ORIGINAL ARTICLE

LUNG RESECTION FOR NON-SMALL-CELL LUNG CANCER - A NEW RISK SCORE TO PREDICT MAJOR PERIOPERATIVE COMPLICATIONS

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Abstract

Objectives: *Identify risk factors for major perioperative complications (MPC) after anatomical lung resection for Non-Small-Cell Lung Cancer (NSCLC) and establish a scoring system.*

Methods: *Single center retrospective study of all consecutive patients diagnosed with NSCLC submitted to anatomical lung resection from 2015 to 2019 (N=564). Exclusion criteria: previous lung surgery, concomitant non-lung cancer related procedures, urgency surgery. Study population: 520 patients. Primary end-point: MPC defined as a composite endpoint including at least one of the in-hospital complications. Univariable and Multivariable analyses were developed to identify predictors of perioperative complications and create a risk score. Discrimination was assessed using the C-statistic. Calibration was evaluated by Hosmer and Lemeshow test and internal validation was obtained by means of bootstrap replication.*

Results: *Mean age of 65 years and 327 (62.9%) were males. Mean hospital stay of 9 days after surgery. Overall MPC rate was 23.3%. Male gender, hypertension, FEV1<75%, thoracotomy, bilobectomy/pneumectomy and additional resection were independent predictors of MPC. A risk score based on the odds ratios was developed - Major Perioperative Complications of Lung Resection (MPCLR) scoring system - and ranged between 0 and 14 points. It was divided in 5 groups: 1-2 points (positive preditive value 15%); 3-4 (PPV 25%); 5-7 (PPV 35%); 8-9 (PPV 60%); >10 points (PPV 88%). The score showed reasonable discrimination (C-statistic=0.70), good calibration (P=.643) and it was internally validated (C-statistic=0,70 BCa95% CI,0.65-0.79).*

Results: *This study proposes a simple and daily-life risk score system that was able to predict the incidence of perioperative complications.*

Keywords: *Risk score; Major perioperative complications, Non-small-cell lung cancer*

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Based on clinical factors including tumor stage, up to 40% of patients with lung cancer are candidates for potentially curative resection[2].

Despite the improvements in surgical techniques and perioperative management, postoperative complications still occur in 20%–30% of lung cancer surgical patients[2,3]. The development of these complications is associated with an increase in the duration of hospital stay, in the cost of hospitalization and an increased incidence of operative mortality [2].

Several scoring systems for quantifying surgical risks have been proposed but most of them are outdated, require large and complex information or regard specific groups or only postoperative mortality[1-7].

This study reviews the experience with anatomical

Table 1 **Patient demographics and comorbidities**

Demographics	n (%)
Male sex	327 (62.9)
Mean age (years)	65
Adenocarcinoma	343 (66.0)
TNM III-IV	116 (22.3)
Neoadjuvancy	74 (14.2)
DLCO% (mean)	80.4
FEV1% (mean)	89.2
FEV1% < 75%	94 (18.1)
Serum Hb g/dL (mean)	13.4
Serum Hb < 10 g/dL	17 (3.3)
Comorbidities	
Previous tumor	93 (17.9)
Arterial Hypertension	288 (55.4)
DM	78 (15.0)
Dyslipidemia	217 (41.7)
Smoker/ex-smoker	359 (69.0)
Smoking index (mean pack-year)	37.5
Hemodialysis	1 (0.2)
Serum Creatinine mg/dL (mean)	0.91
Stroke	31 (6.0)
Coronary artery disease	43 (8.3)
Chronic heart Failure	10 (1.9)
Peripheral vascular disease	18 (3.5)
Respiratory disease	151 (29.0)
Gastrointestinal disease	63 (12.1)
Anticoagulant therapy	22 (4.2)
Atrial fibrillation	26 (5.0)

DLCO%: diffusing capacity for carbon monoxide; DM: Diabetes Mellitus; FEV1%: forced expiratory volume in 1 s; Hb: Hemoglobin.

Table 2 **Operative data**

Procedure	n (%)
Thoracotomy	352 (67.7)
VATS	168 (32.3)
Segmentectomy	15 (2.9)
Lobectomy	461 (88.7)
Bilobectomy	30 (5.8)
Pneumectomy	14 (2.7)
Additional resection	87 (16.7)

VATS: video-assisted thoracoscopic surgery.

lung resection for non-small-cell lung cancer (NSCLC) at a single center with the aim to identify risk factors for in-hospital major perioperative complications (MPC) and establish a scoring system to identify patients at a high risk and facilitate clinical decision-making related to treatment strategy selection.

