Impact of surgical approach on 90-day mortality after lung resection for nonsmall cell lung cancer in high-risk operable patients

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Studying the impact of surgical approaches on 90-day mortality on a nationwide database, preoperative FEV_1 and/or D_{LCO} <50% is associated with higher 90-day mortality that can be mitigated by the use of minimally invasive surgical approaches. https://bit.ly/3QOl4Jn

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Abstract

Introduction Non-small cell lung cancer (NSCLC) is often associated with compromised lung function. Real-world data on the impact of surgical approach in NSCLC patients with compromised lung function are still lacking. The objective of this study is to assess the potential impact of minimally invasive surgery (MIS) on 90-day post-operative mortality after anatomic lung resection in high-risk operable NSCLC patients.

Methods We conducted a retrospective multicentre study including all patients who underwent anatomic lung resection between January 2010 and October 2021 and registered in the Epithor database. High-risk patients were defined as those with a forced expiratory volume in 1 s (FEV_1) or diffusing capacity of the lung for carbon monoxide (D_{LCO}) value below 50%. Co-primary end-points were the impact of risk status on 90-day mortality and the impact of MIS on 90-day mortality in high-risk patients.

Results Of the 46 909 patients who met the inclusion criteria, 42 214 patients (90%) with both preoperative FEV_1 and D_{LCO} above 50% were included in the low-risk group, and 4695 patients (10%) with preoperative FEV_1 and/or preoperative D_{LCO} below 50% were included in the high-risk group. The 90-day mortality rate was significantly higher in the high-risk group compared to the low-risk group (280 (5.96%) *versus* 1301 (3.18%); p<0.0001). In high-risk patients, MIS was associated with lower 90-day mortality compared to open surgery in univariate analysis (OR=0.04 (0.02–0.05), p<0.001) and in multivariable analysis after propensity score matching (OR=0.46 (0.30–0.69), p<0.001). High-risk patients

operated through MIS had a similar 90-day mortality rate compared to low-risk patients in general (3.10% *versus* 3.18% respectively).

Conclusion By examining the impact of surgical approaches on 90-day mortality using a nationwide database, we found that either preoperative FEV_1 or D_{LCO} below 50% is associated with higher 90-day mortality, which can be reduced by using minimally invasive surgical approaches. High-risk patients operated through MIS have a similar 90-day mortality rate as low-risk patients.

Introduction

Non-small cell lung cancer (NSCLC) accounts for around 80% of all lung cancers, with surgical resection being the optimal treatment for early-stage disease [1]. Surgical treatment of NSCLC is associated with 90-day mortality rates that vary between 0 and 5%, depending on the patient's characteristics, tumour extension and surgical management [2]. Previous studies have identified pre-operative forced expiratory volume in 1 s (FEV_1) and diffusing capacity of the lung for carbon monoxide (D_{LCO}) as a simple and effective tool for stratifying surgical risk of operable patients, with preoperative FEV_1 and/or D_{LCO} below 50% of the predicted value, thus defining high-risk operable patients [3].

After surgical resection of NSCLC, post-operative complications are usually due to post-operative pain, leading to atelectasis and pneumonia, which can lead to acute respiratory distress syndrome and prolonged stay in the intensive care unit, ultimately altering survival and quality of life [2]. Minimally invasive surgery (MIS), including video-assisted thoracic surgery (VATS) and robotic-assisted thoracic surgery (RATS), has been associated with significant improvements in post-operative pain, complications and quality of life compared with open surgery in low-risk patients [4, 5]. These improvements are associated with a similar overall survival and relapse-free survival [5].

In the specific context of high-risk operable patients, MIS may reduce operative risk and allow for anatomic lung resection rather than non-anatomic resection, but real-world data are currently lacking. We therefore hypothesised that MIS might be associated with a survival benefit at 90 days in operable high-risk patients. The objective of this study is to evaluate 90-day mortality as a function of patient surgical risk using the French Epithor database and then to evaluate the impact of MIS on post-operative mortality after anatomic lung resection in high-risk operable patients.

Patients and methods

Study design

We conducted a multicentre retrospective study of the French nationwide prospective database Epithor [6], including all adult patients who underwent anatomical lung resection for primary NSCLC from January 2010 to October 2021 in 83 French thoracic centres (supplementary table S1). Adult patients who underwent an anatomical lung resection for primary NSCLC were included. Patients who had wedge resection or extended resection (to the superior vena cava, superior sulcus, carina, ribs, spine and subclavian vessels) were excluded. Patients with preoperative FEV_1 and/or D_{LCO} value below 50% were defined as high-risk operable patients [3]. Patients with both preoperative FEV_1 and D_{LCO} above 50% were defined as low-risk operable patients. The co-primary end-points were: 1) the impact of risk status on 90-day mortality and 2) the impact of the surgical approach on 90-day mortality in high-risk operable patients.

Ethical consideration

All data came from the French registry Epithor managed by the French Society of Thoracic and Cardiovascular Surgery [6]. Created in 2002 under a specific authorisation by the National Commission of Information and Liberties (CNIL # 809833), this registry aims at collecting data from every patient who underwent thoracic surgery in France. The study was approved by the Ethical Committee of the French Society of Thoracic and Cardiovascular Surgery (Société Française de Chirurgie Thoracique et Cardiovasculaire, SFCTCV IRB DELIBERE_CS-SFCTCV-2023–05-11_28684_Harry Etienne). Since this was a retrospective study, all data were anonymised and direct patients' consent was waived.

