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Thoracoscopic lobectomy for non-small-cell lung cancer in patients with impaired pulmonary function: analysis from a national database

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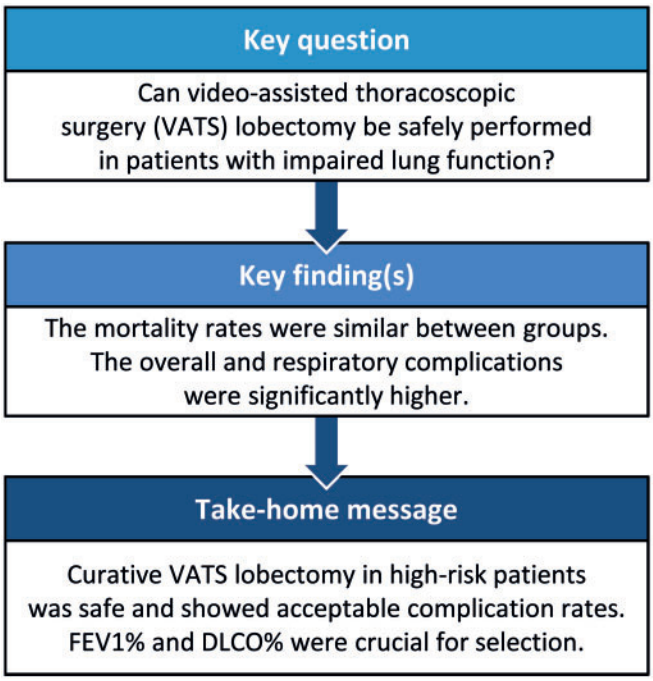

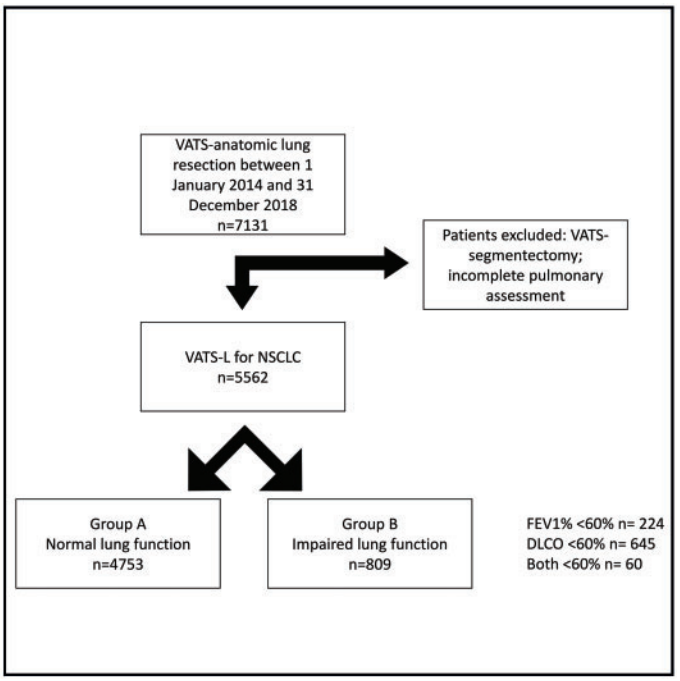

Abstract

OBJECTIVES: The objective of this retrospective multi-institutional study was to evaluate the postoperative outcomes of video-assisted thoracoscopic surgery (VATS)-lobectomy (VATS-L) for non-small-cell lung cancer (NSCLC) in patients with impaired lung function. The second end point was to illustrate the effective role of forced expiratory volume in 1 s (FEV1%) and the diffusing capacity of the lung for carbon monoxide (DLCO%) in predicting complications in this population.

METHODS: Data from patients who underwent VATS-L at participating centres were analysed and divided into 2 groups: group A comprised patients with FEV1% and/or DLCO% >60% and group B included patients with impaired lung function defined as FEV1% and/or DLCO% ≤60%. To define clinical predictors of death and complications, we performed univariate and multivariable regression analyses.

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RESULTS: A total of 5562 patients underwent VATS-L, 809 (14.5%) of whom had impaired lung function. The postoperative mortality rate did not differ between the 2 groups (2.3% vs 3.2%; $P = 0.77$). The percentage of patients who had any complication (21.4% vs 34.2%; $P \leq 0.001$), the complication rate (28% vs 49.8%; $P \leq 0.001$) and the length of hospital stay ($P \leq 0.001$) were higher for patients with limited pulmonary function. Impaired lung function was a strong predictor of overall and pulmonary complications at multivariable analysis.

CONCLUSIONS: VATS-L for NSCLC can be performed in patients with impaired lung function without increased risk of postoperative death and with an acceptable incidence of overall and respiratory complications. Our analysis suggested that FEV1% and DLCO% play a substantial role in estimating the risk of complications after VATS-L, but their role was less reliable for estimating the mortality.

