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Assessment of the 90-day mortality risk score after video-assisted thoracoscopic lobectomy in the Italian VATS Group cohort

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Abstract

A five classes (A-E) aggregate risk score predicting 90-day mortality after video-assisted thoracoscopic lobectomy for lung cancer, including as independent factors male sex (3 points), DLCO <60% (1 point) and operative time >150 minutes (1 point), has been recently published. This study aims to assess the effectiveness and reliability of this risk model in a large, independent cohort of patients, to confirm its generalizability. From the Italian VATS Group Database, we selected 2,209 patients [60% males; median age 69 years (IQR:63-74)] who underwent video-assisted thoracoscopic lobectomy for non-small cell lung cancer. We calculated the aggregate risk score and the corresponding class of 90-day mortality risk for each patient. The correlation between risk classes and mortality rates was tested by Spearman's ρ-test. Model calibration was evaluated by Hosmer-Lemeshow goodness-of-fit test. Class A-E 90-day mortality rates were 0.33%, 0.51%, 1.39%, 1.31% and 2.56%, respectively. A strong uphill correlation was identified between risk classes and 90-day mortality (ρ=0.90; p=0.037), showing a positive correlation between increased mortality rate and class A to E. Hosmer-Lemeshow chi-squared value was 67.47 (p<0.001) with overall, Class D and E significantly lower 90-day mortality in our cohort than in the original one [1.04% *vs* 2.5% (p=0.018), 1.31% *vs* 5.65% (p=0.005) and 2.56% *vs* 18.75% (p=0.007), respectively]. Despite our data show a positive correlation between 90-day mortality and risk classes from A to E with modest discriminatory performance, the poor calibration suggests the need for model recalibration using local data to better manage and counsel lung cancer patients eligible for video-assisted thoracoscopic lobectomy.

Key words: non-small cell lung cancer, VATS lobectomy; 90-day post-operative mortality; risk score; validation.

Introduction

Lung lobectomy and lymph node dissection is the "gold standard" treatment for early-stage non-small cell lung cancer (NSCLC) [1]. However, the 90-day mortality rate after this surgical procedure still ranges between 0.3% and 4.6%, despite the introduction of video-assisted thoracoscopic approach (VATS) has significantly enhanced postoperative recovery, reduced morbidity, length of stay and, in some studies, mortality [2-12]. Thus, being aware of individual 90-day mortality risk after VATS lobectomy is fundamental for NSCLC patients' management and preoperative counseling, mainly when patients have borderline clinical conditions for surgery.

In order to address this issue, Brunelli *et al*. have published a five-class aggregate risk score predicting 90-day mortality after VATS lobectomy for NSCLC, including as independent factors male sex, carbon monoxide lung diffusion capacity (DLCO) and operative time [12]. This model has been found promising in a single-center series of patients but a solid test in a more extended independent cohort is recommended to confirm its generalizability before clinical application.

This study aims to assess the reliability and the validity of this aggregate risk score predicting 90-day mortality after VATS lobectomy for NSCLC in the independent multicenter cohort of the Italian VATS Group registry.

Materials and Methods

From the Italian VATS Group registry (a database containing prospectively collected data on VATS anatomical lung resection performed in 58 certified thoracic surgery centers from January 1st 2014) we selected patients who underwent VATS lobectomy and lymphadenectomy for NSCLC from January 1st 2014 to November 27th 2018. After a quality inspection of data, the VATS Group database was awarded by the European Society of Thoracic Surgeons in 2017. Patients with incomplete data for risk score calculation, tumor size >5 cm, follow-up <3 months and those who underwent neoadjuvant treatment and/or extended resection were excluded from the study, according to the original study [12]. The Ethics Committee approved the study (protocol number: 0033034; ClinTrials.gov ID: NCT04799509) and all patients signed informed consent. This research is being reported in line with the STROCSS guideline [13].

Patients' records included: age, gender, comorbidity, Eastern Cooperative Oncology Group performance status, forced expiratory volume in 1 second (FEV_1), DLCO, tumor clinical 7th edition TNM stage, surgical approach, surgical procedure, operating time, tumor histology, size

and pathological 7th edition TNM stage, postoperative complications, postoperative length of stay, follow-up at 30 and 90-day after surgery.

For each patient, we calculated the corresponding risk class of postoperative 90-day mortality [A (0 point); B (1-2 points); C (3 points); D (4 points); E (5 points)] summing the score related to the following variables included in Brunelli *et al*.'s aggregate risk score [12]:

- Male sex = 3 points;
- DLCO <60% = 1 point;
- Operating time >150 minutes = 1 point.

