Spontaneous versus mechanical ventilation during video-assisted thoracoscopic surgery for spontaneous pneumothorax: A randomized trial

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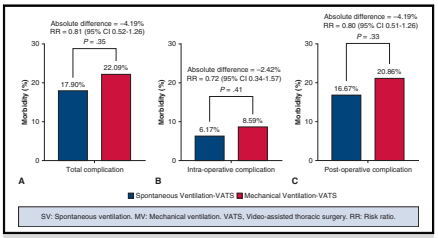
ABSTRACT

Objective: Spontaneous ventilation video-assisted thoracic surgery (SV-VATS) is reported to have superior or equal efficacy on postoperative recovery to mechanical ventilation VATS (MV-VATS). However, perioperative safety of the SV-VATS blebectomy is not entirely demonstrated.

Methods: We performed a noninferiority, randomized controlled trial (No. NCT03016858) for primary spontaneous pneumothorax patients aged 16 to 50 years undergoing a SV-VATS and the MV-VATS procedure. The trial was conducted at 10 centers in China from April 2017 to January 2019. The primary outcome was the comparison of intra- and postoperative complications between SV-VATS and MV-VATS procedures. Secondary outcomes included total analgesia dose, change of vital sign during surgery, procedural duration, recovery time, postoperative visual analog pain scores, and hospitalization length.

Results: In this study, 335 patients were included. There was no significant difference between the SV-VATS group and the MV-VATS group in the intra- and postoperative complication rates (17.90% vs 22.09%; relative risk, 0.81; 95% confidence interval, 0.52-1.26; $P = .346$). The SV-VATS group was associated with significantly decreased total dose of intraoperative opioid agents; that is, sufentanil (11.37 μg vs 20.92 μg; $P < .001$) and remifentanil (269.78 μg vs 404.96 μg; $P < .001$). The SV-VATS procedure was also associated with shorter extubation time (12.28 minutes vs 17.30 minutes; $P < .001$), postanesthesia care unit recovery time (25.43 minutes vs 30.67 minutes; $P = .02$) and food intake time (346.07 minute vs 404.02 minutes; $P = .002$). Moreover, the SV-VATS procedure deceased the anesthesia cost compared with the MV-VATS ($297.81 vs $399.81; $P < .001$).

Conclusions: SV-VATS was shown to be noninferior to MV-VATS in term of complication rate and in selected patients undergoing blebectomy for primary spontaneous pneumothorax. (J Thorac Cardiovasc Surg 2021;■:1-13)



Intra/postoperative complications were similar between the SV-VATS and MV-VATS groups.

CENTRAL MESSAGE

SV-VATS is safe, noninferior to MV-VATS, and has a decreased consumption of intravenous opioids and therefore, decreased cost for anesthesia.

PERSPECTIVE

Spontaneous ventilation video-assisted thoracic surgery for primary pneumothorax is safe and feasible. This approach may enhance the recovery from surgery, decreasing the intraoperative consumption of intravenous opioid analgesia and the cost for anesthesia.

See Commentary on page XXX.

THOR

Video-assisted thoracoscopic surgery (VATS) has emerged as a minimally invasive alternative to thoracotomy over the past 3 decades.[1] Conventional VATS is commonly performed following double-lumen intubated anesthesia with mechanical ventilation (MV) during surgery, leading to intubation and MV-induced injuries.[2,3] Besides, the use of muscle relaxants may cause muscle paralysis, leading to increased susceptibility to postoperative respiratory failure

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Abbreviations and Acronyms

BIS = bispectral index
LMA = laryngeal mask airways
MV = mechanical ventilation
MV-VATS = mechanical ventilation video-assisted thoracoscopic surgery
NLR = neutrophil to lymphocyte ratio
OLV = 1-lung ventilation
PACU = postanesthesia care unit
$PaCO_2$ = arterial carbon dioxide tension
$PetCO_2$ = end tidal carbon dioxide pressure
PLR = platelet to lymphocyte ratio
PSP = primary spontaneous pneumothorax
RCT = randomized controlled trial
SpO_2 = pulse oxygen saturation
SV-VATS = non-intubated spontaneous ventilation video-assisted thoracoscopic surgery
TCI = target-controlled infusion
VAS = visual analog scale
VATS = video-assisted thoracoscopic surgery

Scanning this QR code will take you to the table of contents to access supplementary information.

and prolonged dependence on MV.[4] Moreover, the use of large quantities of opioid analgesia like remifentanil and sufentanil during surgery may cause postoperative hyperalgesia and even opioid abuse and opioid dependence.[5-7]

Since 2011, we have taken the lead in implementing of spontaneous ventilation (SV-VATS) in China.[8] This technique has potential advantages, including that spontaneous ventilation avoids any injury induced by mechanical ventilation during surgery; laryngeal mask airways (LMA) or face masks can avoid the damage to the airway; muscle relaxants use is avoided to maintain spontaneous ventilation, thus reducing the possibility of postoperative muscle paralysis; and regional anesthesia such as intercostal and vagus nerve block decreases the need for intravenous opioid analgesia. Many retrospective, single-center prospective studies and meta-analyses have also shown this technique to have enhanced postoperative recovery, reduced complications, decreased hospital stay, and reduced health care costs.[9,10]

However, the safety and physical changes during surgery between the SV-VATS and mechanical ventilation VATS (MV-VATS) have never been explored. Thoracoscopic blebectomy for primary spontaneous pneumothorax (PSP) was selected to be the model surgery in this study because the simple operation in thoracic surgery has low procedural heterogeneity and is thus better able to reflect the reality of patents' physical index intraoperatively and postoperatively, offering the best view for comparison of 2 thoracic surgery modes.

We hypothesized that SV-VATS is noninferior to MV-VATS on intra- and postoperative complications in thoracoscopic blebectomy for PSP patients. A randomized controlled trial (RCT) was conducted to evaluate the physical changes during surgery and the short-term outcomes between SV-VATS and MV-VATS.

METHODS

Study Design

This prospective, multicenter, noninferiority RCT comparing SV-VATS versus MV-VATS for patients with PSP was completed at 10 hospitals in China. The present trial was designed to assess the noninferiority of the safety and feasibility of SV-VATS. The protocol of this trial was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (Date: December 14, 2016; institutional review board approval No: 2016 NO.53) and 9 other medical centers in accordance with the Declaration of Helsinki.[11] The protocol has published elsewhere.[12] Participants were informed of any potential risks associated with their participation, and their written informed consent was obtained before they entered the trial. Participants could withdraw their consent at any time during the study. The details of the methodology are available in the Online Data Supplement.

Inclusion and Exclusion Criteria

A patient diagnosed with PSP in an emergency room or thoracic outpatient clinic was first evaluated by chest radiograph. Observation was suggested for patients with PSP size <30%. Smaller bore (11-13 Fr) tubes were placed if >30%. A computed tomography scan was done at this time to diagnose pulmonary blebs. Then, thoracic surgeons evaluated the patient's status and surgical intervention determination followed the European Respiratory Society statement[13]; that is, second episode of PSP; the first time of PSP, but persisting air leak longer than 3 to 5 days; hemopneumothorax; bilateral pneumothorax; or professions at risk (eg, aircraft personnel or divers). Therapeutic options were discussed and decided with the patient and his/her family. In the case that the patient decided to undergo surgery, he or she was introduced to this project and if amenable signed the informed consent.

Inclusion criteria were voluntary participation in the trial and ability to personally sign a written informed consent, aged between 16 and 50 years, preoperative chest computed tomography-diagnosed localized lung bullae needing surgical treatment, Eastern Cooperative Oncology Group score standard ≤ 1, American Society of Anesthesiologists score ≤ 2, and cardiopulmonary function and other important organ functions basically normal and able to endure surgery.

Exclusion criteria were refusal to participate in clinical trials; history of ipsilateral thoracic surgery, body mass index ≥ 25; other conditions, including absolute surgical contraindications, pregnancy, or other unsuitable conditions for recruitment as determined by the investigators; and allergic history to cephalosporin, morphine, or any drugs involved in the programs.

Interventions

SV-VATS group. Dexmedetomidine (1.0 μg/kg/h for 15 minutes), target-controlled infusion (TCI) of propofol (2-3.5 μg/mL), and intravenous infusion sufentanil (0.2 μg/kg) were used for anesthesia induction. The third-generation double-tube LMA was used for ventilation management. If there was no spontaneous ventilation in the SV-VATS group,

manual ventilation or simultaneous intermittent mandatory ventilation mode was used to assist ventilation during anesthesia induction. A bispectral index (BIS) sensor was used for evaluation of sedation level.

During the anesthesia maintenance period, intercostal incision local anesthesia, visceral pleural surface anesthesia, and vagus nerve block were performed with lidocaine or ropivacaine in SV-VATS to decrease the use of remifentanil, maintaining spontaneous breathing. Cis-atracurium was not used in the SV-VATS group to maintain spontaneous breathing. TCI of propofol, remifentanil, and dexmedetomidine were administered at 1.5 to 4 μg/mL, 0.03 to 0.08 μg/kg/min, and 0.5 to 1.0 μg/kg/h, respectively. BIS was maintained between 45 and 60 during the operation. Dexmedetomidine was stopped directly after the pleural cavity closure, and propofol and remifentanil were stopped at the end of the operation. The anesthetic was not inhaled during the procedure (Video 1).

