CHEST

Original Research

PULMONARY PROCEDURES

Complications, Consequences, and Practice Patterns of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Results of the AQuIRE Registry

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Background: **Few studies of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) have been large enough to identify risk factors for complications. The primary objective of this study was to quantify the incidence of and risk factors for complications in patients undergoing EBUS-TBNA.**

Methods: **Data on prospectively enrolled patients undergoing EBUS-TBNA in the American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education (AQuIRE) database were extracted and analyzed for the incidence, consequences, and predictors of complications.**

Results: **We enrolled 1,317 patients at six hospitals. Complications occurred in 19 patients (1.44%; 95% CI, 0.87%-2.24%). Transbronchial lung biopsy (TBBx) was the only risk factor for complications, which occurred in 3.21% of patients who underwent the procedure and in 1.15% of those who did not (OR, 2.85; 95% CI, 1.07-7.59; *P* = .04). Pneumothorax occurred in seven patients (0.53%; 95% CI, 0.21%-1.09%). Escalations in level of care occurred in 14 patients (1.06%; 95% CI, 0.58%-1.78%); its risk factors were age > 70 years (OR, 4.06; 95% CI, 1.36-12.12; *P* = .012), inpatient status (OR, 4.93; 95% CI, 1.30-18.74; *P* = .019), and undergoing deep sedation or general anesthesia (OR, 4.68; 95% CI, 1.02-21.61; *P* = .048). TBBx was performed in only 12.6% of patients when rapid onsite cytologic evaluation (ROSE) was used and in 19.1% when it was not used (*P* = .006). Interhospital variation in TBBx use when ROSE was used was significant (*P* < .001).**

Conclusions: **TBBx was the only risk factor for complications during EBUS-TBNA procedures. ROSE significantly reduced the use of TBBx.** ***CHEST 2013; 143(4):1044–1053***

Abbreviations: AQuIRE = American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education; EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; ROSE = rapid onsite cytologic evaluation; TBBX = transbronchial lung biopsy

Mediastinal lymph node sampling is a critical step in the staging of lung cancer[1-3] and in the diagnosis of inflammatory conditions, such as sarcoidosis.[4-8] Over the past decade, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has emerged as a minimally invasive, highly accurate technique for sampling intrathoracic lymph nodes, with a sensitivity of 88% to 93% in distinguishing lymph node metastases from benign conditions.[9,10] Comparative studies have demonstrated the superiority of EBUS-TBNA to conventional TBNA.[11] EBUS-TBNA can reach multiple nodal stations, including

the hilar nodes, and one randomized trial found EBUS-TBNA to be superior to mediastinoscopy for lung cancer staging.[12] As a result, EBUS-TBNA is becoming widely adopted as the standard of care for sampling mediastinal lymph nodes.

Although the initial studies of EBUS-TBNA focused on evaluating diagnostic performance, many of these studies conducted at centers of excellence also reported impressively low complication rates.[6,11-17] Whether these results can be generalized to everyday clinical practice is unknown because the study sample sizes were too small for a formal analysis of complications. Additional outcomes data on EBUS-TBNA complications in everyday clinical practice are, therefore, needed to establish benchmarks for quality improvement and clinical effectiveness.

Bronchoscopy registries are well suited for this purpose because they provide a more generalized snapshot of outcomes and clinical effectiveness than do clinical trials, which by their nature are more selective and not necessarily reflective of everyday practice.[13,18,19] We used the American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education (AQuIRE) program to evaluate EBUS-TBNA complications, their clinical consequences, and the relationship between complications and practice patterns. The primary objective was to quantify the incidence of and risk factors for complications in patients undergoing EBUS-TBNA. The secondary objectives were to quantify the incidence and risk factors for pneumothorax, to evaluate the consequences of complications as measured by escalation in the level of care, and to assess differences in complication rates among hospitals and the impact of practice pattern variations, such as the use of transbronchial biopsy (TBBx).