Surgery

All patients underwent a complete work-up including chest computed tomography (CT), brain imaging (either magnetic resonance imaging or enhanced CT), abdominal imaging (enhanced CT), positron emission tomography–computed tomography (PET-CT) and bronchoscopy. Preoperative assessment was made according to the 2009 European Respiratory Society (ERS)/European Society of Thoracic Surgery (ESTS) guidelines and included a pulmonary function test (PFT) and echocardiography when indicated [1]. After assessing cardiac function, operability was decided on lung function testing (FEV_1 and D_{LCO}). If their values were not satisfying to authorise a major lung resection, the assessment would be completed by spiroergometry and/or a single-photon emission computed tomography scan. All patients were then

discussed during multidisciplinary team meetings including a pulmonologist, an oncologist, a radiation therapist, a radiologist, a pathologist and a board-certified thoracic surgeon. The surgical approach and type of anatomical resection were left at the discretion of the senior surgeon responsible for the patient. Systematic lymph node dissection was associated with the anatomical lung resection. Post-operative management included daily chest radiograph for early detection of atelectasis and assessment of drain removal.

Data collection

The following data were gathered: age, sex, past medical history, surgical approach, type of anatomical lung resection, peri-operative management (induction chemotherapy or radiotherapy), PFT (FEV_1 and D_{LCO}), preoperative staging, post-operative staging, upstaging, pathology results and 90-day mortality (supplementary table S2). The anatomic extent of the tumour was based on the IASLC (International Association for the Study of Lung Cancer) 7th edition tumour, node, metastasis (TNM) classification for NSCLC in patients operated before 2016, and it was based on the IASLC 8th edition TNM classification for patients operated after 2016 [7, 8]. Missing data are summarised in supplementary table S3. The missing data were kept in the database, except for the variable smoking status, which has been replaced by 0 and for the variable age, which has been replaced by the mean age of all patients.

Statistical analysis

Univariate analysis of baseline characteristics by type of risk was performed. Categorical variables were reported as percentages and analysed with Chi-square tests. Continuous data were reported as mean±SD and analysed using independent sample t-tests for normally distributed variables and using Mann–Whitney U-tests otherwise. Survival curves were plotted during the first 90 days following surgery and compared with the logrank test. Univariate analyses were performed by surgical approach between RATS, VATS and open thoracotomy, with one analysis considering all patients and another one considering only high-risk patients. As before, categorical variables were reported as percentages and analysed with Chi-square tests. Continuous data were reported as mean±SD and analysed using one-way ANOVA, for normally distributed variables, and using Kruskal–Wallis tests otherwise. Stepwise multivariable logistic regression analysis was conducted to identify the factors predicting 90-day mortality. Interaction terms between variables were considered and reported whenever needed.

To minimise the effects of confounding factors, a 1:1 propensity score matching (PSM) with a caliper at 0.1 was performed using logistic regression analysis. The surgical approach was grouped into two classes: open surgery and MIS (including VATS and RATS) and used as a dependent variable while the baseline characteristics were included as independent variables. The variables included were sex, age, body mass index (BMI), dyspnoea, smoking status, FEV_1 %, D_{LCO} %, type of intervention, tumour size, nodal status and cancer pathology. The c-statistics were calculated as a measure of accuracy of the propensity score prediction. The histogram of the propensity score by type of surgery was plotted (supplementary figure S1). The standardised mean differences before and after matching were reported (supplementary figure S2). The logistic regression model was then used to estimate the association between baseline characteristics, including type of surgery (MIS *versus* open surgery), and 90-day mortality rate in the PSM sample. Odds ratios, 95% confidence intervals (CIs) and p-values were reported.

We then used artificial intelligence algorithms to investigate whether this method could be used to build a predictive model for 90-day mortality in high-risk patients. The data were randomly divided into training (70% of the data, 3286 observations) and test (30% of the data, 1409 observations) samples. The split was done while maintaining the 90-day mortality rate in each sample. Because the variable of interest is binary, we chose logistic regression, an interpretable random forest classifier, and an optimised random forest classifier [9, 10]. For the interpretable random forest, we set the number of trees to 10 and the maximum depth of each tree to 3 to make its predictions interpretable. The parameters of the optimised random forest were determined by cross-validation search over the parameter settings. The models are fitted to the training set and tested on the test set. The deployment of these algorithms was done in Python using the Scikit-Learn packages.

Results

Overall population

A study flowchart is shown in figure 1. All together 52 240 patients were included in the Epithor database during the study period. After exclusion of 5331 patients who underwent non-anatomical or extended surgery, data from 46 909 patients were used for analysis. There were 7391 patients aged 75 years or more (15.75%). The high-risk group included 4695 patients (10.0%) with preoperative FEV_1 and/or preoperative D_{LCO} below 50%, and the low-risk group included 42 214 patients (90.0%) with preoperative FEV_1 and D_{LCO} above 50%.

