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

JH Fisher, S Shapera, T To, TK Marras, A Gershon, S Dell

-- Online Data Supplement --

ADDITIONAL METHODS

Data Sources

The following databases 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 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 SLB 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

S1. Juurlink D, Preyra C, Croxford R, Chong A, Austin P, Tu J, Laupacis A. Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. Toronto: Institute for Clinical Evaluative Sciences; 2006.

S2. Iron K, Zagorski BM, Sykora K, Manuel DG. Living and dying in Ontario: An opportunity for improved health information. ICES Investigative Report. Toronto: Institute for Clinical Evaluative Sciences; 2008.

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.

S5. Sorahan T, Gilthorpe MS. Non-differential misclassification of exposure always leads to an underestimate of risk: an incorrect conclusion. *Occup Environ Med.* 1994;51(12):839-40.

S6. Snijders TAB, Bosker RJ. Multilevel analysis: an introduction to basic and advanced multilevel modeling. London: Sage Publications Ltd; 2012.

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%)
≥ 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%)
≥ 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.