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Current Practices and Considerations in Lung Biopsy for Suspected Granulomatous-Lymphocytic Interstitial Lung Disease: A Clinician Survey

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Keywords
Common variable immunodeficiency · Granulomatous-lymphocytic interstitial lung disease · Diagnosis · Lung biopsy

Abstract

Introduction: This study explores clinicians' diagnostic practices and perceptions in the context of granulomatous-lymphocytic interstitial lung disease (GLILD), a pulmonary manifestation of common variable immunodeficiency disorder. The aim was to gain valuable insights into key aspects, such as the utilization of radiological features for diagnostic purposes, indications for lung biopsy, preferred biopsy techniques, and the relative importance of different histopathological findings in confirming GLILD. ***Method:*** A survey targeting expert clinicians was conducted, focusing on their experiences, practices, and attitudes towards lung biopsy in suspected GLILD cases. ***Results:*** The survey revealed that the majority of respondents accepted high-resolution computed tomography as a sufficient alternative to biopsy for making a probable GLILD diagnosis in most patients. There was a consensus among most respondents that the presence of extrapulmonary granulomatous disease is adequate for making a diagnosis of GLILD where the chest imaging and clinical picture are consistent. When a biopsy was recommended, there was notable variation in the preferred initial biopsy technique, with 35% favouring transbronchial biopsy. ***Conclusion:*** Our findings underscore the complexity of diagnosing GLILD, indicating varied clinician opinions on

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the necessity and efficacy of lung biopsies. They highlight the need for further research and the development of consistent diagnostic criteria and management protocols, ultimately aiming to enhance the accuracy and safety of GLILD diagnosis and treatment strategies.

Introduction

Common variable immunodeficiency disorder (CVID) is one of the most common primary immunodeficiencies, characterized by a decreased ability to produce serum immunoglobulin IgG, IgA, and/or IgM, most commonly manifested by susceptibility to acute infections [1, 2]. With the introduction of immunoglobulin replacement therapy, infectious complications are no longer the leading cause of morbidity and mortality [3]. In contrast, the most significant impact on prognosis is caused by non-infectious complications such as chronic lung diseases, granulomas, autoimmunity, liver and gastrointestinal diseases, and increased risk of malignancy [4–6].

Granulomatous-lymphocytic interstitial lung disease (GLILD) describes pulmonary manifestation of systemic immune dysregulation in CVID. It affects around 10–20% of CVID patients, resulting in worsening prognosis and reduced survival [3, 7]. The diagnosis and management of GLILD present considerable challenges even for expert clinicians due to the uncertain natural history and heterogeneity of the disease. Chest imaging, lung function tests, and laboratory investigations are non-invasive methods that could help identify the presence and severity of GLILD [8]. These serve as the foundation of recent GLILD diagnostic prediction models [9–13]. However, conceptually, people living with CVID could develop other interstitial lung diseases (ILDs), and thus, it would be challenging to confirm GLILD without histological confirmation. Specifically, pulmonary sarcoidosis is often considered in the differential diagnoses [14] – although sarcoid is typically characterized by hypergammaglobulinaemia. Moreover, when abnormalities typical of GLILD are present on chest imaging in a person with CVID, it is difficult to exclude acute infections and pulmonary lymphoma. Thus, when radiological and clinical observations are not thought sufficient to establish a confident diagnosis of GLILD with a high probability, a lung biopsy revealing typical histological features of GLILD may be considered [8, 15]. However, the role of lung biopsies in suspected GLILD cases, particularly their utility and impact on management strategies, remains a subject of active discussion among clinicians [16]. This ongoing debate highlights the complexity of managing GLILD and underscores the importance of further investigation into the role of biopsies in different clinical scenarios.

To address this, we conducted a survey targeting expert clinicians specialized in pulmonology, immunology, pathology, and radiology to explore their experiences, practices, and attitudes towards lung biopsy in suspected GLILD. The primary purpose of our survey was to gain valuable insights into key aspects, such as the utilization of radiological features for diagnostic purposes, the indications for lung biopsy, the preferred biopsy techniques, and the relative importance of different histopathological findings in confirming GLILD.

