Risk factors associated with prolonged air leak after video-assisted thoracic surgery pulmonary resection: a predictive model and meta-analysis

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Background: This study aimed to establish a predictive model for prolonged air leak (PAL) after video-assisted thoracic surgery (VATS) lung resection; and additionally, to present a meta-analysis of the relevant literature to estimate the association between various clinical factors and PAL.

Methods: A retrospective, case-control study was conducted using univariate analysis and logistic regression based on 493 medical records from patients who underwent VATS lung resection between January 2015 and August 2017 at our institution. PAL was defined as air leak more than 5 days after lung surgery. Subsequently, a nomogram was established as a predictive model. Relevant studies were screened from PubMed, Embase and Cochrane for relevant studies and data was extracted from those enrolled. Pooled odds ratios or weighted mean differences with corresponding 95% confidence intervals were calculated to estimate the association between various clinical factors and PAL.

Results: Incidence of PAL after VATS lung resection was observed in 54 (10.8%) of 493 patients. Logistic regression revealed that smoking (P=0.014), pulmonary function (P=0.011), pleural adhesion (P<0.001), stapling length (P<0.001), early postoperative drainage (P=0.002) were significantly associated with PAL. Our meta-analysis, including 17 eligible studies and 14 potential risk factors, further validating our findings. Upper lobectomy was determined to be a significant risk factor for PAL in Europeans and North Americans (OR =2.03, P<0.001), but not in Asians (OR =1.04, P=0.610). Importantly, the constructed nomogram demonstrated a good predictive ability (C-index =0.858).

Conclusions: Lung stapling length and early postoperative drainage are important indicators for the evaluation of PAL occurrence. Upper pulmonary resection is a factor with particular regional differences as its association with PAL is not significant within Asian populations. Our nomogram, incorporating multiple factors, provided a simple and practical predictive model with value for clinical application.

Keywords: Prolonged air leak (PAL); pulmonary resection; risk factors

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Introduction

Prolonged air leak (PAL) is a condition where air escapes from the lung parenchyma into the pleural space for more than 5 days after lung surgery (1). PALs are considered to be the most common postoperative complication of the lung surgery with an incidence of 6–26% (2-17). Previous studies have found that PAL is associated with other pulmonary complications such as atelectasis and pneumonia, which often translate into longer hospital stays and more hospitalization costs (18,19). In recent years, the enhanced recovery pathway after surgery (ERAS) has become a focus of surgery as a perioperative program to speed up patient recovery, was shown to reduce potential complications and decrease the length of hospital stays (20,21). The Italian ERAS Group (21) recommended that air leak prevention was a crucial part of ERAS, and certain measures, such as pleural tent, surgical sealant, staple-line reinforcement, should be taken in high-risk patients (e.g., those with severe emphysema or intraoperative air leak). This study contributes to research on the risk factors for PAL after video-assisted thoracic surgery (VATS) by conducting a retrospective, case-control study and providing a literature review and the first meta-analysis of published clinical data on this topic.

Methods

Data source and patient selection

Consecutive medical records of consecutive patients who underwent major pulmonary resection (lobectomy, sleeve lobectomy and segmentectomy) between January 2015 and August 2017 at the Department of Thoracic Surgery, Xiangya Hospital, Central South University were retrospectively collected. This project was reviewed and approved by the Ethics Committee of the Xiangya Hospital, Central South University, and informed consent was waived as it was a retrospective study (IRB number: 2017121009). Three individuals were excluded from this study: patients who underwent thoracotomy or pneumonectomy, patients with postoperative bronchopleural fistula, and patients who died before chest tube removal. PAL was defined as an air leak persisting for more than 5 days after lung surgery.

The meta-analysis part of this research conformed to the guidelines set out in the PRISMA Statement. We systematically searched for relevant studies indexed in PubMed, Embase and Cochrane Library. The search dates ranged from January 1, 1984 to November 1, 2017. The following combinations of terms were used: "PAL or prolonged air leak OR persistent air leak", "risk factor OR predict*", "pulmonary resection OR lung resection OR pulmonary lobectomy" (*Table S1*). We also scrutinized previous reviews for additional studies. For studies with incomplete data, we tried to contact the corresponding author to obtain further details. The inclusion criteria were: (I) case-control studies related to risk factors of PAL after lung resection and (II) analysis of air leaks at least 5 days in duration. The exclusion criteria were: (I) studies without sufficient data; (II) reviews or meta-analysis; (III) low-quality publications with an unrepresentative cohort or inadequate methods (*Figure S1*). Two investigators (H Pan and Y Cheng) independently scrutinized the final included studies.

Surgical protocol

The most common anesthesia strategies included of general anesthesia, a central venous catheter, or double-lumen tube. Systemic lymph node dissection was performed for lung cancer in all studies. Two types of mechanical staplers were used to close incomplete fissures (The ECHELON FLEX™ GST System or Endo GIA™ Tri-Staple™). After lung resection, a lung inflation test was performed to determine the presence of a significant air leak; any leaks were repaired by suturing. No biological glue, hemostatic gauze, or other materials were used during surgery. Additionally, one or two 28-Fr chest tubes were then placed after surgery. The indications for the removal of chest tube included: no leakage, drainage volume less than 100–200 mL/24 h (or 2–4 mL/kg/24 h). According to Cerfolio classification of air leaks (22,23), assessment of air leak are classified in 4 grade. If there was an air leak greater than forced expiratory (FE) leak on the classification system after surgery, biologic sealants were routinely used for treatment.

