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High BODE Index Score and Low Albumin Serum Level Identify Patients with Chronic Obstructive Pulmonary Disease (COPD) at Higher Risk for Complications after Major Lung Cancer Resection: A Retrospective Study

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Abstract:

Introduction *- Lung cancer is significantly more common in patients with chronic obstructive pulmonary disease (COPD) than in those without obstruction. Of note, in COPD patients, who underwent major resection for lung cancer, postoperative pulmonary complications and mortality are considerably frequent. Thus, accurate preoperative identification of risk factors for lung resection postoperative complications is greatly needed to improve COPD patient care.*

Materials and Methods *- The study included 104 consecutive COPD patients who underwent pulmonary lobectomy for non-small cell lung cancer (NSCLC). Several functional and metabolic preoperative parameters were retrospectively evaluated and correlated with postoperative, not cardiovascular, complications and mortality occurring within 30 days after surgery or later if the patient was still hospitalized.*

Results *- Two independent factors were associated with the occurrence of postoperative complications in COPD patients resected for lung cancer: the BODE index ≥3 (odd ratio, OR, 2.01; 95% confidence interval, CI, 1.07-3.925; p<0.001) and the albumin serum level <2.9 g/dL (OR 0.084; 95% CI 0.019-0.364; p<0.001).*

Conclusions *- High BODE index score and low albumin serum level identify, among COPD patients who underwent major pulmonary resection for NSCLC, those at higher risk for postoperative complications. As the nutritional status significantly affects morbidity in COPD patients undergoing major lung resection for cancer, its preoperative improvement may be justified to reduce complications. Moreover, it could be considered an appropriate recommendation the measurement of the BODE index, a simple and low cost procedure, for better identify, before lung cancer resection, COPD patients at higher risk for complications and, thus, candidates for postoperative intensive care.*

Keywords: ***Lung cancer surgery; COPD; Surgery, complications; Statistics, risk analysis/modelling; BODE index; Postoperative care.***

Introduction

Lung cancer is significantly more common in patients with chronic obstructive pulmonary disease (COPD) than in those without obstruction.[1] Of note, in COPD patients, who underwent major resection for lung cancer, the risk of postoperative pulmonary complications and mortality is considerably higher than in non-COPD patients.[2] Thus, accurate preoperative identification of risk factors for lung resection postoperative complications is greatly needed to improve COPD patient care.

COPD clinical manifestations are chronic bronchitis or emphysema; however, like other chronic inflammatory conditions, COPD also causes systemic alterations.[3] Thus, in patients with emphysema, biochemical signs of inflammation can be detected in the systemic circulation, the generalized inflammatory state causing important non-pulmonary alterations, the most prominent being the loss of skeletal muscle mass.[4] Muscle and body weight loss (and body mass index, BMI, decrease) establish the cachectic state, usually characterizing severe emphysematous patients, consequence of the respiratory failure causing chronic tissue hypoxia and, in turn, persistent high serum concentration of inflammatory mediators.[5] In detail, cachexia is the result of an imbalance between protein synthesis and degradation, this imbalance affecting, indeed, not only skeletal muscle proteins but also bone collagen. Skeletal muscle and bone loss not only lead to physical activity reduction, poorly affecting life quality, but also unfavourably influences health state and ultimately prognosis. Remarkably, tough, bad

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prognosis does not correlate with airflow obstruction degree; moreover, it is potentially reversible with an appropriate therapy.[6] Thus, it is critical to accurately evaluate respiratory and systemic COPD signs and symptoms to better determine the disease state and to predict its clinical course. To this aim a simple multidimensional index, the BODE index, has been established, combining four parameters in a simple scale.[7] The BODE index measures: 1) BMI, a predictor of death risk *per se*;[8] 2) airflow obstruction degree, quantified by the forced expiratory volume in one second (FEV_1). FEV_1 alone is essential for the diagnosis and for the quantification of the respiratory COPD dysfunction and its reduction is a good marker of disease progression and mortality; however, it does not adequately reflect all the disease systemic manifestations; 3) dyspnoea, quantified according to the Medical Research Council-modified scale.[9] Of note, it has been observed that in COPD patients the degree of dyspnoea predicts death risk more accurately than the FEV_1 value;[10] 4) exercise capacity, measured by the six-minutes walk test (6MWT),[11] a simple and well-standardized method to predict death risk in patients with other chronic diseases such as pulmonary hypertension.[12]

In the present study, we retrospectively evaluated BODE index and several other functional and metabolic preoperative parameters in COPD patients who underwent major pulmonary resection for non-small cell lung cancer (NSCLC), correlating them with the occurrence of postoperative complications. We established high BODE index score and low albumin serum level as predictive of higher risk of postoperative complications in COPD patients resected for lung cancer.

