INTERSTITIAL LUNG DISEASE IN THE CONTEXT OF SYSTEMIC DISEASE: PATHOPHYSIOLOGY, TREATMENT AND OUTCOMES

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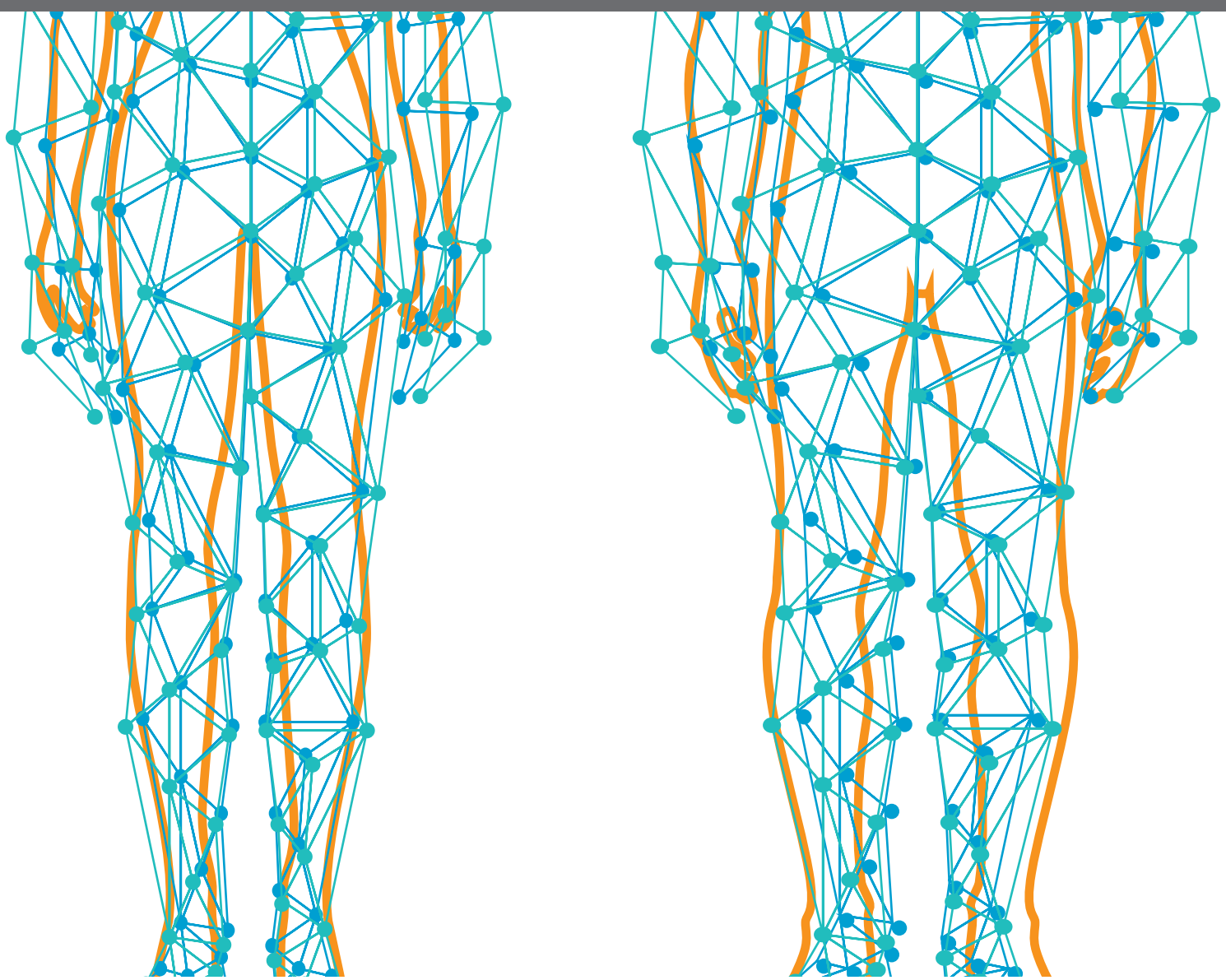

frontiers Research Topics

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INTERSTITIAL LUNG DISEASE IN THE CONTEXT OF SYSTEMIC DISEASE: PATHOPHYSIOLOGY, TREATMENT AND OUTCOMES

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Table of Contents

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EDITORIAL
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Editorial: Interstitial Lung Disease in the Context of Systemic Disease: Pathophysiology, Treatment and Outcomes

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Keywords: interstitial lung disease, autoimmune diseases, rheumatoid arthritis, systemic sclerosis (scleroderma), myositis

Editorial on the Research Topic

Interstitial Lung Disease in the Context of Systemic Disease: Pathophysiology, Treatment and Outcomes

INTRODUCTION

Interstitial lung disease (ILD) is an umbrella term for many different disease entities causing inflammation and fibrosis of the lung parenchyma. These can be broadly divided into five categories based on etiology (1): (1) ILD related to a distinct primary disease (e.g., sarcoidosis), (2) ILD related to environmental factors (e. g., hypersensitivity pneumonitis), (3) ILD induced by drugs or irradiation, (4) idiopathic interstitial pneumonias (e.g., idiopathic pulmonary fibrosis), and (5) ILD related to connective tissue diseases (CTD) (1). While all these entities require thorough and multidisciplinary assessment to ascertain a diagnosis, establish the need for diagnostic procedures, and recommend a patient-specific treatment plan, ILDs associated with systemic diseases are particularly challenging. In many cases, optimal treatment for involvement of other organ systems needs to be balanced with the choice of ILD-directed therapies.

