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RESEARCH ARTICLE

Diagnostic Techniques in Sarcoidosis-Past, Present and the Future

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ABSTRACT:

Introduction: Sarcoidosis has historically been a challenging disorder to diagnose secondary to its non-specific symptoms and multi-system nature of organ involvement. Since the description of Kviem test in 1941, the diagnostic investigations have evolved substantially over time. We have witnessed refinement of the procedures to detect granulomatous inflammation with increasing utilisation of image guided modalities and more recently Transbronchial Lung Cryo-biopsy with an acceptable diagnostic yield.

Methods: In this review, we aim to describe the utility of diagnostic techniques over the decades and propose an algorithm to help General Physicians as well as Pulmonologists. We used search terms including Sarcoidosis, Diagnosis, Transbronchial as well as endobronchial biopsy, Ultrasound guided core biopsy, Endobronchial ultrasound, Transbronchial Lung Cryo-biopsy, Fine Needle Aspiration as well as peripheral lymph node biopsy.

Results: There has been significant advancement in the diagnostic techniques with improvement in the diagnostic yield for histological confirmation of Sarcoidosis. clinical evidence and diagnostic utility of salient diagnostic investigations has been evaluated in this review. The description of diagnostic methods and clinical evidence is deliberately kept brief. Ultrasound guided core biopsy of cervical lymph nodes (even in the absence of palpable glands) should be considered as least invasive test in suspected cases of mediastinal sarcoidosis. Transbronchial Lung Cryo-biopsy is relatively recent development in the diagnostic pathway and is an advantageous tool when lung parenchymal abnormalities are coupled with lack or minimal mediastinal and or hilar adenopathy.

Conclusion: We propose a diagnostic algorithm for patients with suspected Sarcoidosis. The choice of investigation should be decided following discussion in a multi-disciplinary meeting. In appropriate clinical/radiological setting and expertise, core biopsy of cervical lymph nodes should be considered the first line investigation as it may prevent the need for more invasive bronchoscopic procedures. However, in the absence of mediastinal/cervical lymphadenopathy, Cryobiopsy (if available) should be considered, in preference to more invasive thoracic surgical procedure (s) associated with higher morbidity and mortality.

Introduction:

Sarcoidosis is a chronic inflammatory disease of uncertain aetiology characterised by granulomatous inflammation in the affected organ (s). It was first described by Jonathan Hutchinson in 1869, when a 58-year-old worker presented with purple plaques on the skin[1] and Dr Hutchinson described it as a case of "livid papillary psoriasis".

Sarcoidosis has been a challenging disorder to diagnose due to its non-specific symptoms and multi-system nature of organ involvement. The diagnosis is best supported by the histological confirmation of non-caseating granulomatous inflammation of the affected organ (s). However, there is a proportion of patients where the clinical/radiological features are pathognomonic for Sarcoidosis and histological proof may not be required and decision to monitor the patients with close clinical follow up would be appropriate, following discussion in multi-disciplinary meeting (MDM). Scadding criteria has been devised to stage Sarcoidosis based on chest radiographic appearances as shown in Figure 1[2,3].

Stage	*Chest radiograph findings*
0	No chest abnormality
I	Hilar lymphadenopathy
II	Hilar lymphadenopathy and parenchymal abnormality
III	Parenchymal abnormality without hilar lymphadenopathy
IV	Fibrosis with volume loss

Figure 1: Scadding staging for pulmonary sarcoidosis

Historically, Kviem test was utilised to diagnose Sarcoidosis following first report by Norwegian Pathologist Morten Ansgar Kviem in 1941. The diagnostic investigations to confirm evidence of granulomatous inflammation have evolved significantly since, with refinement and increasing utilisation of image guided techniques ranging from fine needle aspiration (FNA), Transbronchial lung biopsy (TBLB) and Endobronchial biopsy (EBB) with or without Broncho-alveolar lavage (BAL), Core biopsy of peripheral lymph glands, Video-assisted thoracoscopic biopsies (VATs), Open Lung Biopsy (OLB), Endobronchial ultrasound guided Transbronchial needle aspiration (EBUS-TBNA) and more recently Transbronchial Lung Cryo-biopsy (TBLCB). These investigations have been shown to have a variable diagnostic yield in research studies and trials.

In this review, we aim to describe the utility of various diagnostic techniques over the years and propose an algorithm for the diagnosis of Sarcoidosis to help the generalists as well as Pulmonologists dealing with the patients with possible Sarcoidosis. We propose that patients with suspected Sarcoidosis should be considered for the least invasive procedure, particularly in the early Stages (Stage I and II) and discussion in an MDM should be the gold standard for decision about the most appropriate initial diagnostic investigation.