Material and Methods

Study Population

All patients were evaluated by a multidisciplinary team and investigated by computed tomography (CT), bronchoscopy, and, when necessary, mediastinoscopy. According to the guideline, lobectomy eligibility was evaluated with pulmonary function tests, arterial blood gas analysis, electrocardiogram, echocardiogram, and, when necessary, with more invasive cardiology procedures.[13] According to the European Respiratory Society criteria, patients included in the study had a predicted postoperative FEV_1 (ppo-FEV_1) value <70% with a FEV_1/forced vital capacity ratio <89%, indicating a predominant functional airway obstruction.[14] BMI was calculated as bodyweight in kilograms divided by height in meters squared. Surgery was performed in patients with ppo-FEV_1 >40%, in agreement with the cut-off value proposed.[2] All patients were subjected, through lateral, video-assisted, muscle-sparing minithoracotomy, to lobectomy with radical lymphadenectomy; then, in the postoperative intensive care unit, they were monitored with invasive cardiovascular tests, continuous body temperature measurement and daily chest x-ray.

We considered postoperative, not cardiovascular, complications and mortality occurring within 30 days after surgery or later if the patient was still hospitalized. Postoperative complications included in this study were:

1. Acute respiratory failure that required mechanical ventilatory support for more than 24 hours or reintubation for controlling ventilation;
2. Nosocomial pneumonia, diagnosed in mechanically ventilated patients if presenting purulent tracheobronchial secretions and new and persistent pulmonary infiltrate. The diagnosis was confirmed by a bacteriological culture of $>10^3$ or $>10^4$ cfu/mL in case of brushed samples collected in sterile containers or of bronchoalveolar lavage specimens, respectively. On the contrary, patients with lower bacterial counts were considered as having bronchitis. In the spontaneously breathing patients nosocomial pneumonia, if radiologically compatible, was diagnosed in case of Gram staining and culture positive purulent sputum;
3. Prolonged air leak, lasting longer than seven days and requiring persistent endopleural drainage;
4. Lobar or lung atelectasis, detected by chest x-ray, that required a bronchoscopy;
5. Acutely worsening Respiratory Distress Syndrome (ARDS) with a partial oxygen tension (PaO_2)/fraction of inspired oxygen (FIO_2) <200 mmHg, with radiological signs of bilateral pulmonary infiltrates and no evidence of atrial hypertension;
6. Pulmonary embolism diagnosed by CT angiogram;
7. Drain bleeding requiring surgical intervention or the transfusion of at least three bags of packed red blood cells;
8. Sepsis diagnosed in accordance with the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Committee criteria;[15]
9. Shock, defined as a reduction in systolic blood pressure below 90 mmHg despite vascular filling or vasoactive drug administration (dopamine >5μg/kg/min, dobutamine, epinephrine, or norepinephrine).

The following variables were evaluated for the association with postoperative complications: age, PaO_2, partial carbon dioxide tension ($PaCO_2$), history of cigarette smoking (packs/year), hemoglobin concentration, hematocrit, serum albumin level, FEV_1, ppo-FEV_1, lung diffusing capacity for carbon monoxide determined by the single-breath technique (DLCOsb), predicted postoperative DLCOsb (ppo-DLCOsb),

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lobectomy site, tumour pathological stage, concomitant heart disease (i.e., previous cardiac surgery, previous myocardial infarction, history of coronary artery disease, treated arrhythmia, heart failure or high blood pressure), BMI, degree of dyspnoea, 6MWT result and BODE index (a 0 to 10 score with the higher indicating the worst prognosis).