For the highly heterogeneous group of patients who cannot be given a definite diagnosis of an autoimmune rheumatic disease but who demonstrate certain clinical, radiographic, and/or serological features suggestive of a CTD, the term interstitial pneumonia with autoimmune features (IPAF) has been coined (2), but its clinical value remains to be defined. Due to its complexity, management of ILDs associated with systemic disease requires multidisciplinary care, including pulmonologists, rheumatologists, and radiologists, often with critical input from other specialties, such as pathologists, dermatologists, or neurologists. In this Research Topic, we hope to present novel research and state-of-the-art reviews as relevant to the care of patients with ILD and systemic diseases.

FREQUENTLY ENCOUNTERED ILDS ASSOCIATED WITH SYSTEMIC DISEASES

The most frequently encountered ILDs in the setting of systemic diseases include parenchymal lung involvement with myositis (Myo-ILD), systemic sclerosis (SSc-ILD), and rheumatoid arthritis

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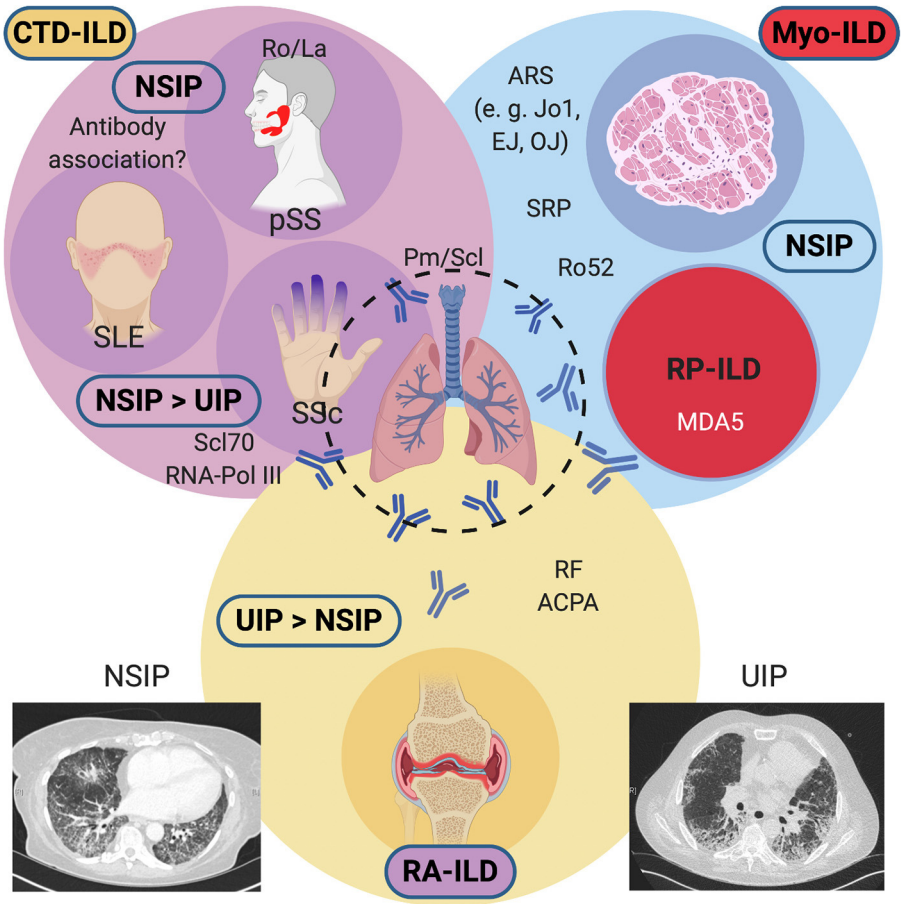

FIGURE 1 | Overview of systemic diseases causing interstitial lung diseases (ILDs) and their associated antibodies. Conditions associated with a predominant NSIP pattern on HRCTs include Myositis-associated ILD (antisynthetase syndrome, anti-RO52 positive overlap myositis, or RP-ILD), Systemic Sclerosis, primary Sjögren's syndrome, and rarely, Systemic Lupus Erythematosus. In SSc, a UIP pattern may also be commonly found. RA-ILD frequently shows a UIP pattern and confers a guarded prognosis. An NSIP pattern may also be encountered on HRCTs. ACPA, anti-citrullinated peptide antibodies; ARS, aminoacyl-tRNA synthetase antibodies; CTD, connective tissue disease; HRCT, high-resolution computed tomography; MDA5; melanocyte-differentiation antigen 5; Myo, myositis; NSIP, non-specific interstitial pneumonia; Pm/Scl, polymyositis-scleroderma; pSS; primary Sjögren's syndrome; RA, rheumatoid arthritis; RF, rheumatoid factor; RNA Pol III, RNA polymerase III; RP, rapidly progressive; Scl70, topoisomerase I; SLE, systemic lupus erythematosus, Sm, Smith; SRP, signal recognition particle; SSc, systemic sclerosis; U1-snRNP, U1 small nuclear ribonucleoprotein; UIP, usual interstitial pneumonia. Created with BioRender.com.