Keywords: Video-assisted thoracoscopic surgery-lobectomy • Non-small-cell lung cancer • Impaired lung function • Forced expiratory volume in 1 s • Diffusing capacity of the lung for carbon monoxide • Complications

ABBREVIATIONS

CCI	Charlson Comorbidity Index
DLCO%	Diffusing capacity of the lung for carbon monoxide
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FEV1%	Forced expiratory volume in 1s
NSCLC	Non-small-cell lung cancer
ppo	Predicted postoperative
VATS	Video-assisted thoracoscopic surgery
VATS-L	Video-assisted thoracoscopic surgery lobectomy

INTRODUCTION

The risk evaluation of lung resection is based on the results of pulmonary function tests. The forced expiratory volume in 1 s (FEV1) and the diffusing capacity of the lung for carbon monoxide (DLCO) are the parameters that correlate most accurately with postoperative morbidity and mortality [1, 2]. Current preoperative guidelines for the risk assessment [1–3] were established according to the evidence obtained from large studies on patients undergoing lung resection through open thoracotomy. However, nowadays pulmonary lobectomy is frequently performed through a minimally invasive video-assisted thoracoscopic surgery (VATS) approach [4–6], and some researchers have demonstrated that VATS-lobectomy (VATS-L) is associated with better outcomes than lobectomy via thoracotomy [4–11], even in patients with suboptimal lung function [12–19]. To clarify the effective role of VATS-L in this fragile population, we performed a multi-institutional study to evaluate the postoperative outcomes of VATS-L for non-small-cell lung cancer (NSCLC) in patients with impaired pulmonary function and to identify the role of preoperative FEV1% and DLCO% in predicting mortality rates and overall and respiratory complications.

MATERIALS AND METHODS

Data source

The Italian VATS Group database is a multicentre, web-based data system for collecting and reporting clinical characteristics, patterns of care and outcomes data of patients with NSCLC treated with a VATS-L. The Italian VATS Group has maintained this prospective database since January 2014. At the time of the latest report, there were 55 participating centres (general thoracic surgery units or services, not individual surgeons, which have joined on a voluntary basis) and ∼8000 collected cases. An institutional review board at each centre has provided the approval for data collection, transmission, storage and analyses. The current analysis was reviewed and approved for scientific merit and feasibility by the VATS Group Scientific Committee and presented at the annual VATS Group meeting. To maintain a high level of accuracy and security of the data, a specific committee implements rigorous quality assurance and safety procedures for the VATS Group database [20]. Furthermore, the Italian VATS Group database received awards from the European Society of Thoracic Surgeons in September 2017 for data quality and auditing [21]. To be included in the database, patients must meet the criterion of a VATS-L using a standard approach as defined by VATS Group policy.

Patient population and methods

The study population comprised patients who received VATS-L with curative intent as the primary procedure for treating NSCLC at VATS Group participating centres and who were included in the VATS Group database between 1 January 2014 and 31 December 2018. We analysed the short-term outcomes of patients with impaired preoperative lung function who underwent VATS-L by comparing results from 2 groups: Group A comprised patients with normal preoperative lung function and Group B included patients with limited preoperative lung function. Impaired lung function was defined as preoperative FEV1% <60% or preoperative DLCO% <60% or both. The threshold of 60% was chosen based on previous studies demonstrating that patients with these FEV1% or DLCO% values have an increased risk of morbidity and death after lung resection [12, 13, 17, 22, 23]. We excluded patients without complete pulmonary function evaluation and patients who underwent VATS segmentectomy.

Mortality was defined as death within 30 days or during the same hospital stay; complications were defined as any event that altered or changed the postoperative course and associated with therapeutic procedures. The following respiratory complications were considered 'any event': atelectasis, prolonged air leak for 7 days, pulmonary embolism, adult respiratory distress syndrome, pneumonia, need for mechanical ventilation, atelectasis and sputum retention. All clinical variables (technical and oncological variables, definitions of complications) were defined by the scientific committee and accepted by each participating centre [20].

Univariate and multivariable analyses were performed regarding postoperative mortality and morbidity rates for selected clinical variables [age, impaired lung function, Eastern Cooperative Oncology Group Performance Status (ECOG PS), Charlson

