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Outcomes of patients with non-diagnostic bronchoscopy

A clinico-radiological comparison of patients with diagnostic and non-diagnostic bronchoscopy

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Abstract

Bronchoscopy is one of the most common diagnostic procedures in pulmonary practice. Data on the outcome of patients following a non-diagnostic bronchoscopy are sparse. Diagnostic yield depends on indication, the characteristics of patients, and the chest imaging. The aim of this study was to evaluate the outcomes of patients with a non-diagnostic bronchoscopy and to compare patients who had a diagnostic with those that had a non-diagnostic bronchoscopy.

Retrospective, single-center study of adult patients who underwent bronchoscopy with transbronchial biopsy (TBBX) and/or endobronchial biopsy (EBBX), endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA), or brushing. A strict definition for a "diagnostic" bronchoscopy was used. Univariate and multivariate analyses were performed.

A total of 684 patients were identified, 350 (51%) had a diagnostic procedure. Of the 334 patients with a non-diagnostic bronchoscopy, 196 (58.6%) were followed, but only 172 (88%) completed 1 year of follow-up. Most of the patients (57.8%) had resolution or stabilization of the condition; in the remaining patients, malignancy was most commonly diagnosed after further investigation followed by diffuse lung diseases and infections. Pulmonary tuberculosis was diagnosed in 8 patients. EBUS-TBNA and EBBX were the procedures associated with a diagnostic bronchoscopy. Presence of bilateral interstitial infiltrates predicted a non-diagnostic bronchoscopy.

A significant number of patients with non-diagnostic bronchoscopy may have serious treatable disease that is identified upon further investigation. Close follow up of patients with a non-diagnostic procedure is warranted. Our study found no clear clinical or radiological predictors of diagnostic bronchoscopy.

Abbreviations: AIDS = acquired immunodeficiency syndrome, CXR = chest roentgenogram, EBBX = endobronchial biopsy, EBUS = endobronchial ultrasound, FFB = flexible fiberoptic bronchoscopy, OR = operating room, TBBX = transbronchial biopsy, TBNA = transbronchial needle aspiration.

Keywords: bronchoscopy, endobronchial ultrasound, non-diagnostic, transbronchial biopsy, yield

1. Introduction

Flexible fiberoptic bronchoscopy (FFB) is a valuable tool for the diagnosis of pulmonary disorders. The diagnostic yield of FFB varies depending on the indications and the diagnostic techniques employed.[1–3] Several studies have evaluated the diagnostic yield of FFB for different clinical conditions, including the presence of masses or nodules and diffuse lung diseases, and in immunocom-

promised patients, among others; however, none has examined the relationship between the clinical and radiological predictors and outcomes of a non-diagnostic bronchoscopy.[4,5] Confounding factors that impact the interpretation of these studies include the different methodologies and techniques used during bronchoscopy and lack of consensus on the definition of a "diagnostic" bronchoscopy, especially for those patients where the tissue biopsy does not indicate a specific diagnosis. Data regarding outcomes of patients considered to have a non-diagnostic bronchoscopy remain sparse.

In this study, we reported the follow-up and outcomes of patients who had a non-diagnostic bronchoscopy. In addition, we compared diagnostic and non-diagnostic bronchoscopies and evaluated predictors for a diagnostic bronchoscopy.

2. Materials and methods

2.1. Study design and patients

This was a retrospective cohort study conducted in an inner-city hospital. All adult patients who underwent FFB with transbronchial biopsy (TBBX), endobronchial biopsy (EBBX), or transbronchial needle aspiration (TBNA) from January 2012 to January 2017 at our institution were included. BronxCare Hospital Center is a community teaching hospital with 972 beds,

serving the South and Central Bronx. This area is one of the poorest in the nation composed of a large minority and immigrant population.

