Risk Factors for the Development of Intraoperative Hypoxia in Patients Undergoing Nonintubated Video-Assisted Thoracic Surgery: A Retrospective Study from a Single Center

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AE 1 Lan Lan
BD 1 Yanyi Cen
BF 2,3 Long Jiang
C 4 Huazhang Miao
B 2,3 Weixiang Lu

1 Department of Anesthesiology, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, P.R. China
2 Department of Cardiothoracic Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, P.R. China
3 Guangzhou Institute of Respiratory Disease and China State Key Laboratory of Respiratory Disease, Guangzhou, Guangdong, P.R. China
4 Department of Healthcare, Guangdong Women and Children Hospital, Guangzhou, Guangdong, P.R. China

Corresponding Author: Lan Lan, e-mail: lanlan@gzhmu.edu.cn
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Background: Nonintubated video-assisted thoracic surgery (NIVATS) has been demonstrated to be safe and effective in patients. However, the risk factors for intraoperative hypoxia are unclear. This retrospective study aimed to identify the risk factors for the development of intraoperative hypoxia in patients undergoing NIVATS.

Material/Methods: The study included patients who underwent NIVATS between January 2011 and December 2018. Intraoperative hypoxia was defined as $SpO_2 \leq 93\%$. Risk factors for hypoxia were identified by binary logistic regression analysis, and the characteristic distribution of patients with and without hypoxia was elaborated.

Results: Of 2742 included patients, age, anesthesia method, the technical level of surgeons, stair-climbing ability, and type of thoracic procedure were associated with intraoperative hypoxia ($P<0.05$). The characteristics of patients with hypoxia were older age ($P=0.011$), higher body mass index and revised cardiac risk index level ($P=0.033$ and $P=0.031$), and lower composition of stair-climbing ≥22 m ($P<0.001$). These patients also had more anatomical lung surgery and mediastinal mass resection ($P=0.033$) and more epidural anesthesia ($P=0.005$). The surgeries were more likely to be performed by surgeons with less than 10 years of VATS training ($P=0.009$) and to have increased intraoperative maximum end-expiratory carbon dioxide partial pressure ($P<0.001$). These patients had a longer Intensive Care Unit stay ($P<0.001$), duration of chest-tube drainage ($P=0.019$), and postoperative hospitalization ($P=0.003$).

Conclusions: The current study suggests that old age and stair-climbing ability of patients, anesthesia method, thoracic procedures, and surgeon experience are risk factors for intraoperative hypoxia in patients undergoing NIVATS.

Keywords: Risk Factors • Hypoxia, Brain • Intraoperative Complications • Thoracic Surgery, Video-Assisted

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Background

The successful debut of nonintubated video-assisted thoracic surgery (NIVATS) for wedge resection under thoracoscopy was first reported in 1997 [1]. With the enhancement of surgical instruments and advances in minimally invasive thoracoscopic techniques, NIVATS has been widely adapted for different types of thoracic procedures [2,3], including lobectomy [4], bullectomy [5], lung volume reduction surgery [6], and tracheal reconstruction [7], and it has even been used with a uniportal approach [8].

NIVATS is reported to shorten surgery time and hospital stay [9,10] and to enhance rehabilitation by having fewer complications [2-5,11]. The perioperative surgical outcomes of NIVATS for lobectomy have been confirmed to be comparable to those of the intubated technique [12-14]. These benefits may be due to NIVATS minimizing the adverse effects of intubation-induced airway trauma, ventilation-related lung injury, and residual muscle relaxation [3]. Use of NIVATS may also reduce postoperative nausea and vomiting and decrease the stress hormones and proinflammatory mediators related to mechanical ventilation [15]. Furthermore, patients may benefit from the low risk of intrapulmonary shunt due to the efficient contraction of the dependent hemidiaphragm and preserved hypoxic pulmonary vasoconstriction in spontaneous ventilation [16].