Data collection

Several clinical data were extracted from the included studies: basic patient characteristics, pulmonary function test, intraoperative factors, postoperative factors, postoperative pathology and malignant tumor stage (*Table 1*). The extent of pleural adhesion was obtained from the surgical records and judged directly by the surgeon. Early postoperative drainage was defined as the sum of pleural fluid for the 3 days after surgery. Stapling length was calculated by the number of staples multiplied by the length of a staple.

Two investigators (H Pan and Y Cheng) extracted the data from the eligible studies independently. Disagreements between investigators were resolved by discussion with the research team. Odds ratios (OR) with associated 95% confidence intervals (CIs) of each risk factor were extracted from eligible studies. Finally, study quality was assessed by two investigators (*Table S2*).

Table 1 Basic characteristics and results of univariable analysis in PAL and non-PAL patients

Variable	PAL	Non-PAL	P
Total, n (%)	54 (11.0)	439 (89.0)	–
Age (years)	61.1±10.2	55.4±10.6	<0.001
Male, n	45	296	0.017
Smoking (pack-year)	30.4±30.3	18.6±25.1	0.001
BMI (kg/m^2)	22.4±2.8	23.3±3.0	0.042
Comorbidities, n			
Tuberculosis	10	60	0.120
Diabetes	6	39	0.775[a]
Chemotherapy	4	22	0.978[a]
Lung function			
FEV1 (L)	2.26±0.58	2.47±0.60	0.014
FVC (L)	3.31±0.69	3.21±0.73	0.358
%FEV1 (%)	83.8±20.2	90.6±17.2	0.009
FEV1/FVC (%)	68.4±11.8	77.3±9.9	<0.001[b]
MVV (L)	88.9±23.6	98.1±29.1	0.032
%MVV (%)	91.1±26.2	100.0±24.0	0.016
Intraoperative information			
Upper lobectomy, n	28	222	0.910[a]
Right-sided operation, n	38	261	0.121
Pleural adhesion, n	41	149	<0.001
Device type, n			0.893
ECHELON	29	240	
Endo GIA	25	199	
Stapling length (mm)	210.0±83.4	145.4±76.9	<0.001
Postoperative information			
Drainage (mL)	846.8±363.5	647.2±269.2	<0.001
Albumin (g/L)	32.0±3.7	33.6±3.7	0.003
Leukocyte (10^9/L)	12.8±3.9	12.7±3.5	0.876
Hemoglobin (g/L)	116.6±18.3	123.6±15.7	0.002
Malignant tumor, n	40	323	0.938
Disease stage, n			0.787
I	18	164	
II	5	46	
III	13	92	
Hospital stay (days)	16±6.0	8±3.7	<0.001[b]

Results are expressed as mean ± SD or as integers. [a], Fisher's exact test; [b], Mann-Whitney U-test. BMI, body mass index; FEV1, forced expiratory volume in 1 second; %FEV1, percentage of predicted value of forced expiratory volume in 1 second; FVC, functional vital capacity; MVV, maximum ventilatory volume; PAL, prolonged air leak.

Table 2 Results of logistic regression analysis

Variables	OR	95% CI	Coefficient	P
Age >60 years	1.830	0.902–3.712	0.604	0.094
BMI <22 kg/m^2	1.922	0.962–3.838	0.653	0.064
Smoking >15 pack-year	2.499	1.200–4.999	0.896	0.014
FEV1/FVC <76%	2.517	1.241–5.106	0.923	0.011
Right-sided operation	1.387	0.674–2.851	0.327	0.374
Pleural adhesion	2.361	1.518–3.671	0.859	<0.001
Stapling length >158 mm	3.845	1.828–8.084	1.357	<0.001
Early postoperative drainage >800 mL	3.030	1.503–6.111	1.109	0.002
Albumin <33.6 g/L	1.003	0.476–2.112	0.003	0.994
Hemoglobin <125 g/L	1.429	0.661–3.091	0.357	0.364

BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, functional vital capacity; OR, odds ratio.

Statistical analysis

Categorical variables were compared by either the χ^2 test or Fisher's exact test, while continuous variables were compared using the *t*-test or Mann-Whitney U-test. Receiver operating characteristic (ROC) curve were used to obtain cutoff values and areas under the ROC curves (AUC). Variables with less than a 0.05 significance level in the univariate analysis were entered into the logistic regression for multivariate analysis. Continuous variables were converted into binary variables based on their respective cutoff values. All data were analyzed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). According to their contribution, the corresponding variables of each factor were analyzed in the regression model and a nomogram point scoring system was built as a predictive model. A concordance index (C-index) and the calibration curve were constructed to measure the performance of the nomogram. R version 3.4.3 (http://www.r-project.org/) was used to construct the nomogram.

For binary variables, we calculated pooled ORs and 95% CIs; pooled weighted mean differences (WMDs) were calculated for continuous variables. Each risk factor in the meta-analysis must have been evaluated in at least three included studies. We used the Q-test and I^2 index (24) to assess the heterogeneity. We then assessed publication bias with Egger's test. Subgroup analyses were performed to identify heterogeneity. The meta-analysis was completed with StataSE version 12.0 (Stata Corp., Texas, USA).

All statistical tests were two-sided, and a P value of <0.05 was considered to be statistically significance.