The 90-day mortality rate was calculated for each risk class. In order to assess the effectiveness and reliability of this risk model in our cohort of patients, the correlation between risk classes and 90-day mortality rates, and overall model calibration were assessed in our multistitutional cohort. Then, our results were compared to Brunelli *et al*.'s ones.

Statistical analysis

Continuous data were reported as median with interquartile range (IQR). Categorical and count data were presented as frequencies and percentages and compared by Chi-square test (Fisher's exact test if any expected frequency <5). The correlation between risk classes and the mortality rate was tested by Spearman's ρ-test. Model calibration was evaluated by Hosmer-Lemeshow goodness-of-fit test. Significance was defined as a p-value <0.05. Statistical analysis was performed using SPSS 24.0 software (IBM Corp, Armonk, NY) and R software (version 3.6.1, Action of the Toes) with standard, *rcmdr*, and *irr* packages (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.).

Results

In the study period (from January 1st 2014 to November 27th 2018), the Italian VATS Group Database included 6,019 patients who underwent VATS lobectomy for NSCLC. According to the study inclusion/exclusion criteria, we excluded 3,810 patients leaving 2,209 records for statistical analysis (Figure 1). Patients' demographic and clinicopathological characteristics are listed in Table 1.

All patients underwent lobectomy. Lymph node radical dissection was performed in 1,503 (69%) patients, lymph node sampling in 691 (31%) and 15 cases this data was not available. Surgical approach was tri-portal VATS in 1,458 (66%) cases, bi-portal VATS in 397 (18%),

uniportal VATS in 228 (10%). In 126 (6%) patients, lobectomy was approached by four ports. Conversion to open thoracotomy occurred in 190 (8.6%) cases. Median operating time was 180 (IQR: 140-220) minutes.
Adjuvant treatment was performed in 239 (11%) patients: 201 chemotherapy; 16 radiotherapy; 22 both chemo and radiotherapy.

Overall postoperative morbidity rate was 28% (610/2,209 patients). In details, the most frequent complications were: 176 (8.0%) cardiovascular; 176 (8.0%) prolonged air-leak (>7days); 159 (7.2%) respiratory; 41 (1.9%) surgical hemo/chylothorax. Median postoperative length of stay was 5 days (IQR: 4-7). Eleven patients died within 30 days after surgery: 4 for acute respiratory failure; 2 for cardiovascular disease; 1 hemorrhage; 1 for multiple organ failure; 1 for abdominal disease; 1 for other cancer hemorrhage and in 1 case the cause of death was not specified. Moreover, further 12 patients died between the 31st and the 90th postoperative day: 6 for cardiovascular disease; 1 for acute respiratory failure; 1 for sepsis; 1 for trauma; 1 for alimentary intoxication and in 2 cases the cause of death was not reported. Overall postoperative mortality rates at 30 and 90 days were 0.50% (11/2,209) and 1.04% (23/2,209) respectively.

After calculating the aggregate risk score of postoperative 90-day mortality for each patient in our cohort, 301 (14%) patients fitted in Class A, 593 (27%) in Class B, 359 (16%) in Class C, 839 (38%) in Class D and 117 (5%) in Class E. The rates of 90-day mortality per classes in our cohort and Brunelli *et al.*'s one are reported in Table 2.
The Spearman's ρ-test showed a strong uphill correlation between risk classes and 90-day mortality rate in our cohort (ρ=0.90; p=0.037) as in the original one (ρ=1.00; p<0.001), showing an increased mortality risk from class A to E, as shown in Figure 2. However, in our cohort, Class C and Class D had similar rates of 90-day mortality after surgery (1.39% and 1.31%, respectively).
To better understand the reason for a similar 90-day mortality rate in Class C and D we analyzed the impact of each risk factor on 90-day mortality in our cohort and the distribution of these risk factors in Class C and D. Regarding the relationship between 90-day mortality and every risk factor, 90-day mortality rate was 0.47% (4/894) among female versus 1.44% (19/1,315) among male (p=0.034); 0.82% (16/1,941) among patients with DLCO ≥60% versus 2.61% (7/268) among those with DLCO <60% (p=0.008); 1.2% (9/749) when surgery lasted ≤150 minutes versus 0.96% (14/1,460) when it lasted >150 minutes (p=0.60). In Class C all patients were male with DLCO ≥60% and surgery lasting ≤150 minutes. In Class D all patients were

male, in 5.8% (49/839) cases DLCO was <60% and in 94% (790/839) surgery lasted >150 minutes.