However, the perioperative risk factors for hypoxia in NIVATS are unclear. NIVATS requires spontaneous breathing of 1 lung and the iatrogenic pneumothorax-induced collapse of the other lung to facilitate the operation, which tends to bring about intraoperative hypoxia and hypercapnia. Severe intraoperative hypoxia can jeopardize tissue oxygenation and hemodynamic stability [17-19] and may increase the incidence of postoperative complications [20,21]. Moreover, patients may have to transfer to endotracheal intubation when the hypoxia cannot be corrected in NIVATS. Therefore, it is important to identify the preoperative risk factors for intraoperative hypoxia to exclude high-risk patients and to permit early and timely intervention in others. However, many medical centers fail to do so due to their cases being scarce.

This retrospective study aimed to identify the risk factors for the development of intraoperative hypoxia in patients who underwent NIVATS between 2011 and 2018, and it compared patients' perioperative characteristics with nonhypoxia and hypoxia events.

Material and Methods

A large single-center retrospective cohort was conducted with a post hoc reanalysis. Exposures and outcomes were defined a priori. This study was reviewed and approved by the Medical Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. K-51; Guangzhou, China) on November 5, 2019. Patient consent was waived due to the study's retrospective design. The study included adult patients who underwent NIVATS between January 1, 2011, and December 30, 2018, at the Guangzhou Institute of Respiratory Diseases. All data were obtained from medical electronic records, anesthesia record sheets, and the hospital examination system. Patients were excluded if they were <18 years old and if they underwent thoracic surgery under endotracheal intubation anesthesia. Patients were also excluded if they underwent simultaneous operations on organs other than the lungs, proceeded to thoracotomy and tracheal tumor resection under NIVATS, or had intraoperative conversion to endotracheal intubation due to bleeding, pleural adhesions, or other nonhypoxia factors. Patients were also excluded if intraoperative values were missing or postoperative medical records were incomplete. All perioperative data were collected.

Anesthesia Procedure

All patients received thoracoscopic surgery with nonintubated anesthesia under the 3-portal approach as described previously [22,23]. Some patients received a target-controlled infusion of propofol 2-4 µg/mL and remifentanil 1-3 ng/mL and intravenous dexmedetomidine 0.5-1 µg/kg/h. A bispectral index value between 40 and 60 was maintained. Laryngeal mask airway (LMA) was placed when patients became unconscious, and end-expiratory carbon dioxide partial pressure ($P_{ET}CO_2$) was continuously monitored via capnography. The other patients received epidural anesthesia by placing an epidural catheter into the T5-T6 or T6-T7 epidural space, and anesthesia was maintained with 0.375% ropivacaine with the anesthesia plane titrated to between the 2nd and 10th ribs. All patients received standard monitoring, but $P_{ET}CO_2$ was not monitored in patients who received epidural anesthesia. Arterial catheterization was used for arterial pressure monitoring and to examine arterial blood gas analysis when SpO_2 ≤93%, while central venous catheterization was dependent on the conditions of operation and patients.

The gas flow was inhaled at 4-5 L/min with FiO_2 of 100% during the operation. Synchronous intermittent mandatory ventilation was implemented after the main procedures were completed to exhale carbon dioxide. The main procedures were defined as the removal of the lung lesion, lymph node dissection, and pleural lavage. Dopamine or norepinephrine was used to maintain mean arterial pressure >60 mmHg. Patients were transferred to the Postanesthesia Care Unit to remove the LMA or epidural catheter after the operation. Self-controlled intravenous analgesia was used for all patients after the operation. After that, patients were sent to the Intensive Care Unit or General Ward according to their conditions.

Surgical Procedure

The thoracoscopic procedures followed the consensus guidelines of the American Association for Thoracic Surgery [24]. Skin local anesthesia was performed with 2% lidocaine. After the pleura opening, the surface of the visceral pleura was sprayed with 5 mL of 2% lidocaine, and the intercostal nerve and left vagus nerve were infiltrated with 2.5 mL of 2% lidocaine and 2.5 mL of 0.75% ropivacaine under direct vision for inhibition of pain and the coughing reflex. Lung collapse was achieved through iatrogenic pneumothorax. The patient's condition and surgical procedures determined whether a chest tube would be placed. All thoracic procedures were classified into 5 types: nonanatomical lung surgery, including wedge resection, bullectomy, and lung volume reduction surgery; anatomical lung surgery, including lobectomy and segmentectomy; mediastinal mass resection; bilateral sympathectomy; and other surgery, including thoracoscopic exploration, lung biopsy, pericardial cyst resection, and so forth.

