Aggregate risk score for predicting mortality after surgical biopsy for interstitial lung disease†

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Abstract

In order to develop a practical risk score for 90-day mortality following surgical lung biopsy (SLB) for interstitial lung disease (ILD) we reviewed 311 consecutive patients undergoing SLB for ILD between 2002 and 2009. Postoperative complication, 30-day and 90-day mortality rates were 11.5%, 9% and 10.6% respectively. Univariable and multivariable analyses, validated by bootstrap statistics, were used to identify factors associated with 90-day mortality. A scoring system was developed by proportionally weighting the regression coefficients of the significant predictors of 90-day mortality: age >67 ($P < 0.0001$, weighted score 1.5), preoperative intensive care unit (ICU) admission ($P = 0.006$, weighted score 2), immunosuppressive treatment ($P = 0.004$, weighted score 1.5) and open surgery ($P = 0.03$, weighted score 1). Patients were grouped in four classes showing incremental risk of death at 90 days: class A, score 0 (2%); class B, score 1–2 (12%); class C, score 2.5–3 (40%); class D, score >3 (86%); $P <0.0001$. SLB entails a considerable surgical risk with an overall 90-day mortality around 10%. We were able to develop a practical risk score which, if validated by other independent studies, can be easily used to stratify the risk of SLB candidates and assess the cost-effectiveness of this procedure.

Keywords: Interstitial lung disease • Surgical lung biopsy • Risk scores

INTRODUCTION

Interstitial lung disease (ILD) comprises a varied group of processes, which range from acute inflammatory disorders to progressive fibrotic conditions. ILD diagnosis is obtainable using a stepwise and methodical approach including progressively more invasive tests, such as transbronchial biopsy, transthoracic needle biopsy and, finally, surgical lung biopsies (SLB), either open or thoracoscopic [1].

The current guidelines and classification of ILD support SLB for definite diagnosis of ILD but encourage physicians to balance the benefit carefully against the risks to patients of performing the surgery [2]. Indeed, the decision to perform SLB is based on the likelihood that pathological examination of tissues obtained will yield specific information about the cause of the disease process [3].

The shift from conventional thoracotomy towards video-assisted thoracoscopic surgery (VATS) has favoured the new technique in regard to mortality and hospital stay, increasing the number of patients sent for SLB [4]. However, VATS SLB is not innocuous and, according to recent studies, postoperative mortality ranges from 4.3% to 4.8% [5]. In some subgroups of patients, such as immunocompromised patients or patients with severe respiratory failure, this operative mortality rate is substantially higher [6]. In addition, increased quality of both high-resolution

computerized tomography (HRCT) and bronchoscopy has raised the question of the real necessity for SLBs [7–9].

To address this question, we reviewed our SLB database to create a risk score model for mortality that could be useful to ponder risk–benefits in patients with suspected ILD and potential candidates for SLB.

METHODS

This retrospective study included 311 consecutive patients submitted for SLB for suspected ILD in the Mayo Clinic General Thoracic Surgery division between 2002 and 2009. Patients' records and histological specimens were reviewed. The following perioperative variables were initially screened for a possible association with 90-day postoperative mortality by univariable analysis: age, forced expiratory volume in one second (FEV_1)%, forced vital capacity (FVC)%, FEV_1/FVC ratio, diffusing capacity for carbon monoxide (D_{LCO})%, coronary artery disease (CAD), preoperative intensive care unit (ICU) stay, open surgery, immunosuppressive treatment, steroid treatment and number of biopsies >2.

The Shapiro-Wilk normality test was used to assess normal distribution of numeric variables. The unpaired Student's t-test was used for comparison of numeric variables with normal distribution and the Mann-Whitney test for those with non-normal distribution. The chi-square or Fisher's exact tests were used for categorical variables, as appropriate. Those variables with a $P <0.1$ were used as independent predictors in a stepwise logistic

regression analysis. Logistic regression was validated using bootstrap statistics with 1000 samples of the same number of patients as the original dataset. Predictors resulting in significantly more than 50% of bootstrap samples were regarded as stable and included in the final model.

For the purpose of building the score, a threshold effect was sought for significant numeric variables by using receiver operating characteristic (ROC) analysis. The scoring system was then built by proportionally weighting the regression coefficients; assigning one point to the factor with the smallest effect.

The final score for each patient was determined by the sum of the individual factors. All statistical tests were two-tailed, with a significance level of 0.05. Stata™ 9.0 statistical software (Stata Corp., College Station, TX, USA) was used for the analysis.

RESULTS

A total of 311 patients were analysed. The average age at diagnosis was 60.9 (Standard Deviation [SD] 14; range 18–91). The gender distribution was 164 males (52.7%) and 147 females (47.3%). Smoking history showed 143 non-smokers (46%), 30 current smokers (9.6%) and 138 past smokers (44.4%).