The FEV_1 and ppo-FEV_1 values were expressed as percentage of those expected for age, sex and weight, according to the European Community for Steel and Coal equation.[16] The ppo-FEV_1 was calculated using the Juhl and Frost formula: ppo-FEV_1= (preoperative FEV_1 x (1 - (S x 5.26)/100) where S is the number of lung segments removed.[17]

The Charlson comorbidity index was calculated for each patient.[18]

Study Design

Only the patients expected to successfully overcome surgery were admitted to the study. Thus, in addition to the strictly selective respiratory criteria, we included only patients medically stable, able to perform moderate physical activity, well-fed in terms of protein supply, not treated with oxygen or corticosteroids with a daily dosage equivalent to >15mg of prednisolone. The exercise capacity was assessed using the 6MWT, the standardized test to indirectly evaluate, from a clinical point of view, COPD severity.[11] Moreover, we excluded from the study patients with coexistence of other diseases. Thus, in detail, the inclusion criteria were:

1. Clinical negativity for bronchiectasis and asthma;
2. ppo-FEV_1 > 40%;
3. ppo-DLCOsb > 40%;
4. Absence of unstable angina or ventricular arrhythmia;
5. Echocardiography value of systolic pulmonary arterial pressure <50 mmHg;
6. $PaCO_2$ <50 mmHg;
7. American Society of Anaesthesiologists score ≤□ □
8. Absence of major comorbidities that can increase the preoperative risk (CCI<2);[19]
9. No previous pleurodesis or thoracotomy in the hemithorax site of the disease.

The respiratory physiology was preoperatively evaluated not only by spirometry and plethysmography but also by DLCOsb measurement and by hemogasanalysis.

Ethics

With the approval of the Institutional Review Board, the study included 104 consecutive COPD patients who underwent pulmonary lobectomy for NSCLC.[20,21]

Statistics

Data were computerized and analysed using the SPSS 13.0 software (SPSS Inc., Chicago, IL). The categorical and the continuous variables were compared using the x^2 or the Fisher exact test and the Student t or the Mann-Whitney U test, respectively. The variables, significant in the univariate analysis, were then evaluated as independent variables in a logistic regression analysis, setting 0.05 as significant value. The risk of postoperative complications associated with certain factors was assessed using logistic regression analysis to estimate the odd ratios (ORs) and their 95% confidence intervals (CIs). Continuous variables were divided using the median as cut-off. The results are expressed as means ± standard deviation for continuous variables and as percentages for categorical variables.

Results

Table 1 - Characteristics of patients with and without postoperative complications

Variables	Total of patients (n=104)	Patients with complications (n=19)	Patients without complications (n=85)	*p* value
Sex (M/F)	**79/25**	**15/4**	**64/21**	**0.1**
Age (years)	**63±8.6**	**64.9±6.5**	**62.6±8.9**	**0.3**
Weight (kg)	**69.9±12.5**	**69±11.7**	**70±12.7**	**0.7**
Height (m)	**1.6±0.1**	**1.7±0.1**	**1.6±0.1**	**0.1**
Smoking history (packs/year)	**50.5±34.7**	**52.6±35.7**	**50.7±34.5**	**0.1**
Hemoglobin (g/dL)	**13.7±1.4**	**14.4±1.4**	**13.5±1.3**	**0.2**
Hematocrit (%)	**42.3±3.9**	**42.8±3.4**	**42.2±4.1**	**0.6**
Albumin (g/dL)	**3.7±0.7**	**2.8±0.6**	**3.9±0.5**	**0.001**
Cardiac comorbidity	**11/104**	**8/19**	**3/85**	**0.01**
Lobectomy				**0.4**
Upper	**63 (60.6%)**	**14**	**49**	
Lower	**40 (38.5%)**	**5**	**35**	

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Medium and/or Lingula	**1 (0.9%)**	**0**	**1**	
Histological diagnosis				**0.2**
Squamous carcinoma	**38 (36.5%)**	**8**	**30**	
Adenocarcinoma	**54 (51.9%)**	**11**	**43**	
Other	**12 (11.6%)**	**0**	**12**	
Pathological stage				**0.2**
Ia	**27 (25.9%)**	**8**	**19**	
Ib	**44 (42.3%)**	**7**	**37**	
IIa	**3 (2.8%)**	**0**	**3**	
IIb	**30 (28.8%)**	**4**	**26**	

Table 2 - Type and incidence of postoperative complications: their percentage respect to the total number of patients

Complications	Total of patients N°	%
Prolonged air leak	**10**	**9.6**
Nosocomial pneumonia	**7**	**6.7**
Acute respiratory failure	**5**	**4.8**
Bleeding	**4**	**3.8**
Atelectasis	**4**	**3.8**
Pleural effusion	**2**	**1.9**
ARDS	**1**	**0.9**
Pulmonary embolism	**1**	**0.9**
Sepsis	**1**	**0.9**
Shock	**1**	**0.9**
Total	**36**	

