New models for prediction of postoperative pulmonary complications in lung resection candidates

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Shareable abstract (@ERSpublications)
Two models with improved ability to predict postoperative pulmonary complications in patients scheduled for lung resection surgery may improve preoperative algorithms as they stratify risk based on more relevant parameters https://bit.ly/3xUzdyY

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Abstract

Introduction In recent years, ventilatory efficiency (minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2}) slope) and partial pressure of end-tidal carbon dioxide (P_{ETCO_2}) have emerged as independent predictors of postoperative pulmonary complications (PPC). Single parameters may give only partial information regarding periprocedural hazards. Accordingly, our aim was to create prediction models with improved ability to stratify PPC risk in patients scheduled for elective lung resection surgery.

Methods This *post hoc* analysis was comprised of consecutive lung resection candidates from two prior prospective trials. All individuals completed pulmonary function tests and cardiopulmonary exercise testing (CPET). Logistic regression analyses were used for identification of risk factors for PPC that were entered into the final risk prediction models. Two risk models were developed; the first used rest P_{ETCO_2} (for patients with no available CPET data), the second used V'_E/V'_{CO_2} slope (for patients with available CPET data). Receiver operating characteristic analysis with the De-Long test and area under the curve (AUC) were used for comparison of models.

Results The dataset from 423 patients was randomly split into the derivation (n=310) and validation (n=113) cohorts. Two final models were developed, both including sex, thoracotomy, "atypical" resection and forced expiratory volume in 1 s/forced vital capacity ratio as risk factors. In addition, the first model also included rest P_{ETCO_2}, while the second model used V'_E/V'_{CO_2} slope from CPET. AUCs of risk scores were 0.795 (95% CI: 0.739–0.851) and 0.793 (95% CI: 0.737–0.849); both p<0.001. No differences in AUCs were found between the derivation and validation cohorts.

Conclusions We created two multicomponental models for PPC risk prediction, both having excellent predictive properties.

Introduction

Surgery remains the preferred treatment of early-stage (IA–IIIA) lung cancer due to benefits on long-term survival [1]. However, postoperative pulmonary complications (PPC) remain a major problem within the 30-day postoperative period, contributing to increased morbidity and mortality, decreased quality of life, prolonged duration of hospitalisation and intensive care unit (ICU) stay, and economic burden [2–4]. 30-day postoperative mortality rates after lung resection range from 2.3% to 3% [5, 6] and from 6.6% to 7.5% [4, 7], depending on surgical technique and extent of resection.

A recognised factor associated with PPC is patient preoperative functional status. Guidelines of the European Respiratory Society (ERS) and the American College of Chest Physicians (ACCP) [8, 9] emphasise the important role of spirometry and assessment of diffusing capacity of the lungs for carbon monoxide (D_{LCO}). Patients with impaired lung function may also benefit from risk stratification by cardiopulmonary exercise testing (CPET) [8, 9]. Despite adherence to the ERS/ACCP guidelines, postoperative morbidity and mortality rates remain high, especially when compared to other elective surgeries including reported 30-day mortality rates of 0.15% for cholecystectomy [10] and 0.08% for appendectomy [11].

In recent years, it has been demonstrated that for patients evaluated by CPET, peak oxygen consumption (peak V'_{O_2}), previously considered to be the gold standard exercise parameter for risk assessment, is a suboptimal predictor of PPC [7, 12–14]. In contrast, ventilatory efficiency (minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2}) slope) and partial pressure of end-tidal carbon dioxide (P_{ETCO_2}) have been demonstrated to be independent predictors of PPC [7, 12, 15, 16]. Indeed, V'_E/V'_{CO_2} slope has been proposed to be included in preoperative functional assessments [17].

Single parameters for clinical risk prediction may give only partial information regarding periprocedural hazards. Accordingly, our aim was to identify factors associated with the development of PPC and create prediction models with improved ability to stratify PPC risk in patients scheduled for elective lung resection surgery. We created two scores – the first for patients able to undergo CPET (for patients with available CPET data) and the second for patients unable (or unwilling) to undergo CPET (for patients with no available CPET data).

