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Diagnostic Yield of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration for Sarcoidosis

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Abstract

Objective: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a relatively safe and minimally invasive procedure frequently used to investigate mediastinal lymphadenopathy of unknown etiology. Due to its safety in comparison to mediastinoscopy, which is the diagnostic gold standard, EBUS-TBNA can be used as the first-line diagnostic modality for approaching mediastinal lymphadenopathy in suspected sarcoidosis. In this study, we evaluated the diagnostic yield and safety of EBUS-TBNA for sarcoidosis at our institution.

Methods: A retrospective review was performed for all patients who presented with mediastinal lymphadenopathy and underwent EBUS-TBNA for presumed sarcoidosis for a three-year period and subsequently diagnosed with sarcoidosis. Twenty-five patients were included, and parameters such as nodal station sampled, radiographic stage, adverse events, alternative diagnosis method, and symptoms were recorded.

Results: Thirteen of 25 patients had non-caseating granulomas on EBUS-TBNA with a diagnostic yield of 52%. Of 12 patients not diagnosed via EBUS-TBNA, a diagnosis was made in four patients (33%) via transbronchial lung biopsy, in three (25%) via mediastinoscopy, in one (8%) via video-assisted thoracoscopic surgery, in three (25%) with an elevated bronchoalveolar lavage (BAL) CD4/CD8 ratio and response to therapy, and in one (8%) via muscle biopsy. The average BAL CD4/CD8 ratio was 5.4 for all patients with sarcoidosis. All patients tolerated the procedure without major complications.

Conclusion: EBUS-TBNA is a useful and minimally invasive tool for the diagnosis of sarcoidosis. It should be used as the first-line diagnostic study in suspected sarcoidosis if mediastinal lymphadenopathy is present.

Keywords: Bronchoscopy, endobronchial ultrasonography, lymphadenopathy, mediastinum, sarcoidosis

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease characterized by diffuse non-caseating granulomas predominantly consisting of epithelioid cells and macrophages (1, 2). There have been numerous environmental associations proposed, but the exact etiology remains unknown. Sarcoidosis can affect many organ systems, but it most commonly affects the eyes, lungs, and skin. It frequently presents with hilar lymphadenopathy and pulmonary infiltrates (3). The clinical course is variable and can range from life- and organ- threatening manifestations to self-limiting diseases in some variants, including Löfgren's syndrome, characterized by arthritis, hilar adenopathy, and erythema nodosum (1, 4).

The diagnosis of sarcoidosis is based on clinical suspicion and radiographic findings and is supported by the histologic detection of non-caseating granulomas. Tissue biopsy is typically required to exclude etiologies with similar presentation, most notably infectious etiologies such as fungal infections or mycobacterial disease.

As pulmonary and mediastinal involvement is seen in 90% of patients with sarcoidosis, these areas are among the most commonly biopsied for tissue confirmation of the diagnosis. Transbronchial and endobronchial lung biopsies have a diagnostic yield of 62% in pulmonary sarcoidosis, with a

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relatively low complication rate (5, 6). When evaluating mediastinal lymphadenopathy for sarcoidosis, potential diagnostic tools include mediastinoscopy and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) (7). Though mediastinoscopy is the gold standard for evaluating mediastinal lymphadenopathy of unknown etiology, it requires general anesthesia and has associated risks including recurrent laryngeal nerve injury, bleeding, and tracheal injury (8). A second option for mediastinal nodal tissue sampling includes EBUS-TBNA.

EBUS-TBNA utilizing a curvilinear ultrasound probe is a bronchoscopic procedure used to visualize and biopsy mediastinal structures and pulmonary masses under real-time guidance (9). It has been shown to have a diagnostic yield of approximately 80% in previous studies on granulomatous diseases (6, 10, 11). EBUS-TBNA is a relatively safe procedure with potential complications including bleeding, vocal cord injury, and hypoxia, with minimal risks of major complications (12).

The purpose of this study was to evaluate the diagnostic yield of EBUS-TBNA and its safety profile by performing a retrospective review of patients with confirmed sarcoidosis who underwent EBUS-TBNA at our institution. Additionally, we evaluated the diagnostic yield of each nodal station and the utility of concomitantly performing EBUS-TBNA with transbronchial biopsy and other bronchoscopic procedures.

