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Review Article

RISK STRATIFICATION OF POSTOPERATIVE PULMONARY COMPLICATIONS (PPCS) IN ELDERLY PATIENTS AFTER LUNG CANCER RESECTION

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ABSTRACT

Postoperative pulmonary complication (PPC) incorporates an array of complications affecting the respiratory system following curative-intent pulmonary resection for lung carcinoma, especially seen in elderly patients. Current apprehensions of the risk stratification for PPC is not uniform; only a handful of high quality studies are available and have emphasized on different variables, leading to an inadequate consensus for them to be practiced clinically. Risk must be evaluated based on a proper history, physical examination, and supportive diagnostic tests. Once a pattern of risk is estimated and its severity measured, that information, adjoined with other patient data, often leads to an early recognition and management of the modifiable preoperative variables. This review encapsulates the published observational studies and clinical trials showing importance of the role of risk stratification in patients with lung cancer being considered for curative-intent pulmonary resection; and emphasizes on the further need for validation of these predictive risk score in clinical use.

Keywords: Lung Cancer Surgery, Postoperative Pulmonary Complications (PPC), Preoperative evaluation, Risk factors, Risk Stratification

INTRODUCTION

Risk stratification is an estimation of the possibility of a patient's risk of suffering a particular complication and the need for preventive intervention determined by clinical and lab data. Postoperative pulmonary complications (PPCs) following lung cancer surgery are seen in 10-50% [1, 2] of patients, contingent on the clinical criteria being evaluated, the category of pulmonary complications studied and the surgical procedure done. In case of pulmonary cancer patients, pulmonary resection provides the optimal chance for cure, but patients especially elderly cases with lung carcinoma have various coexistent preoperative clinical variables namely age, co-morbidities, smoking status, pulmonary function, ASA score, preoperative staging, etc. that can increase the manifestation of PPCs, which have a vital influence on the patient's recovery process. [3] PPCs are the most typical variety of postoperative morbidity in thoracic surgery [2].

There is divergence in the definition of diagnostic criteria for postoperative pulmonary complications in the face of physiopathological disorders particular to the condition and type of surgery, and studies applying a variety of research designs and definitions have fluctuating outcomes. However, patient selection and preoperative risk stratification and perioperative management in particular seems to reduce the incidence of PPCs. Therefore, it is imperative to appraise the PPC risk through clinical variables in the preoperative period, to identify risks for PPCs, change modifiable factors, discuss risks with patients, optimize health before surgery, and plan appropriate perioperative and postoperative care. [4, 5]

Considering the preoperative variables, this review aims to furnish a literature update and clinical overview of the role of risk stratification in lung cancer candidates advised for thoracic surgery.

Risk factors for postoperative pulmonary complications (PPCs):

Preoperative clinical variables:

Age:

As life expectancy grows, the prevalence of lung cancer has been observed to increase. In elderly patients, underlying comorbidities (such as COPD, Hypertension, Diabetes, etc.), emphysematous and inflammatory changes, impaired physical activity level complicates their procedures, thus increasing the risk of developing PPCs.

Studies have outlined advanced age (≥65 years) as an independently powerful predictive element for higher occurrence of PPCs. [5-10], In a prospective observational study, Agostini, P. and colleges identified age≥75 years as one of the non-modifiable risk factors associated with PPCs. These patients are customarily submitted to sublobar resections rather than lobectomy and have reduced resection rates compared to younger population [5, 11]. Similarly, Miura, N., et al. reported that, in octagenerians 80 years of age or older with severe complications, limited surgery is not a poor prognostic factor, and showed acceptable rates of postoperative morbidity and mortality and length of stay [12]. However, few studies speak of age as a single factor not a risk predictor, although in association with other risk factors it was. [13, 14]

Prior to surgery, patients with advanced age need to be assessed vigorously, so as to manage any modifiable risk factors that can avoid the occurrence of PPCs, and provide them equal access to lung cancer treatment regardless of their age.