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Materials and Methods

All patients undergoing bronchoscopy with lymph node sampling by TBNA at six centers from February 13, 2009, to August 31, 2010, were entered consecutively into AQuIRE at the time of their procedure.[20] Institutional review board approval was obtained at each site (e-Appendix 1). Informed consent or a waiver of consent was obtained in accordance with institutional guidelines. Data were entered through the AQuIRE Web-based interface using standardized definitions, quality control checks, and protocols as previously described.[19]

Information extracted from AQuIRE included patient demographics, clinical characteristics, physician and hospital information, sedation information, procedural information, pathology results, complications, and outcomes of complications. The use of rapid onsite cytologic evaluation (ROSE) was recorded, but the results of the onsite reading were not entered; only the final reading by the pathologist was recorded.

The primary outcome was procedural morbidity, defined as any of the following events within 24 h: bleeding that required additional intervention, pneumothorax, clinically significant airway injury (defined as airway injury requiring either escalation of care or additional intervention), sustained hypoxia (defined as oxygen saturation $<90\%$ for >1 min), hypotension, cardiac arrest, arrhythmia, or respiratory failure requiring positive pressure ventilation. Secondary outcomes were the clinical consequences of complications as measured by the need for an escalation in level of care, the need for further interventions to manage these complications, or death. An escalation in level of care was defined as admission to the hospital if the patient was an outpatient or transfer to the ICU if the patient was an inpatient.

Categorical data were compared using the Fisher exact test. Stratified analysis was done using the Cochrane Mantel-Haenszel test. Logistic regression was used to examine the association of outcomes with patient and clinical characteristics. Hierarchical models, with patients nested within hospitals, were compared with ordinary logistic regression models by removing the hospital variance component. Hospital experience was modeled by using annual hospital volume of TBNA procedures as a hospital-level variable; all other variables were considered patient-level variables. We decided a priori that variables with $P \leq .20$ on univariate analysis would be candidate variables for the multivariate models. A backward elimination strategy was used, and factors were retained if $P < .05$. $P < .05$ was considered significant; all tests were two sided. All statistical analyses were performed with SAS version 9.1 (SAS Institute Inc) software.

Results

A total of 1,317 patients were enrolled by 12 physicians from six hospitals. Baseline patient characteristics are summarized in Table 1.

Any Complication

Among the 1,317 patients, 19 (1.44%; 95% CI, 0.87%-2.24%) had a complication of EBUS-TBNA; one patient died after experiencing complications (Table 2). Hospital-specific 24-h complication rates ranged from 0.50% to 3.26% ($P = .37$) (e-Table 1). Univariate and multivariate analyses showed that only TBBx was associated with an increased risk of complications, which occurred in 3.21% of patients who underwent TBBx compared with 1.15% of those who

Table 1—*Patient Demographics and Clinical Characteristics*

Variable	Value
No. patients	1,317
Age, y	
Mean ± SD	63 ± 13.2
Median (range)	65 (11-94)
> 70 y	393 (29.8)
Male sex	685 (52)
Ethnicity	
American Indian or Alaskan Native	2 (0.2)
Asian	44 (3.3)
Black/African American	151 (11.5)
Hispanic/Latino	51 (3.9)
White	1,069 (81.2)
ASA score	
1	22 (1.7)
2	475 (36.1)
3	778 (59.1)
4	42 (3.2)
Zubrod score	
0	160 (12.1)
1	800 (60.7)
2	292 (22.2)
3	53 (4)
4	12 (0.9)
Service	
Inpatient	94 (7.1)
Outpatient	1,223 (92.9)
Smoking status	
≤ 20 pack-y	580 (44)
> 20 pack-y	737 (56)
Fellow involvement in procedure	
≥ 50% of the procedure	1,084 (82.3)
< 50% of procedure	17 (1.3)
Did not participate in procedure	216 (16.4)
No. comorbidities	
≤ 2	1,165 (88.5)
> 2	152 (11.5)
No anticoagulation	1,317 (100)
Forceps biopsy performed	
None	995 (75.6)
Endobronchial only	135 (10.3)
Transbronchial only	164 (12.4)
Both endobronchial and transbronchial	23 (1.7)
BAL performed	
No	1,050 (79.7)
Yes	267 (20.3)
BAL volume instilled	
≤ 120 mL	1,269 (96.4)
> 120 mL	48 (3.6)
Procedure	
Only TBNA	843 (64)
Any additional procedure	474 (36)
Any high paratracheal (2R or 2L) lymph node sampled	
No	1,282 (97.3)
Yes	35 (2.7)
Any left-side low paratracheal (4L) lymph node sampled	
No	964 (73.2)
Yes	353 (26.8)
No. sites of TBNA	
1	426 (32.3)
2	403 (30.6)
3	304 (23.1)
4	114 (8.7)
5	55 (4.2)
6	15 (1.1)
No. TBNA passes	
Mean ± SD	9.2 ± 5.3
Median (range)	8 (1-34)
Median (range) TBNA passes	
≤ 3	452 (34.3)
> 3	865 (65.7)
Lymph node size	
1-10 mm	565 (42.9)
11-20 mm	543 (41.2)
21-30 mm	137 (10.4)
> 30 mm	72 (5.5)
Anesthesia type	
Moderate sedation	484 (36.8)
Deep sedation or general anesthesia	833 (63.2)
Positive pressure ventilation	
No	587 (44.6)
Yes	730 (55.4)
Bronchoscopy type	
Flexible	1,302 (98.9)
Rigid	4 (0.3)
Both flexible and rigid	11 (0.8)
Duration of bronchoscopy	
≤ 30 min	286 (21.7)
> 30 min	1,031 (78.3)
Total duration of procedure	
≤ 60 min	538 (40.9)
> 60 min	779 (59.1)

