Persistent alveolar air leak following pulmonary lobectomy: an old problem in a modern era

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Abstract

Persistent alveolar air leak (PAAL) after major lung resection remains a common complication in thoracic surgery. The aim of this study was to identify a subset of patients with high risk of developing PAAL after pulmonary lobectomy. Another objective was to evaluate the influence of PAAL on postoperative complications and length of hospital stay. A retrospective analysis on 895 patients undergoing pulmonary lobectomy from January 2014 to December 2019 was performed. PAAL was defined as air leak lasting more than 5 days after lung surgery. Univariate analyses and logistic regressions were performed to identify the predictors of PAAL. A backward selection algorithm was used to identify the optimal set of predictors. The incidence of PAAL was 8.2% (74/895). Male gender ($p=0.017$), BMI ($p<0.001$), transient ischemic attack ($p=0.031$), FEV_1 ($p=0.018$), lobectomy combined with adjacent subsegmentectomy ($p=0.018$), partial and extended pleural adhesions ($p=0.033$ and $p=0.038$, respectively) were identified as independent risk factors for PAAL through logistic regression. A weak positive correlation was found between video-assisted thoracic surgery (VATS) and PAAL following pulmonary lobectomy ($p=0.100$). PAAL was found to be associated with higher risk of postoperative morbidity ($p=0.002$) and with longer hospital stay ($p<0.001$). Both preoperative and intraoperative risk factors may be responsible for PAAL after pulmonary lobectomy. VATS does not appear to prevent this postoperative complication. An alveolar air leak lasting beyond 5 days after pulmonary lobectomy is associated with worse postoperative outcomes.

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Introduction

Alveolar air leak is caused by an abnormal communication between the pulmonary parenchyma distal to a segmental bronchus and the pleural space [1]. A persistent alveolar-pleural fistula is one of the most common complications after pulmonary resection and may be associated with increased postoperative morbidity, as pneumonia, pleural empyema, causing distress to both the patient and the thoracic surgeon [2]. An incidence of persistent alveolar air leak (PAAL) between 4 and 25% has been reported in patients with benign or malign tumors undergoing pulmonary resections and even if in the literature there is no single agreed definition of such complication, in most investigations recently an air leak has been defined as prolonged if it lasts more than 5 days after lung surgery, in line with modern recommendations and fast-tracking pulmonary resections protocols [3,7-9]. The objective of this study is to identify a subset of patients with high risk of developing PAAL following pulmonary lobectomy and assess whether this complication is associated with worse postoperative outcomes.

