Incidence and Risk Factors for Chronic Postsurgical Pain Following Video-assisted Thoracoscopic Surgery: a Retrospective Study

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Research Article

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Abstract

Backgroud: Video-assisted thoracoscopic surgery (VATS) has been widely used as an alternative for thoracotomy, but the reported incidence of chronic postsurgical pain (CPSP) following VATS varied widely. The purpose of this study was to investigate the incidence and risk factors for CPSP after VATS.

Methods: We retrospectively collected preoperative demographic, anesthesiology, and surgical factors in a cohort of patients undergoing VATS between January 2018 and October 2020. Patients were interviewed via phone survey for pain intensity, and related medical treatment 3 months after VATS. Univariate and multivariate analysis were used to explore independent risk factors associated with CPSP.

Results: 2,348 patients were included in our study. The incidence of CPSP after VATS were 43.99% (n = 1,033 of 2,348). Within those suffering CPSP, 14.71% (n = 152 of 1,033) patients reported moderate or severe chronic pain. Only 15.23% (n = 23 of 152) patients with moderate to severe chronic pain sought active analgesic therapies. According to multivariable analysis, age ≥ 65 years (OR 1.278, 95% CI 1.057-1.546, $P = 0.011$), female (OR 1.597, 95% CI 1.344-1.898, $P < 0.001$), education level less than junior school (OR 1.295, 95% CI 1.090-1.538, $P = 0.003$), preoperative pain (OR 2.564, 95% CI 1.696-3.877, $P < 0.001$), consumption of rescue analgesia postoperative (OR 1.248, 95% CI 1.047-1.486, $P = 0.013$), consumption of sedative hypnotic postoperative (OR 2.035, 95% CI 1.159-3.574, $P = 0.013$), subcutaneous emphysema of chest wall postoperative (OR 1.255, 95% CI 1.000-1.575, $P = 0.050$), and history of postoperative wound infection (OR 5.949, 95% CI 1.344-1.898, $P < 0.001$) were independent risk factors for CPSP development.

Conclusions: CPSP remains a challenge in clinic because half of patients may develop CPSP after VATS.

Trial registration: Chinese Clinical Trial Registry (ChiCTR2100045765), 2021/04/24

Introduction

Chronic postsurgical pain (CPSP) is defined as chronic pain that develops or increases in intensity after a surgical procedure or a tissue injury and persists beyond the healing process, ie at least 3 months after the surgery or tissue trauma by International Classification of Diseases-11 (ICD-11) [1], and its incidence varies from 3–85% according to surgery type [2]. As traumatic as thoracotomy, the reported incidence of CPSP can be up to 57% [3]. Since video-assisted thoracoscopic surgery (VATS) was introduced into clinical practice in the early 1990s, it has been widely used as an alternative to thoracotomy over the past 30 years [4]. Though it was considered less injury than thoracotomy and with relief of postoperative acute pain, the incidence of CPSP after VATS has been reported to range from 7.7–50% [1]. Limited by small sample size and inconsistent follow-up time, the reported incidence of CPSP following VATS varies widely and we can't reach a comprehensive summary about the occurrence of CPSP after VATS at present.

The aetiology of CPSP after VATS is multifactorial and may involve both patient- and treatment-related factors. Although some studies have examined perioperative risk factors for the development of CPSP

after VATS, most of them focused on a limited number of variables [5–7]. Since CPSP has been associated with long-term opioids use, unnecessary psychological pressure and reduced quality of life, identifying risk factors related to CPSP after VATS will be helpful for clinicians to carry out targeted prevention and help patients to form appropriate expectations [8].

Based on the above reasons, the primary aim of this study was to investigate the incidence of CPSP after VATS in a large sample of patients. The second aim was to identify independently predictors of CPSP from a comprehensive evaluation of demographic, anesthesiology, and surgical factors in a retrospective cohort.

