Approach to diagnosing and managing granulomatous-lymphocytic interstitial lung disease

Jessica Galant-Swafford,[a] Jason Catanzaro,[b] Rosane Duarte Achcar,[c] Carlyne Cool,[d] Tilman Koelsch,[e] Tami J. Bang,[e] David A. Lynch,[e] Rafeul Alam,[a] Rohit K. Katial,[a] and Evans R. Fernández Pérez[f,*]

[a]Department of Medicine, Division of Allergy and Immunology, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA
[b]Department of Pediatrics, Division of Allergy and Immunology, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA
[c]Department of Medicine, Division of Pathology, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA
[d]Department of Pathology, University of Colorado Health Sciences Center, 12605 East 16th Avenue, Denver, CO 80045, USA
[e]Department of Radiology, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA
[f]Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Interstitial Lung Disease Program, National Jewish Health, Denver, CO 80206, USA

eClinicalMedicine
2024;75: 102749
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102749

Summary

Granulomatous-lymphocytic interstitial lung disease (GLILD) is a lymphoproliferative and granulomatous pulmonary manifestation of primary immune deficiency diseases, notably common variable immunodeficiency (CVID), and is an important contributor of excess morbidity. As with all forms of ILD, the significance of utilizing a multidisciplinary team discussion to enhance diagnostic and treatment confidence of GLILD cannot be overstated. In this review, key clinical, radiological, and pathological features are integrated into a diagnostic algorithm to facilitate a consensus diagnosis. As the evidence for diagnosing and managing patients with GLILD is limited, the viewpoints discussed here are not meant to resolve current controversies. Instead, this review aims to provide a practical framework for diagnosing and evaluating suspected cases and emphasizes the importance of a multidisciplinary approach when caring for GLILD patients.

Keywords: Interstitial lung disease; Granulomatous-lymphocytic interstitial lung disease; Common variable immunodeficiency; Diagnosis; Treatment; Multidisciplinary discussion

Introduction

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders with different pathophysiologic causes and genetic etiologies which all lead to hypogammaglobulinemia and inadequate responses to vaccination.[1] As many as 85% of patients with CVID will develop infectious pulmonary complications,[2] specifically recurrent and/or severe lower respiratory bacterial infections. The infectious complications should be excluded before a noninfectious CVID-associated pulmonary diagnosis is rendered. Common non-infection CVID complications include autoimmune cytopenias, enteropathies such as nonceliac sprue, inflammatory bowel disease and lymphocytic colitis, ILD, lymphadenopathy and a predisposition to lymphoma. Noninfectious pulmonary manifestations can be divided into primary or secondary malignancies, airway-limited entities, interstitial lung disease (ILD), and benign lymphoproliferative disorders.

Patients with CVID can develop ILD in various pathologic patterns, with GLILD being the most commonly described in the literature. GLILD is a significant cause of morbidity and premature mortality among patients with CVID.[3,4] Although several large registries of patients with primary immunodeficiency (PID) have been established globally,[1] because of methodological limitations, it is not possible to describe the epidemiology of GLILD precisely. Nevertheless, rough estimates from several cohorts suggest GLILD occurs in 8–20% of patients with CVID.[5–7]

In 2017, the British Lung Foundation and United Kingdom Primary Immunodeficiency Network published a consensus statement that defined GLILD as "a distinct clinico-radio-pathologic interstitial lung disease occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma of the lung, and in whom other conditions have been considered and where possible excluded."[8]

Evaluating suspected GLILD cases requires a probabilistic diagnostic approach that considers the impact of the heterogeneous disease course and patient-centered decision-making. This review focuses on the current

*Corresponding author. National Jewish Health, Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Interstitial Lung Disease Program, Southside Building, Office G12, 1400 Jackson Street, Denver, CO 80206, USA.
E-mail address: Fernandezevans@njhealth.org (E.R. Fernández Pérez).

Research in context

Evidence before this study

Searches were conducted to identify previous GLILD diagnostic and treatment studies. Appraisal of the quality of the evidence from previous studies on the diagnosis and treatment of GLILD was very low. While a systematic review provided a consensus statement on the definition, diagnosis, and management of GLILD in adults, it lacked a clear, step-by-step approach to establishing diagnostic confidence before deciding on the need for testing such as surgical lung biopsy in individual patients. Additionally, an international survey of clinicians revealed a lack of uniformity in diagnostic and treatment approaches, highlighting the importance of our review in synthesizing the existing knowledge in this area.

Added value of this study

We provide a contemporary review of the diagnosis and management of GLILD. The main clinical, radiological, and histopathological features that help differentiate GLILD from other ILDs are summarized and integrated into a simplified diagnostic algorithm. We propose an imaging and histopathological confidence criterion for evaluating suspected GLILD cases within multidisciplinary discussions, aiming to facilitate the consensus diagnosis process. Also, our review highlights areas where the evidence for GLILD is absent or unclear.

Implications of all the available evidence

Our review highlights the importance of using Bayesian reasoning to gauge disease probability before and after diagnostic testing and in formulating and revising the differential diagnosis when facing complex disorders such as GLILD. This approach facilitates more informed decision-making regarding the necessity for invasive diagnostic tests and the selection of appropriate treatment. However, future evidence collection should prioritize studies evaluating diagnostic test performance characteristics in GLILD. Additionally, advancements in CVID-GLILD endotyping may improve and streamline the approach to diagnosis and guide targeted therapy. We also identify areas of unmet need and highlight questions for future research.

approach to diagnosis and management of GLILD and is not intended to provide an exhaustive approach to screening or managing inborn errors of immunity (IEI). The target audience primarily includes pulmonologists, immunologists, and other clinicians who diagnose and manage suspected or confirmed GLILD cases.

Laboratory

GLILD has been described in the setting of CVID, CVID-like disorders (IEI with CVID phenotype), and also non-CVID PIDs including combined immunodeficiency and thymic hypoplasia syndromes.[9,10]

Radiologic findings suggestive of GLILD should prompt immunologic laboratory investigations if not already completed, specifically for CVID. CVID is defined by hypogammaglobulinemia (low IgG with low IgA or IgM) and functional antibody deficiency as measured by poor responses to immunization.[11–13] CVID has several different genetic etiologies[13] and a sizable subset of patients with GLILD are found to have extra-thoracic autoimmune and lymphoproliferative manifestations,[5] more often than CVID without GLILD.[14] Although immunologic laboratory testing is not required to diagnose GLILD, patients with GLILD may have lower IgA, IgG, and IgM serum levels at CVID diagnosis, lower percentage of switched-memory B cells and marginal zone B cells, and increased circulating CD21^{lo} B cells compared to those with CVID but without GLILD.[14–16]

A number of gene mutations have been associated with GLILD including histone-lysine N-methyltransferase 2D (*KMT2D*),[17] recombination-activation gene 1 (*RAG1*),[18] cytotoxic T-lymphocyte associated protein 4 (*CTLA-4*), LPS-responsive beige-like anchor protein (*LRBA*),[19] nuclear factor kappa B subunit 1 (*NFKB1*),[20] tumor necrosis factor superfamily member 13b (*TNFRSF13B*),[17] signal transducer and activator of transcription 3 (*STAT3*)[21] and 1 (*STAT1*).[9] GLILD has also been identified in 22q11.2 deletion syndromes.[10] It is not clear that particular gene mutations are correlated with disease onset, disease severity and progression, and response to therapy. It is presumed that patients with *LRBA* or *CTLA-4* variants will benefit greater from abatacept, but this has not been demonstrated in a placebo-controlled trial.

Gene panel testing is often used as an initial approach, sequencing approximately 400 genes with variants known to be pathogenic in IEIs. Next generation sequencing technologies, including whole exome/genome sequencing may be employed if panel testing is unremarkable. At the very minimum, looking for variants in *LRBA* and *CTLA-4* is critical as targeted therapy, abatacept, is available. However, as a genetic etiology for GLILD has yet to be established, genetic testing in every case of identified or suspected GLILD contributes to the research effort for the future of personalized therapy for this disease.

Immunopathogenesis

Substantial knowledge gaps remain in understanding the immunopathogenesis of GLILD. Available studies are few, use heterogenous diagnostic criteria, and many focus on peripheral blood analysis using flow cytometry to enumerate T, B, and NK cell subsets, which may not accurately reflect the lung pathology.

