; (2) Patients with a history of preoperative sleep disorders and chronic pain; (3) Patients with a history of sedative, analgesic, and antidepressant drug use; (4) Patients with sleep apnea or obstructive sleep apnea-hypopnea syndrome.

3. Anesthesia, surgical and post-anesthetic care protocol

General anesthesia was induced with propofol (2.0–2.5 mg/kg), sufentanil (0.1–0.3 µg/kg), and rocuronium bromide (0.6–1.0 mg/kg). Orotracheal intubation was performed 3 min later with a double-lumen tube under video laryngoscopic guidance. End-tidal carbon dioxide pressure was maintained between 35 and 45 mmHg. Intraoperative anesthesia was administered as follows: 2–5 mg/kg/h continuous infusion of propofol and 0.1–0.2 µg/kg/min remifentanyl to maintain sedation and analgesia; and inhaled sevoflurane (0.5–2%) to maintain minimum alveolar concentration (MAC) \geq 0.7. Ramosetron (0.3 mg) was given prophylactically, and ketorolac tromethamine 45 mg was given 30 min before surgery to relieve postoperative pain. Before chest wall closure, 0.1 % ropivacaine solution (7 ml each) was infused proximally to the fourth, fifth, and sixth intercostal nerves under thoracoscopic guidance. All patients were transferred to the post-anesthesia care unit until full recovery of consciousness. The patient-controlled analgesia (PCA) system was attached after surgery (propanatamol hydrochloride 3g, protoxestron mesylate 12 mg and nalbuphine 1 mg/kg in 100 ml saline, continuous pumping at 2 ml/h, every pump press resulting in a 2 ml infusion with a 15-min lockout interval if the patient self-reported postoperative pain with VAS \geq 4).

4. Outcomes

4.1. Primary observation outcomes

The patients, attending anesthesiologists, surgeons, and data collector were all blinded to the assignment. Postoperative pain intensity was measured by using the visual analog scale (VAS). Conducting of VAS, the patient is asked for visualization of his pain as a point on 10 cm line presented on paper, The higher the score, the more severe the pain is (0–4 mm: No pain, 5–44 mm: mild pain, 45–75 mm: moderate pain, 75–100 mm: severe pain). The data collector was responsible for rest and coughing pain, which were recorded on the day before surgery, 3 h postoperatively, and 24 h on the first day after surgery [16]. The total dose of PCA was also

recorded 24 h on the first day after surgery.

5. Secondary observation outcomes

The same data collector was also responsible for postoperative sleep quality. Postoperative sleep quality was measured by the Athens Insomnia Scale (AIS) score on the night before surgery (Sleep Pre 1), the first night after surgery (Sleep POD 1) and the third night after surgery (Sleep POD 3) [17,18]. The AIS is a self-administered psychometric instrument consisting of eight items. Each item of the AIS can be rated 0 ± 3 , (with 0 corresponding to “no problem at all” and 3 “very serious problem”, 0 to 24 points, with ≥ 6 points indicating a diagnosis of insomnia). Perioperative peripheral blood inflammatory markers system inflammation Index (SII): platelet count \times neutrophils number/lymphocyte count was recorded on the second day before surgery and first day after surgery. Adverse effects within 24 h after surgery, such as hypotension, bradycardia, nausea and vomiting, and dizziness were also collected and treated.

5.1. Statistical analyses

SPSS 23.0 and GraphPad Prism 6.0 software were used for the statistical analyses of study data. Quantitative data are presented as means \pm standard deviations, and the comparison between Male Group and Female Group was performed with independent sample *t*-tests. We constructed multivariate proportional odds logistic models to determine which factors were related to postoperative pain