The surgery time was the interval from skin incision to surgical dressing covering. Blood testing was done before the operation and on the first day after the operation. Postoperative clinical complications, including pleural effusion, dyspnea, air leakage, and reoperation, were recorded.

Outcome Definition

Due to the respiratory volume reduction and rebreathing effect in NIVATS [25], the primary concern is the intraoperative hypoxia values. Since SpO_2 reacts to hypoxia quickly and effectively, we chose continuous monitoring of SpO_2 as the main observation indicator instead of intermittent monitoring of PaO_2. An intraoperative SpO_2 ≤93% lasting for 5 min was taken as evidence of hypoxia [26]. Manual assisted ventilation or synchronous intermittent mandatory ventilation was initiated when SpO_2 ≤90%. The intraoperative SpO_2 was continuously monitored and recorded in the anesthesia record sheet.

Statistical Analysis

Statistical analyses were performed with SPSS software (version 26.0, Chicago, IL, USA). Continuous variables are presented as mean±standard deviation or as median (interquartile range). Dichotomous variables are presented as percentages of the total number of data points available for that field. The variables for different patients with and without hypoxia were analyzed by an independent-samples t test for continuous variables and the Mann-Whitney U test for dichotomous variables. Preoperative values with a P value <0.05 were included in the logistic regression analysis. The variables evaluated for inclusion in the logistic regression analysis were age, body mass index (BMI), revised cardiac risk index (RCRI), stair-climbing ability, types of thoracic procedure, technique level of surgeons, anesthesia method, preoperative values of leukocytes and neutrophils. Binary logistic regression analysis was used to determine the risk factors of the preoperative variables with intraoperative hypoxia. A propensity score-matching analysis was used to counterbalance the discrepancies between the nonhypoxia and hypoxia groups to further analyze whether hypoxia affected the intraoperative outcomes and postoperative recovery. The propensity score model development was done by including age, BMI, RCRI, stair-climbing ability, types of thoracic procedure, technique level of surgeons, anesthesia method, and preoperative values of leukocytes and neutrophils. A P value of <0.05 indicated statistical significance.

Results

A total of 2742 patients who underwent thoracic surgery between 2011 and 2018 met the inclusion criteria (**Figure 1**), with 2497 patients in the nonhypoxia group and 245 patients in the hypoxia group. Two comparable patient groups (n=240 for each group) were identified by using propensity score-matching analysis to counterbalance the discrepancies (**Tables 1-3**). No patient was converted to endotracheal intubation due to hypoxia.

Risk Factors of Intraoperative Hypoxia

Logistic regression analysis showed that age, anesthesia method, technical level of surgeons, stair-climbing ability, and types of thoracic procedures were the risk factors for intraoperative hypoxia (P<0.05). Moreover, the technical level of surgeons with VATS training ≤5 years (P=0.029) and the thoracic types of nonanatomical and anatomical lung surgery were risk factors for intraoperative hypoxia (P=0.015, and P=0.002) (**Table 4**).