Maglione et al. studied 29 patients with lung biopsy-proven GLILD.[22] Patients with progressive ILD had a statistically significant rise in serum IgM from their baseline level compared to those patients with stable disease as measured by pulmonary function testing (PFT). This IgM was presumably produced from apoptosis-resistant plasmablasts from extrafollicular sites in the lung in response to B cell-activating factor (BAFF). BAFF, a cytokine essential for the activation and survival of B cells, was driven by the production of IFN-γ, a known driver of inflammatory complications in CVID.[23] This IgM increase reflected pulmonary B cell hyperplasia and was associated with a significant decline in forced vital capacity and diffusing capacity for carbon monoxide (DLCO) over a twenty-month period. They extended the idea of the likely pathological nature of these B cells and the use of IgM increase over time as a biomarker of active disease by showing stabilization and/or improvement of these PFT parameters and reduction of serum IgM in those treated with rituximab.

Expansion of autoreactive $CD21^{lo}$ B cells, seen in a variety of autoimmune conditions, have been identified in the peripheral blood,[21] lymph nodes[24] and bronchoalveolar lavage (BAL) fluid[25] of patients with CVID and ILD. This B cell subset has been characterized by decreased expression of CXC chemokine receptor type (CXCR) 5, a chemokine receptor important for proper homing to secondary lymphoid tissues, and increased expression of inflammatory chemokine receptors CXCR3 and CXCR6.[26,27] These autoreactive B cells are the end result of naïve B cells that evade central and/or peripheral B cell tolerance checkpoints and subsequently secrete autoantibodies while also producing pro-inflammatory cytokines in response to self-antigens.[28] Recently, using mass cytometry, Lui et al. demonstrated that $CD21^{lo}$ B cells in 23 CVID patients with GLILD had modestly disturbed B-cell receptor signaling and altered downstream extracellular signal-regulated kinase activation, important for a variety of cellular processes including growth and migration.[29] Lui et al. hypothesized that abnormal signaling patterns in these B as well as in activated and senescent T cells may help to differentiate CVID with GLILD from uncomplicated CVID though larger studies are necessary to confirm this theory.[27]

Fraz et al. evaluated an additional 29 serum markers including those related to inflammation, lymphocyte activation, and pulmonary epithelial injury.[21] Compared to CVID patients with only infections or other autoimmune phenomena, patients with GLILD had significant elevation of serum inflammatory cytokines (tumor necrosis factor [TNF] and interferon [IFN]-γ) as well as markers reflecting T cell activation (soluble interlukin-2 receptor alpha chain [IL-2Ra/CD25]) and exhaustion (stromal interaction molecule 3). While IFN-γ was a strong predictor of GLILD and all four markers were stably elevated over time, they failed to identify a distinction between those with stable or progressive disease and they were unable to be correlated with imaging.

The presence of T cells in histologic sections,[30] increased populations of activated, memory and effector T cell populations,[21,27] increased type 1/3 cytokines (IFNγ, TNF, CXCL10, and interlukin-17A) and the efficacious use of combination immunosuppression for therapy[17] support an integral role of T cells in the pathogenesis of GLILD. Given the importance of properly coordinated T and B cell interactions for immune homeostasis and documented abnormalities in these cell types, it supports that immune dysregulation is at the heart of GLILD pathogenesis (Fig. 1).

Clinical manifestations

The age at presentation of GLILD commonly ranges between 20 and 50 years, with a higher prevalence among females. GLILD may be detected incidentally on imaging, and up to 15% of patients may be asymptomatic.[14] When symptoms are present, they typically manifest insidiously as exertional dyspnea and cough. The severity of dyspnea is often due to the extent of the restrictive lung disease. However, reduced exercise capacity as well as fatigue and malaise due to expiratory airflow limitation, increased physiologic dead space, hypoxemia, hypercapnia, or deconditioning may often contribute. Patients frequently have a persistent nonproductive cough. Yet, the production of sputum on most days and sometimes wheezing can be seen in patients with concomitant bronchiectasis in up to 80% of patients with GLILD.[31] These respiratory symptoms early on can be a diagnostic challenge due to overlap with other common chronic diseases such as chronic obstructive pulmonary disease. When bronchiectasis is clinically suspected (e.g., chronic productive cough with positive sputum cultures for potentially pathogenic microorganisms) in at-risk groups (e.g., PID), a high-resolution computed tomography (HRCT) is recommended to confirm the diagnosis.[32] In this scenario, the HRCT findings may also provide the first indication to a GLILD diagnosis.

The systemic symptoms of CVID and respiratory infections can complicate the clinical presentation of GLILD. Therefore, a comprehensive medical history with focus on the severity and course of respiratory symptoms and a thorough physical examination are necessary to establish a pre-test likelihood diagnosis (Table 1).

On chest auscultation, the presence of inspiratory crackles may indicate the presence of pulmonary fibrosis. Wheezing can also be heard, but may not correlate with the severity of airway narrowing. Digital clubbing and signs of secondary pulmonary hypertension are rarely found. However, among extrapulmonary exam findings for patients with CVID and ILD and a

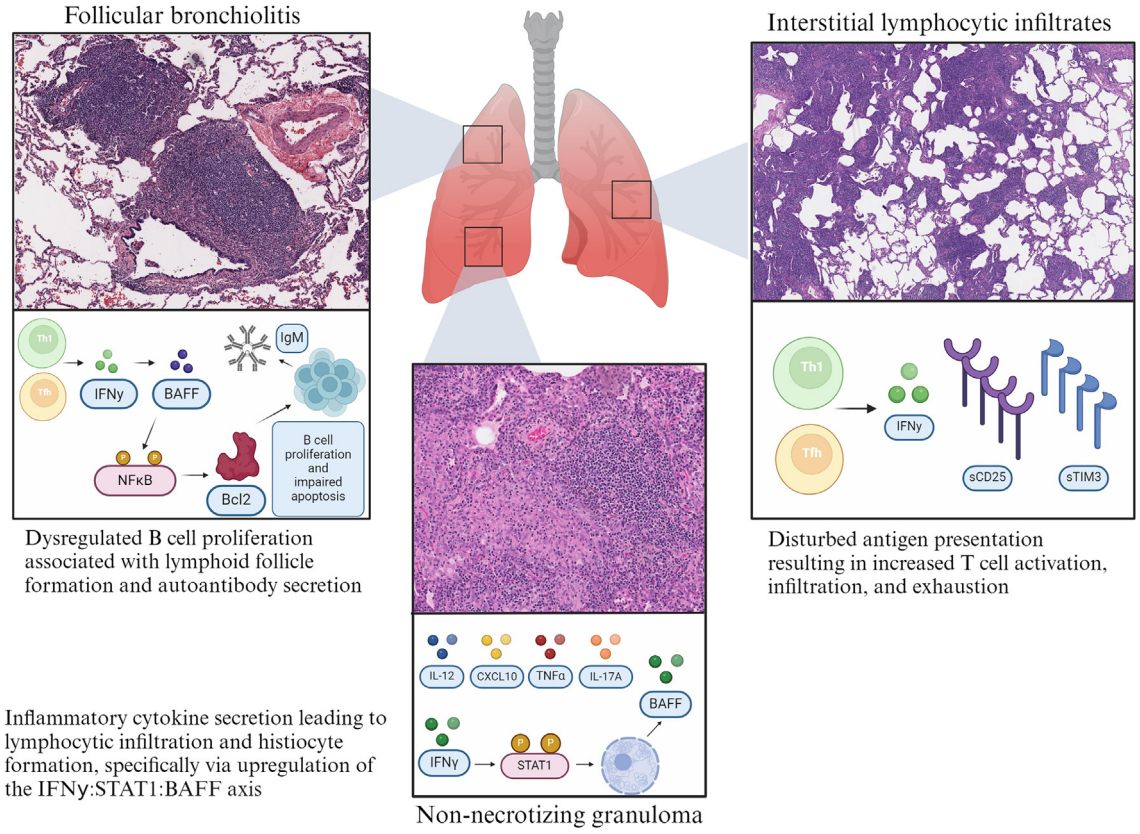

Fig. 1: Immunopathogenesis of GLILD. Figure made using BioRender.com.

chest HRCT pattern typical for GLILD, the presence of splenomegaly and lymphadenopathy, which are surrogates of systemic granulomatous and lymphocytic organ infiltration, point strongly toward a diagnosis of GLILD within the appropriate clinical context.[14,15]

Imaging

Typical manifestations

Chest HRCT is recommended for the initial imaging evaluation of CVID patients with suspected ILD. Patients with CVID may have several presentations on HRCT: 1) No evidence of lung involvement; 2) CVID-related airways disease, characterized by airway thickening, bronchiectasis, mucus plugs and tree-in-bud nodularity; 3) GLILD; and 4) other interstitial lung disease, including organizing pneumonia (OP), nonspecific interstitial pneumonia (NSIP) and lymphocytic interstitial pneumonia.[6,33] Typical GLILD CT findings include pulmonary nodularity, ground-glass opacities, consolidation, and interlobular septal thickening, typically with lower lung and peribronchovascular predominance[6,8,14,34,35] (Fig. 2a and b). The pulmonary nodules may be solid, ground-glass or mixed density,[14,15] and a ground-glass halo may be present around solid nodules.[35] Notably, GLILD almost always manifests with lymphadenopathy and splenomegaly, which may increase the confidence of radiological diagnosis.[8,14,15,33,35]

A subset of patients with GLILD may present with pulmonary fibrosis, with findings of reticulation, traction bronchiectasis, and pulmonary volume loss.[15,33,36] Similar to other forms of non-idiopathic pulmonary fibrosis, the presence of pulmonary fibrosis, especially if it is progressive, is associated with worse prognosis compared to non-fibrotic cases.