(RA-ILD). Less frequently reported are ILDs secondary to primary Sjögren's syndrome (pSS) or systemic lupus erythematosus (SLE). **Figure 1** gives an overview of systemic diseases and frequently encountered autoantibodies that have been associated with the development of ILD in these diseases. For practical reasons, we find it helpful to distinguish these based on their predominant pattern on high-resolution computed tomography (HRCT), most frequently usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP). UIP changes tend to be less reversible and tend to confer a worse prognosis, whereas changes in NSIP (particularly in patients with non-fibrotic NSIP) may be more responsive to treatment. In different diseases, these lung disease patterns occur with varying frequency. In RA, UIP is often more frequently encountered than NSIP, although both may occur. Anti-cyclic citrullinated peptide (CCP) antibodies and rheumatoid factor (RF), present in 70–80% of patients with RA, are associated with RA-ILD. The same applies to SSc, where NSIP is common, but UIP also occurs. In pSS, pulmonary manifestations are relatively rare but have been reported to occur in about 16% of patients, and a consensus guideline on the diagnostic and therapeutic approach has recently been published (3). In pSS, the occurrence of a lymphocytic interstitial pneumonitis (LIP) is rare, but this radiologic pattern should prompt a search for other manifestations of pSS if ILD is the first presenting manifestation (4). ILD is common in myositis, especially in patients with antibodies directed against different aminoacyl-tRNA synthetases, a group collectively called the antisynthetase syndrome (ASyS), but also those with anti-Ro52 antibodies (5, 6). Anti-MDA5 antibodies are associated with clinically amyopathic dermatomyositis (CADM) which can present as a rapidly progressive ILD with high mortality despite aggressive

immunosuppressive therapy (7). The following summarizes the papers publishes within this Research Topic.

A MULTIDISCIPLINARY APPROACH IS USEFUL FOR THE DIAGNOSIS AND MANAGEMENT

In the first paper, Furini et al. systematically investigated the evidence for multidisciplinary conferences (MDC) to assess ILDs. They found that most MDC evaluated patients with history taking and clinical assessment, HRCT, pulmonary function tests (PFTs), lung biopsy (in most MDCs), and serological testing. Less consensus existed on the use of additional tests, such as nailfold video capillaroscopy (NVC) and 6-min walking distance. Only seven studies evaluated the rheumatologist's role in MDCs, but the authors suggest that MDCs include serological testing and rheumatology expertise to help classify CTD-ILD and IPAF with more certainty. The second paper by Tirelli et al. reported results from a retrospective cohort study from Pavia, Italy. In their cohort, the authors found that 15% of all patients were diagnosed with CTD-ILD, 33% were classified as IPAF; the remainder had no underlying systemic disease. They found the application of a standardized screening questionnaire, laboratory testing, and the inclusion of NVC useful for detecting these entities. Karampitsakos et al. summarized the current use and ongoing clinical trials of biological therapies in sarcoidosis and idiopathic pulmonary fibrosis, which emphasizes a potentially useful role of rheumatologists in the management of ILDs given their extensive expertise in the use of these drugs and management of complications.

CONNECTIVE TISSUE DISEASE-ASSOCIATED ILD

One paper specifically reported findings in SLE, pSS, and SSc patients. Patients with SLE and pSS tend to have less ILD. Therefore, it is even more critical to identify individuals at risk and potential overlap syndromes among patients with these relatively common autoimmune rheumatic diseases. Amarnani et al. reviewed the pulmonary manifestations of SLE, including ILDs. Interestingly, the development of an ILD in SLE has not been associated with anti-dsDNA antibodies but rather anti-Ro or anti-U1-snRNP antibodies, which are also associated with mixed connective tissue disease (MCTD). It is, therefore, unclear whether these patients instead represent an overlap population. Sogkas et al. reported their single-center experience from a large cohort of pSS patients with ILD. At their center, 13% of patients were eventually diagnosed with ILD. Of note, almost two thirds (61%) were diagnosed with ILD at presentation and, surprisingly, UIP was the most commonly encountered pattern on HRCT (43%). Lastly, Mirsaeidi et al. reviewed the current treatment options for SSc-ILD, an emerging and rapidly changing topic with the recently approved anti-fibrotic nintedanib, and several ongoing clinical trials.

MYOSITIS-ASSOCIATED ILD

The majority of papers addressed Myo-ILD. The review by Hervier and Uzunhan represents a timely and current overview of the diagnostic and therapeutic approach to Myo-ILD. This is expanded by original data from Asian cohorts on rapidly-progressive ILD (Li et al.), acute exacerbations of ILD in Myo-ILD (Liang et al.), and the understudied role of plasma exchange in the treatment of refractory Myo-ILD (Ning et al.). Finally, Korsten et al. report their findings on the efficacy of immunosuppression in ASyS-ILD. They specifically report equal usefulness of rituximab (RTX) compared to other conventional immunosuppressive drugs, especially in patients with more frequent clinical myositis and progressive or relapsing pulmonary involvement.

RHEUMATOID ARTHRITIS-ASSOCIATED ILD

The recent observation of *MUC5B* promoter variants as a risk factor for RA-ILD, similar to patients with idiopathic pulmonary fibrosis, has generated significant interest in understanding the potential role of antifibrotic strategies in the treatment of this subset of ILD (8). Emerging data from cohort studies examining different immunosuppressive drugs [e.g., abatacept or RTX; (9, 10)] is of similar interest. Fragoulis et al. provided an overview of the difficult topic of RA-ILD, which is an area of active investigation. The authors summarize data on methotrexate-induced pneumonitis and pulmonary fibrosis associated with RA.

AUTHOR CONTRIBUTIONS

PK wrote the first draft and created the figure. BT, MK, and MM edited and reviewed the draft. All authors approved the final version of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Biologic Treatments in Interstitial Lung Diseases

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Interstitial lung diseases (ILD) represent a group of heterogeneous parenchymal lung disorders with complex pathophysiology, characterized by different clinical and radiological patterns, ultimately leading to pulmonary fibrosis. A considerable proportion of these disease entities present with no effective treatment, as current therapeutic regimens only slow down disease progression, thus leaving patients, at best case, with considerable functional disability. Biologic therapies have emerged and are being investigated in patients with different forms of ILD. Unfortunately, their safety profile has raised many concerns, as evidence shows that they might cause or exacerbate ILD status in a subgroup of patients. This review article aims to summarize the current state of knowledge on their role in patients with ILD and highlight future perspectives.