METHODS

Patients

The medical records of all patients who underwent EBUS-TBNA for suspected sarcoidosis from January 1, 2011 to December 1, 2013 were reviewed. Suspicion for sarcoidosis was based on symptoms, including cough, dyspnea, and extra-pulmonary symptoms, along with radiographic findings. Patients who had a previous proven diagnosis of sarcoidosis, had a suspected or diagnosed malignancy, a negative EBUS-TBNA result without a confirmatory test, or were lost to follow-up were excluded. Parameters such as age, symptoms, radiographic sarcoidosis stage, bronchoalveolar lavage (BAL) fluid CD4/CD8 lymphocyte ratio, biopsy results, other diagnostic procedures, mediastinal nodal station sampled, and adverse events were collected. The study was approved by Institutional Review Board and Ethics Committee at the University of Kansas Medical Center. Radiographic sarcoidosis staging was as follows: stage I, bilateral hilar lymphadenopathy (BHL) without pulmonary infiltrates; stage II, BHL with pulmonary infiltrates; stage III, parenchymal infiltrates without BHL; and stage IV, extensive fibrosis with distortion or bullae (13, 14).

Procedure

All endobronchial ultrasound (EBUS) procedures were performed by faculty at the University of Kansas Medical Center. Procedures were performed in a dedicated endoscopy suite. Prior to performing the procedure, a patient received topical and nebulized 0.5% tetracaine. Once this was applied, the patient was placed in the supine position, sedated by a staff anesthesiologist, and had either an laryngeal mask airway or endotracheal tube placed, depending on the patient's anatomy and the location of nodal station to be biopsied. The EBUS bronchoscope was then advanced into the trachea, and all nodal stations were systemically identified. Nodal stations were chosen for biopsy at the discretion of the performing physician based on size, location, and presence of obscuring tracheal rings. At least three separate transbronchial needle aspirations (TBNAs) were performed at each biopsied location. The number of nodal stations biopsied was at the discretion of the performing physician. An on-site cytologist was present to evaluate each TBNA pass for quality and the presence of lymphoid tissue, and cell blocks were also prepared. Biopsy sites were evaluated for bleeding, and hemostasis was confirmed prior to the completion of the procedure.

All EBUS-TBNA procedures were performed using a curvilinear EBUS bronchoscope (EB-1970UK; PENTAX medical, Tokyo, Japan). All TBNA specimens were collected using a disposable 22 or 25 gauge needle (Echotip® Ultra, Cook Medical, Ireland). The use of suction and number of featherings performed during each biopsy attempt were variable and at the discretion of the performing physician.

Statistical Analysis

Statistical analysis was not performed. Sensitivity analysis was performed by comparing the number of patients diagnosed with a certain procedure by the total number of patients undergoing the procedure.

RESULTS

Twenty-five patients were identified who underwent EBUS-TBNA because of mediastinal lymphadenopathy for suspected sarcoidosis and were eventually diagnosed with sarcoidosis. Diagnosis was confirmed by finding non-caseating granulomas on biopsy specimens without associated infectious causes in the proper clinical scenario or was made on clinical grounds based on the response to corticosteroids, BAL CD4/CD8 ratio, and exclusion of other diagnoses. Full background information is shown in Table 1.

Of these 25 patients, 18 were men and 7 were women, with ages between 24 and 71 (mean, 54.5) years. Presenting pulmonary symptoms included 10 patients (40%) with cough and nine (36%) with dyspnea. Eight (32%) patients were asymptomatic, whereas four (16%) had ex-

Table 1. Patient characteristics

Patient characteristics		Number
Female (Male)		7 (18)
Patient characteristics	Dyspnea	9
	Cough	10
	Extrapulmonary symptoms	4
	Asymptomatic	8
Radiographic stage	Stage I	12
	Stage II	11
	Stage IV	1
	Unknown	1
Other procedures	Concurrent TBB alone	2
	Concurrent EBB alone	5
	Concurrent EBB and TBB	4
Total patients		25

