ERJ Express. Published on November 28, 2018 as doi: 10.1183/13993003.01164-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Fisher JH, Shapera S, To T, *et al*. Procedure volume and mortality after surgical lung biopsy in interstitial lung disease. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.01164-2018).

Procedure volume and mortality after surgical lung biopsy in interstitial lung disease

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Take home message: Higher hospital surgical lung biopsy volume was associated with lower post-operative mortality in patients with ILD. Mortality for non-elective procedures was much higher than elective procedures.

ABSTRACT

Surgical volume outcome relationships are well established but have not been studied in patients with interstitial lung disease (ILD) undergoing surgical lung biopsy. Our study objective was to determine if hospital surgical lung biopsy volume is associated with post-operative mortality in patients with ILD.

A cohort study using administrative, population-based data from Ontario, Canada was performed in adults with ILD who underwent a surgical lung biopsy between 2001 and 2014. The association between yearly hospital surgical lung biopsy volume and 30-day post-operative mortality was assessed using multilevel logistic regression modeling.

3057 surgical lung biopsies for ILD were performed during the study period with a median yearly hospital volume of 73 (IQR 34,143) procedures. 30-day mortality was 7.1%, 20.2% and 1.9% in overall, non-elective and elective patients, respectively. Higher yearly hospital surgical lung biopsy volume was associated with lower odds of 30-day post-operative mortality after adjusting for patient characteristics [OR 0.84 95% CI (0.73, 0.97), p=0.02)], with the association appearing stronger for non-elective procedures [OR 0.84 95% CI (0.69, 1.02), p=0.08) versus OR 0.94 95% CI (0.74, 1.18), p=0.57) in elective procedures].

Higher yearly hospital surgical lung biopsy volume was associated with lower post-operative mortality in patients with ILD with the association appearing to be mainly driven by non-elective cases. Surgical lung biopsy mortality was significantly higher for non-elective cases.

INTRODUCTION

Interstitial lung diseases (ILDs) are a diverse collection of lung diseases with varying epidemiology, clinical course and management [1-3]. Determining the correct ILD subtype is essential for appropriate clinical decision making, patient counseling and meaningful research. The diagnosis of a specific ILD is made based on a combination of clinical, radiologic and sometimes pathologic features [1-4]. Transbronchial biopsy is usually inadequate for definitive diagnosis of ILDs, and the role of cryobiopsy remains controversial, often necessitating a surgical lung biopsy (SLB) when histopathology is required [1-4]. Although SLB is the preferred method of obtaining pathologic samples in patients with ILD, prior research suggests substantial and extremely variable post-operative mortality rates, ranging from 3 to 16.7% at 30 to 60-days [5-8]. The reasons behind such wide variability in SLB mortality in the literature is not well studied to date. Individual studies have found certain patient clinical characteristics to be associated with higher mortality [5-7,9,10], however it is unclear if these can completely account for the mortality variability seen in the literature.

Surgical volume outcome relationships are well established and have been studied for many procedures. A US study of 2.5 million patients undergoing 1 of 14 procedure types (6 cardiovascular and 8 cancer related), found that mortality consistently decreased as procedure volume increased [11]. A Canadian Institute for Health Information commissioned systematic review of 161 volume outcome relationship studies found that higher volume was associated with better outcome in

the majority, although the strength of association varied with procedure type [12]. Several other studies and systematic reviews have similar findings, with higher volumes often being associated with better outcomes [13,14]. The volume outcome relationship has been used as evidence to support the regionalization of care for certain conditions, such as lung cancer, in Canada [11,15].

Interstitial lung diseases comprise a group of complex disorders often cared for in expert centers and hospitals with a higher volume of SLBs are likely to have more experience with these patients. This variation in experience could theoretically result in pre, intra and post-operative care differences between hospitals that influence mortality. Factors including surgeon and anesthetist expertise, patient selection, availability of non-invasive techniques (equipment and staffing) and experience of the post-operative care team may all affect patient outcome. Therefore, the aim of this study was to evaluate the association between hospital SLB volume and post-operative mortality in patients with ILD undergoing SLB using large, population based databases. Our pre-specified hypothesis was that higher hospital SLB volume would be associated with lower 30-day mortality after SLB in patients with ILD.

METHODS

Study Design and Setting

An observational cohort study using Ontario administrative, population-based data available through the Institute for Clinical Evaluative Sciences (ICES) was

performed. Ontario is the single insurer for a universal healthcare system which provides essential healthcare services to Ontario's 13.6 million residents. As a result, healthcare data is collected and maintained of on almost all of the province's residents. This study was approved by the University Health Network, Toronto, Canada institutional review board.

Study population

All patients with a first admission for SLB in Ontario between April 2001 and March 2014 were identified using Canadian Classification of Health Interventions (CCI) and Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP) codes (**Table S1,** online supplement) and screened for eligibility. The beginning of the study period was chosen based on the earliest date that all key study variables were collected in ICES databases. Patients were included if they (1) underwent a SLB, (2) were $\geq$ 18 years of age and (3) had a diagnosis of ILD any time prior to or 1 year after SLB. International Classification of Diseases (ICD) 9 or 10 codes were used to define ILD (**Table S2,** online supplement). Individuals with lung cancer and those with CCI or CCP codes for pneumonectomy, lobectomy and lung transplant were excluded (**Table S3,** online supplement).

Data sources

All data were ascertained by deterministic linkage of ICES databases using unique encrypted patient identifiers (see online supplement for database descriptions).

Exposure, outcome and covariable definitions

The primary exposure was defined as the number of SLBs performed at the hospital in the fiscal year of the index SLB. The primary outcome was 30-day mortality after SLB. Procedure type was defined as open thoracotomy versus video-assisted thoracoscopic surgery (VATS) and determined using CCP codes prior to 2002 and CCI codes 2002 and onwards (**Table S1,** online supplement).

Covariates included in analyses were selected *a priori* based on clinical relevance and prior evidence and included age, sex, Long Term Oxygen Therapy, Charlson Comorbidity Index, socioeconomic status (as determined by income quintile), procedure type, procedure year and non-elective versus elective procedure. Long Term Oxygen Therapy was defined as continuous supplemental oxygen for home use. Charlson Comorbidity Index is a validated tool using patient comorbidities to predict 1-year mortality in adults [16]. Non-elective procedure was defined as a SLB in a patient that was admitted to hospital prior to the procedure date. Patients who were admitted to hospital on the day of SLB were considered elective.

Analysis

Population characteristics by hospital SLB volume were described using mean $\pm$ standard deviation (SD), median [interquartile range (IQR)], frequencies and proportions, as appropriate.