(Continued)

Table 1—*Continued*

Data are presented as No. (%), unless otherwise indicated. ASA = American Society of Anesthesiologists; TBNA = transbronchial needle aspiration.

did not (OR, 2.85; 95% CI, 1.07-7.59; $P = .04$) (Table 3). There was a trend suggesting that lower functional status was associated with higher complication rates because complications occurred in 2.5% of patients with Zubrod scores ≥ 2 compared with 1.04% of patients with scores < 2 (OR, 2.42; 95% CI, 0.97-6.02; $P = .06$).

Pneumothorax

Pneumothorax occurred in seven patients (0.53%; 95% CI, 0.21%-1.09%). Four of these patients required tube thoracostomy, whereas pneumothorax was resolved in three patients without intervention. In both univariate and multivariate analyses, only TBBx was associated with increased risk of pneumothorax, which occurred in 2.7% of patients who underwent TBBx compared with 0.2% of those who did not (OR, 15.49; 95% CI, 2.98-80.46; $P = .001$) (Table 4). Among the 187 patients who underwent TBBx, positive pressure

Table 2—*Complications Following EBUS-TBNA*

Outcome	No. Events (N = 1,317)	Complication Rate, % (95% CI)
Any complication within 24 h	19	1.44 (0.87-2.24)
Bleeding requiring intervention[a]	3	0.2 (0.05-0.7)
Pneumothorax	7	0.53 (0.21-1.1)
Clinically significant airway injury	1	0.1 (0.002-0.4)
Sustained hypoxia	4	0.3 (0.08-0.8)
Hypotension	1	0.1 (0.002-0.4)
Cardiac arrest	0	…
Arrhythmia	0	…
Respiratory failure within 24 h	3	0.23 (0.05-0.7)

EBUS = endobronchial ultrasound. See Table 1 for expansion of other abbreviation.

[a]One death occurred in a patient who had bleeding after endobronchial biopsy.

ventilation was not associated with pneumothorax, which occurred in 2.0% of patients receiving positive pressure compared with 2.9% who received spontaneous ventilation ($P = 1.0$).

Escalation in Level of Care

Escalation in level of care occurred in 14 patients (1.06%; 95% CI, 0.58%-1.78%). Hospital-specific escalation of care rates ranged from 0% to 4.4% ($P = .07$) (e-Table 1). Univariate analysis showed that escalation occurred in 2% of patients aged > 70 years compared with 0.6% of patients aged ≤ 70 years ($P = .04$) (Table 5). Trends suggested that escalation of care was associated with certain characteristics (3.2% vs 0.9% inpatients vs outpatients [$P = .074$]; 2.6% vs 0.9% patients with multiple comorbidities vs two or fewer comorbidities [$P = .068$]; 1.4% vs 0.4% patients undergoing deep sedation or general anesthesia vs moderate sedation [$P = .1$]). In multivariate analysis, age > 70 years (OR, 4.06; 95% CI, 1.36-12.12; $P = .012$), inpatient status (OR, 4.93; 95% CI, 1.30-18.74; $P = .019$), and use of deep sedation or general anesthesia (OR, 4.68; 95% CI, 1.02-21.61; $P = .048$) were all associated with increased risk of requiring escalation of care (Table 6). An individual patient could have more than one complication, such as pneumothorax and sustained hypoxia, requiring escalation of care, but the attribution of escalation to any particular complication was not possible from the available data.