Sarcoidosis has propensity for involving lungs and lymph nodes in majority of cases (>90%). The incidence of organ system involvement is demonstrated in Figure 2 as reported by a study using World Association for Sarcoidosis and Other Granulomatous disorders (WASOG) tool[4]. Although the traditional staging of sarcoidosis has been based on the chest radiographic appearances (as described by Scadding Criteria), High-resolution computed tomography (HRCT) is the imaging modality of choice for suspected pulmonary or mediastinal/hilar lymph node involvement with Sarcoidosis. Radiographic imaging including Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET-CT) has been increasingly utilised in recent times and provide an enormous value to the assessment of disease activity and monitoring of response to therapies such as oral corticosteroids and other immunosuppressants such as Methotrexate, particularly in the context of cardio-pulmonary involvement with sarcoidosis. However, the role of specialist imaging techniques such as MRI or PET-CT scan for the diagnosis and or monitoring of disease activity is beyond the scope of this review.

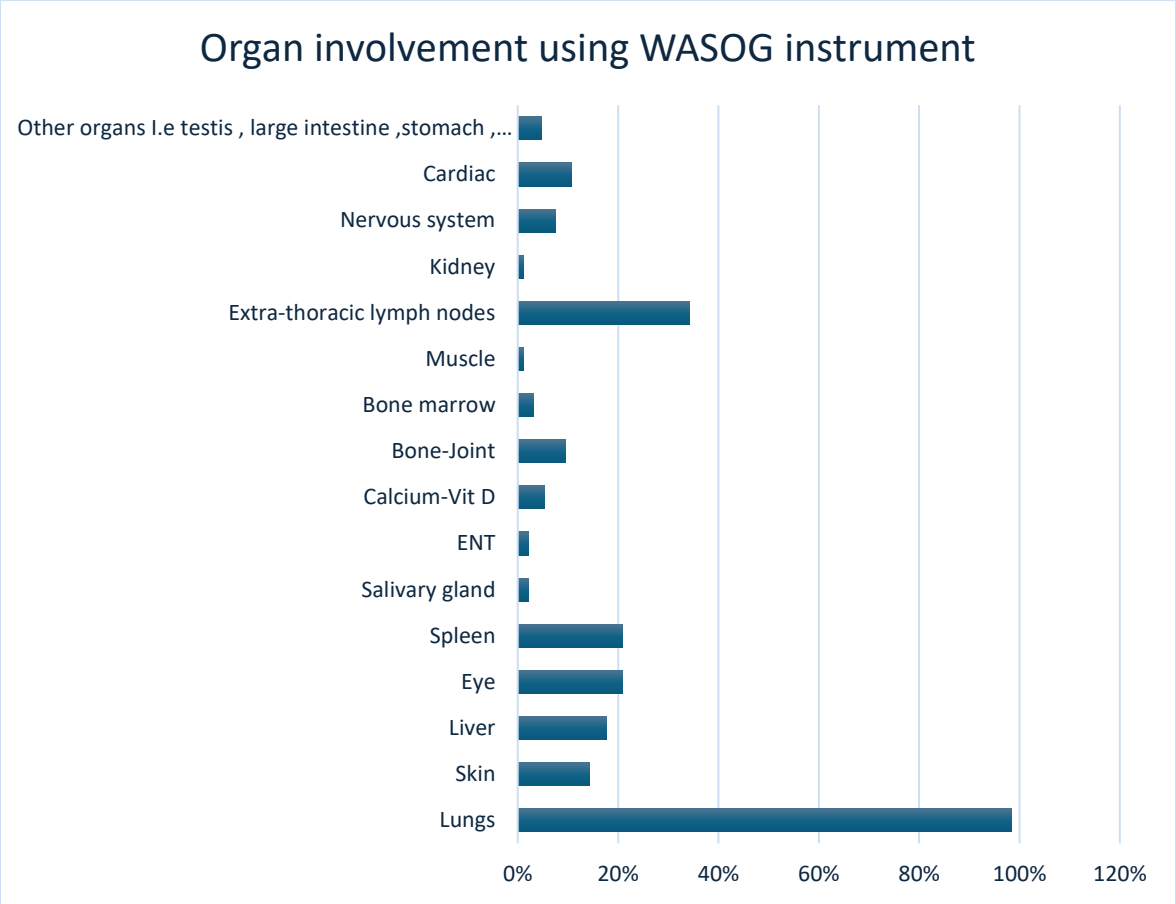


Figure 2: Organ involvement in Sarcoidosis reflecting multi-systemic nature with propensity to affect lungs in the majority (Reference 4)