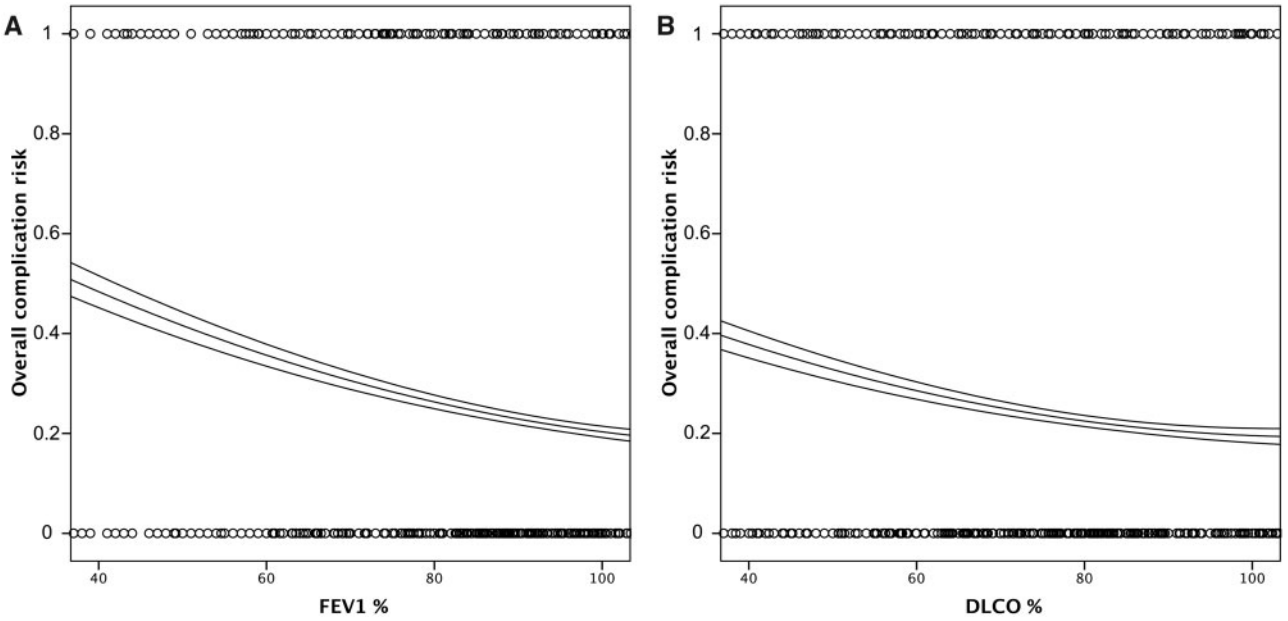

Figure 1: Univariate regression line showing the probability of overall complications as a function of preoperative FEV1% (**A**) and DLCO% (**B**) for patients undergoing video-assisted thoracoscopic surgery-lobectomy. The middle line represents the regression line, whereas the 2 lines above and below represent the 95% confidence limits. The circles show the actual observed occurrence (at the top) and lack of occurrence (at the bottom) associated with the pulmonary function value for each patient in the study. DLCO%: diffusing capacity of the lung for carbon monoxide; FEV1%: forced expiratory volume in 1 s.

Comorbidity Index (CCI), NSCLC clinical stage] in order to identify preoperative risk factors.

Statistical analyses

Statistical analyses were performed using SPSS 24.0 (IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY, USA). Standard descriptive statistics have been used to summarize data with respect to demographic and oncological characteristics. Continuous variables, expressed as mean values ± standard deviation and approximately normally distributed, were compared using the unpaired Student's *t*-tests; differences between the median CCI and ECOG PS were evaluated with the Mann–Whitney test; categorical variables were analysed using the χ^2 test or the Fisher's exact test as appropriate. A *P*-value below 0.05 was considered statistically significant. To define predictors of death, overall morbidity and pulmonary complications, a univariate exact logistic regression analysis was performed for clinical variables including patient demographics, comorbidities and performance status, pulmonary function tests (preoperative FEV1% and DLCO%) and clinical stage. The logistic model was checked with the Hosmer–Lemeshow test, which yielded the following *P*-values: 0.55, 0.42 and 0.61, respectively. Variables associated with a *P*-value <0.20 were selected for the multivariable logistic regression analysis.

RESULTS

During the same period, 43 921 lung resections for NSCLC (www.ape.agenas.it) were performed in the selected centres; of these, 5562 patients were included in the Italian VATS Group database and underwent planned VATS-L with complete pulmonary function assessment. A total of 809 (14.5%) were defined as patients with impaired lung function (Fig. 1). Of these, 224 patients had preoperative FEV1% <60%; 645 had DLCO% <60%; and 60 had both values lower than 60% of the predicted value.

Patient demographics, clinical and pathological stages, preoperative functional status and comorbidities of the 2 groups are summarized in Table 1.

In group B, we noted a higher proportion of men ($P < 0.001$), a higher incidence of chronic obstructive pulmonary disease and connective disease (both $P < 0.001$) and significant differences in the median ECOG PS and CCI (both $P < 0.001$). The preoperative absolute values of FEV1 and forced vital capacity in litres and the preoperative FEV1%, forced vital capacity % and DLCO% were different between the 2 groups ($P < 0.001$ respectively). Patients with poor preoperative pulmonary function more frequently underwent upper lobectomy ($P = 0.025$) and had a more advanced clinical stage ($P < 0.001$).

Postoperative results

The postoperative outcomes of the 2 groups are depicted in Table 2. The postoperative mortality rates were 2.3% and 3.2% ($P = 0.77$), respectively. Representing the lung function on a 10%-based scale for FEV1% and DLCO% (Table 3), we observed a progressive reduction in the mortality rate and in the overall and respiratory complications rate as lung function improved.