EBB: endobronchial biopsy; TBB: transbronchial biopsy

Table 2. Diagnostic yield based on stations sampled

Station sampled	Number of patients	Number of patients with non-caseating granulomas on FNA	Diagnostic yield
2R	1	0	0%
4R	5	3	60%
4L	1	1	100%
7	19	11	58%
10R	1	0	0%
11R	9	2	22%
11L	6	2	33%

2R: right upper paratracheal; 4R: right lower paratracheal; 7: carinal; 10R: right hilar; 11L: left interlobar; 11R: right interlobar; 4L: left lower paratracheal

Table 3. Diagnostic yield of different bronchoscopic procedures

Procedure	Number of samples	Diagnoses made	Diagnostic yield
EBUS	25	13	52%
EBUS+EBB	5	2	40%
EBUS+TBB	2	2	100%
EBUS+EBB+TBB	4	3	75%
EBB	9	1	11%
TBB	6	4	67%

EBB: Endobronchial biopsy; EBUS: endobronchial ultrasound-guided needle biopsy; EBUS+EBB: EBUS with EBB alone; EBUS+EBB+TBB: EBUS in combination with both TBB and EBB; EBUS+TBB: EBUS with TBB alone; TBB: transbronchial biopsy

Table 4. Diagnostic yield based on the number of stations sampled per patient

Number of sampled stations	Number of patients	Diagnostic Yield
1	10	50%
2	12	42%
3	2	100%
4	1	100%

trapulmonary symptoms. Radiographically, most patients had Stage I disease (48%), followed by Stage II (44%) and IV (4%), whereas the stage was unknown in one patient (4%). Of all 25 patients, five underwent concurrent endobronchial biopsy (EBB) alone, two underwent concurrent transbronchial biopsy (TBB) alone, and four underwent concurrent EBB and TBB.

EBUS-TBNA was able to detect non-caseating granulomas in 13 patients with a diagnostic yield of 52%. Patients who underwent EBUS-TBNA with EBB (n=5) had a diagnostic yield of 40%, while those who underwent EBUS with TBB (n=2) had a diagnostic yield of 100%. When EBUS-TBNA was combined with both EBB and TBB (n=4), there was a diagnostic yield of 75%. Other diagnostic modalities included muscle biopsy (1), video-assisted thoracic surgery (VATS) (1), mediastinoscopy (3), and clinical response to steroids (3). The average CD4/CD8 ratio on flow cytometry of BAL specimen was 4, 6, and 5.4 in the EBUS-positive, EBUS-negative, and total patient population, respectively. The sensitivities of EBB and TBB, when considered alone, were 11% (1/9) and 67% (4/6), respectively, for the detection of granulomas in sarcoidosis. Table 2 outlines the diagnostic yield at different stations sampled. Station 7 was most commonly sampled station with a diagnostic yield of 58%. The diagnostic yield for TBNA of mediastinal lymph nodes, 15 diagnostic sampling from 26 lympyh node stations (58%), was higher than that of hilar lymph nodes, with 4 fold diagnostic sampling from 16 hilar lymph nodes (25%). Table 3 displays the various diagnostic rates for EBUS-TBNA, EBB, and TBB.

Table 4 outlines the diagnostic sensitivity based on the number of stations sampled. The rate of the detection of granulomas on EBUS-TBNA increased if multiple nodal stations were sampled and was as high as 100% if three or four stations were sampled. There were no associated complications from EBUS-TBNA in any of our patients.

DISCUSSION

Our study showed that EBUS-TBNA alone had a diagnostic yield of 52% for mediastinal lymphadenopathy associated with sarcoidosis. EBUS-TBNA is a safe procedure, and when combined with standard bronchoscopic modalities such as TBB and EBB, it can improve the diagnostic yield further for sarcoidosis. The diagnostic yield was 100% with only concurrent TBB and was 75% in patients who had undergone EBUS-TBNA, TBB, and EBB. This diagnostic utility is higher than what was calculated for TBB (67%) and EBB (11%) alone. Station 7 was the most commonly sampled station with a diagnostic yield close to the overall yield of EBUS-TBNA. Although sample size was low, lower paratracheal lymph nodes had a higher yield than hilar nodes. The diagnostic yield was significantly higher when three or more nodal stations were sampled and reached 100%. However, most patients had only one or two stations sampled, which may have contributed toward a lower overall yield. In patients not diagnosed with bronchoscopic techniques, VATS, mediastinoscopy, muscle biopsy, or clinical grounds were used to establish the diagnosis.