Methods:

We searched Medline for the clinical trials in English literature evaluating the diagnostic utility of investigations focusing on image guided techniques over the last 25 years. Both authors have extensive clinical experience of managing Sarcoidosis in a multi-disciplinary setting and performed literature search to extract currently available evidence in terms of diagnostic sensitivity of certain modalities. The review is deliberately kept brief to outline important randomised clinical trials (RCTs) to evaluate endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) to confirm histological features of Sarcoidosis. Furthermore, as Transbronchial lung Cryobiopsy (TBLCB) is increasingly being utilised in the diagnosis of interstitial lung disease (ILD), including Sarcoidosis, published studies in English literature on the role of TBLCB for the diagnosis of Sarcoidosis and ILD were evaluated.

The following relevant controlled vocabulary (MeSH Headings) and natural language terms where selected and combined to conduct the search:

- Transbronchial lung cryobiopsy
- Transbronchial cryobiopsy
- TBLCB
- Broncho-alveolar lavage (BAL)
- EBUS-TBNA
- Sarcoidosis
- Diagnosis
- Diagnosing
- Diagnostics

Data sources searched included: CINAHL Complete and Medline on the Ebsco platform, Embase and Emcare on the OVID platform, PubMed, Cochrane Library, TRIP database, UpToDate, BMJ Best Practice, Google and Google Scholar. Items were scanned for relevance and limited to English language and Humans. Relevant references were saved and exported into RefWorks (reference management software) and then deduplicated.

Results:

There have been a wide range of diagnostic modalities being utilised across the globe with myriad of studies ranging from small case series to prospective as well as large scale RCTs evaluating diagnostic value of bronchoscopic techniques in suspected Sarcoidosis. The saliant features of RCTs evaluating EBUS-TBNA are summarised in Table 1.

Table 1: Randomised Controlled Trials of EBUS-TBNA in Sarcoidosis

Study year	Number of participants	Study focus	Comments
2021[5]	358	EBUS-TBNA and EBUS FNA	No significant difference in granuloma detection rate and sensitivity.
2017[6]	253	EBUS-TBNA and c-TBNA (conventional)	The sensitivity of EBUS-TBNA was higher than Conventional (c-TBNA). No major adverse events occurred.
2018[7]	150	Effect of 10 vs 20 revolutions inside lymph node on diagnostic yield of EBUS-TBNA	No difference in specimen adequacy and diagnostic yield between the two groups.
2014[8]	130	EBUS-TBNA and c-TBNA	EBUS-TBNA had the highest diagnostic yield but it should be combined with TBLB for optimal yield. The diagnostic yield of c-TBNA (plus EBB and TBLB) was similar to EBUS-TBNA and TBLB. No major adverse events.
2015[9]	100	TBNA, EBUS-TBNA and Endoscopic Ultrasound (EUS-FNA)	Sensitivity and accuracy of EBUS-TBNA were higher and of EUS-FNA were significantly higher compared to TBNA. In stage 1 and 2 of pulmonary sarcoidosis, EUS-FNA seems to be method of choice.
2021[10]	100	Pro-core and standard EBUS-TBNA needle	No difference found in sensitivity, specimen adequacy or safety with either pro-core or Olympus needle.
2017[11]	80	Utility of rapid on-site evaluation (ROSE) in EBUS-TBNA and c-TBNA	EBB and TBB performed in all patients. Sedation requirements and duration were significantly lower in c-TBNA. c-TBNA with ROSE and EBUS (with and without ROSE) were superior than c-TBNA alone.
2014[12]	62	TBNA and EBUS-TBNA	Diagnostic yield was significantly higher in EBUS-TBNA (93%) compared to TBNA (64%). However, TBNA had similar diagnostic yield if lymph nodes located on 4th and 7th group or shortest diameter was greater than 15mm.
2009[13]	50	EBUS-TBNA and TBNA	Diagnostic yield of EBUS-TBNA was higher (83.3%) compared to TBNA (53.8%).
2012[14]	50	Cytologic assessments of EBUS aspirates	Liquid based cytology and cell block specimens are equally important in maximising diagnostic yield in EBUS-TBNA and c-TBNA.
2022[15]	30	22G Crown-cut needle vs conventional 22G needle	Equal diagnostic accuracy.

