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Development of a Risk Scoring Model to Predict Unexpected Conversion to Thoracotomy during Video-Assisted Thoracoscopic Surgery for Lung Cancer

Ga Young Yoo, M.D.¹, Seung Keun Yoon, M.D.¹, Mi Hyoung Moon, M.D., Ph.D.¹, Seok Whan Moon, M.D., Ph.D.¹, Wonjung Hwang, M.D. Ph.D.², Kyung Soo Kim, M.D., Ph.D.¹

Departments of ¹Thoracic and Cardiovascular Surgery and ²Anesthesiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

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Corresponding author

Kyung Soo Kim Tel 82-2-2258-6139 Fax 82-594-8644 E-mail cskks@catholic.ac.kr ORCID https://orcid.org/0000-0002-3680-9851

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Background: Unexpected conversion to thoracotomy during planned video-assisted thoracoscopic surgery (VATS) can lead to poor outcomes and comparatively high morbidity. This study was conducted to assess preoperative risk factors associated with unexpected thoracotomy conversion and to develop a risk scoring model for preoperative use, aimed at identifying patients with an elevated risk of conversion.

Methods: A retrospective analysis was conducted of 1,506 patients who underwent surgical resection for non-small cell lung cancer. To evaluate the risk factors, univariate analysis and logistic regression were performed. A risk scoring model was established to predict unexpected thoracotomy conversion during VATS of the lung, based on preoperative factors. To validate the model, an additional cohort of 878 patients was analyzed.

Results: Among the potentially significant clinical variables, male sex, previous ipsilateral lung surgery, preoperative detection of calcified lymph nodes, and clinical T stage were identified as independent risk factors for unplanned conversion to thoracotomy. A 6-point risk scoring model was developed to predict conversion based on the assessed risk, with patients categorized into 4 groups. The results indicated an area under the receiver operating characteristic curve of 0.747, with a sensitivity of 80.5%, specificity of 56.4%, positive predictive value of 1.8%, and negative predictive value of 91.0%. When applied to the validation cohort, the model exhibited good predictive accuracy.

Conclusion: We successfully developed and validated a risk scoring model for preoperative use that can predict the likelihood of unplanned conversion to thoracotomy during VATS of the lung.

Keywords: Video-assisted thoracic surgery, Conversion, Thoracotomy, Lung neoplasms

Introduction

Major advances in both equipment and technique have led to the increased use of minimally invasive surgical approaches [1]. Video-assisted thoracoscopic surgery (VATS) has become increasingly common in the surgical treatment of lung cancer [2]. This method is now established as the gold-standard approach for early-stage non-small cell lung cancer (NSCLC) [3]. A review of the database of the Society of Thoracic Surgeons revealed an increase in the use of VATS for lobectomies from 21.6% in 2004 to 32% in 2006, with this rate reaching 45% by 2010 [4]. Since multiple studies have demonstrated that minimally invasive approaches result in lower morbidity [5,6] and higher survival rates [7], we can reasonably expect this trend to become even more pronounced over time.

However, since VATS is a technically demanding procedure with a learning curve, the risk of unplanned conversion to thoracotomy during VATS lung resection remains a substantial concern. Unplanned conversion has been reported in up to 43% of cases [8] and may result in longer operation times, increased risk of injury to surrounding tissues, and greater blood loss [9]. Although the long-term effects of conversion are a matter of debate [10], these con-

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sequences can ultimately lead to increased morbidity and mortality [11]. Therefore, identifying patients who are likely to require thoracotomy conversion can provide valuable information in terms of patient selection, thus helping to mitigate the risk of this event and enhancing surgical outcomes.

Older age, male sex, fibrocalcified lymph nodes, clinically node-positive disease, large tumor size, and the use of neoadjuvant therapy have been identified as risk factors for unexpected conversion to thoracotomy [12-14]. In this study, we examined risk factors among patients who underwent unplanned thoracotomy conversion and sought to determine the impact of preoperative patient-related factors on conversion. Utilizing the identified risk factors, we created a risk scoring model, which, to our knowledge, is novel. We believe that this model will be useful in predicting the likelihood of unexpected thoracotomy conversion.