Major comorbidities were present in 91 patients (29.3%); ischaemic heart disease in 67 (21.5%), arrhythmia in 24 (7.7%) and chronic renal failure in 23 (7.4%).

Ten patients (3.2%) had undergone a prior transplant: four for bone marrow transplantation and six for solid organ transplant.

Seventy-eight patients (25%) were on steroids and 26 patients (8.4%) were immunosuppressed at the time of the SLB.

All the patients analyzed had undergone HRCT before SLB. Bronchoscopy had been carried out in 202 patients (65%). A pulmonary function test was done in 259 patients (83.3%). The mean values were as follows: FEV_1 = 70.2% (SD 16.3%); FVC = 70.1% (SD 16%); FEV_1/FVC = 79.8% (SD 8.8%) and D_{LCO} = 52.1% (SD 14.7%).

Regarding admission characteristics, 292 patients (93.9%) were hospitalized and 19 patients (6.1%) were in the ICU before the SLB.

Mortality rates were: SLB 30-day operative mortality, 28 patients (9%); SLB 9-day mortality, 33 patients (10.6%).

The types of operation were: open SLB in 32 patients (10.3%) and VATS in 279 patients (89.7%). Reasons for open SLB were: adhesions in 27 subjects (84%) and patient unable to tolerate single lung ventilation in five (16%). No intraoperative complications were reported.

The mean number of biopsies performed per patient was 2.05 (SD 0.6). One biopsy was performed in 50 (16%), two in 198 (63.7%), three in 59 (19%) and four in four subjects (1.3%).

The mean length of stay was 2.5 days. Twenty-five (8%) patients were transferred to another department after the SLB.

Histopathological diagnosis was definitive (specific) in 232 patients (74.6%) and descriptive (non-specific) in 76 (25.4%). The most frequent diagnoses were idiopathic pulmonary fibrosis 122 patients (39%), cryptogenic organising pneumonia in 31 (10%) and respiratory bronchiolitis ILD in 16 (5%) (Table 1).

There were postoperative complications in 36 patients (11.5%) (Table 2). The most frequent complications were (i) acute exacerbation for respiratory failure (26.1%), (ii) postoperative need for intensive care (not already in ICU) (22.7%), (iii) requirement for intubation (not already intubated) (13.6%) and (iv) prolonged air leakage (>7 days) (10.2%).

Table 1: Histological diagnosis

Histology	No. of patients
UIP/Idiopathic pulmonary fibrosis	122 (39.2%)
Cryptogenic organising pneumonia	31 (10%)
Respiratory bronchiolitis interstitial lung disease	16 (5.1%)
Nonspecific interstitial pneumonia	13 (4.2%)
Hypersensitivity pneumonitis	12 (3.9%)
Lymphoma	12 (3.9%)
Acute interstitial pneumonia	10 (3.2%)
Sarcoidosis	10 (3.2%)
Infection	10 (3.2%)
Others	60 (19.3%)

Table 2: Type of complications

Respiratory failure (acute exacerbation)	23 (26.1%)
Required ICU (not already in ICU)	20 (22.7%)
Required intubation (not already intubated)	12 (13.6%)
Prolonged air leakage (>7 days or Heimlich)	9 (10.2%)
Pneumothorax	5 (5.7%)
Required tracheostomy (not already trached)	2 (2.2%)
Renal failure requiring dialysis	2 (2.2%)
Pneumonia	2 (2.2%)
Haemothorax	1 (1.1%)
Reoperation (bleeding)	1 (1.1%)

Table 3: Death rates adjusted per variable

	Dead 90 days (33 pts)	Alive 90 days (278)	P-value
Age	68.8 (9.7)	59.9 (14.2)	0.0003
FEV_1%	74.8 (17)	69.7 (16)	0.2
FVC%	73.1 (15)	69.8 (16)	0.3
FEV_1/FVC ratio	80.9 (7.8)	79.7 (9)	0.8
D_{LCO}%	51 (15.1)	52.3 (14.6)	0.9
CAD	10	26	0.3
Pre-ICU	9	10	<0.0001
Open surgery	12	20	<0.0001
Immunosuppressive tx	9	17	<0.0001
Steroids tx	12	66	0.1
Number biopsies >2	8	55	0.5

A threshold effect was searched for significant numeric variables by using ROC analysis.

Treatment modifications resulting from the surgical LB results were present in 280 patients (90%): initiation of a new treatment in 216 (77%), change in treatment strategy in 114 (40.7%) and cessation of previous treatment in 19 (6.8%).

Death rates were adjusted per variable. A threshold effect was searched for significant numeric variables by using ROC analysis (Table 3). Age >67 was identified as the best cut-off value for predicting mortality at 90 days (c-index 0.68).