Results

A total of 493 patients were included in this study. Basic characteristics and univariate analysis are shown in *Table 1*. The occurrence of PAL was 11.0% (54/493), patients with complication of PAL had significantly longer postoperative hospital stays (16±6.0 *vs.* 8±3.7, P<0.001). Age, gender, smoking, BMI, pulmonary function, pleural adhesion, stapling length, drainage, albumin, hemoglobin also showed significant statistical differences. Since males accounted for 96% of smoking patients (226/235), we reanalyzed the effect on PAL for smoking male patients (P=0.044). For this reason, the gender was not included in the later multivariate analyses. ROC curve indicated that forced the first second of expiratory volume/forced vital capacity (FEV1/FVC) was an optimal variable of pulmonary function (AUC =0.72, *Table S3*). Excluding cases of missing information, a total of 463 patients were included in the logistic regression model. The results of regression analysis are shown in *Table 2*. Multivariate analyses indicated that age, smoking, FEV1/FVC, pleural adhesion, stapling length and drainage were factors significantly associated with PAL. All independent factors analyzed in this study and three factors found significant in previous study (BMI, smoking, right-side operation) were integrated into the construction of a nomogram (*Figure 1*). The C-index for PAL prediction was 0.858 and the calibration curve showed good consistency between prediction and observation (*Figure 2*).

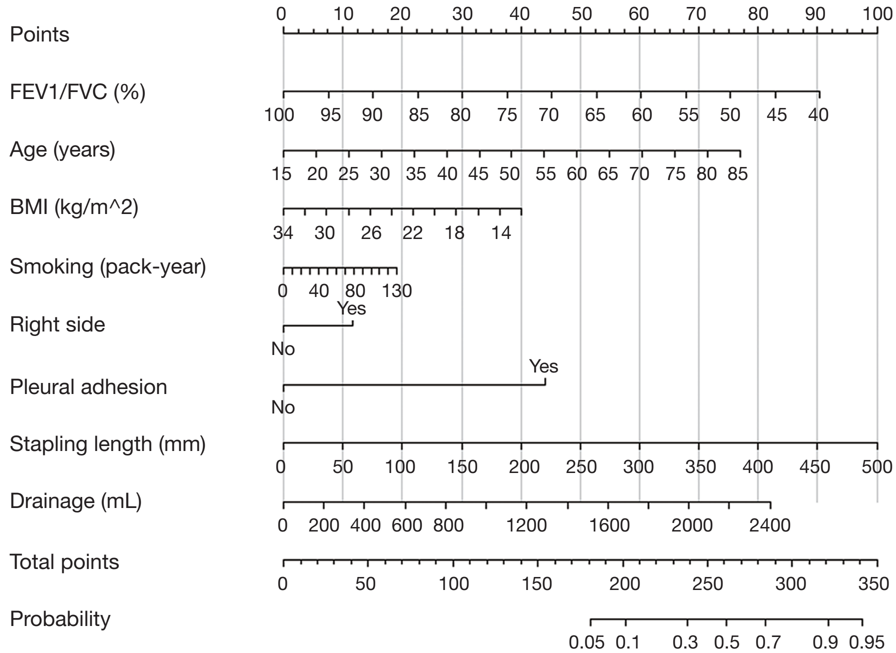

Figure 1 Nomogram predicting PAL after VATS lung resection. For one patient, the corresponding point is derived from each variable axis. The sum of points is located on the Total Points axis, corresponding to a probability below. PAL, prolonged air leak; VATS, video-assisted thoracic surgery.

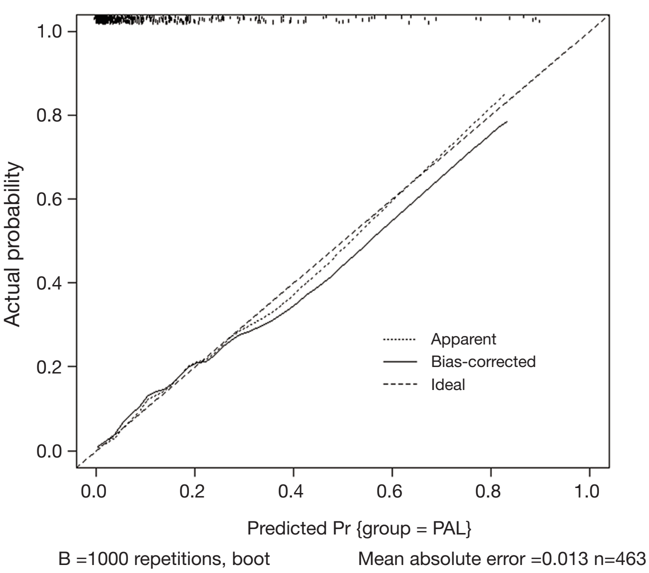

Figure 2 Calibration curve predicting PAL. X-axis: nomogram-predicted probability of PAL; y-axis: actual probability of PAL. The apparent curve and bias-corrected curve is close to the ideal curve indicating a good prediction ability. PAL, prolonged air leak.

After searching and screening, there were 17 eligible studies for meta-analysis, including 2 multicenter database analyses, 2 prospective studies and 13 retrospective studies (*Table S4*). Variability in study design and risk of bias may lead to substantial heterogeneity. Therefore, the results of meta-analysis were shown in *Table 3*, which were based on random-effects model. Fixed-effect meta-analysis were presented in *Table S5*. We calculated pooled unadjusted ORs for 12 risk factors. Factors included male, smoking, %FEV1, FEV1/FVC, and malignancy had statistical significance and heterogeneity was acceptable (I^2 =0–41.5%). To avoid studies with large sample sizes from dominate the overall results, we re-analyzed the corresponding factors after removing Rivera's (7) study. The results were not significantly changed, except for the obvious difference with regards to the right-sided operation factor. Egger's test did not indicate any significant publication bias in this analysis. Subgroup analyses stratified by region showed that upper lobectomy was a risk factor for PAL in Europe and America, but not in Asia. Furthermore, in subgroup analysis