Patients who had at least 1 postoperative complication (21.4% vs 34.2%; $P \leq 0.001$), the overall complication rate (28% vs 49.8%, $P \leq 0.001$), the incidence of pulmonary complications (13.3% vs 23.4%, $P \leq 0.001$) and the length of hospital stay (6.5 ± 5.5 vs 7.9 ± 6.6, $P \leq 0.001$) were higher in group B. In particular, we observed a significantly higher incidence of atrial arrhythmias ($P < 0.001$), prolonged air leak ($P < 0.001$), pneumonia ($P < 0.001$), atelectasis ($P < 0.001$), sputum retention ($P < 0.001$), need for mechanical ventilation ($P < 0.001$), bleeding ($P = 0.02$) and need for blood transfusions ($P < 0.001$) in patients with poor lung function. Patients with both FEV1% and DLCO% <60% were more prone to

Table 1: Demographic and preoperative data, clinical and pathological stages, surgical approaches and perioperative outcomes

Variables	Non-impaired lung function (*n* = 4753)	Impaired lung function (*n* = 809)	*P*-value
Male gender, *n* (%)	2850 (60)	547 (67.6)	<0.001
Age (years), mean ± SD	67.8 ± 9.5	68.1 ± 8.8	0.31
FEV1 (l), mean ± SD	2.4 ± 0.6	2.0 ± 0.6	<0.001
FEV1%, mean ± SD	97.4 ± 18.5	79.4 ± 21.7	<0.001
FVC (l), mean ± SD	103.5 ± 25.1	93.7 ± 31.9	<0.001
FVC%, mean ± SD	103.5 ± 25.1	93.7 ± 31.9	<0.001
FEV1/FVC, mean ± SD	76.2 ± 11.8	68.5 ± 15.8	<0.001
DLCO%, mean ± SD	87.6 ± 16.4	58.7 ± 17.1	<0.001
ECOG PS, median (range)	0 (0–4)	0 (0–4)	<0.001
CCI, median (range)	4 (0–15)	5 (0–13)	<0.001
Comorbidities, *n* (%)			
CAD	490 (10.3)	110 (13.6)	0.07
COPD	882 (18.6)	357 (44.1)	<0.001
Connective disease	121 (2.5)	28 (4.7)	<0.001
Peripheral artery disease	763 (16.1)	158 (19.5)	0.016
Diabetes mellitus	640 (13.5)	102 (12.6)	0.53
Other solid tumour	987 (20.8)	169 (20.9)	0.92
Induction treatment	130 (2.7)	46 (5.7)	<0.001
Side, *n* (%)			0.81
Left	1840 (38.7)	317 (39.2)	
Right	2913 (61.3)	492 (60.8)	
Lower bilobectomy, *n* (%)	45 (0.9)	5 (0.6)	0.025
Lower lobectomy, *n* (%)	1673 (35.2)	262 (32.4)	
Middle lobectomy, *n* (%)	384 (8.1)	47 (5.8)	
Upper bilobectomy, *n* (%)	44 (0.9)	6 (0.7)	
Upper lobectomy, *n* (%)	2607 (54.8)	489 (60.4)	
Surgical approach, *n* (%)			0.027
Copenhagen	3474 (73.1)	585 (72.3)	
D'Amico	615 (12.9)	111 (13.7)	
Uniportal	471 (9.9)	74 (9.1)	
Other	193 (4)	39 (4.8)	
Systematic lymph node dissection, *n* (%)	3113 (65.5)	532 (65.8)	0.62
Sampling, *n* (%)	1617 (34)	271 (33.5)	
No dissection, *n* (%)	23 (0.4)	6 (0.7)	
Pathological diagnosis, *n* (%)			<0.001
ADC	3444 (72.5)	553 (68.4)	
SCC	729 (15.3)	177 (21.9)	
NET	468 (9.8)	62 (7.6)	
Other	112 (2.3)	17 (2.1)	
Clinical stage, *n* (%)			<0.001
IA	3101 (65.2)	480 (59.3)	
IB	799 (16.8)	139 (17.2)	
IIA	177 (3.7)	46 (5.7)	
IIB	323 (6.8)	52 (6.4)	
IIIA	255 (5.4)	66 (8.2)	
IIIB	43 (0.9)	12 (1.5)	
IIIC	2 (0.1)	0	
IV	53 (1.1)	14 (1.7)	
Pathological stage, *n* (%)			0.01
IA	2462 (51.8)	378 (46.7)	
IB	1064 (22.4)	205 (25.3)	
IIA	208 (4.4)	39 (4.8)	
IIB	545 (11.5)	86 (10.6)	
IIIA	390 (8.2)	73 (9)	
IIIB	47 (1)	18 (2.2)	
IIIC	1 (0.1)	0	
IV	36 (0.8)	10 (1.2)	
Operative time (min), mean ± SD	184.4 ± 71.1	180.8 ± 61.8	0.17
Estimated blood loss (ml), mean ± SD	140.8 ± 165.6	146.9 ± 193.1	0.36
Number of N1 lymph nodes resected, mean ± SD	6.2 ± 4.4	6.43 ± 4.4	0.16
Number of N2 lymph nodes resected, mean ± SD	7 ± 5.1	7.6 ± 5.7	<0.001

ADC: adenocarcinoma; CAD: coronary artery disease; CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; DLCO%: diffusing capacity of the lung for carbon monoxide; ECOG PS: Eastern Cooperative Oncological Group Performance Status; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; NET: neuroendocrine tumour; SCC: squamous cell carcinoma; SD: standard deviation.