Keywords: interstitial lung diseases, biologic treatments, pulmonary fibrosis, treatment, safety

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INTRODUCTION

Interstitial lung diseases (ILD) are a group of heterogeneous parenchymal lung disorders, characterized by different clinical and radiological patterns (1, 2). Despite an exponential increase in our knowledge and the advent of novel therapies, treatment remains ineffective for a considerable proportion of patients (3–13). Biologic treatments comprise a wide group of compounds with natural origin produced by biotechnology and other cutting-edge technologies (14); yet, this term mainly refers to the subgroup of complex molecules representing targeted therapy, such as monoclonal antibodies and receptor fusion proteins (15). The last years have seen the emergence of biologic treatments for the treatment of several immune and oncologic disorders (16–18). The most extensively used are tumor necrosis factor-α (TNF-a) inhibitors, B-cell-targeted therapies, T cell co-stimulatory molecule blockers, and immune check point inhibitors. With regards to ILDs, there is established knowledge on the use of biologic therapies in patients with connective tissue disorders (CTD-ILDs) and sarcoidosis (12, 16, 19–21). Despite old skepticism (7, 22–27), there has been recently a shift toward targeting the immune system as a therapeutic option for different forms of interstitial lung inflammation and fibrosis (9, 28–33). Unfortunately, their safety profile has raised many concerns, as evidence shows that they might exacerbate or cause *de novo* development of ILD in a subgroup of patients (34–36) **(Table 1)**. This review article aims to summarize the current state of knowledge on their role in patients with ILD and highlight future perspectives.

TABLE 1 | Lung toxicity of biologic treatments.

Biologic treatment	Radiologic findings	References
Anti-TNFα	Aseptic granulomatous pulmonary nodules Interstitial lung infiltrates Incidence of DI-ILD:0.5–3%	(37–40)
Rituximab	Organizing Pneumonia ARDS	(41)
Tocilizumab	Organizing Pneumonia Exacerbation of ILD Pneumonitis	(42–44)
Abatacept	Rarely causes or exacerbates ILD	(45)

ARDS, Acute Respiratory Distress Syndrome; DI-ILD, Drug Induced- Interstitial Lung Disease; TNF, Tumor Necrosis Factor.

SARCOIDOSIS (TABLE 2)

Prednisolone remains the cornerstone of sarcoidosis treatment (55). Biologic therapies currently represent a fruitful therapeutic alternative in sarcoidosis cases refractory to first line immunomodulatory agents including corticosteroids, methotrexate, azathioprine, leflunomide and mycophenolate mofetil (56). TNFα inhibitors in combination with low dose prednisolone or methotrexate have been suggested in: (i) chronic progressive pulmonary disease, (ii) debilitation by lupus pernio, (iii) persistent neurosarcoidosis, (iv) persistent cardiac sarcoidosis (55). Infliximab has shown superior response rates in pulmonary sarcoidosis compared to etanercept and adalimumab (46, 47, 50, 51, 57). In particular, a randomized controlled trial (RCT) enrolling 148 patients with chronic pulmonary sarcoidosis showed that infliximab led to a statistically significant 2.5% improvement in forced vital capacity (FVC%pred) after 24 weeks of treatment (46). Results from other non-randomized trials were rather conflicting (47, 48). Unfortunately, almost 2/3 of patients with sarcoidosis receiving infliximab demonstrated relapse following drug-cessation (49). Adalimumab has shown acceptable tolerability and efficacy profile as indicated by improvements in FVC% pred, 6 Minute-Walk-Distance (6MWD) and Borg scale over a period of 52 weeks in a small cohort of patients with refractory pulmonary sarcoidosis (50). A phase 2 trial of etanercept in patients with pulmonary sarcoidosis was prematurely terminated due to unfavorable outcomes (51). Furthermore, golimumab (TNFα inhibitor) and ustekinumab (a monoclonal antibody targeting both IL-12 and IL-23) failed to show efficacy in patients with pulmonary and/or cutaneous sarcoidosis in an RCT with 173 patients (52). Finally, rituximab had an acceptable safety profile but inconsistent efficacy in a small cohort of patients with different genetic backgrounds and refractory pulmonary sarcoidosis; thus, its use through a personalized medicine approach could be viable in the future (53).

Elevated C-reactive protein (CRP) levels and TNFα Gly308Ala polymorphisms have been found to be predictive of response to anti-TNFα therapy, while soluble IL-2 receptor serum levels $\geq$4,000 pg·mL^{-1} at start of therapy were predictive of relapse (49, 58). Moreover, ^{18}8F-FDG-PET showed remarkable predictive accuracy in identifying patients that responded or relapsed following infliximab treatment (48, 49).

A broad spectrum of adverse events have been associated with the use of TNF-α inhibitors including anaphylactic reactions, reactivation of latent infections, neurological (i.e., demyelinating diseases) and autoimmune disorders and maybe in some cases malignancy (55, 59, 60). The paradoxical response, denominated sarcoid-like granulomatosis, has also been reported (61).

In conclusion, current evidence based on expert opinion suggests the use of biologic treatments in severe refractory pulmonary sarcoidosis. TNFα-inhibitors are preferred for patients with persistent disease despite treatment with corticosteroids and other second-line immunomodulatory compounds, especially in cases of life-threatening disease. However, such strategies need thorough pre-treatment evaluation and multidisciplinary approaches (12).