To account for the hierarchical nature of healthcare data and clustering by hospital, multilevel logistic regression was used evaluate the association between

hospital SLB volume and 30-day post-operative mortality. A series of 2 level models were fitted with 3 models specified for the outcome (null, hospital level covariate and hospital and patient level covariates). The intraclass correlation coefficient (ICC) was calculated to determine the amount of variability observed in 30-day mortality attributable to between hospital differences. Hosmer and Lemeshow Goodness-of Fit test and c-statistic were used evaluate model fit. The primary analysis was stratified by non-elective and elective patients and hospital SLB volume was secondarily modeled using quartiles to identify a volume threshold (additional details available in the online supplement). Statistical significance was defined by a two-tailed p-value <0.05. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

3057 patients met study criteria and were included in the final cohort (**Figure 1**). There were 216 deaths within 30-days after SLB, with an overall mortality of 7.1% for the entire study cohort. Mortality rate varied by procedure year but in general remained similar over time (**Figure 2**). 174 deaths occurred in non-elective procedures, with an overall mortality in this group of 20.2%. Amongst elective procedures, there were 42 deaths with an overall mortality of 1.9%. Median time to death was 12 (IQR 6,18) days. Median hospital length of stay was 3 (IQR 2,7) days. Readmission within 30-days of procedure occurred in 331 patients (10.8%).

Patient Characteristics

Patient characteristics overall, stratified by SLB volume quartile and stratified by non-elective and elective procedure are summarized in **Table 1** and **Table S4** in the online supplement. Most patients were older adults with similar proportions of men and women and a low Charlson Comorbidity Index. The 4th (highest) SLB volume quartile had the highest proportion of elective procedures. Age, sex and Charlson Comorbidity Index were similar throughout the study period, however, Long Term Oxygen Therapy appeared to increase over time. Individual comorbidity data is available in the online supplement (**Table S5**).

Procedural details for the overall cohort and stratified by non-elective and elective procedure are summarized in **Table 2** and **Table S6** in the online supplement. Video-assisted thoracoscopic surgery was more common than open thoracotomy during the study period in the overall cohort but was less common in non-elective procedures. Median yearly and cumulative hospital SLB volume was 73 (IQR 34,143) and 1219 (IQR 462,2252), respectively.

Primary Outcome

Results of the full multilevel model for 30-day post-operative mortality in the overall cohort and stratified by non-elective and elective patients are shown in **Table 3**. Higher yearly hospital SLB volume was significantly associated with lower odds of 30-day post-operative mortality in the overall cohort [OR 0.84 95% CI (0.73, 0.97), p=0.02, unit for OR is per 50 SLBs], after adjusting for patient level characteristics. In other words, for every additional 50 SLBs performed per year, the odds of dying

within 30-days of the procedure decreased by 16%. After stratification by non-elective and elective patients, the odds ratio for yearly hospital SLB volume was unchanged in non-elective patients as compared to the overall cohort, although the confidence intervals widened slightly and the p value was no longer significant [OR 0.84 95% CI (0.69, 1.02), p=0.08, unit for OR is per 50 SLBs]. Amongst elective patients, hospital SLB volume was no longer significantly associated with 30-day post-operative mortality and the odds ratio increased compared to the overall cohort [OR 0.94 95% CI (0.74, 1.18), p=0.57, unit for OR is per 50 SLBs], although there was still a trend towards lower mortality. The ICCs were negligible, suggesting variability in 30-day post-operative mortality was accounted for by patient characteristics as opposed to between hospital differences.

Older age group, male sex, non-elective procedure, Long Term Oxygen Therapy, later year of procedure, higher Charlson Comorbidity Index and open thoracotomy were significantly associated with a greater odds of 30-day post-operative mortality in the overall cohort. The odds of death within 30-days was 8.76 times higher in non-elective procedures compared to elective procedures [OR 8.76 95% CI (6.19, 12.39), p<0.0001]. Interestingly, open thoracotomy, older age and later procedure year remained significantly associated with 30-day post-operative mortality in non-elective patients only, while Long Term Oxygen Therapy remained significantly associated with 30-day post-operative mortality in only elective patients on stratified analysis. Results of the null and hospital level models are shown in

Table S7 in the online supplement. Adjusted odds ratios for each year of procedure in the overall cohort are shown in Figure S1 in the online supplement.

Assessment of model fit yielded excellent c-statistics of 0.86, 0.86 and 0.80 for the overall cohort, non-elective and elective patients, respectively. Hosmer and Lemeshow Goodness-of Fit test was not significant (p=0.50, p=0.50 and p=0.84 for the overall cohort, non-elective and elective patients, respectively), suggesting the models were well calibrated.

Surgical lung biopsy volume by quartiles

Range of yearly hospital SLB volume by increasing quartile was 1-34, 35-73, 74-143 and 144-258. The difference in 30-day mortality was greatest between extremes of volume (10.0% in quartile 1 versus 3.2% in quartile 4). Model results analyzing yearly hospital SLB volume by quartiles for the overall cohort and stratified by non-elective and elective patients are shown in **Table S8** in the online supplement. In the overall cohort, the odds of death within 30-days after SLB was significantly lower for the highest volume (4^{th}) quartile [OR 0.45 95% CI (0.25, 0.79, p=0.005), reference is quartile 1, unit for OR is per 50 SLBs]. No significant difference was seen for the 2^{nd} and 3^{rd} volume quartiles as compared to quartile 1, although there was a trend towards lower odds of 30-day post-operative mortality for the higher volume quartiles.

DISCUSSION

Previous research has shown that mortality after SLB is variable and may be unacceptably high for some patients and in some settings [5-9]. We used multilevel modeling to demonstrate that higher hospital SLB volume was associated with lower 30-day post-operative mortality after SLB in a large cohort of patients with ILD. The stratified analysis suggested this relationship was stronger for non-elective patients and may be less likely to apply in elective situations. The highest volume quartile group was significantly associated with a lower odds of 30-day post-operative mortality, resulting in a volume threshold of 144 SLBs per hospital per year. It is likely that different volume thresholds could be safely applied to elective versus non-elective SLBs, however we were not powered to assess this. To our knowledge this is the first study to evaluate the volume outcome relationship for SLB in ILD. The variability in post-operative mortality attributable to between hospital differences was small, suggesting that the wide range of mortality described in the literature may be explained by patient level factors. Specifically, non-elective procedure appears to be the most important prognosticator of post-operative outcome.

Similar volume outcome relationships have been found with many surgeries and have been used to support the regionalization of care for certain procedures such as lung cancer resection [11,15]. The volume outcome relationship is likely more complicated than purely surgical expertise and there are several factors specific to SLB in ILD patients to consider. Previous studies have suggested that an acute exacerbation of ILD (AE-ILD) may be precipitated by SLB and contribute to

high mortality rates seen in this population [8,17]. In-hospital mortality from AE-ILD is as high as 50%-80% [18-20]. The trigger for an AE-ILD after SLB is unclear and may be related to factors other than surgical expertise. For example, hyperoxia and mechanical stress during ventilation of the fibrotic lung and intra-operative fluid balance have been proposed as potential etiologic factors in AE-ILD after SLB [21,22]. Institutional factors may also influence the volume outcome relationship, with higher volume centers having processes in place that better equip them for the peri-operative management of these patients. The experience of support staff working in the operating room, post-operation unit, intensive care unit and surgical ward may all play a role in patient outcome. Higher volume centers may also be more likely to have ILD experts that influence patient referral and selection for SLB. Given the volume outcome association we observed appeared to be stronger for non-elective cases, variations on the basis of expertise within hospitals are perhaps not unexpected. However, identifying the mechanisms driving a specific volume outcome relationship remains important for implementing system changes aimed at improving patient outcomes.