Atypical manifestations

Understanding atypical presentations of GLILD is essential for identifying patients with unusual imaging patterns and differentiating them from other lung diseases.

A small subset of GLILD may have an upper lung predominance or diffuse distribution of typical findings,[14,33,34,37] which may prompt consideration of other lung diseases. However, these atypical features do not exclude the diagnosis of GLILD. Features typically seen in CVID-associated airways disease are also less common in GLILD.[8] In GLILD, bronchiectasis is typically mild. Airway wall thickening, mosaic attenuation, mucus plugging, and tree-in-bud nodularity are also less commonly seen in the setting of GLILD.[14,15,33,35,37] This

	Favors GLILD or CVID-related ILD	Also observed in other ILDs	Favors alternative diagnosis
CVID or CVID-like disorder	– Prerequisite		– Established secondary cause, e.g., infection, immunosuppressive drugs, malignancy, malnutrition, non-primary immunodeficiency genetic syndromes
Demographics		– Female, any race – Younger age – Childhood	– Older age, e.g., hypersensitivity pneumonitis – Male older, e.g., unclassifiable – Female older e.g., idiopathic NSIP
Exposure history			– Temporal relation of symptoms/ILD to exposure, e.g., hypersensitivity pneumonitis, chronic beryllium disease
Family history	– Consanguinity – CVID, CVID-like disorders, or other primary immunodeficiencies	– Rarely	– First degree relative with pulmonary fibrosis, e.g., familial pulmonary fibrosis
Respiratory symptoms		– Cough, dyspnea at rest and/or with exertion	
Extrapulmonary manifestations	– Recurrent, severe, or atypical infections (e.g., sinopulmonary, gastrointestinal)	– Otitis, sinusitis, e.g., granulomatosis with polyangiitis – Sicca, e.g., Sjogren's related lymphocytic interstitial pneumonia – Enteropathy, e.g., inflammatory bowel disease related-ILD – Polyarthritis/synovitis, e.g., connective tissue diseases	
Physical exam	– Facial dysmorphism – Splenomegaly particularly alongside CVID-related liver disease and enteropathy (e.g., ascites), lymphadenopathy	– Fever, tachypnea, hypoxemia – Crackles on chest exam – Wheezing – May have normal exam – Hepatosplenomegaly, e.g., sarcoidosis	– Specific autoimmune findings, e.g., sclerodactyly and abnormal nailfold capillaries – Lofgren's syndrome, Heerfordt's syndrome, lupus pernio, erythema nodosum, e.g., sarcoidosis
Physiology		– Restrictive, obstructive or mixed pattern on pulmonary function testing[a] – Resting hypoxemia, or exertional desaturation on walk oxygen titration and 6-min walk test[b] – Ventilatory limitation[c]	
Laboratory	– Hypogammaglobulinemia, impaired vaccine responses[11–13]	– Transaminitis, e.g., sarcoidosis – Autoimmune cytopenias may occur in sarcoidosis and autoimmune-related ILD.	– Hypergammaglobulinemia – Specific autoimmune serology, e.g., anti-tRNA synthetase – Hypercalcemia or hypercalciuria, e.g., sarcoidosis – Elevated serum IgG4 levels, e.g., IgG4-related disease
Genetics	– Pathogenic variants in genes including *LRBA*, *CTLA-4*, *NFKB1*, *TNSFR13B*, *KMT2D*, *RAG1*, *STAT3* and *STAT1* and others yet to be determined		
Bronchoalveolar lavage		– Lymphocytosis – Mixed cell count pattern	
Clinical course		– May be stable and/or slowly progressive over years	– Progressive fibrotic course over weeks to months, e.g., fibrotic hypersensitivity pneumonitis, fibrotic NSIP, idiopathic pulmonary fibrosis

CVID, combined immunodeficiency disorder; GLILD, granulomatous lymphocytic interstitial lung disease; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; LBRA, LPS-responsive beige-like anchor protein; CTLA, cytotoxic T-lymphocyte associated protein; NFKB, nuclear factor kappa B subunit; TNSFR, tumor necrosis factor superfamily member; KMT2D, histone-lysine N-methyltransferase 2D; RAG, recombination activating gene; STAT, signal transducer and activator of transcription. [a]Pulmonary function test is a valuable tool for measuring the level of pulmonary impairment and for monitoring the response to treatment in GLILD. In CVID patients with spirometric restriction, a low diffusing capacity of the lungs for carbon monoxide increases the likelihood of an ILD. [b]The minimal clinically important difference in the 6-min walk test is estimated to be between 30 and 50 m. In addition to distance, ancillary information such as oxygen saturation profile, Borg dyspnea score, and pulse rate also provides helpful information. [c]Specialized centers can perform maximal cardiopulmonary exercise testing (CPET) which can help detect early signs of subtle pulmonary gas exchange abnormalities and predict the degree of impairment in functional capacity in individuals with ILD. Compared to the 6-six-minute walk test and pulmonary function tests, CPET is more sensitive to changes in patient health status.

Table 1: **Clinical characteristics supportive of a diagnosis of GLILD.**

contrasts with CVID-associated airways disease, where these are typical features.

Another atypical feature of GLILD is cavitary disease,[15,33,38] although cavities can be seen with atypical and fungal infections. Pulmonary cysts are also atypical, and are more common in LIP.[8,36] Lastly, lack of lymphadenopathy and splenomegaly would be atypical (Table 2). Lymphadenopathy in GLILD is not typically calcified,[15] and calcification may suggest other causes of lung disease, or a co-existing pulmonary process.

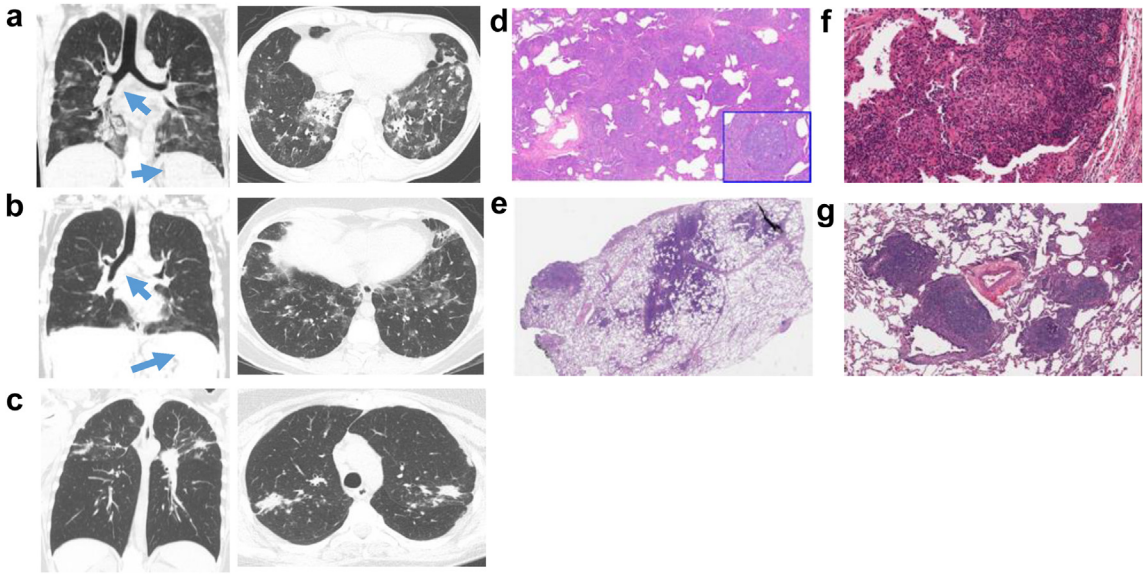

Fig. 2: (a) Typical HRCT findings of GLILD; coronal (left) and axial (right) images show lower lung predominant ground glass abnormality and consolidation, with scattered nodules. Splenomegaly and adenopathy are present (arrows). (b) Findings compatible with GLILD; coronal (left) and axial (right) images show patchy lower lung ground glass abnormality. Nodules are not present. Splenomegaly and adenopathy are present (arrows). (c) Findings suggesting an alternative diagnosis; coronal (left) and axial (right) images show upper lung predominant perilymphatic nodules with areas of conglomeration in a patient with pulmonary sarcoidosis. Spleen size is normal. (d) Interstitial inflammatory infiltrates composed predominantly of small mature lymphocytes and scattered lymphoid aggregates, some of which contain reactive germinal centers (insert), that widens the alveolar walls. The right lower corner inset is a high magnification view showing a reactive germinal center. (e) Lower magnification view of (d) showing lymphoid hyperplasia with nodular to irregular distribution. (f) Granulomas composed of epithelioid histiocytes. (g) Follicular bronchiolitis characterized by the presence of bronchiolocentric lymphoid follicles with germinal centers.