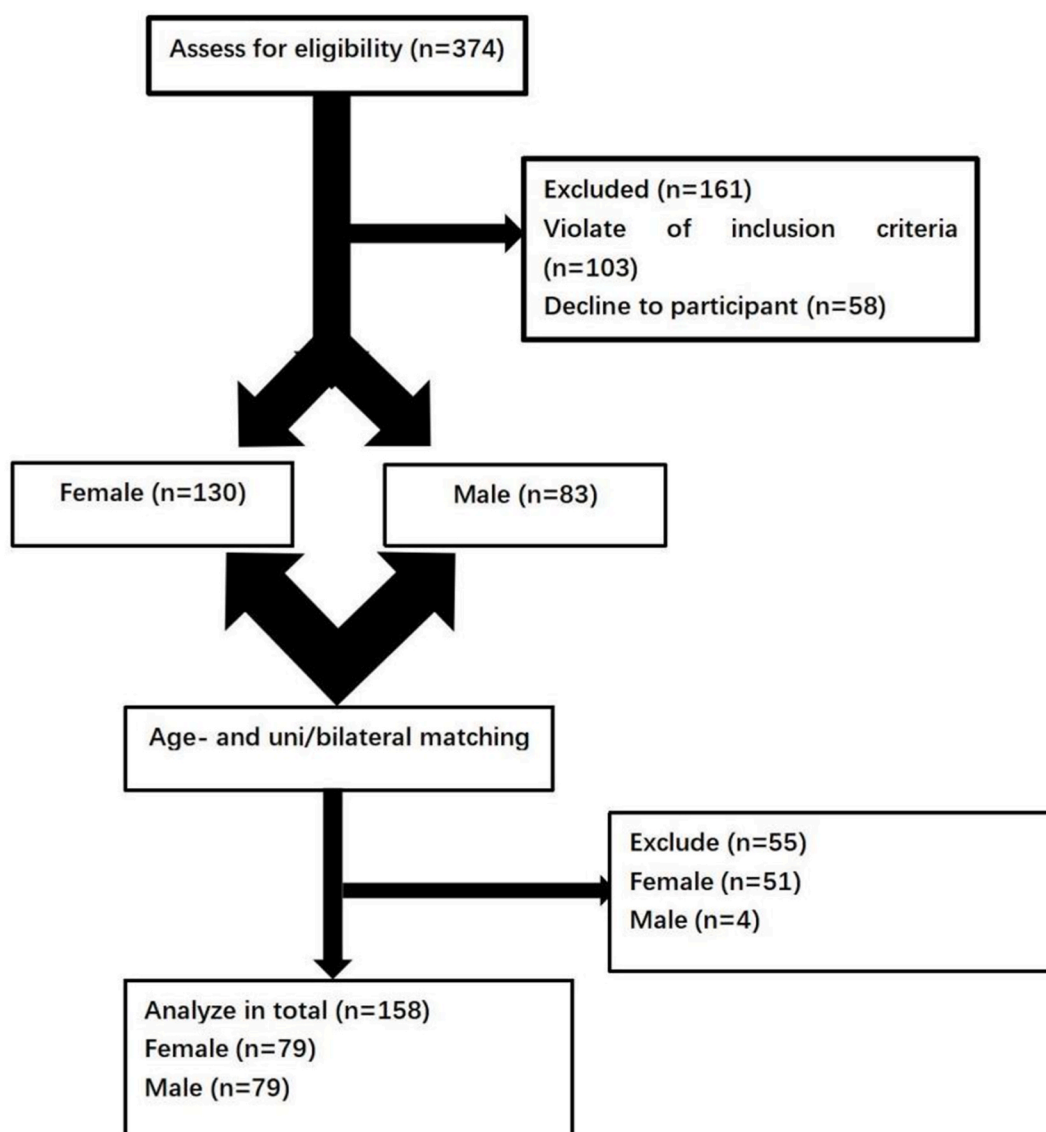


Fig. 1. Flow diagram showing the patients that were included and excluded in this study.

level. Use chi-square test to analyze qualitative data. $P < 0.05$ was considered to be statistically significant.

6. Results

6.1. Demographic characteristics

374 participants received VATS. Among them, 161 participants were excluded due to one or more of the exclusion criteria. In the 213 eligible participants (83 males and 130 females), the males and the females were matched for both age (within ± 1 years). During the procedure, 4 males and 51 females were excluded because an age-matched partner was not available, and 79 males and 79 females were consecutively included in this prospective cohort study. The flow chart is shown in Fig. 1.