MV-VATS group. Dexmedetomidine (1.0 μg/kg/h for 15 minutes), TCI of propofol (2-3.5 μg/mL), intravenous infusion of sufentanil (0.3 μg/kg), and cis-atracurium (0.2 mg/kg) were used for anesthesia induction. A double-lumen bronchial catheter (Mallinckrodt Pharmaceuticals, Staines-upon-Thames, United Kingdom) was used for ventilation management. TOF-WACTH (Organon, Swords, Ireland) and TOF-GUARD (Organon, Oss, The Netherlands) are currently considered the accepted standard neuromuscular function monitoring devices in clinical trials, and the neuromuscular block was monitored using train-of-four stimulation,[14] which was adopted to evaluate neuromuscular transmission in this trial; the BIS sensor was used for evaluation of sedation level.

One-lung ventilation (OLV) under intermittent positive pressure ventilation model was applied for the anesthesia maintenance period. Parameters during intermittent positive pressure ventilation mode were fraction of inspired oxygen, 1; tidal volume, 4 to 6 mL/kg; respiratory rate, 12 to 18 times/min; and oxygen flow, 4 to 5 L/min. TCI of propofol (1.5-4 μg/mL), remifentanil (0.03-0.08 μg/kg/min), dexmedetomidine (0.5-1.0 μg/kg/h), and cis-atracurium (0.05 mg/kg) were administered. BIS was maintained between 45 and 60 during the operation. Dexmedetomidine was stopped directly after the pleural cavity closure, and propofol and remifentanil were stopped at the end of the operation. The anesthetic was not inhaled during the procedure.

Before the project began, surgeons and anesthesiologists from each center discussed the surgery type; all surgeons agreed that uniportal technique should be adopted in such surgery. All qualified surgeons had experience with uniportal VATS in this trial, and they were trained for 1 to 3 days about nonintubated surgery at the First Affiliated Hospital of Guangzhou Medical University before the project was started. The anesthesiologists from each center also attended the training course before the trial.

Operation and follow-up. The surgical procedure was identical both in the SV-VATS and MV-VATS groups. Lateral position was adopted. Single-port VATS was adopted for resection of pulmonary bullae. An incision $\leq$2 cm was made in the fourth or fifth intercostal space on the anterior axillary line as the working port. No pleurodesis was needed intraoperatively. During the operation, electrocardiogram, heart rate, invasive blood pressure, oxygen saturation (SpO_2), respiratory rate, BIS, end-tidal carbon dioxide pressure ($PetCO_2$), arterial carbon dioxide tension (PaCO2), fraction of inspired oxygen, and muscle relaxation monitoring (only in the MV-VATS group) should always be monitored continuously. After the surgery, irrigation of the pleural cavity with warm sterile saline solution or warm water, and reinflation of the operated lung by manual positive pressure ventilation at a pressure of 2 kPa through LMA or bronchial catheter was carried out to test for the presence of air leaks. A 20 Fr chest tube was placed on the top of the chest, then the pleura, muscle, and skin were sutured in turn. Patients were restored to the horizontal position, then 2 kPa pressure was applied to expand the lung. Treatments for intraoperatively special cases are shown in Appendix E1, including mediastinal flutter (movement of the surgical field that interferes substantially with the operation) after artificial pneumothorax, intraoperative hypercapnia, intraoperative hypoxemia, laryngeal mask malposition, and anesthesia conversion.

Patient-controlled analgesia was used after the operation using 1 mg/mL morphine. A visual analog scale (VAS) was applied to analyze the analgesia efficacy. Standard of care postoperative monitoring was provided. Preoperative and postoperative status daily score (see Figure E1) was evaluated every day for each patient. The time in post-anesthesia care unit (PACU) refers to the time from which the anesthesia was stopped to Steward score $\geq$ 4 (0-6 points; an unresponsive immobile patient whose airway requires maintenance [score = 0] to a fully recovered patient [score = 6]).[15] The grip strength test was used to evaluate muscle weakness and continuously monitored after surgery. The chest tube was removed after reexamination via chest radiograph within 4 hours postoperatively if there was no obvious air leakage, no active bleeding, and the radiograph suggested good lung expansion. Thoracentesis was required after chest tube removal if there was poor lung expansion or significant pleural effusion postoperatively. All patients visited the surgical outpatient clinic 1 week and 1 month after discharge from the hospital for follow-up.

Primary Outcomes

The main purpose of this trial was to evaluate the noninferiority of safety and feasibility of SV-VATS. The primary outcome was the intra- and postoperative complications comparison between SV-VATS and MV-VATS, which included intraoperative hypoxia, conversion to intubation (only accessed in SV-VATS group), air leak, and postoperative pneumonia as well as other intraoperative and postoperative adverse events that could be recorded in the 2 groups. The definition of each complication is listed in Table E1.

Secondary Outcomes

Secondary outcomes included total analgesia dose; changes of vital signs during surgery, including heart rate, temperature, respiratory rate, and blood pressure, and blood gas analysis tested every 30 minutes during the operation. Procedural duration, recovery time, postoperative VAS pain scores, and length of hospitalization were also calculated.

Post Hoc and Cost Analysis

Post hoc analysis was performed to investigate the inflammatory index level perioperatively in the SV-VATS group and the MV-VATS group. The neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and systemic immune-inflammation (SII) index (defined as platelet count $\times$ neutrophil count/lymphocyte) were calculated according to a blood test at each time point to show perioperative systemic inflammation level.

The cost evaluation was conducted according to relative costs of anesthesia, surgical procedure, nursing, drugs, surgical consumables, diagnostic evaluations, and physiotherapy between groups.

Randomization

We use the SAS version 9.2 software package (SAS Institute, Cary, NC) to generate random numbers in a 1:1 ratio, with a block size of 4. Randomization was stratified by centers. The results were sealed in envelopes and stored at the study site until the end. A study coordinator assigned from each center saved and distributed randomization results according to the order of recruited patients, and coordinated among the investigators. Each enrolled patient was grouped in the operating room on the day of surgery; the designated anesthesiologist performed anesthesia management and intraoperative data collection. The clinicians managing the patients postoperatively and patients themselves were blinded to the treatment modality the patient received. Postoperative follow-up was performed by researchers who received follow-up training but were not involved in patient care. Anesthesiologists and researchers did not communicate with each other when collecting data.

Sample Size Calculation and Statistical Analysis

The sample size was calculated based on the primary outcome. We set the noninferiority margin at 15%, meaning that when the upper limit of the 95% confidence interval (CI) for the estimated difference in the intra- and postoperative complication rate between the SV-VATS group and the MV-VATS group exceeded 15%, the SV-VATS would be inferior to the MV-VATS group. We assumed the intra- and postoperative complication rate of MV-VATS was 27%, as estimated in a recent meta-analysis from our team,[9] and a single-sided alpha risk of 0.05. With 2 groups of 158 patients each, the trial had 85% power with a prespecified noninferiority margin of 15% to assess the noninferiority of SV-VATS. Considering a dropout rate, a total of 355 patients was the planned enrollment for this study.

All primary and secondary data were analyzed according to an intention-to-treat principle. Normality was checked using the Shapiro-Wilk test for continuous variables. We used independent-sample *t* test for continuous variables that were normally distributed and Mann-Whitney tests for continuous variables that were not normally distributed. The χ^2 test or Fisher exact test were used for categorical variables. Recovery-related indexes were drawn by the Kaplan-Meier curve and tested by the log-rank test. Hazard ratios were calculated with 95% CI. We did not attempt to estimate missing data. All patients, including those with missing values, were included in the analyses using the data available.

We used SPSS version 25.0 (IBM SPSS Inc, Armonk, NY) for all statistical analyses. GraphPad Prism 6.0 software (La Jolla, Calif) was used for drawing figures. PASS 15.0 (NCSS LLC, Kaysville, Utah) was used to calculate the sample size.[16]

RESULTS

Study Patients

Between April 10, 2017, and January 3, 2019, we screened 355 patients with PSP scheduled for thoracoscopic blebectomy. In total, 172 were randomly assigned to SV-VATS and 176 to MV-VATS. Twenty-three patients were excluded after randomization from all analyses, and 3 patients (1 in MV-VATS group and 2 in SV-VATS group) refused to enter the trial. Three hundred twenty-five patients were included in the final analysis (Figure 1). One patient was converted from SV-VATS to MV-VATS. Baseline characteristics are shown in Table 1. Complete data for 317 (97.54%) patients was available for the first follow-up at 1 week after discharge (160 in SV-VATS group and 157 in MV-VATS group). Two hundred seventy-six (84.92%) complete datasets were available for the second follow-up at 28 days after discharge (145 in the SV-VATS group and 131 in the MV-VATS group).