Methods

We used a self-administered questionnaire to gather data regarding indications for biopsy and the preferred technical procedure for patients suspected of having GLILD. The survey consisted of 28 questions covering demographic data, clinical experience, high-resolution computed tomography (HRCT) findings and their value in diagnosing GLILD, indications for biopsy, biopsy techniques, outcomes, and complications, as well as current practices and factors influencing decision-making. Five questions were designed using branching logic, allowing for targeted questions based on the answer to a biopsy modality question to assess efficacy, determine the consideration of re-biopsy, and explore recommended alternative approaches. A total of 92% of the questions were closed, and respondents had the option to leave comments on 35% of questions. A total of 25% of the questions utilized a five-point Likert scale with options including always, most of the time, frequently, sometimes, rarely, and never.

Two pulmonologists and immunologists were asked to review the initial draft questionnaire and provide feedback that was used to shape the final version. The final version was sent via e-mail to 53 experts who were members of eGLILDnet, an ERS Clinical Research Collaboration dedicated to GLILD, and also distributed electronically on X, formerly Twitter, and Threads. The survey was open between June and August 2023. Data are presented as frequencies and percentages.

Results

In total, 26 respondents (50% female) from 12 countries registered and took part in the survey (Table 1). The four most common countries were the USA and Italy (n = 5 each), the Netherlands and the UK (n = 4 each), accounting for 69% of respondents. Fourteen (54%) of the respondents were immunologists, 10 (38%) were pulmonologists, and 2 (8%) were radiologists. They had a

Table 1. Demographic characteristics of the participants

	Frequency, *n*	Percentage
Gender		
Female	13	50
Male	13	50
Type of care setting		
University/academic/tertiary referral centre	25	96
Specialty hospital	1	4
Primary role		
Immunologist	14	54
Pulmonologist	10	38
Radiologist	2	8
Patient population		
Adult patients	21	81
Paediatric patients	2	8
Both adult and paediatric patients	3	11
Total responses	26	

mean experience of 16 years in their specialties, and 21 (80%) were specialized in adult patients only; more information about the number of GLILD patients they treated are summarized in Table 2. Respondents most often worked in university, academic, or tertiary referral centres.

Radiology

Respondents were asked which radiological features of GLILD they had ever observed. Overall, 88% of the respondents had observed ground glass opacities and 88% had observed nodules or masses (Fig. 1). A total of 85% had observed interlobular septal thickening, while 73% had ever observed the presence of lymphadenopathy. Consolidation had been seen by 58% of respondents. Free-standing bronchiectasis was observed by 42% of the respondents. Traction bronchiectasis (i.e., as part of fibrosis) has also been observed by 42%, while honeycombing was only seen by 12% of the respondents.

Acceptability of a CT Diagnosis

Next, we wanted to understand when clinicians would or would not decide to recommend biopsy. Overall, 58% of respondents said that a CT scan in the appropriate clinical setting is frequently or most of the time sufficient to make a probable diagnosis, and no respondents answered that this clinic-radiological diagnosis was never sufficient (Fig. 2). For the decision to initiate treatment for GLILD, more than half of the respondents (57%) indicated that a clinical-radiological diagnosis, most of the time or frequently, provides adequate grounds for treatment initiation.

Table 2. Average number of patients participated treated last year, divided by their years of experience

Years of experience	Participants, *n*	Mean±SD
1–10	8	7±6
11–20	10	19±15
>21	7	12±9

Indications for Biopsy

The two most common reasons cited to proceed to biopsy were diagnostic uncertainty and suspicion of malignancy (both mentioned by 88% of respondents; Table 3). Next, we asked clinicians how frequently a lung biopsy confirmed GLILD in those situations where a biopsy had been performed. Overall, 80% of the respondents said that a diagnosis of GLILD was confirmed in more than half of patients.

Preferred Biopsy Technique for Initial Diagnosis and Repeat Biopsy

Clinicians were asked about the factors that influenced their choice of biopsy technique. Overall, 88% of respondents said that, overall, an individual patient-level risk benefit was the most important factor to affect their decision. Patient-specific factors such as comorbidities and lung function, lesion location and accessibility, and availability of the procedure were also considered very important by 77%, 69%, and 50%, of respondents, respectively. Other factors including costs, the presence of granulomas in extrapulmonary tissues such as lymph