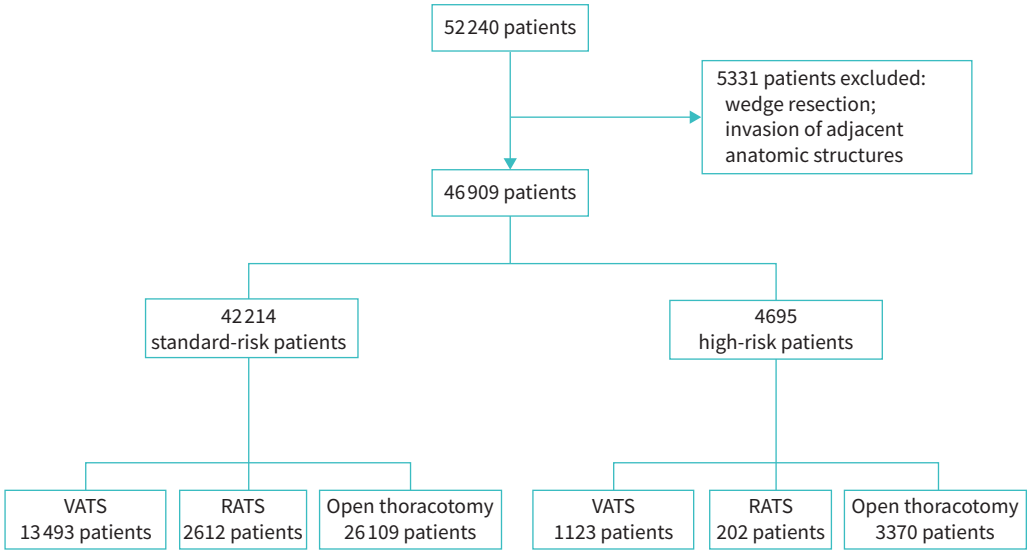


FIGURE 1 Study flowchart. VATS: video-assisted thoracic surgery; RATS: robotic-assisted thoracic surgery.

High-risk group

The characteristics of the overall population according to risk groups are shown in table 1. Briefly, as compared to low-risk patients, high-risk patients were characterised by a younger age (63.8±8.8 *versus* 65.0±9.3 years; $p<0.0001$), more squamous cell carcinoma (37.6% *versus* 24.9%; $p<0.0001$), more open surgery (71.8% *versus* 61.9%; $p<0.0001$) and more pneumonectomies (18.7% *versus* 6.4%; $p<0.0001$) but a similar rate of nodal upstaging (6.4% *versus* 6.8%). The rate of 90-day mortality was higher in the high-risk group compared to the low-risk group (5.96% *versus* 3.18%; $p<0.0001$). Between 2010 and 2020, 90-day mortality remained higher in the high-risk group throughout the years (figure 2). Survival curves during the first 90 days are shown in figure 3.

Surgical approaches

We then investigated the high-risk group according to the surgical approaches, classified as three categories (open surgery, VATS, RATS, table 2) and then two categories (open surgery, MIS including VATS and RATS, table 3). As compared with open surgery, MIS group was characterised by a lower 90-day mortality (3.1% *versus* 7.09%, respectively, $p<0.0001$).

Logistic regression

We then performed a multivariable logistic regression in the high-risk group as shown in table 4. In univariate analysis, factors associated with 90-day mortality in the high-risk group included sex, age, BMI, FEV_1, D_{LCO}, Ipal score and surgical approach. In multivariable analysis, the factors associated with 90-day mortality in the high-risk group included sex, D_{LCO} and surgical approach.

Propensity score analysis

We then performed a propensity score analysis (PSM) to investigate the impact of MIS on 90-day mortality of high-risk patients. The results are summarised in table 5. The PSM sample had 2168 patients. The area under the receiver operating curve (ROC) for the predicted propensity score was 0.82. The distribution of propensity score was similar between MIS and open surgery (supplementary figure S1) with a mean±SD score of 0.57±0.20 for MIS and 0.58±0.20 for open surgery. In the PSM sample the 90-day mortality rate was 3.0% for MIS and 6.0% for open surgery. The propensity score matched odds ratio (OR) of 90-day mortality was lower in high-risk patients who received MIS compared to those who received open surgery (OR 0.46; 95% CI 0.30–0.69, $p<0.001$). The area under the ROC for the predicted 90-day mortality rate (fitted on the PSM sample) was 0.66. High-risk patients operated through MIS had a 90-day mortality rate similar to low-risk patients in general (3.10% *versus* 3.18% respectively).

In the low-risk group, we did a similar analysis to investigate the impact of MIS on 90-day mortality. The PSM sample had 24 408 patients. The distribution of propensity score was similar between MIS and open surgery with a mean score of 0.46±0.19 for MIS and 0.45±0.20 for open thoracotomy. In the PSM sample

TABLE 1 Descriptive characteristics of overall population (n=46 909)