Comparing our overall and per classes postoperative 90-day mortality rate to those of Brunelli *et al.* we observed a significantly lower overall 90-day mortality rate in our cohort than in Brunelli *et al*.'s one (1.04% *vs* 2.5%; p =0.018). The same difference was detected for Class D and Class E whose 90-day mortality rates were lower in our population than in the original one (Table 2) (p=0.005 and p=0.007, respectively). No differences were observed comparing Class A, Class B and Class C 90-day mortality rates between the two cohorts (Table 2) (p=1.00, p=1.00 and p=1.00, respectively). Hosmer-Lemeshow chi-squared value in our cohort was 67.47 (p<0.001).

Discussion

In the era of VATS affirmation as the preferred approach even for lobectomy and lymph node dissection for NSCLC, the estimation of individual mortality risk after this surgical procedure is crucial to decide the most appropriate treatment strategy for each patient with NSCLC. Numerous data have been reported regarding in-hospital/30-day mortality after VATS lobectomy in lung cancer patients, and several postoperative 30-day mortality risk scores have been proposed comprising major anatomical lung resections performed either by thoracotomy or by VATS [14-16]. However, according to recent studies, mortality between the 30th and the 90th postoperative day is still relevant, suggesting surgery effects last probably longer than 30 days after surgical procedure and empathizing the need of moving clinician attention to 90-day mortality and factors associated with it [2-11].

Brunelli *et al*.'s study is the first one analyzing 90-day mortality in the specific cohort of VATS lobectomy for NSCLC; they propose a five classes (Class A-E) aggregate risk score of postoperative 90-day mortality [12]. Our study tested Brunelli *et al*.'s model in the large, multicenter, independent cohort of the Italian VATS Group Registry and showed that the proposed aggregate risk score is predictive of 90-day mortality after VATS lobectomy, with mortality rate increased significantly from Class A to Class E. Moreover, risk class calculation for each patient appeared to be simple requiring only to sum the score related to three easily identifiable parameters: gender, DLCO and operative duration. These findings apparently suggest the possible introduction of Brunelli *et al*.'s aggregate risk score in our daily clinical practice as an additional tool in the management of NSCLC patients.

However, our results require some observations. Overall and higher-risk classes (Class D and E) 90-day mortality risk rates are significantly lower in our cohort than in the original one. This is probably due to the worse respiratory function of Brunelli *et al.*'s population (mean FEV_1= 88.0±21.1%; mean DLCO= 71.8±16.4%) [12]. In fact, in their cohort the half of postoperative deaths are due to respiratory complications. However, both overall 90-day mortality values are consistent with literature reports which assess 90-day mortality after lobectomy up to 4.6% [2-8]. Moreover, in our population no difference in terms of mortality rate was observed between Class C and Class D, probably due to the overall better condition of our patients and to the absence of impact of surgical duration, defined by the 150 minutes cut-off value.
The discrepancies in patients' clinical status explain the model poor calibration revealed by the Hosmer-Lemeshow goodness-of-fit test and suggest the need for model recalibration using local data in order to better manage and counsel NSCLC patients eligible for VATS lobectomy.

Another essential observation concerns the aggregate risk score itself and specifically one of its three variables: duration of surgery. Prolonged surgical time and anesthesia have been largely proven to negatively influence the postoperative course [12]. However, the cut-off value of 150 minutes for the operative time may not be generalizable to all institutions because it varies with surgeon experience, individual surgical volume, and case complexity. Thus, before calculating the risk score, operative time cut-off value should be recalibrated locally in order to better fit each institution setting. Moreover, surgical duration is not known preoperatively, suggesting that the surgical risk can be discussed during the multidisciplinary meeting and presented to the patient only as a range of estimates depending on whether the surgical time will be longer or shorter than the referral one, taking into consideration the possibility of changing the surgical choices and approaches mainly in male patients with a DLCO <60% (Class D).