Materials and Methods

From January 2014 to December 2019, 1010 consecutive patients underwent pulmonary lobectomy via open thoracotomy or video-assisted thoracoscopic surgery (VATS) at our institution for the treatment of lung cancer or suspected tumor. Exclusion criteria included: lobectomy with chest wall resection (15 patients), lobectomy and lung decortication (5 patients), lobectomy combined with volume reduction of one additional lobe (7 patients), ipsilateral reoperation for completion lobectomy (5 patients), after prior lobectomy (3 patients) and for management of postoperative hemothorax (7 patients), contralateral reoperation after prior lobectomy (8 patients), bronchopleural fistula (6 patients), in-hospital postoperative mortality (9 patients), incomplete data (50 patients). A total of 895 patients (583 males, 312 females) were retrospectively analyzed. The preoperative work-up for lung resection included: computed tomography (CT) scan, positron emission tomography (PET) scan, bronchoscopy, pulmonary function studies, cardiac assessment, basic laboratory tests and other evaluations as indicated by anamnestic information and physical examination. The patients were divided into two groups based on the absence or presence of persistent alveolar air leak (PAAL). The presence of peripheral air leak after pulmonary resection for more than 5 consecutive days was defined as persistent. Several variables were analyzed including demographic factors and preoperative factors such as: forced expiratory volume at first second (FEV_1), carbon monoxide lung diffusion capacity (DLCO), maximal oxygen consumption (VO_2max), predicted postoperative (ppo) values of FEV_1, DLCO and VO_2max, neoadjuvant chemotherapy, body mass index (BMI), diabetes mellitus, chronic ischemic cardiomyopathy and so. In all patients, pulmonary function tests were done with measurement of both FEV_1 and DLCO expressed as percentages of predicted values for age, gender and height. Predicted postoperative values of FEV_1 and DLCO, expressed as percentage of predicted values, were obtained through split function studies based on lung segment counting. The formal high-tech cardiopulmonary exercise test (CPET) was performed to assess exercise limitation, expressed as maximal oxygen consumption (VO_2max), in patients with either FEV_1 or DLCO lower than 80% of predicted values. VO_2max and ppoVO_2max were expressed as mL/kg/min. The following intraoperative factors were considered: type of resection (lobectomy *vs* larger parenchymal resections), site of resection (upper *vs* lower), side (access) (right *vs* left), surgical access (open *vs* VATS), conversion from VATS to open lobectomy, pleural adhesions, fissure status and fissure dissection technique. Five hundred fifty-nine patients (62.4%) had preoperative comorbidity. We performed VATS lobectomy, using a standardized three-port anterior approach, in 680 patients (76%) and the conversion rate was 5.3%. Forty patients (4.5%) underwent lobectomy with wedge resection of other lobe; 48 patients (5.4%) underwent lobectomy combined with adjacent subsegmentectomy. Right side was involved in 61.2% of cases. Absent fissures and extended adhesions obliterating the pleural cavity were found respectively in 13.9% and 7.9% of patients. By absent fissure and extended pleural adhesions we mean complete fusion between interlobar planes and diffuse symphysis between the two pleural layers involving more than half of the pleural cavity respectively. At the end of all procedures the remaining lung was reinflated under direct vision and a water submersion test was used to detect air leaks from the lung parenchyma; intraoperative techniques to treat the areas with visible leaks included the use of simple or pledgeted sutures, stapling devices and surgical sealants. More than half of the patients (59.6%) had two chest tubes (28Fr and 32Fr). Underwater seal drains were used for the management of postoperative air leaks and suction of -10 cm H_2O was applied only in case of gradually enlarging pneumothorax or extensive subcutaneous emphysema developed on water seal. The tubes were removed when the chest drainage was less than 200 mL in 24 h and when air leak was resolved.

Statistical analysis

Quantitative variables were expressed as mean plus/minus standard deviation (SD) or through median and interquartile range (in brackets) if normality could not be assumed, i.e., after rejection of the null hypothesis for the Shapiro-Wilk normality test. Differences between PAAL+ and PAAL– groups were tested using Student's *t*- or Mann-Whitney-test (the latter used when normality could not be assumed). Qualitative variables were expressed as raw numbers and percentages (in brackets). Differences between PAAL+ and PAAL– groups were detected by the Chi-Square test or Fisher's exact test if the conditions for Cochran's theorem were not met. We remark that variable VO_2max was registered for only 459 patients (52.3%). A logistic regression was performed to identify the determinants of PAAL using both preoperative and operative information, discarding variables that were totally not associated with PAAL in the univariate analysis (p=1). Histology was not considered due to multicollinearity problem. A full model was estimated using 17 covariates, while a backward selection algorithm was performed to select the "optimal" set of regressors. The reference sample included 893 patients, due to missing data on the parameters of two patients. Odds ratio (OR) and 95% confidence interval (CI) were estimated. R Software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2016) was used to perform the statistical analyses. The multicollinearity of proposed models (full and backward) was checked through generalized variance inflated factors (GVIFs).