Table 2: Postoperative results

Complications	Non-impaired lung function (*n* = 4753)	Impaired lung function (*n* = 809)	*P*-value
AF, *n* (%)	343 (7.2)	85 (10.5)	<0.001
Myocardial infarction, *n* (%)	8 (0.2)	4 (0.5)	0.08
Cerebrovascular disease, *n* (%)	14 (0.3)	2 (0.2)	1
Peripheral vascular disease, *n* (%)	4 (0.1)	1 (0.1)	0.54
Cardiac arrest, *n* (%)	2 (0.0)	1 (0.1)	1
PAL, *n* (%)	355 (7.5)	111 (13.7)	<0.001
Pulmonary embolism, *n* (%)	5 (0.1)	1 (0.1)	1
ARDS, *n* (%)	19 (0.4)	3 (0.4)	1
Pneumonia, *n* (%)	142 (3)	44 (5.4)	<0.001
Mechanical ventilation, *n* (%)	11 (0.2)	10 (1.2)	<0.001
Atelectasis, *n* (%)	81 (1.7)	29 (3.6)	<0.001
Sputum retention, *n* (%)	129 (2.7)	42 (5.2)	<0.001
Haemothorax, *n* (%)	59 (1.2)	19 (2.3)	0.02
Bronchopleural fistula, *n* (%)	7 (0.1)	2 (0.2)	0.62
Chylothorax, *n* (%)	15 (0.3)	1 (0.1)	0.49
Phrenic nerve injury, *n* (%)	8 (0.2)	2 (0.2)	0.64
Laryngeal nerve injury, *n* (%)	25 (0.5)	7 (0.9)	0.21
Blood transfusions, *n* (%)	94 (2)	31 (3.8)	<0.001
Renal failure, *n* (%)	27 (0.6)	8 (1)	0.15
Deaths, *n* (%)	109 (2.3)	26 (3.2)	0.77
Complication rate, *n* (%)	1348 (28)	403 (49.8)	<0.001
At least 1 complication, *n* (%)	1016 (21.4)	277 (34.2)	
FEV1 <60%, *n* (%)	1207 (22.6)	86 (38.4)	<0.001
DLCO <60%, *n* (%)	1069 (21.7)	224 (34.7)	<0.001
Both, *n* (%)	1260 (22.9)	33 (55)	<0.001
Pulmonary complication, *n* (%)	634 (13.3)	189 (23.4)	<0.001
FEV1 <60%, *n* (%)		34 (20.7)	
DLCO <60%, *n* (%)		131 (22.4)	
Both, *n* (%)		24 (40)	
Length of hospital stay (days), mean ± SD	6.5 ± 5.5	7.9 ± 6.6	<0.001
Conversion rate, *n* (%)	412 (8.7)	74 (9.1)	0.63

AF: atrial fibrillation; ARDS: adult respiratory distress syndrome; DLCO: diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in 1 s; PAL: prolonged air leak; SD: standard deviation.

Table 3: Deaths, overall and respiratory complications and length of hospital stay using a 10%-based scale

Variables	FEV1% <40	FEV1% 40–50	FEV1% 50–60	FEV1% 60–70	FEV1% 70–80	FEV1% >80
Deaths, *n* (%)	0	0	4/171 (2.3)	8/424 (1.8)	13/717 (1.8)	110/4197 (2.6)
At least 1 complication, *n* (%)	5/10 (50)	20/43 (46.5)	61/171 (35.6)	136/424 (32)	214/717 (29.8)	857/4197 (20.4)
Pulmonary complication, *n* (%)	3/10 (30)	12/43 (27.9)	43/171 (25.1)	102/424 (24)	158/717 (22)	505/4197 (12)
Length of hospital stay (days), mean ± SD	7.2 ± 3.3	10.9 ± 10	8.1 ± 7.7	7.5 ± 5.9	7.5 ± 7.1	6.4 ± 5.2
Variables, *n* (%)	DLCO% <40%	DLCO% 40–50	DLCO% 50–60	DLCO% 60–70	DLCO% 70–80	DLCO% >80
Deaths, *n* (%)	1/54 (1.8)	11/171 (6.4)	12/420 (2.8)	16/765 (2)	25/1092 (2.2)	70/3060 (2.2)
At least 1 complication, *n* (%)	14/54 (25.9)	70/171 (40.9)	140/420 (33.3)	197/765 (25.7)	238/1092 (21.7)	634/3060 (20.7)
Pulmonary complications, *n* (%)	11/54 (20.3)	44/171 (25.7)	100/420 (23.8)	142/765 (18.5)	159/1092 (14.5)	367/3060 (11.9)
Length of hospital stay (days), mean ± SD	6.9 ± 5.2	9 ± 7.7	7.9 ± 6.7	7.3 ± 6.7	6.7 ± 5.6	6.3 ± 5.1

DLCO: diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in 1 s; SD: standard deviation.

develop overall and respiratory complications ($P < 0.01$, respectively).