30-day post-operative mortality was 7.1% in our overall study cohort. Mortality was much higher for non-elective procedures (20.2%) as compared to elective procedures (1.9%). These results are consistent with those seen in US administrative data, where in-hospital mortality was 6.4% for a large cohort of ILD patients undergoing SLB and mortality for non-elective procedures was much higher than for elective procedures (16.0% versus 1.7%, respectively) [9]. The authors of

that study were unable to ascertain 30-day mortality, but our data on 30-day mortality would be expected to be higher than in-hospital mortality, suggesting our data is likely generalizable to other settings in North America. Interestingly, 30-day mortality after SLB for ILD in administrative data from the United Kingdom was similar to ours among elective procedures (1.5%) but lower (6.3%) in non-elective procedures [10]. This mortality difference may reflect variation in practice and non-elective patient selection patterns between the United Kingdom and North America. Regardless, a 30-day post-operative mortality rate of around 2% for elective SLB is consistent across European and North American data.

In keeping with previous research, we also found several patient level factors that were independently associated with 30-day post-operative mortality on multilevel modeling [9,10]. These included older age, male sex, higher Charlson Comorbidity Index, Long Term Oxygen Therapy, non-elective procedure and open thoracotomy. The ICC was negligible in all 3 of the full multilevel models (overall cohort, non-elective and elective patients). The lack of variability in outcome related to hospital variation suggests that patient characteristics are important drivers in post-operative mortality after SLB for ILD and should be carefully considered when assessing operative risk. Non-elective procedures had a strikingly higher 30-day mortality compared to elective procedures. It is difficult to know whether this finding is attributable to high baseline risk and post-operative complications or if these patients would have died regardless because of their clinical trajectory. In either case, the clear risk of SLB in non-elective patients with ILD should be carefully weighed

against the potential a SLB will significantly alter treatment decisions and clinical course before deciding to proceed in such individuals.

Interestingly, while unadjusted mortality appeared to be stable over time, we found that later procedure year was associated with higher odds of SLB mortality on multilevel modeling in the overall cohort and non-elective patients. At first glance this is counterintuitive as operative mortality has fallen over time for many procedures, such as aortic valve replacement, carotid endarterectomy, and several cancer resections [23,24]. One hypothesis for the unexpected finding is that clinicians have become more aggressive with pursuing SLB over time. Our patient population appeared similar over time regarding age, sex and comorbidity burden. We were limited in our ability to determine the severity of lung disease but the use of Long Term Oxygen Therapy increased over time, suggesting that patients may have had progressively more severe lung disease during the study period. Several key publications on ILD occurred during our study period that may have influenced trends in pursuing SLB. In 2002, the first international guidelines on the diagnosis and classification of ILDs was published jointly by the American Thoracic and European Respiratory Societies. This guideline placed an emphasis on obtaining a SLB to aid in diagnosis in the absence of contraindications and noted that with the advent of VATS, SLB should be associated with less risk than historically seen [1]. Furthermore, this guideline stated that TBBs were generally not useful and discouraged the traditional practice of a trial of therapy to determine prognosis rather than pursuing SLB. The authors also made note of low SLB rate in patients with ILD

at that time. In 2011, interim results from the PANTHER trial were available showing increased mortality in idiopathic pulmonary fibrosis (IPF) patients treated with prednisone, azathioprine and NAC [25,26], providing further discouragement for the clinical practice of a trial of immunosuppressive therapy in situations of diagnostic uncertainty. In 2012, pirfenidone, an antifibrotic agent was approved for use in IPF by Health Canada, and, since this class of medication is not indicated in non-IPF ILD, further emphasis may have been placed on the importance of SLB after 2012 [27]. It is possible that these changes to the landscape of ILD in Canada resulted in clinicians pursuing SLB more aggressively in higher risk patients over time and thus increasing in post-operative mortality. Specifically, it is possible that patients with IPF were biopsied more frequently in recent years and were more likely to have higher post-operative mortality [9]. Expanding on the recent IPF diagnostic guidelines [28] with the development of a statement advising physicians on when SLB is contraindicated and outlining specific pre-operative considerations should be considered to avoid potentially harmful trends associated with inappropriate SLBs.

There are several limitations to our study. First, large-scale validation studies in ICES databases have not been performed for ILD codes. As a result, we were unable to assess the relationship between ILD subtype and 30-day post-operative mortality after SLB. However, we felt the specificity of an ILD diagnosis in our cohort was likely to be high, given that individuals had both a diagnostic code for ILD and underwent a SLB. Second, there is always potential for unmeasured confounding when using administrative databases for research. We were unable to ascertain lung

function or intra-operative ventilator management. These may be important factors in outcome after SLB in ILD and difficult to tease out given the limitations of administrative data. Third, the stratified analysis should be interpreted with caution given an interaction term for surgical volume and non-elective versus elective procedure was non-significant and the sample size was not large enough to excluded a volume outcome relationship for elective procedures. Lastly, while we showed a volume outcome relationship between SLB and post-operative mortality, recommending system changes aimed at improving outcomes remains a challenge. We cannot be sure of the exact mechanisms behind the volume outcome relationship. Surgical expertise is an attractive and straightforward theory which can lead to minimum volume recommendations for procedures. However, previous studies have found that increasing surgical volume does not always translate into a decrease in post-operative mortality [15], suggesting the relationship is more complicated than what research can sometimes elucidate. Despite these limitations, we were able to reliably ascertain 30-day post-operative mortality, a clinically meaningful endpoint, expanding on previous administrative data that has relied on in-hospital mortality estimates.

We applied multilevel modeling to show that higher yearly hospital SLB volume is associated with lower 30-day mortality after SLB for ILD. Non-elective SLB was associated with a significantly higher mortality rate than elective SLB and should therefore be discouraged unless there is a clear indication.

ACKNOWLEDGEMTS

This study made use of de-identified data from the ICES Data Repository, which is managed by the Institute for Clinical Evaluative Sciences with support from its funders and partners: Canada's Strategy for Patient-Oriented Research (SPOR), the Ontario SPOR Support Unit, the Canadian Institutes of Health Research and the Government of Ontario. The opinions, results and conclusions reported are those of the authors. No endorsement by ICES or any of its funders or partners is intended or should be inferred. Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.

SUPPORT

Financial support for this study was provided by a patient donation to the University Health Network Foundation.