Methods

Subjects

This *post hoc* analysis comprised consecutive lung resection candidates (with confirmed or highly suspected lung tumour) from two prior prospective trials conducted at two sites in the Czech Republic (St. Anne's University Hospital in Brno and University Hospital Brno). Inclusion requirements were ability to undergo CPET and age ⩾18 years. Exclusion criteria included inoperable tumour (lung resection not performed) and/or contraindication for lung resection due to low predicted postoperative peak V'_{O_2} [8]. Both studies were registered at ClinicalTrials.gov (NCT03498352 and NCT04826575), conducted in accordance with the Declaration of Helsinki, and approved by the local Ethics Committees of St. Anne's University Hospital in Brno (reference No. 19JS/2017; reference No. 2G/2018; reference No. 03G/2021) and University Hospital Brno (references No. 150617/EK and No. 14-100620/EK). All participants provided written informed consent for participation in the study.

Pulmonary function tests

All patients completed pulmonary function tests as reported previously [12] in accordance with the ERS and American Thoracic Society (ATS) technical standards [18, 19]. The tests included D_{LCO} with PowerCube Diffusion+ (Ganshorn Medizin Electronic GmbH, Germany) and spirometry with the ZAN100 device (nSpire Health, Inc., USA). The analysed spirometry measures included forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and the FEV_1/FVC ratio. FEV_1 and FVC were analysed as % of the predicted values, with FEV_1/FVC analysed as a ratio. In the 2017–2021 period, the ECCS93 reference values were used [20], while after 2021, the Global Lung Function Initiative (GLI) equations were introduced in both centres [21]. D_{LCO} values were recorded as % of the predicted values; in the 2017–2021 period, the Crapo reference values were used [22], while after 2021, the GLI equations were introduced in both centres [23].

Z-scores for FEV_1, FVC and FEV_1/FVC were calculated using the official ERS online calculator [24].

Cardiopulmonary exercise testing

All individuals had a symptom-limited CPET as previously reported [12] prior to surgery on an electronically braked bicycle ergometer (Ergometrics 800®, Ergoline, Bitz, Germany) with a 12-channel electrocardiography unit (AT-104®, Schiller AG, Baar, Switzerland). For the analysis of expired gases and quantities, a PowerCube-Ergo® cardiopulmonary exercise system (Ganshorn Medizin Electronic GmbH, Niederlauer, Germany) was used. At the end of the rest period and during maximal effort, blood gas analyses were performed using the ABL90 Flex Plus® (Radiometer Medical ApS, Denmark) system. Carbon dioxide output (V'_{CO_2}), V'_{O_2}, tidal volume (VT), dead space to tidal volume ratio (V_D/V_T), breathing frequency (f_b), V'_E, P_{ETCO_2}, respiratory exchange ratio and V'_E/V'_{CO_2} slope were among the analysed CPET measures.

Postoperative pulmonary complications

Pulmonary complications were defined as in previous studies [4, 12, 15, 25, 26] and assessed from the first 30 postoperative days or from the hospital stay, and included the following conditions: pneumonia (chest radiograph infiltrates+fever and/or leukocytosis/leukopenia and/or purulent sputum production); atelectasis (chest radiograph signs+bronchoscopy with plug being removed); respiratory failure requiring mechanical ventilation (noninvasive or invasive ventilation); adult respiratory distress syndrome (bilateral chest radiograph infiltrates+arterial partial pressure of oxygen/fraction of inspired oxygen <300) [27], prolonged air leak (presence of air leak from the chest tube on the 5th postoperative day) [28] and tracheostomy. In addition, hospital length of stay (LOS), ICU LOS and type (thoracotomy *versus* video-assisted thoracic surgery (VATS)) and extent of surgical procedure (atypical resection, lobectomy, bilobectomy, pneumonectomy) were recorded. In the multivariate model, "atypical resection" included wedge resection or segmentectomy, while "atypical resection – no" included lobectomy or larger anatomical resection.

Statistical analyses

Categorical parameters were described by absolute and relative frequencies. Independence of two categorical parameters was tested by the Pearson chi square test or the Fisher exact-test. Numerical parameters were described by valid n, mean±SD and median supplemented by the 5th and 95th quantile. Differences between the two groups were tested by the independent t-test or Mann–Whitney U-test, depending on normality of the data that was evaluated by the Shapiro–Wilk test.

Univariate and multivariate logistic regression were used for identification of risk factors for PPC. Statistically significant parameters from basic description (potential confounding factors) were included in univariate regressions. Multivariate models included statistically significant parameters identified by univariate regression. The forward stepwise method for selection was used. Odds ratios (OR) were supplemented by 95% confidence intervals (CI). Spearman correlation coefficients were calculated to assess correlation of these parameters. Statistically significant parameters ($p<0.05$) from multivariate logistic regression were entered into the final risk prediction models. Two risk models were developed: the first used rest P_{ETCO_2} (for patients with no available CPET data); the second used V'_E/V'_{CO_2} slope (for patients with available CPET data). Receiver operating characteristic (ROC) analysis with the DeLong test and area under the curve (AUC) were used for comparison of these models (scores). ROC analysis was also used for comparison of results from the derivation and validation cohorts.