Body mass index (BMI) and nutrition:

Although obesity (BMI≥30 kg/m2) has been cited as a risk factor [5], low body weight (BMI ≤18.5) or recent weight loss (> 5%) and low serum albumin are found in various studies to be directly related to nutritional status, mortality and risk of developing PPC [2, 4, 9, 15-17]. Saad, I.A., et al. in a prospective study of cohorts stated that the average BMI of the patients with postoperative pulmonary complications was 22.2 kg/m2 with 62.9% eutrophic and 37.1% dystrophic, of whom 33.3% were undernourished and 3.7% obese patients. For every one-unit reduction in body mass index (in kilograms), the possibility for occurrence of complications increased 1.15-fold [2]. Moreover, in postoperative period a decrement of 25% in protein albumin levels can also be observed in non-malnourished groups. So, nutritional support is recommended in patients with <4.5mg/dl preoperative albumin [16, 17]. As seen with many cancer types, lung carcinoma patients present with cachexia, low protein albumin levels, leads body functions to slow down, even stop.

Therefore, nutritional assessment should be included in the routine preoperative selection in order to modify the impending risk for postoperative pulmonary complications. Nutritional support for malnourished patients both in the preoperative and postoperative period is beneficial for fast recovery.

Neoadjuvant therapy:

With neoadjuvant therapy, there is a risk of long-term pulmonary disability; especially negative impact on diffusion capacity among other PFTs. [1] As chemoradiotherapy induces a decrement in DLCO, a marker of gas exchange, by 20 to 30%, it is suggested that repeat lung function test (PFT) with diffusing capacity be performed after completion with noeadjuvant therapy. [6] Matsubara et al. [18] in a retrospective design analysed morbidity (55.4%) and mortality (5.4%) following extended resection are both significantly elevated after induction therapy (IT). Therefore, the influence of neoadjuvant therapy on risk stratification should be emphasized in preoperative care.

History of smoking:

Smoking has demonstrated to pose an increase in incidence of primary lung cancer and a crucial predictor of development of PPCs [1, 19]. PCC rates are remarkably higher for patients with at least a 20 pack-year smoking history than for those with a lesser pack-year smoking. [20] Current smoking was seen associated with a nearly six-fold increase in risk for PPC. [21] Saad, I.A., et al. [2], in a prospective study concluded that for every year of smoking the risk of complications increased 1.04-fold. Also, smoking cessation for more than 4 weeks (at least 6-8 weeks) preoperatively reduces the occurrence of PPCs, and longer cessation duration may be even more effective [2, 5, 15, 20, 22, 23]. A lesser period of preoperative cessation confers less protection against PPCs; recent quitters may even have a higher frequency of complications postoperatively than current smokers. This may be explained by an increase in tracheobronchial secretions, a decrease in mucociliary clearance, sputum retention, delayed improvement in inflammatory functions and possible decrease in poor

ciliary activity leading to reduction in irritant induced coughing. Furthermore, there is a compounding effect of anesthesia and smoking on suppression of intraoperative antimicrobial/phagocytic activity in alveolar macrophages. Abstinence of smoking for 6 months normalizes proinflammatory function, however only 3 months normalizes phagocytic function. [5, 7, 21, 23, 24] In contrast with earlier reports, more recent analyses indicate that briefer durations of cessation do not actually increase PPC risk. [4] However, a reduced survival, poorer quality of life and a higher risk for subsequent lung cancers can be observed in those who continue to smoke regardless.

Lifestyle factor like smoking is susceptible to modification and a longer duration of preoperative cessation seems as a favored strategy for improving a number of outcomes, such as mortality and respiratory, arterial and venous events.

Pulmonary function test characteristics:

Pre-existing pulmonary function and the proportion of the planned resection can depict the risk of respiratory insufficiency following lung surgery. The most commonly performed test in clinical practice, Spirometry, to predict one's pulmonary function can be influenced by the patient's age, sex, BMI, and hemoglobin level.