No statistically differences were found between the two groups in patients' age ($p = 0.931$), total dose of propofol (mg) ($p = 0.394$), total dose of remifentanyl (mg) ($p = 0.347$), duration of surgery ($p = 0.621$), duration of anesthesia ($p = 0.918$), type of surgery ($p = 0.466$), number of endoscopic ports ($p = 0.528$), bleeding volume ($p = 0.166$) and intraoperative fluid volume ($p = 0.260$). Male's BMI were significantly higher than female's BMI ($p = 0.006$) (Table 1).

6.2. Sex differences in postoperative pain and perioperative peripheral blood inflammatory response

There was no significant difference in VAS score during rest and coughing on the day before surgery between the two groups ($p = 0.315$; $p = 0.151$). Women scored significantly higher VAS pain during rest and coughing at 3 h after surgery compared with men (3.85 ± 1.2 vs. 3.16 ± 1.1) (rest) ($p < 0.001$) and 5.10 ± 1.3 vs. 4.46 ± 1.6 (coughing) ($p = 0.006$) (Table 2). Women's postoperative VAS pain score (coughing) at 24 h on the first day after surgery was still significantly higher compared with men ($p = 0.002$) but not during rest ($p = 0.247$). The total dose of PCA in the female group was more than that in the male group ($p < 0.001$). As for perioperative peripheral blood inflammatory response, no differences were found in SII on the second day before surgery between the two groups ($p = 0.128$). In both groups, postoperative SII was increased and statistically significant compared to preoperative SII ($p < 0.001$, respectively) (Fig. 2). Women presented higher levels of SII on the first day after surgery, and the increase of postoperative SII in females groups was significantly higher than that in male group when compared to preoperative SII (1806.33 ± 1314.8 vs 1430.55 ± 958.4) ($p = 0.042$).

6.3. Sex differences in postoperative sleep quality and postoperative adverse effects

Patients suffered from obvious sleep disturbance after surgery. Compared to Sleep-preop 1, a significant higher AIS subjective sleep quality were presented at Sleep POD 1 and Sleep POD 3 in both of the two groups ($p < 0.001$ respectively). In addition, no differences were found in the AIS scores at Sleep-preop 1 between patients in the male group and female group ($p = 0.503$). Patients in the male group had significantly lower AIS scores than those in the female group at Sleep POD 1 and Sleep POD 3 ($p = 0.024$ and $p = 0.045$) (Fig. 3). The incidence rate of postoperative nausea and vomiting was higher in the female group than that in the male group ($p < 0.001$). No significant differences were found in other adverse effects such as dizzy, polypnea and bradycardia ($p = 0.151$, $p = 0.632$, $p = 0.316$) (Table 2).

6.4. The association between relevant factors and VAS pain after surgery

As shown in Table 3, we included sex, type of surgery, number of endoscopic ports, duration of surgery and preoperative sleep

Table 1

Comparison of demographic characteristics between the two groups.

	Male Group (n = 79)	Female Group (n = 79)	P
Age (years)	58.19 \pm 9.2	58.32 \pm 9.2	0.931
BMI (Kg/m ²)	25.11 \pm 3.8	23.53 \pm 3.4	0.006
Intraoperative fluid input volume (ml)	830.38 \pm 386.1	774.05 \pm 216.6	0.260
Total dose of propofol (mg)	522.56 \pm 110.5	506.19 \pm 129.4	0.394
Total dose of remifentanyl (mg)	1.29 \pm 0.5	1.36 \pm 0.5	0.347
Duration of surgery (min)	111.85 \pm 46.1	108.41 \pm 41.1	0.621
Duration of anesthesia (min)	132.01 \pm 48.5	132.76 \pm 42.1	0.918
Type of surgery (n,%)			0.466
Thorascopic wedge resection of the lobectomy	32 (40.5)	32 (40.5)	
Thorascopic lobectomy of lung	43 (54.4)	39 (49.4)	
Thorascopic mediastinectomy	4 (5.1)	8 (10.1)	
Number of endoscopic ports (n,%)			0.528
Single-hole thoracoscopy	28 (35.4)	23 (29.1)	
Double-hole thoracoscopy	33 (41.8)	40 (50.6)	
Three-hole thoracoscopy	18 (22.8)	16 (20.3)	
Intraoperative bleeding volume (ml)	65.70 \pm 91.2	50.71 \pm 29.4	0.166

Note: variables were presented as Mean \pm SD or frequency (percentage).