Due to the low number of events (deaths) in both cohorts, we were unable to develop any model for prediction of death risk. However, 30-day and 90-day mortality rates were summarised by survival analysis methods. Kaplan–Meier curves were constructed for visualisation of survival probability. Cox models for proportional hazards were used for hazard ratio (HR) calculation.

Analysis was performed using SPSS Statistics 24 and R 4.2.0 software; p-values <0.05 were considered statistically significant.

Results

In total, data from 423 patients were included in the analysis. This dataset was randomly split into the derivation (n=310) and validation (n=113) cohorts on a 3:1 ratio basis. The derivation cohort (three-quarters of dataset) was used for models and risk scores development while the validation cohort (a quarter of dataset) was used to test the models.

Basic characteristics of study cohorts

Basic demographic characteristics of the derivation cohort are presented in table 1. 75 (24.2%) patients from the derivation cohort (n=310) had PPC. Patients with PPC were significantly more likely to have COPD, lobectomy or thoracotomy (all $p<0.001$) compared to the group without PPC. In contrast, patients without PPC more frequently underwent atypical lung resection. Patients with PPC had significantly worse lung function, lower rest P_{ETCO_2}, higher V'_E/V'_{CO_2} slope and a longer hospital LOS and ICU LOS (table 1).

Univariate logistic regression and ROC analysis – identification of risk factors

A total of 44 factors or parameters were entered in the univariate logistic regression and ROC analysis. Of these, a total of seven factors were included in the multivariate analysis; the other parameters were omitted due to collinearity or correlation of similar parameters (*e.g.*, V'_E/V'_{CO_2} slope and V'_E/V'_{CO_2} ratio or FEV_1 % predicted, FEV_1 Z-score and FEV_1/FVC). The results of ROC analysis are presented in supplementary table S1.

TABLE 1 Subject characteristics of study group (derivation cohort; n=310)

	Pulmonary complications		
	No[#]	Yes[¶]	p-value
Age years	n=235	n=75	0.324
Mean±SD	61.6±13.8	64.4±9.3	
Median (5th and 95th quantile)	65.0 (30.0–77.0)	66.0 (48.0–76.0)	
Sex, male	121 (51.5)	51 (68.0)	**0.012**
BMI kg·m^{-2}	n=235	n=75	0.654
Mean±SD	27.9±5.4	28.5±6.0	
Median (5th and 95th quantile)	27.7 (19.8–37.4)	27.2 (19.9–41.4)	
COPD	48 (20.4)	31 (41.3)	**<0.001**
Pneumonectomy	6 (2.6)	0 (0.0)	0.342
Bilobectomy	7 (3.0)	2 (2.7)	0.999
Lobectomy	92 (39.1)	59 (78.7)	**<0.001**
Atypical resection	128 (54.5)	17 (22.7)	**<0.001**
Thoracotomy	112 (47.7)	53 (70.7)	**<0.001**
FEV_1 % pred	n=232	n=74	**0.004**
Mean±SD	93.2±19.9	85.5±19.1	
Median (5th and 95th quantile)	93.0 (59.0–127.0)	83.5 (46.0–118.0)	
FEV_1 Z-score	n=229	n=73	**0.013**
Mean±SD	−0.73±1.20	−1.12±1.11	
Median (5th and 95th quantile)	−0.84 (−2.90–1.16)	−1.10 (−2.95–0.67)	
FVC % pred	n=231	n=74	0.136
Mean±SD	95.4±18.1	92.1±19.3	
Median (5th and 95th quantile)	94.0 (67.0–129.0)	91.0 (63.0–128.0)	
FVC Z-score	n=225	n=73	0.234
Mean±SD	−0.81±1.08	−0.92±1.18	
Median (5th and 95th quantile)	−0.82 (−2.71–1.00)	−1.01 (−2.76–1.17)	
FEV_1/FVC %	n=225	n=74	**<0.001**
Mean±SD	78.6±8.5	73.8±9.7	
Median (5th and 95th quantile)	79.3 (63.0–91.5)	73.5 (56.6–88.7)	
FEV_1/FVC Z-score	n=225	n=73	**< 0.001**
Mean±SD	0.07±1.14	−0.45±1.19	
Median (5th and 95th quantile)	0.10 (−1.91–2.01)	−0.42 (−2.57–1.31)	
D_{LCO} % pred	n=224	n=73	**0.024**
Mean±SD	84.7±21.5	78.1±22.1	
Median (5th and 95th quantile)	83.0 (51.2–123.0)	78.5 (46.0–120.0)	
Rest P_{ETCO_2} mmHg	n=235	n=75	**<0.001**
Mean±SD	29.8±4.5	27.4±4.4	
Median (5th and 95th quantile)	30.0 (21.7–37.0)	27.6 (19.2–34.7)	
V'_E/V'_{CO_2} slope	n=235	n=75	**<0.001**
Mean±SD	29.5±6.2	32.8±7.0	
Median (5th and 95th quantile)	28.8 (21.1–39.9)	31.6 (23.0–44.1)	
Length of hospitalisation, days	n=235	n=75	**<0.001**
Mean±SD	6.54±3.11	13.65±7.82	
Median (5th and 95th quantile)	6.00 (3.00–12.00)	11.00 (7.00–30.00)	
Length of stay in intensive care unit, days	n=235	n=75	**<0.001**
Mean±SD	3.12±1.82	6.60±4.69	
Median (5th and 95th quantile)	3.00 (1.00–7.00)	5.00 (2.00–16.00)	

