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Population-based risk of complications following transthoracic needle lung biopsy of a pulmonary nodule

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Abstract

Background—Because pulmonary nodules are found in up to 25% of patients undergoing chest computed tomography, the question of whether to biopsy is becoming increasingly common. Data on complications following transthoracic needle lung biopsy are limited to case series from selected institutions.

Objective—To determine population-based estimates of risks of complications following transthoracic needle biopsy of a pulmonary nodule.

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Design—Cross-sectional analysis.

Setting—The 2006 Healthcare Cost and Utilization Project's State Ambulatory Surgery Databases and State Inpatient Databases for California, Florida, Michigan, and New York.

Patients—15,865 adults who underwent transthoracic needle biopsy of a pulmonary nodule.

Measurements—Percent of biopsies complicated by hemorrhage, any pneumothorax, and pneumothorax requiring chest tube, and adjusted odds ratios for these complications associated with various biopsy characteristics, calculated using multivariable population-averaged generalized estimating equations.

Results—Although hemorrhage was rare, complicating 1.0% (95% CI 0.9-1.2%) of biopsies, 17.8% (95% CI 11.8-23.8%) of patients with hemorrhage required a blood transfusion. By contrast, the risk of any pneumothorax was 15.0% (95% CI 14.0-16.0%), and 6.6% (95% CI 6.0-7.2%) of all biopsies resulted in a pneumothorax requiring chest tube. Compared to patients without complications, those who experienced hemorrhage or pneumothorax requiring chest tube had longer lengths of stay ($p<0.001$) and were more likely to develop respiratory failure requiring mechanical ventilation ($p=0.02$). Patients aged 60-69 years (as opposed to younger or older patients), smokers, and those with chronic obstructive pulmonary disease had higher risk of complications.

Limitations—Estimated risks may be inaccurate if coding of complications is incomplete. The databases analyzed contain little clinical detail (e.g., nodule characteristics, biopsy pathology) and cannot determine whether biopsies produced useful information.

Conclusion—While hemorrhage is an infrequent complication of transthoracic needle lung biopsy, pneumothorax is common and often necessitates chest tube placement. These population-based data should help patients and doctors make a more informed choice on whether to biopsy a pulmonary nodule.

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INTRODUCTION

With rising use of chest computed tomography (CT) for indications ranging from ruling out a pulmonary embolism to lung cancer screening, several hundred thousand Americans are diagnosed each year with a pulmonary nodule (1). Patients and doctors then face the dilemma of whether to biopsy the nodule. Although most nodules are benign incidental findings, some are lung cancer. Unfortunately, the invasive procedures to conclusively make this determination can cause harm.

Transthoracic needle lung biopsy (i.e., CT-guided biopsy) is recommended for suspicious peripheral nodules (2). In 2004, over 58,000 such biopsies were performed among Medicare fee-for-service patients (3). CT-guided biopsy may cause hemorrhage or pneumothorax, which may then require hospitalization. Consequently, doctors and patients must carefully weigh whether the risk of cancer justifies the risk of potential harms of biopsy.

Because the literature contains only case series from selected centers (4-13), estimated risks of CT-guided biopsy are highly variable. For example, over the past 10 years, published reports of pneumothorax risk range from 4% (11) to 42% (13). To provide patients and physicians with representative data to inform decision-making, we determined population-based estimates of risk of complications following CT-guided biopsy of a pulmonary nodule.

METHODS

Study Design

We performed a cross-sectional analysis of discharge records in four large, geographically diverse states in 2006. Our primary outcomes were risk of complications of CT-guided biopsy of a pulmonary nodule: the percent of biopsies complicated by hemorrhage, pneumothorax, or pneumothorax requiring chest tube. (The Appendix Table shows all diagnosis and procedure codes used in this study). At our institutions, studies using de-identified, publicly available data are deemed exempt from institutional board review.

Data Source

We used the 2006 Healthcare Cost and Utilization Project State Inpatient Databases (14) and State Ambulatory Surgery Databases (15) from the largest participating state in each census region (California, Florida, Michigan, New York). These states had a combined estimated adult population of 63,340,236, representing 28.2% of the 2006 United States (US) population (16).