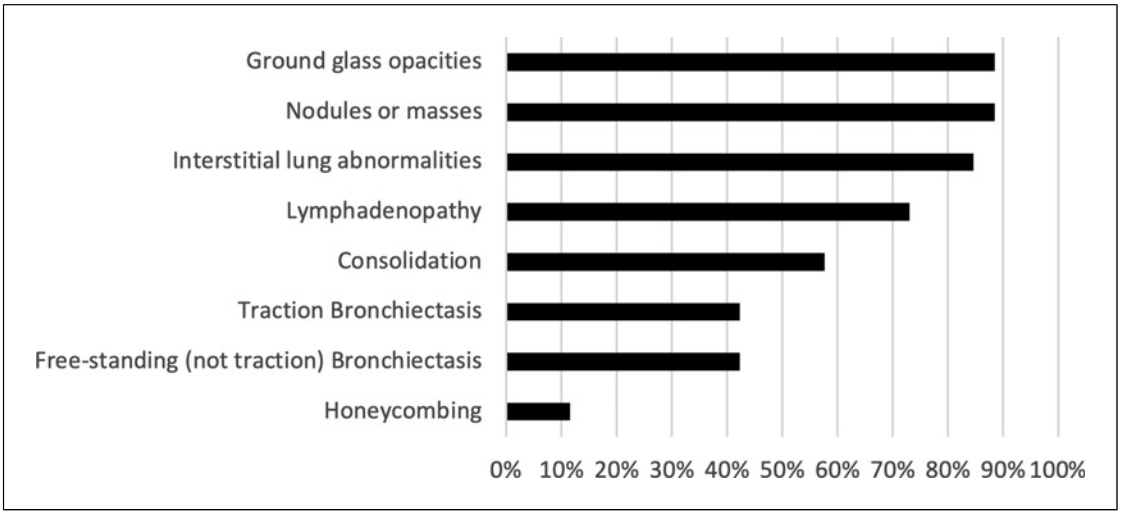

Fig. 1. Radiological features in GLILD patients. The percentages indicate the proportion of respondents who have observed these radiological features (n = 26).

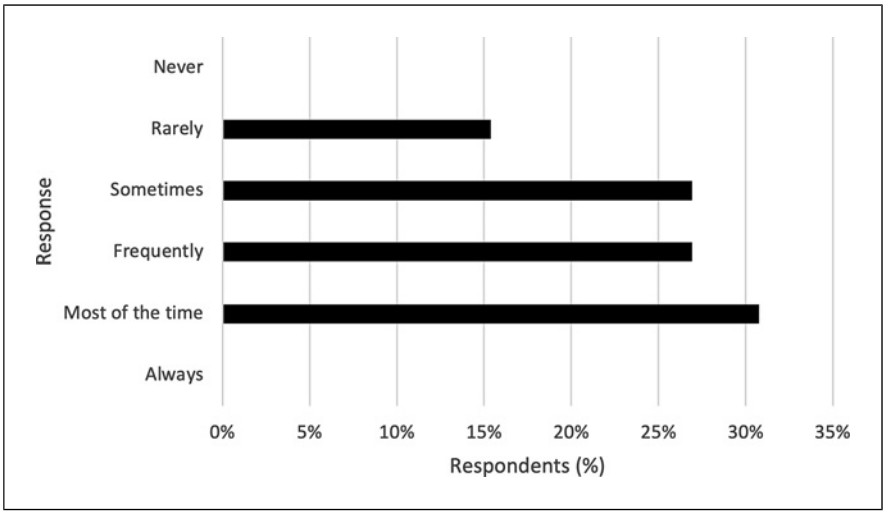

Fig. 2. Frequency of responses to the following survey question: "compared to biopsy, is a lung CT in the context of an appropriate clinical picture sufficient to diagnose probable GLILD?" (n = 26).

nodes (reducing the perceived need to biopsy the lung), and the availability of surgical expertise were reported by one respondent each.

Following that, we asked about the initial biopsy technique that clinicians would prefer when radiological and laboratory investigations failed to provide a confident diagnosis. The responses from clinicians varied, making interpretation challenging (Table 2). Overall, 35% (9 clinicians) would prefer transbronchial biopsy (TBB) as first choice for obtaining tissue. When asked about how often TBB confirmed the diagnosis, 55% (5/9) indicated that TBB was frequently or most of the time sufficient to detect multiple GLILD histological features.