Data are presented as n (%) unless indicated otherwise. Bold type for p-values indicates statistical significance. "Atypical resection" includes segmentectomy and wedge resection. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; FEV_1/FVC: Tiffeneau index; D_{LCO}: diffusion capacity of the lungs for carbon monoxide; P_{ETCO_2}: pressure of end-tidal carbon dioxide; V'_E/V'_{CO_2}: ventilatory efficiency (for carbon dioxide). [#]: n=235; [¶]: n=75.

Multivariate logistic regression – risk scores development

Two final models (multivariate logistic regression) are presented in table 2. Numerical parameters were categorised according to the best cut-off value (FEV_1/FVC ⩽75%, rest P_{ETCO_2} ⩽28 mmHg and V'_E/V'_{CO_2} slope ⩾33) based on ROC analysis and our previous studies [12]. Both models included sex, thoracotomy, resection other than wedge ("atypical") and FEV_1/FVC ratio as risk factors. In addition, the first model

TABLE 2 Risk factors for pulmonary complications: multivariate regression (derivation cohort; n=310)

	Model 1				Model 2			
	Primary model		Final model		Primary model		Final model	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex, male	2.459 (1.293–4.673)	**0.006**	2.455 (1.292–4.665)	**0.006**	2.281 (1.218–4.273)	**0.010**	2.281 (1.218–4.273)	**0.010**
Thoracotomy – yes	1.934 (1.023–3.659)	**0.042**	1.907 (1.014–3.585)	**0.045**	1.857 (0.992–3.478)	0.053	1.856 (0.999–3.456)	**0.050**
Atypical resection – no	0.228 (0.115–0.454)	**<0.001**	0.229 (0.115–0.456)	**<0.001**	0.250 (0.128–0.489)	**<0.001**	0.250 (0.128–0.489)	**<0.001**
FEV_1/FVC %	0.945 (0.913–0.979)	**0.002**	0.947 (0.915–0.980)	**0.002**	0.953 (0.921–0.987)	**0.007**	0.953 (0.921–0.987)	**0.006**
D_{LCO} % pred	1.002 (0.987–1.018)	0.748			1.000 (0.985–1.015)	0.990		
Rest P_{ETCO_2} ⩽28 mmHg	0.878 (0.816–0.943)	**<0.001**	0.881 (0.822–0.943)	**<0.001**				
V'_E/V'_{CO_2} slope ⩾33					1.052 (1.002–1.104)	**0.040**	1.052 (1.005–1.101)	**0.029**

Statistically significant differences are indicated in bold. "Atypical resection" includes segmentectomy and wedge resection. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; FEV_1/FVC: Tiffeneau index; D_{LCO}: diffusion capacity of the lungs for carbon monoxide; P_{ETCO_2}: pressure of end-tidal carbon dioxide; V'_E/V'_{CO_2}: ventilatory efficiency (for carbon dioxide).

also included rest P_{ETCO_2}, while the second model used V'_E/V'_{CO_2} slope from CPET. ORs for risk of PPC for all included factors are presented in table 2.