The State Inpatient Databases include all discharge records from each state's community hospitals, defined by the American Hospital Association as "all nonfederal, short-term, general and other specialty hospitals, excluding hospital units of institutions" (14). The State Ambulatory Surgery Databases contain all discharge records from ambulatory surgical procedures performed in non-federal community hospitals and free-standing ambulatory surgery centers. These databases are fairly comprehensive; for example, the proportion of community hospitals represented in the 2006 State Inpatient Database ranges from 92% (Michigan) to 99.5% (New York) (14). Each record contains information on patient demographics; hospital characteristics; up to 31 International Classification of Diseases, 9th revision diagnosis codes, up to 31 International Classification of Diseases, 9th revision procedure codes, and/or up to 21 current procedural terminology codes.

Population

We first identified all adults who underwent CT-guided lung biopsy. We then restricted analysis to patients with a pulmonary nodule, defined by codes for coin lesion, chest mass, or lung neoplasm. Although some coding experts recommend using diagnosis code 518.89 ("Other diseases of lung not elsewhere classified") for pulmonary nodules (17), we did not include this code in our definition due to its non-specific nature. Because our data showed that patients who underwent concomitant chest surgery or multiple CT-guided lung biopsies were almost twice as likely to suffer complications, we also excluded these patients from our analyses.

Analyses

We calculated the overall rate of CT-guided lung biopsies per 100,000 adults in the selected states, and also age-standardized each state's rate using the 2006 estimated US adult population (16).

We then measured our primary outcome: the percent of biopsies complicated by hemorrhage, pneumothorax, or pneumothorax requiring chest tube. We investigated whether presence of each complication was associated with clinically important adverse outcomes including need for blood transfusion (for the complication of hemorrhage), increased mean length of stay, respiratory failure (defined by presence of codes for mechanical ventilation and intubation within one day following the biopsy), or hospital death. We used the SVY mean and proportion functions in STATA 10.1 (College Station, Texas), clustered by hospital and stratified by state, with post-estimation Wald tests to compare these outcomes

among patients with versus without complications. P-values <0.05 were considered statistically significant.

We next explored the association between each biopsy characteristic and each complication using logistic regression. We examined patient characteristics (age, sex, co-morbid pulmonary disease), visit characteristics (scheduled procedure, concurrent bronchoscopy), and hospital characteristics (volume of CT-guided biopsies performed per year, hospital state). Comorbid pulmonary disease was defined by codes for current or former tobacco use, chronic obstructive pulmonary disease (COPD), or pleural effusion. We considered “scheduled procedures” to be those in which the CT-guided biopsy was performed as an ambulatory procedure or within one day of hospital admission (as opposed to those biopsies performed in the midst of a hospital stay). We defined “concurrent bronchoscopy” as a bronchoscopy performed on the same day as CT-guided biopsy.

Adjusted odds ratios and 95% confidence intervals (CI) for complications were calculated based on robust standard error estimates including all biopsy characteristics (i.e., patient, visit, and hospital characteristics) described above as covariables. We investigated but did not identify interactions between state and patient characteristics. We used generalized estimating equations to account for clustering by hospital assuming the binomial family, a logit link function and an exchangeable correlation structure. Analyses were performed in STATA 10.1 using the xtgee function. To determine whether residual variation across hospitals was important we ran a random effects model with a random intercept for hospital.

Sensitivity Analyses

We performed 2 sensitivity analyses to address potential limitations of using administrative databases. To address the possibility that a discharge diagnosis of pneumothorax may not represent a complication of CT-guided biopsy, we performed a sensitivity analysis for the outcome of any pneumothorax using the more specific code for “iatrogenic pneumothorax” and eliminating discharges that included other procedures that could cause pneumothorax (e.g., central venous catheterization, bronchoscopy with transbronchial biopsy). To address the possibility that pneumothorax requiring chest tube may not be a complication of CT-guided biopsy, we repeated the first sensitivity analysis for the outcome of pneumothorax requiring chest tube, this time also excluding patients with a pleural effusion to ensure chest tube placement was for pneumothorax.

Role of the Funding Source

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RESULTS

Of 22,176 CT-guided lung biopsies in the 4 states, 15,865 met our criteria of a single biopsy of a pulmonary nodule (Figure 1). Table 1 displays characteristics of the study population, stratified by state. As shown, there were statistically significant differences among states in patient, visit, and hospital characteristics.