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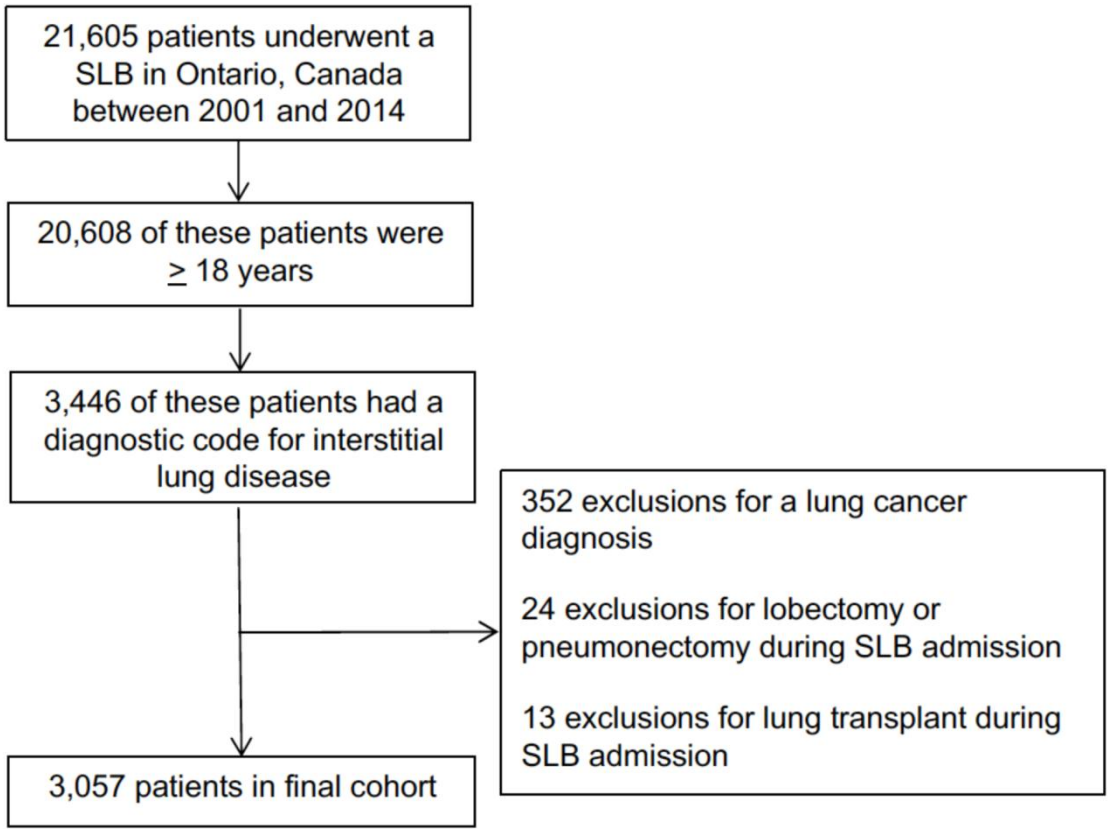
Travis WD, Walsh S, Wilson KC. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med* 2018;198:e44-e68.

FIGURE CAPTIONS

Figure 1. Study cohort selection.

Figure 2. 30-day mortality after surgical lung biopsy in interstitial lung disease patients by procedure year.



Abbreviations: SLB, surgical lung biopsy.
Of the 17,162 patients who underwent SLB and did not have a diagnostic code for interstitial lung disease, 8,345 had a diagnosis of lung cancer in the Ontario Cancer Registry.

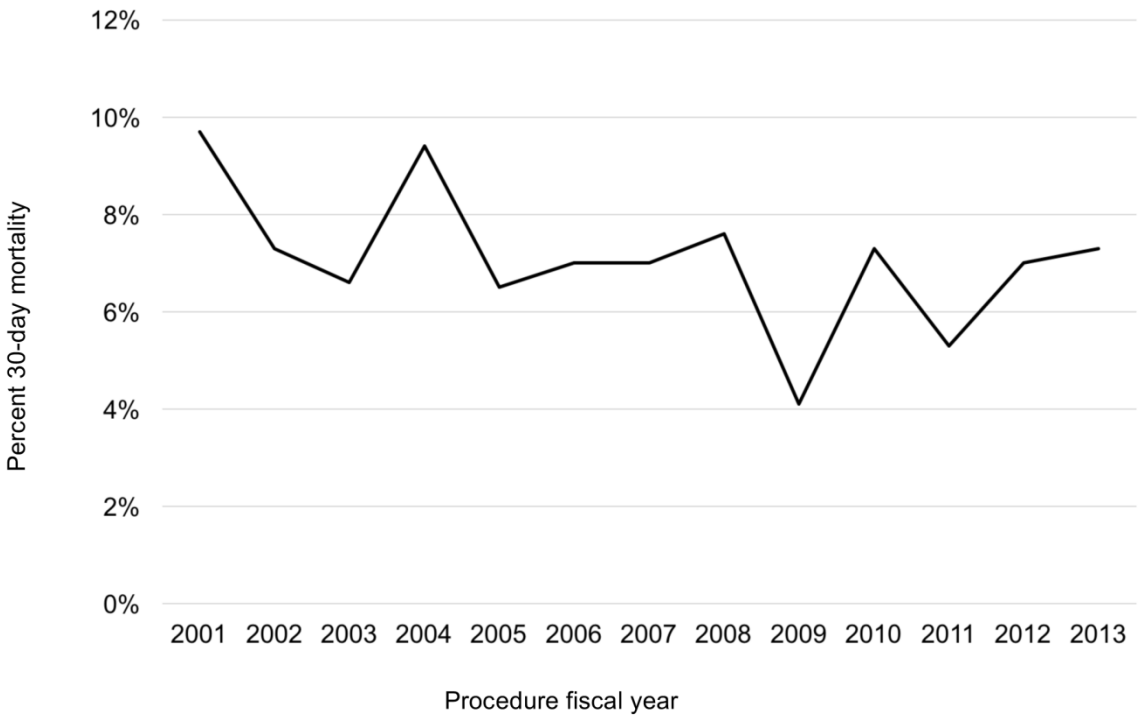

12%
10%
8%
6%
4%
2%
0%
Percent 30-day mortality
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
Procedure fiscal year

Table 1. Baseline characteristics of patients with interstitial lung disease undergoing surgical lung biopsy by hospital surgical volume.