Table 3 - Preoperative respiratory and metabolic parameters in patients with and without postoperative complications

Parameters	Total of patients (104)	Patients with complications (19)	Patients without complications (85)	*p* value
FEV_1 (L)	**1.9±0.2**	**1.7±0.2**	**1.9±0.1**	**0.01**
FEV_1 (%)	**65.3±5.6**	**61.2±7.2**	**66.3±4.7**	**0.01**
ppo-FEV_1 (L)	**1.6±0.1**	**1.51±0.2**	**1.63±0.1**	**0.01**
ppo-FEV_1 (%)	**51.5±6.1**	**48.5±7.8**	**52.2±5.5**	**0.01**
DLCOsb (%)	**73.1±10.3**	**75.5±5.9**	**72.6±11.2**	**0.3**
ppo-DLCOsb (%)	**57.6±9.4**	**59.8±7.2**	**57.2±9.8**	**0.3**
PaO_2 (at FIO_2 0.21 mmHg)	**82.1±7.8**	**81±7.6**	**82.4±7.9**	**0.4**
$PaCO_2$ (mmHg)	**40.7±3.4**	**41.2±3.4**	**40.6±3.3**	**0.5**
BMI (Kg/m^2)	**25.5±5.2**	**22.8±4.5**	**26.1±5.3**	**0.01**
Dyspnoea score	**0.71±0.8**	**1.42±1.1**	**0.55±0.7**	**0.01**
6MWT (m)	**336.4±90.7**	**267.5±80.9**	**351.8±85.8**	**0.01**
BODE index	**1.58±1.3**	**3.37±1.5**	**1.18±0.9**	**0.001**

The preoperative characteristics of 104 COPD patients (mean age 63 ± 8.6 years; 79 men and 25 women), who underwent pulmonary resection for NSCLC, are listed in table 1. Upper lobectomy was the most common procedure, performed in 63 patients (60.6%). The cancer histology was adenocarcinoma in 54 patients (51.9%), squamous cell carcinoma in 38 (36.5%) and other types in 12 (11.6%). The stage was: Ia (n = 27; 25.9%), Ib (n = 44; 42.3%), IIa (n = 3; 2.8%), IIb (n = 30; 28.8%).

The incidence of thoracic surgery postoperative complications varies widely, from 7 to 49%, 15-40% of them occurring during the first five days.[22,23] As shown in table 2, we observed postoperative complications in 19 patients (18.3%) for a total of 36 complications. It has been reported that the incidence of air leak ranges from 4% to 26%.[24] Accordingly, prolonged air leak, causing a longer hospitalization, was the predominant complication we observed (27.8%), followed by bacterial pneumonia (19.4%), acute respiratory failure that required mechanical ventilatory

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assistance (13.9%), postoperative bleeding (11.1%), requiring surgical revision in two cases, and lobar atelectasis that required fibrobronchoscopy (11.1%). In the tenth patients with a prolonged air leak (13.7 ± 6.2 days, range 8 to 22 days) we observed a bronchopleural fistula treated conservatively with endoscopic instillation of biological glue; none of these patients required mechanical ventilatory assistance. In six out of seven (85.7%) pneumonia patients we found gram-negative bacilli: *Pseudomonas aeruginosa* (n=3; 50%), *Escherichia coli* and *Haemophilus influenzae* (n= 2; 33.3%), *Klebsiella pneumoniae* e *Acinetobacter baumannii* (both n=1; 16.7%). The gram-positive *Staphylococcus aureus* was isolated in the seventh case. Acute respiratory failure was the third most common complication we observed with an incidence of 4.8%, in accordance to the incidence, ranging 2.4-9%, reported in other studies.[25,26] Five patients were subjected to mechanical ventilation for > 24 hours (10 ± 11.4 days, range 4-28 days), one requiring tracheotomy. As advised,[27] we evaluated this complication severe; accordingly, among the five patients, three developed nosocomial pneumonia; in one case sepsis occurred leading to multiple organ failure and death in the 28th postoperative day.