We also asked clinicians about the percentage of patients who had inconclusive TBB results and so required further evaluation to confirm the diagnosis. Overall, 44% (4/9) indicated that this occurred in less than 30% of the patients, while 22% (2/9) stated this occurred in more than half. Overall, 55% (5/9) believed that re-biopsy was essential for accurate diagnosis and management in cases of inconclusive TBB. Finally, we asked about the best alternative biopsy techniques in case of re-biopsy. Overall, 44% (4/9) preferred video-assisted thoracoscopic surgery (VATS), whereas 33% (3/9) considered transbronchial lung cryobiopsy (TBLC) in this situation.

Table 3. Indications and preferred initial biopsy modalities (n = 26)

	Frequency, n	Percentage
Indications for lung biopsy in patients with suspected GLILD		
Diagnostic uncertainty	23	88
Suspicion of malignancy	23	88
Assessment of disease activity	4	15
Assessment of disease phenotype to guide therapy	5	19
Evaluation of treatment response	2	8
Initial consideration when the radiological and laboratory investigations are inadequate to provide a confident diagnosis		
Endoscopic biopsy approach		
TBB	9	35
EBUS	5	19
TBLC	4	15
Percutaneous biopsy approach		
VATS	5	19
CT-guided needle biopsy	3	12

GLILD, granulomatous lymphocytic interstitial lung disease; TBB, transbronchial biopsy; EBUS, endobronchial ultrasound-guided biopsy; TBLC, transbronchial Lung cryobiopsy; VATS, video-assisted thoracoscopic surgery.

Whilst acknowledging that the selection of biopsy technique and site will vary depending on the individual clinical presentation, VATS and endobronchial ultrasound-guided biopsy (EBUS) were the preferred first choice of biopsy for 19% (5 each) of respondents. All respondents said that VATS, most of the time or always, provides sufficient diagnostic evidence for GLILD, while 60% (3/5) said EBUS sometimes does. Additionally, 80% (4/5) reported that VATS usually reveals multiple histological features of GLILD, as opposed to 60% (3/5) for EBUS. All clinicians preferring VATS reported that fewer than 30% of patients who underwent VATS had inconclusive biopsy results and required further evaluation. In contrast, 80% (4/5) of clinicians preferring EBUS stated that between 30% and 50% of patients needed re-evaluation.

The responses regarding TBLC and CT-guided needle biopsy were low and diverse, which makes drawing conclusions challenging. VATS was the preferred option by 42% of the respondents in case of a repeat biopsy for suspected GLILD patients, followed by TBLC (27%). Repeated TBB and EBUS were infrequently chosen.

Additionally, we sought responses from respondents regarding the complications they encountered post-biopsy in patients with GLILD. Of the total respondents, 14 (54%) provided information on observed complications. The data revealed that the greatest number of clinicians had encountered complications with TBLC: pneumothorax (reported by 6 respondents), clinically significant bleeding (4 respondents), and haemoptysis (3 respondents). VATS followed with pneumothorax and pneumonia observed by 5 and 3 respondents, respectively. In contrast, TBB and CT-guided needle biopsy were indicated as having fewer complications, with pneumothorax reported by 3 and 4 respondents, respectively. These responses reflect the perceived frequency of various complications associated with different biopsy methods in the context of GLILD.

Histological Features Observed

We aimed to understand how frequently clinicians observed abnormal histological features. The frequencies reported for these features varied. The categories "always," "most of the time," and "frequently" were combined and categorized as "often" for reporting. Non-necrotizing granulomas were often observed by 77% of clinicians. Both lymphoid interstitial pneumonitis and organizing pneumonia were often seen by 64%, while 55% of the respondents often observed lymphoid hyperplasia. The presence of interstitial fibrosis and follicular bronchiolitis varied among clinicians: 41% often diagnosed interstitial fibrosis while 27% rarely did; follicular bronchiolitis was observed among 41% and rarely among 23%.

Acceptability of Extrapulmonary Biopsy

In conjunction with positive radiological findings, the presence of biopsy-confirmed extrapulmonary granulomatous disease was most of the time or frequently sufficient to confirm the diagnosis of GLILD in 69% of respondents. Overall, 52% of respondents answered it was rare to make a different diagnosis after performing a biopsy for suspected GLILD, and 26% said it had never happened. Additionally, 88% reported that the biopsy results were discussed at a multidisciplinary meeting.