A meta-analysis of previous studies showed a diagnostic yield of EBUS-TBNA for the sampling of mediastinal adenopathy in sarcoidosis to be between 54% and 93%, with a pooled diagnostic yield of 79% (10). A recent retrospective study with a large sample size revealed a diagnostic yield of 84% for EBUS-TBNA (14). Various studies have demonstrated that EBUS-TBNA has a diagnostic yield of approximately 80–90% in detecting granulomas in suspected sarcoidosis (15-22). Our diagnostic yield of 52%, while lower than that in previously reported studies, is reflective of a real-world experience and might be due to the sampling of too few nodal stations in majority of the patients. It can be explained by multiple factors such as the use of a 25-G needle, which has not been studied for granulomatous diseases, multiple providers with different skillsets, the learning curve associated with a training program, and fellow involvement.

A key finding of our study was the improved diagnostic yield in mediastinal lymph nodes compared to hilar lymph nodes (58% vs. 25%). Additionally, our highest diagnostic yield was in patients who under-

went nodal sampling of three stations or more. Trisolini et al. (23), in a prospective study, found that paratracheal and subcarinal lymph nodes had higher yields than hilar nodes. They also found improvement in the diagnostic yield when two or more nodal stations were sampled. Sampling of multiple nodal stations has an association with better overall diagnostic yield and should be employed when sampling mediastinal and hilar lymphadenopathy of unknown etiology.

Several authors have evaluated the diagnostic utility of EBUS-TBNA in combination with other bronchoscopic procedures. The current standard for obtaining tissue to diagnose sarcoidosis is by TBB, which has a lower diagnostic yield (50–75%) than EBUS-TBNA (80%) (6, 24). EBB has the lowest diagnostic yield ranging from 30% to 60% but is noted to be up to 90% when mucosal abnormalities are present (14, 19, 25). In one large retrospective study, Dziedzic et al. (14) compared EBUS-TBNA, TBB, and EBB for the evaluation of sarcoidosis and found that when EBUS-TBNA was combined with TBB, the diagnostic yield increased from 84% with EBUS-TBNA alone to 89% with the combination. Various studies have also shown an improved diagnostic yield if other bronchoscopic modalities were utilized with EBUS-TBNA to diagnose sarcoidosis (26-28). It is important to note that although TBB has a higher diagnostic yield in more advanced stages, it can show granulomas even in patients with normal parenchyma on high-resolution computerized thomography (CT) scans (28). Therefore, TBB has become the standard of care for all stages. From the available data, it can be inferred that EBUS-TBNA, despite its high diagnostic yield, should be combined with TBB and/or EBB to maximize the detection of non-caseating granulomas of sarcoidosis.

EBUS-TBNA is a relatively safe procedure with a low complication rate (29, 30). While all our patients underwent the procedure with the assistance of an anesthesiologist, it can also be performed under conscious sedation. Potential complications can include hypoxemia, hypotension, bleeding, pneumothorax, cardiac arrhythmias, bronchospasm, and laryngospasm (31). In our study, only one patient had reported a sore throat after the procedure; no other complications were noted. In one multicenter study, the complication rate for various bronchoscopic procedures was 1% with a very low mortality rate of 0.02% (31). In a meta-analysis evaluating the effectiveness and complication rate of EBUS-TBNA, it was found that no studies reported serious complications. However, three studies reported having observed agitation, cough, and presence of blood at the puncture site (12). In another retrospective study analyzing 3123 patients undergoing EBUS, the complication rate was found to be low at 0.16% that included pneumomediastinum with empyema, mediastinal abscess, fever lasting longer than 24 h, infection of a bronchogenic cyst, and pericarditis (7). These data suggest that EBUS-TBNA is a safe procedure when compared to mediastinoscopy, with an associated morbidity rate of 1% and mortality rate of 0.05%, or VATS, with an associated morbidity rate of 4% and mortality rate of 2% (8, 32). These surgical procedures carry a high expense and significant complication rate which should lead to EBUS-TBNA being the first-line diagnostic study in the sampling of mediastinal lymphadenopathy of unknown etiology.