	Total	Low risk	High risk	p-value
Patients n	46 909	42 214	4695	
Sex, female	15 460 (32.96)	14 177 (33.58)	1283 (27.33)	<0.0001
Age years	64.9±9.3	65.04±9.36	63.82±8.88	<0.0001
FEV_1 %	82.8±20.5	85.69±18.57	58.30±19.85	<0.0001
D_{LCO} %	70.7±19.2	75.74±16.16	44.92±11.08	<0.0001
Thoracoscore	2.6±2.6	2.45±2.35	3.63±3.94	<0.0001
Score Ipal	6.7±4.8	6.60±4.56	7.69±6.38	<0.0001
Neoadjuvant therapy	2145 (4.57)	1927 (4.56)	218 (4.64)	0.007
Surgical approach				
Thoracotomy	29 479 (62.84)	26 109 (61.85)	3370 (71.78)	<0.0001
VATS	14 616 (31.16)	13 493 (31.96)	1123 (23.92)	
RATS	2814 (6.0)	2612 (6.19)	202 (4.3)	
Resection extent				< 0.0001
Segmentectomy	4278 (9.12)	3734 (8.85)	544 (11.59)	
Lobectomy	37 236 (79.38)	34 179 (80.97)	3057 (65.11)	
Bilobectomy	1824 (3.89)	1607 (3.81)	217 (4.62)	
Pneumonectomy	3571 (7.61)	2694 (6.38)	877 (18.68)	
Pathology				< 0.0001
Adenocarcinoma	32 423 (69.12)	29 751 (70.48)	2672 (56.91)	
SCC	12 289 (26.20)	10 525 (24.93)	1764 (37.57)	
Large cell carcinoma	1831 (3.90)	1610 (3.81)	221 (4.71)	
SaCa	366 (0.78)	328 (0.78)	38 (0.81)	
Post-operative staging	26 666 (56.85)			<0.0001
Stage I	9320 (19.87)	24 323 (57.62)	2343 (49.90)	
Stage II	9765 (20.82)	8304 (19.67)	1016 (21.64)	
Stage III	1158 (2.47)	8553 (20.26)	1212 (25.81)	
Stage IV		1034 (2.45)	124 (2.64)	
Nodal upstaging	3163 (6.74)	2861 (6.78)	302 (6.43)	0.80
90-day mortality	1581 (3.37)	1301 (3.18)	280 (5.96)	< 0.0001

Data are presented as mean±SD or n (%). FEV_1: forced expiratory volume in 1 s. D_{LCO}: diffusing capacity of the lung for carbon monoxide; VATS: video-assisted thoracic surgery; RATS: robotic-assisted thoracic surgery; SCC: squamous cell carcinoma; SaCa: sarcomatoid carcinoma.

the 90-day mortality rate was 0.02±0.14 for MIS and 0.03±0.17 for open thoracotomy. The propensity matched odds ratio of 90-day mortality was, in low-risk patients, in favour of MIS compared to open thoracotomy (OR 0.709; 95% CI 0.602–0.835, p<0.001). The area under the ROC for the predicted 90-day mortality rate (fitted on the PSM sample) was 0.68.

We then performed a propensity score analysis to decipher the impact of MIS on the 90-day mortality of high-risk patients aged 75 years or more. The area under the ROC for the predicted propensity score was 0.77. The PSM sample had 282 patients (550 in the full sample). The distribution of propensity score was similar between MIS and open surgery with a mean score of 0.41±0.19 for MIS and 0.39±0.19 for open surgery. In the PSM sample the 90-day mortality rate was 0.06±0.25 for MIS and 0.11±0.32 for open surgery, but this difference was not statistically significant (p=0.16). Similarly, the propensity matched odds ratio of 90-day mortality was, in high-risk patients aged ⩾75 years, in favour of MIS compared to open thoracotomy who received open surgery compared to those who received MIS, but this difference was not statistically significant (OR 0.456; 95% CI 0.172–1.213).

Machine learning algorithms

The ROC, the area under the curve (AUC) and the F1 score (recommended for imbalanced data sets) of the machine learning approaches performed in the high-risk group are summarised in figure 4. As compared with logistic regression associated with PSM, the interpretable random forest classifier was not associated with any improvement in F1 score or AUC, while the optimised random forest classifier was associated with a limited improvement in both values.

Discussion

Studying the impact of surgical approach on 90-day mortality following lung surgery for NSCLC on a nationwide database, we found that patients with FEV_1 or D_{LCO} values below 50% preoperatively were