Logistic regression: univariate and multivariable analyses

Univariate predictors of mortality, morbidity and pulmonary complications with *P*-value >0.20 were entered into a multivariable model. No preoperative factors were significantly associated with mortality. We observed a trend of significance for patients with PS >1 ($P = 0.07$) (Table 4). Excluding the preoperative clinical stage, all variables entered into the model demonstrated a significant association with overall complications (Table 5). When we looked at postoperative respiratory complications (Table 6), the multivariable analysis showed a significant association between impaired lung function ($P < 0.001$), CCI <4 ($P < 0.001$), male sex ($P < 0.001$), FEV1 <60% ($P < 0.001$), DLCO <60% ($P < 0.001$) and both values <60% ($P < 0.001$). Figures 1 and 2 represent in a visual manner the association between preoperative FEV1% or DLCO% and the incidence of overall and respiratory complications.

Table 4: Univariate and multivariable analysis on mortality

Variables	Univariate analysis			Multivariable analysis		
	OR	CI 95%	*P*-value	OR	CI 95%	*P*-value
Male gender	1.15	0.81–1.62	0.42			
Impaired lung function	1.41	0.91–2.18	0.12	1.94	0.47–7.97	0.35
Age >70	1.24	0.88–1.75	0.21			
ECOG PS >1	2.08	0.95–4.53	0.065	2.05	0.94–4.49	0.070
CCI >4	1.01	0.71–1.42	0.96			
cIA	0.99	0.69–1.42	0.98			
FEV1 <60%	1.38	0.51–3.77	0.52			
DLCO <60%	1.67	1.06–2.62	0.025	3.17	0.74–13.58	0.12
Both >60%	1.39	0.33–5.76	0.64			

CCI: Charlson Comorbidity Index; cIA: clinical stage IA; CI 95%: confidence interval at 95%; DLCO: diffusing capacity of the lung for carbon monoxide; ECOG PS: Eastern Cooperative Oncological Group Performance Status; FEV1: forced expiratory volume in 1 s; OR: odds ratio.

Table 5: Univariate and multivariable analyses on overall complications

Variables	Univariate analysis			Multivariable analysis		
	OR	CI 95%	*P*-value	OR	CI 95%	*P*-value
Impaired lung function	1.91	1.63–2.25	<0.001	1.87	1.58–2.2	<0.001
Age >70	1.69	1.49–1.92	<0.001	1.62	1.43–1.84	<0.001
CCI >4	2.08	1.83–2.62	<0.001	1.76	1.53–2.03	<0.001
ECOG PS >1	1.86	1.32–2.62	<0.001	1.56	1.1–2.23	<0.001
Men	1.61	1.4–1.83	<0.001	1.49	1.31–1.71	<0.001
cIA	0.99	0.87–1.12	0.87			
FEV1 <60%	2.13	1.61–2.81	<0.001	2.35	1.36–4.06	<0.001
DLCO <60%	1.91	1.61–2.28	<0.001	2.68	1.36–4.06	<0.001
Both <60%	4.11	2.46–6.87	<0.001	2.56	1.39–4.68	<0.001

CCI: Charlson Comorbidity Index; cIA: clinical stage IA; CI 95%: confidence interval at 95%; DLCO: diffusing capacity of the lung for carbon monoxide; ECOG PS: Eastern Cooperative Oncological Group Performance Status; FEV1: forced expiratory volume in 1 s; OR: odds ratio.

DISCUSSION

In the last decades, the advantages of VATS-L over a traditional lobectomy via thoracotomy were assessed in large multi-institutional retrospective analyses and randomized controlled trials [4–11, 19, 24]. However, in these studies, patients with poor lung function were under-represented or not included, so the outcomes in this fragile population could not be extrapolated. Consequently, the objective of our study was to report the post-operative outcomes of VATS-L for NSCLC in patients with impaired lung function, defined as preoperative FEV1% and/or DLCO% <60%, using a web-based Italian VATS-L database (www.vatsgroup.org).

The major findings of our retrospective multi-institutional study were as follows: (i) VATS-L is feasible in patients with marginal lung function without an increased number of deaths; (ii) postoperative complications were more frequent in this population and were strongly associated with preoperative lung function; and (iii) predicted FEV1% and predicted DLCO% values maintained their role in predicting the incidence of adverse events but not of deaths.