Risk of complications

Among all CT-guided biopsies of a pulmonary nodule, 1.0% (95% CI 0.9-1.2%) were complicated by hemorrhage, 15.0% (95% CI 14.0-16.0%) by any pneumothorax, and 6.6% (95% CI 6.0-7.2%) by pneumothorax severe enough to require a chest tube. When we

performed sensitivity analyses, the estimated risks changed little: for the outcome of any pneumothorax, risk was 13.6% (95% CI 12.6-14.6%); for the outcome of pneumothorax requiring chest tube, risk was 6.1% (95% CI 5.4-6.7%).

Risk of complications varied across hospitals, ranging from 0-100% for each complication (95% CI = 0-5.9% for hemorrhage, 0-50% for any pneumothorax, and 0-25% for pneumothorax requiring chest tube). After accounting for the fixed effects in our models, there was significant residual variation across hospitals for each complication ($p = .0199$ for hemorrhage, $p < .0001$ for any pneumothorax, and $p < .0001$ for pneumothorax requiring chest tube). While the estimated residual correlation within hospital appeared quite small ($\rho = .003$, $.03$ and $.03$ for the three outcomes, respectively), these results are consistent with meaningful variation in outcomes across hospitals.

Several findings suggest that these complications were clinically important. Eighteen percent (95% CI 11.8-23.8%) of patients with hemorrhage from biopsy required a blood transfusion, compared to 4.3% of patients with no documented complication ($p < .001$). As shown in Table 2, complications were significantly associated with other adverse outcomes as well. Patients with complications more often required hospitalization (if performed in the outpatient setting) or had longer lengths of stay (if performed in the inpatient setting), as compared to patients without complications. Among all patients who underwent CT-guided biopsy, respiratory failure requiring mechanical ventilation occurred more often in patients with complications of hemorrhage (4.3%, $p = 0.02$) or pneumothorax requiring chest tube (1.4%, $p = 0.02$) compared with patients without recorded complications (0.6%).

Characteristics associated with complications

Characteristics associated with complications are shown in Table 3. Age (60-69 years, versus age < 60 or age ≥ 80), female sex, and comorbid pulmonary disease (COPD or pleural effusion) were significantly associated with hemorrhage. Age 60-69 years, tobacco use, and COPD were significantly associated with both any pneumothorax and pneumothorax requiring chest tube, while patients undergoing concurrent bronchoscopy had a lower risk of any pneumothorax ($p < .001$) and pneumothorax requiring chest tube ($p < .01$). Patients undergoing a scheduled procedure (ambulatory or within one day of hospital admission) had significantly higher rates of all complications than patients who had a biopsy performed in the midst of a hospital stay. Figure 2 shows adjusted rates of complications stratified by age, illustrating that patients aged 60-69 years experienced significantly more complications than younger or older patients.

Variation among states

Overall, 25.0 CT-guided biopsies of a pulmonary nodule were performed per 100,000 adults (95% CI 24.7-25.4). Table 4 highlights the substantial variation between states in biopsy utilization rates and complication rates. Age-standardized biopsy rates in New York (14.7 per 100,000) and California (17.5) were less than half those in Michigan (35.9) and Florida (36.2). As shown in Table 4, low biopsy utilization states had lower relative rates of complications at the population level, but higher relative rates of complications at the biopsy level (e.g., higher odds of pneumothorax requiring chest tube among patients who underwent biopsy in New York versus Florida).

DISCUSSION

In this paper we provide population-based complication risks following CT-guided biopsy of a pulmonary nodule. While hemorrhage was infrequent (1%), pneumothorax was common (15%). Complications were associated with adverse outcomes including longer length of

stay and higher rates of respiratory failure. We confirmed prior reports that older age and COPD increase complications (4, 8, 9, 13). Perhaps most importantly, we show that over 6% of CT-guided biopsies result in pneumothorax requiring chest tube. This is a clinically important complication that entails pain, serial imaging and radiation exposure, and hospitalization averaging 2-5 days (18).

A recent study showed that doctors do not accurately predict pneumothorax risk following CT-guided biopsy (12); this may in part be due to a lack of representative data. Case series over the last decade report hemorrhage in 2-10% and pneumothorax in 4-42% (4-13). Some estimates are clearly lower than the risk the typical patient faces, reflecting the expertise of specialized centers. Other estimates seem high, perhaps because all complications visualized under CT-guidance were included, regardless of their clinical relevance.