Methods

Study design and population

This retrospective, observational study was approved by the Institutional Review Board (IRB) for Clinical Investigations at Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School (2020-297-02) and retrospective requirement for written informed consent was waived. This study was registered at Chinese Clinical Trial Registry (ChiCTR2100045765). Patients who underwent VATS between January 2018 and December 2020 at our institution (Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School) were identified. Study inclusion criteria were as follows: (1) age ≥ 18 years; (2) American Society of Anesthesiologists(ASA) □-□ grade; (3) non-emergency VATS surgery. The exclusion criteria were as follows: (1) patients with previous thoracodorsal surgery; (2) patients underwent bilateral surgery or converted to thoracotomy; (3) patients who developed □/□/□ complications according to Clavien-Dindo grade system; (4) patients with inadequate medical records perioperatively.

Data collection

Data on demographics, medical history, anesthesia/surgery related parameters, perioperative pain-related parameters were collected from an electronic medical records retrieval system.

Total intravenous anesthesia protocol was performed. No premedication was administered before surgery. Anesthesia was induced by intravenous midazolam 0.05 mg/kg, 1% propofol 1–2 mg/kg (or etomidate 0.3–0.5 mg/kg), fentanyl 3–8 μg/kg, vecuronium bromide 0.08–0.12 mg/kg. Double-lumen endotracheal intubation was performed under visual laryngoscope. Anesthesia was maintained with continuous infusion of propofol 4–12 mg/kg/h, remifentanil 0.05–0.2 μg/kg/min, cisatracurium 1–3ug/kg/min. Intravenous patient-controlled analgesia consisted of a combination of sufentanil 1 μg/mL, ondansetron 8 mg, and dexmedetomidine 10 mg at a continuous infusion rate of 2 mL/hour and a bolus of 0.5mL with a lockout interval of 15 min. Based on the anesthesia record sheet, whether using nerve block, dexmedetomidine, and sevoflurane, dosage of fentanyl and remifentanil per kilogram, and intraoperative blood transfusion were collected.

VATS was performed by a two-port technique, one port was used as an operating hole and the other as an observation hole. The location of the chest wall incision was selected by surgeons according to the clinical features of patient's lesion. At the end of surgery, the chest tube was disposed for postoperative thoracic drainage. The etiology of the operation, duration of the operation, whether lymph node dissection was performed and the amount of intraoperative blood loss were collected according to the surgery records.

If there were no contraindications, all patients received intravenous injection of propacetamol hydrochloride after operation routinely. If patients complained severe pain, surgeons choosed indomethacin, flurbiprofen axetil injection, codeine phosphate, pethidine or tramadol as rescue analgesics according to the patient's pain severity. The use of rescue analgesics was extracted from the electronic medical system.

The primary outcome was whether CPSP developed after VATS. Patients were contacted by telephone about whether they felt pain at or around the surgical incision 3 months after VATS. The intensity and the relevant treatment measures were recorded. Pain intensity was evaluated by Numerical Rating Scale (NRS), with 0 representing painless and 10 representing unbearable pain. The peak value of pain (when rest,coughing, moving or others) was recorded. Pain score ≥ 1 were diagnosed as CPSP according to ICD-11 [9]. The relevant pain treatment measures were rated as no treatment, having a rest or reducing daily activity, taking medicine on themselves and asking help from doctors [10].

Statistical analysis

Data were analyzed using SPSS 19.0 (SPSS, Inc., Chicago, IL, USA). The results were expressed as means ± standard deviation for continuous variables or as number and percentages for categorical variables. The independent t test or Mann-Whitney U-tests were used for between-group testing, depending on the distribution of the variables. Chi-square test tests or Fisher’s exact tests were applied for categorical variables.

Univariable logistic regression analysis was applied to examine predictors of CPSP after VATS, and candidate covariates were chosen based on statistical significance or possible clinical importance. Multivariate model was developed using a stepwise forward approach. The discriminatory power of the multivariate model was evaluated by using the area under the receiver operating characteristic curve and its 95% confidence interval (CI). The calibration of the multivariate model was evaluated using the Hosmer-Lemeshow goodness-of-fit statistic, where a high *P*-value indicates good calibration. A significance level of 5% ($P < 0.05$), and confidence intervals of 95% were used [11].