Table 3 Results of meta-analysis

Variable	Region	Patients, n	OR	95% CI	P	Heterogeneity		Egger's test	
						I^2 (%)	P	t	P
Male	Overall	13	1.75	1.52–2.01	<0.001	41.5	0.058	2.19	0.051
	Europe & Americas	8	1.52	1.39–1.67	<0.001	0	0.778		
	Asia	5	2.39	1.93–2.96	<0.001	0	0.695		
FEV1/FVC <70%	Overall	6	2.41	1.93–3.01	<0.001	25.7	0.242	0.24	0.822
	Europe & Americas	3	2.00	1.59–2.52	<0.001	0	0.800		
	Asia	3	3.09	2.35–4.06	<0.001	0	0.735		
Right-sided	Overall	9	1.36	1.10–1.69	0.004	54.5	0.025	1.47	0.191
	Europe & Americas	5	1.31	1.02–1.68	0.034	54.6	0.066		
	Asia	4	1.43	0.94–2.19	0.098	58.1	0.067		
Upper lobectomy	Overall	11	1.49	1.13–1.96	0.005	84.3	<0.001	–0.93	0.380
	Europe & Americas	6	2.03	1.85–2.24	<0.001	0	0.474		
	Asia	5	1.04	0.90–1.21	0.601	0.4	0.404		
Pleural adhesion	Overall	9	2.10	1.68–2.62	<0.001	60.9	0.009	0.36	0.73
	Europe & Americas	4	1.79	1.25–2.56	0.002	61.6	0.050		
	Asia	5	2.42	1.72–3.39	<0.001	59.6	0.042		
Smoking	Overall	6	1.83	1.45–2.31	<0.001	0	0.642	7.93	0.001
Chemotherapy	Overall	5	0.97	0.73–1.30	0.845	0	0.732	0.98	0.431
Diabetes	Overall	6	0.85	0.67–1.09	0.209	0	0.797	0.44	0.688
%FEV1 <80%	Overall	5	1.73	1.50–2.00	<0.001	0	0.503	1.25	0.299
Thoracotomy	Overall	4	2.30	1.61–3.29	<0.001	81.2	0.001	–0.40	0.726
Lobectomy	Overall	5	2.24	1.20–4.21	0.012	91.3	<0.001	1.81	0.168
Malignancy	Overall	4	1.53	1.38–1.69	<0.001	0	0.481	–0.54	0.684

CI, confidence interval; FE, fixed effect; FEV1, forced expiratory volume in 1 second; %FEV1, percentage of predicted value of forced expiratory volume in 1 second; FVC, functional vital capacity; OR, odds ratio; RE, random effect.

by region heterogeneity disappeared (*Figure 3*). Subgroup analyses of other factors were consistent with the overall results (*Figure 4*).

Age and BMI were analyzed using pooled WMD. As part of age subgroup analysis (*Figure 4A*), 8 studies were included to yield a pooled WMD of 2.17 (P=0.004, 95% CI: 0.86–3.48, I^2 =66.7%). In BMI analysis (*Figure S2*), 7 studies were included and pooled WMD was −1.35 (P<0.001, 95% CI: −1.81 to −0.89, I^2 =60.6%). Subgroup analysis did not reduce the heterogeneity, but consistency was reflected in the forest plot.

In subgroup analysis using the definition of PAL, heterogeneity did not decrease and there was no difference in results between subgroups (*Table S6*).

Discussion

The risk factors of PAL after lung resection have been the subject of previous study, with many prediction models proposed. However, the relevant independent risk factors in such a clinical situation remain controversial. Pre- and intra-operative identification of high-risk patients contributes the success of intraoperative interventions such as pleural tenting, prophylactic pneumoperitoneum, sealing material and the buttressing of staple lines (25). However, few studies have examined postoperative risk factors of PAL which could

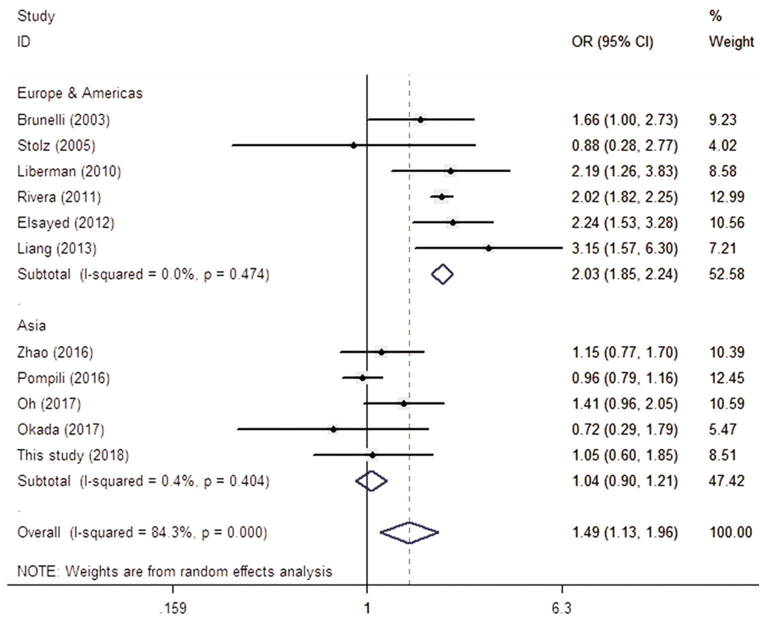

Figure 3 Forest plot of the relationship between upper lobectomy and PAL. PAL, prolonged air leak.

help determine interventional indications. There may be yet undiscovered associations and geographical differences among various clinical factors and PAL.

Consistent with previous study (4,7,10,11,14,16), we found that poor pulmonary function, smoking, intraoperative pleural adhesion were all risk factors for PAL. Additionally, three variables of pulmonary function (%FEV1, FEV1/FVC, %MVV) were found to be potential predictors in preliminary analysis. Using the ROC curve method, we found that, unlike previous studies, FEV1/FVC had better identification ability than %FEV1 (AUC =0.72). A possible explanation for this finding might be that patients undergoing lobectomy required acceptable pulmonary function. In our study, 99% (407/412) of lobectomy patients had %FEV1 >50%. Therefore FEV1/FVC could be indicative of airflow obstruction and elastic recoil pressure (26,27). According to the result of meta-analysis, pulmonary function was the most consistent risk factor for postoperative PAL.