As shown in table 3, among the 19 patients experiencing complications, BMI was 22.8±4.5 kg/m^2 (range 18.2-34.2), well below the median value, calculated in all 104 patients, of 25.5±5.2 kg/m^2 (range 18.2-57). Importantly, four of the patients presenting complications were underweight (BMI <18.5 kg/m^2). The non-optimal nutritional state of the 19 patients with postoperative complications was highlighted also by the albumin serum level (table 1) that was 2.8±0.6 g/dL (range 2.1-4.8), below the median value, calculated in all 104 patients, of 3.7±0.7 g/dL (range 2.1-5). Notably, the majority of the patients (12/19) presenting complications had an albumin serum level <3 g/dL. The complications were more serious in the three patients with both a preoperative BMI <18.5 kg/m^2 and a serum albumin level <3 g/dL (p = 0.01), the deceased patient in the 28th postoperative day having BMI= 18.2 Kg/m^2 and albumin serum level=2.1 g/dL. Thus, our study indicates that low serum albumin levels were predictors of postoperative complications by univariate analysis.

As shown in table 3, univariate analysis also revelled FEV_1 and ppo-FEV_1 as predictors of postoperative pulmonary complications.

Moreover, the preoperative BODE index was also significantly related to the occurrence of postoperative complications (p≤0.001). Thus, based on the BODE index score, we divided our patients into three groups: Group one with a score 0-2, group two with a score 3-6 and group three with a score 7-10. The risk of postoperative complications was much higher in patients with a BODE index score between 3 and 6, the BODE index predicting the appearance of postoperative complications better than BMI, FEV_1, ppo-FEV_1, dyspnoea severity and 6MWT result taken individually.

In conclusion, our study demonstrates that two independent factors are associated with the occurrence of postoperative complications in COPD patients resected for lung cancer: the BODE index ≥3 (OR 2.01; 95% CI 1.07-3.925; p<0.001) and the albumin serum level <2.9 g/dL (OR 0.084; 95% CI 0.019-0.364; p<0.001).

Discussion

An accurate preoperative pathophysiological evaluation of the patients, candidate to major resection for lung cancer, is of great importance to predict postoperative complications and, thus, surgical risk. Ideally, the preoperative assessment should rely on non-invasive, easily available, costly affordable tests, performed following a rational flowchart.

In this study, we evaluated the preoperative respiratory function and the nutritional status of patients affected by COPD and lung cancer and candidates for lung surgery to identify those at greater risk of complications and, therefore, eligible for a more intensive postoperative monitoring.

Between the two parameters most commonly used for the preoperative pulmonary function evaluation of patients considered for lung resection, ppo-FEV_1 is the most indicative to consider further testing or even to exclude patients from surgery.[28,29] Many studies have demonstrated an increased perioperative risk in case of ppo-FEV_1 <40%, with a mortality rate ranging 16-50%.[2,30-32] Accordingly, ppo-FEV_1 has been validated by multivariate analysis as the best predictor of complications.[33] However, even in patients with normal ppo-FEV_1 (> 80%), also DLCOsb should always be measured for its accuracy in predicting postoperative complications.[34] Stimulation tests assessing the cardiorespiratory reserve before lung resection are recommended only in selected cases,[28,29] even if a recent meta-analysis showed correlation between low exercise capacity, expressed as $VO_{2,peak}$, and the onset of cardiorespiratory complications in patients after lung surgery.[35] The European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) have recently proposed to modify the Bolliger et al. algorithm,[13] emphasizing the cardiac evaluation relevance and, therefore, recommending a complete spirometry with DLCOsb measurement for all lung resection candidates and, for the patients with a ppo-FEV_1 and/or ppo-DLCOsb <80%, the oxygen peak consumption assessment during a cardiopulmonary exercise test.[36,37] However, cardiopulmonary exercise tests are not available in all the hospitals; moreover, many patients are not able to perform them, thus limiting the attainment to the ERS/ESTS

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guidelines. In the present study, we retrospectively evaluated 104 COPD patients who underwent surgery for NSCLC with ppo-FEV_1 and ppo-DLCOsb >40%. We confirmed the relevance of the respiratory parameters FEV_1 and ppo-FEV_1 to identify patients at higher risk for postoperative complications.

A complication incidence, ranging 10-20%, has been observed in patients with a poor nutritional status undergoing lung cancer resection,[38,39] a low BMI (<18.5 kg/m^2) having been associated with an increased risk of early postoperative complications.[40] Our study confirms the relationship between the poor nutritional status and the occurrence of complications, as we observed more, and more severe, complications in malnourished patients. For example, although the incidence of bacterial nosocomial pneumonias, the most important risk factor for morbidity and mortality, was in our study lower than reported in the literature (6.7% *vs.* 15-22%),[41] four out of seven pneumonias occurred in patients with a BMI <18.5 kg/m^2 and were particularly severe in presentation and poor responsive to antibiotic treatment.