All bronchoscopies were performed using a standard flexible bronchoscope (Olympus America Inc; Melville, NY) either under local anesthesia with conscious sedation in the bronchoscopy suite or under general anesthesia in the operating room (OR) based on pre-operative risk assessment. All endobronchial ultrasound (EBUS)-TBNA are performed in the OR under general anesthesia. Bronchoscopies were performed by any of the 8 full-time pulmonologists with any of the 6 pulmonary fellows. All TBBXs were fluoroscopically guided. This study was conducted in accordance with the amended Declaration of Helsinki. The study was approved by the Institutional Review Board (approval number 04090904).

2.2. Data abstraction

Demographic and clinical information, as well as data from the bronchoscopic procedure, were abstracted from the medical record. Radiological characteristics of thoracic findings were obtained from the radiology reports.

2.3. Definition of diagnostic bronchoscopy

As part of the bronchoscopy quality and safety review of the pulmonary division and for purposes of practice standardization and training, we define a diagnostic bronchoscopy when at least 1 of the following criteria is met:

1. A specific histo-pathological diagnosis is established.
2. Histopathology excludes the primary indication for bronchoscopy and follow-up reveals radiological stability or resolution.
3. EBUS sampling of mediastinal lymph nodes provides a histological diagnosis or excludes malignant involvement of the sampled lymph nodes and follow-up reveals radiological stability or resolution.
4. No further diagnostic procedure is considered necessary to pursue a specific diagnosis and follow up of a minimum of 6 months reveals radiological stability or resolution.

All other bronchoscopies are categorized as non-diagnostic.

2.4. Definition of complications

1. Bleeding: documented blood loss of ≥50 ml or the requirement of specific interventions, such as a balloon tamponade, surgery, or blood transfusion.
2. Pneumothorax: radiological pneumothorax on a post-procedure chest roentgenogram (CXR).
3. Respiratory failure: need for mechanical ventilation post-procedure regardless of duration of ventilator support.

The diagnostic yield of the bronchoscopy was defined as the ratio of the total number of patients in whom a diagnosis was obtained to the total number of patients undergoing the procedure. Patients were followed up for at least 1 year after bronchoscopy.

2.5. Statistical analysis

The statistical software R (version 3.4.1) was used for all descriptive and inferential analyses. Categorical variables were expressed as counts (percentage), while continuous variables were expressed as means ± standard deviations (SD) except for data on biopsies which were expressed as medians. Fisher exact tests were used to evaluate the association between categorical variables and diagnostic/non-diagnostic FFB. Analysis of variance (ANOVA) tests were used to assess the association between continuous variables besides data on biopsies and having diagnostic or non-diagnostic FFB. Multivariable Logistic regression was conducted to identify the risk factors associated with having diagnostic bronchoscopy.

All inferential analyses were set at a 95% level of significance ($\alpha = 0.05$).

3. Results

3.1. Outcome of patients with non-diagnostic bronchoscopy

A total of 334 (49%) patients had a non-diagnostic bronchoscopy, and 196 (58.7%) of those patients were available for follow-up. Of those, 11 patients did not comply with subsequent work up and follow ups; 9 refused any additional work up and were lost for follow-up, and 4 patients died before any intervention. The remaining 172 (87.7%) patients were followed for at least 1 year.

Imaging and further procedures were the 2 most common interventions performed to achieve a final diagnosis. Of the 172 patients followed for at least 1 year, radiological resolution or stability was observed in 99 (57.5%) patients, malignancy in 33 (19.2%), infections in 12 (7%), and other diagnosis in 28 (16.2%). See Figure 1. The most common malignancies were primary lung cancer (25 of 33; 75.7%) followed by lymphoma and metastatic lung disease in 3 (9%) patients each. In addition, 12 patients had a final diagnosis of infection, 8 had tuberculosis, and 4 had pulmonary Mycobacterium complex. Respiratory cultures after the initial FFB yielded a final diagnosis in 3 of those patients.

3.2. Comparison of diagnostic and non-diagnostic bronchoscopy

We identified a total of 684 patients who underwent FFB with either TBBX, EBBX, or EBUS-TBNA during the study period. Of these, 350 (51.1%) were considered diagnostic bronchoscopies according to our definition. A comparison of the demographics and selected comorbidities are shown in Table 1. There was no difference in demographic data, smoking history, or comorbid conditions between the groups. Weight loss was the only significant presenting symptom in patients with diagnostic bronchoscopy (22.9% vs 15.1%; $P = .01$; Table 2).