Baseline characteristic	**Overall** (n = 3057)	**1st quartile** *1-34 SLBs/yr* (n= 782)	**2nd quartile** *35-73 SLBs/yr* (n= 763)	**3rd quartile** *74-143 SLBs/yr* (n= 818)	**4th quartile** *144-258 SLBs/yr* (n= 694)
30-day mortality	216 (7.1%)	78 (10.0%)	52 (6.8%)	64 (7.8%)	22 (3.2%)
Age group, years					
18-29	96 (3.1%)	23 (2.9%)	18 (2.4%)	33 (4.0%)	22 (3.2%)
30-39	157 (5.1%)	39 (5.0%)	45 (5.9%)	44 (5.4%)	29 (4.2%)
40-49	466 (15.2%)	94 (12.0%)	142 (18.6%)	125 (15.3%)	105 (15.1%)
50-59	827 (27.1%)	222 (28.4%)	189 (24.8%)	212 (25.9%)	204 (29.4%)
60-69	861 (28.2%)	219 (28.0%)	222 (29.1%)	234 (28.6%)	186 (26.8%)
$\geq$ 70	650 (21.3%)	185 (23.7%)	147 (19.3%)	170 (20.8%)	148 (21.3%)
Male sex	1582 (51.8%)	413 (52.8%)	391 (51.3%)	436 (53.3%)	342 (49.3%)
Income quintile					
1 (lowest)	602 (19.8%)	152 (19.5%)	178 (23.4%)	153 (18.8%)	119 (17.2%)
2	604 (19.8%)	158 (20.3%)	145 (19.1%)	169 (20.8%)	132 (19.1%)
3	594 (19.5%)	161 (20.6%)	148 (19.5%)	155 (19.1%)	130 (18.8%)
4	669 (22.0%)	170 (21.8%)	163 (21.4%)	185 (22.8%)	151 (21.9%)
5 (highest)	576 (18.9%)	139 (17.8%)	127 (16.7%)	151 (18.6%)	159 (23.0%)
Charlson Comorbidity Index					
0	1682 (55.1%)	416 (53.3%)	432 (56.7%)	421 (51.5%)	413 (59.8%)
1	702 (23.0%)	180 (23.1%)	165 (21.7%)	205 (25.1%)	152 (22.0%)
2	307 (10.1%)	89 (11.4%)	83 (10.9%)	88 (10.8%)	47 (6.8%)
$\geq$ 3	360 (11.8%)	96 (12.3%)	82 (10.8%)	103 (12.6%)	79 (11.4%)
Charlson Comorbidity Index overall	0 (0,1)	0 (0,1)	0 (0,1)	0 (0,1)	0 (0,1)
Long Term Oxygen Therapy	210 (6.9%)	48 (6.1%)	43 (5.6%)	65 (8.0%)	54 (7.8%)
Non-elective	860 (28.1%)	284 (36.3%)	223 (29.2%)	238 (29.1%)	115 (16.6%)

Data are shown as number (percent) or median (interquartile range). Abbreviations: SLB, surgical lung biopsy, yr, year.

Table 2. Surgical lung biopsy details for patients with interstitial lung disease by hospital surgical volume.

Characteristic	**Overall** (n = 3057)	**1st quartile** *1-34 SLBs/yr* (n= 782)	**2nd quartile** *35-73 SLBs/yr* (n= 763)	**3rd quartile** *74-143 SLBs/yr* (n= 818)	**4th quartile** *144-258 SLBs/yr* (n= 694)
Open thoracotomy	1158 (37.9%)	321 (41.1%)	273 (35.8%)	312 (38.1%)	252 (36.3%)
Yearly hospital SLB volume	73 (34,143)	23 (13,30)	50 (41,64)	115 (96,137)	208 (170,220)
Total hospital SLB volume	1219 (462,2252)	306 (219,514)	655 (516,1219)	1575 (1453,2252)	2345 (2082,3681)

Data are shown as number (percent) or median (interquartile range).
Abbreviations: SLB, surgical lung biopsy, yr, year.

Table 3. Full multilevel models* of the association between yearly hospital surgical lung biopsy volume and 30-day post-operative mortality in patients with interstitial lung disease undergoing surgical lung biopsy in the overall cohort and stratified by non-elective and elective patients.

Variable	Overall cohort (n = 3039)		Non-elective patients† (n = 858)		Elective patients† (n = 2181)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Yearly hospital SLB volume‡	0.84 (0.73, 0.97)	0.02	0.84 (0.69, 1.02)	0.08	0.94 (0.74, 1.18)	0.57
Non-elective	8.76 (6.19, 12.39)	<0.0001	-	-	-	-
Open thoracotomy	2.70 (1.95, 3.75)	<0.0001	3.29 (2.18, 4.95)	<0.0001	1.35 (0.70, 2.61)	0.37
Long Term Oxygen Therapy	1.93 (1.19, 3.13)	0.008	1.05 (0.55, 2.03)	0.88	5.48 (2.70, 11.12)	<0.0001
Male sex	1.64 (1.20, 2.22)	0.002	1.51 (1.04, 2.17)	0.03	2.05 (1.08, 3.91)	0.03
Age group, years	1.36 (1.20, 1.55)	<0.0001	1.38 (1.19, 1.61)	<0.0001	1.34 (1.00, 1.79)	0.05
Charlson Comorbidity Index	1.17 (1.09, 1.26)	<0.0001	1.12 (1.03, 1.22)	0.007	1.37 (1.19, 1.56)	<0.0001
Procedure year	1.08 (1.04, 1.13)	0.0005	1.09 (1.03, 1.15)	0.002	1.03 (0.94, 1.13)	0.53
Income quintile	0.95 (0.86, 1.05)	0.33	0.96 (0.85, 1.09)	0.52	0.90 (0.73, 1.12)	0.35
ICC§	0.02		0.05		0.00	

*The full multilevel model includes hospital (yearly hospital SLB volume) and patient level covariates. †An interaction term for yearly hospital surgical lung biopsy volume and non-elective versus elective patients was non-significant. ‡Unit for odds ratio is per 50 surgical lung biopsies performed. §The ICC represents the variability in 30-day post-operative mortality that is accounted for by the hospital differences. For example, in the overall cohort, 2 percent of the variability in 30-day post-operative mortality is accounted for by between hospital differences, leaving 98% of the variability attributable to patient characteristics.

Odds ratios > 1 represent higher odds of 30-day post-operative mortality, odds ratios < 1 represent lower odds of 30-day post-operative mortality. Age and income were analyzed as ordinal variables, with increasing age group being associated with higher 30-day post-operative mortality in the overall cohort and non-elective patients. Age groups used were 18-29, 30-39, 40-49, 50-59, 60-69 and $\geq$ 70 years. Charlson Comorbidity Index and procedure year were analyzed as continuous variables, with higher Charlson Comorbidity Index being associated with higher 30-day post-operative mortality in all 3 groups and later procedure year being associated with higher 30-day post-operative mortality in the overall cohort and non-elective patients. All other variables were analyzed as categorical (yes versus no).

Abbreviations: OR, odds ratio, CI, confidence interval, SLB, surgical lung biopsy, ICC, intraclass correlation coefficient.

There were 18, 2 and 16 patients excluded from the overall cohort, non-elective patients and elective patients, respectively due to missing data.