Results

Of 3,147 patients who were screened for inclusion, 2,738 met the inclusion criteria. When we attempted to contact these patients and assess their postoperative pain, 348 patients were excluded due to unanswered phone calls/refusal to answer, and 42 were excluded due to death. Finally, 2,348 patients

were included in our analysis (Fig. 1). According to the CPSP definition from ICD-11, 43.99% (n = 1,033 of 2,348) patients reported characteristics of CPSP after surgery with approximately 14.71% (n = 152 of 1,033) reported moderate to severe pain (NRS > 3). Within those who reported moderate to severe pain, 22.52% (n = 34 of 152) did not take any treatment, 62.25% (n = 94 of 152) relieved their pain by resting or reducing activity, only 15.23% (n = 23 of 152) sought active analgesic therapies (medicine or consultation to doctors).

Sociodemographic and medical history of patients were presented in Table 1. Factors associated with CPSP included age, sex, smoking history, drinking history, education level, and preoperative pain ($P < 0.05$).

Data about surgery and anesthesia were summarized in Table 2. Statistically significant differences were observed, including the consumption of fentanyl dose per kilogram (μg/kg), blood loss volume intraoperative (ml/kg), the consumption of rescue analgesia postoperative, the consumption of sedative hypnotic postoperative, and history of postoperative wound infection ($P < 0.05$).

Based on statistical significance or possible clinical implication, variates with $P < 0.25$ in the univariate analysis were entered in the multivariate model. As showed in Fig. 2, eight risk factors were identified for CPSP after VATS: age < 65 years (OR 1.278, 95% CI 1.057–1.546, $P = 0.011$), female (OR 1.597, 95% CI 1.344–1.898, P < 0.001), education level less than junior school (OR 1.295, 95% CI 1.090–1.538, $P = 0.003$), preoperative pain (OR 2.564, 95% CI 1.696–3.877, $P < 0.001$), consumption of rescue analgesia postoperative (OR 1.248, 95% CI 1.047–1.486, $P = 0.013$), consumption of sedative hypnotic postoperative (OR 2.035, 95% CI 1.159–3.574, $P = 0.013$), subcutaneous emphysema of chest wall postoperative (OR 1.255, 95% CI 1.000-1.575, $P = 0.050$), and history of postoperative wound infection (OR 5.949, 95% CI 1.344–1.898, $P < 0.001$) .

The predictive model for CPSP after VATS yield the area under the receiver operating characteristic curve of 0.622 (95% CI 0.599–0.644) (Fig. 3), and the model showed good calibration by Hosmer-Lemeshow goodness-of-fit statistic with $X^2 = 4.956$, $P = 0.665$.

Table 1
Sociodemographic and medical history of subjects without and with CPSP (n = 2,348)

Variables	Non-CPSP (n = 1,315)	CPSP (n = 1,033)	P value
Age, n (%)			**0.008**
< 65	897 (68.2)	757 (73.3)	
≥ 65	418 (31.8)	276 (26.7)	
Female, n (%)	627 (47.7)	623 (60.3)	**< 0.001**
BMI, n (%)			0.076
< 24 kg/m^2	722 (54.9)	605 (58.6)	
≥ 24 kg/m^2	593 (45.1)	428 (41.4)	
ASA, n (%)			0.118
□/□	156 (11.9)	98 (9.5)	
□	1,159 (88.1)	931 (90.5)	
Smoking history, n (%)	200 (15.2)	121 (11.7)	**0.014**
Drinking history, n (%)	143 (10.9)	84 (8.1)	**0.026**
Hypertension, n (%)	358 (27.2)	273 (26.4)	0.666
Diabetes mellitus, n (%)	128 (9.7)	92 (8.9)	0.494
CHD, n (%)	36 (2.7)	20 (1.9)	0.206
Surgery history, n (%)	413 (31.4)	413 (31.2)	0.903
Preoperative pain, n (%)	36 (2.7)	75 (7.3)	**< 0.001**
Education level less than junior school, n (%)			
	658(50.0)	591(57.2)	**0.001**
Consumption of sedative hypnotic preoperative, n (%)			
	458 (34.8)	338 (32.7)	0.284