Primary Outcome

The total intra- and postoperative complication rate was not significantly different between the SV-VATS group

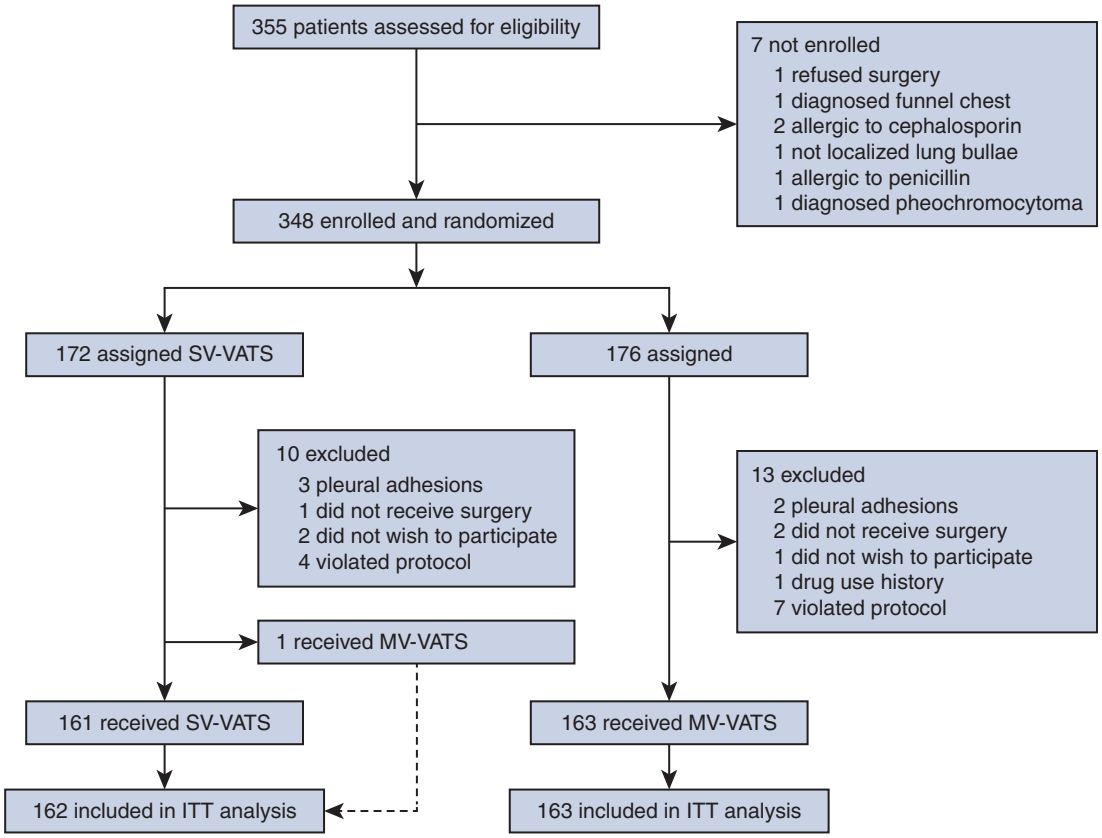


FIGURE 1. Consolidated Standards of Reporting Trials diagram. *SV-VATS*, Spontaneous ventilation video-assisted thoracoscopic surgery; *MV-VATS*, mechanical ventilation video-assisted thoracoscopic surgery; *ITT*, intention to treat.

TABLE 1. Patient characteristics

Characteristic	SV-VATS (n = 162)	MV-VATS (n = 163)	*P* value
Age (y)	22.63 ± 6.84	23.10 ± 7.56	.38
Gender			.62
Male	152 (93.83)	155 (95.09)	
Female	10 (6.17)	8 (4.91)	
Weight (kg)	56.08 ± 7.25	55.68 ± 8.03	.46
Height (cm)	172.70 ± 9.80	172.09 ± 14.89	.68
Body mass index	18.68 ± 2.14	18.57 ± 2.09	.49
Temperature (°C)	36.50 ± 0.81	36.48 ± 1.61	.38
Heart rate (n)	78 ± 11.01	78 ± 13.84	.16
Respiratory rate (n)	20 ± 1.20	19 ± 1.26	.31
Systolic blood pressure (mm Hg)	115.28 ± 10.78	115.90 ± 11.69	.67
Diastolic blood pressure (mm Hg)	72.43 ± 9.21	72.44 ± 9.31	.71
Preoperative status score*	1.28 ± 1.19	1.21 ± 1.17	.88
Comorbidities	14 (8.64)	20 (12.27)	.37
Hepatitis B virus	5 (3.09)	5 (3.01)	
Rhinitis	3 (1.85)	2 (1.23)	
Cholelithiasis	2 (1.23)	3 (1.84)	
Nephritis	1 (0.62)	2 (1.23)	
Gastric ulcer	3 (1.85)	3 (1.84)	
Renal calculi	0	3 (1.84)	
Gallbladder polyps	0	1 (0.61)	
Arrhythmia	0	1 (0.61)	
American Society of Anesthesiologists score			.57
I	103 (63.58)	88 (53.99)	
II	59 (36.42)	75 (46.01)	
Preoperative oxygen saturation (%)	96.99 ± 4.89	96.76 ± 3.78	.58
Preoperative HCO_3^- (mmol/L)	25.22 ± 2.21	25.57 ± 2.67	.26
Preoperative oxygenation	426.39 ± 145.46	451.07 ± 329.11	.13
History of pneumothorax or bullae†			.31
Yes	22 (13.58)	14 (8.59)	
No	140 (86.42)	149 (91.41)	

Values are presented as mean ± standard deviation or n (%). Percentages are calculated for the whole population. *SV-VATS*, Spontaneous ventilation video-assisted thoracoscopic surgery; *MV-VATS*, mechanical ventilation video-assisted thoracoscopic surgery. *Details of the preoperative status score are presented in Table E7. †History of pneumothorax or bullae means second episode of pneumothorax.

and MV-VATS group (17.90% vs 22.09%; relative risk [RR], 0.81; 95% CI, 0.52-1.26; $P = .346$) (Figure 2, *A*). Specifically, the intraoperative (6.17% vs 8.59%; RR, 0.72; 95% CI, 0.33-1.57; $P = .405$) (Figure 2, *B*) and postoperative (16.67% vs 20.86%; RR, 0.80; 95% CI, 0.51-1.26; $P = .333$) (Figure 2, *C*) complication rates were also similar between the SV-VATS group and the MV-VATS group.

One (0.62%) patient in the SV-VATS group was converted to MV-VATS during surgery; the patient experienced LMA movement during surgery. One patient experienced hypoxia with temporary peripheral SpO_2 <90% in the SV-VATS group; this condition was reversed, so conversion to MV was avoided. SpO_2 <90% occurred in 2 patients who underwent MV-VATS. Details of postoperative complications are presented in Table 2.

Secondary Outcomes

Intraoperative ventilation variables appear in Table 3. Higher arterial oxygen tension and SpO_2 levels were observed in the first 15 minutes after opening the pleura in the SV-VATS group. However, SV-VATS was associated with higher $PetCO_2$ and $PaCO_2$ during the whole operative process; meanwhile, more patients with $PetCO_2$ >60 mm Hg were found in the SV-VATS group (17.90% vs 0.62%; relative risk, 29.18; 95% CI, 4.02-211.67; $P < .001$). Consequently, lower pH levels during surgery were found in patients who underwent SV-VATS. Although

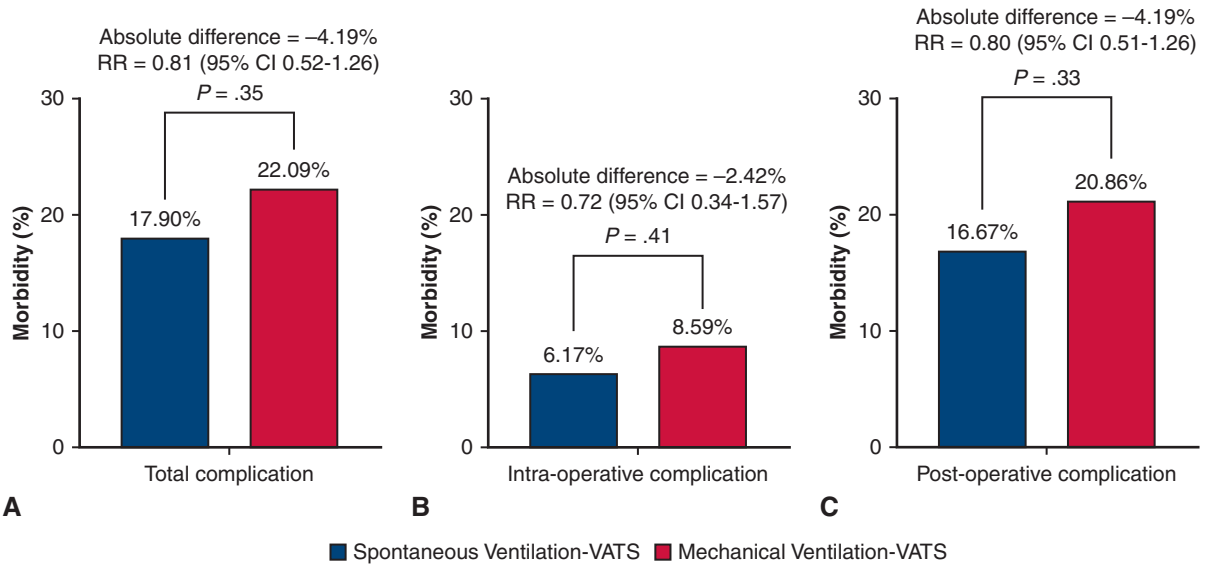


FIGURE 2. Total, intraoperative, and postoperative complications. A, Total complication rate. B, Intraoperative complication rate. C, Postoperative complication rate. *RR*, Risk ratio; *CI*, confidence interval; *VATS*, video-assisted thoracic surgery.

intraoperative cough was more frequent in SV-VATS (14.81% vs 3.07%; RR, 4.83; 95% CI, 1.89-12.35; $P < .001$), the operative view score ($P = .435$) (1-5 points; that is, very poor surgical field exposure [score = 1] to a clear surgical field exposure [score = 5]) was similar between SV-VATS and MV-VATS patients. Other vital signs are summarized in Table E2.

