

Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997-2008

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30-day mortality after surgical lung biopsy for interstitial lung disease is 2.4% - similar to lobectomy for lung cancer

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ABSTRACT

Introduction: International guidelines and new targeted therapies for idiopathic pulmonary fibrosis have increased the need for accurate diagnosis of interstitial lung disease, which may lead to more surgical lung biopsies. This study aims to assess the risk of this procedure in patients from the United Kingdom.

Methods: We used Hospital Episodes Statistics data from 1997-2008 to assess the frequency of surgical lung biopsy for interstitial lung disease in England. We identified cardiothoracic surgical patients using ICD-10 codes for interstitial lung disease and OPCS-4 codes for surgical lung biopsy. We excluded those with lung resections or lung cancer. We estimated in-hospital, 30-day and 90-day mortality following the procedure, and linked to cause of death using data from the Office of National Statistics.

Results: We identified 2,820 patients with interstitial lung disease undergoing surgical lung biopsy during the 12 year period. The number of biopsies increased over the time period studied. In-hospital, 30-day and 90-day mortality were 1.7%, 2.4% and 3.9% respectively. Male sex, increasing age, increasing co-morbidity and open surgery were risk factors for mortality.

Discussion: Surgical lung biopsy for interstitial lung disease has a similar mortality to lobectomy for lung cancer, and clinicians and patients should understand the likely risks involved.

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INTRODUCTION

Achieving an accurate diagnosis of interstitial lung disease (ILD) is important, as it can help guide treatment options and prognosis (1). This is particularly true for idiopathic pulmonary fibrosis (IPF), where the introduction of Pirfenidone and Nintedanib as targeted therapies has the potential to slow the rate of decline in lung function, offering hope to patients who face a median survival of only three years (2, 3). While diagnosis can often be made after review of high-resolution computed tomography imaging at a multi-disciplinary team meeting, a surgical lung biopsy may be required to confirm the histological diagnosis (1).

Surgical lung biopsy has associated risks, in part due to the impaired lung function of the patients involved. Case series have reported 30-day mortality rates of around 1.5-4.5%, although these may be biased by careful case selection or local expertise, and are not necessarily generalizable to other centres (4-7). Other case series note much higher mortality rates (8, 9).

We have recently published data from a large secondary care dataset from the United States, identifying in-hospital mortality of 1.7% following elective surgical lung biopsy for ILD (10). However, there are no comparable studies from Europe, and this study was not able to assess mortality following hospital discharge, meaning it is likely to underestimate the 30-day and 90-day mortality statistics commonly reported elsewhere. In this study, we aim to assess the use of surgical lung biopsy for ILD in England, using a national secondary care dataset linked to national mortality statistics, to estimate the in-hospital, 30-day and 90-day mortality associated with the procedure.

METHODS

We used the Hospital Episodes Statistics database, which contains details of all admissions to National Health Service hospitals in England (11). This is managed by the Health and Social Care Information Centre, a body linked to the UK Department of Health. We requested data on all admissions of patients with interstitial lung disease (see supplementary material for specific codes used) from 1989-2008. We requested linked data from the Office of National Statistics (ONS) on date of death and underlying cause of death for all patients, where available, to establish mortality after discharge.

We excluded patients from years prior to 1997 as these did not have a unique identifier that allowed pairing with ONS data. We selected all patients who had undergone a surgical lung biopsy using the following OPCS-4 procedural codes: E593 (biopsy of lesion of lung), E552 (open excision of lung), E548 (other specified excision of lung), and E549 (unspecified excision of lung); in addition we required a treating specialty of 'cardiothoracic surgery' to exclude patients undergoing radiological biopsies, who were unlikely to be under a surgical team. We identified additional codes suggestive of imaging involvement and excluded those mentioning 'radiological', 'ultrasound' or 'computed tomography' approaches. We retained records specifying approach under 'imaging' or 'video' control, which could reflect video-assisted thoracoscopic surgery, but performed a sensitivity analysis excluding the less specific 'imaging' codes. We identified codes for 'open' and 'thoracoscopic' procedures where available. We excluded any patients undergoing repeat operations, those with additional codes for lung resections that suggested the intention of the operation was therapeutic rather than diagnostic, and also those with codes for lung cancer in the current or subsequent record, to ensure we did not include diagnostic procedures for the cancer rather than the ILD. We also excluded patients where surgical lung biopsy was not the primary operation coded and there was any doubt about the nature of the biopsy (see supplementary material). Finally, we excluded any patient without a clear age or sex record.