Comparison of findings on chest imaging is shown in Table 3. Bilateral infiltrates on CXR were more common in patients with diagnostic bronchoscopy (29.4% vs 21%; $P = .01$), while interstitial infiltrates were associated with a non-diagnostic procedure (1.1% vs 6.8%; $P < .001$). Computed tomography (CT) of the chest was performed in 672 (98%) patients; findings of bilateral interstitial infiltrates (3.7% vs 8.6%; $P = .01$) and multiple nodules (5.1 vs 9.5; $P = .02$) were predictive of a non-diagnostic bronchoscopy. Evaluation for possible infections and malignancy followed by evaluation for non-infectious diffuse lung diseases were the most common indications for FFB. The main indications for FFB in patients with normal imaging or
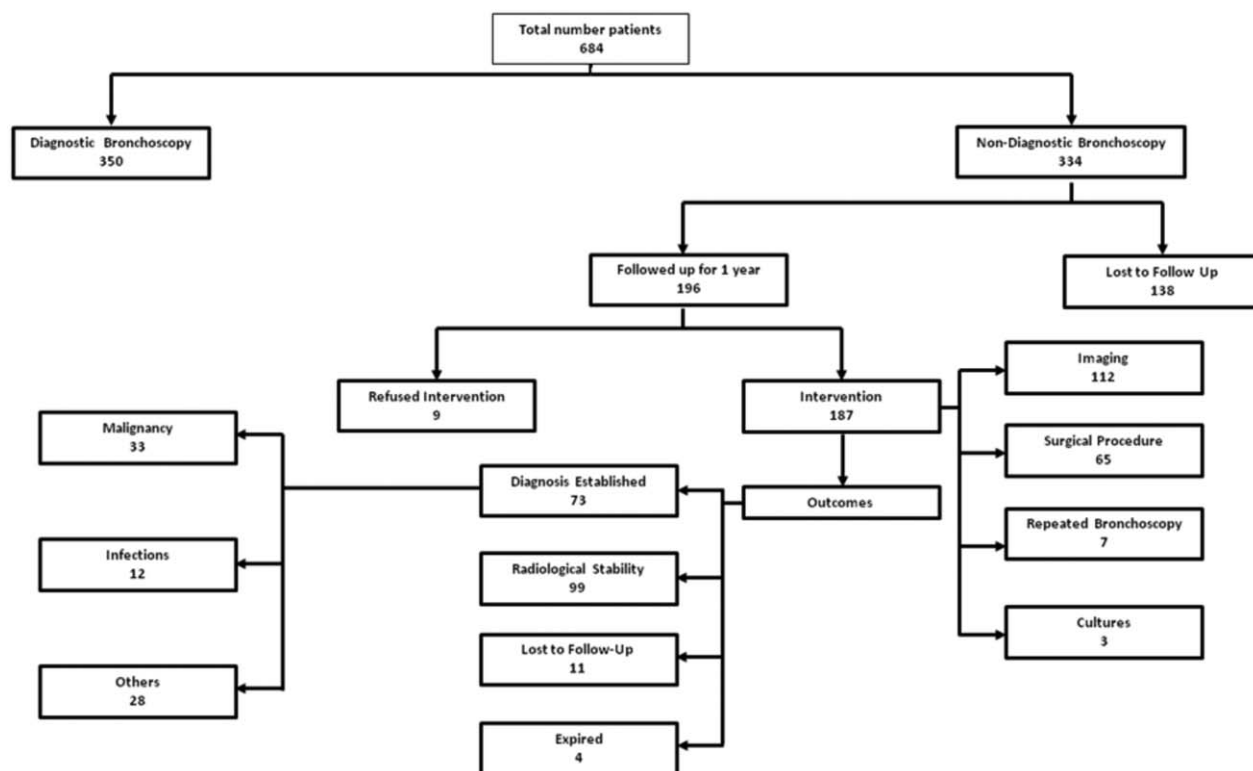
Figure 1. Flow chart showing outcome of patient with non-diagnostic bronchoscopy.

pleural effusion were evaluation of possible endobronchial disease, hemoptysis, and infections. There was no correlation between indications for bronchoscopy and diagnostic bronchoscopy (Table 4).