Preoperative Characteristics of Patients with and without Hypoxia

Further analysis revealed that patients with intraoperative hypoxia were older and a higher proportion were over 60 years (47.32 vs 44.48 years, P=0.011 and 27% vs 22%, P=0.046), and they had higher BMI (21.99 vs 21.55 kg/m^2, P=0.033), a higher level of RCRI (P=0.031), and a higher proportion of stair-climbing ability <22 m (4 vs 1%, P<0.001). These patients were also more likely to have undergone anatomical lung surgery and mediastinal mass resection (29% vs 25% and 11% vs 7%, P=0.033) and to have received epidural anesthesia (29% vs 21%, P=0.005), and fewer of the surgeons had VATS training ≥10 years (52% vs 63%, P=0.009) (**Table 1**).
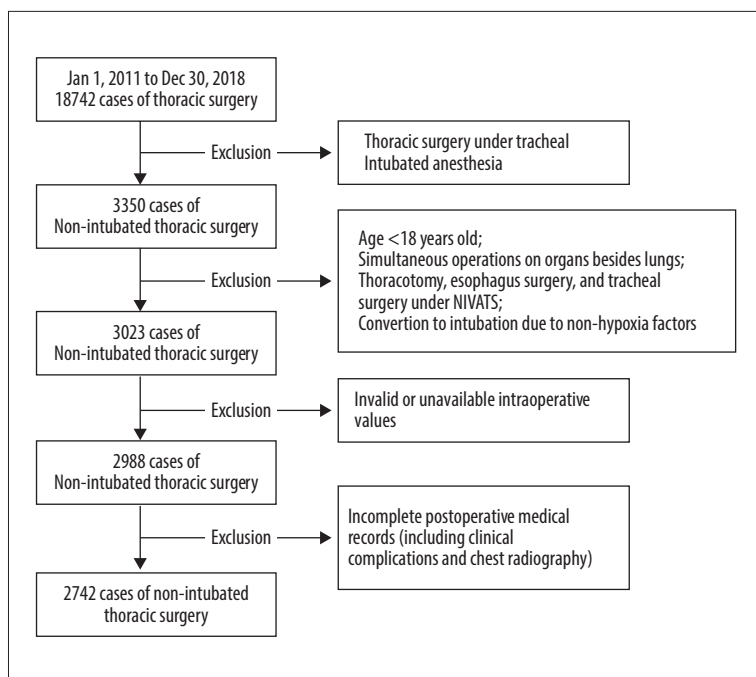
Figure 1. Flow chart of data collection. NIVATS, nonintubated video-assisted thoracic surgery.

Table 1. Preoperative characteristics of patients with or without hypoxia.

Variables	Before matching			After matching		
	Nonhypoxia (n=2497)	Hypoxia (n=245)	P value	Nonhypoxia (n=240)	Hypoxia (n=240)	P value
Age, y	44.48±16.71	47.32±16.68	0.011	46.24±17.46	47.02±16.62	0.619
Age, n (%)			0.046			0.883
18-44 y	1149 (46)	101 (41)		105 (43)	100 (42)	
45-59 y	810 (32)	78 (32)		69 (29)	78 (32)	
60-74 y	497 (20)	59 (24)		60 (25)	55 (23)	
≥75 y	41 (2)	7 (3)		6 (3)	7 (3)	
Sex, n (%)			0.435			0.310
Male	1444 (58)	148 (60)		133 (55)	144 (60)	
Female	1053 (42)	97 (40)		107 (45)	96 (40)	
BMI, kg/m^2	21.55±3.02	21.99±3.09	0.033	21.85±3.08	21.95±3.08	0.213
ASA physical status, n (%)			0.140			0.331
I	1984 (80)	185 (76)		193 (80)	184 (77)	
II	470 (19)	54 (22)		41 (17)	50 (21)	
III	43 (2)	6 (2)		6 (3)	6 (2)	
Previous medical history, n (%)						
Smoking history	450 (18)	37 (15)	0.254	41 (17)	36 (15)	0.534
Cardiovascular disease	187 (8)	23 (9)	0.286	20 (8)	22 (9)	0.747
Diabetes	79 (3)	7 (3)	0.793	11 (5)	5 (2)	0.127
Pulmonary operation history	73 (3)	7 (3)	0.953	3 (1)	7 (3)	0.202
Pulmonary disease	129 (5)	14 (6)	0.713	12 (5)	12 (5)	1.000
Hepatic dysfunction	33 (1)	5 (2)	0.358	6 (3)	5 (2)	0.761

Table 1 continued. Preoperative characteristics of patients with or without hypoxia.