Intraoperative opioid agents consumption was explored in this study (Table 4). The SV-VATS group was associated with significantly decreased total consumption of both sufentanil (11.37 μg vs 20.92 μg; $P < .001$) and remifentanil (269.78 μg vs 404.96 μg; $P < .001$) compared with MV-VATS group patients. The average total dosage of cis-atracurium in the MV-VATS group was 13.6 mg, whereas no muscle relaxant (eg, cis-atracurium) was used in the SV-VATS group ($P < .001$). The total dose of other perioperative anesthesia agents, including propofol and dexmedetomidine, were similar between the SV-VATS group and the

TABLE 2. Intra- and postoperative complications (primary outcomes)

Complication	SV-VATS (n = 162)	MV-VATS (n = 163)	Total (N = 335)	*P* value
Intraoperative				
Converted to intubation	1 (0.62)	–	1 (0.31)	-
Hypoxia	1 (0.62)	2 (1.23)	3 (0.92)	.569
Arrhythmia/bradyarrhythmia	10 (6.17)	14 (8.59)	24 (7.16)	.405
Postoperative				
Incision pain	15 (9.26)	12 (7.36)	27 (8.31)	.535
Fever	7 (4.32)	16 (9.82)	23 (7.08)	.053
Dyspnea	6 (3.70)	11 (6.75)	17 (5.23)	.218
Weakness	7 (4.32)	5 (3.07)	12 (3.69)	.549
Sore throat	5 (3.08)	7 (4.29)	12 (3.69)	.564
Nausea	6 (3.70)	5 (3.07)	11 (3.38)	.751
Upper respiratory infection	4 (2.47)	7 (4.29)	11 (3.38)	.363
Air leak	4 (2.47)	5 (3.07)	9 (2.77)	.742
Pneumothorax	5 (3.08)	1 (0.61)	6 (1.85)	.098
Pleural effusion	3 (1.85)	1 (0.61)	4 (1.23)	.311
Urinary retention	1 (0.62)	0	1 (0.31)	.315
Constipation	0	1 (0.61)	1 (0.31)	.318
Blood loss (mL)	6.12 (3.83)	7.03 (5.85)	–	.099

Values are presented as n (%). Percentages are calculated for the whole population. *SV-VATS*, Spontaneous ventilation video-assisted thoracoscopic surgery; *MV-VATS*, mechanical ventilation video-assisted thoracoscopic surgery.

TABLE 3. Intraoperative ventilation characteristics

Characteristic	SV-VATS (n = 162)	MV-VATS (n = 163)	*P* value
Arterial oxygen tension (mm Hg)			
Baseline	102.67 ± 28.46	101.02 ± 31.82	.624
After anesthesia	457.78 ± 120.25	416.41 ± 138.50	.004*
Immediately after opening pleura	448.50 ± 130.95	320.23 ± 133.15	<.001
15 min after opening pleura	357.93 ± 137.74	296.51 ± 128.22	<.001
30 min after opening pleura	365.57 ± 151.65	327.53 ± 129.45	.150
After closing pleura	366.69 ± 131.60	362.09 ± 160.95	.780
After awake	131.18 ± 83.10	118.74 ± 70.73	.151
Oxygen saturation (%)			
After anesthesia	99.16 ± 1.10	99.09 ± 1.13	.611
Immediately after opening pleura	99.15 ± 1.27	98.80 ± 1.48	.025*
15 min after opening pleura	99.06 ± 1.24	98.49 ± 1.96	.004*
30 min after opening pleura	99.11 ± 1.08	98.73 ± 1.64	.116
After closing pleura	98.85 ± 1.59	98.64 ± 2.10	.308
After awake	98.14 ± 2.10	97.87 ± 2.39	.276
End tidal carbon dioxide pressure (mm Hg)			
After anesthesia	42.87 ± 7.23	37.27 ± 6.21	<.001
Immediately after opening pleura	48.18 ± 7.88	33.51 ± 5.95	<.001
15 min after opening pleura	48.94 ± 8.41	34.95 ± 8.01	<.001
30 min after opening pleura	49.11 ± 9.53	34.11 ± 6.38	<.001
After closing pleura	44.78 ± 8.31	33.16 ± 5.84	<.001
Arterial carbon dioxide tension (mm Hg)			
Baseline	42.27 ± 4.10	42.64 ± 4.54	.452
After anesthesia	51.91 ± 10.68	45.52 ± 7.77	<.001
Immediately after opening pleura	62.92 ± 11.78	41.66 ± 7.96	<.001
15 min After opening pleura	64.59 ± 11.65	42.54 ± 7.90	<.001
30 min After opening pleura	63.18 ± 12.51	45.20 ± 8.50	<.001
After closing pleura	58.97 ± 11.35	44.19 ± 8.29	<.001
After awake	51.39 ± 7.96	48.63 ± 7.03	.001
Perioperative end tidal carbon dioxide pressure >60 mm Hg			<.001
Yes	29 (17.90)	1 (0.62)	
No	133 (82.10)	162 (99.38)	
pH			
After anesthesia	7.34 ± 0.06	7.38 ± 0.05	<.001
Immediately after opening pleura	7.27 ± 0.06	7.40 ± 0.05	<.001
15 min after opening pleura	7.25 ± 0.06	7.39 ± 0.05	<.001
30 min after opening pleura	7.25 ± 0.06	7.38 ± 0.06	<.001
After closing pleura	7.27 ± 0.06	7.37 ± 0.06	<.001
After awake	7.33 ± 0.04	7.31 ± 0.16	<.001

Values are presented as mean ± standard deviation or n (%). Percentages are calculated for the whole population. *SV-VATS*, Spontaneous ventilation video-assisted thoracoscopic surgery; *MV-VATS*, mechanical ventilation video-assisted thoracoscopic surgery. *$P < .05$.

MV-VATS group. No intraoperative awareness happened in either group; meanwhile, the anesthesia effect score level (1-4 points; that is, anesthesia conversion is required for surgery performance [score = 1] to complete, painless, and quiet anesthesia providing good conditions for surgery [score = 4]) ($P = .082$) and BIS score (P values = .053-.741) were similar in both groups during the entire process of surgery (Table E2).

We explored the postoperative recovery time and pain status in the 2 groups, as shown in Figure 3 and Table E3. SV-VATS was associated with shorter extubation (ie, LMA) time (12.28 minutes vs 17.30 minutes; $P < .001$) (Figure 3, *A*), PACU recovery time (25.43 minutes vs 30.67 minutes; $P = .02$) (Figure 3, *C*), and food intake time (346.07 minutes vs 404.02 minutes; $P = .002$) (Figure 3, *D*) than patients who underwent MV-VATS. The time to consciousness (Figure 3, *B*), ambulation (Figure 3, *E*), hospitalization (Figure 3, *F*), as well as the chest tube duration and chest drainage were comparable between the groups.

TABLE 4. Intraoperative anesthesia agent assumption

Agent	SV-VATS (n = 162)	MV-VATS (n = 163)	*P* value
Sufentanil (μg)	11.37 (12.35)	20.92 (15.17)	<.001
Remifentanil (μg)	269.78 (183.01)	404.96 (224.33)	<.001
Cis-atracurium (mg)	0.00 (-)	13.67 (15.85)	<.001
Propofol (mg)	459.95 (163.82)	490.09 (182.44)	.118
Dexmedetomidine (μg)	74.01 (91.65)	67.37 (55.03)	.429

Values are presented as n (%). Percentages are calculated for the whole population. *SV-VATS*, Spontaneous ventilation video-assisted thoracoscopic surgery; *MV-VATS*, mechanical ventilation video-assisted thoracoscopic surgery.

Table E4 summarizes postoperative pain status. Perioperative VAS was evaluated at different time points. No significant difference was observed between the SV-VATS group and the MV-VATS group. Postoperative morphine analgesia was also similar in the groups. Cough status after surgery is shown in Table E5; no difference was found in the groups at either follow-up.

Post Hoc Analysis

We investigated the level of inflammatory index perioperatively. We found SV-VATS was associated with lower levels of inflammation than MV-VATS according to the SII index (1913.44 vs 2487.70; $P = .009$), PLR index (196.71 vs 232.51; $P = .023$), and NLR index (8.59 vs 12.02; $P = .001$) at 4 hours after surgery, but not at other time points (Table E6).

Cost Evaluation

The cost evaluation was based on data from all 325 patients. There was no difference between the mean cost per patient between the SV-VATS group and the MV-VATS group ($4723.26 vs $4891.44; $P = .263$). SV-VATS