A total of 255 (37.3%) patients underwent bronchoscopy with conscious sedation, and 429 (62.7%) with general anesthesia. The type of sedation did not predict a diagnostic bronchoscopy.

Bronchoscopy with TBBX was the most common procedure followed by brushing, EBBX, and EBUS-TBNA. In total, 381 (55%) of patients had multiple bronchoscopic procedures. The EBBX and EBUS-TBNA procedures were predictive of a diagnostic bronchoscopy, while TBBX, brushing, and performance of more than 1 procedure were not (Table 5). No correlation between the number of TBBXs or EBUS-TBNA passes

Table 1

Comparison of patients demographics.

Variable	Diagnostic n = 350	Non diagnostic n = 334	Total n = 684	P value
Male, No	192 (54.9)	162 (48.5)	354 (51.8)	.108
Age, Mean ± SD, yr	56.7 ± 14.5	56.3 ± 13.7	56.5 ± 14.1	
Ethnicity				.194
Black	168 (48)	135 (40.4)	303 (44.3)	
Hispanic	141 (40.3)	160 (47.9)	301 (44)	
White	8 (2.29)	6 (1.8%)	14 (2.05)	
Other	33 (9.43)	33 (9.88%)	66 (9.65)	
BMI Mean ± SD	26.1 ± 6.94	28.1 ± 26.3	27.1 ± 19.1	.177
Comorbidities				
HIV	109 (31.1)	101 (30.2%)	210 (30.7%)	.804
CD4 Mean ± SD	162 ± 175	220 ± 233	190 ± 207	.041
Diabetes Mellitus	100 (28.6)	78 (23.4)	178 (26)	.138
Hypertension	175 (50)	174 (52.1)	355 (49)	.593
Obstructive airway disease	129 (36.9)	136 (40.7)	265 (38.7)	.308
Malignancy	67 (19.1)	59 (17.7)	126 (18.4)	.623
Liver Disease	54 (15.4)	67 (20.1)	121 (17.7)	.133
Heart Failure	22 (6.29)	22 (6.59)	44 (6.43)	.878
Pulmonary Hypertension	66 (18.9)	63 (18.9)	129 (18.9)	1.000
Current or former smoker	227 (64.9)	222 (66.5)	449 (65.6)	.687

Values are No. (%) or as otherwise indicated. BMI = body mass index, HIV = human immunodeficiency virus.

Table 2

Symptoms at presentation.

	Diagnostic N=350	Non diagnostic N=334	Total N=684	P value
Cough	215 (61.6)	183 (55)	398 (58.4)	.087
Shortness of breath	152 (43.6)	140 (42.2)	292 (42.9)	.757
Chest pain	52 (14.9)	40 (12)	92 (13.5)	.313
Fever	82 (23.5)	60 (18.1)	142 (20.9)	.090
Weight loss	80 (22.9)	50 (15.1)	130 (19.1)	.011
Hemoptysis	24 (6.88)	18 (5.42)	42 (6.17)	.524

Values are No. (%) or as otherwise indicated

Table 3

Chest imaging findings.