Methods

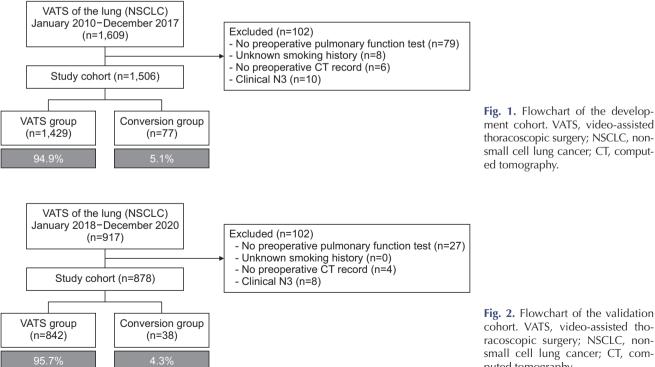
Patients

We reviewed the medical records of 2,526 patients who underwent VATS for NSCLC at Seoul St. Mary's Hospital between January 2010 and December 2020. We excluded patients who underwent planned open thoracotomy; those lacking preoperative medical records such as pulmonary function tests, data on smoking history, or computed tomography (CT) scans; and those diagnosed with clinical N3 disease. Ultimately, 1,506 patients from January 2010 to December 2017 were included in the primary cohort for the development of a scoring model to predict unplanned conversion to thoracotomy (Fig. 1). Additionally, 878 patients from January 2018 to December 2020 were included in the validation cohort (Fig. 2).

Preoperative patient evaluation typically included CT imaging of the chest with contrast enhancement, unless contraindicated. If cancer was suspected based on the CT findings, additional staging evaluations were conducted using positron emission tomography-CT, bone scans, and brain magnetic resonance imaging. When multilevel N2 disease was suspected, either endobronchial ultrasoundguided transbronchial needle aspiration or mediastinoscopic lymph node biopsy was performed. The clinical stage was classified according to the most recent version of the tumor, node, and metastasis staging system, which was the eighth edition [15].

Operative technique

For the typical VATS approach, all patients were placed under general anesthesia using a double-lumen endotra-



ment cohort. VATS, video-assisted thoracoscopic surgery; NSCLC, nonsmall cell lung cancer; CT, computed tomography.

cheal tube and situated in the lateral decubitus position. Two monitors were positioned near the patient's head. A 5-mm or 10-mm trocar for the thoracoscope was inserted into the seventh or eighth intercostal space along the midaxillary line. A working incision, ranging from 3 to 6 cm, was made on the anterior axillary line in the fourth or fifth intercostal space under thoracoscopic guidance, and 1 to 3 additional instrument ports, each 5 to 10 mm, were placed as needed. The exact location of the working incision was determined based on the location of the lesion. Rib retractors were not employed in the initial VATS setup. Vascular and bronchial structures were typically divided using an endoscopic stapling device, and mediastinal lymphadenectomy was performed. At the conclusion of surgery, a single chest tube was inserted, and most patients were extubated in the operating room.

Definitions

Thoracotomy conversion was performed at the discretion of the attending surgeon, typically by extending the working incision. An unplanned conversion to open thoracotomy was defined as a conversion that occurred during surgery initially intended as VATS. If the decision to convert was made immediately after the initial VATS exploration, it was not considered an unplanned conversion. Our analysis included only total open conversions, which were indicated by the use of a rib retractor or full thoracotomy incision. We reviewed the medical records of our study cohort to identify cases of thoracotomy conversion. The surgical records of these patients were then examined to determine the cause of conversion. Fibrocalcified lymph nodes and pleural calcifications were identified on preoperative CT scans when the official radiology report described abnormally enlarged lymph nodes or pleural calcifications. Preoperative CT scans were also utilized to assess fissure completeness. A complete fissure was defined as one for which continuity could be identified on at least 1 plane (sagittal, coronal, or axial) [16].