INTRODUCTION

Materials and Methods

A retrospective research was conducted to identify all consecutive patients diagnosed with NSCLC submitted to anatomical lung resection at the Hospital Pulido Valente, between January 2015 and June 2019. The initial population included 564 patients. Patients with previous lung surgery (29), concomitant procedures (10) and urgency surgery (5) were excluded. These exclusion criteria were selected *a priori*. Therefore, the study population consisted of 520 patients operated during a 5 year interval.

Patient's characteristics

There were 327 (62.9%) men and 193 (37.1%) women (N=520) with mean age of 65 (standard deviation (SD) 10.8) years. Patient demographics and comorbidities are delineated in Table 1.

Operative technique

Operability was determined based on the existing guidelines for pulmonary resection. The operative data are listed in Table 2. Thoracotomy was performed in 352 (67.7%) patients. All other patients were submitted to video-assisted thoracoscopic surgery (VATS). The type of the approach was selected by the surgeon of each patient. Lobectomy was performed in 461 (88.7%) patients. Forty-four (8.5%) underwent bilobectomy or pneumectomy. An endoscopic stapler was used to divide the fused fissures/ intersegmental planes and to section the hilar structures. All patients were submitted to mediastinal lymph node dissection. Additional resection (wedge resection, sleeve resection and ribs resection) was performed in 87 (16.7%) patients.

All patients received epidural analgesia or an intercostal nerve block for pain control. Chronic medication was continued after surgery.

Outcomes

Primary outcome analyzed was MPC defined as a composite endpoint including at least one of the following 13 in-hospital variables: myocardial infarction, cardiac arrest,

de novo Atrial Fibrillation, stroke, acute kidney lesion (according to Acute Kidney Injury Network (AKIN) classification), bleeding requiring surgery, acute pulmonary edema, primary respiratory failure (defined as mechanical ventilation or unplanned reintubation beyond 48 hours after surgery), respiratory infection, empyema, sepsis and need for reoperation.

Statistical Analysis

Categorical variables were expressed as absolute numbers and percentages and continuous variables were expressed as mean (SD) because they all followed a normal distribution. Kolmogorov-Smirnov test was used to access the normal distribution.

Twenty-six clinical variables were selected: male gender, previous tumor, neoadjuvant treatment, TNM III-IV, thoracotomy, bilobectomy/pneumectomy, additional resection, non-adenocarcinoma, hypertension, Diabetes Mellitus (DM), smoking (included ex-smokers), stroke, peripheral vascular disease, coronary artery disease, chronic heart failure, hemodialysis, respiratory disease, gastrointestinal disease, atrial fibrillation, anticoagulant therapy, diffusing capacity for carbon monoxide (DLCO%) <80%, age >65 years, serum hemoglobin <10 g/dL, FEV1% <75%, smoking index >29 pack-year.

For continuous variables, the cutoff value was assessed through the analysis of receiver operating characteristics curve (ROC curve), turning these variables into categorical ones. Categorical variables were compared using $_X2$ test. Variables with a univariate p <0.05 were included in the multivariable logistic regression model to identify risk factors for MIPC.

We assigned weighted points to risk factors based on their odds ratios. A risk score was then calculated for each patient and it ranged between 0 and 14 points. Model discrimination was evaluated by ROC curves and concordance statistics (C-statistics). The Hosmer-Lemeshow goodness-of-fit test was used to evaluate the model calibration. A value of p> .05 indicated satisfactory calibration. Internal validation was obtained by means of bootstrap method involving 1000 resampling and Mersenne Twister seed with bias corrected and accelerated (BCa) confidence intervals.

The scoring system was divided in 5 groups and positive predicted value (PPV) of MIPC was obtained for each group.

All analyses were performed using IBM SPSS Statistics for Windows, Version 23.0. (IBM Corp. Armonk, NY).