Table 2

Degree of postoperative pain and incidence of adverse effects between the Male Group and Female Group.

	Male Group (n = 79)	Female Group (n = 79)	P
VAS scores			
One day before surgery (Rest)	0.03 ± 0.2	0.08 ± 0.4	0.315
One day before surgery (Coughing)	0.22 ± 0.6	0.38 ± 0.8	0.151
3 h postoperatively (Rest)	3.16 ± 1.1	3.85 ± 1.2	<0.001
3 h postoperatively (Coughing)	4.46 ± 1.6	5.10 ± 1.3	0.006
24h on the first day after surgery (Rest)	2.09 ± 0.9	2.25 ± 0.9	0.247
24h on the first day after surgery (Coughing)	2.66 ± 1.1	3.23 ± 1.1	0.002
Total PCA dose at 24 h after surgery	53.53 ± 4.8	57.73 ± 4.7	<0.001
Adverse effects			
Nauseated and vomiting, n (%)	7 (8.9)	27 (34.2)	<0.001
Dizzy, n (%)	7 (8.9)	13 (16.5)	0.151
polypnea, n (%)	9 (11.4)	11 (13.9)	0.632
Bradycardia, n (%)	1 (1.3)	0 (0)	0.316

Notes: VAS: visual analog scale; PCA: patient control analgesia; variables were presented as Mean ± SD or frequency (percentage).

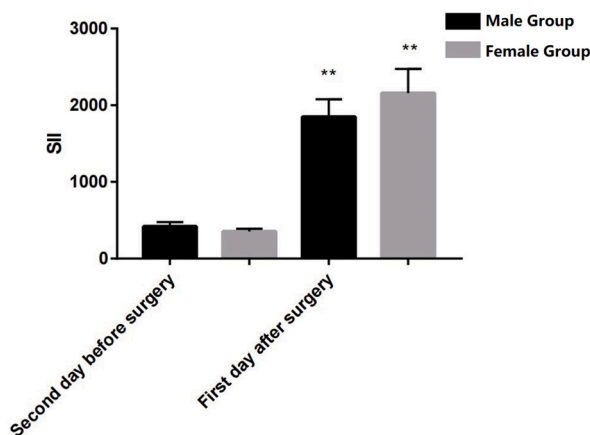


Fig. 2. Comparison of SII during perioperative periods in the two groups. SII: Perioperative peripheral blood inflammatory markers system inflammation Index. In the same group, ** vs the previous time point: $p < 0.001$.

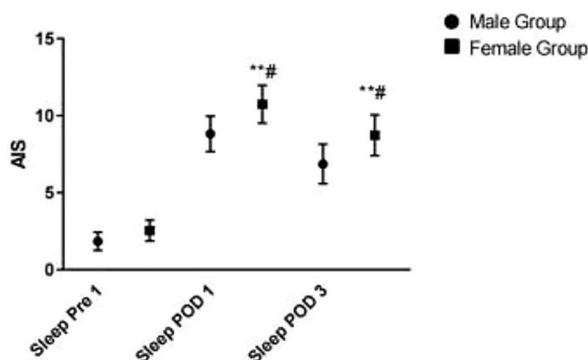


Fig. 3. Comparison of AIS scores between the female group and the male group. AIS: The Athens Insomnia Scale; Sleep-preop 1: the first night before surgery; Sleep POD 1: the first night after surgery; Sleep POD 3: the third night after surgery. In the same group, ** vs the previous time point: $p < 0.001$. At the same time point, # vs the Male Group: $p < 0.05$.

quality to construct a multivariate logistic regression equation. After setting rest VAS pain score (≤ 4) as a reference, we found that sex difference was an independent risk factor which was correlated with postoperative pain, and male are less likely to experience pain after surgery than female (OR = 0.246, 95 % CI = 0.101–0.6; $p = 0.002$). However, information regarding the surgical procedures such as type of surgery, number of endoscopic ports and duration of surgery and preoperative sleep quality showed no significant correlation with postoperative pain ($p > 0.05$, respectively).