IDIOPATHIC PULMONARY FIBROSIS (FIGURE 1, TABLE 3)

The treatment of IPF has been revolutionized by the advent of two novel compounds, pirfenidone and nintedanib (3–11). Nevertheless, both compounds only slow down disease progression; thus, at best leave patients with considerable functional disability. Therefore, the need for alternative therapeutic options remains amenable (75–78).

Biologic agents represent one such option, yet with disappointing results. The clinical trial of carlumab, a monoclonal antibody against CC-chemokine ligand 2 (CCL2), was stopped prematurely as patients in the carlumab-treatment-arm experienced greater functional decline compared to the patients in the placebo-treatment-arm (62). TNFa-blocking agents such as etanercept showed no efficacy in patients with IPF (63). Imatinib, a tyrosine kinase inhibitor with multiple biologic properties, did not affect survival or lung function of patients with IPF (64). The study of simtuzumab, a monoclonal antibody against lysyl oxidase-like 2 (LOXL2), was also a negative study (69). Most recently, two anti-IL-13 monoclonal antibodies have entered the pipeline of clinical trials for IPF. Tralokinumab had an acceptable safety and tolerability profile; yet, key efficacy endpoints were not met (70). Monotherapy with lebrikizumab, another anti-IL-13 monoclonal antibody, did not result in a benefit on lung function or mortality over 52 weeks (65). Combination of lebrikizumab and pirfenidone was well-tolerated but did not meet the primary endpoint of FVC% decline; yet, a trend toward beneficial effects on mortality and acute exacerbations was observed (66, 67). Furthermore, SAR156597, a monoclonal bispecific antibody targeting IL-4 and IL-13, failed to halt disease progression either as monotherapy or in combination with standard-of-care antifibrotics (72). A Phase 2 open label trial of pamrevlumab (FG-3019), a monoclonal antibody blocking the downstream effects of connective tissue growth factor (CTGF), showed an acceptable safety and efficacy profile and thus a phase III clinical trial is currently anticipated (68, 79, 80). Safety and efficacy of VAY736, a monoclonal antibody against the cytokine

TABLE 2 | Biologic treatments in pulmonary sarcoidosis.

Study	Biologic agent	Mechanism of action	Number of patients/Outcome	References
Baughman et al.	Infliximab	Chimeric monoclonal antibody against TNF	148 patients Improvement of 2.5% in FVC over 24 weeks	(46)
Rossman et al.	Infliximab	Chimeric monoclonal antibody against TNF	19 patients No significant improvement over 6 and 14 weeks	(47)
Vorselaars et al.	Infliximab	Chimeric monoclonal antibody against TNF	56 patients Improvement of 6.6% in FVC Uptake value on ^{18}F-FDG-PET predictive of response	(48)
Vorselaars et al.	Infliximab	Chimeric monoclonal antibody against TNF	47 patients Relapse 62% Increased SUV, IL-2r predictors	(49)
Sweiss et al.	Adalimumab	Humanized monoclonal antibody against TNF	11 patients Improvement in FVC (4), stabilization in FVC (7), improvement in 6MWD (5), improvement in Borg (9) over 24/52 weeks	(50)
Utz et al.	Etanercept	Receptor antagonist of TNF	17 patients Excessive treatment failure	(51)
Judson et al.	Ustekinumab/ golimumab	Humanized monoclonal antibody against IL12,IL23/and against TNF, respectively	173 patients (pulmonary or cutaneous) No significant improvement over 28 weeks	(52)
Sweiss et al.	Rituximab	Humanized monoclonal antibody against CD20	10 patients >5% improvement in FVC (5) improvement by >30 m in 6MWD (5) over 24/52 weeks	(53)
NCT02888080	Canakinumab	Human monoclonal antibody against IL-1 b	Change in PFTs from baseline to week 24/Recruiting	(54)

CD, Cluster of Differentiation; IL, interleukin; ^{18}F-FDG-PET, Fludeoxyglucose (^{18}F) Positron Emission Tomography; FVC, Forced Vital Capacity; PFTs, Pulmonary Function Tests; SUV, Standardized Uptake Value; TNF, Tumor Necrosis Factor; 6MWD, 6 Minute Walk Distance.