Calculated risk of PPC during the first 30 postoperative days is summarised in figure 1. The two prediction tools yielded similar results. Women with higher values of FEV_1/FVC and rest P_{ETCO_2} (or lower values of V'_E/V'_{CO_2} slope, respectively) undergoing a wedge resection *via* VATS approach had the lowest risk of PPC – around 2%. In contrast, men with decreased FEV_1/FVC and rest P_{ETCO_2} (or higher values of V'_E/V'_{CO_2} slope, respectively) undergoing lobectomy or bilobectomy *via* open thoracotomy had the greatest risk of PPC development – >75% (figure 1). The concordance of the two risk scores was also shown by ROC analysis (figure 2), where AUCs of risk scores were 0.795 (95% CI: 0.739–0.851) and 0.793 (95% CI: 0.737–0.849), respectively (figure 2). There was no significant difference between the AUCs of the two models (p=0.867).

Validation of risk scores

Validation of risk scores was performed on the independent validation cohort (n=113). Comparison of parameters included in the scores for both cohorts is presented in table 3. There were no statistically significant differences between the cohorts. Figure 3a,b summarises the comparison of the discrimination ability of these scores between derivation and validation cohorts. There were no statistically significant differences in AUCs on comparison of the derivation and validation cohorts (p=0.063 and p=0.173, respectively).

90-day overall survival according to PPC

As an additional exploratory analysis, 90-day overall survival was evaluated and patients without PPC were compared with those with PPC. Only two patients (0.9%) without PPC died within the first 90 postoperative days, while eight patients (10.7%) died in the group with PPC. Kaplan–Meier curves are presented in supplementary figure S1. PPC were observed to be a statistically significant risk factor of 90-day postoperative mortality (HR 13.04; 95% CI: 2.77–61.40; p=0.001).

Discussion

We developed two novel risk models for prediction of PPC in lung resection candidates. The two models had comparable predictive properties for both the derivation and validation cohorts. Both models are composed of five parameters (sex, FEV_1/FVC, extent of resection, surgical technique and V'_E/V'_{CO_2} slope for patients with CPET, and sex, FEV_1/FVC, extent of resection, surgical technique and rest P_{ETCO_2} if CPET is not available).

As PPC have been found to be the main determinant of 30-day postoperative mortality [3], identification of patients at risk is a key strategy to improve postoperative outcomes. The current ERS/ACCP guidelines recommend FEV_1 and D_{LCO} measurements as part of routine preoperative evaluation [8, 9]. While spirometry and D_{LCO} assessment have a reasonable negative predictive value in patients with preserved lung function [29], patients with a predicted postoperative (ppo) FEV_1 of <40% or <30% were observed with 16–50% [30, 31] and approaching 60% rates of postoperative mortality [32], respectively. FVC

a)

			Women	Men
Thoracotomy – no	Atypical resection – yes	FEV_1/FVC >75 and rest P_{ETCO_2} >28	2.1	4.6
		FEV_1/FVC >75 and rest P_{ETCO_2} ≤28	5.0	10.3
		FEV_1/FVC ≤75 and rest P_{ETCO_2} >28	5.5	11.3
		FEV_1/FVC ≤75 and rest P_{ETCO_2} ≤28	12.3	23.5
	Atypical resection – no	FEV_1/FVC >75 and rest P_{ETCO_2} >28	8.4	16.7
		FEV_1/FVC >75 and rest P_{ETCO_2} ≤28	18.0	32.4
		FEV_1/FVC ≤75 and rest P_{ETCO_2} >28	19.6	34.9
		FEV_1/FVC ≤75 and rest P_{ETCO_2} ≤28	37.0	56.3
Thoracotomy – yes	Atypical resection – yes	FEV_1/FVC >75 and rest P_{ETCO_2} >28	4.9	10.1
		FEV_1/FVC >75 and rest P_{ETCO_2} ≤28	11.0	21.3
		FEV_1/FVC ≤75 and rest P_{ETCO_2} >28	12.1	23.2
		FEV_1/FVC ≤75 and rest P_{ETCO_2} ≤28	24.8	42.0
	Atypical resection – no	FEV_1/FVC >75 and rest P_{ETCO_2} >28	17.7	32.0
		FEV_1/FVC >75 and rest P_{ETCO_2} ≤28	34.0	53.1
		FEV_1/FVC ≤75 and rest P_{ETCO_2} >28	36.5	55.8
		FEV_1/FVC ≤75 and rest P_{ETCO_2} ≤28	58.0	75.2

b)