Meta-analysis also showed that patients with the older age, male gender, and low BMI were more likely to have PAL. In China, males account for 90.1% of all smokers in the general population (28), and this proportion was up to 96% in our center; hence, gender variable was not included in our regression analysis. Additionally, age and BMI showed a non-significant trend in our regression analysis (P=0.094, 0.064, respectively). Pulmonary function results were adjusted for age as they are representative. Low BMI may imply poor nutritional status and obesity was found to be protective against PAL, which was shown to be due to a variation in respiratory rates and tidal volumes in obese patients (10).

We identified upper lobectomy as a risk factor for PAL. Interestingly, subgroup analysis indicated that this surgical procedure was of significance in European and North American studies but not in Asian ones. This difference might be due to differences in thorax morphology and pulmonary anatomy among ethnic groups. Researchers believe that residual pleural spaces with incomplete visceral-parietal apposition in the upper thoracic cavity account for air leakage after upper lobectomy (1); however, this cannot completely explain our results. Currently there is no research to confirm this interpretation and thus should be an area of interest in the future.

Extensive adhesions increase parenchymal injury during surgery. However, as this factor is assessed by subjective judgment, the literature remains inconsistent. Clearly on the forest plot (*Figure 4D*), Gilbert's (11) result was the main source of heterogeneity, as the other seven studies showed good consistency. Pleural adhesion may be a good predictor of postoperative PAL when strictly defined. Lobectomy, right-side operation, malignancy and thoracotomy were also found to be significant upon analysis, but were not convincing enough, because of the obvious heterogeneity or

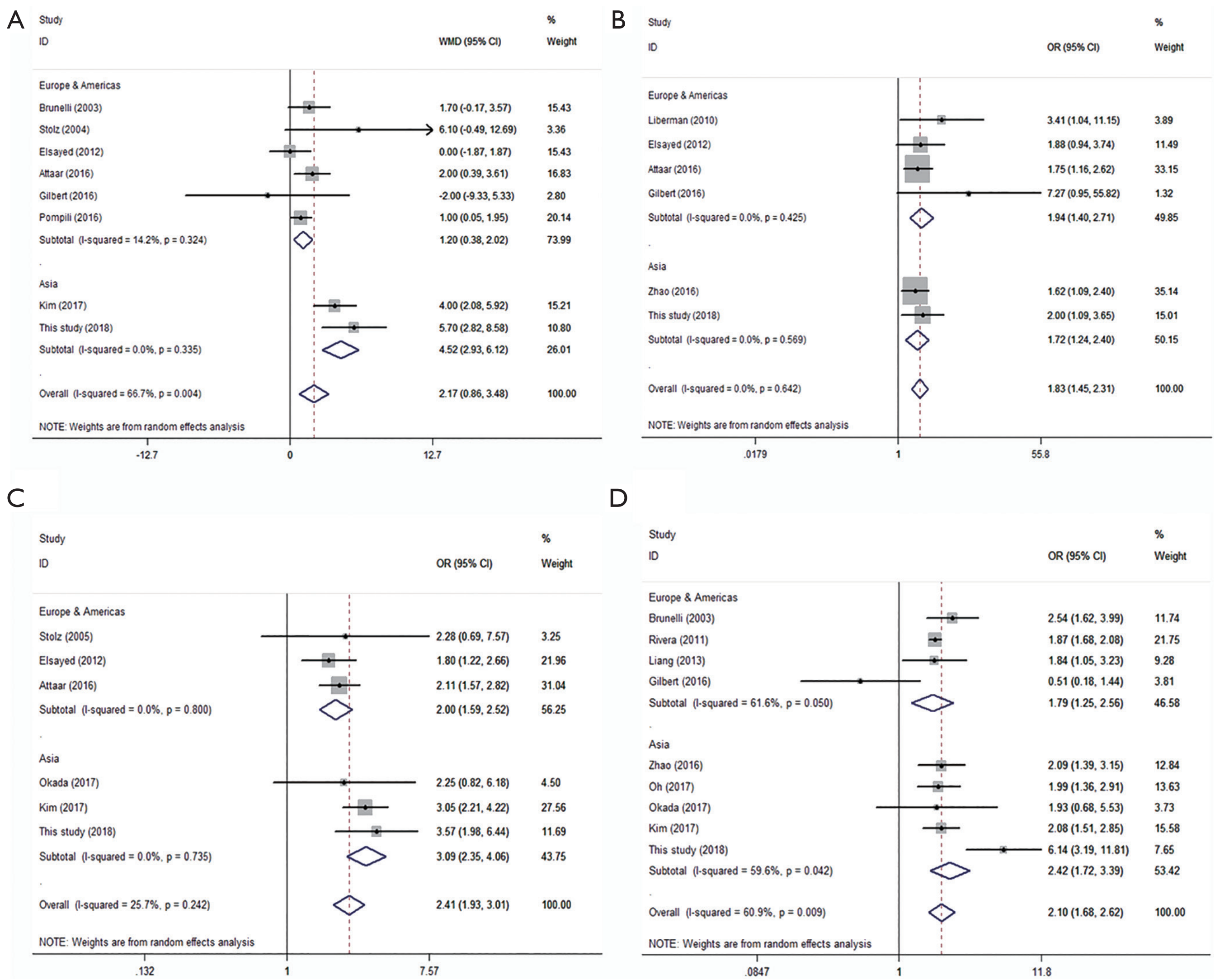

Figure 4 Forest plot of several previously identified critical clinical factors. Relationship between PAL and (A) age, (B) smoking, (C) FEV1/FVC, and (D) pleural adhesion. PAL, prolonged air leak; FEV1/FVC, forced the first second of expiratory volume/forced vital capacity.

the limited number of studies.