Other Complications

Hypoxia, respiratory failure, bleeding, airway injury, cardiac complications, and death were infrequent, so univariate and multivariate analyses of risk factors for these complications were not feasible (Table 2).

Hospital Variability

We used hierarchical models to investigate the effect of hospital-level variation on outcomes. Tests for homogeneity demonstrated no differences among hospitals in complications ($P = .99$), pneumothorax (model failed to converge because of sparse data), or escalation of care ($P = .77$). Hospital volume was not associated with complications or their outcomes, and TBBx remained the main risk factor (e-Table 2).

Practice Patterns

Because TBBx was the strongest risk factor for complications, we analyzed practice patterns to identify factors associated with the frequency of TBBx use with EBUS-TBNA. There were significant variations among hospitals in use of TBBx (range, 4.4%-42.5%; $P < .001$) and ROSE ($P < .001$) (e-Table 3). The use of ROSE for EBUS-TBNA was associated with less use of TBBx, which was performed in 12.6% of patients when ROSE was used compared with 19.1% of patients when ROSE was not used ($P = .006$), indicating that one TBBx was avoided for each 16 ROSEs performed (e-Tables 4, 5).

The effect of ROSE on TBBx use depended on whether a specific diagnosis was made by EBUS-TBNA (Mantel-Haenszel $P = .049$). Among patients for whom a specific diagnosis was made by EBUS-TBNA, TBBx was performed in 6.4% when ROSE was used compared with 14.8% when ROSE was not used (OR, 0.39; 95% CI, 0.22-0.70; $P = .001$). Among patients for whom no diagnosis was made by EBUS-TBNA, TBBx was performed in 19.3% of patients when ROSE was used compared with 22.9% of patients when ROSE was not used (OR, 0.81; 95% CI, 0.53-1.23; $P = .32$). However, there were significant differences among hospitals in the use of TBBx, even after adjustments for ROSE and for whether a specific diagnosis was made by EBUS-TBNA ($P < .001$) (e-Table 4). Among the 517 patients in whom ROSE was used and EBUS-TBNA established a specific diagnosis, hospital use of TBBx ranged from 0% to 32%. In these 517 patients, TBBx was performed in 16.1% of those with sarcoidosis and in 5.1% of those with something other than sarcoidosis ($P = .003$).

Discussion

To our knowledge, this is the first report of EBUS-TBNA complications and consequences from a multicenter registry. It shows that EBUS-TBNA is a reassuringly safe procedure with an overall complication rate of only 1.4% in participating centers. The complications noted were most often secondary to concurrent TBBx. Escalations in level of care resulting from these complications were more frequent in older patients, inpatients, and patients receiving deep sedation or general anesthesia. Also to our knowledge,

Table 3—*Patient and Clinical Characteristics by Occurrence of Any Complication Within 24 h After Procedure*