Forced expiratory volume in one second (FEV1) >1.5L for lobectomy and >2 L for pneumonectomy, in general practice is considered safe for operability, provided there is no evidence of interstitial lung disease or unexpected disability due to shortness of breath [9] .A range of values between 40% to 70 % has been recommended as the best cutoff value for predicting PPCs following resection of lung ,FEV1/FVC <70% [25] , FEV1 <60% [26] , ppo-DLCO < 40% [3, 6, 27, 28] , ppo-FEV1< 40% [29, 30] . However, percentage predicted rather than absolute lung function values should be used in assessing patients for lung cancer surgery, as it is correlated significantly with both complicated post-operative course and poor surgical outcome [31]. Patients with otherwise normal FEV1> 80% may have a DLCO < 80%; 7% of them may also have a PPO DLCO < 40%, a predictor of cardiopulmonary complication and mortality [6].

The purpose of preoperative risk stratification is to ascertain that there will be sufficient pulmonary reserve and decreased risk of becoming respiratory cripple after lung resection. Pulmonary function testing using spirometry may help predict the risk of PPCs and mortality.

American Society of Anesthesiologist's (ASA) score:

Higher ASA physical status (ASA score ≥2) has been associated with postoperative respiratory complications following thoracic surgeries [5, 32]. Advanced ASA score increases rates of pneumonia, unplanned intubation and prolonged ventilator support for 48 hours or longer. [4] Since the ASA functional status classification is a good instrument to evaluate overall physical condition and burden of comorbidities, it is an important variable to be assessed for PPC risk stratification.

Comorbidities:

Patients with lung cancer are predisposed to various pulmonary and non-pulmonary complications postoperatively. The underlying pulmonary disease, onset of an acute pulmonary process or a recent

exacerbation of a preexisting lung condition is considered important risk factors for developing PPCs, particularly COPD and bronchial asthma [4, 5, 19, 24, 25, 29]. However, other non-pulmonary comorbidities such as coronary disease, hypertension, and diabetes mellitus, have also been related with higher risks of mortality after resection for lung carcinoma. [25, 33]

Lung cancer patients with a history of cigarette smoking are predisposed to atherosclerotic cardiovascular disease (11%-17%), pulmonary hypertension which confers an increased risk of congestive heart failure, cardiac arrhythmias, hemodynamic instability, sepsis, and respiratory failure [4]. However, Lakshminarasimhachar, A. and G.W. Smetana emphasized on the fact that the risk of PPCs may be higher in patients with congestive heart failure than those with COPD, stating "CHF is present in 10% of the individuals ≥65 years of age and is a leading cause of postoperative morbidity and mortality." [4] Also, renal function is an important variable to stratify risk; a serum blood urea nitrogen level of 21 mg/dl or greater; a preoperative creatinine of ≥1.5 mg/dl has been associated with an increased risk of postoperative respiratory failure [4, 33] Conversely, few studies found no significant impact of comorbidities s/a CAD,CHF, HTN, Diabetes on the impending risk of PPCs. [32]

The inter-relation between patient's life expectancy, performance status, and presence of underlying comorbidities should be taken into account in the surgical decision-making process.

Upper respiratory tract infection (URTI) in last month before surgery:

In adults, the risk of bronchospasm, laryngospasm, and desaturation are associated with an URTI only if symptoms are present or occur in the last 2 weeks before surgery [4, 7, 20]. In patients with a history of bronchospasm, the risk of complications increases 6.2- fold [2]. Hence, respiratory infection in the last month is another avoidable risk factor which should be focused on during risk evaluation and surgical selection.