Variables	Before matching			After matching		
	Nonhypoxia (n=2497)	Hypoxia (n=245)	*P* value	Nonhypoxia (n=240)	Hypoxia (n=240)	P value
Neurologic diseases	39 (2)	5 (2)	0.569	2 (1)	5 (2)	0.254
Nonpulmonary cancer	66 (3)	8 (3)	0.566	7 (3)	8 (3)	0.793
RCRI, n (%)			0.031			0.704
1 point	2479 (99)	240 (98)		236 (98)	237 (99)	
2 points	18 (1)	5 (2)		4 (2)	3 (1)	
Stair climbing			<0.001			0.001
≥22 m	2473 (99)	235 (96)		240 (100)	230 (96)	
<22 m	24 (1)	10 (4)		0	10 (4)	
LVEF, n (%)	n=2127 71.02±5.35	n=212 71.44±7.15	0.292	n=208 71.08±5.14	n=207 71.48±7.14	0.511
Pulmonary function tests, n (%)	n=1659	n=178		n=154	n=170	
FVE$_1$% predicted	92.90±18.47	92.04±18.70	0.555	91.98±17.94	92.06±18.82	0.968
FVC% predicted	95.31±18.37	93.63±18.41	0.245	92.99±19.39	94.02±18.21	0.616
FEV$_1$/FVC% predicted	96.88±11.72	97.90±11.72	0.272	96.88±12.30	98.08±11.38	0.354
Types of thoracic procedure, n (%)			0.033			0.895
Nonanatomical lung surgery	1482 (59)	127 (52)		131 (54)	126 (53)	
Anatomical lung surgery	615 (25)	70 (29)		54 (22)	68 (28)	
Mediastinal mass resection	174 (7)	27 (11)		23 (10)	27 (11)	
Bilateral sympathectomy	81 (3)	9 (4)		23 (10)	10 (4)	
Other surgery	145 (6)	12 (5)		9 (4)	9 (4)	
Surgical location, n (%)			0.241			0.801
Left lung	1042 (42)	85 (35)		90 (37)	83 (34)	
Right lung	1086 (44)	132 (54)		108 (45)	130 (54)	
Mediastinum	340 (14)	24 (10)		42 (18)	23 (10)	
Left and right lung	29 (1)	4 (2)		0	4 (2)	
Anesthesia methods, n (%)			0.005			0.540
TCI+LMA	1975 (79)	175 (71)		177 (74)	171 (71)	
EA	522 (21)	70 (29)		63 (26)	69 (29)	
Technical level of surgeons, n (%)			0.009			0.819
VATS training ≤5 y	355 (14)	31 (13)		49 (20)	30 (12)	
VATS training 6-10 y	559 (22)	85 (35)		49 (20)	81 (34)	
VATS training ≥10 y	1583 (63)	129 (52)		142 (60)	129 (54)	
Technical level of anesthetists, n (%)			0.203			0.050
Attending	2082 (83)	212 (87)		192 (80)	208 (87)	
Residents	415 (17)	33 (13)		48 (20)	32 (13)	

ASA – American Society of Anesthesiologists; BMI – body mass index; EA – epidural anesthesia; FEV$_1$% predicted – the forced expiratory volume in the first second in percent of predicted; TCI – target-controlled infusion; FVC% predicted – the forced vital capacity in percent of predicted; LMA – laryngeal mask airway; LVEF – left ventricular ejection fraction; RCRI – revised cardiac risk index; VATS – video-assisted thoracic surgery.

Table 2. Intraoperative comparisons of patients with or without hypoxia.

Variables	Before matching			After matching		
	Nonhypoxia (n=2497)	Hypoxia (n=245)	P value	Nonhypoxia (n=240)	Hypoxia (n=240)	P value
Surgery time, min	80 (50, 125)	80 (50, 135)	0.453	75 (50, 130)	80 (50, 135)	0.306
Blood loss, mL	15 (5, 45)	15 (10, 50)	0.057	15 (5, 45)	15 (10, 50)	0.143
Intraoperative minimum SpO_2, %	98.26±1.76	90.68±3.05	<0.001	98.32±1.78	90.68±3.07	<0.001
Level of intraoperative SpO_2, n (%)			<0.001			<0.001
94-100%	2493 (100)	0		240 (100)	0	
90-93%	0	211 (86)		0	207 (86)	
≤89%	0	34 (14)		0	33 (14)	
Intraoperative maximum $P_{ET}CO_2$, mmHg	n=1975 45.62±7.24	n=175 49.82±9.65	<0.001	n=177 45.25±6.73	n=159 49.90±9.46	<0.001
Level of intraoperative $P_{ET}CO^2$, n (%)	n=1975	n=175		n=177	n=159	
30-45 mmHg	1192 (60.4)	76 (43.4)		107 (61)	67 (42)	
46-60 mmHg	724 (36.7)	75 (42.9)		68 (38)	70 (44)	
61-80 mmHg	59 (3.0)	23 (13.1)		2 (1)	21 (13)	
>81 mmHg	0	1 (0.6)	<0.001	0	1 (1)	<0.001

$P_{ET}CO_2$ – End-expiratory carbon dioxide partial pressure; SpO_2 – pulse oxygen saturation.