Results

Five hundred eighty-three men and 312 women, with a median age of 65,7 years (range, 19 to 88 years), were included in this analysis. Characteristics of these patients are listed in Table 1. PAAL occurred in 74 patients (8.2%) and in all cases was managed conservatively with chest tube drainage. Eight hundred and twelve lobectomies (90.8%) were done for primary malignant lung tumor, 37 (4.1%) for lung metastasis and 46 (5.1%) for benign lung disease. According to the 8th edition of the TNM staging system for lung cancer, 499 patients (55.8%) were pathologically diagnosed as stage I, 195 (21.8%) as stage II, and 118 (13.2%) as stage IIIA. In patients with pathological tumor node metastasis (TNM) stage III, PAAL wasn't observed more frequently compared to those with TNM stage I/II. Male gender ($p<0.001$), BMI ($p<0.001$), FEV_1 ($p=0.002$), age ($p=0.032$), TIA ($p=0.029$), pleural adhesions ($p<0.001$), fissure status ($p=0.020$) and operation time ($p<0.001$) were identified as potential risk factors for PAAL through univariate analysis (Tables 1 and 2). Moreover, the results of this analysis showed association between postoperative prolonged alveolar air leak and lobectomy with wedge resection of other lobe ($p=0.040$) or lobectomy combined with adjacent subsegmentectomy ($p=0.013$). Multivariate analysis was performed to assess the overall risk factors for PAAL excluding operation time due to its strong relationship with adhesions (perfect collinearity): higher lengths of operation (in minutes), in summary, are always associated with cases of pleural adhesions. Logistic regression analysis indicated that significant independent predictors of PAAL following pulmonary lobectomy were male gender ($p=0.017$), BMI ($p<0.001$), transient ischemic attack (TIA) comorbidity ($p=0.031$), FEV_1 ($p=0.018$), lobectomy combined with adjacent subsegmentectomy ($p=0.018$), partial and extended pleural adhesions ($p=0.033$ and $p=0.038$, respectively) (Table 3). The probability of air leak decreased on average by about 13% for each additional point of BMI (OR: 0.87), while males were on average more than twice as likely to develop an air leak. Finally, for each (percentage) additional point of FEV1, the probability of air leaks decreased on average by 12%, going from 3% to 30% in 95% of the samples. In the backward selection procedure, the main results were substantially in line with the full model. PAAL occurred in 59 of 680 patients (8.7%) and in 15 of 215 patients (7%) undergoing respectively VATS and open lobectomy. When considered in the multiple logistic regression models, VATS was weakly correlated with PAAL after lung resection (p=0.100). The postoperative course was uneventful in 780 patients. Postoperative complications occurred in 18.9% of patients with PAAL and 12.3% of those without.

PAAL was associated with a higher risk of postoperative morbidity (p=0.002) and significantly prolonged the length of hospital stay (14 *vs* 4 days; p<0.001) (Table 4).

Discussion

PAAL remains a frequent complication after major lung resection and represents an important cause of morbidity. Most recently it has been defined as an air leak lasting beyond the postoperative fifth day according to enhanced recovery after surgery (ERAS) programs and The Society of Thoracic Surgeons General Thoracic Surgery Database (STS GTSD) queried to assess the risk of these postoperative complications in patients undergoing elective lung cancer resection [10,11]. Taking this definition into consideration, the incidence of PAAL after lobectomy in our study is 8.2% and it is slightly lower than previously reported [2-4]. In this investigation, the logistic regression analysis procedure demonstrates that significant preoperative predictors of PAAL are low BMI, reduced FEV_1 and male gender. The latter, among variables associated with persistent pleuropulmonary air leak after lobectomy, was found even by the European Society of Cardiovascular and Thoracic Surgery database [12,13]. A low BMI is considered a marker of malnutrition and some authors have estimated cut-off values, for predicting increased risk of PAAL, less than or equal to 25 kg/m^2 [7,10]. In our study, 50% of patients with PAAL have a BMI below 25.5 kg/m^2. A reduced FEV_1, expression of increased airways resistance and pathologic parenchymal changes, has been frequently associated with the occurrence of PAAL [7,12,14]. Prolonged air leak scores have reported values of FEV_1 lower than 86%, 80% or 70% [8,10,15]. In our investigation, 50% of patients with PAAL have a preoperative FEV_1 less than 83% and 25% a preoperative FEV_1 below 68%. In multivariate analysis, we identify lobectomy combined with adjacent subsegmentectomy as an independent operative risk factor for PAAL: a surgical procedure that, due to a roughly divided pulmonary parenchyma, may potentially create a source for peripheral air leak. In our work, both partial and extended pleural adhesions are factors significantly associated with PAAL: in such instances, maneuvers of traction and blunt dissection may lead to lung parenchyma injuries. This result is in line with previous articles focusing on the contribution of pleural adhesions to increase hospital stay after pulmonary resection [4,7,13,15,16]. Our data show a weak positive correlation between VATS and PAAL following pulmonary lobectomy but conversion to thoracotomy surprisingly has no clinical impact on postoperative prolonged air leak.