Statistical analysis

Patient characteristics and surgical outcomes were compared between the patients who underwent complete VATS and those who required conversion. This was accomplished using chi-square tests, Student t-tests, or Wilcoxon ranksum tests, as appropriate. Univariate logistic regression analysis was applied to identify variables that may influence the likelihood of conversion from VATS. This analysis included patient demographics, body mass index, the results of pulmonary function tests, clinical staging, and the use of neoadjuvant therapy, yielding odds ratios (ORs) with 95% confidence intervals (CIs). Any variable with a univariate p-value of less than 0.2 was additionally examined using multivariable logistic regression analysis. A risk scoring model to predict the probability of unexpected conversion to thoracotomy was developed based on the variables identified through multivariable logistic regression analysis. This model was subsequently validated using data from a patient population selected under the same criteria, who underwent surgery between January 2018 and December 2020.

Ethical considerations

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The institutional review board of Seoul St. Mary's Hospital reviewed and approved the study protocol (IRB approval no., KC23RISI0743) and granted a waiver for the requirement of informed consent.

Results

Patient characteristics

A total of 2,532 patients with NSCLC who underwent VATS pulmonary resection between January 2010 and December 2020 were initially considered for inclusion in the study. The exclusion criteria included patients who underwent planned open thoracotomy, those without preoperative medical records, and those diagnosed with clinical N3 disease. After applying these criteria, 2,378 patients remained and were included in the study cohort. The development cohort included 1,506 individuals who underwent surgery between 2010 and 2017, while the validation cohort included 878 patients from 2018 to 2020. Within the development cohort, 77 patients (5.1%) experienced unexpected conversion to thoracotomy during surgery (Fig. 1). Table 1 presents the baseline characteristics of the development cohort. The mean age of patients in the conversion group was 66.4±9.8 years, with a male predominance (61 patients, 79.2%). Compared to the VATS group, those who required conversion displayed a higher proportion of male patients (p<0.001), a more frequent history of smoking (p<0.001), a higher T stage (p<0.001), a higher rate of lymph node metastasis (p<0.001), and a higher frequency of neoadjuvant treatment (p<0.001). In the validation cohort, 38 patients (4.3%) underwent unexpected thoracotomy conversion during surgery (Fig. 2). The baseline characteristics of the validation cohort are shown in Table 2, while Table 3 displays the contingency table for the development and validation cohorts.

The reasons for unexpected conversion to thoracotomy are detailed in Table 4. The most common of these reasons was the presence of fibrocalcified lymph nodes, which accounted for 29 cases (37.7%). This was followed by pleural adhesions, with 23 cases (29.9%). Vascular injury was found in 9 patients (11.9%). Other factors that necessitated conversion included invasion into vessels or adjacent structures (9.1%), large tumor size (2.6%), the requirement for additional procedures (2.6%), poor oxygenation (1.3%), and instances where the tumor was not located (1.3%). In 3 cases (3.9%), the reason for conversion was not recorded.

Risk factors for thoracotomy conversion

A univariate analysis of the preoperative clinical data from both groups revealed several factors significantly associated with conversion to thoracotomy: older age at the

Table 1. Baseline characteristics of development cohort (n=1,506)