Intraoperative Comparison of Patients with and without Hypoxia

The total incidence of hypoxia ($SpO_2 \leq 93\%$) was 9% (245/2742) and only 1.2% of patients (34/2742) experienced severe hypoxia (<90%). The total incidence of hypercapnia ($P_{ET}CO_2 \geq 46$ mmHg) was 41% (882/2150), and only 3.8% of patients (83/2150) had moderate hypercapnia ($P_{ET}CO_2 \geq 61$ mmHg).

The results of propensity score-matching analysis showed that the patients with hypoxia were also combined with a higher-level proportion of $P_{ET}CO_2 \geq 46$ mmHg ($P < 0.001$). The intraoperative maximum $P_{ET}CO_2$ was higher (49.90 vs 45.25 mmHg, $P < 0.001$) (**Table 2**). Arterial blood gas was analyzed when $SpO_2 \leq 93\%$ and the mean values of PaO_2 and $PaCO_2$ were 62.28±4.23 mmHg and 56.59 ± 12.84 mmHg in patients with hypoxia (**Figure 2**).

Postoperative Comparison of Patients with and without Hypoxia

The results of propensity score-matching analysis showed that the patients who experienced intraoperative hypoxia had a longer Intensive Care Unit stay ($P=0.039$), but the chest-tube drainage, postoperative hospital stay, and the incidence of postoperative clinical complications were similar to those without hypoxia ($P=0.077$, $P=0.059$, and $P=0.216$) (**Table 3**).

Discussion

This retrospective study revealed that the total incidence of intraoperative $SpO_2 \leq 93\%$ was 9%. The main risk factors for intraoperative hypoxia were age, anesthesia method, technical level of surgeons, stair-climbing ability, and the type of thoracic procedure. The overall distribution of characteristics in this study indicated that NIVATS was mostly performed in young-to middle-aged patients with normal BMI, American Society of Anesthesiologists (ASA) level grade I or II, RCRI grade I, and normal cardiopulmonary function. Comorbidities of smoking history, cardiopulmonary disease, and a history of pulmonary operation were not absolute exclusion criteria. The procedure of NIVATS was mainly nonanatomical lung surgery, and it also had no limitation with regard to the sex of the patient or the surgical location.

NIVATS is a safe and feasible alternative procedure and improves postoperative rehabilitation by reducing postoperative complications, hospital stay, and attenuating stress and inflammatory responses [10,13,14]. However, few specific analyses of risk factors for NIVATS have been conducted even though the procedure has been used in a large number of patients [27-31]. The distribution characteristics of patients with intraoperative hypoxia revealed that older patients with higher BMI and inferior cardiopulmonary function who underwent anatomical

Table 3. Postoperative comparisons of patients with or without hypoxia.

Variables	Before matching			After matching		
	Nonhypoxia (n=2497)	Hypoxia (n=245)	P value	Nonhypoxia (n=240)	Hypoxia (n=240)	P value
Mean ICU stay, d	0 (0, 1)	0 (0, 1)	<0.001	0 (0, 1)	0 (0, 1)	0.039
Duration of chest-tube drainage, d	2 (0, 3)	2 (0.5, 3)	0.019	2 (0, 3)	2 (0.5, 3)	0.077
Postoperative hospital stay, d	4 (3, 6)	5 (3, 7)	0.003	4 (3, 7)	5 (3, 7)	0.059
Postoperative clinical complications, n (%)			0.724			
None	2310 (92.5)	225 (92)		227 (94.6)	220 (91.7)	0.216
Pleural effusion	125 (5)	15 (6.1)		8 (3.3)	15 (6.3)	
Mechanical ventilation	3 (0.1)	2 (0.8)		0	2 (0.8)	
Dyspnea	13 (0.5)	0		0	0	
Arrhythmia	5 (0.2)	0		1 (0.4)	0	
Air leakage in chest tube	23 (0.9)	0		3 (1.3)	0	
Fever	6 (0.2)	1 (0.4)		1 (0.4)	1 (0.4)	
Reoperation	4 (0.2)	2 (0.8)		0	2 (0.8)	
Cardio-dysfunction	2 (0.1)	0		0	0	
Chylothorax	4 (0.2)	0		0	0	
Pulmonary embolism	1	0		0	0	
Death	1	0		0	0	

ICU – Intensive Care Unit.