-- Online Data Supplement --

ADDITIONAL METHODS

Data Sources

The following databases were used held at the Institute for Clinical Evaluative Sciences (ICES) were used:

1. Canadian Institute of Health Information Discharge Abstract Database (CIHI-DAD)

The CIHI-DAD contains demographic, clinical and administrative data for hospital admissions and day surgeries in Canada. Data for all Ontario facilities is available from 1988 for hospital admissions and 1991 for same day surgeries. The CIHI-DAD was used to identify patients who underwent a surgical lung biopsy (SLB), determine hospital SLB volume, year of procedure, hospital length of stay, readmission rates and patient comorbidities. A validation study of the CIHI-DAD found high agreement and sensitivity of coding for lung biopsy (kappa of 0.85, sensitivity of 92%) and a 97.3% agreement for procedure date. Overall agreement for diagnostic codes was 85% [1].

2. Assistive Devices Program (ADP)

Data on Long Term Oxygen Therapy was obtained using the ADP. The ADP funds Oxygen in Ontario for those who qualify and collects data on several parameters,

including Long Term Oxygen Therapy, blood gas results and Oxygen saturation. Long Term Oxygen Therapy data was first available in 2001 for our study cohort.

3. Registered Persons Database (RPDB)

30-day post-operative mortality, age and sex were determined using the RPDB. The RPDB is a population based registry that contains demographic data and vital status for almost all Ontario residents. Date of birth, date of death, sex and address is collected and changes are tracked over time. An algorithm is used by ICES to search other health services data sets with potentially more up to date address and death information to further enrich the RPDB. The data sets searched include the CIHI-DAD, National Ambulatory Care Reporting System, Continuing Care Reporting System, Levels of Care Classification System and the National Rehabilitation System [2].

4. Ontario Health Insurance Claims (OHIP)

The OHIP database captures data on all physician claims for insured services. Almost 95% of Ontario physicians are paid 'fee-for-service' and submit claims to OHIP for reimbursement. Physicians who are not reimbursed in a fee-for-service fashion, usually submit 'shadow billings', which still allows for capture of their services. Data collected includes the service provided, patient diagnosis, the service provider, the individual that received the service and the date the service was provided. This database was used to determine patient comorbidities.

5. Ontario Cancer Registry (OCR)

A diagnosis of cancer (lung and non-lung) was determined using the Ontario OCR. The OCR contains information on all newly diagnosed invasive cancers in Ontario. All lung cancer diagnoses 5 years prior to or within 60 days following SLB and non-lung cancer diagnoses 5 years prior to SLB were identified.

6. Census Canada

2006 Census Canada data was used to determine socioeconomic status using income quintiles.

Potential limitations of variable definitions

Inaccurate coding of variables by data abstractors can result in misclassification bias. While validation research of the CIHI-DAD suggests the overall level of agreement for diagnostic coding is high, specific data on ILD codes is not available. However, misclassification of ILD or other variables, should be non-differential between hospitals. Since the outcome (30-day mortality) should be at low risk of misclassification, we would expect any misclassification to bias results toward the null [3-5].

Analysis

Intensive care unit admission and intubation at the time of SLB were considered *a priori* for inclusion but ultimately excluded from analysis as they were not reliably

available. All variables were assessed for multicollinearity using a variance inflation factor of 4 as the threshold for exclusion of a variable from the model. The multilevel model included 3 models specified for the outcome. The null model, representing the variability in 30-day post-operative mortality that is explained by between hospital differences without any covariates (as measured by the intra-class correlation coefficient (ICC); the hospital level model, including yearly hospital SLB volume as the only covariate; and the full multilevel model, including yearly hospital SLB volume and patient level covariates. The ICC was calculated using 3.29 as the level-1 error variance.[6] The omnibus likelihood ratio test was used to confirm a significant relationship between predictors and 30-day post-operative mortality.

We performed an additional stratified primary analysis separating elective and non-elective patients. We assessed for an interaction between yearly hospital surgical lung biopsy volume and elective versus non-elective patients and it was not significant. However, we hypothesized that elective patients would be a different study population compared to non-elective patients undergoing SLB. Subsequently we wished to separately evaluate the factors influencing post-operative mortality in the different populations. Given high volume centers would be more likely to also be lung transplant centers, we compared the date of lung transplant to the date of SLB for the 13 patients in our cohort that underwent a lung transplant during the same admission as the SLB to ensure our results were not biased based on the presumably easier access to lung transplant post-operatively. No patient received a lung transplant after SLB.

Missing data for the outcome and key variables was assessed and reported. It was anticipated that missing data would be at random and a threshold for list wise

deletion was set at 10% for key variables and 5% for outcome data. We pre-specified an additional analysis using imputation or direct maximum likelihood estimation if missing data exceeded this threshold. Missing data in our study was extremely small, with no key variable or outcome meeting the predefined threshold in isolation or in combination during multilevel modeling.

ONLINE SUPPLEMENT REFERENCES

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S3. Rothman KJ, Greenland S, Lash TL. Modern epidemiology, 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2008.

S4. Wacholder S, Hartge P, Lubin JH, Dosemeci M. Non-differential misclassification and bias towards the null: a clarification. *Occup Environ Med.* 1995;52(8):557-8.

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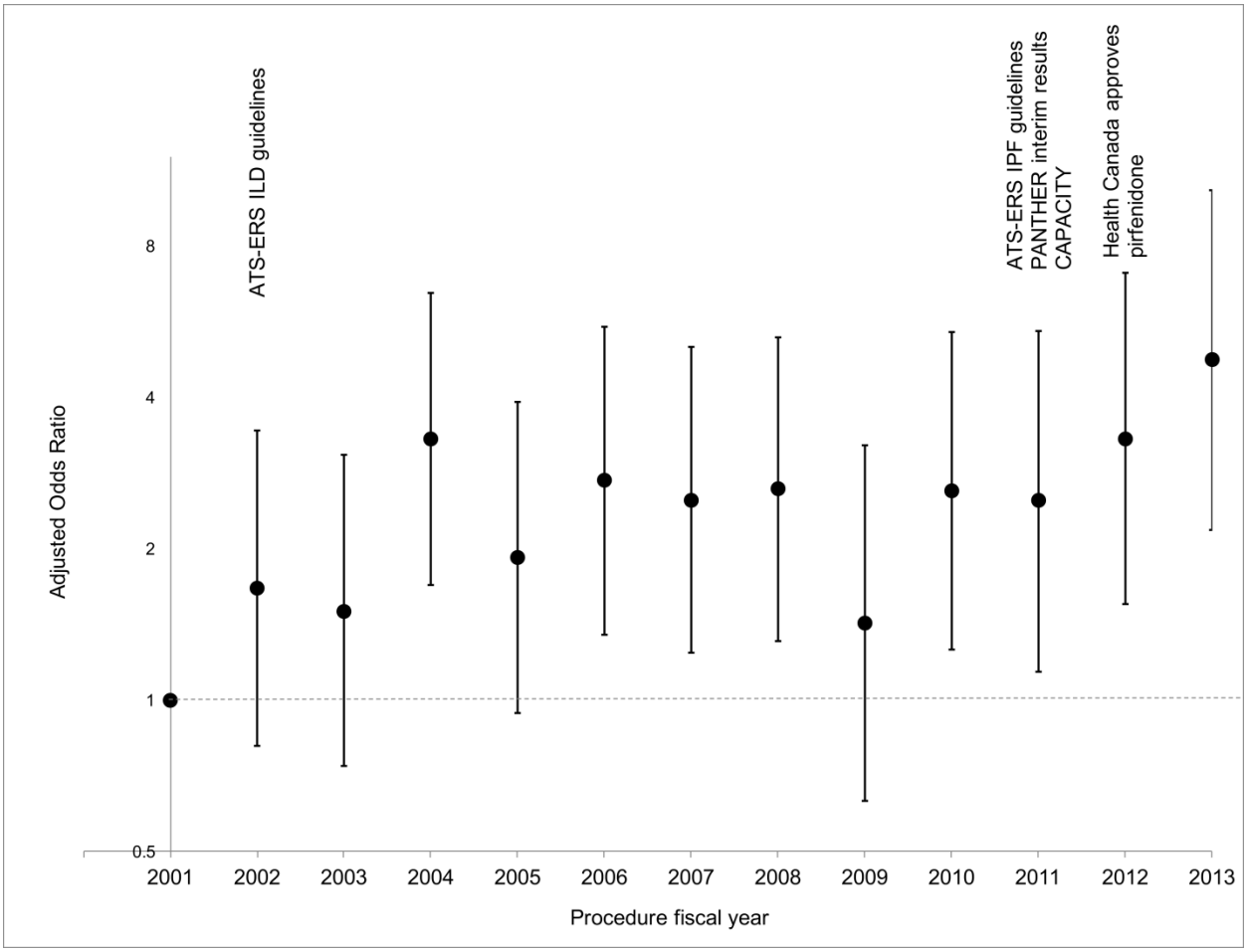
ONLINE SUPPLEMENT FIGURE CAPTION