Variable	No 24-h Morbidity (n = 1,298)	Yes 24-h Morbidity (n = 19)	*P* Value[a]
Age			.31
≤ 70 y	913 (98.8)	11 (1.2)	
> 70 y	385 (98)	8 (2)	
Sex			.82
Female	622 (98.4)	10 (1.6)	
Male	676 (98.7)	9 (1.3)	
Ethnicity			1.00
Nonwhite	245 (98.8)	3 (1.2)	
White	1,053 (98.5)	16 (1.5)	
ASA score			.81
1-2	489 (98.4)	8 (1.6)	
3-4	809 (98.7)	11 (1.3)	
Zubrod score			.06
0-1	950 (99)	10 (1.0)	
2-4	348 (97.5)	9 (2.5)	
Smoking status			.35
≤ 20 pack-y	574 (99)	6 (1)	
> 20 pack-y	724 (98.2)	13 (1.8)	
No. comorbidities			.47
≤ 2	1,149 (98.6)	16 (1.4)	
> 2	149 (98)	3 (2)	
Service			.15
Outpatient	1,206 (98.7)	16 (1.3)	
Inpatient	92 (96.8)	3 (3.2)	
Fellow involvement in procedure			.54
No involvement	212 (98.1)	4 (1.9)	
Any involvement	1,086 (98.6)	15 (1.4)	
Procedures performed			.34
Only TBNA	833 (98.8)	10 (1.2)	
Other procedures	465 (98.1)	9 (1.9)	
Transbronchial biopsy performed			.04
No	1,117 (98.8)	13 (1.2)	
Yes	181 (96.8)	6 (3.2)	
Endobronchial biopsy performed			1.00
No	1,142 (98.5)	17 (1.5)	
Yes	156 (98.7)	2 (1.3)	
No. sites of TBNA			.55
1	418 (98.1)	8 (1.9)	
2	396 (98.3)	7 (1.7)	
3	302 (99.3)	2 (0.7)	
4-6	182 (98.9)	2 (1.1)	
Median lymph node size			.73
1-10 mm	558 (98.8)	7 (1.2)	
11-20 mm	533 (98.2)	10 (1.8)	
21-30 mm	135 (98.5)	2 (1.5)	
> 30 mm	72 (100)	0 (0)	
Median lymph node size			.65
> 10 mm	740 (98.4)	12 (1.6)	
≤ 10 mm	558 (98.8)	7 (1.2)	
Anesthesia			.81
Moderate sedation	478 (98.8)	6 (1.2)	
Deep sedation or general anesthesia	820 (98.4)	13 (1.6)	
Positive pressure ventilation			.49
No	577 (98.3)	10 (1.7)	
Yes	721 (98.8)	9 (1.2)	
Bronchoscopy type			.20
Flexible only	1,284 (98.6)	18 (1.4)	
Rigid and flexible	14 (93.3)	1 (6.7)	
Duration of bronchoscopy			.58
≤ 30 min	281 (98.3)	5 (1.7)	
> 30 min	1,017 (98.6)	14 (1.4)	

Data are presented as No. (%). See Table 1 for expansion of abbreviations.
[a]Fisher exact test.

Table 4—*Patient and Clinic Characteristics by Occurrence of Pneumothorax as a Complication*

Characteristic	No 24-h Pneumothorax (n = 1,310)	Yes 24-h Pneumothorax (n = 7)	*P* Value[a]
Age			1.00
≤ 70 y	919 (99.5)	5 (0.5)	
> 70 y	391 (99.5)	2 (0.5)	
Sex			.72
Female	628 (99.4)	4 (0.6)	
Male	682 (99.6)	3 (0.4)	
Ethnicity			.36
Nonwhite	248 (100)	0 (0)	
White	1,062 (99.3)	7 (0.7)	
Service			1.00
Outpatient	1,216 (99.4)	7 (0.6)	
Inpatient	94 (100)	0 (0)	
Any high paratracheal (2R or 2L) lymph node sampled			1.00
No	1,275 (99.5)	7 (0.5)	
Yes	35 (100)	0 (0)	
Any left-side low paratracheal (4L) lymph node sampled			.68
No	958 (99.4)	6 (0.6)	
Yes	352 (99.7)	1 (0.3)	
Transbronchial biopsy performed			< .001
No	1,128 (99.8)	2 (0.2)	
Yes	182 (97.3)	5 (2.7)	
Endobronchial biopsy performed			1.00
No	1,152 (99.4)	7 (0.6)	
Yes	158 (100)	0 (0)	
No. TBNA passes			.70
≤ 3	449 (99.3)	3 (0.7)	
> 3	861 (99.5)	4 (0.5)	
Median lymph node size			.15
> 10 mm	750 (99.7)	2 (0.3)	
≤ 10 mm	560 (99.1)	5 (0.9)	
Anesthesia			.11
Moderate sedation	479 (99)	5 (1)	
Deep sedation or general anesthesia	831 (99.8)	2 (0.2)	
Positive pressure ventilation			.25
No	582 (99.1)	5 (0.9)	
Yes	728 (99.7)	2 (0.3)	
Duration of bronchoscopy			.36
≤ 30 min	286 (100)	0 (0)	
> 30 min	1,024 (99.3)	7 (0.7)	

Data are presented as No. (%). See Table 1 for expansion of abbreviation.
[a]Fisher exact test.

this is the first prospective study to evaluate hospital variables as well as patient and procedural variables associated with EBUS-TBNA complications. In contrast to diagnostic yield,[19] there was less variance among hospitals in terms of safety. There was significant interhospital variation in the use of ROSE as well as TBBx with EBUS-TBNA. This finding is important because we were able to demonstrate that the use of ROSE for EBUS-TBNA resulted in fewer TBBxs.