In our study, the mortality rate after VATS-L for patients with poor lung function was 3.2%, a value similar to that of the control group of patients with normal lung function ($P = 0.77$) and in line with the mortality rates (0–14.3%) reported in a previously published meta-analysis [14]. Furthermore, we observed an increased mortality rate (6.2%) in patients who had preoperative DLCO% values of 40–50%. However, no other paper showed a statistically significant increase in deaths for patients with impaired lung function because the overall number of postoperative deaths after VATS-L was low and the proportion of patients with poor lung function was too small to identify their statistical impact on the mortality rate, as was also shown in a multi-institutional analysis [13]. The debate about the safety of VATS-L in high-risk patients is on-going. Several historical, single-centre studies demonstrated that, in carefully selected patients, outcomes for patients who had VATS-L were acceptable and not different in comparison with the outcomes of patients with standard postoperative risk [15, 18, 25]. Our study showed that VATS-L in this fragile cohort of patients is safe and feasible and that the multi-institutional nature of this study decreased the influence of individual algorithms for patient selection. Therefore, our outcomes can be generally accepted.

Despite the poor lung function and the presence of comorbid conditions in our cohort of patients, overall morbidity was 49.8%, although a large portion of patients had an uneventful postoperative course (65.8%). Furthermore, as shown in Table 2, the majority of complications were not life-threatening. The incidence of pulmonary complications was significant, about twice that of the control group (23.4% vs 13.3%; $P < 0.001$). We reported a high incidence of prolonged air leak (13.7%), pneumonia (5.4%), sputum retention (5.2%) and atelectasis (3.6%). As reported by other

Table 6: Univariate and multivariable analyses on pulmonary complications

Variables	Univariate analysis			Multivariable analysis		
	OR	CI 95%	*P*-value	OR	CI 95%	*P*-value
Impaired lung function	1.82	1.51–2.19	<0.001	1.81	1.51–2.18	<0.001
ECOG PS >1	0.80	0.53–1.22	0.31			
Age >70	1.11	0.94–1.31	0.21			
cIA	1.03	0.88–1.2	0.7			
CCI >4	1.59	1.34–1.89	<0.001	1.68	1.43–1.96	<0.001
FEV1 <60%	2.9	1.53–2.84	<0.001	1.7	1.15–2.5	<0.001
DLCO <60%	2.01	1.65–2.45	<0.001	1.87	1.51–2.31	<0.001
Both <60%	3.92	2.32–6.61	<0.001	2.31	1.33–4.01	<0.001
Male gender	1.53	1.29–1.81	<0.001	1.53	1.29–1.81	<0.001

CCI: Charlson Comorbidity Index; cIA: clinical stage IA; CI 95%: confidence interval at 95%; DLCO: diffusing capacity of the lung for carbon monoxide; ECOG PS: Eastern Cooperative Oncological Group Performance Status; FEV1: forced expiratory volume in 1 s; OR: odds ratio.