Imaging differential diagnosis

When the dominant pattern of GLILD is nodules with lymphadenopathy, the primary differential consideration is sarcoidosis (Fig. 2c). However, the nodules of sarcoidosis are usually upper lobe predominant, in contrast to the lower lung predominance of GLILD, and consolidation or ground glass abnormality are not usually prominent.[39] When the dominant pattern is multifocal ground glass or consolidation, the differential diagnosis would include organizing pneumonia, which is not usually associated with significant adenopathy or splenomegaly.[8] Infectious pneumonia should be considered and excluded clinically. Lymphoma, a primary issue of concern in CVID,[40] typically presents with progressively enlarging nodules or consolidation,[40,41] in contrast to the fluctuating course of GLILD nodules. However, nodule biopsy may be necessary in some cases to exclude lymphoma.[42]

Histopathology

In addition to screening for infection, bronchoscopy with BAL can be a valuable tool in evaluating ILD in patients with CVID. The BAL's effluent differential cell counts may hint at the presence of a lymphocytic alveolitis, a key component of GLILD. However, BAL lymphocytosis alone does not confirm GLILD. Other ILDs may also have lymphocyte-predominant BAL, such as NSIP, OP, hypersensitivity pneumonitis, sarcoidosis, drug-induced pneumonitis and lymphoproliferative disorders. Flow cytometry and gene rearrangement studies can identify a monoclonal population of lymphocytes, which could indicate a lymphoproliferative disorder.

Transbronchial biopsies (TBBx) may help in diagnosing peribronchovascular processes, such as lymphoma, sarcoidosis, infection, and airspace-filling diseases. However, small specimen size and sampling error are significant limitations, and in general, a highly confident histopathologic diagnosis of GILID cannot be made from TBBx specimens. Video-assisted thoracoscopic surgery remains the surgical procedure of choice when a diagnosis cannot be obtained by less invasive methods. However, a final diagnosis requires integrating histologic data with clinical and radiographic information. The diagnostic yield of less invasive transbronchial cryobiopsy in comparison to surgical lung biopsy remains uncertain in the context of multidisciplinary discussion (MDD) for patients with suspected GLILD.

The key histopathologic findings of GLILD are the presence of granulomas associated with all forms of

HRCT Pattern[a]	
Typical GLILD	Distribution – Axial: peribronchovascular predominance – Craniocaudal: lower lung zones Features – All of the following features: nodularity, ground-glass opacity, consolidation Other findings – Hilar, mediastinal lymphadenopathy, splenomegaly
Compatible with GLILD	Distribution – Heterogeneous or diffuse Features – Some, but not all, of the following features: nodularity, ground-glass opacity, consolidation Other findings – Hilar, mediastinal lymphadenopathy, splenomegaly
Favors alternative diagnosis	Distribution – Upper lung predominant, e.g., hypersensitivity pneumonitis, sarcoidosis – Patchy unilateral or bilateral but asymmetric e.g., aspiration, infection Features – Progressively enlarging focal nodule or mass progressively enlarging over 3–6 months despite treatment (raises concern for lymphoma) Other findings – Absence of adenopathy, splenomegaly
Histopathological Pattern[b]	
Typical GLILD	Major features – Presence of two major features in at least one of the sampled lobe(s) of the lung (surgical lung biopsy): 1. Pulmonary lymphoid hyperplasia with reactive germinal centers in the form of: – Follicular bronchiolitis, And/or – Nodular lymphoid hyperplasia, And/or – Any interstitial lymphocytic infiltrates 2. Granulomas (well, moderately, or poorly-formed) Secondary features 1. Organizing pneumonia 2. Interstitial scarring – Lack of features of an alternative diagnosis
CVID-related ILD without granulomas	Major features Presence of two major features in at least one of the sampled lobe(s) of the lung (surgical lung biopsy): – Follicular bronchiolitis And/or – Nodular lymphoid hyperplasia, And/or – Any interstitial lymphocytic infiltrates Secondary features 1. Organizing pneumonia 2. Interstitial scarring – Lack of granulomas and features of an alternative diagnosis
Favors alternative diagnosis	A biopsy favoring other processes such as: – Infection: well-formed granulomas often with necrosis, positive infection work-up (e.g., positive special stains [GMS and AFB] and tissue cultures) – Lymphoproliferative disorders: atypical lymphocytic proliferation with the diagnosis of lymphoma stablished by immunohistochemical stains, flow cytometric immunophenotyping, and monoclonality confirmed by positive gene rearrangement – Hypersensitivity pneumonitis: bronchiolocentric distribution/accentuation with poorly formed granulomas and prominent peribronchiolar metaplasia – Sarcoidosis: coalescent well-formed granulomas associated with hyaline fibrosis with lymphatic distribution and no significant interstitial inflammation – Berylliosis: histology similar to sarcoidosis. Exposure history; positive lymphocyte proliferation test to beryllium – Cellular nonspecific interstitial pneumonia: idiopathic or secondary to other causes/associations (e.g., drug toxicity, connective tissue disease), absence of granulomas – IgG4 disease: marked plasma cell infiltrate with increased proportion IgG4+ cells; absence of granulomas

CVID, combined immunodeficiency disorder; GLILD, granulomatous lymphocytic interstitial lung disease; ILD, interstitial lung disease. The suggested terminology and proposed criteria for these patterns are intended for use within the scope of multidisciplinary discussion when evaluating suspected GLILD cases. These patterns are not discrete as they seek to categorize a complex spectrum of HRCT and histologic findings that may share common features. [a]While features of fibrosis including reticulation, and airway disease including bronchiectasis and/or bronchial wall thickening are often present, these are not distinguishing features in patient with CVID. Some cases of GLILD may be indistinguishable on CT from sarcoidosis, and cryptogenic or other causes of organizing pneumonia and are ultimately diagnosed based on clinical and/or histological features. In contrast to GLILD, lymphocytic interstitial pneumonia, whether idiopathic or due to other causes (e.g., Sjogren's syndrome, rheumatoid arthritis), frequently demonstrates diffuse thin-walled cysts, predominantly in the lower lung and with peribronchovascular distribution on CT. [b]CVID cases may exhibit other ILD histopathological patterns, including organizing pneumonia. (6) The GLILD CT findings of consolidation and ground glass often indicate organizing pneumonia, but the histopathological pattern may not always match. Although organizing pneumonia is a common feature in histopathology, its presence is unnecessary for a confident histopathological diagnosis of GLILD.

***Table 2*: Chest HRCT and histopathological GLILD pattern.**

pulmonary lymphoid hyperplasia including follicular bronchiolitis, nodular lymphoid hyperplasia, and interstitial lymphocytic infiltrates, which are usually associated with reactive germinal centers (Table 2, Fig. 2d–g). The granulomas are typically non-necrotizing, well-, moderate-, or poorly-formed, and composed of epithelioid histiocytes with occasional multinucleated giant cells. A component of OP, pulmonary interstitial fibrosis, and cases of CVID-related ILD not associated with granulomas have also been described (Table 2).[30,43]

Surgical lung biopsies should be stained at least for CD3 and CD20, and evaluated for bacteria (e.g., acid-fast stain), fungi (e.g., GMS stain), and clonality to exclude lymphoma. Lymphoid interstitial pneumonia (LIP) due to other causes/associations, should be clinically excluded. Granulomas are usually absent in cellular NSIP, but this diagnosis should also be clinically excluded. Sarcoidosis and hypersensitivity pneumonitis are also differential considerations for granulomatous disease. However, sarcoidosis in contrast to GLILD, is not associated with significant interstitial inflammation, and is typically associated with hypergammaglobulinemia, and specific (lymphatic upper zone predominant) distribution of nodules within the lung. Hypersensitivity pneumonitis usually has a primarily bronchiolocentric distribution or a diffuse distribution with bronchiolocentric accentuation. It is not commonly associated with lymphoid hyperplasia with reactive lymphoid follicles containing germinal center or follicular bronchiolitis, as seen in GLILD.