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Table 1. Comparison of preoperative variables between patients with (PAAL+) and without (PAAL-) persistent alveolar air leak (n=895).

Variables	Summary	PAAL+	PAAL-	p-value
Male gender	583 (65.1)	63 (85.1)	520 (63.3)	<0.001***
Age	67 (11)	70 (11)	67 (12)	0.032*
BMI	27 (6)	25.5 (4)	27 (6)	<0.001***
Comorbidities				
None	336 (37.5)	21 (24.8)	315 (34.8)	0.115
Other	31 (3.5)	2 (2.7)	29 (3.5)	1.000
Hypertension	475 (53.1)	43 (58.1)	432 (52.6)	0.433
Chronic ischemic heart disease	107 (12.0)	10 (13.5)	97 (11.8)	0.807
Chronic atrial fibrillation	25 (2.8)	2 (2.7)	23 (2.8)	1.000
Diabetes mellitus	145 (16.2)	18 (24.3)	127 (15.5)	0.069.
Peripheral artery disease	40 (4.5)	3 (4.1)	37 (4.5)	1.000
Transient ischemic attack	15 (1.7)	4 (5.4)	11 (1.3)	0.029*
Histology				0.379
Metastasis	37 (4.1)	1 (1.4)	36 (4.4)	
Benign disease	46 (5.1)	5 (6.8)	41 (5.0)	
Primary malignant tumor	812 (90.8)	68 (91.9)	744 (90.6)	
Pathological stage				0.334
I	499 (55.8)	46 (62.2)	453 (55.2)	
II	195 (21.8)	17 (23.0)	178 (21.7)	
III	118 (13.2)	5 (6.8)	113 (13.8)	
Neoadjuvant chemotherapy	33 (3.7)	3 (4.1)	30 (3.7)	1.000
FEV_1 (%)	89.5±20.5	82.2±19.9	90.1±20.5	0.002**
DLCO (%)	80 (25)	79.5 (20)	80 (26)	0.306
VO_2max*	16 (3)	17 (3)	16 (3)	0.177
ppoFEV_1 (%)	70.9±16.9	65 (15.9)	71.4 (16.8)	0.006**
ppoDLCO (%)	62 (21)	61.5 (16)	63 (22)	0.249
ppoVO_2max*	13 (3)	13 (3)	13 (3)	0.194

PAAL, persistent alveolar air leak; BMI, body mass index; FEV_1, forced expiratory volume at first second; DLCO, carbon monoxide lung diffusion capacity; VO_2max, maximal oxygen consumption; ppo, predicted postoperative; *p<0.05; **p<0.01; ***p<0.001.

Table 2. Comparison of operative variables between patients with (PAAL+) and without (PAAL-) persistent alveolar air leak (n=895).