The present study adds to the existing body of evidence regarding bronchoscopic complications.[21-25] We found that most of the risk in EBUS-TBNA procedures

Table 5—*Patient and Clinical Characteristics by Escalation in Level of Care as a Result of Complication*

Variable	No Escalated Care (n = 1,303)	Escalated Care (n = 14)	*P* Value[a]
Age			.04
≤ 70 y	918 (99.4)	6 (0.6)	
> 70 y	385 (98)	8 (2)	
Sex			1.00
Female	625 (98.9)	7 (1.1)	
Male	678 (99)	7 (1)	
Ethnicity			1.00
Nonwhite	246 (99.2)	2 (0.8)	
White	1,057 (98.9)	12 (1.1)	
ASA score			.59
1-2	493 (99.2)	4 (0.8)	
3-4	810 (98.8)	10 (1.2)	
Zubrod score			.07
0-1	953 (99.3)	7 (0.7)	
2-4	350 (98.0)	7 (2.0)	
Smoking status			.29
≤ 20 pack-y	576 (99.3)	4 (0.7)	
> 20 pack-y	727 (98.6)	10 (1.4)	
No. comorbidities			.07
≤ 2	1,155 (99.1)	10 (0.9)	
> 2	148 (97.4)	4 (2.6)	
Service			.074
Outpatient	1,212 (99.1)	11 (0.9)	
Inpatient	91 (96.8)	3 (3.2)	
Transbronchial biopsy performed			.44
No	1,119 (99.0)	11 (1.0)	
Yes	184 (98.4)	3 (1.6)	
Procedures performed			1.00
Only TBNA	834 (98.9)	9(1.1)	
Other	469 (98.9)	5(1.1)	
BAL performed			1.00
No	1,039 (99)	11(1)	
Yes	264 (98.9)	3(1.1)	
BAL volume instilled			.41
≤ 120 mL	1,256 (99)	13 (1)	
> 120 mL	47 (97.9)	1(2.1)	
Median lymph node size			.42
> 10 mm	742 (98.7)	10(1.3)	
≤ 10 mm	561 (99.3%)	4 (0.7)	
Anesthesia			.10
Moderate sedation	482 (99.6)	2 (0.4)	
Deep sedation or general anesthesia	821 (98.6)	12 (1.4)	
Duration of bronchoscopy			.52
≤ 30 min	282 (98.6)	4 (1.4)	
> 30 min	1,021 (99)	10 (1)	
Duration of procedure			.79
≤ 60 min	533 (99.1)	5 (0.9)	
> 60 min	770 (98.8)	9 (1.2)	

Data are presented as No. (%). See Table 1 legend for expansion of abbreviations.
[a]Fisher exact test.

Table 6—*Multivariate Logistic Regression Models*

Outcome and Covariates	OR (95% CI)	*P* Value
Outcome: any complication within 24 h		
Transbronchial biopsy: yes vs no	2.85 (1.07-7.59)	.04
Outcome: pneumothorax		
Transbronchial biopsy: yes vs no	15.49 (2.98-80.4)	.001
Outcome: escalation in level of care		
Age: > 70 vs ≤ 70 y	4.06 (1.36-12.12)	.012
Service: inpatient vs outpatient	4.93 (1.30-18.74)	.019
Anesthesia type: deep sedation or general anesthesia vs moderate sedation	4.68 (1.02-21.61)	.048