Managing patients who are candidates for VATS lobectomy for NSCLC, Brunelli *et al.*'s model may be used several times: during multidisciplinary boards in choosing the most adequate treatment strategy; during surgery, to evaluate conversion of the surgical procedure from VATS to thoracotomy; after surgery to better modulate high-risk patients' cure and monitoring before and after discharge.
More in detail, after estimating the predicted mortality rates per risk class in its own institution, patients' 90-day mortality risk should be calculated preoperatively using as surgical duration reference its own median surgical time for VATS lobectomy and lymphadenectomy. High-risk patients should be discussed and possibly proposed for sublobar resection, stereotactic

radiotherapy or radiofrequency. For surgical candidates, surgeons should evaluate conversion of surgical procedure from VATS to thoracotomy whenever surgery delays over regular timetable, upgrading patient to a higher risk class. Finally, since the leading causes of death were respiratory failure within 30-day after surgery and cardiovascular disease during the following 60 days, high-risk patients may benefit from a more intensive postoperative respiratory physiotherapy program during their early postoperative course in order to reduce respiratory complications and form a cardiological check before discharge in order to assess heart function after surgery and to eventually introduce an appropriate cardiac therapy, preventing respectively respiratory and cardiac deaths.

This study has some limitations. First, its retrospective nature. A prospective validation study may overcome the issue; however, the Italian VATS Group Registry comprises prospectively collected data, granting a better reconstruction of patients' clinical history and limiting missing information. The quality of these data was awarded by the European Society of Thoracic Surgeons in 2017, after a proper inspection. A second limitation is that the number of events is low, suggesting that few events can drive results in different ways. Though statistical analysis and results evaluation have been performed aware of this limitation. We also underline that the use of the Spearman Rank Correlation Coefficient recognizes some limitations. Values of both variables are assumed to describe a linear relationship rather than a non-linear one; a sizeable computational time is required when the number of pairs of values of two variables exceeds 30 and assigning ranks to each numerical value is very time-consuming. This method cannot be applied to measure the association between two variables whose distribution is given as a grouped frequency distribution.
Finally, we could not compare Brunelli *et al*.'s model to the available scores for mortality prediction after lung resection (the Thoracoscore, the EuroLung2 and the STS score) because these models have been developed with the specific aim to predict 30-day and not 90-day mortality after surgery [16-18]. Furthermore, Brunelli *et al*.'s score exclusively focuses on lung lobectomy performed by VATS, while the Thoracoscore the EuroLung2 and the STS score referred to various kinds of lung resections (from wedge resection to pneumonectomy) mostly approached by thoracotomy [16-18].

To conclude, when tested in the Italian VATS Group dataset, the aggregate risk score of 90-day mortality after VATS lobectomy, proposed by Brunelli *et al*., showed a positive correlation with mortality rate from Class A to Class E, with modest discriminatory performance, but poor

calibration. This suggests that the applicability of this risk model to manage and counsel NSCLC patients eligible for VATS lobectomy is easy and feasible; however, to obtain a better performance, operating time cut-off values may be revised and adjusted according to local data.

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Table 1. Demographic and clinical characteristics of 2,209 patients from the Italian VATS Group Registry who underwent video-assisted thoracoscopic lobectomy for non-small cell lung cancer.

Patients' characteristics	
Age, median (IQR) years	69 (63-74)
Male, n (%)	1,315 (60%)
FEV_1, median (IQR) %	96 (82-109)
DLCO, median (IQR), n (%)	82 (68-94)
Significant co-morbidity	
Myocardial infarction, n (%)	212 (10)
Congestive heart failure, n (%)	68 (3)
Cerebrovascular disease, n (%)	141 (6)
Diabetes, n (%)	275 (12)
COPD	383 (17)
ECOG, n (%)	
0	1,708 (77)
1	432 (20)
2-3	69 (3)
Side right, n (%)	1,355 (61)
Side upper, n (%)	1,285 (58)
Histology, n (%)	
Adenocarcinoma	1,605 (73)
Squamous cell carcinoma	331 (15)
Adenosquamous carcinoma	24 (1)
Large cell carcinoma	14 (1)
Large cell neuroendocrine carcinoma	28 (1)
Carcinoid	183 (8)
Others	24 (1)
pStage, n (%)	
I	1,782 (81)
II	249 (11)
III	178 (8)

COPD, chronic obstructive pulmonary disease; DLCO, carbon monoxide lung diffusion capacity; ECOG, Eastern Cooperative Oncology Group performance status; FEV_1, forced expiratory volume in 1 second; IQR, interquartile range; pStage, pathological stage (according to 7^{th} edition TNM stage).

Table 2. 90-day mortality rates by risk aggregate score classes: the Italian VATS Group cohort and Brunelli *et al*.'s cohort [12].