US guided core-biopsy of cervical lymph nodes

Ultrasound (US) has been utilised for decades to establish suitable target for histological confirmation of lymphadenopathy in benign as well as malignant diseases including lymphoma[16]. However, it can be of significant value in patients referred to pulmonologists with *suspected sarcoidosis* based on mediastinal and or hilar lymph node enlargement as part of systemic screening of cases with acute uveitis, granulomatous disease affecting the skin, cardiac investigations raising possibility of sarcoidosis or incidental lymphadenopathy when patients are scanned for other reasons. The value of this technique was evaluated in a retrospective study of 25 patients with mediastinal adenopathy referred for sonographic evaluation of head and neck without apparently enlarged or clinically palpable cervical lymph nodes[17]. Most cases biopsied following US scan had minimal enlargement of lymph nodes (short axis diameter of <10 mm) without pathological features on ultrasound. However, all cases where a biopsy was attempted, confirmed non-caseating granulomatous inflammation confirming the diagnosis of sarcoidosis with clear evidence of cost effectiveness of this technique as otherwise these patients would have been referred for EBUS-TBNA for confirmatory histology. Hence, there is huge value of this technique (in expert hands) in the initial diagnostic work up of sarcoidosis. Furthermore, availability of ultrasound in most healthcare settings makes it an attractive *first line investigation* in appropriately trained hands.

Bronchoalveolar Lavage (BAL)

BAL is utilised in the diagnostic work up of ILD by sampling distal airways with flexible bronchoscope and 100-250 ml of sterile saline is instilled with an aim to obtain at least 30% of aspirate back. It has a potential role in the diagnostic work up in ILD and sarcoidosis[18-20]. A lymphocytosis of >15% with associated CD4/CD8 ratio of >3.5 provides specificity of 93 to 96% for the diagnosis of sarcoidosis[21]. We do not recommend routine use of BAL in the diagnostic work up. However, it should be considered in patients on a case-by-case basis following MDM discussion, where radiological changes are predominantly affecting upper to mid zones and differentials being considered are either Sarcoidosis or Hypersensitivity Pneumonitis based on distribution of radiological changes on thoracic computed tomography.

Transbronchial Lung Cryobiopsy

Traditional transbronchial biopsies (TBB) have been utilised via flexible bronchoscope for diffuse as well localised lung disease since 1970s[22]. There have been several studies demonstrating variable diagnostic yield of TBB with or without endobronchial biopsy (EBB) for histological confirmation of diffuse parenchymal lung diseases[23-28]. These studies lack uniformity in selection criteria of patients and are limited to case series and retrospective study designs, making it difficult to establish their role in the diagnostic algorithm of sarcoidosis. The procedure (s) are associated with complications including pneumothorax, chest pain and need for intercostal drain insertion in a proportion of cases. Furthermore, the samples obtained are small and frequently crushed- making histological assessments challenging, meaning that patients may require further invasive investigations such as mediastinoscopy and or surgical lung biopsies, adding to the morbidity and mortality as well as delay in the diagnosis.

Transbronchial lung Cryobiopsy (TBLCB) is an emerging and attractive diagnostic tool in the evaluation of ILD and sarcoidosis. It provides a significantly larger sample compared to the traditional methods. The sample is obtained by using a cryoprobe and is performed under general anaesthesia[29,30]. It provides lung tissue in non-crushed form making histological assessment easier and sample being suitable for additional studies such as genetic evaluation as well as detailed histological analysis for underlying ILD including Idiopathic Pulmonary Fibrosis with usual interstitial pneumonia pattern. Table 2 summarises the published studies in English literature to evaluate TBLCB in ILD and Sarcoidosis. The list is not exhaustive and provides key information about the studies including diagnostic yield (where reported) and complication rates associated with the procedure.