Moreover, pulmonary fissure was another risk factor discussed in past (5,14), but no accurate measurement of such a complication has been proposed. To control for bias, we calculated the stapling length as an objective measurement for incomplete fissures of lung. We found that stapling length was an independent risk factor for PAL. Future studies should take steps to be scrutinize this factor.

Postoperative factors could be assessed for the timing of intervention after air leak. Okada *et al.* (12) and Oh *et al.* (16) emphasized the importance of quantifying air leakage in the postoperative period. Postoperative albumin, leukocyte, hemoglobin and three days postoperative drainage was not previously considered clinically relevant. However, our data indicated that a large amount of early postoperative drainage was related to the occurrence of PAL, presumably because more pleural effusion would hamper the healing of alveolar fistula and the formation of pleural adhesions.

Several predictive models have been proposed for PAL, including scoring systems (6,11,15,29) based on two or three risk factors (e.g., %FEV1, male, BMI, pleural adhesions, smoking) which could be further divided into demographic features and pulmonary function. However, the predictive power of these models has been unsatisfactory. At present, nomograms have been applied widely and have proven to be more accurate than the conventional scoring systems (30). Attaar *et al.* (10) derived a nomogram for PAL with good discriminatory accuracy in 2016, but they ignored postoperative factors. In contrast, we drew a nomogram based on the significant variables in multivariate analysis and, while using the previous risk models from Attaar *et al.* (10) and Gilbert *et al.* (11) as references, right-side operation and BMI variables were also included. Our nomogram, with 86% discriminatory accuracy and a calibration curve close to the ideal, had better predictive value than previous studies. Notably, we were not able to validate other models using our data because of significant differences in baseline characteristics. Application of a predictive model widely or across geographical regions should be done cautiously before a multi-center, large sample size study come out.

This study provided the first meta-analysis to identify the relationship between various factors and PAL. Subgroup analysis was performed to minimize heterogeneity, as well as to explore regional differences in risk factors. VATS has been widely accepted as part of thoracic surgery because it is minimally invasion and requires smaller incisions (31,32). Unfortunately, the difference between thoracotomy and VATS was not analyzed in our meta-analysis because only four studies focused on VATS. Nonetheless, our results involving thoracotomy and VATS were meaningful and convincing, even with some heterogeneity.

There are limitations to our study that should be noted. First, in order to minimize the differences in baseline characteristics, we did not analyze all types of pulmonary surgery (lung volume reduction surgery and bulla resections were excluded). Secondly, our prediction model requires prospective external validation, which will be done as part of our follow-up research. Finally, only a few studies were included in the meta-analysis for some factors (e.g., lobectomy, chemotherapy, malignancy) and detailed data was unavailable in some studies.

Conclusions

Taken together, in order to speed patient recovery and decrease hospital stay lengths, preoperative, intraoperative, and postoperative factors should be taken into account and analyzed for prevention and early treatment of PAL after VATS lung resection. Researchers should also pay close attention to the differences in surgical risk factors among ethnic groups when using a predictive model.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This project was reviewed and approved by the Ethics Committee of the Xiangya Hospital, Central South University (IRB number: 2017121009), and informed consent was waived as it was a retrospective study.

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Supplementary

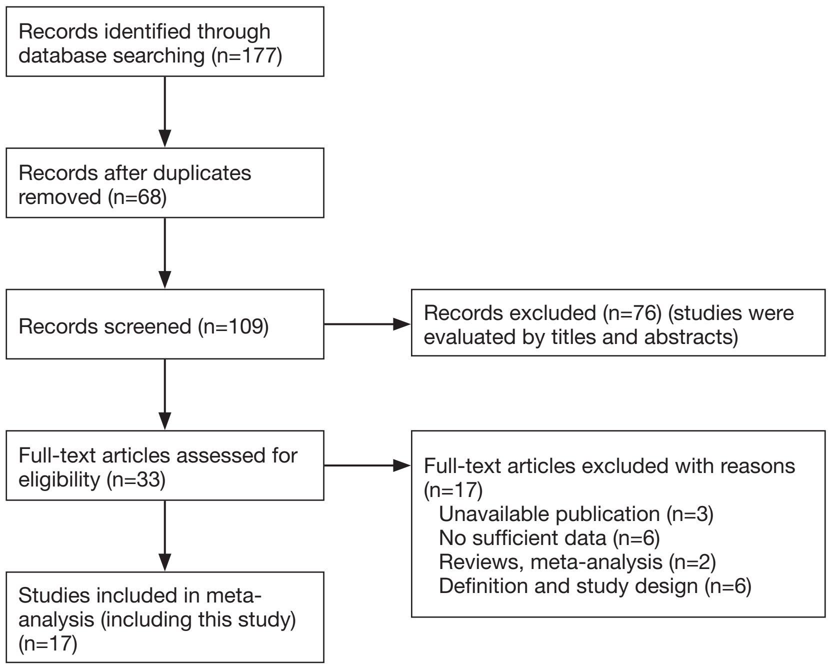

Figure S1 Study flow diagram and selection of included studies with specific reasons.