We attempted to assess whether procedures were elective (scheduled) or non-elective (emergency). All patients with a decision-to-admit date prior to their actual admission date were classed as elective. Those without a valid decision-to-admit date or where this was the same as the operation date were classed as non-elective (see supplementary material for further details). We explored the number of operations performed across England, as well as in-hospital, 30-day and 90-day mortality, cause of death, post-procedural complications, length of stay and re-admission rates. Complications were derived from additional diagnostic codes on the operation record that would be consistent with a post-operative complication; for conditions that could be a co-morbidity (for example, arrhythmia), these had to be absent from the preceding admission record (if available). We assessed the frequency of different types of operation (video-assisted thoracoscopic surgery (VATS) or open thoracotomy) where this information was available, and attempted to assess the impact of provisional type of ILD diagnosis, accepting this might be modified by subsequent biopsy results. Patients with more than one ILD diagnostic code were pragmatically coded as 'unclassified' ILD.

We looked at risk factors for early death by logistic regression, adjusting for age, sex, level of co-morbidity, level of deprivation, type of operation, and provisional diagnosis. Co-morbidities were derived from additional diagnostic codes present in either the operation record or previous records, and scored using the updated Charlson score (12), a modified version of the Charlson Co-morbidity Index (13) that takes into account advances in disease management since the original score was published almost 30 years ago. Using this score, patients with no or minor co-morbidities are assigned a score of '0', whereas those with notable co-morbidities receive points depending on the number and severity of co-morbidities present. We categorised patients into those with scores of '0', '1', '2' and '3 or more'. Further information on how to calculate the updated Charlson score is available in the supplementary material. Deprivation was measured using the Index of Multiple Deprivation 2010 (IMD) (14): this score, which reflects indicators such as income, employment, education and crime (with a low score given to areas that are least deprived), was analysed as a continuous rather than categorical variable, as the latter was no more effective using the likelihood

ratio test. Overall p values and p-for-trend values were calculated using the likelihood ratio test. We assessed survival from the date of operation using the Cox proportional hazards model, with censoring of data in survivors on 22 June 2010 (last date of ONS data) or on date of lung transplantation, and examination of the proportional hazards assumption by the Schonfeld test. Statistical analysis was performed using Stata, version 13.1 (StataCorp, Texas, USA). Ethical approval for the use of the data was obtained from the NHS Health and Social Care Information Centre.

RESULTS

After exclusions, our dataset contained 2,820 patients with a diagnosis of ILD undergoing a surgical lung biopsy between 1997 and 2008 (Figure 1). 55% of these were male, with 73% below age 65. 81% of biopsies were classified as elective, and 19% were non-elective. The number of biopsies increased over the years in the study period (Table 1, Figures 2-3). The biopsy rate ranged from 0.27-0.74 per 100,000 across the English regions (See Table E1, supplementary material).

Table 1 – Demographics of biopsy cohort

Total cohort = 2,820 patients	Number (percentage)
Sex	
Male	1,546 (54.8)
Female	1,274 (45.2)
Age group (years)	
<44	576 (20.4)
45-54	636 (22.6)
55-64	843 (29.9)
65-74	588 (20.9)
>74	177 (6.3)
Year of biopsy	
1997 [April onwards]	104 (3.7)
1998	169 (6.0)
1999	191 (6.8)
2000	185 (6.6)
2001	213 (7.6)
2002	195 (6.9)

2003	197 (7.0)
2004	239 (8.5)
2005	262 (9.3)
2006	261 (9.3)
2007	345 (12.2)
2008	367 (13.0)
2009 [up until March]	92 (3.3)

Codes specifying whether operations were performed via open thoracotomy or video-assisted thoracoscopic surgery (VATS) were available for 38% of operations. Of these, 66% were VATS. No VATS codes were listed prior to 2006, with 80% of patients having a code for the type of operation from 2007 onwards, suggesting the code for VATS came into practice at this time. The most common provisional diagnosis was J84.1 (the most specific code for IPF, but also including other idiopathic interstitial pneumonias) which comprised 50.8% of codes, followed by J84.9 ('unclassified ILD') with 28.8% of codes. This included 81 patients who had more than one diagnostic code listed.