This study has several limitations, the most notable of which are its retrospective design and small sample size. Further, we had no control group available for comparison. Additionally, not all patients underwent EBB or TBB with EBUS-TBNA. The effectiveness of using all three modes of diagnosis can be better evaluated with a larger sample size of patients undergoing all three procedures in one setting.

CONCLUSION

EBUS-TBNA is a safe and effective procedure when it comes to evaluating mediastinal lymphadenopathy. Its role in lung cancer is well established. It should be widely used to sample mediastinal lymphadenopathy of unknown etiology when a diagnosis of sarcoidosis is suspected. Sampling of multiple nodal stations and performing concomitant EBB and TBB will improve the diagnostic yield. Sampling of mediastinal lymph nodes using TBNA appears to be higher yield than sampling of hilar lymphadenopathy.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Institutional Review Board of the University of Kansas Medical Center and its Ethics Committee.

Informed Consent: Informed consent was not obtained as this was a retrospective review, and many of the patients were unable to be located to provide consent or were lost to follow up. As all patient identifiers were protected and de-identified from the clinical study data, the study was approved by the local review board and Ethics Committee as there was minimal risk for patient harm.

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REFERENCES

1. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999; 160: 736-55.
2. Ma Y, Gal A, Koss MN. The pathology of pulmonary sarcoidosis: update. Semin Diagn Pathol 2007; 24: 150-61. [CrossRef]
3. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. New Engl J Med 2007; 357: 2153-65. [CrossRef]
4. Siltzbach LE, James DG, Neville E, Turiaf J, Battesti JP, Sharma OP, et al. Course and prognosis of sarcoidosis around the world. Am J Med 1974; 57: 847-52. [CrossRef]
5. Agarwal R, Aggarwal AN, Gupta D. Efficacy and safety of conventional transbronchial needle aspiration in sarcoidosis: a systematic review and meta-analysis. Respir Care 2013; 58: 683-93.
6. von Bartheld MB, Dekkers OM, Szlubowski A, Eberhardt R, Herth FJ, in't Veen JC, et al. Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. JAMA 2013; 309: 2457-64. [CrossRef]
7. Caglayan B, Yilmaz A, Bilaceroglu S, Comert SS, Demirci NY, Salepci B. Complications of Convex-Probe Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration: A Multi-Center Retrospective Study. Respir Care 2016; 61: 243-8. [CrossRef]
8. Lemaire A, Nikolic I, Petersen T, Haney JC, Toloza EM, Harpole DH Jr, et al. Nine-year single center experience with cervical mediastinoscopy: complications and false negative rate. Ann Thorac Surg 2006; 82: 1185-9. [CrossRef]