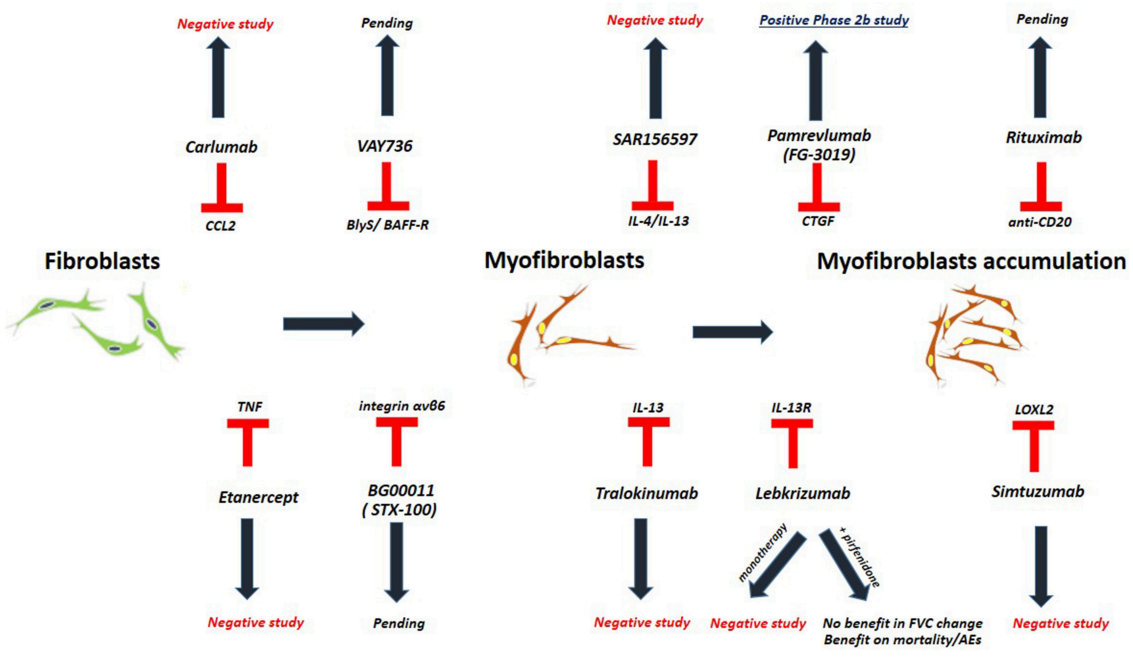

FIGURE 1 | Studies investigating biologic treatments in patients with IPF.

BlyS, a B cell activating factor, is also currently being tested in a phase 2 study (71). BG00011 (STX-100), a humanized monoclonal antibody against integrin αvβ6, demonstrated an acceptable safety profile and its efficacy is currently investigated in a phase 2b study (66, 81). Finally, rituximab ± intravenous immunoglobulin showed 1-year survival benefit in a small cohort of patients with IPF undergoing acute exacerbation compared to historical controls (82). A Phase 2 trial of rituximab in IPF aiming to reduce titers of autoantibodies to HEp-2 Cells over a 9-months period of follow up, has been recently

TABLE 3 | Phase 2 clinical trials for biologic treatments in patients with IPF.

Biologic agent	Mechanism of action	Outcome	References
Carlumab	CCL2 inhibitor	Negative study	NCT00786201 (62)
Etanercept	Receptor antagonist of TNF	Negative study	NCT00063869 (63)
Imatinib	Tyrosine kinase inhibitor	Negative study	NCT00131274 (64)
Lebrikizumab	anti- IL13	Monotherapy: Negative study Combination with pirfenidone: Trend for benefit on AE/mortality	NCT01872689 (65–67)
Pamrevlumab (FG-3019)	Monoclonal antibody against CTGF	Positive phase 2 open label trial	NCT01262001 (68)
simtuzumab	Anti-LOXL2	Negative study	NCT01769196 (69)
Tralokinumab	Anti-IL13	Negative study	NCT01629667 (70)
BG00011 (STX-100)	Humanized monoclonal antibody against integrin αvβ6	Pending	NCT01371305 (66)
VAY736	Monoclonal antibody against BlyS/ BAFF-R	Pending	NCT03287414 (71)
SAR156597	Bispecific monoclonal antibody against IL-4 and IL-13	Negative study	NCT02921971 (72)
Rituximab	anti-CD20	Pending	NCT01969409 NCT03286556 (73, 74)

BAFF-R, B cell activating factor; CCL2, chemokine (C-C motif) ligand 2; CTGF, Connective Tissue Growth Factor; IL, interleukin; LOXL2, Lysyl oxidase homolog 2; RCT, Randomized Controlled Trial; TNF, Tumor Necrosis Factor.

completed (73, 83). In addition, the results of autoantibody reduction for acute exacerbations of IPF (STRIVE-IPF) are greatly anticipated (74).

CONNECTIVE TISSUE DISEASE-ASSOCIATED INTERSTITIAL LUNG DISEASE (CTD-ILD)

RHEUMATOID ARTHRITIS

Pulmonary complications represent an important extra-articular feature of rheumatoid arthritis and a major cause of mortality and worse quality of life (16). The decision to treat them requires a multidisciplinary approach weighting: (i) the disease severity and patients' clinical status, (ii) the potential benefits of early therapy (i.e., treatment of inflammation before fibrosis is established) and (iii) the risk of adverse events (i.e., immunosuppression especially for patients with established fibrosis or severe bronchiectatic lesions). Given the lack of consensus over clinical trials, management is currently based on expert opinion. The recent emergence of novel anti-fibrotic compounds for the IPF-UIP-lung holds promise for the RA-UIP-lung (84–87) and the first randomized trial of antifibrotics in RA-ILD (TRAIL trial) is currently under investigation (84). To this end, biologic treatments may present with beneficial outcomes in a proportion of patients with refractory RA-ILD.

Rituximab represents the most widely used biologic treatment in patients with rapidly progressive RA-ILD who are unresponsive to first line therapeutic compounds including corticosteroids and methotrexate (88). Unfortunately, evidence is based on small observational studies and thus further data is required (89–97). A recent prospective, observational cohort study enrolling 43 patients on rituximab and 309 patients on TNF-α inhibitors, demonstrated better long-term survival in patients receiving rituximab than in those receiving TNF-α inhibitor, as event rates were 53.0 and 94.8 per 1,000 person years, respectively (98).