Table 4. Risk factors of intraoperative hypoxia.

Complications	Variables	P value	OR (95% CI)
Intraoperative hypoxia	Age	0.002	1.013 (1.005-1.022)
	Anesthesia method	0.021	1.438 (1.057-1.956)
	The technical level of surgeons	<0.001	
	VATS training ≤5 y	0.029	1.642 (1.051-2.565)
	Stair climbing	<0.001	4.329 (1.988-9.428)
	Types of thoracic procedure	0.011	
	Nonanatomical lung surgery	0.015	1.492 (1.082-2.058)
	Anatomical lung surgery	0.002	2.046 (1.299-3.222)

CI – confidence interval; OR – odds ratio; VATS – video-assisted thoracic surgery.

lung surgery under epidural anesthesia by thoracic surgeons with <10 years of VATS training had a high incidence of hypoxia. A logistic regression analysis of these risk factors confirmed these inferences. As reported by the ASA, the risk of morbidity and mortality from general anesthesia is always present, and the risk of laryngotracheal injuries caused by double-lumen tube should not be underestimated [32]. Nevertheless, NIVATS was sometimes advocated for patients with inferior pulmonary function in less invasive procedures. Although the difficulty of intraoperative management increased, the patients recovered quickly after the operation, due to less sedative and analgesic drugs, and the probability of postoperative mechanical ventilation and weaning difficulty was reduced [32-35]. At present, most patients who have undergone NIVATS are successful case
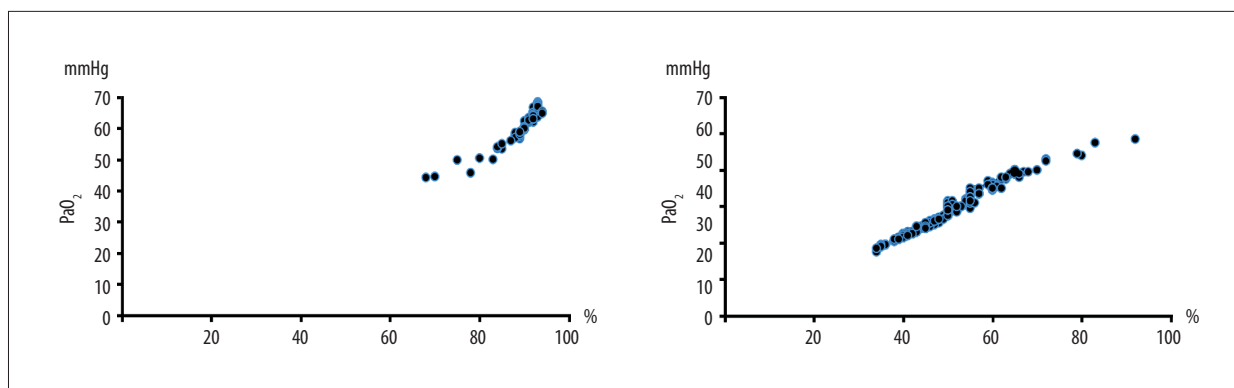
Figure 2. The values of PaO_2 and $PaCO_2$ in patients with hypoxia. Arterial blood gas was analyzed when SpO_2 ≤93%, and the mean values of PaO_2=62.28±4.23 mmHg and $PaCO_2$=56.59×12.84 mmHg.

reports, but whether NIVATS is suitable or not still needs to be verified. Therefore, NIVATS must be carefully evaluated to attain more advantages than disadvantages for patients with inferior pulmonary function or those who cannot tolerate tracheal intubation general anesthesia.