9. Balamugesh T, Herth FJ. Endobronchial ultrasound: A new innovation in bronchoscopy. Lung India 2009; 26: 17-21. [CrossRef]
10. Agarwal R, Srinivasan A, Aggarwal AN, Gupta D. Efficacy and safety of convex probe EBUS-TBNA in sarcoidosis: a systematic review and meta-analysis. Respir Med 2012; 106: 883-92. [CrossRef]
11. Zhu J, Zhang HP, Ni J, Gu Y, Wu CY, Song J, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for diagnosing mediastinal lymphadenectasis: a cohort study from a single center. Clin Respir J 2015. doi: 10.1111/crj.12317. [Epub ahead of print] [CrossRef]
12. Varela-Lema L, Fernandez-Villar A, Ruano-Ravina A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. Eur Respir J 2009; 33: 1156-64. [CrossRef]
13. Lynch JP, 3rd, Kazerooni EA, Gay SE. Pulmonary sarcoidosis. Clin Chest Med 1997; 18: 755-85. [CrossRef]
14. Dziedzic DA, Peryt A, Orlowski T. The role of EBUS-TBNA and standard bronchoscopic modalities in the diagnosis of sarcoidosis. Clin Respir J 2015. doi: 10.1111/crj.12304. [Epub ahead of print] [CrossRef]
15. Cetinkaya E, Gunluoglu G, Ozgul A, Gunluoglu MZ, Ozgul G, Seyhan EC, et al. Value of real-time endobronchial ultrasound-guided transbronchial needle aspiration. Ann Thorac Med 2011; 6: 77-81. [CrossRef]
16. Garwood S, Judson MA, Silvestri G, Hoda R, Fraig M, Doelken P. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. Chest 2007; 132: 1298-304. [CrossRef]
17. Navani N, Booth HL, Kocjan G, Falzon M, Capitanio A, Brown JM, et al. Combination of endobronchial ultrasound-guided transbronchial needle aspiration with standard bronchoscopic techniques for the diagnosis of stage I and stage II pulmonary sarcoidosis. Respirology 2011; 16: 467-72. [CrossRef]
18. Oki M, Saka H, Kitagawa C, Tanaka S, Shimokata T, Kawata Y, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration is useful for diagnosing sarcoidosis. Respirology 2007; 12: 863-8. [CrossRef]
19. Plit M, Pearson R, Havryk A, Da Costa J, Chang C, Glanville AR. Diagnostic utility of endobronchial ultrasound-guided transbronchial needle aspiration compared with transbronchial and endobronchial biopsy for suspected sarcoidosis. Intern Med J 2012; 42: 434-8. [CrossRef]
20. Tremblay A, Stather DR, Maceachern P, Khalil M, Field SK. A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis. Chest 2009; 136: 340-6. [CrossRef]
21. Wong M, Yasufuku K, Nakajima T, Herth FJ, Sekine Y, Shibuya K, et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. Eur Respir J 2007; 29: 1182-6. [CrossRef]
22. Eckardt J, Olsen KE, Jorgensen OD, Licht PB. Minimally invasive diagnosis of sarcoidosis by EBUS when conventional diagnostics fail. Sarcoidosis Vasc Diffuse Lung Dis 2010; 27: 43-8.
23. Trisolini R, Tinelli C, Cancellieri A, Paioli D, Alifano M, Boaron M, et al. Transbronchial needle aspiration in sarcoidosis: yield and predictors of a positive aspirate. J Thorac Cardiovasc Surg 2008; 135: 837-42. [CrossRef]
24. Descombes E, Gardiol D, Leuenberger P. Transbronchial lung biopsy: an analysis of 530 cases with reference to the number of samples. Monaldi Arch Chest Dis 1997; 52: 324-9.
25. Chapman JT, Mehta AC. Bronchoscopy in sarcoidosis: diagnostic and therapeutic interventions. Curr Opin Pulm Med 2003; 9: 402-7. [CrossRef]
26. Hong G, Lee KJ, Jeon K, Koh WJ, Suh GY, Chung MP, et al. Usefulness of endobronchial ultrasound-guided transbronchial needle aspiration for diagnosis of sarcoidosis. Yonsei Med J 2013; 54: 1416-21. [CrossRef]
27. Goyal A, Gupta D, Agarwal R, Bal A, Nijhawan R, Aggarwal AN. Value of different bronchoscopic sampling techniques in diagnosis of sarcoidosis: a prospective study of 151 patients. J Bronchology Interv Pulmonol 2014; 21: 220-6. [CrossRef]
28. Raddaoui E, Alhamad EH, Zaidi SN, Arafah M, AlHabeeb FF. Utility of endoscopic ultrasound-guided transbronchial fine-needle cytology in the diagnosis of sarcoidosis: A Saudi experience. Cytojournal 2014; 11: 31. [CrossRef]
29. Facciolongo N, Patelli M, Gasparini S, Lazzari Agli L, Salio M, Simonassi C, et al. Incidence of complications in bronchoscopy. Multicentre prospective study of 20,986 bronchoscopies. Monaldi Arch Chest Dis 2009; 71: 8-14.
30. Jin F, Mu D, Chu D, Fu E, Xie Y, Liu T. Severe complications of bronchoscopy. Respiration 2008; 76: 429-33. [CrossRef]
31. Jalil BA, Yasufuku K, Khan AM. Uses, limitations, and complications of endobronchial ultrasound. Proc (Bayl Univ Med Cent) 2015; 28: 325-30.
32. Imperatori A, Rotolo N, Gatti M, Nardecchia E, De Monte L, Conti V, et al. Peri-operative complications of video-assisted thoracoscopic surgery (VATS). Int J Surg 2008; 6 (Suppl 1): S78-81. [CrossRef]