Multidisciplinary team diagnosis

In light of the intricate clinical presentation, multidisciplinary evaluation is recommended to integrate the clinical context, the immunodeficiency history, the information contributed by the HRCT and the histology data to arrive at a diagnosis of GLILD (Fig. 3). The ILD MDD is a formal team meeting of pulmonologists, chest radiologists, and pathologists experienced in ILD, along with an immunologist, when assessing a patient with a PID. The MDD aims to enhance the accuracy and confidence of ILD diagnosis through consensus and provide recommendations on additional testing and management plans for each patient.[8,36]

When there is diagnostic and management uncertainty, referral to an ILD center should be considered at an early stage. These centers can provide expert diagnosis and management based on a multidisciplinary team consensus. Additionally, they can offer specialized care for extra-pulmonary complications, disease education, access to clinical research studies, and support groups.

Patients without a confident diagnosis but in whom GLILD is suspected have a provisional or working diagnosis. For instance, in a never-smoker patient with confirmed CVID, with suggestive extra-pulmonary manifestations and a chest HRCT pattern typical for GLILD and BAL lymphocytosis for whom there is a high clinical suspicion for GLILD and when alternative diagnoses have been reliably excluded during the initial diagnostic evaluation (e.g., sarcoidosis, cryptogenic organizing pneumonia, identifiable connective tissue disease or infections such as pulmonary tuberculosis and atypical mycobacterial infections), then a provisional high-confidence diagnosis can be established. Although most cases can be provisionally diagnosed with high confidence, a subgroup of cases remains indeterminate (i.e., provisional low-confidence) or more suggestive of an alternative ILD such as CVID-OP. Once the evaluation for alternative diagnoses has been completed and all available data, such as clinical, laboratory, and radiologic findings along with bronchoscopic results fail to provide a confident diagnosis for patients with suspected GLILD, a surgical lung biopsy may be necessary for additional diagnostic evaluation. However, it is critical to note that although the term "GLILD" suggests that a confirmed diagnosis of GLILD requires the presence of histopathological findings (see Table 2), this does not mandate recommending video-assisted thoracoscopic surgery for all patients, particularly for those with a provisional high confidence diagnosis, especially if they are asymptomatic and with preserved physiology. Furthermore, considering the disease severity, behavior, and patient-related factors (e.g., comorbidities, views, and preferences), refining the working diagnosis by surgical lung biopsy sampling is unnecessary if a definite GLILD diagnosis is unlikely to alter management.

Pharmacological treatment

Immunoglobulin replacement therapy (IGRT) should be optimized before the initiation of immunosuppressive therapy for GLILD as it is essential in patients with CVID and has reduced the frequency of respiratory infections since it became available.[8,44] The relationship of IGRT to progression of GLILD is not clear, specifically whether earlier age of initiating IGRT and higher dosing is associated with less disease progression. Doses of IGRT are 0.4 g/kg/month to 0.6 g/kg/month are typically recommended for individuals with CVID without lung disease.[45] While there is not high-quality data to support this clinical practice, higher doses (0.6 g/kg/month to 1.2 g/kg/month) are sometimes used in patients with chronic lung disease owing to an association with reduced respiratory infections with IgG troughs up to 1000 mg/dL[46] and improved lung function.[44,47]

Not all patients with GLILD require immunosuppressive treatment. Asymptomatic patients with normal and stable PFT do not require treatment. Immunosuppressive treatment is generally reserved for those with persistent respiratory symptoms and/or evidence of radiographic or physiologic progressive lung disease.

Corticosteroids are considered first line therapy for remission induction (Supplementary Table S1). The

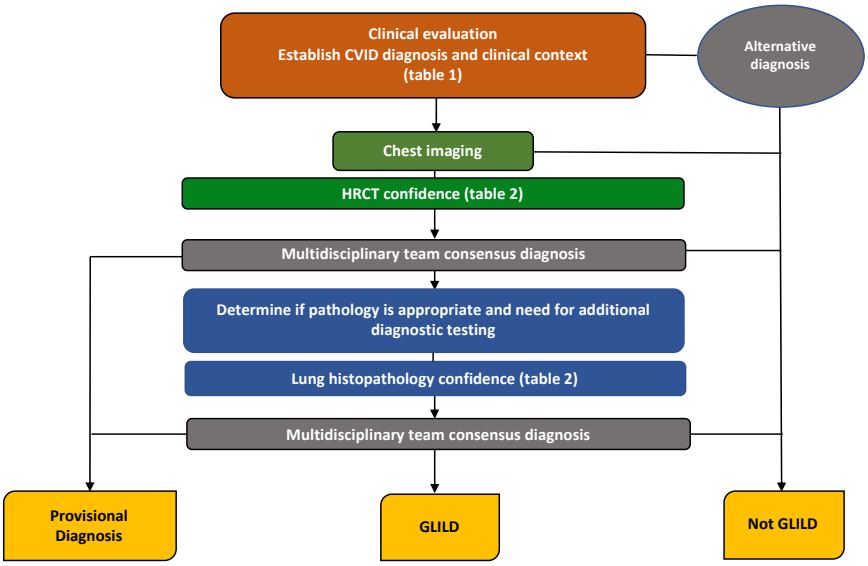

Fig. 3: Diagnostic approach. The multidisciplinary team discussion and consensus diagnosis is the reference standard for the clinical diagnosis of GLILD, allowing the diagnosis to be made with higher confidence than clinicians alone. Multidisciplinary decisions are also important when managing CVID patients with ILD diagnostic uncertainty who cannot undergo surgical lung biopsy to establish a diagnosis. Multiple domains must be incorporated into the diagnostic pathway, including clinical, radiological, and histopathological information. After thoroughly examining all the available data, a decision to conduct a lung biopsy should be made if it can help establish a confident diagnosis and guide the patient's management plan. Before proceeding with invasive testing, after considering patient preferences and the procedure's risks and benefits, it is essential to note that background treatment for CVID-related comorbidities, such as corticosteroids to treat overlapping autoimmune complications, can affect histology results.

quality of evidence informing the use of glucocorticoids is based on observational uncontrolled data.[8,48–52] Oral corticosteroids in the form of prednisone typically is initiated with a tapering schedule to minimize toxicity. Case studies have shown variable degrees of improvement in clinical symptoms, chest radiographic findings, and PFTs. In a multicenter study,[53] corticosteroid monotherapy (≥0.3 mg/kg prednisone equivalent) led to induction of prolonged remission for at least 2 years in 72% of patients with primary response for whom follow-up data was available.

Corticosteroid-sparing drugs such as azathioprine (AZA) and mycophenolate mofetil (MMF) are widely used to treat GLILD patients who are steroid-resistant or -intolerant in an effort to reduce steroid dose and its associated adverse effects while preserving lung function and may be considered on a case-by-case basis (Supplementary Table S1).[8,54]

Rituximab as monotherapy is another corticosteroid-sparing agent utilized in patients with progressive disease despite treatment with prednisone (Supplementary Table S1), AZA, or MMF.[55–58] There are other anti-CD20 drugs available, but they have not yet been studied in GLILD patients. While randomized trials are yet to be completed, uncontrolled studies have reported an association between using rituximab and improved symptoms and lung function in patients with GLILD. The presence of concomitant extra-pulmonary disorders, such as autoimmune cytopenias, may favor the introduction of rituximab. The simultaneous administration of rituximab and AZA[17,59–61] or MMF[17,54,62,63] aims to target both B- and T-lymphocytes in order to effectively deplete the lymphoproliferative and autoimmune pathophysiology present in the lung. This approach has been proposed as a means to achieve better therapeutic outcomes and disease remission.

CTLA-4 haploinsufficiency and LRBA deficiency result in CVID-like disorders characterized by immunodeficiency, autoimmunity, and lymphoproliferation. Abatacept, an IgG1-CTLA-4 fusion protein, prevents excessive T-cell proliferation and has been effective in controlling autoimmunity in individuals with CTLA-4 and LRBA mutations.[64,65] Abatacept has been shown to improve clinical symptoms, PFTs, and CT findings in patients with LRBA deficiency and CTLA-4 haploinsufficiency, including those who have failed immunosuppressive therapy.[19,66–68] The efficacy of abatacept in GLILD without identified causative gene mutations or in patients without CTLA-4 or LRBA-related disease is currently under investigation in a multicenter study (NCT04925375). A promising report of patients with GLILD with unrestricted genetics in an open-label nonrandomized trial of abatacept 125 mg/week for 12 months found that five of eight patients treated per

protocol had stable or improved DLCO, improved nodules and ground-glass opacities on CT, ability to wean systemic corticosteroids, and improved quality of life and fatigue.[69]

Several other immunosuppressants may have a role in treating patients with GLILD, but little clinical information is available to support their use.