Discussion

This survey has revealed insights into the practices and perceptions of clinicians on the diagnostic utility of lung biopsy in GLILD, including the preferred techniques and factors that affect the decision-making process in managing suspected GLILD. The key findings include the following: (1) a majority of respondents accepted HRCT as a sufficient alternative to biopsy for making a probable GLILD diagnosis in most patients; (2) there was consensus among most respondents that the presence of extrapulmonary granulomatous disease was adequate for making a diagnosis of GLILD where the chest imaging and clinical picture were consistent; (3) when a biopsy was recommended, there was notable variation in the preferred initial biopsy modality, with 35% favouring TBB.

Utility of CT in the Diagnosis of GLILD

CT scans are predominantly utilized as a diagnostic modality in patients with GLILD [15]. The majority of the respondents stated that HRCT presentations in the context of an appropriate clinical picture was frequently or most of the time sufficient to enable a diagnosis and to initiate treatment without the need for histopathological confirmation, while 27% felt that HRCT findings were sometimes sufficient. Nonetheless, the opinions of these expert clinicians did not align with the British Lung Foundation/United Kingdom Primary Immunodeficiency Network (BLF/UKPIN) consensus statement, which suggests that HRCT changes and lung function tests can indicate suspicion of GLILD but that biopsy is required to confirm the diagnosis [8]. A classification that distinguishes between probable and biopsy confirmed (definite) has been applied to other subtypes of ILD such as idiopathic pulmonary fibrosis [17, 18]. Adapting a similar classification for GLILD could be beneficial.

There was a consensus on the typical radiological features observed in suspected GLILD patients aligning with previous studies [19–21]. Scarpa et al.'s [11] recent study reported that features such as small nodules, ground-glass opacities, consolidations, reticulations, fibrotic ILD, and enlarged lymph nodes are reliable diagnostic indicators of GLILD.

Necessity, Indications, and Preferred Approach of Lung Biopsy

The value of lung biopsies in cases of suspected GLILD remains a subject of debate, and this was also reflected by our results. This question was identified as a top-ten research priority in an international research prioritization for GLILD [22]. More than 85% agreed that diagnostic uncertainty and suspicion of malignancy were the primary indications for obtaining a confirmatory tissue diagnosis.

There was also diversity among clinicians in their choice of preferred biopsy modalities, which, in part, may reflect what techniques are available. TBB was preferred by 35% of respondents as the first invasive approach. This indicates a preference for less invasive methods despite lower diagnostic conclusiveness with TBB compared to VATS [15]. The responses on diagnostic sufficiency showed greater reliability with VATS but raises questions about the more invasive nature and potential complications.

Despite the high accuracy of VATS in diagnosing lung conditions, TBLC may offer a less invasive alternative [23]. TBLC achieves a diagnostic yield of higher than 70%, according to the European Respiratory Society's guidelines on TLBC in the diagnosis of ILD [23]. Rodrigues et al. [24], in their recent meta-analysis, found that the diagnostic yield increased from 77% to 81% in experienced centres with multidisciplinary discussion. This highlighted the benefits of multidisciplinary discussion in enhancing diagnostic accuracy and patient outcomes. Moreover, the post-procedure mortality rate within 30 days following TBLC was lower, ranging from 0.3% to 0.6%, compared to 1.7%–2.3% for surgical lung biopsy, making it a safer option [23, 24].

The use of TBLC for diagnosing GLILD has been reported in several case studies with mixed outcomes. It yielded conclusive results in 2 case reports [25, 26], however produced inconclusive findings in another patient [27], with no complications reported. We cannot comment on the complication rate with individual tests in people with GLILD, but the greatest number of clinicians had encountered complications with TBLC. This limitation underlines the need for further research with larger cohorts to accurately assess the safety profile and diagnostic efficacy of TBLC in GLILD.

Moreover, our results emphasize the ongoing discussion regarding whether the benefits of lung biopsy, such as helping confirm diagnoses, outweighs risks, such as pneumothorax. It is important to note that there was no distinct preference in the preferred approach between the more experienced expert clinicians and those with less experience (data not shown), or between immunologists and pulmonologists. This may reflect expert clinicians being aware that there are little comparative data available and less expert clinicians not being so familiar with tests such as TBLC.