Findings	Diagnostic N=350	Non diagnostic N=334	Total N=684	P value
Chest Roentgenogram				
Bilateral Alveolar Infiltrates	103 (29.4)	70 (21)	173 (25.3)	.014
Bilateral Interstitial Infiltrates	4 (1.14)	23 (6.89)	27 (3.95)	<.001
Bilateral Multiple Nodules	11 (3.14)	18 (5.39)	29 (4.24)	.184
Cavitary lesions	14 (4)	13 (3.89)	27 (3.95)	1.000
Enlarged Mediastinum	9 (2.57)	3 (0.898)	12 (1.75)	.144
Solitary Lung Nodule	16 (4.57)	25 (7.49)	41 (5.99)	.146
Mass	43 (12.3)	32 (9.58)	75 (11)	.273
Normal	19 (5.43)	23 (6.89)	42 (6.14)	.524
Pleural effusion	3 (0.857)	3 (0.898)	6 (0.877)	1.000
Unilateral Infiltrate	116 (33.1)	118 (35.3)	234 (34.2)	.573
Chest Computed Tomogram				
Bilateral Alveolar Infiltrates	62 (17.7)	51 (15.3)	113 (16.5)	.411
Bilateral Interstitial Infiltrates	13 (3.71)	29 (8.68)	42 (6.14)	.010
Multiple Nodules	18 (5.14)	32 (9.58)	50 (7.31)	.028
Cavitary lesions	23 (6.57)	17 (5.09)	40 (5.85)	.421
Ground glass opacities	35 (10)	30 (8.98)	65 (9.5)	.697
Lung mass/masses	82 (23.4)	64 (19.2)	146 (21.3)	.192
Mediastinal lymphadenopathy	18 (5.14)	11 (3.29)	29 (4.24)	.259
Solitary Lung Nodule	24 (5.43)	37 (10.5)	61 (7.89)	.060
Not performed	6 (1.71)	6 (1.8)	12 (1.75)	1.000
Unilateral Infiltrate	58 (16.6)	48 (14.4)	106 (15.5)	1.460

Values are No. (%) or as otherwise indicated

Table 4

Indications for bronchoscopy.

Indications	Diagnostic N=350	Non diagnostic N=334	Total N=684	P value
Suspected Infection	111 (31.7)	123 (36.8)	234 (34.2)	.171
Suspected Interstitial Lung Disease	17 (4.86)	10 (2.99)	27 (3.95)	.242
Mediastinal Lymphadenopathy	28 (8)	18 (5.39)	46 (6.73)	.222
Nodule or Mass	132 (37.7)	146 (43.7)	278 (40.6)	.120
Suspected Opportunistic Infections	53 (15.1)	36 (10.8)	89 (13)	.111

Values are No. (%) or as otherwise indicated

Table 5

Types of bronchoscopic procedures.

Procedures	Diagnostic N=350	Non diagnostic N=334	Total N=684	P value
Transbronchial biopsy	277 (79.1)	299 (89.5)	576 (84.2)	.0002
Endobronchial biopsy	106 (30.3)	71 (21.2)	177 (25.9)	.0087
EBUS TBNA	96 (27.4)	65 (19.4)	161 (23.5)	.01
Brushing	118 (33.7)	143 (42.8)	261 (38.1)	.01
More than 1 procedure	182 (52)	199 (59.5)	381 (55.7)	.054

Values are No. (%) or as otherwise indicated

and performance of a diagnostic bronchoscopy was identified; however, the number of EBBX procedures was predictive of a diagnostic bronchoscopy (4 [range 1–14] vs 3 [range 1–10]; $P = .018$).

Multiple logistic regression and odds ratios (OR) of having a diagnostic bronchoscopy was determined. Predictors of a diagnostic FFB included EBUS-TBNA (OR 5.99 [2.45–18.03]; $P < .0001$) and indication of interstitial lung disease (OR 2.71 [1.13–6.96]; $P = .01$). Predictors for a non-diagnostic FFB included bilateral interstitial infiltrates on CXR (0.24 [0.12–0.45]; $P = .0001$), TBBX (0.48 [0.3–0.76]; $P = .001$), and presence of liver disease (0.6 [0.4–0.94]; $P = .01$).

The overall rate of bronchoscopy-related complications was 17% (115/684). Bleeding was the most common complication, seen in 98 (14%) patients (1 patient had a blood loss >200 mL). Respiratory failure requiring mechanical ventilation was observed in 11 (1.6%) patients, pneumothorax in 5 (0.7%) and arrhythmia in 1 (0.1%) patient. All bleeding complications resolved with use of topical epinephrine and/or cold saline. No patient needed transfusion. All patients needing mechanical ventilation were liberated.