Table 2
Surgery and anesthesia data of subjects without and with CPSP (n = 2,348)

Variables	Non-CPSP (n = 1,315)	CPSP (n = 1,033)	*P* value
Anesthesia, n (%)			0.492
general anesthesia	965 (73.4)	771 (74.6)	
combined with nerve block	350 (26.6)	262 (25.4)	
Fentanyl dosage (ug/kg)	11.3 ± 4.8	11.0 ± 4.3	**0.044**
Remifentanil dosage (ug/kg)	11.8 ± 10.1	12.1 ± 9.3	0.478
Dexmedetomidine usage, n (%)	1,214 (92.3)	960 (92.9)	0.573
Sevoflurane usage, n (%)	221 (16.8)	199 (19.3)	0.123
PCIA, n (%)	955 (72.6)	763 (73.9)	0.501
Surgical Procedure, n (%)			0.179
lung	1,235 (93.9)	967 (93.6)	
mediastinal	76 (5.8)	57 (5.5)	
others	4 (0.3)	9 (0.9)	
Lymph node dissection, n (%)	603 (56.2)	470 (43.8)	0.863
Duration of surgery (min)	106.4 ± 47.6	107.9 ± 44.9	0.189
Blood loss (ml/kg)	2.0 ± 4.1	1.8 ± 3.5	**0.013**
Infusion volume (ml/kg)	22.7 ± 8.8	22.1 ± 8.0	0.114
Consumption of rescue analgesia postoperative, n (%)			
	450 (34.2)	411 (39.8)	**0.005**
Consumption of sedative hypnotic postoperative, n (%)			
	22 (1.7)	32 (3.1)	**0.022**
Subcutaneous emphysema postoperative, n (%)			
	210 (16.0)	185 (17.9)	0.212
History of postoperative wound infection, n (%)			
	12 (0.9)	57 (5.5)	**< 0.001**
Postoperative pulmonary infection, n (%)			
	31 (2.4)	37 (3.6)	0.079

Variables	Non-CPSP (n = 1,315)	CPSP (n = 1,033)	*P* value
Postoperative WBC (^10^9)	11.4 ± 3.1	11.3 ± 3.3	0.202
Postoperative CRP (mg/L)	52.9 ± 1.0	51.1 ± 1.1	0.205
PONV, n (%)	180 (13.7)	149 (14.4)	0.610

Discussion

In this study, we investigated the incidence of CPSP after VATS in 2,348 patients. Our study showed that the incidence of CPSP was 43.99%. Most CPSP were mild and bearable, and the incidence of moderate-severe CPSP were 14.71%. The results of multivariate logistic regression analysis showed that age < 65 years, female, education level less than junior school, preoperative pain, consumption of rescue analgesia postoperative, consumption of sedative hypnotic postoperative, subcutaneous emphysema of chest wall postoperative, and history of postoperative wound infection were the risk factors of CPSP.

Previously published meta-analysis reported the incidence of CPSP after thoracotomy was 57%, but data about the risk of developing CPSP after VATS were not sufficient to summarize [3, 12]. Morten et al [9] did a randomized controlled trial to compare postoperative quality of life and pain between thoracotomy and VATS and found although VATS was associated with less postoperative pain for the first year after surgery, the incidence of CPSP after VATS was still as high as 30 to 50%. In Bayman et al's [3] prospective observational study, they found no significant difference in the incidence of CPSP between thoracotomy and VATS (47% vs 33%). The high risk of developing CPSP after VATS may be explained by peripheral and central sensitization caused by local trauma, inflammation, or nerve injury [6]. As indicated, the prevalence of CPSP reported in the present study was comparable to them. In addition to the high prevalence of CPSP, we were surprised to find that the majority of patients deal with CPSP in a negative way, only 15.23% of patients with moderate to severe pain sought active analgesic therapies (medicine or consultation to doctors), most of the remaining patients got relief from CPSP by resting or reducing activity. Overall, our results showed that although VATS significantly reduced the iatrogenic injury caused by surgical procedures, the incidence of CPSP after VATS remained high and most patients had a negative attitude towards CPSP management [8].