Type of Surgery:

Even though, with this era's advances, certain procedures are still high risk and also depends on surgical skills, especially pneumonectomies for lung cancer which are highly associated with development of postoperative pulmonary complications (PPC) and these complications with high mortality rates. [29, 32]

Neurologic Impairment and Dependent functional status:

The correlation between preoperative neurologic impairment and residual deficits from a previous stroke and PPCs could probably be because of an increased risk of occurrence of aspiration of gastric or pharyngeal secretions postoperatively. Postoperative delirium and confusion, altered sensorium increase the risk of pneumonia and respiratory failure. [4] Along with this, patients with the need for help with daily activities have an increased risk for postoperative pulmonary complications, since postoperative early mobilization can be a barrier.

Surgery duration (Perioperative period clinical variables):

One of the risk factors to be ascertained during the perioperative assessment is the duration of the surgery. Prolonged duration of surgery is a persistent risk factor encountered in most studies, and surgical procedures lasting more than 3h are specifically associated with a higher risk of PPCs [4, 15, 34]. For every one-unit increase in surgery duration (in minutes), the risk of complications increases 1.007-fold, according to Saad, I.A.and colleges. [2] Shiono, S. and colleges determined that an important factor in decreasing PCs is the quality of surgery, determined by surgery time. [8] Also, general anesthesia and the duration for which it is used during the course of surgery, leads to a higher risk of clinically important pulmonary complications [4, 29]. The duration of the procedure along with its complexity may play a role in the instigation of PPCs.

PPCs following thoracic surgeries:

Study/year	Year	Design	%PPC	Risk factors	PPC
Bluman, L.G. [21]	1998	Prospective cohort study (n=410)	22.0% (current smokers), 12.8% (past smokers)	smoking	PPCs obtained from medical records
Wang, J., et al[3]	1999	Prospective study (n=40)	32.5%	Impaired DLCO%	Pneumonia, respiratory failure, need for supplemental oxygen
Algar, F.J., et al. [29]	2002	Retrospective study(n=242)	14%	Anesthetic time, low ppo-FEV1, heart disease, no previous record of chest physiotherapy, COPD.	ARF, re-intubation, Nosocomial pneumonia, atelectasis, pulmonary edema, pneumothorax

Saad, I.A., et al. [2]	2003	Prospective cohort study (n=145)	18.6%	History of bronchospasm, BMI, Smoking, surgery duration	Tracheobronchitis, bronchospasm
Agostini, P., et al. [5]	2010	Prospective observational study (n=234)	14.5%	age ≥75 years, BMI ≥30 kg/m2, ASA≥3, smoking history and COPD	Melbourne group scale (MGS) was used to identify high PPC risk patients.
Lugg, S.T., et al. [23]	2017	Prospective observational study (n=111)	13% (Smokers: never 2%, current 22%, ex-smoker <6wk 10.9%, ex-smoker ≥6wk 11.8%)	current smoking	WBC, purulent sputum, CXR findings and reduced oxygen saturations
Agostini, P.J., et al. [24]	2018	Prospective observational study (n=285)	7.4% (in VATS lobectomy)	Current smoking	CXR findings, elevated WBC, SpO2 <90% on room air.
Hino, H., et al. [34]	2018	Single-arm retrospective study(n=337)	35.3%	Male gender, operation time	Pulmonary fistula, pneumonia, arrhythmia, etc. (PPCs obtained from medical records)
Marret, E., et al. [32]			42.6%		

	2010	Retrospective study(n=129)	ASA≥2, liberal fluid administration during surgery	Bacterial pneumonia

Table 1: Studies on PPCs following thoracic surgeries

*n= sample size; PPCs=postoperative pulmonary complications; PAL= prolonged air leak; BMI=Body mass index; ppo-FEV1=predicted postoperative Forced expiratory volume in 1 second; DLCOppo= predicted postoperative Diffusion capacity of lung for carbon monoxide; DLCO%= Diffusion capacity of lung for carbon monoxide expressed as a percent of predicted; ASA score= American society of Anesthesiologist's score