Table 3 **Major perioperative complications**

Morbidity	n (%)
Myocardial infarction	2 (0.4)
Cardiac arrest	2 (0.4)
De novo atrial fibrillation	36 (6.9)
Stroke	2 (0.4)
Acute renal lesion	9 (1.7)
Bleeding	18 (3.5)
Acute pulmonary edema	4 (0.8)
Primary respiratory failure	14 (2.7)
Respiratory infection	63 (12.1)
Empyema	12 (2.3)
Wound infection	5 (1.0)
Sepsis	9 (1.7)
Reoperation	23 (4.4)
Total (%)	**121 (23.3)**

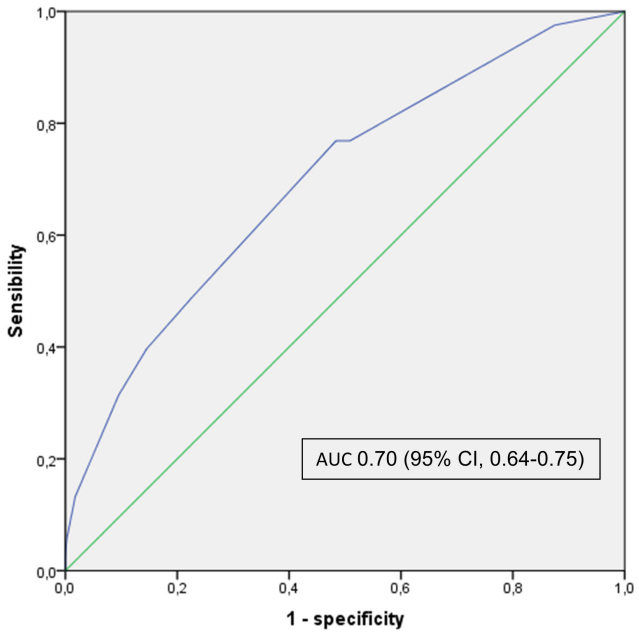

Figure 1 *Receiver operating characteristic curve of new risk score for MPC.*

RESULTS

Major in-hospital perioperative complications

The mean length of stay was 9.2 (SD:7.2) days. MPC was observed in 121 (23.3%) patients. Sixty-three patients (12.1%) presented with respiratory infection and 6.9% of the patients had *de novo* atrial fibrillation. Seven patients required reoperation for any cause other than

Table 4 **Predictors of MPC**

Variable	Univariable analysis	Multivariable analysis		
	p-value	OR	CI 95%	*p*-value
Male sex	0.002	1.9	1.16-3.07	0.010
Age > 65 years	0.008			0.065
Non-adenocarcinoma	0.035			0.735
TNM III-IV	0.032			0.543
Neoadjuvant treatment	0.009			0.194
Thoracotomy	<0.001	2.1	1.19-3.57	0.009
Bilobectomy/pneumectomy	0.005	2.5	1.23-4.90	0.011
Additional resection	0.006	2.1	1.19-3.58	0.009
DLCO% < 80%	0.351			
FEV1% < 75%	<0.001	2.5	1.53-4.17	<0.001
Serum Hb < 10 g/dL	0.025			0.246
Previous tumor	0.402			
Arterial Hypertension	0.008	2.1	1.35-3.37	0.001
DM	0.342			
Dyslipidemia	0.338			
Smoker/ex-smoker	0.132			
Smoking index >29 pack-year	0.031			0.562
Hemodialysis	0.767			
Stroke	0.563			
Coronary artery disease	0.280			
Chronic heart Failure	0.422			
Peripheral vascular disease	0.222			
Respiratory disease	0.003			0.176
Gastrointestinal disease	0.250			
Anticoagulant therapy	0.594			
Atrial fibrillation	0.236			

DLCO%: diffusing capacity for carbon monoxide; DM: Diabetes Mellitus; FEV1%: forced expiratory volume in 1 s; Hb: Hemoglobin.

bleeding; 18 patients due to post-operative bleeding. The list of major complications is registered in Table 3.

Predictors of MPC

As described in table 4, on univariable analysis, male gender (p=0.002), age>65 years (p=0.008), Non-adenocarcinoma type (p=0.035), TNMIII-IV (p=0.032), neoadjuvant treatment (p=0.009), thoracotomy (p<0.001), bilobectomy/pneumectomy (p=0.005), additional resection (p=0.006), FEV1% < 75% (p<0.001), serum Hb < 10 g/dL (p=0.025), arterial hypertension (p=0.008), smoking index >29 pack-year (p=0.031) and respiratory disease (p=0.003) increased the risk of MPC.