Variables	Summary	PAAL+	PAAL-	P-value
Operation type				0.143
RUL	317 (35.4)	34 (45.9)	283 (34.5)	
ML	66 (7.4)	2 (2.7)	64 (7.8)	
RLL	163 (18.2)	9 (12.2)	154 (18.8)	
LUL	199 (22.2)	18 (24.3)	181 (22.0)	
LLL	150 (16.8)	11 (14.9)	139 (16.9)	
Lobectomy + WR	40 (4.5)	7 (9.5)	33 (4.0)	0.040*
Lobectomy + AS	48 (5.4)	9 (12.2)	39 (4.8)	0.013*
VATS	680 (74.0)	59 (79.7)	621 (75.6)	0.518
Conversion	36 (5.3)	3 (5.1)	33 (5.3)	1.000
Pleural adhesions				<0.001***
Absent	609 (68.1)	35 (47.3)	574 (70.0)	
Partial	214 (23.9)	27 (36.5)	187 (22.8)	
Extended	71 (7.9)	12 (16.2)	59 (7.2)	
Fissure status				0.020*
Complete	135 (15.1)	6 (8.1)	129 (15.7)	
Incomplete	635 (70.1)	63 (85.1)	572 (69.8)	
Absent	124 (13.9)	5 (6.8)	119 (14.5)	
Fissure dissection				0.625
Blunt+ED	181 (20.2)	12 (16.2)	169 (20.6)	
ED+Stapler	406 (45.5)	34 (45.9)	372 (45.4)	
Stapler	307 (34.3)	28 (37.8)	279 (34.0)	
Operation time (min)	150 (40.0)	190 (47.5)	150 (40.0)	<0.001***

PAAL, persistent alveolar air leak; RUL, right upper lobectomy; ML, middle lobectomy; RLL, right lower lobectomy; LUL, left upper lobectomy; LLL, left lower lobectomy; WR, wedge resection; AS, adjacent subsegmentectomy; VATS, video-assisted thoracoscopic surgery; ED, energy device; *p<0.05; ***p<0.001.

Table 3. Multivariate logistic-regression analysis of risk factors of PAAL.

	Full model			Backward model		
Variables	OR	95% CI's	p-value	OR	95% CI's	p-value
Intercept	2.667	(0.067; 101.561)	0.599	1.069	(0.088; 12.826)	0.958
Male gender	2.395	(1.209; 5.138)	0.017*	2.859	(1.487; 5.987)	0.003**
Age	1.005	(0.973; 1.040)	0.770			
BMI	0.868	(0.802; 0.935)	<0.001***	0.885	(0.822; 0.948)	0.001**
Comorbidity: None	0.735	(0.298; 1.905)	0.512			
Comorbidity: Hypertension	0.921	(0.428; 2.139)	0.839			
Comorbidity: Diabetes mellitus	1.367	(0.693; 2.629)	0.356			
Comorbidity: TIA	4.347	(1.030; 15.702)	0.031*	5.264	(1.313; 17.813)	0.011*
Pathological stage: I	0.856	(0.337; 2.512)	0.758			
Pathological stage: II	0.742	(0.258; 2.366)	0.593			
Pathological stage: III	0.368	(0.094; 1.399)	0.140			
FEV_1	0.983	(0.969; 0.997)	0.018*	0.985	(0.972; 0.997)	0.016*
DLCO	1.004	(0.988; 1.020)	0.605			
Operation type: ML	0.239	(0.034; 1.004)	0.084°			
Operation type: RLL	0.410	(0.145; 1.088)	0.081°			
Operation type: LUL	0.625	(0.267; 1.407)	0.267			
Operation type: LLL	0.505	(0.180; 1.348)	0.181			
Lobectomy + WR	2.502	(0.918; 6.108)	0.055°	2.385	(0.891; 5.682)	0.063°
Lobectomy + AS	2.880	(1.142; 6.725)	0.018*	2.159	(0.890; 4.800)	0.071°
VATS	1.898	(0.905; 4.193)	0.100°	1.701	(0.932; 3.294)	0.097°
Pleural adhesions: Partial	1.852	(1.044; 3.255)	0.033*	1.867	(1.064; 3.246)	0.028*
Pleural adhesions: Extended	2.299	(1.014; 4942)	0.038*	2.692	(1.224; 5.614)	0.010*
Fissure status: Incomplete	3.336	(0.893; 12.733)	0.071°	1.798	(0.792; 4.860)	0.197
Fissure status: Absent	1.163	(0.202; 6.330)	0.862	0.612	(0.166; 2.167)	0.443
Fissure dissection: ED+stapler	0.454	(0.162; 1.404)	0.147			
Fissure dissection: Stapler	0.383	(0.095; 1.595)	0.179			