Our findings also confirm the previously reported diversity of histological patterns in GLILD, as evidenced by the different frequencies of non-necrotizing granulomatous, lymphoid interstitial pneumonitis, and organizing pneumonia features that have been reported. This indicates that GLILD is a complex and diverse ILD, requiring a detailed comprehension of its histopathology. Interestingly, a significant majority (69%) of the study respondents believed that having biopsy-confirmed extrapulmonary granulomatous disease was most of the time or frequently sufficient to support a diagnosis of GLILD. However, the presence of granulomas in other organs does not always correlate with their presence in the affected areas, which suggests that other organs may not reliably reflect the condition of the lungs, and the single lesion of concern might still represent a malignant manifestation even within GLILD [28, 29].

The variance in clinicians' opinions might be attributed to their assessment of the risk-benefit ratio for their patients. The risk of performing a lung biopsy increases with age, comorbidities, and lung disease severity [30]. It is known that managing patients with ILD is challenging, and it becomes more difficult if it involves a rare disease such as GLILD. Clinicians sometimes deal with diagnostic uncertainty. However, they still need to make the best decisions for the management of their patients. Discussing suspected cases with a multidisciplinary team (MDT), comprising pulmonologists, immunologists, radiologists, and pathologists, clearly enhances the accuracy of diagnosis [31]. This allows the decision to be based on MDT consensus rather than individual opinion. Additionally, future research focusing on the place of lung biopsy and the development of practice guidelines involving an MDT is crucial for improving diagnosis and management of GLILD.

We acknowledge several limitations in this study. First, the generalizability of our findings may be restricted due to the low number of respondents, which may not accurately represent a wider range of perspectives. However, few clinicians have much experience in GLILD. Second, according to our survey results, clinical decisions are heavily influenced by case specifics and according to answering specific items also influenced by recall bias. Finally, although our goal is to maintain objectivity, the complexities in interpreting and representing the viewpoints of clinicians might lead to some level of bias in interpretation.

Conclusion

When considering the diagnosis of GLILD, most clinicians would accept a clinico-radiological diagnosis of GLILD. However, lung biopsy is often performed in cases of diagnostic uncertainty or to rule out malignancy and can result in a positive diagnosis of definite GLILD. Notably, there was no clear consensus on the preferred biopsy modality, which could be attributed to the many factors, including individual patient risk-benefit assessments and local experience. In summary, the observed complexities and variabilities in diagnosing GLILD emphasizes the necessity for additional research to establish consistent criteria and protocols for diagnosing and managing GLILD, enhancing both the accuracy and safety of GLILD diagnosis and management.

Statement of Ethics

Ethical approval was not required for this study in accordance with local guidelines. Written informed consent was obtained from participants prior to their participation in the survey.

Conflict of Interest Statement

- Jesper Rømhild Davidsen reports grants and honoraria from Boehringer Ingelheim DK outside the submitted work.
- Annick A.J.M. van de Ven's institution has received honoraria by Takeda for presentations on this topic.
- Sarah Goddard has received honoraria by Takeda to co-lead a workshop relating to immunodeficiency.
- Klaus Warnatz reports honoraria for advisory board meetings and teaching and educational activities from TAKEDA, LFB biomedicaments, CSL Behring, Grifols, and Bristol-Myers Squibb outside the submitted work. In addition, KW has received a research grant by Bristol-Myers Squibb for the investigation of Abatacept for interstitial lung disease in CVID.
- John R. Hurst has received support to attend meetings and personal payment and payment to his employer from companies that make medicines to treat respiratory disease and immunoglobulin products.
- The rest of authors have nothing to disclose.

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Author Contributions

The study conception and design was contributed by H.M.B. and J.R.H. Material preparation and data collection were performed by H.M.B., J.R.H., J.R.D., S.G., and A.A.J.M.V. Initial analysis, interpretation, and evaluation of data was led by H.M.B. and J.R.H. The first draft of the manuscript was written by H.M.B. Previous versions of the manuscript were commented by J.R.H., J.R.D., A.A.J.M.V., S.G., S.O.B., and K.W. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author H.M.B. upon reasonable request.