Characteristic	VATS group (n=1,429)	Conversion group (n=77)	p-value	
Age (yr)	64.3±10.2	66.4±9.8	0.065	
Sex			< 0.001	
Female	665 (46.5)	16 (20.8)		
Male	764 (53.5)	61 (79.2)		
Smoking status			< 0.001	
Never	745 (52.1)	23 (29.9)		
Ever	684 (47.9)	54 (70.1)		
Body mass index (kg/m²)	24.0±3.1	24.2±2.7	0.616	
Diabetes mellitus	246 (17.2)	19 (24.7)	0.128	
Liver disease	54 (3.8)	5 (6.5)	0.371	
Chronic kidney disease	31 (2.2)	2 (2.6)	1.000	
Chronic obstructive lung disease	154 (10.8)	16 (20.8)	0.012	
Cerebrovascular disease	65 (4.5)	3 (3.9)	1.000	
Hypertension	550 (38.5)	28 (36.4)	0.800	
Coronary artery disease	109 (7.6)	8 (10.4)	0.507	
Tuberculosis	148 (10.4)	10 (13.0)	0.587	
Interstitial lung disease	22 (1.5)	0	0.542	
FEV1 (L)	2.4±0.6	2.4±0.6	0.766	
DLCO (%predicted) (%)	85.3±17.9	79.0±16.4	0.003	
Location of tumor			0.233	
Right upper lobe	441 (30.9)	21 (27.3)		
Right middle lobe	113 (7.9)	4 (5.2)		
Right lower lobe	324 (22.7)	18 (23.4)		
Left upper lobe	315 (22.0)	25 (32.5)		
Left lower lobe	236 (16.5)	9 (11.7)		
Clinical tumor stage			< 0.001	
0 or 1	850 (59.5)	24 (31.2)		
2	423 (29.6)	26 (33.8)		
3	123 (8.6)	20 (26.0)		
4	33 (2.3)	7 (9.1)		
Clinical lymph node metastasis	203 (14.2)	31 (40.3)	< 0.001	
Neoadjuvant treatment	103 (7.2)	13 (22.1)	< 0.001	
Previous ipsilateral operation	27 (1.9)	4 (5.2)	0.115	
Fibrocalcified lymph node	519 (36.3)	50 (64.9)	< 0.001	
Pleural calcification	4 (3.2)	4 (5.2)	0.538	
Incomplete preoperative CT fissure	546 (38.2)	38 (49.4)	0.067	

Values are presented as mean±standard deviation or number (%).

VATS, video-assisted thoracoscopic surgery; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity for carbon monoxide; CT, computed tomography.

Table 2. Baseline characteristics of validation cohort (n=880)

Characteristic	VATS group (n=842)	Conversion group (n=38)	p-value
Age (yr)	66.3±10.0 70.2±7.0		0.002
Sex			< 0.001
Female	428 (50.8)	7 (18.4)	
Male	414 (49.2)	31 (81.6)	
Smoking status			< 0.001
Never	471 (55.9)	7 (18.4)	
Ever	371 (44.1)	31 (81.6)	
Body mass index (kg/m²)	24.3±3.2	23.9±3.7	0.453
Diabetes mellitus	163 (19.4)	9 (23.7)	0.654
Liver disease	34 (4.0)	2 (5.3)	1.000
Chronic kidney disease	20 (2.4)	3 (7.9)	0.117
Chronic obstructive lung disease	91 (10.8)	12 (31.6)	< 0.001
Cerebrovascular disease	50 (5.9)	3 (7.9)	0.883
Hypertension	326 (38.7.5)	19 (50.0)	0.221
Coronary artery disease	86 (10.2)	4 (10.5)	1.000
Tuberculosis	82 (9.7)	8 (21.1)	0.048
Interstitial lung disease	15 (1.8)	1 (2.6)	1.000
FEV1 (L)	2.6±8.7	2.3±0.5	0.226
DLCO (%predicted) (%)	16.7±4.5	15.2±3.8	0.039
Location of tumor			0.017
Right upper lobe	267 (31.7)	8 (21.1)	
Right middle lobe	52 (6.2)	0	
Right lower lobe	186 (22.1)	7 (18.4)	
Left upper lobe	202 (24.0)	18 (47.4)	
Left lower lobe	135 (16.0)	5 (13.2)	
Clinical tumor stage			< 0.001
0 or 1	588 (69.8)	13 (34.2)	
2	191 (22.7)	16 (42.1)	
3	51 (6.1)	5 (13.2)	
4	12 (1.4)	4 (10.5)	
Lymph node metastasis	67 (8.0)	11 (28.9)	< 0.001
Neoadjuvant treatment	67 (8.0)	11 (28.9)	< 0.001
Previous ipsilateral operation	16 (1.9)	3 (7.9)	0.055
Fibrocalcified lymph node	229 (27.2)	25 (65.8)	0.055
Pleural calcification	28 (3.3)	2 (5.3)	0.852
Incomplete preoperative CT fissure	426 (50.6)	19 (50.0)	1.000

Values are presented as mean±standard deviation or number (%).