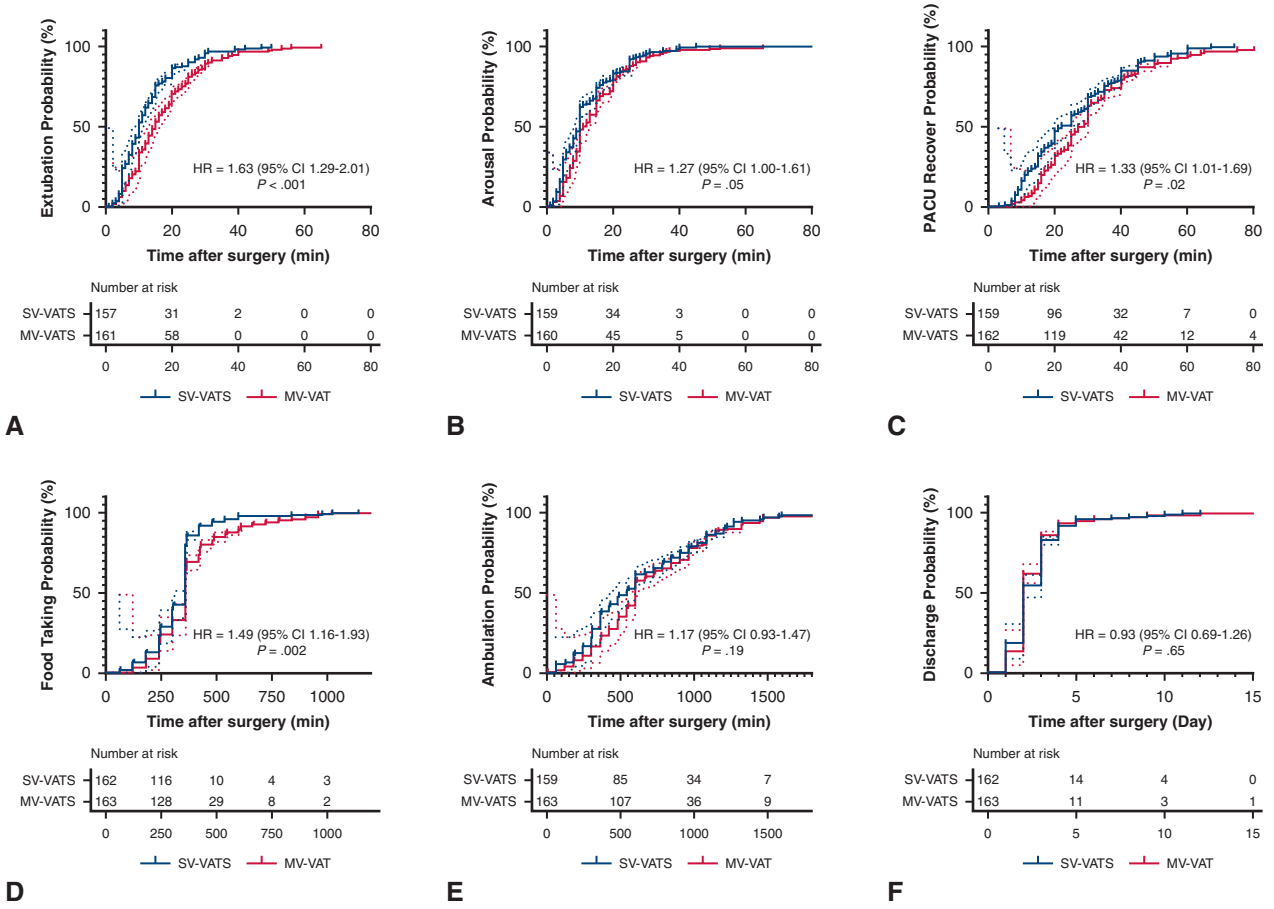


FIGURE 3. Recovery-related evaluation. A, Extubation. B, Arousal. C, Postanesthesia care unit recovery. D, Food taking. E, Ambulation. F, Discharge. *SV-VATS*, Spontaneous ventilation video-assisted thoracoscopic surgery; *MV-VATS*, mechanical ventilation video-assisted thoracoscopic surgery; *HR*, hazard ratio; *CI*, confidence interval; *PACU*, postanesthesia care unit.

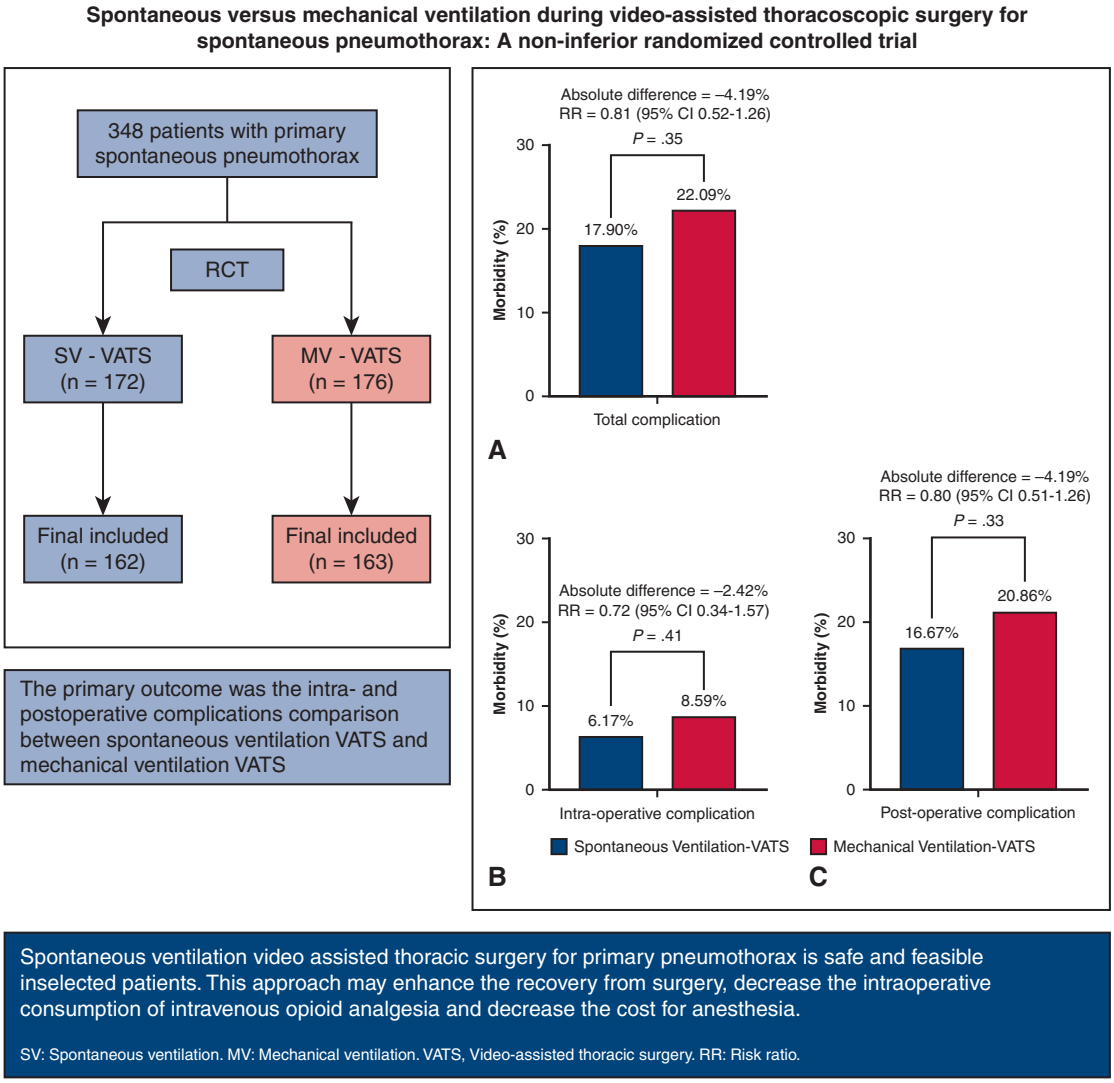


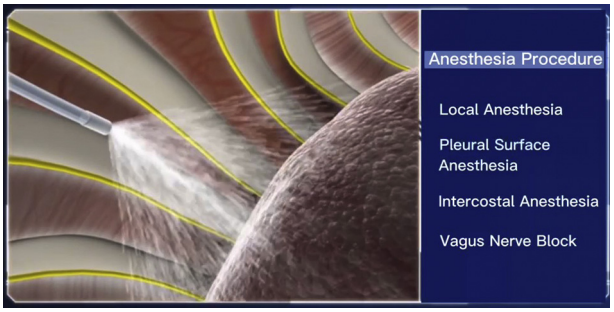
FIGURE 4. Spontaneous ventilation (*SV*) versus mechanical ventilation (*MV*) during video-assisted thoracoscopic surgery (*VATS*) for primary spontaneous pneumothorax (PSP): A non-inferior randomized controlled trial (*RCT*). This multicenter, non-inferiority, RCT showed that SV-VATS blebectomy is a safe and feasible technique in PSP patients. The primary outcome showed that intra- and postoperative complication rates were similar between the SV-VATS group and the MV-VATS group, which suggests that SV-VATS could be an option for blebectomy in selected PSP patients. A, Total complication rate. B, Intraoperative complication rate. C, Postoperative complication rate. *RR*, Risk ratio; *CI*, confidence interval.

significantly decreased the anesthesia cost compared with MV-VATS ($297.81 vs $399.81; $P < .001$). Other costs, including the operation cost, nursing cost, medicine cost, surgical consumables cost, diagnostic evaluation cost, and physiotherapy cost, were comparable between the groups (Table E7).

DISCUSSION

This multicenter, non-inferiority, RCT showed that SV-VATS blebectomy is a safe and feasible technique in PSP patients (Figure 4). The primary outcome showed that intra- and postoperative complication rates were similar between the SV-VATS group and the MV-VATS group. Other outcomes indicated SV-VATS was associated with significantly decreased consumption of intraoperative opioid agents, higher levels of SpO_2, shorter extubating (ie, LMA) time, shorter PACU recovery time, lower levels of the inflammatory index, and cheaper anesthesia expense.