Complications occurred in 13.9% of operations, based on discharge diagnoses for admissions with lung biopsies. The most common were pneumothorax (4.2%), pneumonia (2.8%), other unspecified complications of procedure (1.9%), pleural effusion (1.4%), and failed thoracoscopic approach with conversion to open surgery (1.2%). 8.4% of patients with a valid record for critical care input spent time in a critical care area: for most this was a single stay but 24 patients had more than one stay. The median length of hospital stay was 4 days (range 0-82). 14.1% of patients were re-admitted to hospital within three months, with 28.0% of these having more than one re-admission. Half of re-admissions were due to interstitial lung disease (Table 3).

Table 2 – Cause of re-admissions within 3 months (for first re-admission only; n = 397)

Primary diagnosis	Number of re-admissions (%)
Interstitial lung disease	202 (50.9)
Pneumonia/lower respiratory tract infection	38 (9.6)
Pneumothorax	19 (4.8)
Specified post-procedural issue	15 (3.8)
<i>Haemorrhage complicating a procedure</i>	2 (0.5)
<i>Infection following a procedure</i>	5 (1.3)
<i>Other complication of procedure</i>	8 (2.0)
Cardiac problem (eg myocardial infarction)	16 (4.0)
Other respiratory symptoms (eg 'cough')	10 (2.5)
Chest pain – not otherwise classified	8 (2.0)
Other infection (eg urinary tract infections)	7 (1.8)
Pulmonary embolism	5 (1.3)
Pyothorax	2 (0.5)
Pleural effusion / haemothorax	4 (1.0)
Respiratory failure – other	3 (0.8)
Other respiratory – likely unrelated (eg COPD)	8 (2.0)
Other – unrelated	60 (15.1)

There were 911 deaths (32% of the cohort) until the end of June 2010. The most common cause of death was interstitial lung disease (50%), followed by cancer (18%), and cardiac disease (8%) (Table 4).

Table 3 – Cause of death of biopsy patients

Cause of death <i>n=911</i>	Number of deaths (%)
Interstitial lung disease	451 (49.5)
Cancer (excluding lung cancer)	94 (10.3)
Lung cancer	71 (7.8)
Ischaemic heart disease or heart failure	53 (5.8)
Chronic obstructive pulmonary disease	35 (3.8)
Pneumonia	35 (3.8)
Other respiratory	29 (3.2)
Connective tissue disease	25 (2.7)
Other cardiac cause	21 (2.3)
Stroke	13 (1.4)
Other	65 (7.1)
No data	19 (2.1)

With regards to early deaths, in-hospital mortality was 1.7% (47 deaths), 30-day mortality was 2.4% (68 deaths) and 90-day mortality was 3.9% (111 deaths). Elective biopsies had a lower mortality than non-elective ones: for elective procedures, in-hospital, 30-day and 90-day mortality were 1.0%, 1.5% and 2.8% respectively; for non-elective procedures, the figures were 4.6%, 6.3% and 8.8% respectively.

Risk factors for death within 90 days of biopsy (the time period yielding the most power) were identified as male sex, increasing age, increasing co-morbidity, and use of open thoracotomy (see Table 5). Results were broadly similar for deaths within 30 days or in-hospital, although the effect of co-morbidity was stronger for in-hospital deaths (see Tables E2-E3, supplementary material). Risk factors were less significant when non-elective patients were excluded (See tables E4-E6, supplementary material). In a sensitivity analysis excluding 593 patients who had an additional procedure code specifying 'approach to organ under imaging control' (which could be applied to VATS but was non-specific and therefore unclear), mortality was slightly higher at 1.9% (in-hospital), 2.7% (30 day) and 4.2% (90 day). Interstitial lung disease was the most common cause of early death in each category. After splitting admissions into four time periods, mortality was lowest in the latest time period (2006-2008) for in-hospital, 30-day and 90-day mortality measures; in-hospital mortality of 1.0% in 2006-2008 vs 1.7% in 1997-1999; 30-day mortality of 1.8% in 2006-2008 vs 3.0% in 1997-1999; and 90-day mortality of 2.8% in 2006-2008 vs 4.3% in 1997-1999. Risk factors for death within 90 days of biopsy for the period 2005 onwards are presented in Table E7 in the supplementary material.