			Women	Men
Thoracotomy – no	Atypical resection – yes	FEV_1/FVC >75 and V_E/V_{CO_2} slope <33	2.7	5.4
		FEV_1/FVC >75 and V_E/V_{CO_2} slope ≥33	5.7	11.0
		FEV_1/FVC ≤75 and V_E/V_{CO_2} slope <33	6.7	12.7
		FEV_1/FVC ≤75 and V_E/V_{CO_2} slope ≥33	13.5	24.2
	Atypical resection – no	FEV_1/FVC >75 and V_E/V_{CO_2} slope <33	10.2	18.9
		FEV_1/FVC >75 and V_E/V_{CO_2} slope ≥33	20.0	33.7
		FEV_1/FVC ≤75 and V_E/V_{CO_2} slope <33	22.7	37.4
		FEV_1/FVC ≤75 and V_E/V_{CO_2} slope ≥33	39.1	56.7
Thoracotomy – yes	Atypical resection – yes	FEV_1/FVC >75 and V_E/V_{CO_2} slope <33	5.8	11.1
		FEV_1/FVC >75 and V_E/V_{CO_2} slope ≥33	11.8	21.5
		FEV_1/FVC ≤75 and V_E/V_{CO_2} slope <33	13.6	24.4
		FEV_1/FVC ≤75 and V_E/V_{CO_2}slope ≥33	25.7	41.3
	Atypical resection – no	FEV_1/FVC >75 and V_E/V_{CO_2} slope <33	20.1	33.9
		FEV_1/FVC >75 and V_E/V_{CO_2} slope ≥33	35.5	52.9
		FEV_1/FVC ≤75 and V_E/V_{CO_2} slope <33	39.3	56.9
		FEV_1/FVC ≤75 and V_E/V_{CO_2} slope ≥33	58.6	74.3

FIGURE 1 a) Risk of pulmonary complications (%) during 30 post-operative days – patients with cardiopulmonary exercise testing (CPET) data not available. b) Risk of pulmonary complications (%) during 30 post-operative days – patients with available CPET data. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; FEV_1/FVC: Tiffeneau index; P_{ETCO_2}: pressure of end-tidal carbon dioxide; V'_E/V'_{CO_2}: ventilatory efficiency (for carbon dioxide). "Atypical resection" includes segmentectomy and wedge resection. Part a presents risk assessment for patients with unavailable CPET data, part b for patients with available CPET data.

wasn't significantly different between groups with and without PPC. Indeed, FVC is not included in any of the guidelines on preoperative functional assessment [8, 9]. Similarly, a decreased ppo D_{LCO} has a fair predictive value [33], even in patients with a normal FEV_1 [34]. In our study, both FEV_1 and D_{LCO} were associated with PPC in the univariate model, but compared to FEV_1, the Tiffeneau index (FEV_1/FVC) had better predictive properties. For this reason and considering the limitations of FEV_1 mentioned above, we used FEV_1/FVC in the multivariate model instead of FEV_1. D_{LCO} failed to predict PPC in the multivariate model.

Peak V'_{O_2} predicts PPC and mortality only if calculated ppo peak V'_{O_2} is <10 $mL \cdot min^{-1} \cdot kg^{-1}$. Patients with such values are considered inoperable [8, 9]. Values of ppo peak V'_{O_2} >10 $mL \cdot min^{-1} \cdot kg^{-1}$ are

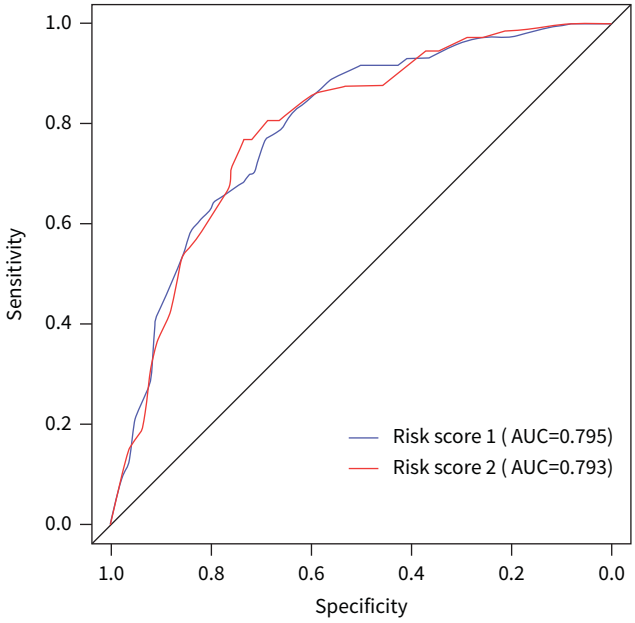

FIGURE 2 Comparison of risk scores – receiver operating characteristic analysis (derivation cohort; n=310). Risk score 1 contains rest P_{ETCO_2}; Risk score 2 contains V'_E/V'_{CO_2} slope. AUC: area under the curve; P_{ETCO_2}: pressure of end-tidal carbon dioxide; V'_E/V'_{CO_2}: ventilatory efficiency (for carbon dioxide).