On multivariable analysis, male gender (OR 1.9CI95: 1.16-3.07; p=0.010), thoracotomy (OR 2.1CI95: 1.19-3.57; p=0.009), bilobectomy/pneumectomy (OR 2.5CI95: 1.23-4.90; p=0.011), additional resection (OR 2.1CI95: 1.19-3.58; p=0.009), FEV1% < 75% (OR 2.5CI95: 1.53-4.17; p<0.001) and arterial hypertension(OR 2.1CI95: 1.35-3.37; p=0.001 were significant predictors of MPC (Table 4).

A new risk score – MPCLR scoring system

The predictors of a risk MPC on multivariable analysis were combined and a risk score based on their odds ratios was developed as follows: 2 X male gender + 2 X thoracotomy + 3 X bilobectomy/pneumectomy+ 2 X additional resection+ 3 X FEV1% < 75%+ 2 X arterial hypertension. The risk score was named MPCLR (Major Perioperative Complications of Lung Resection) scoring system and it ranged between 0 and 14 points (Table 5).

As seen in figure 1, the score C-statistic was 0.70 (95% CI, 0.64-0.75). The model had a good calibration (p=0.64) and it was then internally validated by a bootstrap sampling procedure, which gave a C-statistic of 0.71 (BCa95% CI,0.65-0.79).

The MPCLR scoring system was later divided in 6 groups: 0 points (PPV:6%); 1-2 points (PPV: 15%); 3-4 (PPV: 25%); 5-7 (PPV: 35%); 8-9 (PPV: 60%); >10 (PPV: 88%). We considered patients with a risk score up to 2 points as the low risk groups because their morbidity was less than 20%, those with a risk score of [3-7] as the intermediate-risk groups because their predicted probability of MPC was between 20 and 50%, and those with a risk score greater than 8 points as the high-risk group because their morbidity was over 50% (table 6).

Table 5 **MPCLR scoring system**

Characteristic	Points
Male gender	2
Thoracotomy	2
Bilobectomy/ Pneumectomy	3
Additional resection	2
FEV1% <75%	3
Hypertension	2
TOTAL	0-14

FEV1%: forced expiratory volume in 1s.

Table 6 **Predicted probability of MPC**

Points	n	PPV (%)	Risk
0	3	6	Low risk
1-2	25	15	
3-4	34	25	Intermediate risk
5-7	43	35	
8-9	9	60	High risk
>10	7	88	

DISCUSSION

Regardless of the improvements in current ages, postoperative complications are described in 20%–30% of lung cancer surgical patients[2,3]. Our experience detected a similar morbidity rate (23.3%). Such complications dramatically increase the length of hospital stay, the cost of hospitalization and postoperative mortality[2].

Several factors have been associated with an increased risk of major complications after lung resection including gender, age, diabetes mellitus, cardiovascular disease, smoking, spirometric values or the type of procedure[1-4]. Our research identified male gender, thoracotomy, bilobectomy/pneumectomy, additional resection, FEV1% < 75% and arterial hypertension as risk factors for MPC.

Numerous risk factors have been combined into scoring systems. However, multiple risk scores regard only to specific groups, like older patients[3-5], pulmonary complications solely[1], or require large and complex information[2,6].

To the best of our acknowledgement, the risk scores related to MPC after lung resection are outdated and with a low ability to predict increased risk. CPRI-system[8], published in 1993, has been used in multiple populations with area under the curve (AUC) ranged from 0.51 to 0.62. POSSUM scoring system[7], from 1999, also used to predict postoperative complications, had an AUC of0.66and EVAD system[2], created in 2003, with an AUC of 0.65. MPCLR scoring system has a better ability to quantitate relative risk than the previous mentioned scores, with an AUC of 0.70. This score risk also presented a good calibration (p=0.64) indicating close agreement between predicted and observed event rates and it was internally validated.

This study has multiple limitations. It is based on the retrospective analysis of a population operated by different surgeons. The final decisions to select patients for surgery and the choice of surgical procedure may vary among surgeons. Another limitation is the exclusion of other risk factors, such as nutritional status. We did not have access to prolonged air leakage data. The risk score lacks external validation.

In summary, we propose a simple scoring system, based on clinical and easily accessible variables, which demonstrated ability to predict which patients are at a high risk of developing major perioperative complications. This score can facilitate clinical decision-making related to treatment strategy in order to reduce the incidence of complications.

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