We calculated a rate of death of 6.81 per 100 person-years (95% CI 6.38-7.27) in our biopsy cohort suggesting that about 6% of patients would die in the first year after surgery. For those aged 65 and over, the rate of death was 13.14 per 100 person-years (95% CI 11.86-14.55) suggesting about 13% of patients would die in the first year.

Using Cox regression, we estimated that males had a 52% increased risk of death compared to females, there was a 2-7 fold increased risk of death with increasing age compared to the lowest age category, there was an 2.3 fold increased risk of death with an updated Charlson score of 3 or more compared to 0, and a 61% increased risk of death with open surgery compared to VATS (see Table E8, supplementary material for details).

Table 4 – Multivariable analysis – associations with death within 90 days of biopsy

Variables	Cases	Deaths	Unadjusted Odds Ratio (95% CI)	p value	Adjusted Odds Ratio (95% CI)	p value
Sex						
Female	1,274	36	1.00	0.005	1.00	
Male	1,546	75	1.75 (1.17-2.63)		1.54 (1.02-2.34)	0.038
Age						
<44 yrs	576	10	1.00	<0.001	1.00	<0.001
45-54 yrs	636	21	1.93 (0.90-4.14)	(p for trend)	1.72 (0.79-3.72)	(p for trend)
55-64 yrs	843	31	2.16 (1.05-4.44)		1.85 (0.89-3.82)	
65-74 yrs	588	32	3.26 (1.59-6.69)		2.81 (1.35-5.82)	
>74 yrs	177	17	6.01 (2.70-13.39)		4.33 (1.90-9.89)	
Updated Charlson score						
0	1,947	75	1.00	0.082	1.00	0.037
1	717	23	0.83 (0.51-1.33)	(p for trend)	1.02 (0.61-1.69)	(p for trend)
2	116	8	1.85 (0.87-3.93)		1.63 (0.75-3.54)	
3 or more	40	*	3.57 (1.36-9.36)		3.88 (1.43-10.58)	
IMD score	2,760	109	0.99 (0.98-1.01)	0.381	1.00 (0.98-1.01)	0.521
Type of operation						
VATS	703	14	1.00	0.002	1.00	0.004
Open	362	21	3.03 (1.52-6.03)		2.94 (1.41-6.11)	
<i>Unclear or not specified</i>	1,755	76	2.23 (1.25-3.97)		2.37 (1.29-4.36)	
Provisional diagnosis						
J84.1	1,433	76	1.00	<0.001	1.00	0.008
J84.9	812	28	0.64 (0.41-0.99)		0.76 (0.48-1.20)	
J84.8	99	*	0.18 (0.03-1.32)		0.23 (0.03-1.65)	
RA-ILD	16	0	-		-	
CTD-ILD	38	*	0.99 (0.23-4.20)		0.91 (0.21-3.94)	
HP	162	*	0.34 (0.11-1.08)		0.45 (0.13-1.55)	
Sarcoidosis	260	*	0.07 (0.01-0.50)		0.10 (0.01-0.74)	

* in this table means a number between 1 and 5 – small numbers hidden to aid confidentiality. Higher updated Charlson score reflects greater degree of co-morbidity.

IMD: index of multiple deprivation (lower score = least deprived); VATS: video-assisted thoracoscopic surgery; J84.1: other interstitial pulmonary disease with fibrosis; J84.9: interstitial pulmonary disease, unspecified; J84.8: other specified interstitial pulmonary disease; RA-ILD (J99.0): rheumatoid lung disease; CTD-ILD (J99.1): respiratory disorders in other diffuse connective tissue disorders; HP (J67.9): hypersensitivity pneumonitis due to unspecified organic dust; Sarcoidosis (D86.0): sarcoidosis of lung.