disputed regarding their role in prediction of PPC [7, 12–17]. However, a number of previous studies have demonstrated that both V'_E/V'_{CO_2} slope and resting P_{ETCO_2} are independent predictors of PPC for lung resection surgery candidates [7, 12, 15–17]. These parameters relate more directly to ventilation, sharing nearly the same physiological determinants, *i.e.*, dead-space ventilation and hyperventilation [7, 12, 15]. In our study, V'_E/V'_{CO_2} slope and resting P_{ETCO_2} were independently associated with PPC and constituted important components of the newly developed prediction tools.

TABLE 3 Comparison of derivation and validation cohorts in components of risk scores

	Cohort		
	Derivation[#]	Validation[¶]	p-value
Sex, male	172 (55.5)	65 (57.5)	0.709
Atypical resection	145 (46.8)	54 (47.8)	0.853
Thoracotomy	165 (53.2)	62 (54.9)	0.765
FEV_1/FVC %			0.633
Mean±SD	77.4±9.1	77.8±9.3	
Median (5th and 95th quantile)	78.6 (62.2–91.0)	78.9 (62.9–91.0)	
⩽75%	110 (36.9)	34 (32.4)	0.405
rest P_{ETCO_2} (mmHg)			0.362
Mean±SD	29.2±4.6	29.1±4.6	
Median (5th and 95th quantile)	29.6 (20.7–36.0)	28.8 (22.1–37.0)	
⩽28 mmHg	119 (38.4)	44 (38.9)	0.918
V'_E/V'_{CO_2} slope			0.080
Mean±SD	30.3±6.5	31.4±6.4	
Median (5th and 95th quantile)	29.5 (21.6–42.3)	30.8 (23.2–43.0)	
⩾33	86 (27.7)	41 (36.3)	0.090
Pulmonary complications	75 (24.2)	33 (29.2)	0.296

Data are presented as n (%) unless indicated otherwise. "Atypical resection" includes segmentectomy and wedge resection. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; FEV_1/FVC: Tiffeneau index; P_{ETCO_2}: pressure of end-tidal carbon dioxide; V'_E/V'_{CO_2}: ventilatory efficiency (for carbon dioxide). [#]: n=310; [¶]: n=113.

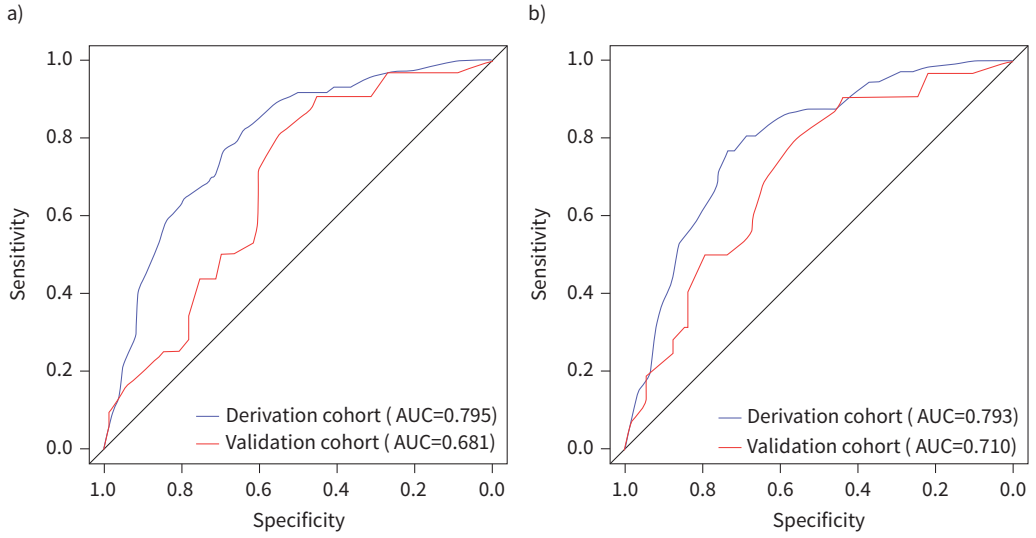

FIGURE 3 a) Risk score 1 (with rest P_{ETCO_2}) – comparison of derivation and validation cohort – receiver operating characteristic (ROC) analysis. b) Risk score 2 (with V'_E/V'_{CO_2} slope) – comparison of derivation and validation cohort – ROC analysis. AUC: area under the curve; P_{ETCO_2}: pressure of end-tidal carbon dioxide; $V'E/V'_{CO_2}$: ventilatory efficiency (for carbon dioxide).