VATS, video-assisted thoracoscopic surgery; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity for carbon monoxide; CT, computed tomography.

Table 3. Contingency table for development and validation cohorts

	VATS group	Conversion group	Total
Development cohort	1,429	77	1,506
Validation cohort	842	38	880
Total	2,271	115	2,386

Values are presented as number.

VATS, video-assisted thoracoscopic surgery.

time of surgery, male sex, history of smoking, higher T stage, presence of lymph node metastasis, prior neoadjuvant therapy, and previous ipsilateral lung surgery (Table 5).

Multivariable logistic regression analysis identified several independent risk factors for unexpected thoracotomy conversion. These included male sex (OR, 2.36; 95% CI, 1.32–4.21; p=0.0036), previous ipsilateral lung surgery (OR, 3.44; 95% CI, 1.11–10.59; p=0.0316), the presence of fibrocalcified lymph nodes on preoperative CT (OR, 2.14; 95% CI, 1.28–3.55; p=0.0035), and clinical T stage. Specifically,

Table 4. Reasons for unexpected conversion to thoracotomy in the development cohort (n=77)

Cause	No. (%)
Fibrocalcified lymph node	29 (37.7)
Pleural adhesions	23 (29.9)
Vessel injury	9 (11.7)
Invasion into vessels or other surrounding structures	7 (9.1)
Not specified	3 (3.9)
Large tumor	2 (2.6)
Need for additional procedure	2 (2.6)
Poor oxygenation	1 (1.3)
Tumor not found	1 (1.3)

clinical T2 stage was associated with an OR of 1.77 (95% CI, 0.99–3.17; p=0.055), clinical T3 stage exhibited an OR of 3.61 (95% CI, 1.79–7.29; p<0.0001), and clinical T4 stage displayed an OR of 1.11 (95% CI, 0.76–1.63; p=0.0020) (Table 5).

Development of a scoring system

The risk score for each factor identified in the multivariate analyses was scaled according to its OR. These 4 factors were incorporated to develop a clinical risk scoring model. The estimated contribution of lymph node calcification was assigned a score of 1, with the other values adjusted accordingly. One point was assigned for male sex, 2 points for previous ipsilateral operative history, and 0 to 3 points for clinical T stage, depending on the stage. The risk scoring model is presented in Table 6. The area under the re-

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (yr)	1.01 (0.97–1.04)	0.7049		
Male sex	2.38 (0.97-5.92)	0.0616	2.36 (1.32-4.21)	0.0036
Body mass index (kg/m ²)	1.04 (0.95-1.13)	0.4056		
Smoking	0.86 (0.40-1.84)	0.6954		
Diabetes mellitus	1.30 (0.71–2.39)	0.3961		
Liver disease	1.61 (0.59-4.39)	0.3562		
Chronic kidney disease	0.68 (0.14-3.22)	0.6298		
Chronic obstructive pulmonary disease	1.29 (0.66–2.53)	0.4506		
Previous ipsilateral operation	3.18 (0.97-10.48)	0.0569	3.44 (1.11-10.59)	0.0316
Fibrocalcified lymph node	1.71 (0.97-3.02)	0.0653	2.14 (1.28-3.55)	0.0035
Pleural calcification	0.89 (0.29-2.72)	0.8404		
Incomplete fissure	1.38 (0.83-2.31)	0.2131		
Hypertension	0.74 (0.43-1.30)	0.3011		
Coronary artery disease	1.07 (0.46-2.45)	0.8791		
Tuberculosis	1.01 (0.48-2.11)	0.9866		
FEV1 (L)	0.92 (0.52-1.60)	0.7624		
DLCO (% predicted) (%)	0.99 (0.98-1.01)	0.4617		
Tumor location				
Right upper lobe	1.00			
Right middle lobe	0.92 (0.29-2.85)	0.8798		
Right lower lobe	0.94 (0.47-1.87)	0.8635		
Left upper lobe	1.73 (0.91-3.30)	0.0940		
Left lower lobe	1.61 (0.88-2.96)	0.7605		
Clinical tumor stage				
1	1.00			
2	1.61 (0.88–2.96)	0.1232	1.77 (0.99-3.17)	0.0551
3	3.61 (1.79–7.29)	0.0003	4.03 (2.10-7.72)	< 0.0001
4	1.11 (0.76–1.63)	0.0064	4.49 (1.73-11.65)	0.0020
Lymph node metastasis	1.11 (0.76–1.63)	0.5902		
Neoadjuvant treatment	1.28 (0.61-2.69)	0.5089		