In terms of demographics data, age < 65 years, female and education level less than junior school were independent risk factors for CPSP. These results were consistent with previously published, known risk factors for CPSP in a variety of surgical procedures, including thoracic surgery [13–15]. A recent meta claimed that patients who developed CPSP after thoracic surgery were tend to be younger than patients without CPSP (mean difference 2.12 years, 95% CI -3.56 to -0.68) and female were found to be at slightly higher risk of CPSP (RR 1.15, 95%CI 1.02–1.30) [16]. The relationship between age and CPSP can be explained by two points. First, young patients are biologically more sensitive to low-intensity noxious stimuli and may having a more heightened central nervous system responsiveness [17]. Second, from a physiological perspective, older adults are more conservative in pain perception and reporting than

younger adults and are more reluctant to report pain when it dose occurs [18]. The association between sex and CPSP can also be explained from these two aspects. From biologically, differences of sex hormone levels, pain-related receptor activity such as *N*-methyl-*D*-aspartic acid receptor or *P*2*X*3 receptor, μ/κ subtype splits in the endogenous analgesic system, and brain structure and function between men and women are related to the mechanism of sex differences in pain perception [8]. And from psychologically, female are more self-conscious and more likely to report pain to others [19]. Association between education level and CPSP has also been proved in several studies, but the specific mechanism is still unclear, pain catastrophizing may be a mediating factor between them [20]. Anyway, the combination of these demographic factors suggests a higher risk of developing CPSP. Recognition of these predictors, although unmodifiable, can help clinicians identify high-risk groups during preoperative evaluation and tailor an individualized pain treatment regimen [21].

As for perioperative pain-related parameters, our findings revealed that preoperative pain, the consumption of rescue analgesics and sedative hypnotic after surgery were independent predictors for CPSP. The association between preoperative pain and CPSP has been reported in several clinical trials. In a prospective study, Bayman et al [3] found those patients who reported higher preoperative pain scores at rest or upon coughing tended to have a higher likelihood of reporting chronic pain related to thoracic surgery at 6 months. Montes et al [14] also reported that preoperative pain at the surgical site and other sites was a risk predictor for the development of postoperative chronic pain in hernia repair, hysterectomy, and thoracotomy, which was confirmed by another risk index for CPSP [22]. The mechanism between preoperative pain and CPSP remains elusive but cumulative evidence has demonstrated that sensitization of the peripheral and central nervous system, which related to the alterations of peripheral nociceptors sensitivity and function of the pain descending inhibitory system may be the possible explanations between them [23]. Since preoperative pain could explain part of the interindividual variance in pain sensitivity, it may sensitize patients to new painful stimuli [24].

Postoperative use of rescue analgesics is an important indicator of postoperative pain intensity, especially when pain scores are performed only once or twice a day, the need for rescue analgesics helps in revealing the true level of postoperative pain intensity [25]. Limited by the characteristics of the retrospective study, we were unable to collect a detailed information about postoperative acute pain score. Therefore, postoperative consumption of rescue analgesics and sedative hypnotic in hospital were investigated to reflect the existence of postoperative acute pain [2, 25]. Consistent with the thoracic surgery and other postsurgical chronic pain conditions, we reported that postoperative consumption of rescue analgesics and sedative hypnotic in hospital (which indicates a higher severity of acute pain) was associated with a greater risk of developing CPSP [26]. Acute postoperative pain represents actual or potential tissue injury and motivates a response that removes the organism from such noxious stimuli [27]. The more severe the postoperative acute pain, the more severe the tissue injury, and the less adequate the pain control, which may induce peripheral sensitization and neuroplastic changes that involves altered pain processing [28]. Although our results did not show that nerve block reduces the risk of CPSP, the latest meta-analysis did report a meaningful change in the incidence of CPSP by controlling postoperative acute pain through regional anesthesia [29]. Discrepancy between results may be related to

differences in sample size, nerve block technique, and the type of study design. Therefore, the attempts to better manage postoperative acute pain are of great clinical significance in CPSP prevention.