Table S1 Search strategy for PubMed (publication date to 2017/11/01)

(I)	"Pneumonectomy"[Mesh]
(II)	pulmonary lobectomy[Title/Abstract]
(III)	pulmonary resection[Title/Abstract]
(IV)	lung resection[Title/Abstract]
(V)	1 OR 2 OR 3 OR 4
(VI)	PAL[Title/Abstract]
(VII)	air leak[Title/Abstract]
(VIII)	6 OR 7
(IX)	risk factors[Title/Abstract]
(X)	predict*[Title/Abstract]
(XI)	predictor[Title/Abstract]
(XII)	prediction[Title/Abstract]
(XIII)	9 OR 10 OR 11 OR 12
(XIV)	5 AND 8 AND 13

Table S2 Quality evaluation of case-control studies by Newcastle-Ottawa Scale (NOS)

Years	Author	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate
1997	Abolhoda	★	☆	★	☆	★	★	☆	☆
2003	Brunelli	★	★	★	☆	★	★	★	☆
2004	Stolz	★	★	☆	★	★	★	★	☆
2010	Liberman	★	★	★	★	☆	★	★	☆
2010	Petrella	★	★	★	☆	★	★	☆	☆
2011	Lee	★	★	★	★	★★	★	★	☆
2011	Rivera	★	★	★	☆	☆	★	☆	★
2012	Elsayed	★	★	★	☆	★	★	★	☆
2013	Liang	★	★	★	☆	★	★	★	☆
2016	Attaar	★	★	★	☆	★★	★	★	☆
2016	Gilbert	★	★	★	☆	★	★	★	☆
2016	Okada	★	★	★	☆	★	★	★	☆
2016	Pompili	★	★	★	☆	★	★	★	★
2017	Oh	★	★	★	☆	★	★	★	☆
2017	Kim	★	★	★	★	★	★	★	★
2017	Zhao	★	★	★	★	★	★	★	★
2018	This study	★	★	★	★	★★	★	★	☆

★ , score 1 in this item; ☆ , no score for this item.

Table S3 ROC curve of significant variables

Variable	Sensitivity	1-specificity	Cutoff	Youden index	AUC
%FEV1	0.66	0.42	84	0.241	0.60
FEV1/FVC	0.59	0.25	76	0.344	0.72
%MVV	0.75	0.56	83.5	0.187	0.59
BMI	0.65	0.44	22	0.305	0.60
Age	0.69	0.41	60	0.281	0.67
Smoking	0.65	0.41	15	0.243	0.62
Stapling length	0.77	0.42	158	0.343	0.72
Drainage	0.50	0.20	803	0.001	0.66
Albumin	0.55	0.27	33.6	0.276	0.62
Hemoglobin	0.48	0.29	125	0191	0.60

AUC, areas under the ROC curves; BMI, body mass index; FEV1, forced expiratory volume in 1 second; %FEV1, percentage of predicted value of forced expiratory volume in 1 second; FVC, functional vital capacity; MVV, maximum ventilatory volume; ROC, receiver operating characteristic.

Table S4 Characteristics of eligible studies in meta-analysis

Years	Author	Country	Methods	Definition (days)*	Case number	Morbidity, n (%)	Surgery	Variables included in this meta-analysis
1997	Abolhoda	USA	SCRS	7	100	26 (26.0)	Thoracotomy	Gender, chemotherapy
2004	Brunelli	Italy	SCRS	7	588	80 (15.6)	Thoracotomy	Age, diabetes, chemotherapy, upper lobectomy, right side, pleural adhesion
2004	Stolz	Czech	SCRS	7	134	13 (9.7)	Thoracotomy	Age, BMI, gender, %FEV1, upper lobectomy, FEV1/FVC
2010	Liberman	USA	SCRS	5	1,393	78 (5.6)	Thoracotomy	Gender, smoking, upper lobectomy, right side
2010	Petrella	Italy	SCRS	5	241	58 (24.1)	Thoracotomy	Gender, right side
2011	Lee	Canada	SCRS	7	580	82 (14.1)	Thoracotomy and VATS	Pleural adhesion
2011	Rivera	France	Database analysis	7	24,113	1,655 (6.9)	Thoracotomy and VATS	Gender, smoking, upper lobectomy, right side, pleural adhesion, pathology, lobectomy
2012	Elsayed	UK	SCRS	6	1,911	129 (6.7)	Thoracotomy	Age, BMI, gender, %FEV1, upper lobectomy, lobectomy, FEV1/FVC
2013	Liang	Canada	SCPS	5	352	65 (18.0)	Thoracotomy	%FEV1, upper lobectomy, right side, pleural adhesion, pathology, lobectomy, FEV1/FVC
2016	Attaar	USA	MCRS	5	2,317	200 (8.6)	Thoracotomy and VATS	Age, BMI, gender, %FEV1, smoking, right side, pathology, chemotherapy, FEV1/FVC
2016	Gilbert	Canada	SCPS	7	225	18 (8.0)	NA	Age, BMI, gender, %FEV1, smoking, pleural adhesion, upper lobectomy
2016	Okada	Japan	SCRS	5	146	23 (16.0)	VATS	Gender, smoking, diabetes, right side, upper lobectomy, pleural adhesion, diabetes, FEV1/FVC
2016	Pompili	UK	Database analysis	7	5,069	504 (9.9)	VATS	Age, BMI, gender, %FEV1, right side, upper lobectomy
2017	Oh	Korea	SCRS	5	720	135 (18.8)	Thoracotomy and VATS	Gender, %FEV1, right side, pleural adhesion, upper lobectomy, chemotherapy
2017	Kim	Korea	SCRS	5	1,060	198 (18.7)	Thoracotomy and VATS	Age, BMI, gender, %FEV1, FEV1/FVC
2017	Zhao	China	SCRS	5	1,051	111 (10.6)	VATS	Gender, age, smoking, pleural adhesion, right side, upper lobectomy, lobectomy
2018	This study	China	SCRS	5	493	54 (10.8)	VATS	Age, BMI, gender, %FEV1, smoking, right side, pleural adhesion, upper lobectomy, lobectomy, FEV1/FVC

*, the number of days to define prolonged air leak. BMI, body mass index; FEV1, forced expiratory volume in 1 second; %FEV1, percentage of predicted value of forced expiratory volume in 1 second; FVC, functional vital capacity; MVV, maximum ventilatory volume; MCRS, multi-center retrospective study; NA, not available; SCRS, single center retrospective study; SCPS, single center prospective stud; VATS, video-assisted thoracoscopic surgery.