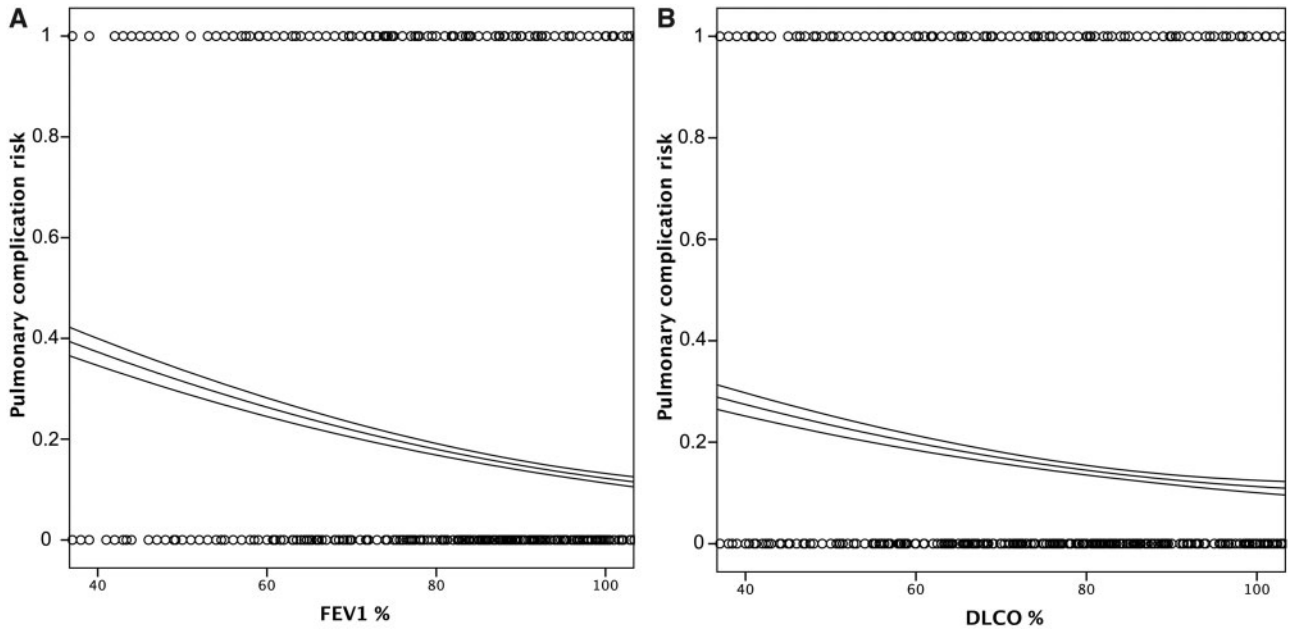

Figure 2: Univariate regression line showing the probability of pulmonary complications as a function of preoperative FEV1% (**A**) and DLCO% (**B**) for patients undergoing video-assisted thoracoscopic surgery-lobectomy. The middle line represents the regression line, whereas the 2 lines above and below represent the 95% confidence limits. The circles show the actual observed occurrence (at the top) and lack of occurrence (at the bottom) associated with the pulmonary function value for each patient in the study. DLCO%: diffusing capacity of the lung for carbon monoxide; FEV1%: forced expiratory volume in 1 s.

authors [10, 17, 26], we also noted that the incidence of pulmonary complications was inversely proportional to the decrease of pulmonary function, as represented in Fig. 2. Also, if both preoperative FEV1% and DLCO% were low, the pulmonary morbidity could increase. These adverse events also caused a significantly prolonged length of hospital stay, and we can assume that it involved an increase in hospital-related costs. The multivariable analysis on overall morbidity demonstrated that the development of complications was multifactorial (Table 5), whereas pulmonary complications were strongly associated with preoperative lung function, as shown by the significant, high level of the hazard ratio for both FEV1% and DLCO% (Table 6).

A large number of authors postulated that the advantages of a VATS-L over a lobectomy through a conventional thoracotomy were secondary to maintained chest wall mechanics, lower postoperative pain and preserved postoperative lung function. All these factors had a positive influence on patients with poor lung function as reported by several authors [12, 13, 25]. Ceppa *et al.* [13], in a multi-institutional study based on data from the General Thoracic Database of the Society of Thoracic Surgeons demonstrated that a thoracotomy *per se* had a strong influence on predicting pulmonary complications in comparison with VATS (21.7% vs 17.8%; $P < 0.001$). Moreover, they showed fewer complications in patients at high risk (with preoperative FEV1% <60%) treated with VATS in comparison to a similar group of subjects who underwent thoracotomy. The effective role of VATS resection in patients with limited lung function was also confirmed by Burt *et al.* [12]. They reaffirmed the strong predictive value of preoperative FEV1%, DLCO%, predicted postoperative (ppo)FEV1% and ppoDLCO% regarding postoperative overall and cardiopulmonary complications, findings comparable to our results. On the other hand, Berry *et al.* [17] showed that the value

of pulmonary function tests in predicting complications in high-risk patients (FEV1% and DLCO% <60%) is still reliable for thoracotomy whereas the correlation between the preoperative low value of both FEV1% and DLCO% and adverse postoperative events is weak for patients who had VATS-L. In conclusion, these data from the literature and from our study suggested that curative resection for NSCLC should not be denied to patients based only on limited pulmonary function; other clinical factors such as performance status and the presence of comorbid conditions should be strongly considered.

Limitations

Our study has several limitations. First, it has all of the inherent biases associated with a retrospective analysis. Second, the absence of a comparison with a cohort of patients treated through thoracotomy represents another limit, but our purpose was to verify the feasibility and to report the outcomes of VATS-L, which is currently the preferred approach for treating early-stage NSCLC. Therefore, we demonstrated the benefits of the minimally invasive approach in patients with impaired preoperative lung function through the comparison with a population with normal lung function. Furthermore, we strongly believe that patients with poor lung function should be referred for minimally invasive resection and that thoracotomy should be avoided in order to decrease the mortality and morbidity risks. Moreover, thoracotomy should be reserved for those with a more advanced stage and after-induction treatment, though these fragile patients often had a worse performance status and comorbid conditions that could preclude any multimodal approach. In these kinds of patients, complete clinical and oncological evaluations are mandatory [8] to identify the correct tailored therapeutic approach. For example, a sublobar lung resection with lymph node assessment could be a reasonable approach [27] or offer to the patient a non-surgical therapy such as stereotactic body radiation therapy or radiofrequency ablation.

The non-use of ppoFEV1% or ppoDLCO% could be interpreted as another limit, but other papers reported FEV1% and DLCO% as valuable and reliable parameters predicting mortality and morbidity rates after VATS-L [15, 19, 21, 22]. Furthermore, the ppoFEV1% or ppoDLCO% calculated with different formulas is not free from biases. We also excluded other parameters used in the preoperative assessment such as the 6-min walking test or the maximum rate of oxygen consumption because they are rarely performed. We did not include them in order to maintain data accuracy and diminish missing data.

CONCLUSION

In conclusion, curative VATS-L for NSCLC can be safely performed in patients with impaired lung function, defined as preoperative FEV1% and/or DLCO% lower than 60%, without an increased risk of postoperative death and an acceptable incidence of overall and respiratory complications. Our analysis suggested that FEV1% and DLCO% still have important roles in predicting and estimating the risk of operative overall and respiratory complications after VATS-L, but their role was less reliable for mortality.

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Author contributions

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