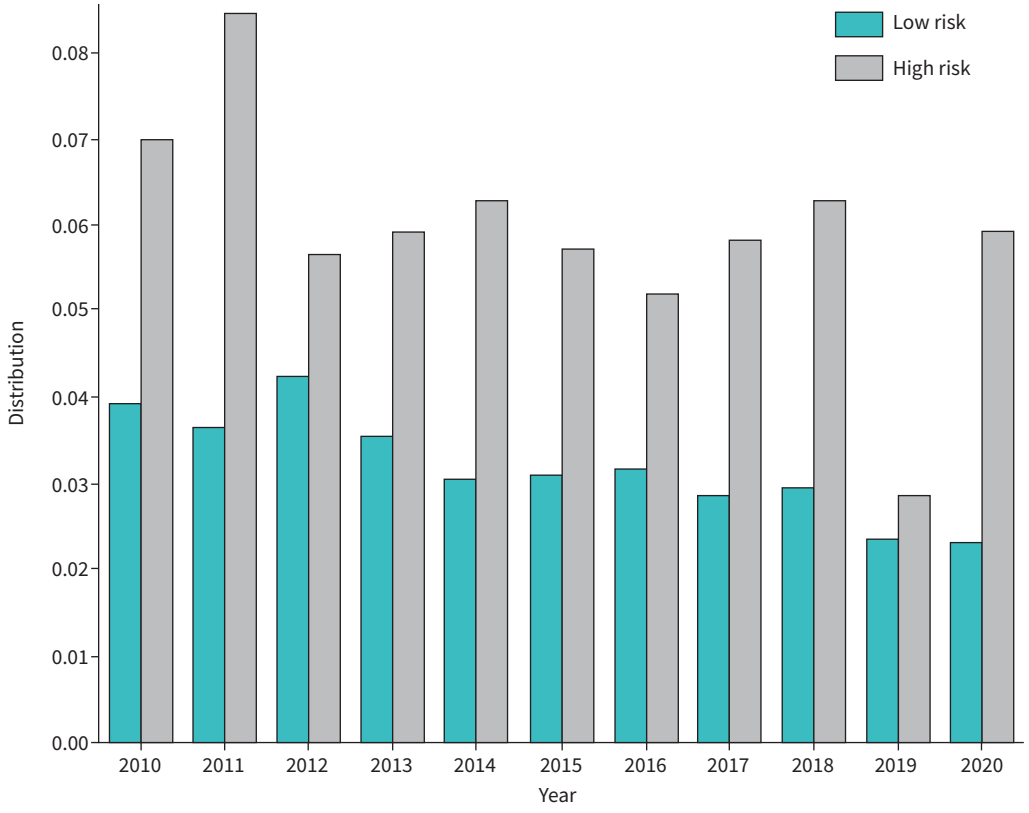
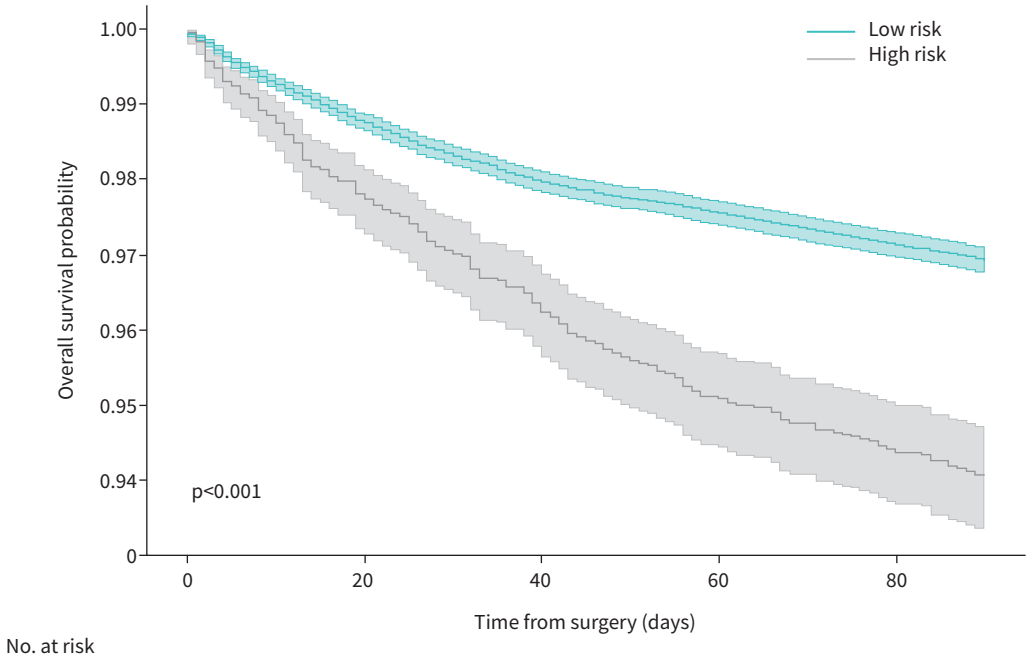


FIGURE 2 90-day mortality rate by risk group and year.



No. at risk					
Low risk	42177	41681	41345	41170	40988
High risk	4692	4589	4518	4465	4431

FIGURE 3 Survival curves during the first 90 days according to risk group.

TABLE 2 Comparison of surgical approaches in high-risk patients (n=4695)

	RATS	VATS	Thoracotomy	p-value
Patients n	202	1123	3370	
Sex, female	57 (28.22)	375 (33.40)	851 (25.25)	<0.0001
Age years	64.27±8.47	64.72±8.60	63.49±8.97	<0.0001
FEV_1 %	66.08±22.95	64.93±20.39	55.62±18.80	<0.0001
D_{LCO} %	44.05±8.44	45.54±11.17	44.69±11.20	0093
Thoracoscore	2.59±1.79	2.62±1.94	4.03±4.43	<0.0001
Ipal score	9.44±5.55	9.31±5.73	7.05±6.52	<0.0001
Neoadjuvant therapy	13 (6.44)	40 (3.56)	165 (4.90)	0.62
Intervention				<0.0001
Segmentectomy	42 (20.79)	232 (20.66)	270 (8.01)	
Lobectomy	160 (79.21)	857 (76.31)	2040 (60.43)	
Bilobectomy	0 (0)	18 (1.60)	199 (5.91)	
Pneumonectomy	0 (0)	16 (1.42)	861 (25.55)	
Pathology				<0.0001
Adenocarcinoma	130 (64.36)	785 (68.12)	1777 (52.73)	
SCC	58 (28.71)	299 (26.63)	1407 (41.75)	
Large cell carcinoma	13 (6.44)	52 (4.63)	156 (4.63)	
SaCa	1 (0.5)	7 (0.62)	30 (0.89)	
Post-operative staging				<0.0001
Stage I	148 (73.27)	793 (70.61)	1402 (41.60)	
Stage II	38 (18.81)	187 (16.65)	791 (23.47)	
Stage III	15 (7.43)	124 (11.04)	1073 (31.84)	
Stage IV	1 (0.50)	19 (1.69)	104 (3.09)	
Nodal upstaging	5 (2.48)	54 (4.81)	111 (3.29)	0.04
Death at 90 days	8 (3.96)	33 (2.94)	239 (7.09)	<0.0001