Table S5 Results of meta-analysis based on fixed-effect model

Variable	Region	Patients, n	OR	95% CI	P
Male	Overall	13	1.64	1.51–1.78	<0.001
	Europe & Americas	8	1.53	1.39– 1.67	<0.001
	Asia	5	2.41	1.94–2.98	<0.001
FEV1/FVC <70%	Overall	6	2.39	2.00–2.84	<0.001
	Europe & Americas	3	2.00	1.60–2.52	<0.001
	Asia	3	3.09	2.35–4.05	<0.001
Right-sided	Overall	9	1.28	1.13–1.44	<0.001
	Europe & Americas	5	1.22	1.06–1.40	0.007
	Asia	4	1.48	1.15–1.91	0.002
Upper lobectomy	Overall	11	1.68	1.55–1.82	<0.001
	Europe & Americas	6	2.03	1.85–2.24	<0.001
	Asia	5	1.04	0.90–1.21	0.595
Pleural adhesion	Overall	9	1.96	1.80–2.15	<0.001
	Europe & Americas	4	1.88	1.69–2.08	<0.001
	Asia	5	2.28	1.88–2.78	<0.001
Smoking	Overall	6	1.88	1.49–2.38	<0.001
Chemotherapy	Overall	5	0.96	0.72–1.28	0.862
Diabetes	Overall	6	0.84	0.66–1.08	0.177
%FEV1 <80%	Overall	5	1.73	1.50–2.00	<0.001
Thoracotomy	Overall	4	2.44	2.14–2.79	<0.001
Lobectomy	Overall	5	2.24	1.20–4.21	0.012
Malignancy	Overall	4	1.53	1.38–1.70	<0.001

CI, confidence interval; FE, fixed effect; FEV1, forced expiratory volume in 1 second; %FEV1, percentage of predicted value of forced expiratory volume in 1 second; FVC, functional vital capacity; OR, odds ratio; RE, random effect.

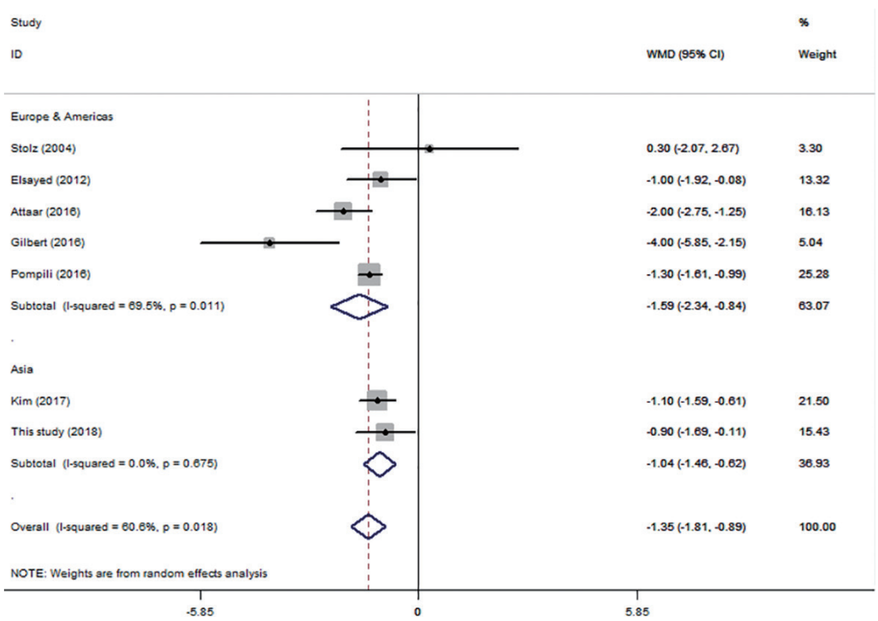

Figure S2 Forest plot of the relationship between BMI and prolonged air leak. BMI, body mass index.

Table S6 Subgroup analysis by the definition of prolonged air leak based on random-effects model

Variable	Definition* (days)	Numbers	OR	95% CI	P	Heterogeneity	
						I^2 (%)	P
Male	Overall	13	1.75	1.52–2.01	<0.001	41.5	0.058
	7	5	1.55	1.40–1.71	<0.001	0	0.860
	5	7	2.00	1.50–2.66	<0.001	62.1	0.015
Upper lobectomy	Overall	11	1.49	1.13–1.96	0.005	84.3	<0.001
	7	5	1.35	0.84–2.16	0.209	71.9	0.014
	5	5	1.48	1.05–2.07	0.024	75.7	0.001
Pleural adhesion	Overall	9	2.10	1.68–2.62	<0.001	60.9	0.009
	7	3	1.69	1.01–2.81	0.044	74.4	0.020
	5	6	2.30	1.73–3.08	<0.001	51.7	0.066
Right side	Overall	9	1.36	1.10–1.69	0.004	54.5	0.025
	7	2	1.05	0.88–1.24	0.611	0	0.933
	5	7	1.54	1.24–1.92	<0.001	27	0.222

*, the number of days to define prolonged air leak.