Table 3
The association between relevant factors and VAS pain after surgery.

	Variables	OR (95 % CI)	P value
Rest VAS pain(>4) at 3h after surgery	Constant		0.604
	Sex		
	male	0.246 (0.101–0.6)	0.002
	female	Reference.	.
	Type of surgery		
	Thoracoscopic wedge resection of the lobectomy	0.506 (0.119–2.155)	0.357
	Thoracoscopic lobectomy of lung	0.749 (0.163–3.429)	0.709
	Thoracoscopic mediastinectomy	Reference.	.
	Number of endoscopic ports		
	Single-hole thoracoscopy	1.085 (0.301–3.910)	0.901
	Double-hole thoracoscopy	0.891 (0.290–2.740)	0.841
	Three-hole thoracoscopy	Reference.	.
	Duration of surgery		
	>2h	1.162 (0.497–2.719)	0.729
	≤2h	Reference.	.
Preoperative sleep quality			
AIS score ≥6	1.803 (0.652–4.989)	0.256	
AIS score <6	Reference.	.	

Notes: VAS: visual analog scale.

7. Discussion

In view of the increasing amount of VATS in the present years, it is important to understand the risk factors for poor prognosis after the operation. In our prospective cohort study, we examined the effects of sex on perioperative inflammatory response, postoperative sleep quality and recovery outcomes among patients undergoing VATS. We found that sleep disturbances, increased inflammation and VAS scores were commonly seen after surgery. And women had worse sleep quality, higher postoperative inflammatory response level and higher pain level than men.

Complete surgical resection is still the gold standard for the curative treatment of early stage non-small cell lung cancer in physiologically suitable patients. In the past two decades, VATS has become a minimally invasive procedure with less tissue trauma, improved postoperative respiratory function, and enhanced patient tolerance [19]. Acute pain following VATS is not rare because of multiple muscle incisions and irritation of the pleura with chest tubes. The incidence of pain in patients undergoing VATS surgery varies widely among related studies, which may be related to different patient characteristics, different types of surgery, and different follow-up periods [20]. Our findings showed that pain scores were highest in both groups at rest and cough at 3 h postoperatively, and then gradually decreased at subsequent time points, but still statistically significant compared to previous time points in each group. Postoperative pain is not only related to inflammation reaction that inflammatory cytokines play an important role in neuronal remodeling and enhancement of nociceptive sensory transduction, and postoperative chronic pain can also lead to cognitive impairment, memory loss and sleep disturbances [21–25]. Recently, a new comprehensive systemic immune-inflammatory index (SII) based on neutrophil, platelet and lymphocyte counts was developed to adequately reflect the balance of host immune and inflammatory status [26,27]. Recently studies have shown that SII is a relatively non-invasive and inexpensive independent prognostic marker for overall survival, disease-free survival, and freedom from recurrence in patients with stage III NSCLC undergoing neoadjuvant chemoradiotherapy followed by surgical resection, SII holds promise in predicting patient prognosis, guiding individualized treatment plans, reducing tumor recurrence and metastasis, and improving the quality of life for NSCLC patients [28,29]. Moreover, one study shows that sleep-related disorders had a stronger correlation with SII [30]. Thus, in this experiment, we also observed the changes in postoperative inflammation of patients by assessing the levels of SII. We found that the postoperative SII levels of the two groups increased compared with those before the operation, and the levels of SII was the higher on the first day after the operation. This result corresponds to an increase in pain scores.