References

1 Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International consensus document (ICON): common variable immunodeficiency disorders. J Allergy Clin Immunol Pract. 2016;4(1):38–59. https://doi.org/10.1016/j.jaip.2015.07.025
2 Salzer U, Warnatz K, Peter HH. Common variable immunodeficiency: an update. Arthritis Res Ther. 2012;14(5):223. https://doi.org/10.1186/ar4032
3 Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012;119(7):1650–7. https://doi.org/10.1182/blood-2011-09-377945
4 Ho HE, Cunningham-Rundles C. Non-infectious complications of common variable immunodeficiency: updated clinical spectrum, sequelae, and insights to pathogenesis. Front Immunol. 2020;11:149. https://doi.org/10.3389/fimmu.2020.00149
5 Cabanero-Navalon MD, Garcia-Bustos V, Nunez-Beltran M, Ciscar Fernandez P, Mateu L, Solanich X, et al. Current clinical spectrum of common variable immunodeficiency in Spain: the multicentric nationwide GTEM-SEMI-CVID registry. Front Immunol. 2022;13:1033666. https://doi.org/10.3389/fimmu.2022.1033666
6 Gathmann B, Mahlaoui N, Ceredih GL, Gérard L, Oksenhendler E, Warnatz K, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol. 2014;134(1):116–26. https://doi.org/10.1016/j.jaci.2013.12.1077
7 Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol. 2004;114(2):415–21. https://doi.org/10.1016/j.jaci.2004.05.057
8 Hurst JR, Verma N, Lowe D, Baxendale HE, Jolles S, Kelleher P, et al. British lung foundation/United Kingdom primary immunodeficiency Network consensus statement on the definition, diagnosis, and management of granulomatous-lymphocytic interstitial lung disease in common variable immunodeficiency disorders. J Allergy Clin Immunol Pract. 2017;5(4):938–45. https://doi.org/10.1016/j.jaip.2017.01.021
9 Hartono S, Motosue MS, Khan S, Rodriguez V, Iyer VN, Divekar R, et al. Predictors of granulomatous lymphocytic interstitial lung disease in common variable immunodeficiency. Ann Allergy Asthma Immunol. 2017;118(5):614–20. https://doi.org/10.1016/j.anai.2017.01.004
10 Mannina A, Chung JH, Swigris JJ, Solomon JJ, Huie TJ, Yunt ZX, et al. Clinical predictors of a diagnosis of common variable immunodeficiency-related granulomatous-lymphocytic interstitial lung disease. Ann Am Thorac Soc. 2016;13(7):1042–9. https://doi.org/10.1513/AnnalsATS.201511-728OC
11 Scarpa R, Cinetto F, Milito C, Gianese S, Soccodato V, Buso H, et al. Common and uncommon CT findings in CVID-related GL-ILD: correlations with clinical parameters, therapeutic decisions and potential implications in the differential diagnosis. J Clin Immunol. 2023;43(8):1903–15. https://doi.org/10.1007/s10875-023-01552-1
12 Cabanero-Navalon MD, Garcia-Bustos V, Forero-Naranjo LF, Baettig-Arriagada EJ, Nunez-Beltran M, Canada-Martinez AJ, et al. Integrating clinics, laboratory, and imaging for the diagnosis of common variable immunodeficiency-related granulomatous-lymphocytic interstitial lung disease. Front Immunol. 2022;13:813491. https://doi.org/10.3389/fimmu.2022.813491
13 Cinetto F, Scarpa R, Carrabba M, Firinu D, Lougaris V, Buso H, et al. Granulomatous lymphocytic interstitial lung disease (GLILD) in common variable immunodeficiency (CVID): a multicenter retrospective study of patients from Italian PID referral centers. Front Immunol. 2021;12:627423. https://doi.org/10.3389/fimmu.2021.627423
14 Verbsky JW, Routes JM. Sarcoidosis and common variable immunodeficiency: similarities and differences. Semin Respir Crit Care Med. 2014;35(3):330–5. https://doi.org/10.1055/s-0034-1376862
15 Bintalib HM, van de Ven A, Jacob J, Davidsen JR, Fevang B, Hanitsch LG, et al. Diagnostic testing for interstitial lung disease in common variable immunodeficiency: a systematic review. Front Immunol. 2023;14:1190235. https://doi.org/10.3389/fimmu.2023.1190235
16 van de Ven A, Alfaro TM, Robinson A, Baumann U, Bergeron A, Burns SO, et al. Managing granulomatous-lymphocytic interstitial lung disease in common variable immunodeficiency disorders: e-GLILDnet international clinicians survey. Front Immunol. 2020;11:606333. https://doi.org/10.3389/fimmu.2020.606333
17 Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198(5):e44–68. https://doi.org/10.1164/rccm.201807-1255ST
18 Ryerson CJ, Corte TJ, Lee JS, Richeldi L, Walsh SLF, Myers JL, et al. A standardized diagnostic ontology for fibrotic interstitial lung disease. An international working group perspective. Am J Respir Crit Care Med. 2017;196(10):1249–54. https://doi.org/10.1164/rccm.201702-0400PP
19 van de Ven AA, de Jong PA, Hoytema van Konijnenburg DP, Kessels OA, Boes M, Sanders EA, et al. Airway and interstitial lung disease are distinct entities in paediatric common variable immunodeficiency. Clin Exp Immunol. 2011;165(2):235–42. https://doi.org/10.1111/j.1365-2249.2011.04425.x
20 Maglione PJ, Overbey JR, Radigan L, Bagiella E, Cunningham-Rundles C. Pulmonary radiologic findings in common variable immunodeficiency: clinical and immunological correlations. Ann Allergy Asthma Immunol. 2014;113(4):452–9. https://doi.org/10.1016/j.anai.2014.04.024
21 Fraz MSA, Moe N, Revheim ME, Stavrinou ML, Durheim MT, Nordoy I, et al. Granulomatous-lymphocytic interstitial lung disease in common variable immunodeficiency-features of CT and ^{18}F-fdg positron emission Tomography/CT in clinically progressive disease. Front Immunol. 2020;11:617985. https://doi.org/10.3389/fimmu.2020.617985