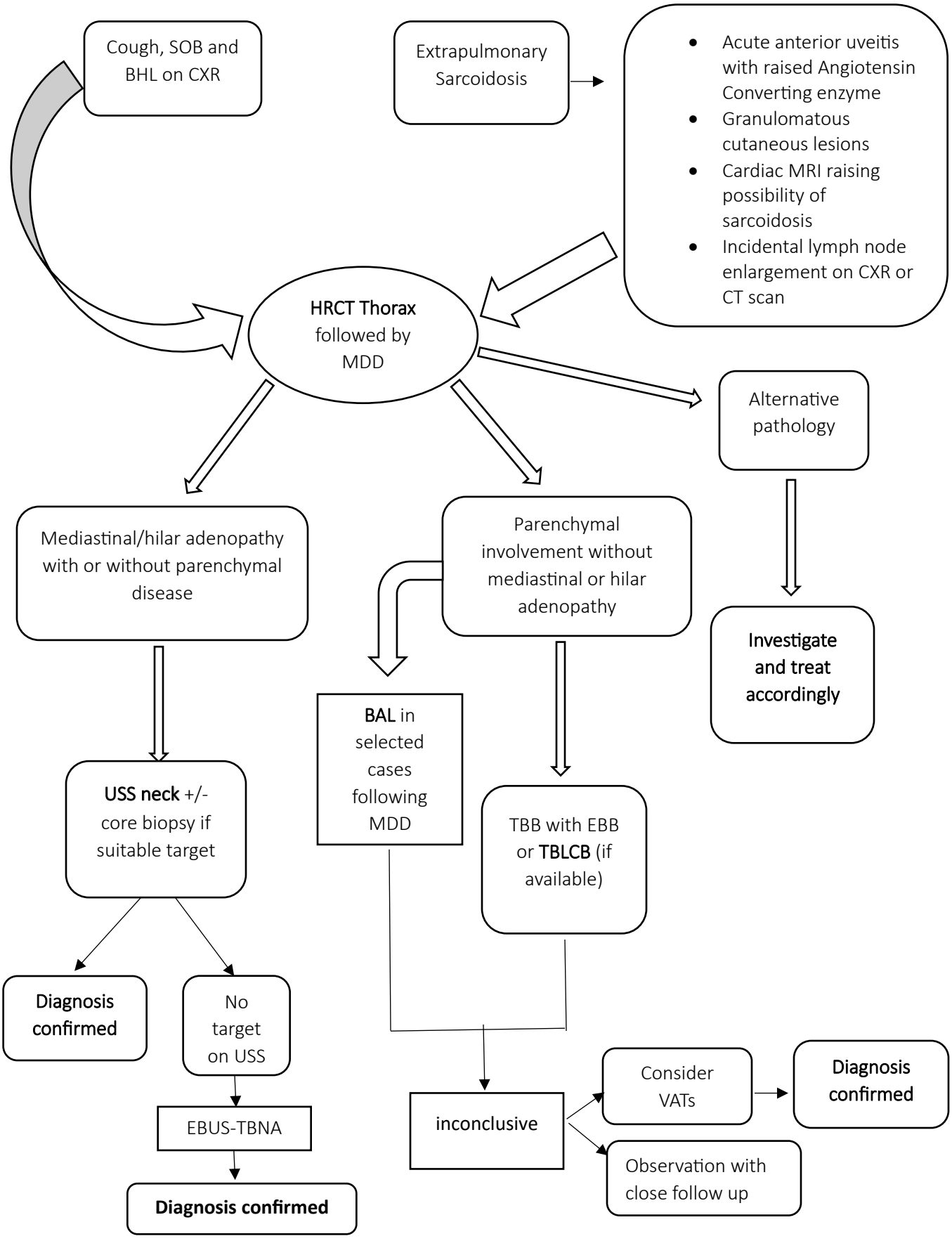
Table 2: Studies evaluating *TBLCB* in ILD and Sarcoidosis

Study year	Number of participants	Type of study	Focus of study	Comments
2022[31]	132	Retrospective	Diagnostic rates, complications and cost effectiveness of VATS and TBLCB	Low diagnostic accuracy in TBLCB compared to VATS but it may be an alternative diagnostic tool due to its acceptable safety profile and cost effectiveness.
2022[32]	431	Retrospective	Sensitivity of TBLCB in different ILDs	Sensitivity of pathological diagnosis with TBLCB was higher in IPF compared to iNSIP, CTD-ILD and fibrotic HP.
2021[33]	359	Prospective	Superiority of TBLCB to TBLB	The histological diagnosis of sarcoidosis better with TBLCB, however with higher bleeding risk.
2021[34]	100	Prospective	Evaluation of TBLCB in combination with BAL, radiological and clinical data	Diagnostic value is high if combined with BAL, radiological and clinical data. Complications included pneumothorax and locally controlled bleeding.
2020[35]	114	Prospective	Safety and diagnostic yield of TBLCB under conscious sedation	79% had conclusive histopathology. Complications included pneumothorax and minor to moderate bleeding.
2019[36]	32	Retrospective	Diagnostic yield and safety of TBLCB in sarcoidosis	Diagnostic yield of 92.6%. Complications included pneumothorax (15.6%) and moderate bleeding (3.1%).
2018[37]	128	Retrospective	Diagnostic yield and safety of TBLCB in ILD	Overall yield 78.1%. Incidence of moderate to severe bleeding and pneumothorax was lower with use of an occlusion balloon and fluoroscopy respectively.
2017[38]	36	Retrospective	Use of TBLCB to diagnose sarcoidosis	TBLCB can be considered part of diagnostic armamentarium. Pneumothorax rate was 11.1%.
2017[39]	74	Retrospective	TBLCB with a 2-scope technique	Diagnostic yield of 87.84%. Pneumothorax occurred in 5 cases and significant bleeding in 1. Death occurred in 3.