Patients who receive OLV during thoracic surgery are prone to volutrauma, barotrauma, atelectrauma, and oxygen toxicity, which are important aspects of ventilator-induced lung injury.[17,18] Therefore, lung protection is of the utmost importance, and protective ventilation is strongly recommended during thoracic surgery.[19] Protective ventilation includes the use of low V_T, positive end-expiratory pressure with the recruitment maneuver, and limiting inspiratory pressure.[20] Compared with protective ventilation supported by a ventilator, SV during thoracic surgery is closer to the



VIDEO 1. The intraoperative regional anesthesia during spontaneous ventilation video-assisted thoracic surgery. Video available at: https://www.jtcvs.org/article/S0022-5223(21)00192-6/fulltext.

physiological state, which avoids mechanical pressure-related pulmonary injury.[21] To prove its safety and explore its effect on patients' physical status, we chose among the simplest operations in thoracic surgery—blebectomy for PSP—as the experiment surgery model. The surgery process is a simple wedge resection of pulmonary bullae, which seldom affects the hemodynamic parameters or immunoinflammatory index of patients. Besides, PSP patients are usually young, thin, male, and have fewer comorbidities.[22] These characteristics of experimental patients decrease the hybrid bias of disease and surgery, enabling better observation of the effect of the ventilation strategy itself. However, enhanced recovery cannot be observed in this study due to the simplicity of the surgical procedure and the relatively young age and health status of the patients, similar to a recent meta-analysis from our team.[9]

We found a higher level of oxygen tension and carbon dioxide tension according to blood gas function during the entire operative process in the SV-VATS group. The ventilator passively gave the oxygen supply for patients in the MV-VATS group through OLV. If the ventilation tube is moved or muscle relaxants were not complete, stable oxygen supply might be interrupted, causing perioperative hypoxia.[23] However, for patients undergoing SV-VATS, spontaneous breathing during the operation is seldom interrupted; slightly elevated levels of carbon dioxide in the blood stimulate the respiratory center; thus the oxygen level of patients in the SV-VATS group is more stable and higher. Another explanation should be clarified for the SV-VATS group when the treated lung had ipsilateral ventilation stopped relative to opening the pleura. This is because ceasing it before that time can cause shunting and reduced oxygenation. Besides, with both lungs being spontaneously ventilated, there is very little ventilation/perfusion mismatch; thus the higher oxygen tension was observed in the SV-VATS group. In our study the average SpO_2 and oxygen tension were both higher in the SV-VATS group than the MV-VATS group during the first 15 minutes of surgery; furthermore, hypoxemia occurred in 2 patients in the MV-VATS group (SpO_2 <90%), but in only 1 patient in the SV-VATS group.

Hypercapnia is among the lung-protective strategies for intervention in acute respiratory distress syndrome.[24] A previous clinical study demonstrated the safety of hypercapnia with the $PaCO_2$ range of 60 to 70 mm Hg and showed that therapeutic hypercapnia inhibits local and systematic inflammation and improves respiratory function after OLV in lobectomy patients.[25] Because no intubation was placed, the SV-VATS group's rate of carbon dioxide exhaustion was slowed down, leading to mild carbon dioxide accumulation. In our trial, $PetCO_2$ and $PaCO_2$ in SV-VATS patients were higher than that of the MV-VATS group, and the average range of $PaCO_2$ of the SV-VATS group was between 51.91 and 64.59 mm Hg, which was a safe level for patients during surgery. The post hoc analysis observed a lower inflammation index in the SV-VATS group, which might be explained by the hypercapnia in the SV-VATS patients. We first observed that SV-VATS was associated with a decreased level of bronchoalveolar lavage fluid inflammatory cytokines in 2014.[26] A rabbit model study was then developed by our team, demonstrating that SV decreased nonoperative lung injury compared with OLV by decreasing the level of messenger RNA and protein of tumor necrosis factor-α.[27] Mineo and colleagues[28] also observed that VATS lung metastasectomy in nonintubated anesthesia (ie, SV) had significantly less influence on both the immunological and inflammatory response than the traditional procedure. A lower SII index, NLR, and PLR level was observed in SV-VATS in our study, which could be partly explained by the mild hypercapnia. Besides, mild hypercapnia increases tissue oxygen tension and temperature, which would reduce infection risk and low-temperature damage.[29] However, the mechanism and clinical significance need to be proved in animal experiments and a larger population cohort study.

To maintain SV, muscle relaxants are avoided; this also potentially speeds-up the recovery postoperatively. In this trial, extubating (ie, LMA) time and PACU recovery time were shorter in SV-VATS patients. However, use of muscle antagonism in the MV-VATS group, ambulation time and postoperative force recovery status were comparable between SV-VATS and MV-VATS. Regional anesthesia and nerve block included incision anesthesia, lung surface anesthesia, and vagus nerve block, which remain effective during the entire surgical procedure, decreasing intravenous opioid analgesia. The low dose of opioid analgesia helped maintain stable SV. Although the setting range of opioid analgesia (ie, sufentanil and remifentanil) in the protocol was the same in the 2 groups, the result showed the total dose of opioid analgesia in SV-VATS was nearly half that of the MV-VATS group. A series of studies in patients undergoing surgery suggest that the administration of a high rather than a low intraoperative opioid dose is associated

with increased pain and or opioid consumption during the postoperative period.[30,31] Although intraoperative opioid dose decreased, the pain score and postoperative morphine analgesia showed no difference between the groups, which showed that regional anesthesia in addition to a low dose of opioid analgesia during the operation was an alternation in SV-VATS strategy.

The total dose of propofol and dexmedetomidine are similar in both groups, which would ensure satisfactory intraoperative sedation. This is reflected by the BIS index, operative view score, and anesthesia effect score; these indexes were all comparable in SV-VATS and MV-VATS patients. However, more cough was observed in patients who underwent SV-VATS; this happened mainly before the vagus nerve block and did not cause operation-related adverse events. After the intrathoracic vagus nerve block, intraoperative cough seldom occurred.[31] The right vagus nerve block is usually enough; left vagus nerve block is more demanding and is avoided by less experienced surgeons to avoid the risk of injury to the aortic arch, thus left SV-VATS could be associated with more cough than right-sided procedures.

Some medical centers may add abrasion of the parietal pleural to blebectomy for decreasing the recurrence of pneumothorax. In the current trial, we did not adopt abrasion, pleurodesis, or pleurectomy after wedge resection. Whether pleurodesis by scrubbing the parietal pleura, or pleurodesis after wedge resection will decrease the recurrence rate for PSP is controversial. Many clinical trials and meta-analyses demonstrated pleural abrasion after thoracoscopic wedge resection may not be regularly recommended for routine application due to the greater incidence of adverse effects than wedge resection alone.[32,33] In clinical practice, we did not adopt this procedure after the blebectomy, thus pleural abrasion was not performed in the current clinical trial. Although we did not perform the pleural abrasion, it certainly could be accomplished under SV.

Several limitations need to be acknowledged. First, we only assessed the perioperative safety between SV-VATS and MV-VATS, rather than the enhanced recovery after surgery. We regard SV-VATS as a novel and challenging technique, and intraoperative safety of SV-VATS is the primary concern; thus, this trial was designed mainly to answer such a question; besides, we did not measure recurrence of PSP in this study, which would miss the long-term evaluation of these 2 techniques. Second, the patients in this trial were PSP patients undergoing thoracoscopic blebectomy, chosen for the simplicity of the operation; thus, the safety of SV-VATS some would argue is only applicable to simple thoracic procedures. Besides, although several retrospective cohort studies have reported the outcomes of SV-VAT used for older, pulmonary function deficiency, and higher body mass index patients, the current clinical trial did not include these populations, which may limit the generalization of this technique.[34-36] Third, PSP patients included in our study were relatively young, with few comorbidities, which might not represent all PSP patients. Another multicenter randomized clinical trial is ongoing in our center and other hospitals in China to investigate the advantage of SV-VATS on postoperative recovery and complications in lung cancer surgery patients (ClinicalTrials.gov ID: NCT03432637). With the increased complexity of the surgery, the advantage of fast recovery of SV-VATS might become obvious. Fourth, the SV-VATS group might benefit from a good local block. The local block is not the necessary procedure in patients who received intubated MV (SV-VATS). With the use of muscle relaxants and the full dose of intraoperative opioid agents, the operation field is satisfied, and the operation field is stable without additional local block.

In contrast, to maintain SV, patients in the SV-VATS group have to omit muscle relaxant use, and only a half dose of intraoperative opioid agents was used. Thus, for the SV-VATS group, the local block was a necessary procedure to decrease the potential intraoperative pain-related irritation and decrease the mediastinal movement for a better surgery filed. The SV-VATS strategy changes the anesthesia from general anesthesia to target anesthesia. We compared 2 anesthesia strategies in this study rather than only airway management. The local block was also a part of the different anesthesia strategies. Fifth, unblinded anesthesiologists and surgeons may cause bias during operation and postoperative care.

CONCLUSIONS

This multicenter, noninferiority, randomized clinical trial demonstrated that nonintubated SV-VATS is as safe and feasible as MV-VATS in selected patients undergoing blebectomy for PSP.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: spontaneous ventilation, mechanical ventilation, video-assisted thoracoscopic surgery, randomized controlled clinical trial, opioid anesthesia

APPENDIX E1: INTRAOPERATIVE TREATMENT IN SPECIAL CASES

Mediastinal Flutter After Artificial Pneumothorax

If the amplitude of mediastinum flutter is obvious, the operation will be affected. The main reason is the effect of single-pulmonary respiration and anesthesia drugs (especially remifentanil and propofol) on respiration after artificial pneumothorax. The ideal parameter of single-lung spontaneous respiration is tidal volume (V_T) 3 to 4 mL/kg and respiratory rate of 20 to 25 per minute. Because dexmedetomidine has a relatively milder effect on respiration, dexmedetomidine is kept at a constant rate intraoperatively. The V_T and respiratory rate of spontaneous respiration will be altered by propofol rate adjustment. While the bispectral index value is maintained at 45 to 60. The improvement of local anesthesia + nerve block anesthesia has contributed to the gradual reduction of the dose of remifentanil, to downgrade the possibility of interference with breathing.