For surgery related parameters, the history of postoperative wound infection and postoperative subcutaneous emphysema of chest wall were independently associated with the occurrence of CPSP.

Postoperative wound infection may be accompanied by severe, persistent, and recurrent inflammation [30]. According to our results, there was no statistically significant difference in the contents of white blood cells, lymphocytes, neutrophils and CRP between the CPSP group and the non-CPSP group after surgery, but this may be related to the fact that we only routinely rechecked relevant biochemical indicators on the first day postoperatively. After discharge, some patients would suffer from out-of-hospital wound infection due to improper nursing or pleural effusion. However, due to the defects of retrospective study, we could not obtain relevant data comprehensively.

In addition, we identified a statistically significant relationship between postoperative subcutaneous emphysema of chest wall and the incidence of CPSP. We diagnosed patients with subcutaneous emphysema of chest wall based on the results of chest radiography (chest computed tomography or chest X-ray) during their postoperative hospitalization. No related literature has been found to prove that subcutaneous emphysema of chest wall is directly related to CPSP. The common causes of subcutaneous emphysema after surgery are leakage of lung tissue and inadequate thoracic drainage [31]. When a patient develops subcutaneous emphysema, the surgeon will extend the indwelling time of the drainage tube or even re-place the thoracic drainage tube after ruling out other causes. The prolonged indwelling time and replacement of thoracic drainage tube may be the possible cause of the increased incidence of CPSP [32]. Since it is the first time an association between subcutaneous emphysema and chronic pain has been found, stronger evidence is needed and the detailed mechanism of the association needs to be further explored. However, this finding reminds us of the importance of patency of postoperative thoracic drainage.

Our study has strengths, including the large sample size and comprehensive range of risk factors collection. However, the results should still be interpreted cautiously for several reasons. First, although we collected relevant data as comprehensive as possible, some potential predictors of CPSP remain missed. Information such as psychological status, the detailed postoperative acute pain score, and prolonged chest tube drainage should be included in future prospective study. And we speculated that the addition of these data may increase the area under the receiver operating characteristic curve. Second, since the incidence of CPSP decreased over time [2], the reported incidence of CPSP of our study may be still underestimated because of the long follow-up time span. Third, for the data collected from in a single institution, the results may be influenced by the selection bias.

Conclusion

Overall, our study found that the incidence of CPSP after VATS was 43.99%. Although the majority of patients reported mild pain, such a high incidence suggests that CPSP after VATS remains an important

challenge that cannot be ignored. In addition, our study found that younger age, female, low education level, preoperative pain, postoperative consumption of rescue analgesics and sedative hypnotic, postoperative wound infection and subcutaneous emphysema of chest wall were important predictors of CPSP, which suggested that clinicians should conducted a throughout evaluation perioperatively in order to identify high-risk groups of CPSP as soon as possible and tailor individualized pain prevention and treatment strategies for them.

Abbreviations

VATS = Video-assisted thoracoscopic surgery;

CPSP = chronic postsurgical pain;

CI = Confidence Interval;

OR = Odds Ratio;

ICD-11 = International Classification of Diseases-11;

IRB = the Institutional Review Board;

ASA = American Society of Anesthesiologists;

NRS = Numerical Rating Scale;

Declarations

Ethics approval and consent to participate

The study was conducted according to the Helsinki Declaration and approved by the ethics community of Institutional Review Board (IRB) for Clinical Investigations at Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School (2020-297-02) and retrospective requirement for written informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

BL H and ZL M contributed to the study conception and design. Material preparation, data collection and analysis were performed by YY Z, RZ, SH T and JH. The first draft of the manuscript was written by YY Z and JZ. All authors read and approved the final manuscript.