4. Discussion

Our study highlights one of the challenges in the provision of care to an underserved community. Despite institutional systems to recall and track patients for their clinic appointments, we were able to have an extended follow up of only 185 of the initial 334 (55.4%) patients who had non-diagnostic bronchoscopy. Our institution serves one of the poorest congressional districts in the nation. It is reported that health in the United States is patterned along both socioeconomic and racial/ethnic lines, suggesting links between hierarchies of social advantage and health.[6] The health care disparities seen is likely responsible for the poor rates of follow up. This low rate of follow up in an inner-city population has been reported by others and causes are multifactorial.[7–9] Causes include ethnicity, type of insurance coverage and undocumented status.[10,11] At our institution, uninsured constitute 7% of our hospital discharges and 18% of clinic visits.

Most of the studies on non-diagnostic bronchoscopy have focused on a specific group of patients or pathologies, and few have provided prolonged follow-up of those patients.[2,12,13] Barrio reported 286 patients with acquired immunodeficiency syndrome (AIDS), who underwent bronchoscopies for the evaluation of diffuse pulmonary disease, and 29% of these patients had a non-diagnostic procedure. The yield of repeated bronchoscopy within a month of the initial procedure was low compared with a 59% yield for patients having the procedure performed after 1 month. Some patients underwent surgical biopsy, and the most commonly missed bronchoscopic diagnoses were cytomegalovirus pneumonia and Kaposi's sarcoma.[14] In our study, 30% of our patients had AIDS with a 48% of non-diagnostic bronchoscopy. One difference between our study and that of Barrios was that we included all imaging findings, not only diffuse lung diseases. Chuang reported 38 patients with diffuse lung disease with non-specific TBBX; 19 (50%) had a specific diagnosis made by open lung biopsy, and these diagnoses included bronchiolitis obliterans, alveolar proteinosis, metastatic carcinoma, lymphoma, tuberculosis, and bronchioloalveolar cell carcinoma.[15]

A negative initial bronchoscopy in a patient with suspected lung cancer carries the potential for excessive delays in diagnosis and treatment. Most of the delay occurs in the interval from the outpatient appointment to decision to treat. Patients with negative bronchoscopy require a concerted effort to achieve a timely diagnosis and treatment plan. We found malignancy in an additional 19% cases during follow-up of patients with a non-diagnostic bronchoscopy.

In 2016, the Bronx, where our study took place, had a rate of 5.5 cases per 100,000 individuals with tuberculosis. Our institution sees approximately 8 to 10 new cases of pulmonary tuberculosis each year, and most of the patients are diagnosed either by sputum analysis or bronchoscopy. In a South American study of 286 patients with suspected tuberculosis and negative or no produced sputum, bronchoscopy identified 144 patients with tuberculosis.[13] In our cohort with non-diagnostic bronchoscopy, we identified pulmonary tuberculosis in an additional 8 patients; although this seems a small number, there are significant social implications for tuberculosis control, especially in an inner-city area.

In addition, this study compared factors that lead to a diagnostic versus a non-diagnostic bronchoscopy. Overall, our findings demonstrate that there are no clear clinical or radiological predictors of diagnostic bronchoscopy. These results add to our understanding of diagnostic bronchoscopy procedures in an inner-city teaching hospital and provide much-needed follow-up data on patients with non-diagnostic bronchoscopy.

The diagnostic yield of bronchoscopies at our institution was 51%, consistent with other studies.[4,5,16,17] Our study did not identify any demographic or clinical factors predictive of a diagnostic bronchoscopy. Presence of bilateral diffuse infiltrates on chest imaging was associated with a lower diagnostic yield. Many of those cases were suspected cases of idiopathic lung disease or associated with collagen vascular diseases, where the yield for bronchoscopy is usually low.[3] Notably, in patients with non-diagnostic bronchoscopy, radiological resolution or stability was observed in the majority of cases.