Intraoperative Hypercapnia

Hypercapnia is common during surgery, but it is well tolerated. When arterial carbon dioxide tension is ≥80 mm Hg, manual or simultaneous intermittent mandatory ventilation mode (inspired oxygen fraction, 1; V_T, 3-5 mL/kg; respiratory rate, 12-15 times/min; oxygen flow, 4-5 L/min) can be used to reduce the hypercapnia while adjusting the speed of propofol and remifentanil. If the above treatment fails to improve hypercapnia, conversion of anesthesia is considered.

Intraoperative Hypoxemia

The incidence of hypoxemia is low. It usually occurs after the complete collapse of the lung on surgical side. If oxygen saturation is <90%, manual or intermittent simultaneous intermittent mandatory ventilation mode (inspired oxygen fraction, 1; V_T, 3-5 mL/kg; respiratory rate, 12-15 times/min; oxygen flow, 4-5 L/min) can be used. When the lung on the surgical side is completely collapsed, the airway resistance of the operation side is higher than that of the contralateral side, and most of the gas will enter the contralateral lung when ventilated by small V_T. Generally, small V_T ventilation does not cause lung expansion on the surgical side and has little effect on the surgical operation.

Laryngeal Mask Malposition

If inspiratory dyspnea occurs during surgery, the end tidal carbon dioxide pressure waveform drops flat or disappears, and V_T drops suddenly, the possibility of a laryngeal mask shift is considered. In this case it is necessary to deepen anesthesia appropriately and adjust the position of the laryngeal mask to relieve the obstruction.

Anesthesia Conversion

If hypoxemia or hypercapnia or other indicated conditions for conversion occur during the surgery and cannot be resolved after noninvasive management, the anesthesiologist must be able to switch the anesthesia mode and perform tracheal intubation. The single-lumen endotracheal tube + bronchial blocker is preferred. If there is intra-airway hemorrhage, lung isolation can be achieved by double lumen endotracheal intubation.

The single-lumen tube should be inserted under the guidance of a fiber optic bronchoscope when the patient is in a lateral position, which is more difficult than normal practice. To achieve this, a small pillow should be placed under the head to allow the front, bottom perspective of the mouth and nose to stay up and the head and neck should be parallel to the central axis of the body.

Indications for anesthesia conversion:

- Hypoxemia: Oxygen saturation <90%, no improvement of blood oxygen saturation after auxiliary ventilation.
- Arterial carbon dioxide tension ≥80 mm Hg, no improvement of hypercapnia after auxiliary ventilation, and any of the following:
  - Circulation change: Heart rate >100 bpm, or change of systolic pressure amplitude >30% of the base value;
  - Arrhythmia occurs, such as frequent atrial or ventricular premature ≥6 beats/min (excluding from surgical stimulation-induced arrhythmia); and/or
  - Arterial blood gases analyses are detected twice at intervals of 15 min or more, and pH values are all <7.25.
- The swing amplitude of surgical field is large which is difficult to perform surgical operation, and is not improved after drug treatment, duration >5 min.
- Severe hemorrhage in the surgical wound and thoracic cavity blurred surgical field.
- A significant increase in endotracheal secretions, especially bloody secretions that cause difficulty in breathing, increased airway resistance, or the reduction of spontaneous ventilation >30%, mechanical ventilation peak airway pressure >20 cm H_20.
- After surface anesthesia and local anesthetic block of the intrathoracic vagus nerve is achieved, coughing still occurs >2 times/min.
- Those who meet the exclusion criteria of this study may consider anesthesia conversion.

Preoperative and postoperative status score table

Patient Name: Patient ID

Daily record of Symptoms and signs (Operation day～4 weeks after discharge)

Symptom		Score	Post-operative days								Discharge	
			0	1	2	3	4	5	6	7	1 week	4 weeks
Systemic symptoms and signs	Mental state	0: Nice	□	□	□	□	□	□	□	□	□	□
		1: Good	□	□	□	□	□	□	□	□	□	□
		2: Bad	□	□	□	□	□	□	□	□	□	□
	Expectoration	0: No manual assistance required	□	□	□	□	□	□	□	□	□	□
		1: Manual assistance required	□	□	□	□	□	□	□	□	□	□
		2: Need bronchoscopy for sputum suction	□	□	□	□	□	□	□	□	□	□
	Fever	0: Normal	□	□	□	□	□	□	□	□	□	□
		1: 37.5-37.9℃	□	□	□	□	□	□	□	□	□	□
		2: 38—40℃	□	□	□	□	□	□	□	□	□	□
	Gastrointestinal motility	0: Yes	□	□	□	□	□	□	□	□	□	□
		1: No	□	□	□	□	□	□	□	□	□	□
Symptoms and signs of lower respiratory tract	Cough	0: No	□	□	□	□	□	□	□	□	□	□
		1: Intermittent cough	□	□	□	□	□	□	□	□	□	□
		2: Severe cough, not disturb sleep	□	□	□	□	□	□	□	□	□	□
		3: Severe cough, disturb sleep	□	□	□	□	□	□	□	□	□	□
	Sputum	0: None	□	□	□	□	□	□	□	□	□	□
		1: White	□	□	□	□	□	□	□	□	□	□
		2: Yellow	□	□	□	□	□	□	□	□	□	□
		3: Red	□	□	□	□	□	□	□	□	□	□
	Dyspnea	0: None	□	□	□	□	□	□	□	□	□	□
		1: Dyspnea on exertion	□	□	□	□	□	□	□	□	□	□
		2: Dyspnea on general activity	□	□	□	□	□	□	□	□	□	□
		3: Dyspnea on quiet	□	□	□	□	□	□	□	□	□	□
	Rhonchus	0: None	□	□	□	□	□	□	□	□	□	□
		1: Occasionally	□	□	□	□	□	□	□	□	□	□
		2: Scattered	□	□	□	□	□	□	□	□	□	□
		3: Dense	□	□	□	□	□	□	□	□	□	□
	Moist rales	0: None	□	□	□	□	□	□	□	□	□	□
		1: Occasionally	□	□	□	□	□	□	□	□	□	□
		2: Persist but not obvious	□	□	□	□	□	□	□	□	□	□
		3: Persist and obvious	□	□	□	□	□	□	□	□	□	□
Total score												
Signature:												
Date												

FIGURE E1. Preoperative and postoperative status score table.

TABLE E1. Definitions of complications

Complication	Criteria
Cardiac	
Cardiac infarction	Confirmed by electrocardiography or echocardiography and cardiac enzyme monitoring
Heart failure	Confirmed by echocardiography or necessitating pressure agents
Arrhythmia	ECG confirmed and necessitating medication
Respiratory	
Hypoxia	Intraoperative oxygen saturation <90%
Upper respiratory infection	Radiograph or CT confirmed and necessitating antibiotic treatment
Air leak	Chest tube maintenance for air leak for >7 d postoperatively
Pulmonary embolus	Confirmed by angio-CT scan
Pleural effusions	Radiograph or CT confirmed and requiring treatment
Chest infection	Supported by positive bacterial culture
Pneumothorax	Radiograph or CT confirmed and requiring treatment
Other complication	
Fever	Temperature above 38.5°C
Nausea	Patient-reported nausea and vomiting
Weakness	Patient not willing to move after surgery because of weakness
Urinary retention	Requiring reinsertion of urinary catheter
Incision pain	Patient reports incision pain >4 degree of visual analog scale
Sore throat	Patient reports sore throat >4 degree of visual analog scale
Wound infection	Requiring opening of wound or antibiotics
Constipation	Fewer than 3 bowel movements per week

ECG, Electrocardiogram; *CT*, computed tomography.

TABLE E2. Intraoperative vital signs

Vital sign	SV-VATS (n = 162)	MV-VATS (n = 163)	*P* value
Respiratory rate			
After anesthesia	13 ± 4.17	14 ± 3.20	.004*
Immediately after opening pleura	13 ± 4.66	14 ± 1.83	.017*
15 min after opening pleura	14 ± 4.91	14 ± 2.11	.497
30 min after opening pleura	15 ± 5.14	14 ± 1.96	.064
After closing pleura	14 ± 4.51	14 ± 2.36	.071
After awake	17 ± 3.78	17 ± 4.03	.238
Heart rate			
After anesthesia	64.43 ± 11.53	69.80 ± 11.85	<.001
Immediately after opening pleura	65.50 ± 11.72	64.92 ± 11.03	.647
15 min after opening pleura	73.92 ± 12.45	66.04 ± 10.73	<.001
30 min after opening pleura	73.00 ± 12.43	63.94 ± 11.35	<.001
After closing pleura	73.73 ± 12.69	65.68 ± 10.82	<.001
After awake	74.49 ± 12.07	69.93 ± 12.43	.001
Systolic blood pressure (mm Hg)			
Baseline	115.28 ± 10.78	115.90 ± 11.68	.617
After anesthesia	102.15 ± 14.01	105.99 ± 17.35	.029*
Immediately after opening pleura	96.89 ± 12.44	108.67 ± 13.90	<.001
15 min after opening pleura	93.99 ± 11.72	102.72 ± 14.93	<.001
30 min after opening pleura	96.75 ± 12.92	99.71 ± 13.12	.181
After closing pleura	98.30 ± 15.29	98.63 ± 14.72	.843
After awake	112.52 ± 14.85	112.36 ± 16.14	.881
Diastolic blood pressure (mm Hg)			
Baseline	72.43 ± 9.21	72.44 ± 9.31	.993
After anesthesia	57.15 ± 9.54	62.13 ± 9.97	<.001
Immediately after opening pleura	57.38 ± 8.86	67.04 ± 9.50	<.001
15 min after opening pleura	55.12 ± 8.20	62.76 ± 9.98	<.001
30 min after opening pleura	56.40 ± 8.65	60.55 ± 10.41	.011*
After closing pleura	58.67 ± 11.67	59.55 ± 12.41	.511
After awake	68.79 ± 12.17	66.83 ± 11.10	.131
BIS			
After anesthesia	51.20 ± 8.97	49.21 ± 9.49	.053
Immediately after opening pleura	48.48 ± 9.90	47.32 ± 10.01	.297
15 min after opening pleura	43.52 ± 8.60	43.86 ± 9.03	.741
30 min after opening pleura	46.12 ± 8.39	45.60 ± 9.31	.725
After closing pleura	50.17 ± 11.46	49.44 ± 10.27	.549
Operative view score			.435
4	6 (3.70)	9 (5.52)	
5	156 (96.30)	154 (94.48)	
Anesthesia effect score			.082
2	2 (1.23)	1 (0.61)	
3	14 (8.64)	5 (3.07)	
4	146 (90.13)	157 (96.32)	
Intraoperative cough			<.001
Yes	24 (14.81)	5 (3.07)	
No	138 (85.19)	158 (96.93)	