Non-pharmacologic interventions

The nonpharmacologic management of GLILD centers on close patient follow-up by a multidisciplinary team that includes a pulmonologist and immunologist and other subspecialties as indicated by the clinical scenario. Supportive measures include (1) supplemental oxygen when needed during the day and/or at night to treat hypoxemia; (2) screening and management of comorbid conditions, such as CVID-related live disease and enteropathy, gastroesophageal reflux, and bronchiectasis (e.g., airway clearance) as they can contribute to symptoms and morbidity; (3) smoking cessation; (4) maintenance of nutrition; and (5) pulmonary rehabilitation.

Hematopoietic stem cell transplantation (HSCT) is a potential definitive therapy for PID and, consequently, GLILD. HSCT carries a considerable risk of severe infections and graft vs. host disease (GVHD). Reports suggest a high risk-to-benefit ratio, with a survival for patients with CVID and GLILD varying between 48% and 70%, compared to other PIDs where the survival nears 90%.[70,71] Though symptoms and radiographic findings may improve, longer-term follow-up with imaging and PFT are needed to determine the precise benefit of HSCT on GLILD.[9,72,73] Tesch et al. followed 76 patients with CVID-like disease due to LRBA deficiency. Out of the 24 individuals who received HSCT, 8 had GLILD.[74] Five of these 8 achieved complete remission from their GLILD, while two experienced partial remission. Two of the 24 patients undergoing HSCT developed GLILD after the HSCT. However, Wehr et al. reported on two patients with CVID and GLILD who underwent HSCT. One died at day 104 after the procedure due to GVHD and severe infection.[75] Seidel et al. reported on seven patients with CVID-like disease due to LRBA deficiency and GLILD who underwent HSCT; four patients with mild-to-moderate disease went into remission and three patients died, two with severe GLILD (part of the indication for transplant) and one with mild-moderate disease.[76]

Disease monitoring

Patients with GLILD may remain clinically stable or progress at a variable rate, which is not necessarily linear in an individual patient. Patients should be regularly monitored to evaluate progression and adjust management and supportive care as needed. Progression of GLILD to a usual interstitial pneumonia-like pattern or a progressive fibrotic phenotype on chest CT is uncommon. It is important to note that the existing evidence on the prognosis, risk factors, and mechanisms driving GLILD progression, as well as the effectiveness and options for pharmacological therapy, is limited and of insufficient quality. This presents a notable opportunity for further research.

Disease progression is usually monitored over periods of 3–6 months. Disease monitoring should include respiratory and extra-pulmonary symptoms evaluation, PFTs, 6-min walk distance and oxygen saturation at rest and with exertion, and repeat imaging where clinically indicated. Also, after initiating immunosuppressive therapy, management of potential side effects is highly advisable. Therefore, if corticosteroids are used, screening, prevention, treatment of side effects and *Pneumocystis* prophylaxis should be considered.

When patients experience sudden respiratory deterioration, prompt evaluation of the potential causes, such as acute exacerbation of the underlying GLILD, micro-aspiration, respiratory infection, or pulmonary embolism is necessary.

A challenging problem in GLILD is the waxing and waning of lung opacities on CT which can also demonstrate hyper-metabolism on an 18F-fluorodeoxyglucose positron emission tomography scan which can be mistaken for malignancy. The differential diagnosis includes OP, eosinophilic lung disorders, infectious and noninfectious granulomatous disorders, alveolar hemorrhage, pulmonary infarct, and lymphoproliferative lesions. The frequently migratory nature of the nodules on serial CT often effectively excludes granuloma, infection, and lymphoma, and suggests OP. CT evaluation of the specific morphologic characteristics, growth rate, and surrounding lung parenchyma of solitary or multifocal pulmonary nodules can help differentiate benign from malignant nodules. It is unclear how to monitor these nodules properly, but it is essential to strike a balance between being diligent and not missing

Search strategy and selection criteria

This Review is a critical synthesis and expert viewpoints of the issues related to the diagnosis and management of GLILD. References for this Review were identified through searches of PubMed with the search terms "GLILD", "granulomatous lymphocytic interstitial lung disease", "Common variable immune deficiency AND interstitial lung disease", "CVID AND ILD", primary immune deficiency AND interstitial lung disease" from inception until March 2024. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. Case reports and conference abstracts were excluded. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

any potential malignant transformation to lymphoma while also avoiding exposing the patient to excessive radiation from repeated low-dose CT scans while weighing the diagnostic yield and potential risks associated with multiple and different lung biopsy procedures.

Conclusions

The diagnostic process of a patient suspected of having GLILD is iterative and benefits from a consensus-based MDD that incorporates all available data. Given the complexity of diagnosing GLILD, as well as the risk of overdiagnosis and misdiagnosis, coupled with management challenges, early referral to an ILD center should be considered. We suggest a probabilistic approach to clinical diagnosis to identify a subgroup of patients with either a high or low probability of GLILD. This can help determine whether additional workup is necessary within the context of MDD and aid in making patient-centric management decisions while considering each patient's disease severity, behavior, and comorbidities. Clinicians managing patients with GLILD should individualize treatment decisions due to insufficient evidence, which does not provide enough confidence in the efficacy and effectiveness of pharmacological treatment on disease progression according to the clinical context.

Outstanding questions

There is a need for better quality evidence to guide the diagnosis and management of GLILD, define the clinical course of the disease, and monitor pulmonary nodules. Unmet needs that require further research include the following:

- Developing preclinical models for studies of GLILD pathogenesis and treatment.
- Facilitating funding and promoting the development and conduct of clinical trials in GLILD to determine the efficacy and safety of immunomodulatory therapy.
- Building large, multisite, rigorously-phenotyped GLILD patient cohorts with long-term clinical and biological data.
- Additionally, there is a need for integrated studies in GLILD using omics data to enhance risk stratification and personalized therapeutic strategies.

Contributors

ERFP conceptualized and organized the article theme. ERFP, and JGS wrote the first draft. JGS, JC, RDDA, CC, TK, TJB, DAL, RA, RKK, and ERFP contributed to the writing, review and editing of the first and subsequent drafts. ERFP, JGS, RDDA, CC, TK, TJB, and DAL produced all the tables and figures. All authors read and approved the final manuscript.

Data sharing statement

The authors agree that the data supporting our findings are present in this manuscript and are available for accessed upon request.

Declaration of interests

JGS reports a Pfizer global medical grant.
ERFP reports research funding grants from the state of Colorado advanced industry accelerator program, the National Heart Lung and Blood Institute and Boehringer Ingelheim.
RKK reports consulting fees from AstraZeneca and GSK.
Other authors have no conflicts of interest to declare.

Acknowledgements

Funding: None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102749.

References

1 Abolhassani H, Azizi G, Sharifi L, et al. Global systematic review of primary immunodeficiency registries. *Expert Rev Clin Immunol*. 2020;16(7):717–732. https://doi.org/10.1080/1744666X.2020.1801422.
2 Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. *J Allergy Clin Immunol*. 2002;109(6):1001–1004. https://doi.org/10.1067/mai.2002.124999.
3 Odnoletkova I, Kindle G, Quinti I, et al. The burden of common variable immunodeficiency disorders: a retrospective analysis of the European Society for Immunodeficiency (ESID) registry data. *Orphanet J Rare Dis*. 2018;13(1):201. https://doi.org/10.1186/s13023-018-0941-0.
4 Fernandez Perez ER, Hunter M, Katial RK. United States trends in mortality rates for primary immunodeficiency diseases. *J Allergy Clin Immunol Pract*. 2019;7(3):1045–1048. https://doi.org/10.1016/j.jaip.2018.09.030.
5 Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. *Blood*. 2012;119(7):1650–1657. https://doi.org/10.1182/blood-2011-09-377945.
6 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):415–421. https://doi.org/10.1016/j.jaci.2004.05.057.
7 Cabanero-Navalon MD, Garcia-Bustos V, Nunez-Beltran M, 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.
8 Hurst JR, Verma N, Lowe D, 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):938–945. https://doi.org/10.1016/j.jaip.2017.01.021.
9 Hartono SP, Vargas-Hernandez A, Ponsford MJ, et al. Novel STAT1 gain-of-function mutation presenting as combined immunodeficiency. *J Clin Immunol*. 2018;38(7):753–756. https://doi.org/10.1007/s10875-018-0554-3.
10 Sood AK, Funkhouser W, Handly B, Weston B, Wu EY. Granulomatous-lymphocytic interstitial lung disease in 22q11.2 deletion syndrome: a case report and literature review. *Curr Allergy Asthma Rep*. 2018;18(3):14. https://doi.org/10.1007/s11882-018-0769-7.
11 Ameratunga R, Woon ST, Gillis D, Koopmans W, Steele R. New diagnostic criteria for common variable immune deficiency (CVID), which may assist with decisions to treat with intravenous or subcutaneous immunoglobulin. *Clin Exp Immunol*. 2013;174(2):203–211. https://doi.org/10.1111/cei.12178.
12 Seidel MG, Kindle G, Gathmann B, et al. The European society for immunodeficiencies (ESID) registry working definitions for the clinical diagnosis of inborn errors of immunity. *J Allergy Clin Immunol Pract*. 2019;7(6):1763–1770. https://doi.org/10.1016/j.jaip.2019.02.004.
13 Bonilla FA, Barlan I, Chapel H, 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.