For EBBX and TBBX samples, the optimal number of biopsy specimens varies depending on the radiologic distribution of disease, bronchoscopy findings, and the specific diagnostic entities under consideration.[18–20] One study by Descombes with 530 bronchoscopy biopsies revealed a direct correlation between the number of biopsies and overall diagnostic yield.[21] We failed to uncover a correlation between the number of biopsies and diagnostic yield. As expected, EBBXs correlated with better diagnostic yield, as most of these biopsies were performed for visible endobronchial lesions or suspected sarcoidosis. For EBUS-TBNA, 3 passes of the needle per biopsy site have been suggested for optimal diagnostic yield;[22,23] however, we found no correlation between the number of passes and diagnostic yield for EBUS-TBNA.

Addition of EBUS-TBNA enables retrieval of cytologic material from hilar and/or mediastinal lesions. Indications for this procedure include the diagnosis and/or mediastinal staging of lung cancer and the evaluation of suspected benign granulomatous diseases. False-negative EBUS-TBNA results have been reported for 15% to 30% of cases, with a negative predictive value ranging from 60% to 80%.[24,25] Our study confirmed that performing an EBUS-TBNA is one of the few predictive factors of a diagnostic bronchoscopy. TBBX can be useful in diagnosing malignancy, infections, and certain interstitial lung diseases. The likelihood of successful sampling and diagnosis depends on whether there are localized (local infiltrates, nodules, and masses) or diffuse radiological abnormalities as well as the immune status

of the patient. In general, TBLB is not recommended in suspected idiopathic pulmonary fibrosis or idiopathic interstitial pneumonia. Our study supports these data, as our diagnosis yield in those patients was low.[24]

Bronchoscopy is considered a low-risk, high-yield procedure with an overall low complication rate, which ranges from 1% to 35%.[5,26,27,28] We noted a higher incidence of bleeding compared with other studies, this may be due to overreporting as it is difficult to exactly quantify of bleeding when diluted with saline and body fluids. Incidence of pneumothorax was similar to published data. Incidence of post-procedure respiratory failure has not been reported in prior studies describing complications of bronchoscopy.[26,27] One study reported incidence of hemodynamic and respiratory instability in mechanically ventilated critically ill patients undergoing BAL.[29] In our study post-bronchoscopy ventilatory support was required in 11(1.6%) patients, all of them had preexisting lung condition and were high-risk procedure.

Our study benefits from several strengths. First, our study design included a clear definition for a diagnostic bronchoscopy. Second, we attempted to follow all patients with a non-diagnostic procedure for an extended period of time. Third, we included only bronchoscopic procedures associated with higher diagnostic yield. Fourth, we examined the relationship between clinical and radiological parameters.

This study is one of few studies comparing diagnostic and non-diagnostic bronchoscopy and following patients with a non-diagnostic procedure for a prolonged period of time, offering new insight into the outcomes of these procedures.

There are limitations of our study. This was a single, retrospective study in an inner-city community teaching hospital and as such, has unique demographic features, including a high incidence of HIV infection. Generalization of findings to other settings should be made with caution. Bronchoscopies were performed by multiple operators, perhaps leading to differences in the yield of the procedure. Nonetheless, the standard recommended number of biopsies for TBBX is 5 to 7 in our division unless contraindicated, likely minimizing this potential difference.

5. Conclusions

In summary, we demonstrated that in a general pulmonary practice, there are no clear clinical or radiological predictors of diagnostic bronchoscopy. The presence of bilateral interstitial infiltrates predicts a non-diagnostic bronchoscopy, and performance of EBUS-TBNA and EBBX, if indicated, increases the chances of diagnosis. Follow-up of those patients with a non-diagnostic bronchoscopy is paramount. Although most of them will improve, resolve, or stabilize, a significant treatable pathology can later be identified in as many as 40% of cases. The clinical implications for the pulmonologist are to follow those patients with a non-diagnostic procedure, to closely monitor them, to perform further diagnostic testing when indicated, and to develop an internal system to improve adherence to care.

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Author contributions

SV is the guarantor of this paper and takes responsibility for the content of the manuscript including the data and analysis. GDF contributed to the design, planning, initiation, data collection, data analysis, data interpretation, and writing of the manuscript. PD and BB contributed to data collection, data analysis, data interpretation, and writing and take responsibility for data integrity. All authors had access to the data and final manuscript for approval before submission.

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