PPCs are defined vastly, which mainly includes respiratory failure, re-intubation within 48 hours, weaning failure, pneumonia, atelectasis, bronchospasm, exacerbation of chronic obstructive pulmonary disease (COPD), pneumothorax, pleural effusion, and various forms of upper airway obstruction. The incidence of these complications varies between hospitals and quality of the procedures. [15] The most common complications after lung surgery in elderly patients are arrhythmia (≈14.3%) [8], postoperative pneumonia, prolonged air leak. [34] and cardiac complications (2% - 3%, including myocardial ischemia, pulmonary edema, ventricular fibrillation or primary cardiac arrest, complete heart block, and cardiac-related death) [6].

A PPC score, the Melbourne Group Scale (MGS), has been used by few researchers to identify PPCs, identified with four or more of the following eight dichotomous factors: "chest x-ray findings of atelectasis or consolidation; raised white cell count(>11.2x10 9/l) or administration of respiratory antibiotics postoperatively (in addition to prophylactic antibiotics);temperature >38.8C; signs of infection on sputum microbiology; purulent sputum differing from preoperative status; oxygen saturations <90% on room air; physician diagnosis of pneumonia; and prolonged HDU stay or readmission to HDU or ITU for respiratory complications." The reliability of the score has been validated in few studies, and shows promising results in identifying high risk patients. [5, 24]

Scientific evidences supporting use of risk stratification tools:

Study/Year	Design	Sample size	% PPC	Risk Score(Independent Risk Factors identified for PCs)
Amar, D., et al./2010[1]	Retrospective study	956	12.7 %	Predictive rule using these 2 independent predictors was formulated
Sekine, Y., et al./2010[7]	Retrospective study	1713	11.1 %	(Preoperative chemotherapy, a lower DLCOppo).
Canet, J., et al./2010[20]	Prospective, multicenter, observational study	2,464	5%	TRI Sekine score (male, advanced age, preoperative interstitial pneumonia, high smoking index, combined resection, and vascular and/ or bronchial reconstruction).
				ARISCAT risk index (low preoperative arterial oxygen saturation, acute respiratory infection during the previous month, age, preoperative anemia, upper abdominal/ intrathoracic surgery, surgical duration of at least 2 h,& emergency surgery).

Table 2: Studies of Risk stratification tools for postoperative complications

*PPC=postoperative pulmonary complications; TRI= Total risk index; DLCOppo= predicted postoperative Diffusion capacity of lung for carbon monoxide; ARISCAT= Assess Respiratory Risk in Surgical Patients in Catalonia Tool

Since the late 1990s several PPC prediction models have been developed, but previous reports have conflicting results concerned with which preoperative clinical, spirometric, or laboratory data to include for risk stratification of PPCs. A standard definition for PPCs has yet to be established. Therefore, at present, any factor associated with the dysfunction of normal endothelial-epithelial barriers of the lungs or other lung abnormality is considered a PPC according to the general diagnostic criteria [35].

Using a single insitution prospective database of 956 patients, Amar, D., et al., [1] formulated a prediction rule using the variables, preoperative chemotherapy (point score 2) and a lower DLCOppo (point score 1 per each 5% decrement of DLCOppo less than 100%) for risk stratification of PPC occurrence. They defined 3 general risk categories for PCs: "low ≤10 points, intermediate 11–13 points, and high ≥14 points". They mainly focused on defining risk factors associated with pulmonary morbidity. However, the overall prediction of this model was moderate, and only examined patients undergoing thoracotomy. Sekine, Y., et al. [7] generated a risk index for PPCs using the significant risk factors identified from logistic regression model. "Each risk factor (male, advanced age, preoperative interstitial pneumonia, high smoking index, combined resection, and vascular and/ or bronchial reconstruction) is scored from 0 to 2 or 3 points according to the frequencies of PPC. Using this, an aggregate score is established for predicting PPC. "TRI (Sekine score) = Sex score+ Age score +SI score+IP score+ Reconstruction score + Combined resection score", where, TRI is total risk index, SI is smoking index, IP is interstitial pneumonia." Even so, since the risk index was not statistically calculated, the efficacy of it remains doubtful.