OR, odds ratio; CI, confidence interval; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity for carbon monoxide.

ceiver operating characteristic curve (AUC) for the model was 0.747, with a sensitivity of 80.5%, specificity of 56.4%, positive predictive value (PPV) of 1.8%, and negative predictive value (NPV) of 91.0% (Fig. 3A).

After developing the scoring system, we stratified the evaluated patients into 4 groups based on their total scores: 0–1 points, 2–3 points, 4–5 points, and 6 points. Under this system, the estimated thoracotomy conversion rate increased as the total risk score increased. Among patients with scores of 0 or 1, only 0.9% underwent unexpected thoracotomy conversion. Among those with scores of 2–3 points, the conversion rate rose to 8.1%; for 4–5 points, it was 16.7%, and a score of 6 points was associated with a

Table 6. Risk scoring model for unexpected thoracotomy conversion

Risk factor	Score	
Sex		
Female	0	
Male	1	
Previous ipsilateral operation		
No previous ipsilateral operation	0	
Previous ipsilateral operation	2	
Clinical T stage		
Tis, T1mi, T1a, T1b, T1c	0	
T2	1	
Т3	2	
T4	3	
Fibrocalcified lymph node		
No fibrocalcified lymph node	0	
Fibrocalcified lymph node	1	

rate of 37.5%.

Assessment of scoring system model

To assess the validity of the developed scoring model, we calculated the score for each of the 872 patients in the validation cohort. The risk model demonstrated good predictive accuracy, with an AUC of 0.819 (sensitivity, 86.8%; specificity, 66.6%; PPV, 0.9%; NPV, 89.5%) (Fig. 3B). Additionally, the risk score exhibited a statistically significant relationship with the rate of unexpected thoracotomy conversion (Fig. 4).

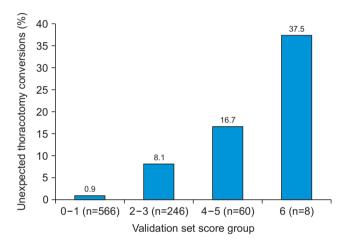


Fig. 4. Percentage of unexpected thoracotomy conversions in the validation set. A significant increase was noted in the rate of unexpected thoracotomy conversion as the risk score increased.

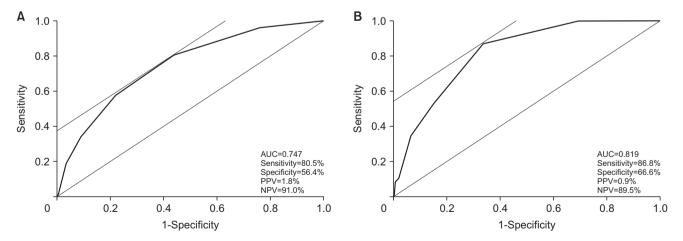


Fig. 3. Assessment of the risk scoring model for predicting the likelihood of unexpected conversion to thoracotomy in the development and validation sets. (A) Receiver operating characteristic curve for the model in the development set. The area under the curve (AUC) was 0.747 (sensitivity, 80.5%; specificity, 56.4%; positive predictive value [PPV], 1.8%; negative predictive value [NPV], 91.0%). (B) Receiver operating characteristic curve for the validation set. The AUC was 0.819 (sensitivity, 86.8%; specificity, 66.6%; PPV, 0.9%; NPV, 89.5%).