Logistic regression analysis had included the following independent predictors: age >67, pre-ICU, open biopsy and immunosuppressive treatment.

Table 4:   ILD risk score. Classes of risk of death at 90 days

ILD score	Dead		Class
0	3 of 146	2%	A
1	1 of 11	16 of 138 (12%)	B
1.5	14 of 121	"	B
2	1 of 6	"	B
2.5	2 of 7	8 of 20 (40%)	C
3	6 of 13	"	C
>3	6 of 7	86%	D

Chi-square statistic = 71.2, $P < 0.0001$.

All turned out significantly associated with mortality at 90 days: Age >67, $P < 0.0001$ (coeff. 1.95, bootstrap frequency 99%); pre-op ICU admission $P = 0.006$ (coeff. 2.16, bootstrap frequency 88%); immunosuppressive treatment $P = 0.004$ (coeff. 1.7, bootstrap frequency 88%); open surgery $P = 0.03$ (coeff. 1.3, bootstrap frequency 74%).

Each variable was then proportionally weighed according to its regression coefficient, assigning one point to the smallest one (open surgery): open surgery = 1, immunosuppressive treatment = 1.3 (rounded to 1.5), age >67 = 1.5, pre-ICU = 1.7 (rounded to 2).

A model for predicting score was created with scores varying from 0 to 6. Patients were grouped in classes of risk showing an increasing risk of death at 90 days. (Table 4).

DISCUSSION

Interstitial lung disease (ILD) refers to a group of diseases with great diversity in respect of diagnosis, treatment options and prognosis [10]. Although great advances have been achieved employing non-surgical methods like HRCT, broncho-alveolar lavage or transbronchial biopsy, lung tissue is still required for the diagnosis of ILD in approximately a third of patients who do not have a clearly defined environmental exposure or obvious systemic illness that frequently involves the lung [7, 8, 9, 11].

Nevertheless, the role of SLB remains controversial. Despite the benefits obtained in the shift from open LB to VATS-LB, many clinicians are still reluctant to allow patients to undergo surgery without assurances that benefits will overcome risks [6]. Safety and diagnostic yield are physicians' main concerns in SLB for ILD cases.

However, despite these concerns, there is no definitive guideline at present to estimate the surgical risk to these patients; in other words, there is no way to objectively advise the patient and his/her family regarding the real hazards of a diagnostic surgery that cannot be guaranteed to lead to a change in treatment and an improvement in life quality/expectancy.

Looking at the literature, different results regarding the safety of SLB have been published. Some authors have shown that SLB can be performed safely in ILD patients [5–6, 12]. Others have reported the contrary: Utz *et al.* noted that SLB, when performed in subjects with interstitial pulmonary fibrosis (IPF), was associated with a nearly 17% short-term mortality rate [13]. Kramer *et al.* also observed a high risk of death following SLB for the diagnosis of any ILD [14]. Kreider *et al.* reported that VATS lung

biopsy for diagnosis of ILD, even in ambulatory patients, is not an entirely benign procedure [15].

To solve this question—and taking advantage of a large ILD database—we decided to develop a risk model for mortality and use it for patient counselling as well as a perioperative guide for selecting patients. We chose to develop an aggregate score, as it is a simple way to evaluate factors.

Our results showed four classes of risk according to the specific weight of every independent predictor. In this way, class A patients would have a 90-day mortality risk of 2%; class B, 12%; class C, 40% and class D, 86% (Table 4). In daily practice, this means that SLB indication could be fairly done in class A patients, but would not be advisable in class D patients.

Class B and C patients would present the challenging cases. A class B 12% risk, although high, would be acceptable if lung samples could revert in a real benefit. However, a class C 40% risk would require an individualization of the case.

The main limitation of the study is its retrospective nature and the inherent problems of definition and recording of variables and outcomes. Nevertheless, to minimize this problem, all variables' definitions were set *a priori* and data abstraction was performed by a trained surgeon and reviewed by a data manager.

Preoperative ICU stay, which is the factor with the highest score, may be a surrogate for unknown conditions associated with severity of illness. Nevertheless, factors such as older age, immunosuppresive therapy and thoracotomy—all of which were more frequently represented in ICU patients—retained their independent significance after logistic regression.

There may be other independent factors—such as oxygen dependency—that were not consistently reported in the electronic medical records and, given the retrospective nature of the study, were not taken into consideration for the analysis.

Ideally, prospective studies are needed to refine the model. The strengths of the manuscript are that it comes from one centre with standard pathways of care and procedures, its large sample size and the limited number of missing data (near-completeness of the data).

In summary, we were able to develop an aggregate risk score from a large surgical ILD database that could be useful to estimate risk–benefit in patients with suspected ILD and potential candidates for SLB. Ideally, prospective independent studies are needed to refine and validate the model.

Funding

Conflict of interest: none declared.

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