Furthermore, the sex differences observed in this study highlight the importance of sex in different postoperative outcomes. Sex difference was an independent risk factor which was correlated with postoperative pain, male are less likely to experience pain after surgery than female. We found that except similar preoperative pain scores, women scored significantly higher VAS pain during rest and coughing at 3 h after surgery compared with men. Women's postoperative VAS pain score at 24h on the first day after surgery during coughing was still significantly higher compared with men but not during rest, which was similar to Nandi M et al.'s findings [31]. Many previous studies have also found higher rates of pain in women than men, increased sensitivity to painful stimuli, and a greater impact of pain on function [32–34]. The possible reasons may be due to that 1) sex differences in pain and analgesia requirements could be explained through gonadal hormones, genetic susceptibility, immune response, pharmacokinetics (liver metabolism and membrane transport) and endogenous pain regulation system [35,36]. 2) as mentioned earlier, it seems that female are more likely to feel greater sensitivity of pain than male. And women's higher sensitivity of early postoperative pain would not be reduced by increased doses of opioids postoperatively [37]. Conversely, in our study, opioids may have been a contributing factor to vomiting and discomfort in women compared with men [38].

In addition, in our study, we also proved that women are at higher risk for worse postoperative sleep quality with higher AIS scores at Sleep POD 1 and Sleep POD 3 than men. Women presented higher levels of SII on the first day after surgery, and the increase of

postoperative SII in females groups was significantly higher than that in male group. Besides sex was significantly associated with inflammation levels and sleep quality [39], pain can also prolong sleep latency and reduce total sleep duration, while sleep disorders can increase pain sensitivity and lower pain threshold or even the level of pain on the second day can be predicted by postoperative sleep quality [40]. Furthermore, similar to the study by Dolan R et al. [41], we found that female patients had poorer sleep quality and higher AIS scores, which may be due to the higher incidence of postoperative nausea and vomiting in female patients [42]. Thus, it is important to identify risk/protective variables that shape the experience of pain in the days and weeks following surgery. The present study found that women had worse sleep quality, higher postoperative inflammatory response level and pain level than men, which highlight the complex multidimensional nature of postoperative pain, nausea and vomiting, sleep quality and the potential contributory role of sex in shaping these outcomes. Further studies are needed to develop and deliver targeted, personalized treatments that can reduce the incidence and impact of persistent postoperative pain among patients with different sex and characteristics.

There are some limitations in this study. Factors such as anxiety, genetic polymorphism, and preoperative pain threshold are predictive factors of postoperative pain and analgesic requirement and were not studied in this research project. And although we tried to minimize interference factors on postoperative sleep quality such as light, noise, or interruptions due to nursing care at night in our study, they might also have other unavoidable factors which may affect postoperative sleep quality. The small sample and single-institution experience limit generalizability of the study findings.

8. Conclusion

These findings highlight the complex multidimensional nature of postoperative pain, nausea and vomiting, sleep quality, and the potential contribution of sex in shaping these outcomes. Equipped with this knowledge, researchers and clinicians will be one step closer to designing precision pain medicine strategies that consider the complexities of a person's sex and gender. We also need to pay more attention on these patients' postoperative recovery to relieve their postoperative pain level and improve their postoperative sleep quality. Overall, early identification of patients at risk may help to allow early application of effective treatment strategies to prevent unexpected suffering in these patients.

Consent for publication

All authors approved the final manuscript and the submission to this journal.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Ethics

The study was approved by the Human Research Ethics Committee of Shengjing Hospital, Shenyang, Liaoning, China (Institutional Review Board registration number 2021PS612K).

CRedit authorship contribution statement

Hongyu Wang: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Man Luo:** Writing – original draft, Resources, Formal analysis, Data curation, Conceptualization. **Yanping Yang:** Software, Resources, Formal analysis, Data curation. **Shiyi Li:** Software, Resources, Data curation. **Song Liang:** Validation, Resources. **Ran Xu:** Visualization, Supervision. **Junchao Zhu:** Project administration, Methodology, Funding acquisition, Conceptualization. **Bijia Song:** Writing – review & editing, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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