In previous years, various composite scores have been introduced for PPC prediction based on demographic, lung function and other score-based data [9, 35], the former having an insufficient focus on PPC if viewed from the perspective of current knowledge. In addition, in prior studies scores were constructed with retrospective or registry-based data. In contrast, the new predictive models described herein are based on prospective multicentre data from two separate cohorts/studies. In addition, the incorporation of V'_E/V'_{CO_2} slope and P_{ETCO_2} measurement introduces more specific parameters associated with PPC; the predictive value of both parameters has been demonstrated in a number of previous studies and replicated in different centres [7, 13–17]. V'_E/V'_{CO_2} slope is a potential therapeutic target, though there remains some potential controversy about its role in lung resection surgery [36]. Due to the shared underlying pathophysiology of V'_E/V'_{CO_2} slope and rest P_{ETCO_2}, the two parameters can be used as mutual surrogates [7, 37]. Despite this fact, rest P_{ETCO_2} shouldn't be viewed as superior to V'_E/V'_{CO_2} slope. Indeed, CPET still has an important role in preoperative assessment as calculated values of ppo peak V'_{O_2} <10 mL·min^{-1}·kg^{-1} are strongly indicative of PPC and mortality risk [8, 9]. Therefore, the most appropriate role of rest P_{ETCO_2} appears to be in those patients unable or unwilling to undergo the test or if CPET is unavailable.

We incorporated surgery-related factors, including technique and extent of resection. The introduction of modern surgical techniques (VATS and robotic-assisted thoracic surgery (RATS)), decreasing volume of lung tissue loss with lung parenchyma-sparing surgery (segmentectomy or atypical/wedge resection) [38] or implementation of the Enhanced Recovery After Thoracic Surgery (ERATS) protocol has clearly resulted in a decreased rate of PPC and postoperative mortality in the last decade [39]. Robotic surgery alone has also decreased the rate of in-hospital postoperative mortality by ∼50%, compared to open thoracotomy [40]. An important consideration is that surgery-related factors are modifiable, *i.e.* the type of surgery and extent of resection can be discussed within the multidisciplinary team and with the patient.

Interpretation of the calculated risk

An important question is what extent of calculated risk should be perceived as acceptable, increased or prohibitive for lung resection. In a recent study, the risk of PPC in patients with preserved lung function was 9% [29], while it was 14.5–17% or even 25% in less selected populations [3, 4, 12]. In view of these data, we suggest that acceptable risk of PPC shouldn't exceed 30%, while a >50% risk is prohibitive for surgical treatment. Patients with a calculated risk of PPC between 31% and 50% should participate in risk-reducing programmes/strategies. However, we can't give an exact guidance, as the latter should routinely be discussed with the patient and within the interdisciplinary team.

Limitations

The main limitation of our work is that the predictive tools have not yet been evaluated in a larger external validation cohort. A second limitation is that the tools are not suitable for mortality risk assessment as they

relate only to PPC, since the limited number of deaths in our cohorts did not permit development of suitable models for mortality prediction. Third, patients with ppo peak $V'_{O_2} < 10\ mL \cdot min^{-1} \cdot kg^{-1}$ have been excluded as they are considered inoperable in agreement with the current guidelines [8, 9]. This might reduce the predictive value of peak V'_{O_2}. Fourth, in ~30% of patients, we lack data on arterial blood gases (ABG). Due to the data incompleteness, we didn't include ABG parameters in the multivariate models. As data for D_{LCO} were recorded only as % of predicted, we were not able to calculate Z-scores for D_{LCO}. Despite these limitations, we believe the models described represent an incremental improvement in PPC prediction and merit consideration for routine use in clinical practice.

Conclusion

We created two multicomponental models/scores for PPC risk prediction, both having excellent predictive properties. We suggest that the models be used in daily clinical practice.

Provenance: Submitted article, peer reviewed.

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Data availability: The datasets generated and analysed during this study are available from the corresponding author on reasonable request.

This study is registered at www.clinicaltrials.gov with identifier number NCT03498352.

Ethics statement: This study was approved by the local Ethics Committees of St Anne's University Hospital in Brno (reference numbers 19JS/2017, 2G/2018 and 03G/2021) and University Hospital Brno (reference numbers 150617/EK and No. 14-100620/EK).

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