Data are presented as mean±SD or n (%). RATS: robotic-assisted thoracic surgery; VATS: video-assisted thoracic surgery; FEV_1: forced expiratory volume in 1 s. D_{LCO}: diffusing capacity of the lung for carbon monoxide; SCC: squamous cell carcinoma; SaCa: sarcomatoid carcinoma.

experiencing a higher risk of post-operative mortality that can be mitigated through MIS. High-risk patients operated through MIS achieved 90-day mortality rate similar to low-risk patients.

Previous randomised studies have shown the post-operative benefits of VATS surgery in post-operative outcomes in low-risk patients [4, 5, 11]. Bendixen *et al.* [4] have shown that VATS significantly decreased early post-operative pain and chronic post-operative pain compared to anterior thoracotomy. Long *et al.* [11] reported no difference in length of stay or any other clinical outcomes. Lim *et al.* [5] confirmed that compared to open surgery, VATS lobectomy results in better physical function at 5 weeks, shorter post-operative hospital stay, fewer serious adverse events after discharge and less pain. Using a data set of nearly 10 000 patients from the Veterans Health Administration, Heiden *et al.* [12] developed a surgical quality score named VALCAN-O for patients diagnosed with resectable early-stage NSCLC. The score reflects the risk-adjusted association between five quality metrics including the surgical approach (MIS and open surgery) and the overall survival and recurrence-free survival. In all these trials, description of the patients included suggests that their expected operative mortality was low, as was the observed mortality in both arms. No secondary analysis was done in patients with compromised pulmonary function. Our study was designed to investigate the benefits of MIS in this subgroup of patients.

No standard definition exists for patients at high risk of post-operative mortality following thoracic surgery. Guidelines advocate that patients being considered for thoracic surgery should undergo a comprehensive preoperative risk assessment to explore possible pulmonary and cardiac comorbidities. The ERS/ESTS 2009 guidelines on preoperative assessment before lung resection insist on both FEV_1 and D_{LCO} as key markers of post-operative functional status, morbidity and mortality [1]. A multivariable analysis by Ceppa *et al.* [13] showed that use of thoracotomy, decreasing predicted post-operative (ppo) FEV_1 and ppoD_{LCO} were independent predictors of increased post-operative morbidity after major lung resection. Risk prediction models have been used to define high-risk patients, but they often lack external validation and their discrimination ability is questionable [14, 15]. Among risk prediction models, the Thoracoscore was constructed using the Epithor database [16, 17]. Looking for a simple definition of high-risk patients, we

TABLE 3 Comparison of surgical approaches in high-risk patients (n=4695)

	Overall	MIS	Thoracotomy	p-value
Patients n	4695	1325	3370	
Sex, female	1283 (27.3)	432 (32.6)	851 (25.3)	<0.001
Age years	63.7±9.2	64.6±8.9	63.4±9.2	<0.001
FEV_1 %	58.4±19.9	65.2±20.8	55.7±18.8	<0.001
D_{LCO} %	53.5±15.1	49.9±13.8	54.9±15.4	0.061
Thoracoscore	3.6±3.3	2.6±1.7	4.0±3.6	<0.001
Ipal score	7.7±6.4	9.3±5.7	7.1±6.5	<0.001
Neoadjuvant therapy	218 (4.64)	53 (4)	165 (4.90)	0.378
Intervention				<0.001
Segmentectomy	544 (11.6)	274 (20.7)	270 (8.01)	
Lobectomy	3057 (65.1)	1017 (76.8)	2040 (60.43)	
Bilobectomy	217 (4.6)	18 (1.4)	199 (5.91)	
Pneumonectomy	877 (18.7)	16 (1.2)	861 (25.55)	
Pathology				<0.001
Adenocarcinoma	2672 (56.9)	895 (67.5)	1777 (52.73)	
SCC	1764 (37.6)	357 (26.9)	1407 (41.75)	
Large cell carcinoma	221 (4.7)	65 (4.9)	156 (4.63)	
SaCa	38 (0.8)	8 (0.6)	30 (0.89)	
Post-operative staging				<0.001
Stage I	2326 (49.54)	924 (69.74)	1402 (41.60)	
Stage II	1016 (21.64)	225 (16.98)	791 (23.47)	
Stage III	1212 (25.81)	139 (10.49)	1073 (31.84)	
Stage IV	124 (2.7)	20 (1.5)	104 (3.09)	
Nodal upstaging	170 (3.6)	59 (4.5)	111 (3.3)	0.068
Death at 90 days	280 (6.0)	41 (3.1)	239 (7.09)	<0.001

Data are presented as mean±SD or n (%). MIS: minimally invasive surgery; FEV_1: forced expiratory volume in 1 s. D_{LCO}: diffusing capacity of the lung for carbon monoxide; SCC: squamous cell carcinoma; SaCa: sarcomatoid carcinoma.