For type of operation, 'unclear or not specified' mainly reflects older data from before a specific code for VATS was available. These cases are likely to be a combination of open and VATS procedures, with increasing numbers of VATS in later years.

DISCUSSION

Our data reveals an increasing number of surgical lung biopsies for interstitial lung disease in England from 1997-2008, with variation according to geographical region. The figure of 367 biopsies in 2008 would equate to an average of 13 annual biopsies per thoracic surgical centre in England (see supplementary material). Assuming our estimate of 51% of biopsies being for a provisional diagnosis of J84.1 (most specific for idiopathic pulmonary fibrosis, but possibly including other idiopathic interstitial pneumonias), this would equate to around 187 biopsies per year for IPF-clinical syndrome, which is 4.5% of the new cases per year in England (based on 5000 new cases in the UK (15), with England comprising 84% of the UK population). Unsurprisingly, there was a higher mortality for non-elective admissions. Complications were reasonably common, and the most common cause for re-admission and death was interstitial lung disease – likely (but not certain) to represent acute exacerbations. 30 day mortality was 2.4%, which is comparable to the 30 day mortality following lobectomy for non-small cell lung cancer (2.3%) – a potentially curative rather than diagnostic operation (16). Male sex, increasing age, increasing co-morbidity, and open surgery were risk factors for mortality.

Our cohort of 2,820 patients is much larger than most case series of surgical lung biopsies for interstitial lung disease, and encompasses multiple centres from across a single country (England). By using the Hospital Episodes Statistics database, we have been able to comprehensively capture all records of admissions to National Health Service hospitals, representing the vast majority of patients who receive healthcare in England, and the ability to link this with national cause of death data means that we were able to reliably assess mortality after discharge. Therefore, unlike other series, we have been able to assess mortality at several stages, as well as re-admissions, complications and ultimate cause of death for patients treated across a large number of surgical units.

However, there are limitations to our analysis. There is no clear diagnostic code for surgical lung biopsy in the OPCS-4 system, and it is possible that some of our procedures were performed via another means, such as medical thoracoscopy or computed tomography guided percutaneous needle biopsy. We attempted to exclude these by specifying cardiothoracic surgery as the treating speciality, but it is possible this may have been miscoded. The increasing number of cases in later years contrasts with a decrease in other studies (17) attributed to the publication of previous American Thoracic Society and European Respiratory Society consensus criteria (18). It is possible we may have included some patients undergoing biopsy for malignancy, despite excluding all patients with codes for lung cancer, however excluding all patients who subsequently died from cancer made little difference to our results. Our provisional diagnosis data should be interpreted with caution, as this originated from index admissions where final histology would likely not be available prior to discharge, and the confidence of this presumptive diagnosis may vary depending on the experience of the doctor completing discharge paperwork.

Our co-morbidity assessment depended on the detail recorded in discharge records, and may not have detected all medical problems. We did not have information on medications such as corticosteroids, immunosuppression, anticoagulation and importantly pre-operative oxygen requirements and lung function, all of which have been associated with adverse outcomes in surgical lung biopsy case series (6, 19, 20). Our mortality data only included the underlying cause of death, which may not reflect the *mode* of death, and therefore the majority of our cases with 'interstitial lung disease' may or may not have had pneumonia, acute exacerbations or sepsis as a final pathway. Finally, our data covered a time period lasting until 2008, and therefore it is likely that surgical practice and patient selection today would be slightly different.

Our estimates for mortality seem comparable with others in the literature. In fact, our overall in-hospital mortality of 1.7% is identical to that for elective patients from our recent large database study from the United States (10), where we identified similar risk factors for increased mortality.