Values are presented as mean ± standard deviation or n (%). Percentages are calculated for the whole population. *SV-VATS*, Spontaneous ventilation video-assisted thoracoscopic surgery; *MV-VATS*, mechanical ventilation video-assisted thoracoscopic surgery; *BIS*, bispectral index. *$P < .05$.

TABLE E3. Postoperative recovery

Variable	SV-VATS (n = 162)	MV-VATS (n = 163)	*P* value
Operation time (min)	54.54 ± 19.09	52.41 ± 20.13	.329
Anesthesia time (min)	99.18 ± 27.87	101.35 ± 32.85	.523
Extubation time (min)	12.28 ± 9.13	17.30 ± 11.38	<.001*
Arousal time (min)	12.36 ± 11.11	15.15 ± 14.74	.050
PACU recovery time (min)	25.43 ± 15.25	30.67 ± 16.52	.020†
Food taking time (min)	346.07 ± 140.49	404.02 ± 219.69	.002†
Ambulation time (min)	225.46 ± 174.06	228.64 ± 174.06	.192
Hospitalization (d)	2.73 ± 1.81	2.69 ± 2.01	.653
Drainage within 4 h of surgery (mL)	28.24 ± 39.63	25.06 ± 27.89	.404
Chest tube removed within 4 h of surgery			.058
Yes	132 (80.98)	145 (88.96)	
No	30 (18.51)	18 (11.04)	
Postoperative force recovery (N)			
Left hand			
Baseline	31.18 ± 7.26	30.34 ± 8.23	.329
2 h after surgery	24.30 ± 9.36	24.19 ± 10.02	.450
4 h after surgery	26.22 ± 9.15	25.44 ± 9.51	.456
6 h after surgery	27.23 ± 8.77	26.15 ± 9.15	.280
Right hand			
Baseline	32.88 ± 8.42	32.55 ± 9.71	.742
2 h after surgery	25.37 ± 9.64	25.24 ± 11.49	.934
4 h after surgery	28.17 ± 9.59	26.52 ± 11.17	.156
6 h after surgery	28.49 ± 8.51	27.57 ± 10.82	.397
Postoperative status score‡			
POD 0	0.91 ± 1.23	1.04 ± 1.32	.360
POD 1	1.15 ± 1.30	1.44 ± 1.49	.065
POD 2	0.79 ± 1.19	1.07 ± 1.40	.079
POD 3	0.70 ± 1.08	0.88 ± 0.97	.315
1 wk after leaving hospital	0.18 ± 0.55	0.17 ± 0.66	.931

Values are presented as mean ± standard deviation or n (%). Percentages are calculated for the whole population. *SV-VATS*, Spontaneous ventilation video-assisted thoracoscopic surgery; *MV-VATS*, mechanical ventilation video-assisted thoracoscopic surgery; *PACU*, postanesthesia care unit; *POD*, postoperation day. *$P < .001$. †$P < .05$. ‡Details of the postoperative status score are presented in Table E7.

TABLE E4. Postoperative pain status and analgesia

Variable	SV-VATS (n = 162)	MV-VATS (n = 163)	*P* value
VAS evaluation			
4 h after surgery	3.16 ± 1.70	3.32 ± 1.82	.407
Before chest tube removal	2.94 ± 1.90	3.30 ± 2.14	.462
2 h after chest tube removal	2.61 ± 1.53	2.65 ± 1.46	.846
24 h after surgery	2.39 ± 1.46	2.36 ± 1.39	.884
48 h after surgery	1.81 ± 1.42	1.64 ± 1.14	.312
72 h after surgery	1.56 ± 1.23	1.65 ± 1.11	.735
Before leaving hospital	1.27 ± 0.84	1.24 ± 0.99	.806
Postoperative morphine analgesia			
4 h after surgery	3.34 ± 3.21	3.81 ± 3.32	.192
24 h after surgery	8.29 ± 7.76	8.42 ± 8.03	.878
48 h after surgery	10.76 ± 9.84	9.84 ± 8.48	.375

Values are presented as mean ± standard deviation. *SV-VATS*, Spontaneous ventilation video-assisted thoracoscopic surgery; *MV-VATS*, mechanical ventilation video-assisted thoracoscopic surgery; *VAS*, visual analog scale.

TABLE E5. Postoperative cough status

Time point	SV-VATS (n = 162)	MV-VATS (n = 163)	*P* value
Baseline			.301
Yes	33 (20.37)	26 (15.95)	
No	129 (79.63)	137 (84.05)	
POD 0			.155
Yes	42 (25.93)	54 (33.13)	
No	120 (74.07)	109 (66.87)	
POD 1			.051
Yes	47 (29.01)	64 (39.26)	
No	115 (70.99)	99 (60.74)	
POD 2			.327
Yes	38 (23.46)	46 (28.22)	
No	124 (76.54)	117 (71.78)	
POD 3			.767
Yes	22 (13.58)	24 (14.72)	
No	140 (86.42)	139 (85.28)	
1 wk after leaving hospital			.859
Yes	14 (8.64)	15 (9.20)	
No	148 (91.36)	148 (90.80)	
1 mo after leaving hospital			.824
Yes	9 (5.56)	10 (6.13)	
No	153 (94.44)	153 (93.87)	

Values are presented as n (%). Percentages are calculated for the whole population. *SV-VATS*, Spontaneous ventilation video-assisted thoracoscopic surgery; *MV-VATS*, mechanical ventilation video-assisted thoracoscopic surgery; *POD*, postoperation day.

TABLE E6. Postoperative inflammatory index

Inflammatory index	SV-VATS (n = 162)	MV-VATS (n = 163)	*P* value
SII			
Baseline	658.88 ± 707.26	630.26 ± 448.77	.664
4 h after surgery	1913.44 ± 1788.72	2487.70 ± 2083.64	.009*
24 h after surgery	1913.28 ± 1278.22	2134.27 ± 1931.57	.236
48 h after surgery	1111.76 ± 600.34	1170.15 ± 540.60	.409
1 wk after leaving hospital	811.86 ± 517.68	787.75 ± 513.37	.687
PLR			
Baseline	131.69 ± 66.23	130.57 ± 64.41	.877
4 h after surgery	196.71 ± 114.07	232.51 ± 161.81	.023*
24 h after surgery	195.44 ± 92.98	188.65 ± 95.24	.527
48 h after surgery	147.66 ± 57.69	149.81 ± 51.95	.752
1 wk after leaving hospital	169.80 ± 70.57	172.30 ± 70.85	.761
NLR			
Baseline	2.81 ± 2.79	2.73 ± 1.78	.748
4 h after surgery	8.59 ± 7.31	12.02 ± 10.13	.001*
24 h after surgery	8.71 ± 5.05	9.63 ± 8.10	.230
48 h after surgery	5.19 ± 2.62	5.37 ± 2.30	.549
1 wk after leaving hospital	2.57 ± 1.61	2.43 ± 1.35	.412

Values are presented as mean ± standard deviation. *SV-VATS*, Spontaneous ventilation video-assisted thoracoscopic surgery; *MV-VATS*, mechanical ventilation video-assisted thoracoscopic surgery; *SII*, systemic immune-inflammation, calculated as platelet count × neutrophil count/lymphocyte; *PLR*, platelet/lymphocyte; *NLR*, neutrophil/lymphocyte. *$P < .05$.

TABLE E7. Cost evaluation

Variable	SV-VATS (n = 162)	MV-VATS (n = 163)	*P* value
Total cost ($)	4723.26 ± 1101.45	4891.44 ± 910.71	.263
Anesthesia cost ($)	297.81 ± 156.65	399.81 ± 131.51	<.001
Operation cost ($)	1841.71 ± 494.16	1894.59 ± 521.64	.486
Nursing cost ($)	119.67 ± 126.59	103.46 ± 74.22	.290
Medicine cost ($)	214.22 ± 251.58	216.73 ± 173.96	.938
Surgical consumables cost ($)	1468.04 ± 871.22	1493.59 ± 738.22	.831
Diagnostic cost ($)	603.57 ± 144.90	591.46 ± 118.19	.537
Physiotherapy cost ($)	163.85 ± 111.86	143.80 ± 115.47	.238
Other cost ($)	60.94 ± 148.42	40.19 ± 92.98	.257

Values are presented as mean ± standard deviation. *SV-VATS*, Spontaneous ventilation video-assisted thoracoscopic surgery; *MV-VATS*, mechanical ventilation video-assisted thoracoscopic surgery.