The use of TNF-α inhibitors yielded controversial safety and efficacy results in patients with RA-ILD. Caveats following their use in CTD-ILD parallel those previously described in sarcoidosis. Despite their effectiveness in improving clinical status and slowing down articular disease progression, lung toxicity remains a major concern (99–103). Small case series of patients with RA-ILD have shown that infliximab and etanercept could improve dyspnea and cough, as well as stabilize disease functional status (104–107). On the other hand, safety concerns have been raised for current TNF-α inhibitors infliximab (108–111), etanercept (112–116), adalimumab (117–121), golimumab (90), and certolizumab (37, 122, 123) considering reports for ILD exacerbation. Importantly, TNF- induced ILD could be rapidly progressive and even fatal, especially in patients with preexisting ILD (34, 124–127). Nonetheless, large cohorts of patients with RA reported no association between anti-TNF agents and ILD development or progression (128, 129). Caution should be used for elderly patients, as they represent a high-risk and frail group of patients (100).

Data for other agents including abatacept, tocilizumab and anakinra are still scarce. Abatacept has shown an acceptable safety and efficacy profile, as assessed by dyspnea, functional indicators and radiological extent of inflammation, in both large RCTs (130) and smaller case studies (45, 90, 102, 131, 132). The use of tocilizumab yielded conflicting results and it seems to be beneficial only in a small subgroup of patients with RA-ILD (42, 90, 102, 126, 133–137). Isolated cases of ILD-exacerbation following treatment with tocilizumab have been described (138). Finally, anakinra, an IL-1 receptor antagonist, is rarely, if ever, employed, in the treatment of patients with RA-ILD (126, 139).

SCLERODERMA

Until recently, the standard treatment for systemic sclerosis-associated ILD (SSc-ILD) was considered to be cyclophosphamide, based on the results of Scleroderma Lung Study (140). However, previously reported data from small-scale studies depicted beneficial effects of mycophenolate mofetil in SSc-ILD (141–143). The recently reported large-scale, randomized, double-blind Scleroderma Lung Study II comparing head-to-head cyclophosphamide vs. mycophenolate mofetil disclosed that mycophenolate mofetil was as effective as cyclophosphamide but with a better safety profile. Thus, mycophenolate mofetil has been established as the current standard of care for SSc-ILD (144). The statistically significant but clinically rather small benefit from the use of such treatment along with the commonly resistant nature of SSc-ILD, clearly underscores the need for novel treatments. Biologic agents, particularly rituximab, have been evaluated in small-scale studies in a minority of patients with progressive, treatment-resistant disease (145). The results of a multicenter, open label, comparative study evaluating rituximab on top of standard treatment ($n = 33$) vs. standard treatment alone ($n = 18$) showed that patients in the rituximab group had a 6% increase of FVC compared to baseline values at 2 years of treatment, a benefit that apparently was preserved later on; however, the number of patients at 7 years of treatment was too small for safe conclusions (146). Direct comparison between the rituximab group and the standard-treatment group disclosed a statistically significant benefit for the rituximab-treated patients. Other studies have reported results along the same lines (19, 20, 145, 147–149). Nevertheless, formal, multicenter, large-scale studies are clearly needed to evaluate the value of B-cell depletion treatment(s) in patients with SSc-ILD. A phase III trial evaluating the effects of the anti-IL-6 receptor monoclonal antibody tocilizumab was terminated despite relatively promising results in the earlier phase trials (150, 151) and the results from the use of belimumab, an anti-BLyS monoclonal antibody, have been evaluated only in one study with a small number of patients ($n = 9$) with clinically non-significant SSc-ILD (152).

MYOSITIS/ ANTISYNTHETASE SYNDROME

ILDs represent a major cause of mortality in dermatomyositis (DM), polymyositis (PM) and antisynthetase syndrome. Most common antibodies in patients with myositis-ILD include anti-EJ, anti-PL12, anti-PL7, anti-Jo1, anti-OJ and anti-KS (153). Biologics have been used in cases of myositis-associated-ILD refractory to more commonly used immunomodulatory agents such as corticosteroids, azathioprine and mycophenolate mofetil (92, 153). Data derived from case series, case reports and retrospective studies suggested clinical, functional and radiologic benefits from rituximab in patients with progressive ILD associated with PM/DM/ antisynthetase syndrome (92, 154–161). Basiliximab, a monoclonal antibody blocking the alpha chain (CD25) of the IL-2 receptor complex, resulted in radiologic and functional improvement in three out of four cases of clinically amyopathic dermatomyositis (CADM) with anti-MDA5 positivity and rapidly progressive ILD (162). However, prior to the application of such therapies, exclusion of other causes of lung function deterioration such as drug-induced pneumonitis, superimposed infection and respiratory muscle weakness is mandatory.

FUTURE PERSPECTIVES AND CONCLUDING REMARKS (TABLE 3)

ILDs represent disease paradigms of unknown pathogenesis, unpredictable clinical course and relatively ineffective therapeutic approaches. Biologic therapies may offer an effective alternative in progressive and refractory cases. Early identification of these patients is of paramount importance. Unfortunately, current physiologic biomarkers neither provide mechanistic insights in disease endotypes nor they predict disease clinical course. While ILDs are associated with several underlying mechanisms, currently applied regimens target specific pathways and thus there is still an amenable need for novel compounds. The development of biologics for the treatment of fibrotic lung diseases may hold promise considering the potential for disease modulation (163).

Biologic agents have shown to have a major impact in severe refractory cases of sarcoidosis. Furthermore, canakinumab, a human monoclonal antibody against IL-1 b, has entered the pipeline of clinical trials for sarcoidosis and the results are greatly anticipated (54). Unfortunately, the majority of biologic agents in IPF have, so far, led to disappointing results mainly due to the fact that they target immune-mediated inflammation and not fibrosis. Application of oncologic and personalized medicine approaches represent crucial steps toward successful implementation of biologic agents in lung fibrosis (164). The advent and implementation of high-throughput computational tools could identify biomarkers able to distinguish patients' endotypes and thus predict the subgroup of patients which are more likely to benefit from specific biologic interventions (165, 166). Biologic enrichment of future clinical trials and implementation of biomarkers as end-points could have a crucial impact toward this direction. Systematic pre-treatment assessment for latent infections and immunocompromise is mandatory prior treatment initiation to avoid undesirable adverse-events. Thoughtful monitoring and multi-disciplinary care with rheumatologists and pulmonologists are strongly encouraged.