Similarly, in a multicenter cohort, Canet, J., et al. [20], identified seven straightforward, objective, and easily assessed factors associated with the appearance of PPCs and developed an ARISCAT risk index. The index includes 7 independent risk factors (mentioned in Table 2) of any severity that predicts PPC rates. Each factor was assigned a weighted score and patients were stratified as low, intermediate, and high risk for developing pulmonary complications. Clinical application of the ARISCAT risk index has the potential to facilitate development of new and improved strategies for minimizing the rate of PPCs following lung cancer resections.

PPC risk-stratification tools are essential for guiding clinical decision-making in the preoperative period, but such tools should ideally be based on prospectively collected data and validated externally before they are considered widely transportable to new settings. [15]

Concluding remarks:

In recent practice, more emphasis has been given to postoperative care due to the complexity of patients with multiple risk factors for postoperative pulmonary complications. Previously, studies have compared variety of risk factors such as age, gender, smoking, impaired pulmonary function variables, comorbidities, ASA class, surgery duration so on to be associated with the occurrence of Postoperative

pulmonary complications (PPCs), which are the second most common postoperative complications. [4] The variation from 2% - 40% in the incidence of PPCs following thoracic surgery is mainly due to the type of pulmonary complications studied, the clinical criteria used in the definition, patient comorbidity, and quality of the procedure done. [4, 5, 15, 36]

Early-stage lung cancer, which benefits from radical surgery, is often diagnosed in patients with multiple comorbidities (concomitant diffuse parenchymal and/or obstructive airway disease and atherosclerotic cardiovascular disease as a consequence of their smoking habit) [6] and in an increasingly older population. Comorbidities have an intrinsic impact on each patient's treatment and its efficacy, especially when referred to a surgical treatment. However, minimally invasive VATS (video-assisted thoracoscopic surgery) approach reduces postoperative morbidity and mortality, shortens the length hospital stay and provides the same long-term prognosis compared with thoracotomy [37].

In an attempt to improve the preoperative assessment of candidates for lung resection, most studies mainly take into account specific data such as spirometric characteristics, whereas there are more variables that are required to be considered together for risk stratification, leading to conflicting results among various studies. The large discordance in the incidence of respiratory complications (air leak, 11% to 22%; pneumonia, 3% to 25%; prolonged ventilation, 2% to 29% or recent oxygen dependency 6% to 28%) and postoperative mortality (1% to 20%) can largely be explained by the lack of standard criteria for defining outcome variables (e.g. pneumonia, atelectasis, etc.), the extent of the resection (e.g. wedge resection, lobectomy, segmentectomy, pneumonectomy) and the type of incision (e.g. muscle-sparing anterior thoracotomy, posterior and lateral thoracotomy, thoracoscopy). [26]

Candidate specific preventive strategies could be set in motion for identified risks, such as delaying surgery if a respiratory infection has occurred during the last month, cutting out smoking at some point before surgery, supplement nutrition if malnourished, shortening the duration of surgery, and scheduling physiotherapy training and incentive spirometry pre- and post-operatively. [15] Preemptive measures can potentially improve outcomes, shorten the postoperative LOS, and reduce hospital costs. However, rigorous studies of the preoperative strategy to reduce the risk of PPC are needed.

In order to identify patients at increased risk for lung cancer resection and to enable the patient to make an informed decision about the appropriate therapeutic approach, a careful preoperative physiological assessment can be helpful in their management [6]. Once risk is estimated, it may be possible to reduce the threat to an individual's health or survival by acting on factors that are modifiable. Therefore, algorithms for PPC risk stratification of lung cancer patients undergoing pulmonary resection are essential for guiding clinical decision-making during the complete length of an individual's hospital stay.

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Footnote:

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