came from concurrent TBBx procedures rather than from the EBUS-TBNA itself. TBBx was performed under fluoroscopy in most cases, but this was left to the individual centers. Because the rate of TBBx and associated pneumothorax was low, no significant difference could be ascertained regarding the impact of fluoroscopy. The incidence of pneumothorax when TBBxs were performed in addition to EBUS-TBNA was 2.7%, which is similar to previous reports.[13,26-32] However, in contrast to previous investigations,[33,34] we found that the use of positive pressure ventilation in patients undergoing TBBx was not associated with increased pneumothorax risk. This contrast likely reflects differences in patient populations; previous studies included patients receiving positive pressure ventilation for respiratory failure, whereas patients in this study received positive pressure ventilation only for the procedure. The difference in complications between these patient populations suggests that there is an interaction among lung injury, positive pressure ventilation, and pneumothorax when TBBx is performed. The results of the present study suggest that positive pressure ventilation during TBBx is low risk in the absence of acute lung injury.

The present study is one of a few that evaluated the consequences of the complications associated with EBUS. Although physiologic status, comorbidities, anesthesia, and hospital variables may not affect the frequency of complications, they do affect the consequences of complications, as reflected by the need for an escalation in level of care. Older age, inpatient status, and the use of deep sedation or general anesthesia were all associated with an increased probability of escalation of care. These factors probably reflect decreased physiologic reserve and become relevant only when a complication occurs, meaning that they have an impact on the consequences of complications, not the incidence. It is probable that other factors are also relevant, such as comorbidities and functional status, although the low frequency of complications limited our ability to demonstrate the effect of these variables, which did not reach statistical significance.

The present findings are directly relevant to the ongoing debate over sedation techniques for EBUS-TBNA.[19,35-38] Currently, EBUS-TBNA is routinely performed under moderate sedation or general anesthesia, depending on local preferences and resources. Advocates of moderate sedation frequently cite the lower risk of complications, particularly pneumothorax, as a potential benefit.[38] Advocates of deep sedation or general anesthesia cite patient comfort, ability to sample more lymph node stations, higher diagnostic yield, and educational benefits for trainees as potential advantages.[19] However, few data confirm or refute most of these claims. In general, use of deep or general anesthesia was associated with a longer bronchoscopy time and procedure time, but these did not affect the incidence of complications. The longer bronchoscopy and procedure time associated with general anesthesia may be reflective of procedure planning where full mediastinal staging may skew the bronchoscopist toward requesting anesthesia support, whereas a single-station diagnostic EBUS-TBNA is more likely to be done under moderate sedation. The present findings suggest that the type of sedation and the method of ventilation do not affect the incidence of complications in patients without preexisting lung injury. However, when complications do occur, the consequence may be more serious and require an escalation in level of care for patients with limited physiologic reserve. It is important to recognize, however, that the absolute risks of both complications and escalation in care from complications are very low. Overall, the 1.44% incidence of complications demonstrates the safety of EBUS-TBNA and should encourage wider adoption of this technology.

We found no other patient-level predictors of complications. TBNA of high paratracheal lymph nodes (2R and 2L) has been anecdotally reported to be associated with increased risk of pneumothorax, but in this study, there was no association. Similarly, smaller lymph nodes and trainee involvement in the procedure did not affect outcomes. These findings support the standard use of complete mediastinal lymph node staging for non-small cell lung cancer with EBUS regardless of lymph node size or location because previous reports suggested that sampling more lymph nodes is associated with an increase in diagnostic yield.[39]

This study adds to the growing body of evidence evaluating the impact of hospital variables on bronchoscopic outcomes. In contrast to the previous AQuIRE report on diagnostic yield,[19] hospital volume was not associated with any differences in complication rates.

We did identify wide interhospital variations in the use of ROSE and the frequency of concurrent TBBx. Of course, in a registry study, it is impossible

to ascertain the decision-making process that guides the individual bronchoscopist to select particular procedures in particular patients. From the data available, we demonstrated that TBBx was more frequently performed when ROSE was not available. Previous studies of ROSE in bronchoscopy have focused primarily on the ability of ROSE to decrease the percentage of cases with inadequate specimens.[40-45] Those studies often included mixed populations, including patients with parenchymal lesions as well as patients with mediastinal lesions, and focused on conventional TBNA rather than on EBUS-TBNA.[41] However, few studies have looked at the impact of ROSE with EBUS-TBNA on use of TBBx. One single-center randomized controlled trial using conventional TBNA found that ROSE reduced the number of parenchymal biopsies and complications (most of which consisted of minor bleeding).[40] The investigators speculated that the impact of ROSE on diagnostic adequacy might decrease as EBUS-TBNA replaces conventional TBNA.[40] A second study found only a trend in favor of a reduced need for biopsies with ROSE.[46] The present finding that the use of ROSE with EBUS-TBNA can help to limit the number of TBBxs is consistent with and builds on the work of these previous investigators.[40-46]