Comprehensive databases offer important advantages over case series. Our analysis of essentially all CT-guided lung biopsies in four states (>15,000 biopsies) offers a more representative picture of complication risk than smaller case series of a few hundred patients. Our estimated risks of complications are more likely to be clinically important than complications defined by imaging findings at the time of biopsy (as is often done in case series), which may be irrelevant to the patient if no symptoms result. For example, in our study, hemorrhage recorded on discharge records was associated with a number of clinically important adverse events, including longer length of stay, need for blood transfusion, and respiratory failure requiring mechanical ventilation. Similarly, our estimated risk of pneumothorax requiring chest tube should be reliable and precise, since it is based on billing for a clinically important invasive procedure with coding specificity and positive predictive value of 99% and 86%, respectively (19). Indeed, our estimated risk of pneumothorax requiring chest tube (6.6%, 95% CI 6.0-7.2%) is consistent with, but far more precise than, estimates from case series (0.2-9.0%) (4-13).

Analyzing administrative databases has disadvantages. While they can be used to estimate short-term risks of procedures like CT-guided biopsy, these data are de-identified and cannot be linked to other sources to provide information on diagnostic yield of biopsy or long-term risks and benefits of the procedure. It is likely that some complications, particularly minor complications, are systematically undercoded. However, there has been increasing emphasis on accurately coding complications (20), and procedure-related adverse outcomes of hemorrhage and pneumothorax have been shown to have positive predictive values over 70% (20-22). Without access to clinical progress notes, we cannot be certain of the sequence of events. For example, one might wonder whether a discharge diagnosis of pneumothorax is truly a complication of CT-guided biopsy. However, our more specific sensitivity analyses, which produced little change in estimated risks, suggest it is highly likely that our reported risks of any pneumothorax and pneumothorax requiring chest tube indeed reflect complications of CT-guided biopsy.

Another disadvantage of de-identified administrative databases is the lack of clinically detailed variables to predict complications, such as previously identified patient risk factors of nodule size and location, physician characteristics such as specialty or years of experience (7, 9), or concentration of physicians or CT scanners in a hospital or region. The comorbidities we tested (e.g., COPD, tobacco use) may be variably coded on discharge records, and it is possible that coding of comorbidities may be more thorough on records that also show a complication. Without clinical detail, some observed associations appear counter-intuitive at first glance. For example, pleural effusion was associated with a five-fold higher likelihood of hemorrhage; however, we could not distinguish whether the effusion increased the risk of complication, or was itself the complication (i.e., hemothorax from biopsy). Although some variables associated with lower complication rates (e.g.,

patients undergoing concurrent bronchoscopy, biopsies performed in the midst of a hospital stay as opposed to a scheduled procedure) initially seem counter-intuitive, we believe the explanation lies in patient selection: doctors choose to perform bronchoscopy and CT-guided biopsy on the same day only in the subset of patients best able to tolerate both procedures (those with lower risk of complications); similarly, doctors tend to defer elective procedures like CT-guided biopsy in patients at high risk of complications (such as those with severe COPD) during acute hospital admissions. We suspect the lower complication risk in younger patients (age<60) represents an overall healthier population, while the lower risk of complications in older patients (age>70) suggests that doctors may reserve biopsy for the subset of older adults who are healthy enough to tolerate treatment if the nodule is malignant.

Interestingly, as shown in Table 4, low biopsy utilization states had a higher complication rate per biopsy than high biopsy utilization states (e.g., odds ratio for pneumothorax requiring chest tube given biopsy = 1.85, 95% CI 1.35-2.54 for New York vs. Florida). High biopsy utilization states likely achieved a lower rate of complications per biopsy by expanding the pool of patients undergoing biopsy to include healthier individuals with a lower risk of both cancer and complications. In support of this hypothesis is the fact that, compared to high biopsy utilization states, a greater proportion of CT-guided biopsies in New York were performed among patients with COPD and patients aged 60-79, factors associated with both lung cancer and biopsy complications. It is important to note, however, that because fewer biopsies were performed at the population level in the low biopsy utilization states, the rate of complications at the population level was lower in the low biopsy utilization states (e.g., age-adjusted relative rate of pneumothorax requiring chest tube at the population level = 0.61, 95% CI 0.50-0.73 in New York vs. Florida).