14 Mannina A, Chung JH, Swigris JJ, et al. Clinical predictors of a diagnosis of common variable immunodeficiency-related granulomatous-lymphocytic interstitial lung disease. *Ann Am Thorac Soc*. 2016;13(7):1042–1049. https://doi.org/10.1513/AnnalsATS.201511-728OC.

15 Cinetto F, Scarpa R, Carrabba M, 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.

16 Sanchez-Ramon S, Radigan L, Yu JE, Bard S, Cunningham-Rundles C. Memory B cells in common variable immunodeficiency: clinical associations and sex differences. *Clin Immunol*. 2008;128(3):314–321. https://doi.org/10.1016/j.clim.2008.02.013.

17 Verbsky JW, Hintermeyer MK, Simpson PM, et al. Rituximab and antimetabolite treatment of granulomatous and lymphocytic interstitial lung disease in common variable immunodeficiency. *J Allergy Clin Immunol*. 2021;147(2):704–712.e17. https://doi.org/10.1016/j.jaci.2020.07.021.

18 Farmer JR, Foldvari Z, Ujhazi B, et al. Outcomes and treatment strategies for autoimmunity and hyperinflammation in patients with RAG deficiency. *J Allergy Clin Immunol Pract*. 2019;7(6):1970–1985.e4. https://doi.org/10.1016/j.jaip.2019.02.038.

19 Lo B, Zhang K, Lu W, et al. Autoimmune disease. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. *Science*. 2015;349(6246):436–440. https://doi.org/10.1126/science.aaa1663.

20 Tuijnenburg P, Lango Allen H, Burns SO, et al. Loss-of-function nuclear factor kappaB subunit 1 (NFKB1) variants are the most common monogenic cause of common variable immunodeficiency in Europeans. *J Allergy Clin Immunol*. 2018;142(4):1285–1296. https://doi.org/10.1016/j.jaci.2018.01.039.

21 Fraz MSA, Michelsen AE, Moe N, et al. Raised serum markers of T cell activation and exhaustion in granulomatous-lymphocytic interstitial lung disease in common variable immunodeficiency. *J Clin Immunol*. 2022;42(7):1553–1563. https://doi.org/10.1007/s10875-022-01318-1.

22 Maglione PJ, Gyimesi G, Cols M, et al. BAFF-driven B cell hyperplasia underlies lung disease in common variable immunodeficiency. *JCI Insight*. 2019;4(5):e122728. https://doi.org/10.1172/jci.insight.122728.

23 Park J, Munagala I, Xu H, et al. Interferon signature in the blood in inflammatory common variable immune deficiency. *PLoS One*. 2013;8(9):e74893. https://doi.org/10.1371/journal.pone.0074893.

24 Unger S, Seidl M, Schmitt-Graeff A, et al. Ill-defined germinal centers and severely reduced plasma cells are histological hallmarks of lymphadenopathy in patients with common variable immunodeficiency. *J Clin Immunol*. 2014;34(6):615–626. https://doi.org/10.1007/s10875-014-0052-1.

25 Friedmann D, Unger S, Keller B, et al. Bronchoalveolar lavage fluid reflects a T(H)1-CD21(low) B-cell interaction in CVID-related interstitial lung disease. *Front Immunol*. 2020;11:616832. https://doi.org/10.3389/fimmu.2020.616832.

26 Rakhmanov M, Keller B, Gutenberger S, et al. Circulating CD21low B cells in common variable immunodeficiency resemble tissue homing, innate-like B cells. *Proc Natl Acad Sci USA*. 2009;106(32):13451–13456. https://doi.org/10.1073/pnas.0901984106.

27 Lui VG, Ghosh T, Rymaszewski A, et al. Dysregulated lymphocyte antigen receptor signaling in common variable immunodeficiency with granulomatous lymphocytic interstitial lung disease. *J Clin Immunol*. 2023;43(6):1311–1325. https://doi.org/10.1007/s10875-023-01485-9.

28 Meffre E, O'Connor KC. Impaired B-cell tolerance checkpoints promote the development of autoimmune diseases and pathogenic autoantibodies. *Immunol Rev*. 2019;292(1):90–101. https://doi.org/10.1111/imr.12821.

29 Lavoie H, Gagnon J, Therrien M. ERK signalling: a master regulator of cell behaviour, life and fate. *Nat Rev Mol Cell Biol*. 2020;21(10):607–632. https://doi.org/10.1038/s41580-020-0255-7.

30 Rao N, Mackinnon AC, Routes JM. Granulomatous and lymphocytic interstitial lung disease: a spectrum of pulmonary histopathologic lesions in common variable immunodeficiency–histologic and immunohistochemical analyses of 16 cases. *Hum Pathol*. 2015;46(9):1306–1314. https://doi.org/10.1016/j.humpath.2015.05.011.

31 Ramzi N, Jamee M, Bakhtiyari M, et al. Bronchiectasis in common variable immunodeficiency: a systematic review and meta-analysis. *Pediatr Pulmonol*. 2020;55(2):292–299. https://doi.org/10.1002/ppul.24599.

32 Hill AT, Sullivan AL, Chalmers JD, et al. British thoracic society guideline for bronchiectasis in adults. *Thorax*. 2019;74(Suppl 1):1–69. https://doi.org/10.1136/thoraxjnl-2018-212463.

33 Scarpa R, Cinetto F, Milito C, 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):1903–1915. https://doi.org/10.1007/s10875-023-01552-1.

34 Fraz MSA, Moe N, Revheim ME, 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.

35 Bang TJ, Richards JC, Olson AL, Groshong SD, Gelfand EW, Lynch DA. Pulmonary manifestations of common variable immunodeficiency. *J Thorac Imaging*. 2018;33(6):377–383. https://doi.org/10.1097/RTI.0000000000000350.

36 Fernandez Perez ER. Granulomatous lymphocytic interstitial lung disease. *Immunol Allergy Clin North Am*. 2012;32(4):621–632. https://doi.org/10.1016/j.iac.2012.08.003.

37 Torigian DA, LaRosa DF, Levinson AI, Litzky LA, Miller WT Jr. Granulomatous-lymphocytic interstitial lung disease associated with common variable immunodeficiency: CT findings. *J Thorac Imaging*. 2008;23(3):162–169. https://doi.org/10.1097/RTI.0b013e318166d32f.

38 Ward GK, Stewart SS, Price GB, Mackillop WJ. Cellular heterogeneity in normal human urothelium: an analysis of optical properties and lectin binding. *J Histochem Cytochem*. 1986;34(7):841–846. https://doi.org/10.1177/34.7.3754881.

39 Nunes H, Uzunhan Y, Gille T, Lamberto C, Valeyre D, Brillet PY. Imaging of sarcoidosis of the airways and lung parenchyma and correlation with lung function. *Eur Respir J*. 2012;40(3):750–765. https://doi.org/10.1183/09031936.00025212.

40 Yakaboski E, Fuleihan RL, Sullivan KE, Cunningham-Rundles C, Feuille E. Lymphoproliferative disease in CVID: a report of types and frequencies from a US patient registry. *J Clin Immunol*. 2020;40(3):524–530. https://doi.org/10.1007/s10875-020-00769-8.

41 Reichenberger F, Wyser C, Gonon M, Cathomas G, Tamm M. Pulmonary mucosa-associated lymphoid tissue lymphoma in a patient with common variable immunodeficiency syndrome. *Respiration*. 2001;68(1):109–112. https://doi.org/10.1159/000050475.

42 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.

43 Larsen BT, Smith ML, Tazelaar HD, Yi ES, Ryu JH, Churg A. GLILD revisited: pulmonary pathology of common variable and selective IgA immunodeficiency. *Am J Surg Pathol*. 2020;44(8):1073–1081. https://doi.org/10.1097/PAS.0000000000001479.

44 Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H. Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. *J Allergy Clin Immunol*. 2010;125(6):1354–1360.e4. https://doi.org/10.1016/j.jaci.2010.02.040.

45 Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the primary immunodeficiency committee of the American academy of allergy, asthma and immunology. *J Allergy Clin Immunol*. 2006;117(4 Suppl):S525–S553. https://doi.org/10.1016/j.jaci.2006.01.015.