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Figures

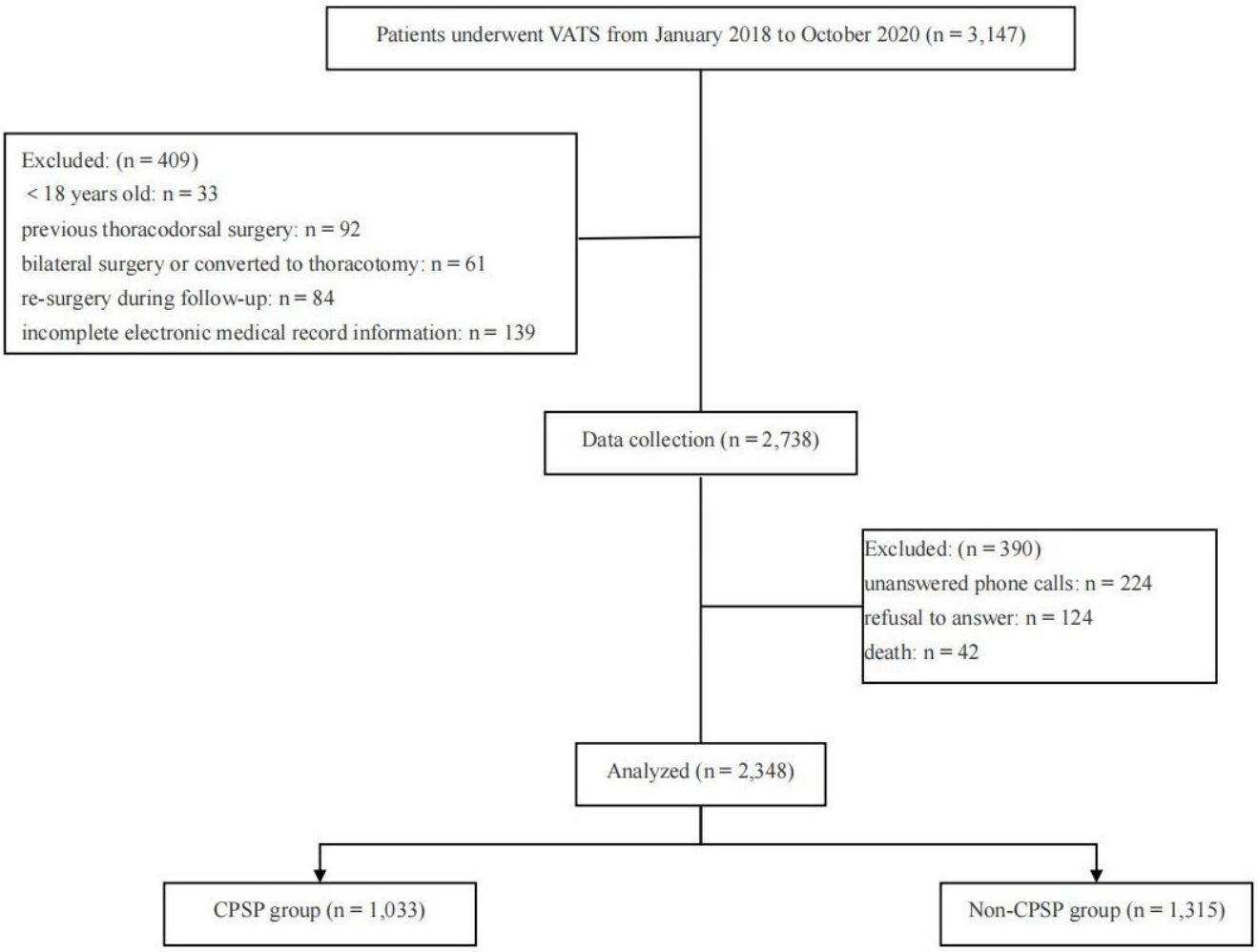

Figure 1

Flow diagram for patient inclusion.