Figure S1. Adjusted odds ratios of 30-day post-operative mortality after surgical lung biopsy for individual procedure year.



ONLINE SUPPLEMENT TABLES

Table S1. CCI and CCP codes for surgical lung biopsy.

CCI code	**Description**
1.GR.87.DA	Excision partial, lobe of lung using endoscopic approach (VATS)
1.GR.87.QB	Excision partial, lobe of lung using open thoracic approach
2.GT.71.DA	Biopsy lung using endoscopic approach (VATS)
2.GT.71.LA	Biopsy lung using open approach
CCP code	**Description**
44.22	Endoscopic excision or destruction of lesion or tissue of lung
44.3	Segmental resection of lung
45.84	Other biopsy of lung

Abbreviations: CCI, Canadian Classification of Health Interventions, CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures. VATS, video-assisted thoracoscopic surgery.

Table S2. ICD 9 and 10 codes for interstitial lung disease.

ICD 10 code	Description
J80	Acute Respiratory Distress Syndrome
J82	Pulmonary Eosinophilia
J84	(all)
J84.0	Alveolar and parietoalveolar conditions
	J84.01, J84.02, J84.03, J84.09
J84.1	Other interstitial pulmonary diseases with fibrosis
	J84.10, J84.11, J84.111, J84.112, J84.113, J84.114, J84.115, J84.116, J84.117, J84.17
J84.2	Lymphoid interstitial pneumonia
J84.8	Other specified interstitial pulmonary diseases
	J84.81, J84.82, J84.83, J84.84, J84.841, J84.842, J84.843, J84.848, J84.89
J84.9	Interstitial pulmonary disease, unspecified
D86.0	Sarcoidosis of lung
D86.2	Sarcoidosis of lung and lymph nodes
J70.0	Acute pulmonary manifestations due to radiation
J70.1	Chronic and other pulmonary manifestations due to radiation
J70.2	Acute drug-induced interstitial lung disorders
J70.3	Chronic drug-induced interstitial lung disorders
J70.4	Drug-induced interstitial lung disorders, unspecified
J60	Coal workers pneumoconiosis
J61	Pneumoconiosis due to asbestos and other mineral fibers
J62	Pneumoconiosis due to dust containing silica
J63	Pneumoconiosis due to other inorganic dusts
J64	Unspecified pneumoconiosis
J67	Hypersensitivity pneumonitis due to organic dust
J69	Pneumonitis due to solids and liquids

M34.81	Systemic sclerosis with lung involvement
M05.10	Rheumatoid lung disease with rheumatoid arthritis of unspecified site
M05.19	Rheumatoid lung disease with rheumatoid arthritis of multiple sites

ICD 9 code	**Description**
515	Postinflammatory pulmonary fibrosis
516.0	Pulmonary alveolar proteinosis
516.1	Idiopathic pulmonary hemosiderosis
516.2	Pulmonary alveolar microlithiasis
516.3	Idiopathic interstitial pneumonia, nos and others
516.4	Lymphangioleiomyomatosis
516.5	Adult pulmonary Langerhans cell histiocytosis
516.8	Other specified alveolar and parietoalveolar pneumonopathies
516.9	Unspecified alveolar and parietoalveolar pneumonopathy
500	Coal workers' pneumoconiosis
501	Asbestosis
502	Pneumoconiosis due to other silica or silicates
503	Pneumoconiosis due to other inorganic dust
505	Pneumoconiosis, unspecified
508.0	Acute pulmonary manifestations due to radiation
508.1	Chronic and other pulmonary manifestations due to radiation
517.1	Rheumatic pneumonia
517.2	Lung involvement in systemic sclerosis
517.8	Lung involvement in other diseases classified elsewhere
517.8 plus 135	Pulmonary sarcoid
518.3	Pulmonary eosinophilia

Abbreviations: ICD, International Classification of Diseases.

Table S3. CCI and CCP codes for excluded procedures.

CCI code	Description
1.GT.87.^^	Excision partial, NEC (includes bilobectomy and lobectomy with partial excision from another lobe)
1.GR.89.^^	Excision total, lobe of lung
1.GR.91.^^	Excision radical, lobe of lung
1.GT.89.^^	Excision total, NEC (includes pneumonectomy)
1.GT.91.^^	Excision radical, lung NEC
1.GT.85.LA.XXJ 1.GT.85.LA.XXK 1.HY.85.LA.XXK	Lung transplant

CCP code	Description
44.4, 444, 4440	Lobectomy
445, 4450	Pneumonectomy
455, 4550, 456, 4560	Lung transplant

Abbreviations: CCI, Canadian Classification of Health Interventions, CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures, NEC, not elsewhere classified.

Table S4. Baseline characteristics of patients with interstitial lung disease undergoing surgical lung biopsy stratified by non-elective and elective procedure.