In theory, hypoxia does not occur easily in spontaneous ventilation when an individual is in a lateral position. The lower diaphragm contracts more efficiently without obviously decreasing the functional residual capacity during spontaneous respiration [36,37], and more blood distribution occurs in the dependent lung by gravity and hypoxic pulmonary vasoconstriction [16,38], which results in a better matching of the ventilation quotient. However, hypoxia still occurred in 9% of patients undergoing NIVATS in our study. Nonintubated anesthesia cannot avoid rebreathing, which easily leads to hypercapnia. Our study also revealed that the patients with intraoperative hypoxia also had a higher proportion of hypercapnia, which reached 41%, but only 1.2% and 3.8% of patients had severe hypoxia (<90%) and moderate hypercapnia ($P_{ET}CO_2$ ≥61 mmHg), which showed that NIVATS was safe. Complex thoracic surgery, such as anatomical lung surgery, may aggravate the extent of hypoxia. In addition, the surgeon's familiarity with the anatomy of the endoscope view is a prerequisite for a quick and accurate operation, which decreases perioperative complications and improves recovery in NIVATS [37,38]. Therefore, to avoid increased incidence of hypoxia and hypercapnia in patients, we recommend against surgeons with <10 years of VATS training proceeding with complicated procedures in NIVATS. It is possible in our study that junior surgeons were more aggressive in manipulating lung tissues or the operations were too complicated for their experience.

The anesthesia method of target-controlled infusion combined with LMA seemed to be safer than epidural anesthesia in our study. Since the lung is innervated by the visceral nerve, the somatic nerve can be blocked under local anesthesia of the skin and intercostal nerve, and then VATS can be completed under the assistance of moderate sedation and mild analgesia [39,40]. LMA is a strong measure to ensure oxygenation in patients receiving nonintubated anesthesia, and it can decrease the incidence of hypoxia, especially in patients with a high risk of upper airway obstruction. As to the high plane block in thoracic epidural anesthesia, it decreases the inspiratory capacity as a consequence of the motor block of the intercostal muscles [41,42], which may lead to hypercapnia and hypoxia during thoracic surgery. It is possible that patients that received an epidural also had a higher RCRI and more complex resections, resulting in the epidural being seen as increasing the incidence of hypoxia. But which anesthesia method is the best suited for NIVATS? A more detailed comparison is still needed to determine the answer [43].

Furthermore, Bellucci and Qiao [20] and Cureley et al [21] proposed that intraoperative hypoxia may increase the incidence of postoperative complications. However, after the propensity score-matching analysis of preoperative basic characteristics in the current study, patients with hypoxia were associated with intraoperative hypercapnia and increased the probability of intensive care, but hypoxia did not affect the overall complications and postoperative hospital stay. This outcome may imply that the impact of intraoperative hypoxia on patients is short-term in NIVATS and has no significant impact on the overall clinical recovery after the operation.

Undoubtedly, this study design could be modified and improved. First, this is a single-center retrospective investigation with data collected over 8 years, and bias (eg, laboratory measurement bias) due to the long period of time was inevitable. In addition, the large sample of data were collected by more than one person, which inevitably led to measurement bias. However, all patients were treated at the same center and a uniform therapeutic regime may have reduced the potential bias. Second, miscellaneous types rather than a specific type of thoracic procedures were included, and cases were consequently less comparable. However, this situation presents a

real-world clinical scenario. Third, patients younger than 18 years old were excluded, and pediatric patients need to be included in future studies to determine whether NIVATS is safe for young patients. Fourth, although the PaO_2 can reflect the real oxygenation status of patients, a change in SpO_2 is recognized much more easily and quickly. Therefore, the continuous monitoring index $SpO_2 \leq 93\%$, not the PaO_2, was chosen as the outcome standard. Fifth, although the propensity score-matching analysis was used to reduce the preoperative bias to the outcomes, prospective studies are still needed to confirm whether intraoperative hypoxia affects the prognosis of patients in NIVATS.

Conclusions

Rigorous preoperative evaluations should be implemented for patients who are scheduled for NIVATS. Identification of risk factors for intraoperative hypoxia in NIVATS may guide recommendations for early identification of high-risk patients

and enable interventions before the operation. The incidence of intraoperative hypoxia in our study was related to the patient's age, anesthesia method, the technical level of surgeons, the stair-climbing ability, and the type of thoracic procedure. However, even if intraoperative hypoxia occurred, it did not affect the postoperative recovery duration.

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Conflicts of Interest

None.

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