Discussion:

Diagnostic modalities and pathways to establish histological confirmation of Sarcoidosis have evolved considerably over the recent decades with advancement in image guided biopsy techniques. It has resulted in better selection of patients for invasive tests to exclude other pathologies considered in differential diagnoses with Sarcoidosis such as malignancy, tuberculosis, other granulomatous diseases as well as lymphoproliferative disorders. American Thoracic Society (ATS) produced guidelines on 'diagnosis and detection of Sarcoidosis' in 2020[40] with no *strong* recommendations for any diagnostic investigation (s) for histological confirmation either in asymptomatic patients with bilateral hilar and or mediastinal adenopathy or in patients for whom it is determined that tissue sampling is necessary. Furthermore, ATS made a conditional recommendation albeit with *very low quality of evidence*, in the latter group, for EBUS guided lymph node sampling (EBUS-TBNA), rather than mediastinoscopy as initial investigation of choice for histological confirmation. This reflects the challenges in standardisation of diagnostic algorithms and quality of evidence available to detect and diagnose Sarcoidosis globally and present opportunity to propose a pragmatic approach to be considered. Furthermore, least invasive tests should be considered in the first instance, before moving on to more complex and invasive diagnostic procedures with associated increased morbidity and complications (including mortality and infection risk).

Figure 3: Proposed algorithm for diagnostic confirmation of suspected sarcoidosis
HRCT: High resolution computed tomography; MDD: Multidisciplinary discussion; USS: Ultrasound scan; TBB: Trans-bronchial biopsy; EBB: Endobronchial biopsy; TBLCB: Transbronchial lung cryobiopsy; VATs: Video assisted thoracoscopic; BHL: bilateral hilar lymphadenopathy; CXR: chest radiograph.



We propose a diagnostic algorithm as shown in Figure 3, when a patient is presented to a pulmonologist or general acute physician where sarcoidosis is a potential consideration. The most common scenario is when a patient presents with respiratory symptoms such as cough, shortness of breath and or chest pain and a thoracic CT scan demonstrates mediastinal lymphadenopathy with or without parenchymal lung involvement. It is envisaged that if all suspected patients are scanned with an US neck at the outset, we are likely to diagnose a third of cases (personal observation) without the need for a bronchoscopic procedure (TBB with EBB or EBUS-TBNA). It will be of enormous value in stage I and II sarcoidosis[41] where the value of recommending more invasive tests is questionable and expert guidance is limited about best plan of action. Moreover, it is cost effective in resource limited healthcare settings where EBUS-TBNA may not be readily available and may result in delay to confirm the diagnosis.

Conclusion:

We have witnessed evolution in diagnostic investigations for sarcoidosis over the last two decades with a significant proportion of patients being able to have histological confirmation via less invasive procedure (s). It is utmost important to have a systematic approach to establish confident diagnosis following MDM discussion amongst pulmonologists with expertise in sarcoidosis, specialist thoracic radiologist and pathologist as well as thoracic surgeon (in selected cases). It is recommended that US guided core biopsy of cervical lymph nodes should be considered in all suspected cases with mediastinal and or hilar lymphadenopathy, where appropriate expertise is available. Furthermore, TBLCB has an acceptable diagnostic yield in ILD and sarcoidosis (78% to 93%) with associated risks of pneumothorax and bleeding, and we are likely to witness its expansion in preference to more invasive surgical techniques such as mediastinoscopy and video assisted or open surgical lung biopsies. Final decision regarding the most appropriate initial diagnostic intervention should be made following detailed clinical and radiological assessment in close collaboration with the patient, about the risks/benefits of currently available tools and need for histological sampling based on severity and organ involvement.

Conflicts of Interests Statement:

The authors confirm no conflicts of interest in relation to this manuscript.

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