Baseline characteristic	Non-elective patients (n = 860)	Elective patients (n= 2197)
30-day mortality	174 (20.2%)	42 (1.9%)
Age group, years		
18-29	38 (4.4%)	58 (2.6%)
30-39	43 (5.0%)	114 (5.2%)
40-49	107 (12.4%)	359 (16.3%)
50-59	211 (24.5%)	616 (28.0%)
60-69	229 (26.6%)	632 (28.8%)
$\geq$ 70	232 (27.0%)	418 (19.0%)
Male sex	477 (55.5%)	1105 (50.3%)
Income quintile		
1 (lowest)	176 (20.5%)	426 (19.5%)
2	166 (19.4%)	438 (20.0%)
3	175 (20.4%)	419 (19.2%)
4	186 (21.7%)	483 (22.1%)
5 (highest)	155 (18.1%)	421(19.3%)
Charlson Comorbidity Index		
0	278 (32.3%)	1404 (64.1%)
1	229 (26.6%)	473 (21.6%)
2	152 (17.7%)	155 (7.1%)
$\geq$ 3	201 (23.4%)	159 (7.3%)
Charlson Comorbidity Index overall	1 (0,2)	0 (0,1)
Long Term Oxygen Therapy	68 (7.9%)	142 (6.5%)

Data are shown as number (percent) or median (interquartile range).

Table S5. Comorbidities in patients with interstitial lung disease undergoing surgical lung biopsy.

Comorbidity	n=3057
Frailty	249 (8.2%)
Diabetes	673 (22.0%)
Cancer (non-lung)	280 (9.2%)
Coronary artery disease	979 (32.0%)
Congestive heart failure	406 (13.3%)
Chronic obstructive pulmonary disease	860 (28.1%)
Hypertension	1458 (47.7%)
Acute myocardial infarction	80 (2.6%)
Cerebrovascular disease	22 (0.7%)
Asthma	545 (17.8%)
Renal disease	215 (7.0%)
Peripheral vascular disease	156 (5.1%)
Pulmonary hypertension	30 (1.0%)
Pulmonary embolism	132 (4.3%)
Gastroesophageal reflux disease	1789 (58.5%)
Liver disease	159 (5.2%)
Connective tissue disease	163 (5.3%)

Data are shown as number (percent). Frailty was determined using the John Hopkins Ambulatory Clinical Groups software. Comorbidities were determined using validated administrative definitions where available. All other comorbidities were defined using International Classification of Diseases 9 and 10 codes from the Canadian Institute of Health Information Discharge Abstract Database or Ontario Health Insurance Claims using a 5-year look back period.

Table S6. Surgical lung biopsy details for patients with interstitial lung disease stratified by non-elective and elective procedure.

Characteristic	Non-elective patients (n = 860)	Elective patients (n= 2197)
Open thoracotomy	459 (53.4%)	699 (31.8%)
Yearly hospital SLB volume	63 (28,124)	85 (37,147)
Total hospital SLB volume	780 (376,2082)	1453 (516,2252)

Data are shown as number (percent) or median (interquartile range).

Abbreviations: SLB, surgical lung biopsy.

Table S7. Null and hospital level models of 30-day post-operative mortality in patients with interstitial lung disease undergoing surgical lung biopsy in the overall cohort and stratified by non-elective and elective patients.

	Null model	Hospital level model
Overall cohort		
Yearly hospital SLB volume*	-	OR 0.82 95% CI (0.69, 0.98 p=0.03)
ICC	0.12	0.09
Non-elective patients		
Yearly hospital SLB volume*	-	OR 0.88 95% CI (0.73, 1.05 p=0.14)
ICC	0.05	0.04
Elective patients		
Yearly hospital SLB volume*	-	OR 0.98 95% CI (0.78, 1.21 p=0.82)
ICC	0.00	0.00

*Unit for odds ratio is per 50 surgical lung biopsies performed. Odds ratios > 1 represent higher odds of 30-day post-operative mortality, odds ratios < 1 represent lower odds of 30-day post-operative mortality.

Abbreviations: OR, odds ratio, CI, confidence interval, SLB, surgical lung biopsy, ICC, intraclass correlation coefficient.

Table S8. Multivariable analysis of 30-day post-operative mortality model with surgical lung biopsy volume analyzed in quartiles in the overall cohort and stratified by non-elective and elective patients.

Variable	Overall cohort (n = 3039)		Non-elective patients (n = 858)		Elective patients (n = 2181)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Non-elective	8.73 (6.16, 12.37)	<0.0001	-	-	-	-
Open thoracotomy	2.70 (1.95, 3.75)	<0.0001	3.27 (2.18, 4.92)	<0.0001	1.39 (0.71, 2.70)	0.34
Long Term Oxygen Therapy	1.92 (1.18, 3.12)	0.008	1.04 (0.54, 2.00)	0.90	5.45 (2.67, 11.12)	<0.0001
Male sex	1.65 (1.21, 2.24)	0.002	1.49 (1.04, 2.15)	0.03	2.05 (1.07, 3.93)	0.03
Age group, years	1.37 (1.20, 1.55)	<0.0001	1.39 (1.19, 1.61)	<0.0001	1.34 (1.00, 1.80)	0.05
Income quintile	0.95 (0.86, 1.06)	0.34	0.96 (0.85, 1.09)	0.51	0.90 (0.73, 1.12)	0.35
Charlson Comorbidity Index	1.17 (1.09, 1.26)	<0.0001	1.12 (1.03, 1.22)	0.007	1.37 (1.19, 1.56)	<0.0001
Procedure year	1.08 (1.03, 1.13)	0.001	1.09 (1.03, 1.15)	0.003	1.04 (0.94, 1.14)	0.46
Yearly hospital SLB volume (reference is Quartile 1)						
Quartile 2	0.79 (0.53, 1.18)	0.25	0.92 (0.56, 1.52)	0.75	0.92 (0.40, 2.12)	0.85
Quartile 3	0.87 (0.57, 1.31)	0.50	0.83 (0.48, 1.45)	0.52	0.72 (0.30, 1.71)	0.45
Quartile 4 (highest volume)	0.45 (0.25, 0.79)	0.005	0.63 (0.32, 1.23)	0.17	0.69 (0.27, 1.74)	0.43
ICC	0.01		0.05		0.00	

Odds ratios > 1 represent higher odds of 30-day post-operative mortality, odds ratios < 1 represent lower odds of 30-day post-operative mortality. Age and income were analyzed as ordinal variables, with increasing age group being associated with higher 30-day post-operative mortality in the overall cohort and non-elective patients. Age groups used were 18-29, 30-39, 40-49, 50-59, 60-69 and $\geq$ 70 years. Charlson Comorbidity Index

and procedure year were analyzed as continuous variables, with higher Charlson Comorbidity Index being associated with higher 30-day post-operative mortality in all 3 groups and later procedure year being associated with higher 30-day post-operative mortality in the overall cohort and non-elective patients. All other variables were analyzed as categorical (yes versus no, unless otherwise specified).

Abbreviations: OR, odds ratio, CI, confidence interval, SLB, surgical lung biopsy, ICC, intraclass correlation coefficient.

There were 18, 2 and 16 patients excluded from the overall cohort, non-elective patients and elective patients, respectively due to missing data.