BODE index has been prospectively validated as mortality index, well correlated with the life quality of patients with severe COPD. Accordingly, upon lung resection, a BODE index change predicts a better prognosis.[42] Accordingly, our study demonstrates the efficacy of the BODE index in identifying patients at higher risk of postoperative complications, in particular of the respiratory ones. Moreover, we observed that the BODE index predicted the postoperative risk of complications more accurately than dyspnoea, BMI, FEV_1, ppo- FEV_1 or 6MWT, taken individually. Thus, the BODE index potential limitation, due to the fact it measures subjective parameters, such as the degree of dyspnoea, seems to be greatly compensated by the use of multiple variables in a multidimensional scale that better assess COPD patient state.

Conclusions

In conclusion, this retrospective study identifies risk factors already present at the time of surgery, critical to foresee and, thus, to better deal with postoperative complications. Moreover, it also identifies prognostic variables that can be modified to reduce the risk of postoperative complications. The nutritional status significantly affects morbidity in COPD patients undergoing major lung resection for cancer; thus, its preoperative improvement may be justified to reduce postoperative complications. Moreover, it could be considered an appropriate recommendation the measurement of the BODE index, a simple and low cost procedure, for better evaluating, before lung cancer resection, COPD patients with FEV_1 and DLCOsb <80% and ppo-FEV_1 and ppo-DLCOsb >40%.

References

1. Tockman MS, Anthonisen NR, Wright EC, Donithan MG. Airway obstruction and the risk for lung cancer. Ann Intern Med 1987;106(4):512-518.
2. Markos J, Mullan BP, Hillman DR, Musk AW, Antico VF, Lovegrove FT, et al. Preoperative assessment as predictor of mortality and morbidity after lung resection. Ann Rev Respir Dis 1989;139(4):902-910.
3. Wouters EF, Creutzberg EC, Schols AM. Systemic effects in COPD. Chest 2002;121(5 Suppl):S127-S130.
4. Agusti AG. Systemic effects of chronic obstructive pulmonary disease. Novartis Found Symp 2001;234:242-249; discussion 250-254.
5. Congleton J. The pulmonary cachexia syndrome: aspects of energy balance. Proc Nutr Soc 1999;58(2):321-328.
6. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157(6 Pt 1):1791-1797.
7. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350(10):1005-1012.
8. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160(6):1856-1861.
9. Mahler D, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988;93(3):580-586.
10. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002;121(5):1434-1440.
11. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166(1):111-117.
12. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 2000;161(2 Pt 1):487-492.
13. Bolliger CT, Perrunchoud AP. Functional evaluation of the lung resection candidate. Eur Respir J 1998;11(1):198-212.