OR, odds ratio; CI, confidence interval; BMI, body mass index; TIA, transient ischemic attack; FEV_1, forced expiratory volume at first second; DLCO, carbon monoxide lung diffusion capacity; ML, middle lobectomy; RLL, right lower lobectomy; LUL, left upper lobectomy; LLL, left lower lobectomy; WR, wedge resection; AS, adjacent subsegmentectomy; VATS, video-assisted thoracoscopic surgery; ED, energy device; °p<0.1; *p<0.05; **p<0.01; ***p<0.001.

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Table 4. Postoperative length of stay and postoperative complications according to presence or absence of PAAL (n=895).

Variables	Summary	PAAL+	PAAL-	p-value
LOS (days)	4 (2)	14 (7)	4 (2)	<0.001***
Complications				0.002**
None	780 (87.2)	60 (81.1)	720 (87.7)	
Pleural empyema	3 (0.3)	3 (4.1)	0 (0.0)	
Atelectasis	24 (2.7)	4 (5.4)	20 (2.4)	
AF	4 (0.4)	0 (0.0)	4 (0.5)	
Atelectasis + AF	48 (5.4)	4 (4.4)	44 (5.4)	
Other	36 (4.0)	3 (4.1)	33 (4.0)	

PAAL, persistent alveolar air leak; LOS, length of stay; AF, atrial fibrillation; **p<0.01; ***p<0.001.

As many authors, we found that an alveolar air leak lasting beyond 5 days after pulmonary lobectomy was associated with greater pulmonary morbidity, including pleural empyema or atelectasis, and that the incidence of total complications was significantly higher in patients with PAAL than those without [2,17]. Persistent alveolar air leak after lung resection has been shown to be one of the main reasons for prolonged hospital stay [8,18,19]. Our results are similar to the findings of previous studies: we found that PAAL increased length of hospital stay (LOS) by 11,7 days. We have not reported non-surgical options for inducing pleurodesis in the management of PAAL because we are hesitant to use this procedure in such cases. Although recent literature suggests that autologous blood patch is an effective option for resolving air leaks, the procedure-related complications rate reported is relatively low, the few studies published have small patient populations, and there is no agreement on the optimal volume of blood required to seal the air leak or the optimal timing for pleurodesis [20].

Limitations

This paper adopted two models in the analysis (full and backward model) that share an accuracy of 92% and 91% respectively, a very high specificity which is close to 100% but a very low or null sensitivity (6% and 0%, respectively). This can be considered a limitation of the present study. Further studies should be conducted to improve the predictive ability of the model, especially out of sample. Additional limitations include the lack of information regarding surgeons' procedural skills and individual surgeons' case volume. The missing information about the intraoperative management of air leak, due to significant heterogeneity in our database on the type of sutures or sealants used, is another important aspect of this study.

Conclusions

Considering preoperative risk factors analysis for PAAL following pulmonary lobectomy, low BMI, low FEV_1 and male gender appear to be statistically significant parameters and this research validates preoperative indicators included in prolonged air leak predictive scores [8,10,12,13]. Although a strong correlation between upper lobectomy and postoperative prolonged air leak has been emphasized repeatedly, in our study a strong intraoperative risk factor of PAAL following lung resection is lobectomy combined with adjacent subsegmentectomy [7,10,13]. One of the key findings of this research is that VATS does not appear to prevent PAAL in patients undergoing pulmonary lobectomy. In such patients, an alveolar air leak lasting longer than 5 days leads to a more complicated postoperative course.

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