Although the distinction between whether biopsies were elective or non-elective was less robust in this study, our estimate for elective in-hospital mortality of 1.0% is slightly lower than in the US data, which may reflect a more cautious approach to biopsies in the UK. Our overall figure of 2.4% 30-day mortality is similar to that reported by Carrillo *et al* in the next largest series, of 722 patients in Mexico from 1986-1990 (21), and also Sigurdsson *et al* in a smaller nationwide series from Iceland from 1986-2007 (20). It is slightly higher than the 2.1% estimate for VATS procedures from a systematic review by Nguyen and Meyer (7) and the 1.5% estimate from a recent case series in Edinburgh, UK (4), but lower than a previous summary estimate reported by Kreider *et al* (4.5%) (although this included studies with varying mortality endpoints) (6). Although comparison of mortality figures depends on case mix, endpoints, and procedure types, this consistency supports our estimates, and the comparison to mortality post lobectomy is not insignificant (16). 90-day mortality was less commonly reported in case series, but our overall estimate of 3.9% was again similar to that in Sigurdsson *et al*'s study (20).

Although our estimate of the proportion of cases of IPF undergoing lung biopsy may seem low, it is consistent with our experience that surgical biopsy is infrequently used to diagnose IPF in the UK if imaging is supportive. The proportion of younger patients undergoing biopsy also seems higher than would be expected, however again this is consistent with our experience that biopsy will be more readily attempted in younger patients with low co-morbidity, whereas clinicians may be more reluctant to offer the procedure to older patients. It is possible though that our caseload may include more younger patients with an inflammatory type of ILD. Given we excluded patients with lung cancer, it is surprising that so many patients eventually died of this: this may reflect uncoded disease before the biopsy, but also that lung cancer is more common in patients with IPF and may develop later on. As noted, if we omitted all patients who ultimately died from any type of cancer, overall mortality was essentially no different (in-hospital, 30-day and 90-day mortality of 1.7%, 2.4% and 4.0% respectively). Given our data includes patients who underwent open surgery (which has a

higher mortality) it is likely that our figures will slightly over-estimate the expected mortality from a VATS procedure carried out today.

The increasing number of biopsies over time in our study may suggest an increasing desire to characterise ILD, but may simply reflect the rising incidence of ILD in the UK (15, 22). It would be useful to extend our analysis to the present day to assess the impact of the availability of targeted treatments for IPF on rates of biopsy.

The mortality following surgical biopsy in interstitial lung disease, combined with improvements and greater experience in imaging studies, suggests that the decision to undergo biopsy should be taken very carefully in older patients with co-morbidities, with clear counselling of risks and awareness of factors associated with poorer outcomes. The limited number of biopsies performed annually per surgical centre in England suggests a national audit would be an effective means of monitoring outcomes: the Society for Cardiothoracic Surgeons now collates some of this data for UK centres, and this could be used to monitor local practice. The possible impact of low surgical centre volume on mortality may be less relevant for thoracic surgery in the UK (23), but should be taken into consideration in other regions (24).

In conclusion, our data suggests there were increasing numbers of surgical lung biopsies for interstitial lung disease in England from 1997-2008, with 4-5% of new cases of IPF-clinical syndrome being biopsied. 30-day and 90-day mortality were estimated at 2.4% and 3.9% respectively.

Increasing age and co-morbidity were risk factors for adverse outcome. Our data suggests a patient aged under 65 with no significant co-morbidities has a 30-day mortality of 1.6%, whereas a patient aged over 65 with co-morbidities has a 30-day mortality of 4.7%. Clearly personal factors such as lung function tests need to be taken into account, but these risks need to be discussed with patients.

COMPETING INTERESTS

RBH and TMM have received academic-industry funding from GSK for the multi-centre PROFILE study, which aims to evaluate biomarkers for IPF. JPH, AWF and VN have no relevant competing interests.

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CONTRIBUTORSHIP

TMM, AWF, VN and RBH conceived the study. VN and JPH requested and had access to the data. JPH prepared and analysed the data, and wrote the first draft. All authors were involved in reviewing the study and developing the final draft. All approved the final draft prior to submission.