**Corresponding author: Gianluca Guggino*

14. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995;8(8):1398-1420.
15. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failures and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101(6):1644-1655.
16. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests. European Community for Steel and Coal. Official statement of the European Respiratory Society. Eur Respir J 1993;16:5-40.
17. Juhl B, Frost N. A comparison between measured and calculated changes in the lung function after operation for pulmonary cancer. Acta Anaesthesiol Scand Suppl 1975;57:39-45.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40(5):373-383.
19. Moro-Sibilot D, Aubert A, Diab S, Lantuejoul S, Fourneret P, Brambilla E, et al. Comorbidities and Charlson score in resected stage I non small cell lung cancer. Eur Respir J 2005;26(3):480-486.
20. Morra F, Luise C, Merolla F, Poser I, Visconti R, Ilardi G, et al. FBXW7 and USP7 regulate CCDC6 turnover during the cell cycle and affect cancer drugs susceptibility in NSCLC. Oncotarget 2015;6(14):12697-12709.
21. Morra F, Luise C, Visconti R, Staibano S, Merolla F, Ilardi G, et al. New therapeutic perspectives in CCDC6 deficient lung cancer cells. Int J Cancer 2015;136(9):2146-2157.
22. Licker MJ, Widikker I, Robert J, Frey JG, Spiliopoulos A, Ellenberger C, et al. Operative mortality and respiratory complications after lung resection for cancer: impact of chronic obstructive pulmonary disease and time trends. Ann Thorac Surg 2006;81(5):1830-1837.
23. Birim O, Kappetein AP, Waleboer M, Puvimanasinghe JP, Eijkemans MJ, Steyerberg EW, et al. Long-term survival after non-small cell lung cancer surgery: development and validation of a prognostic model with a preoperative and postoperative mode. J Thorac Cardiovasc Surg 2006;132(3):491-498.
24. Abolhoda A, Liu D, Brooks A, Burt M. Prolonged air leak following radical upper lobectomy: an analysis of incidence and possible risk factors. Chest 1998;113(6):1507-1510.
25. Deslauriers J, Ginsberg RJ, Piantadosi S, Fournier B. Prospective assessment of 30-day operative morbidity for surgical resection in lung cancer. Chest 1994;106 (6 Suppl):S329-S330.
26. Mitsudomi T, Mizoue T, Yoshimatsu T, Oyama T, Nakanishi R, Okabayashi K, et al. Postoperative complications after pneumonectomy for treatment of lung cancer: multivariate analysis. J Surg Oncol 1996;61(3):218-222.
27. Keagy BA, Lores ME, Starek PJ, Murray GF, Lucas CL, Wilcox BR. Elective pulmonary lobectomy: factors associated with morbidity and operative mortality. Ann Thorac Surg 1985;40(4):349-352.
28. British Thoracic Society; Society of Cardiothoracic Surgeons of Great Britain and Ireland Working Party. BTS guidelines: Guidelines on the selection of patients with lung cancer for surgery. Thorax 2001;56(2):89-108.
29. Colice GL, Shafazand S, Griffin JP, Keenan R, Bolliger CT; American College of Chest Physicians. Physiologic evaluation of the subject with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest 2007;132 (3 Suppl):S161-S177.
30. Bolliger CT, Jordan P, Solèr M, Stulz P, Grädel E, Skarvan K, et al. Exercise capacity as a predictor of postoperative complications in lung resection candidates. Am J Respir Crit Care Med 1995;151(5):1472-1480.
31. Holden DA, Rice TW, Stelmach K, Meeker DP. Exercise testing, 6-min walk, and stair climb in the evaluation of patients at high risk for pulmonary resection. Chest 1992;102(6):1774-1779.
32. Pierce RJ, Copland JM, Sharpe K, Barter CE. Postoperative risk evaluation for lung cancer resection: predicted postoperative product as a predictor of surgical mortality. Am J Respir Crit Care Med 1994;150(4):947-955.
33. Kearney DJ, Lee TH, Reilly JJ, DeCamp MM, Sugarbaker DJ. Assessment of operative risk in patients undergoing lung resection. Importance of predicted pulmonary function. Chest 1994;105(3):753-759.
34. Ferguson MK, Vigneswaran WT. Diffusing capacity predicts morbidity after lung resection in patients without obstructive lung disease. Ann Thorac Surg 2008;85(4):1158-1164.
35. Benzo R, Kelley GA, Recchi L, Hofman A, Sciurba F. Complications of lung resection and exercise capacity: a meta-analysis. Resp Med 2007;101(8):1790-1797.

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36. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J 2009;34(1):17-41.
37. Brunelli A, Refai MA, Salati M, Sabbatini A, Morgan-Hughes NJ, Rocco G. Carbon monoxide lung diffusion capacity improves risk stratification in patients without air flow limitation: evidence for systematic measurement before lung resection. Eur J Cardiothorac Surg 2006;29(4):567-570.
38. Yano T, Yokoyama H, Fukuyama Y, Takai E, Mizutani K, Ichinose Y. The current status of postoperative complications and risk factors after a pulmonary resection for primary lung cancer. A multivariate analysis. Eur J Cardiothorac Surg 1997;11(3):445-449.
39. Hollaus PH, Wilfing G, Wurnig PN, Pridun NS. Risk factors for the development of postoperative complications after bronchial sleeve resection for malignancy: a univariate and multivariate analysis. Ann Thorac Surg 2003;75(3):966-972.
40. Jagoe RT, Goodship TH, Gibson GJ. The influence of nutritional status on complications after operations for lung cancer. Ann Thorac Surg 2001;71(3):936-943.
41. Busch E, Verazin G, Antkowiak JG, Driscoll D, Takita H. Pulmonary complication in patients undergoing thoracotomy for lung carcinoma. Chest 1994;105(3):760-766.
42. Imfeld S, Bloch KE, Weder W, Russi EW. The BODE index after lung volume reduction surgery correlates with survival. Chest 2006;129(4):873-878.

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