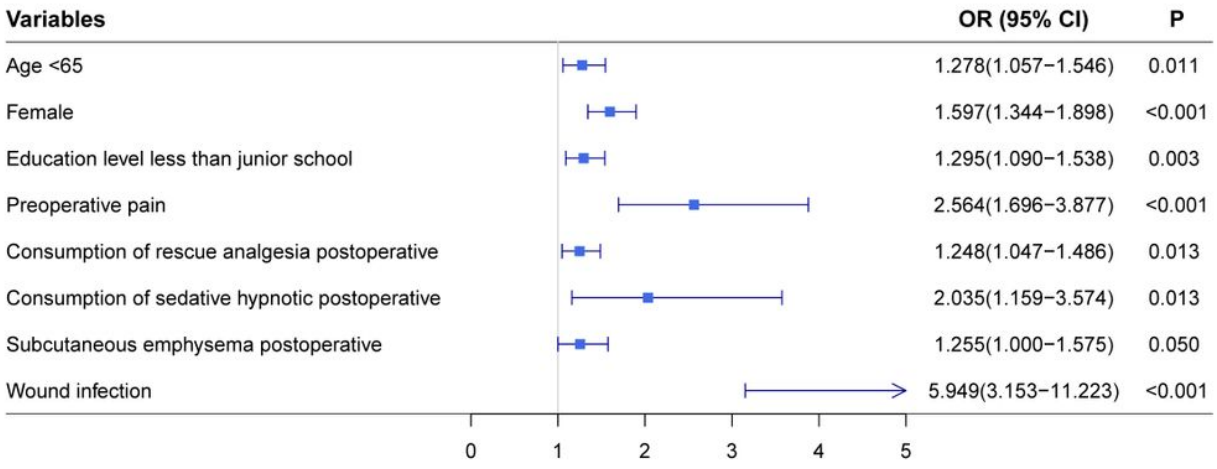

Figure 2

Multivariate model for CPSP after VATS.

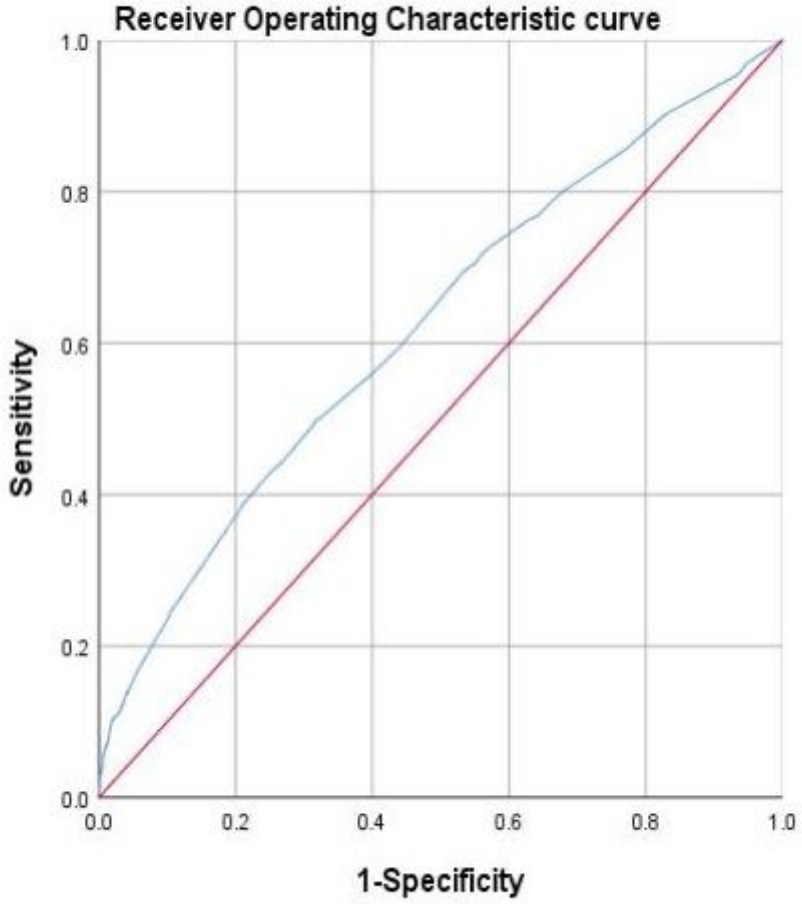

Figure 3

The area under the ROC curve of CPSP multivariate model.