We found that TBBx use varied significantly among hospitals ($P < .001$). Although variations in disease prevalence among hospitals are certainly possible, TBBx use varied even in cases when ROSE was used and a diagnosis was established through EBUS-TBNA, suggesting that the quality of ROSE was a factor. This suggestion is further supported by the finding that a final diagnosis of sarcoidosis was associated with a higher probability of TBBx ($P = .003$) because it is far more difficult to identify granulomas than cancer on EBUS-TBNA.[6]

The present findings also highlight the value of registry data as a quality improvement tool. Measurement of outcomes is a necessary element for all quality improvement programs.[47] Registry data can provide direct feedback to participants about their performance regarding not only diagnostic yield and complications but also the impact of their processes (eg, use of ROSE) and structures (eg, availability, organization, quality of ROSE) on outcomes.

One of the strengths of AQuIRE is that data are collected prospectively from multiple hospitals and physicians. The data, therefore, are more generalizable than that from prior single-center clinical trials,[40,46] and the insights gained can be viewed as complementary to those obtained from randomized trials.

Although these findings are useful, it is important to recognize their limitations. This is the largest prospective multicenter registry study of EBUS-TBNA complications to our knowledge, but complications with EBUS-TBNA are so rare that the power of the study to identify particular risk factors is limited. Thus, the single reported death could not be analyzed meaningfully, but it reminds us that even a procedure as safe as EBUS-TBNA can be associated with catastrophic complications. In addition, because AQuIRE includes only complications occurring within 24 h, late complications such as infections, which have rarely been reported, would have been missed.[48-50] AQuIRE is still relatively small, and most of the data are from major academic centers. The safety profile, therefore, is more reflective of highly experienced centers, suggesting that efforts should be made to enroll additional centers from a variety of practice settings. It will be important to revisit the data when more centers are included.

In conclusion, this report from the AQuIRE registry represents the first multicenter prospective observational study to evaluate patient and hospital predictors of EBUS-TBNA complications. The only patient variable that affected the incidence of complications was concurrent TBBx. When complications did occur, escalations in level of care were more likely to be required in older patients, inpatients, and patients who received deep sedation or general anesthesia. The use of ROSE was associated with a reduced use of TBBx, but there was significant interhospital variation in the use of ROSE and TBBx. Future studies should expand this registry to other hospitals of varying sizes and more diverse practice patterns to verify these findings and to explore the interactions between hospital-level and physician-level variations on complications and their consequences.

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Author contributions: Dr Eapen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Eapen: contributed as the principal investigator (PI) for this study and to project oversight and organization, data collection, and manuscript writing.

Dr Shah: contributed to the study design, data collection and auditing, and writing of the manuscript.

Dr Lei: contributed as the primary biostatistician for the project and to the construction of the multilevel models and analyses and writing of the manuscript.

Dr Jimenez: contributed to the study design, data collection and auditing, and writing of the manuscript.

Dr Morice: contributed to the study design, data collection and auditing, and writing of the manuscript.

Dr Yarmus: contributed to the data collection and writing of the manuscript.

Dr Filner: contributed to the data collection and writing of the manuscript.

Dr Ray: contributed to the data collection and writing of the manuscript.

Dr Michaud: contributed to the data collection and writing of the manuscript.

Dr Greenhill: contributed to the data collection and writing of the manuscript.

Dr Sarkiss: contributed to the data collection and writing of the manuscript.

Dr Casal: contributed to the data collection and writing of the manuscript.
Dr Rice: contributed to writing of the manuscript.
Dr Ost: contributed to the registry design and organization, data collection and auditing, statistical analyses, and writing of the manuscript.

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Additional information: The e-Appendix and e-Tables can be found in the "Supplemental Materials" area of the online article.

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