The striking variability in biopsy utilization rates between states suggests a lack of consensus on optimal management of pulmonary nodules, reflecting the paucity of evidence in this area. There have been no randomized trials comparing strategies of pulmonary nodule management (e.g., serial imaging, biopsy, early surgery) or addressing whether, when, and how to perform biopsy, and guidelines on pulmonary nodule management are based primarily on expert opinion (2). Although full results have yet to be released, the National Cancer Institute recently stopped its National Lung Screening Trial comparing chest CT versus x-ray screening early due to a reported 20% reduction in lung cancer mortality in the CT arm (23). This announcement received substantial media coverage and has led to renewed public and physician enthusiasm for lung cancer screening and aggressive pulmonary nodule management in general. Data from a feasibility study for this trial suggest that a third of smokers who undergo chest CT scanning have a false positive finding (a pulmonary nodule that does not turn out to be malignant over the next year) (24). These patients will then be faced with the choice of whether or not to proceed with biopsy, an area not addressed by the design of the trial. Although our study does not address the long-term risk-benefit trade-off of whether to pursue biopsy, the population-based data we have provided on short-term risk of complications of CT-guided biopsy may help patients with pulmonary nodules and their doctors make a more informed decision.

Our data suggest that several thousand Americans experience complications of CT-guided biopsy each year. These harms will no doubt continue to rise as more patients are diagnosed with nodules and undergo biopsy. For many patients, including those with a low risk of cancer, those too frail to undergo cancer treatment, or those with a high risk of cancer who should proceed directly to surgery, this procedure may be unnecessary. Before exposing patients to potential harm from CT-guided biopsy, it is critical that physicians ensure patients understand the risks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Inclusion and exclusion criteria to create final study population

*Includes open or video-assisted thoracoscopic surgical biopsy, excision, wedge resection, segmentectomy, lobectomy, or pneumonectomy

Figure 2. Adjusted risk of complications following transthoracic needle biopsy of a pulmonary nodule

*Adjusted for all variables shown in Table 3 using generalized estimating equations models.

Table 1
Baseline characteristics of CT-guided biopsies of a pulmonary nodule

Baseline characteristics	Overall (n=15,865)	California (n=4382)	Florida (n=6408)	Michigan (n=2820)	New York (n=2255)	p-value
<i>Patient characteristics</i>						
Female	48.4%	49.4%	47.5%	48.1%	49.8%	p=0.12
Age group, years						p<0.001
18-49	6.9%	8.2%	5.8%	7.6%	6.7%	
50-59	13.4%	14.9%	12.1%	15.5%	11.9%	
60-69	25.4%	23.4%	25.8%	26.2%	27.1%	
70-79	34.1%	32.6%	35.4%	33.0%	34.8%	
80 and older	20.2%	20.9%	21.0%	17.7%	19.4%	
Comorbid pulmonary condition						
Current or former tobacco use	36.4%	40.4%	36.3%	35.5%	30.0%	p<0.001
Chronic obstructive pulmonary disease	27.4%	26.1%	28.4%	25.3%	29.9%	p<0.001
Pleural effusion	4.8%	5.6%	4.0%	4.1%	6.3%	p<0.001
<i>Visit characteristics</i>						
Scheduled procedure	67.1%	59.2%	75.4%	72.9%	51.3%	p<0.001
Concurrent bronchoscopy	1.9%	1.4%	2.0%	0.6%	4.3%	p<0.001
<i>Hospital characteristics</i>						
Number of facilities performing CT-guided biopsies (Total)	713	286	174	90	163	
Number of facilities appearing in both inpatient and ambulatory surgery databases	440	153	146	67	74	
Number of hospitals appearing only in inpatient databases	247	125	22	14	86	
Number of facilities appearing only in ambulatory surgery databases	26	8	6	9	3	
Biopsy volume per year						
Median (range)	55 (1-245)	35 (1-151)	77 (1-245)	77 (1-169)	33 (1-114)	p<0.001
Number of biopsies per year (%)						p<0.001
1-50	46.9%	67.8%	30.4%	27.4%	77.5%	
51-100	26.7%	23.5%	27.8%	37.8%	16.3%	
101-245	26.4%	8.7%	41.8%	34.8%	6.2%	