22 Hurst JR, Abbas SH, Bintalib HM, Alfaro TM, Baumann U, Burns SO, et al. Granulomatous–lymphocytic interstitial lung disease: an international research prioritisation. ERJ Open Res. 2021;7(4):00467-2021–2021. https://doi.org/10.1183/23120541.00467-2021
23 Korevaar DA, Colella S, Fally M, Camuset J, Colby TV, Hagmeyer L, et al. European Respiratory Society guidelines on transbronchial lung cryobiopsy in the diagnosis of interstitial lung diseases. Eur Respir J. 2022;60(5):2200425. https://doi.org/10.1183/13993003.00425-2022
24 Rodrigues I, Estevao Gomes R, Coutinho LM, Rego MT, Machado F, Morais A, et al. Diagnostic yield and safety of transbronchial lung cryobiopsy and surgical lung biopsy in interstitial lung diseases: a systematic review and meta-analysis. Eur Respir Rev. 2022; 31(166):210280. https://doi.org/10.1183/16000617.0280-2021
25 Doan J, Rao N, Kurman JS, Routes JM, Benn BS. Granulomatous and lymphocytic interstitial lung disease diagnosed by transbronchial lung cryobiopsy. Cryobiology. 2020;97:231–4. https://doi.org/10.1016/j.cryobiol.2020.08.004
26 Sasaki J, Tominaga M, Sudou M, Tokisawa S, Nishii Y, Zaizen Y, et al. Granulomatous lymphocytic interstitial lung disease in multiple myeloma. Intern Med. 2022: 9758–22.
27 Ruiz-Alcaraz S, Gaya Garcia-Manso I, Marco-De La Calle FM, Garcia-Mullor MDM, Lopez-Brull H, Garcia-Sevila R. Granulomatous lymphocytic interstitial lung disease: description of a series of 9 cases. Med Clin. 2021;156(7):344–8. https://doi.org/10.1016/j.medcli.2020.11.033
28 Patel S, Anzilotti C, Lucas M, Moore N, Chapel H. Interstitial lung disease in patients with common variable immunodeficiency disorders: several different pathologies? Clin Exp Immunol. 2019; 198(2):212–23. https://doi.org/10.1111/cei.13343
29 Dhalla F, Lochlainn DJM, Chapel H, Patel SY. Histology of interstitial lung disease in common variable immune deficiency. Front Immunol. 2020;11:605187. https://doi.org/10.3389/fimmu.2020.605187
30 Cottin V. Lung biopsy in interstitial lung disease: balancing the risk of surgery and diagnostic uncertainty. Eur Respir J. 2016;48(5):1274–7. https://doi.org/10.1183/13993003.01633-2016
31 Flaherty KR, King TE Jr., Raghu G, Lynch JP 3rd, Colby TV, Travis WD, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med. 2004;170(8):904–10. https://doi.org/10.1164/rccm.200402-147OC