TABLE 4 Logistic regression in high-risk patients (n=4695)

	Univariate				Multivariate			
	OR	Lower CI	Upper CI	p-value	OR	Lower CI	Upper CI	p-value
Sex				<0.001				<0.001
Male	1.00				1.00			
Female	0.08	0.07	0.09		1.69	1.22	2.35	
Age	0.96	0.96	0.96	<0.001	1.01	1.00	1.02	0.18
BMI	0.89	0.89	0.90	<0.001	0.93	0.90	0.97	<0.001
Dyspnoea	0.15	0.13	0.18	<0.001	1.10	0.95	1.28	0.20
Smoking	0.94	0.93	0.94	<0.001	1.00	0.99	1.01	0.88
FEV_1	0.95	0.95	0.96	<0.001	1.00	0.99	1.00	0.23
D_{LCO}	0.94	0.94	0.94	<0.001	0.96	0.94	0.97	<0.001
Surgical approach				<0.001				<0.001
Open surgery	1.00				1.00			
Minimally invasive	0.04	0.02	0.05		0.47	0.32	0.68	
Procedure				<0.001				0.13
Non-pneumonectomy	1.00				1.00			
Pneumonectomy	0.10	0.08	0.13		1.26	0.94	1.70	
Pathology				<0.001				<0.001
Non-adenocarcinoma	1.00				1.00			
Adenocarcinoma	0.04	0.03	0.05		0.60	0.47	0.78	

BMI: body mass index; FEV_1: forced expiratory volume in 1 s. D_{LCO}: diffusing capacity of the lung for carbon monoxide.

TABLE 5 Results of the logistic regression after using propensity score matching in high-risk patients (n=4695)

	Multivariate			
	OR	Lower CI	Upper CI	p-value
Sex				<0.001
Male	1.00			
Female	2.29	1.35	3.87	
Age	1.01	0.99	1.03	0.35
BMI	0.95	0.91	0.99	0.03
Dyspnoea	1.02	0.80	1.28	0.90
Smoking	1.00	0.99	1.01	0.50
FEV_1	1.00	0.99	1.01	0.54
D_{LCO}	0.94	0.92	0.96	<0.001
Surgical approach				<0.001
Open surgery	1.00			
Minimally invasive	0.46	0.30	0.69	
Procedure				0.13
Non-pneumonectomy	1.00			
Pneumonectomy	1.91	0.83	4.43	
Pathology				<0.001
Non-adenocarcinoma	1.00			
Adenocarcinoma	0.59	0.40	0.86	

BMI: body mass index; FEV_1: forced expiratory volume in 1 s. D_{LCO}: diffusing capacity of the lung for carbon monoxide.

decided to use the main criteria of the ACOSOG Z4099/RTOG 1021 and ACOSOG Z4032, both randomised controlled trials [3, 18]. We did not include the minor criteria, as not all those data were necessarily available in the Epithor database. Using this simple risk stratification, we found a significant difference in 90-day mortality between high-risk patients and low-risk patients. The fact that there was a high rate of pneumonectomy in the high-risk group compared to the low-risk group could be a potential bias. It is possibly explained by a higher proportion of squamous cell carcinoma and large cell carcinoma present in the high-risk group: we know that those tumours tend to be more central compared to adenocarcinoma, which are more peripheral. The extent of parenchymal resection was not associated with 90-day mortality in univariate or multivariate analysis in the high-risk group thus relativising the impact of this potential bias. Our study corroborates the results from a study by Donahoe *et al*. [19] with a much larger sample size. In this retrospective study, 72 high-risk patients were compared to 536 low-risk patients. Rates of overall and pulmonary complications were significantly higher in high-risk patients compared to low-risk patients (p=0.0001). Overall, 90-day survival was significantly lower for high-risk patients who had an open thoracotomy compared to the high-risk patients who had MIS. We found similar trends on a larger scale, reinforcing the generalisability of the results.

Propensity matching reduces the confounding bias when comparing two surgical approaches**,** but it does not replace a randomised controlled trial. It is a good compromise when study groups differ not only in numbers but also in various demographic characteristics. Using this technique, an analysis of the ESTS database found a significant reduction in post-operative morbidity and mortality in frail patients (older than 70 years, BMI <18.5 $kg \cdot m^{-2}$ or ASA >2) who had VATS lobectomy instead of open surgery [2]. A subgroup of patients with $ppoFEV_1$ <40% had the same tendency but no mention was made of the D_{LCO}, although it remains a key element in operability assessment as previously mentioned. In our study use of the machine learning approach has been disappointing. As compared to the results for the PSM sample, AI algorithms did not reach any additional predictive value when using the interpretable random forest including 10 trees and a maximum depth of each tree to 3. AI algorithms reached a modest additional predictive value with the optimised random forest, but the results cannot be interpreted due to unintelligible variables. Even though the AUC of the logistic regression is good, the F1 score shows that the raw data is not sufficient to build an effective predictive model. It might be interesting to add a preprocessing step to create more informative feature data and then to test more algorithms. However, the machine learning approach is usually limited by the difficulty to generate synthetic data that prove to be realistic, accurate and to represent the complex state. In this particular field of medicine, the interpretability of a predictive model is required to allow its use in clinical practice.