Discussion

Since its introduction in the 1990s, VATS for pulmonary resection has become increasingly safe and effective for treating early-stage lung cancer [17,18]. VATS lobectomy is associated with comparatively low morbidity and short hospital stay [19]. Studies have consistently shown it to be equivalent or superior to conventional thoracotomy in propensity-matched populations [20]. Despite these benefits, VATS remains technically demanding. Intraoperative complications are possible, most notably unplanned conversion to thoracotomy [21,22].

Conversion rates for attempted VATS have been reported to be as high as 43% [8,23]. These rates tend to decrease with the increasing experience of the surgeon [12]. Additionally, with the advancement of thoracoscopic equipment, VATS conversion rates have been reported to be as low as 4% [10,24]. Our study similarly demonstrated a conversion rate of 5.1%. While surgical experience can reduce the likelihood of conversion from VATS to open thoracotomy, the identification of risk factors for potential conversion is valuable for patient selection and surgical planning.

Older age, male sex, higher clinical T stage, prior ipsilateral lung surgery, and the presence of fibrocalcified lymph nodes on preoperative CT scans were found to be independent risk factors for conversion to thoracotomy. Previous studies of thoracotomy conversion have identified similar risk factors [12,14]; however, no clear biological explanation has been proposed for the higher risk among male patients [25]. Lymph node calcification can complicate hilar dissection, increasing the risk of injury to surrounding tissues, including vascular structures. Prior studies have also reported that ipsilateral reoperation is associated with higher rates of thoracotomy conversion due to adhesions and distorted hilar anatomy [26,27]. Additionally, tumor size has been recognized as a risk factor for thoracotomy conversion because of the technical challenges it presents to manipulation within the confined space of the thoracic cavity [11].

Utilizing the independent risk factors identified, we developed a risk model for predicting unexpected thoracotomy conversion. By computing a score under this model, patients could be categorized into 4 groups, each with a distinct estimate of conversion risk. This tool can be instrumental in patient selection and surgical planning. Based on validation with data collected over 3 years (2018– 2020), the risk scoring model demonstrated good discriminative power in predicting unplanned thoracotomy conversion. This study has several limitations. First, its retrospective design inherently raises the possibility of selection bias, as the inclusion and exclusion of patients may have been influenced by various factors. Second, the procedures included in the study were performed by multiple surgeons, which could lead to discrepancies due to technical differences and varying criteria for conversion. Each surgeon's operative technique also varied according to their preferences and individual methods. Third, the study was limited to patients from a single institution; thus, a multicenter or prospective study would be necessary to further validate the proposed risk scoring model.

Nonetheless, our proposed model may enable surgeons to estimate the likelihood of unexpected conversion from VATS to thoracotomy using routine preoperative evaluation in candidates for VATS pulmonary resection. We believe this risk scoring model to be potentially useful in determining surgical strategies for high-risk patients with NSCLC.

Article information

ORCID

Ga Young Yoo: https://orcid.org/0000-0002-5066-3270 Seung Keun Yoon: https://orcid.org/0000-0002-2609-2148 Mi Hyoung Moon: https://orcid.org/0000-0003-2799-4570 Seok Whan Moon: https://orcid.org/0000-0003-3348-6011 Wonjung Hwang: https://orcid.org/0000-0003-2820-0322 Kyung Soo Kim: https://orcid.org/0000-0002-3680-9851

Author contributions

Conceptualization: GYY, KSK, SKY. Data curation: SKY, KSK, MHM, WH, SKY. Formal analysis: GYY, SKY. Funding acquisition: none. Investigation: GYY, SHM, KSK, MHM, WH, SKY. Methodology: KSK, KYH, SKY. Project administration: KSK, SKY. Resources: SHM, KSK, MHM, WH, SKY. Software: SKY. Supervision: KSK, SKY. Validation: KSK, SKY. Visualization: GYY, SKY. Writing–original draft: GYY. Writing–review & editing: GYY, SKY, KSK. Approval of final manuscript: all authors.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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