CT = computed tomography; SASD = State Ambulatory Surgery Database; SID = State Inpatient Database

Table 2
Clinical outcomes among patients undergoing CT-guided lung biopsy, stratified by presence of complication and timing of biopsy

		Had a complication		
	No complication *	Hemorrhage	Any pneumothorax	Pneumothorax with chest tube
Among all patients who underwent biopsy (n=15,865)				
Number in group, % (95% CI)	84.2% (83.2-85.2%)	1.0% (0.9-1.2%)	15.0% (14.0-16.0%)	6.6% (6.0-7.2%)
Mean length of stay, days (95% CI)	4.8 (4.5-5.2)	7.6 (5.5-9.6) §	5.3 (4.9-5.8) ¶	6.3 (5.6-7.0) ¶
Respiratory failure, % (95% CI)	0.6% (0.4-0.7%)	4.3% (1.3-7.3%) ¶	0.8% (0.5-1.2%)	1.4% (0.7-2.1%) ¶
Hospital death, % (95% CI)	1.8% (1.5-2.0%)	4.3% (1.2-7.4%)	1.6% (1.1-2.2%)	2.0% (1.2-2.9%)
Among patients with a scheduled biopsy (n=10,638)				
Number in group, % (95% CI)	83.8% (82.5-85.1%)	1.0% (0.8-1.2%)	15.4% (14.2-16.7%)	6.8% (6.0-7.6%)
Mean length of stay, days (95% CI)	1.0 (0.8-1.1)	1.7 (1.0-2.4) ¶	1.9 (1.6-2.1) ¶	2.7 (2.3-3.0) ¶
Respiratory failure, % (95% CI)	0.1% (0.1-0.2%)	4.6% (0.1-8.7%) ¶	0.3% (0.0-0.6%)	0.7% (0.1-1.3%)
Hospital death, % (95% CI)	0.4% (0.3-0.6%)	0.9% (0.0-2.7%)	0.5% (0.2-0.8%)	1.0% (0.2-1.7%)
Among patients with a biopsy in midst of a hospital stay (n=5,227)				
Number in group, % (95% CI)	85.0% (84.0-86.1%)	1.1% (0.8-1.3%)	14.1% (13.1-15.2%)	6.1% (5.4-6.8%)
Mean length of stay, days (95% CI)	10.8 (10.4-11.3)	17.1 (13.4-20.7) ¶	11.6 (10.9-12.4)	13.1 (12.0-14.2) ¶
Respiratory failure, % (95% CI)	1.5% (1.1-1.8%)	3.6% (0.0-8.7%)	2.0% (1.0-3.0%)	3.1% (1.2-5.0%)
Hospital death, % (95% CI)	4.3% (3.7-5.0%)	10.9% (2.6-19.3%)	4.2% (2.7-5.7%)	4.4% (2.2-6.6%)

CI = Confidence Interval

* Referent group for p-values is group of patients with no complications; statistically significant differences (p<0.05) are highlighted in bold.

[§] p<0.01

^{//} p<0.05

^{//} p<0.001

Table 3
Odds ratios for complications associated with various characteristics included in multivariable generalized estimating equations models