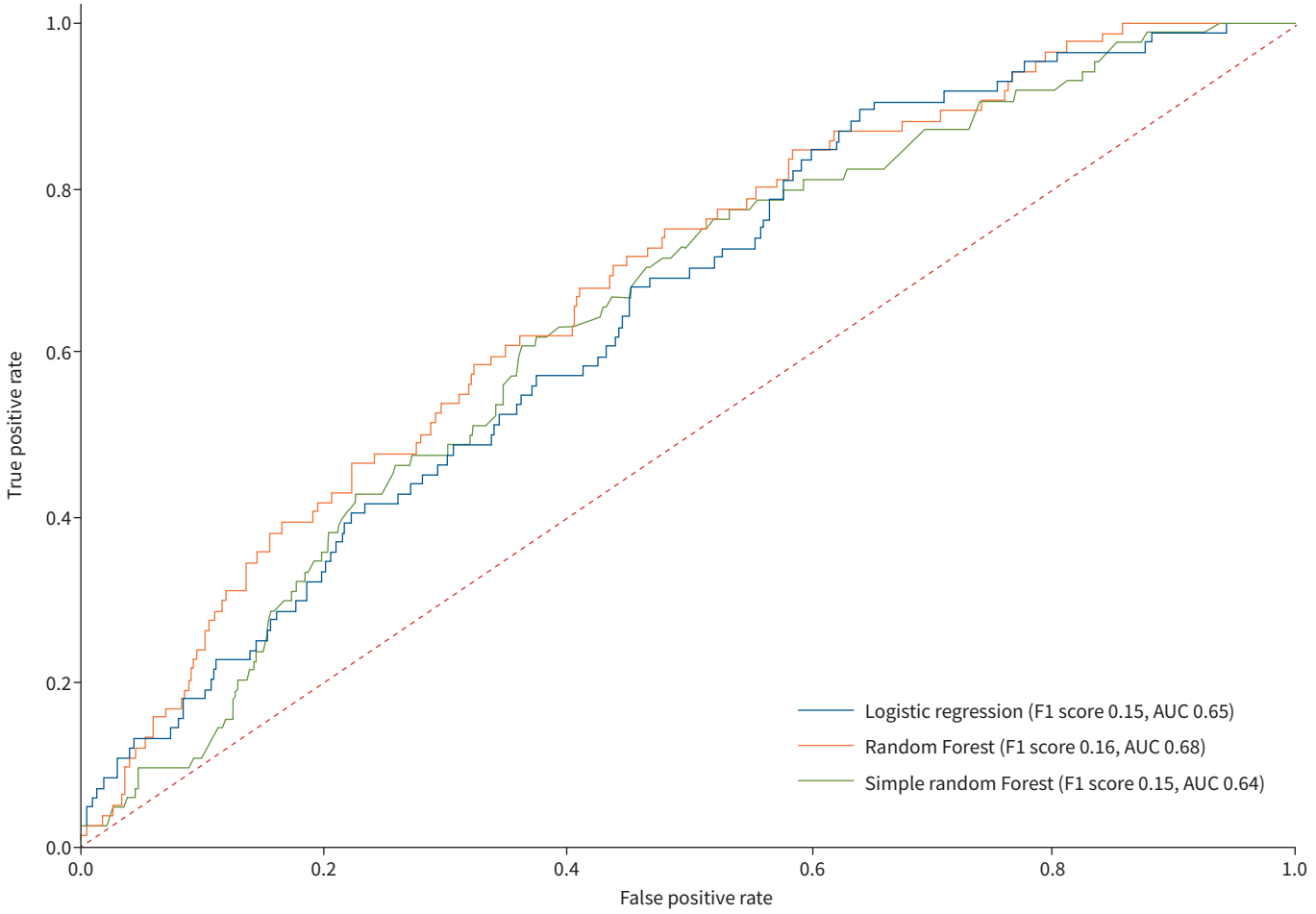


FIGURE 4 Receiver operating characteristic of different models to predict 90-day mortality of high-risk patients. AUC: area under the curve.

The main limitation of this study is its retrospective design. The data come from the French national database Epithor, and its quality depends on the accuracy of the submitted data from the individual participating centres. Depending on the centres, the open surgical approach (postero-lateral thoracotomy, axillary thoracotomy or anterior thoracotomy), VATS approach (anterior approach, totally thoracoscopic approach or subxyphoid approach) or RATS approach (three-arm or four-arm) differ. Moreover, no information was available on the conversion rate from VATS to thoracotomy. Lastly, the 90-day mortality might be underreported in surgical databases. The 90-day mortality has indeed been reported to be less important in the surgeon-based Epithor database than in the administration-based PMSI database, but the difference is less pronounced in high-volume centres, and this bias might affect both the low-risk and the high-risk groups in a similar way [20]. We performed a sensitivity analysis using only the high-volume centres and the results were not changed. The large sample size of our study allows us to have valuable information on the management of high-risk patients. Further randomised controlled studies would still be necessary to confirm these results.

Conclusion

Examining the impact of surgical approaches on 90-day mortality using a nationwide database, we found that preoperative FEV_1 and/or D_{LCO} below 50% were associated with higher 90-day mortality, which can be reduced by using minimally invasive surgical approaches. High-risk patients who underwent MIS had a 90-day mortality rate similar to that of low-risk patients.

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