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Figure Legends

Figure 1 – Flow diagram of patient selection

Figure 2 – Number of biopsies over time, stratified by sex

Figure 3 – Number of biopsies over time, stratified by age category

Figure 1

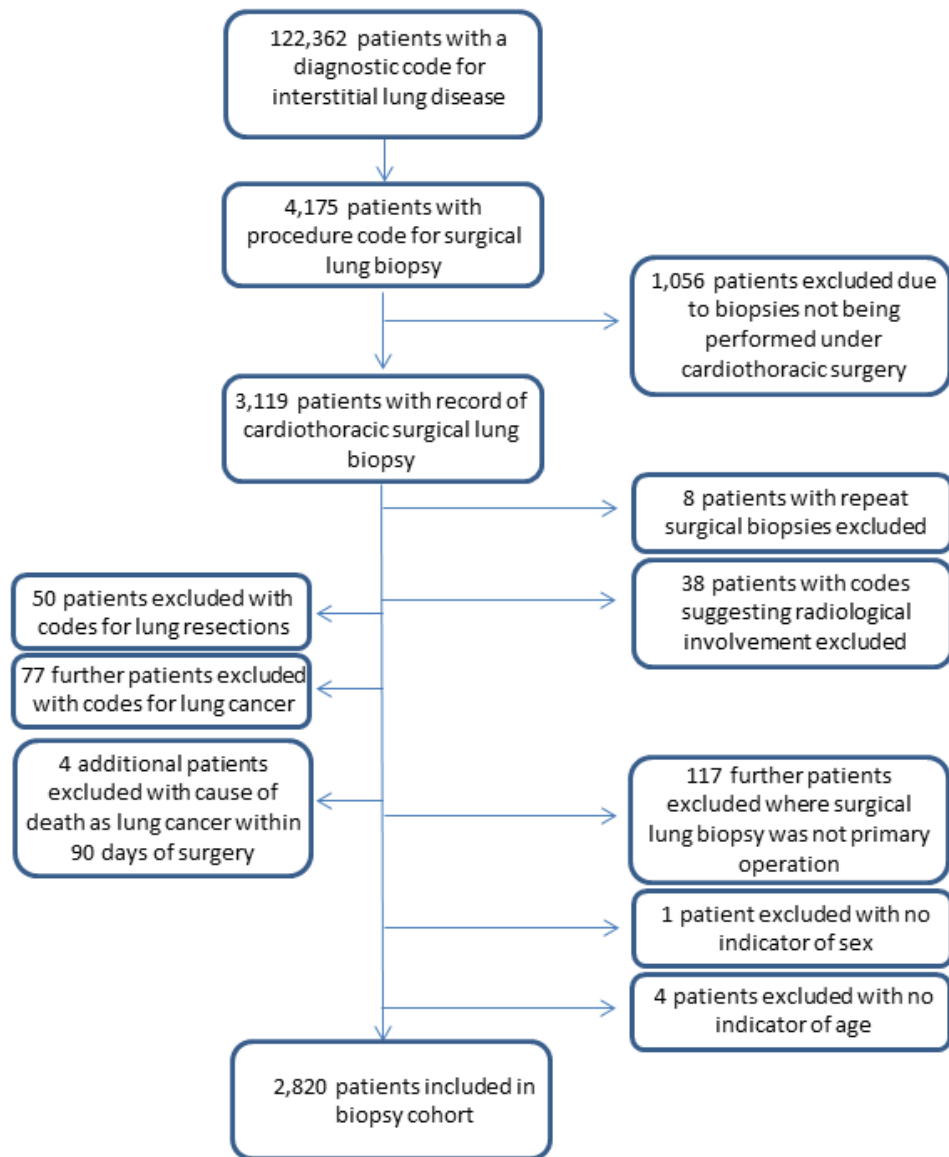


Figure 2

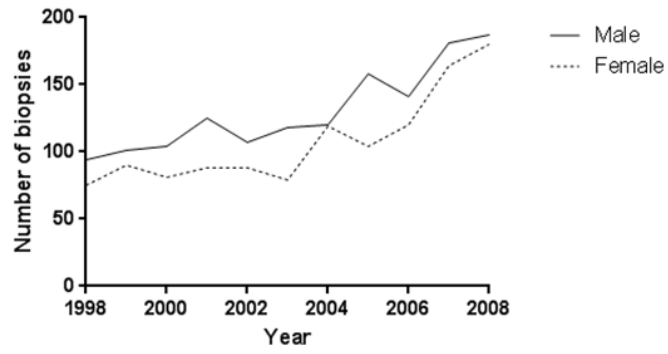


Figure 3