	Italian VATS Group cohort			**Brunelli *et al.*'s cohort [12]**		
Class	**N (%)**	**Death, n**	**90-day mortality**	**N (%)**	**Death, n**	**90-day mortality**
A	301 (14)	1	0.33%	155 (21)	0	0.00%
B	593 (27)	3	0.51%	262 (36)	1	0.38%
C	359 (16)	5	1.39%	107 (15)	1	0.93%
D	839 (38)	11	1.31%	177 (24)	10	5.65%
E	117 (5)	3	2.56%	32 (5)	6	18.75%

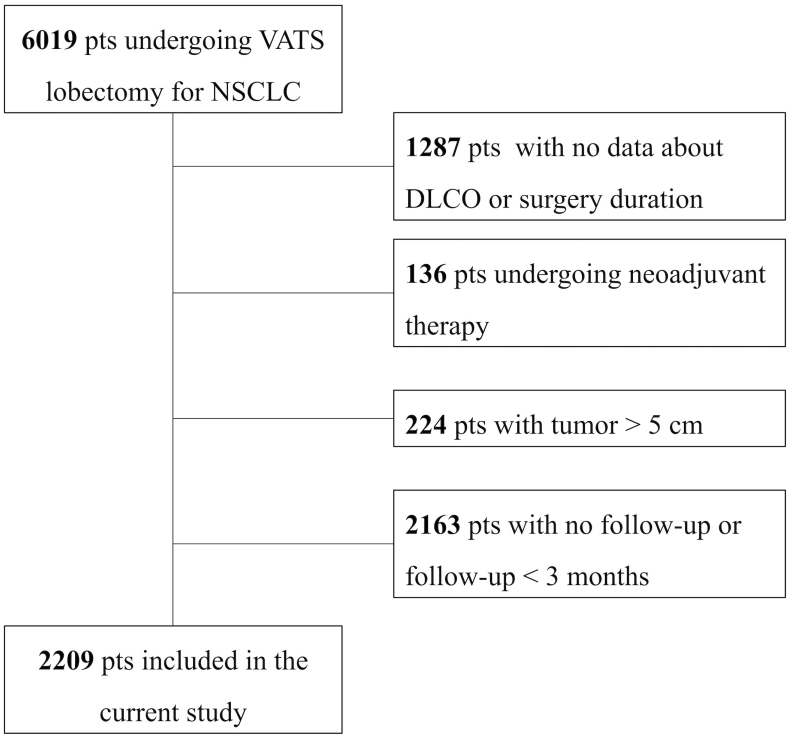

Figure 1. Patients' enrollment in the current study. DLCO, carbon monoxide lung diffusion capacity; NSCLC, non-small cell lung cancer; pts, patients; VATS, video-assisted thoracic surgery.

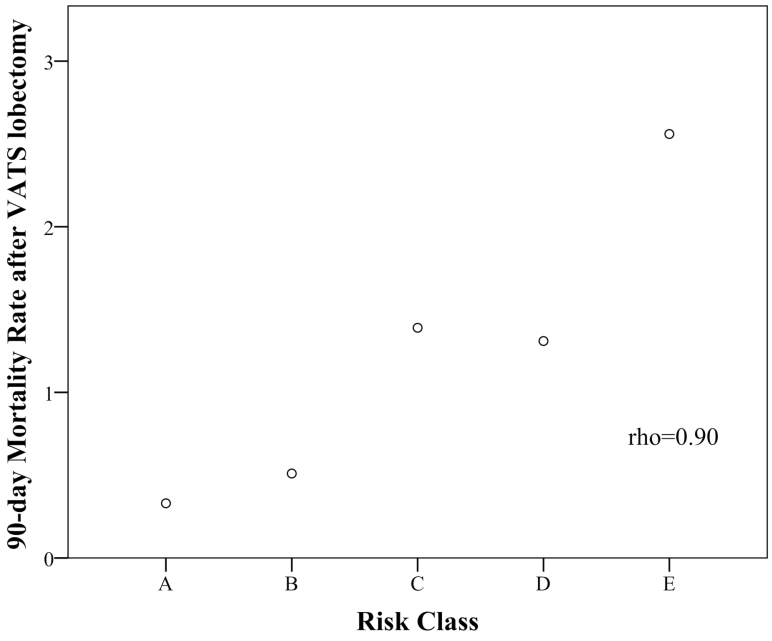

Figure 2. The correlation between risk classes (from Class A to Class E) and 90-day mortality rate after VATS lobectomy for NSCLC in the Italian VATS Group cohort.