46 Orange JS, Grossman WJ, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: a meta-analysis of clinical studies. *Clin Immunol*. 2010;137(1):21–30. https://doi.org/10.1016/j.clim.2010.06.012.

47 Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. *Lancet*. 1987;1(8541):1075–1077. https://doi.org/10.1016/s0140-6736(87)90494-6.

48 Boujaoude Z, Arya R, Rafferty W, Dammert P. Organising pneumonia in common variable immunodeficiency. *BMJ Case Rep*. 2013;2013:bcr2013008905. https://doi.org/10.1136/bcr-2013-008905.

49 Wislez M, Sibony M, Naccache JM, et al. Organizing pneumonia related to common variable immunodeficiency. case report and

literature review. *Respiration*. 2000;67(4):467–470. https://doi.org/10.1159/000029552.
50 Kanathur N, Byrd RP Jr, Fields CL, Roy TM. Noncaseating granulomatous disease in common variable immunodeficiency. *South Med J*. 2000;93(6):631–633. https://www.ncbi.nlm.nih.gov/pubmed/10881789.
51 Kaufman J, Komorowski R. Bronchiolitis obliterans organizing pneumonia in common variable immunodeficiency syndrome. *Chest*. 1991;100(2):552–553. https://doi.org/10.1378/chest.100.2.552.
52 Kohler PF, Cook RD, Brown WR, Manguso RL. Common variable hypogammaglobulinemia with T-cell nodular lymphoid interstitial pneumonitis and B-cell nodular lymphoid hyperplasia: different lymphocyte populations with a similar response to prednisone therapy. *J Allergy Clin Immunol*. 1982;70(4):299–305. https://doi.org/10.1016/0091-6749(82)90066-5.
53 Smits B, Goldacker S, Seneviratne S, et al. The efficacy and safety of systemic corticosteroids as first line treatment for granulomatous lymphocytic interstitial lung disease. *J Allergy Clin Immunol*. 2023;152(2):528–537. https://doi.org/10.1016/j.jaci.2022.12.813.
54 Tashtoush B, Memarpour R, Ramirez J, Bejarano P, Mehta J. Granulomatous-lymphocytic interstitial lung disease as the first manifestation of common variable immunodeficiency. *Clin Respir J*. 2018;12(1):337–343. https://doi.org/10.1111/crj.12511.
55 Tessarin G, Baronio M, Gazzurelli L, et al. Rituximab monotherapy is effective as first-line treatment for granulomatous lymphocytic interstitial lung disease (GLILD) in CVID patients. *J Clin Immunol*. 2023;43(8):2091–2103. https://doi.org/10.1007/s10875-023-01587-4.
56 Kosinski SM, Nachajon RV, Milman E. Rituximab as a single agent for successful treatment of granulomatous and lymphocytic interstitial lung disease in a pediatric patient with common variable immunodeficiency. *J Allergy Clin Immunol Pract*. 2022;10(3):876–878.e1. https://doi.org/10.1016/j.jaip.2021.10.040.
57 Ng J, Wright K, Alvarez M, Hunninghake GM, Wesemann DR. Rituximab monotherapy for common variable immune deficiency-associated granulomatous-lymphocytic interstitial lung disease. *Chest*. 2019;155(5):e117–e121. https://doi.org/10.1016/j.chest.2019.01.034.
58 Cereser L, De Carli R, Girometti R, et al. Efficacy of rituximab as a single-agent therapy for the treatment of granulomatous and lymphocytic interstitial lung disease in patients with common variable immunodeficiency. *J Allergy Clin Immunol Pract*. 2019;7(3):1055–1057.e2. https://doi.org/10.1016/j.jaip.2018.10.041.
59 Routes JM, Verbsky JW. Immunodeficiency presenting as an undiagnosed disease. *Pediatr Clin North Am*. 2017;64(1):27–37. https://doi.org/10.1016/j.pcl.2016.08.007.
60 Pathria M, Urbine D, Zumberg MS, Guarderas J. Management of granulomatous lymphocytic interstitial lung disease in a patient with common variable immune deficiency. *BMJ Case Rep*. 2016;2016:bcr2016215624. https://doi.org/10.1136/bcr-2016-215624.
61 Chase NM, Verbsky JW, Hintermeyer MK, et al. Use of combination chemotherapy for treatment of granulomatous and lymphocytic interstitial lung disease (GLILD) in patients with common variable immunodeficiency (CVID). *J Clin Immunol*. 2013;33(1):30–39. https://doi.org/10.1007/s10875-012-9755-3.
62 Bucciol G, Petrone A, Putti MC. Efficacy of mycophenolate on lung disease and autoimmunity in children with immunodeficiency. *Pediatr Pulmonol*. 2017;52(10):E73–E76. https://doi.org/10.1002/ppul.23757.
63 Jolles S, Carne E, Brouns M, et al. FDG PET-CT imaging of therapeutic response in granulomatous lymphocytic interstitial lung disease (GLILD) in common variable immunodeficiency (CVID). *Clin Exp Immunol*. 2017;187(1):138–145. https://doi.org/10.1111/cei.12856.
64 Kiykim A, Ogulur I, Dursun E, et al. Abatacept as a long-term targeted therapy for LRBA deficiency. *J Allergy Clin Immunol Pract*. 2019;7(8):2790–2800.e15. https://doi.org/10.1016/j.jaip.2019.06.011.
65 Dhunputh C, Ducassou S, Fernandes H, et al. Abatacept is useful in autoimmune cytopenia with immunopathologic manifestations caused by CTLA-4 defects. *Blood*. 2022;139(2):300–304. https://doi.org/10.1182/blood.2021013496.
66 Kostel Bal S, Haskologlu S, Serwas NK, et al. Multiple presentations of LRBA deficiency: a single-center experience. *J Clin Immunol*. 2017;37(8):790–800. https://doi.org/10.1007/s10875-017-0446-y.
67 Schwab C, Gabrysch A, Olbrich P, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. *J Allergy Clin Immunol*. 2018;142(6):1932–1946. https://doi.org/10.1016/j.jaci.2018.02.055.
68 Rodina Y, Deripapa E, Shvets O, et al. Rituximab and abatacept are effective in differential treatment of interstitial lymphocytic lung disease in children with primary immunodeficiencies. *Front Immunol*. 2021;12:704261. https://doi.org/10.3389/fimmu.2021.704261.
69 von Spee-Mayer C, Echternach C, Agarwal P, et al. Abatacept use is associated with steroid dose reduction and improvement in fatigue and CD4-dysregulation in CVID patients with interstitial lung disease. *J Allergy Clin Immunol Pract*. 2021;9(2):760–770.e10. https://doi.org/10.1016/j.jaip.2020.10.028.
70 Lamers OAC, Smits BM, Leavis HL, et al. Treatment strategies for GLILD in common variable immunodeficiency: a systematic review. *Front Immunol*. 2021;12:606099. https://doi.org/10.3389/fimmu.2021.606099.
71 Laberko A, Gennery AR. Clinical considerations in the hematopoietic stem cell transplant management of primary immunodeficiencies. *Expert Rev Clin Immunol*. 2018;14(4):297–306. https://doi.org/10.1080/1744666X.2018.1459189.
72 Slatter MA, Engelhardt KR, Burroughs LM, et al. Hematopoietic stem cell transplantation for CTLA4 deficiency. *J Allergy Clin Immunol*. 2016;138(2):615–619.e1. https://doi.org/10.1016/j.jaci.2016.01.045.
73 Rizzi M, Neumann C, Fielding AK, et al. Outcome of allogeneic stem cell transplantation in adults with common variable immunodeficiency. *J Allergy Clin Immunol*. 2011;128(6):1371–1374.e2. https://doi.org/10.1016/j.jaci.2011.07.055.
74 Tesch VK, Abolhassani H, Shadur B, et al. Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the immune deficiency and dysregulation activity (IDDA) score. *J Allergy Clin Immunol*. 2020;145(5):1452–1463. https://doi.org/10.1016/j.jaci.2019.12.896.
75 Wehr C, Gennery AR, Lindemans C, et al. Multicenter experience in hematopoietic stem cell transplantation for serious complications of common variable immunodeficiency. *J Allergy Clin Immunol*. 2015;135(4):988–997.e6. https://doi.org/10.1016/j.jaci.2014.11.029.
76 Seidel MG, Bohm K, Dogu F, et al. Treatment of severe forms of LPS-responsive beige-like anchor protein deficiency with allogeneic hematopoietic stem cell transplantation. *J Allergy Clin Immunol*. 2018;141(2):770–775.e1. https://doi.org/10.1016/j.jaci.2017.04.023.