Baseline characteristics	Odds Ratio for Complication (95% Confidence Interval)*		
	Hemorrhage (n=163)	Any pneumothorax (n=2381)	Pneumothorax requiring chest tube (n=1047)
<i>Patient characteristics</i>			
Female	1.42 (1.03-1.96) §	0.99 (0.91-1.08)	0.93 (0.81-1.05)
Age group, years			
18-49	0.42 (0.17-1.04)	0.72 (0.58-0.89) ¶	0.63 (0.45-0.88) ¶
50-59	0.43 (0.22-0.83) §	0.83 (0.72-0.97) §	0.83 (0.68-1.00)
60-69	referent	referent	referent
70-79	0.92 (0.63-1.37)	0.89 (0.80-0.99) §	0.78 (0.67-0.91) ¶
80 and older	0.51 (0.30-0.84) ¶	0.93 (0.82-1.05)	0.78 (0.66-0.92) ¶
<i>Comorbid pulmonary condition</i>			
Current or former tobacco use	1.13 (0.78-1.63)	1.37 (1.23-1.54) ¶	1.50 (1.26-1.77) ¶
Chronic obstructive pulmonary disease	1.61 (1.08-2.39) §	1.88 (1.69-2.09) ¶	2.52 (2.16-2.95) ¶
Pleural effusion	6.32 (4.18-9.55) ¶	1.04 (0.83-1.29)	1.09 (0.81-1.47)
<i>Visit characteristics</i>			
Scheduled procedure	1.64 (1.10-2.45) §	1.60 (1.40-1.82) ¶	1.86 (1.53-2.25) ¶
Concurrent bronchoscopy	1.20 (0.43-3.36)	0.27 (0.15-0.49) ¶	0.28 (0.13-0.64) ¶
<i>Hospital characteristics</i>			
Biopsy volume per year			
1-50	referent	referent	referent
51-100	0.75 (0.49-1.14)	0.92 (0.78-1.09)	1.10 (0.86-1.41)
101-245	0.82 (0.47-1.43)	1.02 (0.81-1.27)	1.14 (0.84-1.55)

* Odds ratios with a statistically significant p-value (p<0.05) are highlighted in bold font. Multivariable generalized estimating equations models also included hospital state; please see Table 4 for odds ratios for complications associated with each state relative to the referent state of Florida.

§ p<0.05

¶ p<0.01

¶ p<0.001

Table 4
Rates of complications at the population level and biopsy level, stratified by state*

	High biopsy utilization states		Low biopsy utilization states	
	Florida (n=6408)	Michigan (n=2820)	California (n=4382)	New York (n=2255)
<i>Age-adjusted population biopsy rate per 100,000 adults (95% CI)</i>	36.2 (35.3-37.1)	35.9 (34.6-37.2)	17.5 (16.9-18.0)	14.7 (14.1-15.3)
Population-level analyses				
<i>Age-adjusted complication rate per 100,000 adults (95% CI)</i>				
Hemorrhage	0.33 (0.2-0.4)	0.32 (0.2-0.5)	0.23 (0.2-0.3)	0.15 (0.1-0.2)
Any pneumothorax	5.2 (4.4-5.9)	5.4 (4.6-6.3)	2.7 (2.4-3.0)	2.4 (1.9-2.9)
Pneumothorax requiring chest tube	2.2 (1.8-2.6)	2.0 (1.5-2.4)	1.2 (1.0-1.4)	1.3 (0.9-1.7)
<i>Age-adjusted relative rate of complications in the population (95% CI)</i>				
Hemorrhage	referent	0.98 (0.57-1.63)	0.71 (0.48-1.07)	0.45 (0.26-0.77) §
Any pneumothorax	referent	1.06 (0.94-1.20)	0.53 (0.47-0.59) ¶	0.47 (0.41-0.53) ¶
Pneumothorax requiring chest tube	referent	0.90 (0.74-1.10)	0.54 (0.46-0.64) ¶	0.61 (0.50-0.73) ¶
Biopsy-level analyses				
<i>Age-adjusted complications per 1000 biopsies (95% CI)</i>				
Hemorrhage	7 (5-9)	9 (5-13)	14 (10-18)	10 (5-14)
Any pneumothorax	112 (96-129)	148 (126-172)	166 (145-187)	157 (124-192)
Pneumothorax requiring chest tube	48 (40-57)	54 (42-66)	73 (60-87)	86 (61-113)
<i>Adjusted odds ratio of complications given biopsy (95% CI) €</i>				
Hemorrhage	referent	1.08 (0.64-1.80)	1.45 (0.91-2.29)	1.05 (0.63-1.77)
Any pneumothorax	referent	1.06 (0.89-1.27)	1.17 (0.99-1.38)	1.30 (1.04-1.63) ¶
Pneumothorax requiring chest tube	referent	0.85 (0.67-1.08)	1.32 (1.04-1.68) ¶	1.85 (1.35-2.54) ¶

CI = Confidence Interval

* Statistically significant (p<0.05) comparisons to referent state (Florida) are highlighted with bold font.

€ Odds ratios are result of multivariable generalized estimating equations, adjusted for variables shown in Table 3 as well as state.

¶ p<0.001

§ p<0.01

// p<0.05