AUTHOR CONTRIBUTIONS

TK and AV wrote the manuscript. The manuscript was significantly modified by DB, S-NL, and AT. All authors offered intellectual contribution.

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REVIEW
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Methotrexate-Associated Pneumonitis and Rheumatoid Arthritis-Interstitial Lung Disease: Current Concepts for the Diagnosis and Treatment

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Rheumatoid arthritis (RA) is a type of inflammatory arthritis that affects ∼1% of the general population. Although arthritis is the cardinal symptom, many extra-articular manifestations can occur. Lung involvement and particularly interstitial lung disease (ILD) is among the most common. Although ILD can occur as part of the natural history of RA (RA-ILD), pulmonary fibrosis has been also linked with methotrexate (MTX); a condition also known as MTX-pneumonitis (M-pneu). This review aims to discuss epidemiological, diagnostic, imaging and histopathological features, risk factors, and treatment options in RA-ILD and M-pneu. M-pneu, usually has an acute/subacute course characterized by cough, dyspnea and fever. Several risk factors, including genetic and environmental factors have been suggested, but none have been validated. The diagnosis is based on clinical and radiologic findings which are mostly consistent with non-specific interstitial pneumonia (NSIP), more so than bronchiolitis obliterans organizing pneumonia (BOOP). Histological findings include interstitial infiltrates by lymphocytes, histiocytes, and eosinophils with or without non-caseating granulomas. Treatment requires immediate cessation of MTX and commencement of glucocorticoids. RA-ILD shares the same symptomatology with M-pneu. However, it usually has a more chronic course. RA-ILD occurs in about 3–5% of RA patients, although this percentage is significantly increased when radiologic criteria are used. Usual interstitial pneumonia (UIP) and NSIP are the most common radiologic patterns. Several risk factors have been identified for RA-ILD including smoking, male gender, and positivity for anti-citrullinated peptide antibodies and rheumatoid factor. Diagnosis is based on clinical and radiologic findings while pulmonary function tests may demonstrate a restrictive

pattern. Although no clear guidelines exist for RA-ILD treatment, glucocorticoids and conventional disease modifying antirheumatic drugs (DMARDs) like MTX or leflunomide, as well as treatment with biologic DMARDs can be effective. There is limited evidence that rituximab, abatacept, and tocilizumab are better options compared to TNF-inhibitors.

Keywords: rheumatoid arthritis, interstitial lung disease, methotrexate, biologics, immunosuppressive therapies

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory arthritis with a worldwide prevalence of about 1% and a female predominance of about 3:1 (1). While there are numerous synthetic and biologic disease-modifying antirheumatic drugs (DMARDs) that can halt progression of the articular manifestations of the disease, data on extraarticular manifestations are less conclusive. Over the past few years, the lung has become a major focus in terms of pathophysiology and overall prognosis (2). In clinical practice, there are perceived discrepancies regarding pulmonary toxicity between pulmonologists and rheumatologists, especially regarding methotrexate (MTX) and the potential risks of long-term pulmonary fibrosis. Over the past few years, more evidence has evolved adding to the controversy. To make matters more complex, the pulmonary toxicity of biological therapies is less clear. Therefore, rheumatologists are frequently faced with the situation of how to treat joint manifestations effectively in the presence of interstitial lung disease (ILD) since evidence regarding pulmonary safety is sparse. In this review article, we aim to summarize the available evidence regarding MTX-associated pneumonitis (M-pneu), RA-ILD, and discuss treatment options based on available evidence.

METHODS AND LITERATURE SELECTION

A focused literature review including the keywords "methotrexate," "pneumonitis," "interstitial lung disease," and "rheumatoid arthritis" was performed. In addition, articles from the personal archives of the authors or references from key papers were included if deemed relevant by the authors.

PULMONARY DISEASE PATTERNS IN RHEUMATOID ARTHRITIS

Methotrexate-Associated Pneumonitis

Epidemiology

The frequency of M-pneu has been reported to range between 0.3 and 11.6% (3–6), depending on the methodology used and the criteria applied for M-pneu diagnosis. Interestingly, since 2001, no cases of M-pneu have been reported in randomized clinical trials of MTX in RA (7). M-pneu generally has an acute or subacute course and is usually observed within the first year of treatment (8). However, cases of late-onset M-pneu have been also described (9, 10).

Clinical Symptomatology and Laboratory Findings

Symptomatology mainly pertains to dry cough and dyspnea observed in more than 80% of the patients. Fever also occurs in more than 60% of them (3, 11, 12). Some authors have suggested that mild peripheral blood eosinophilia is present in about 25–40% of patients with sub-acute M-pneu (4, 9–11). Also, in case-series from patients with M-pneu it was demonstrated that peripheral blood lymphocytes dropped at the time of M-pneu and went back to normal after recovery (13). These findings, although very useful in everyday clinical practice, remain to be confirmed in larger studies.

Pathogenesis and Risk Factors for the Development of M-Pneu

Pathogenic mechanisms underlying M-pneu are unclear. It is considered by many investigators to be a hypersensitivity reaction, while interleukin-8 has been implicated in the pathogenesis (14). It should also be noted that patients receiving MTX are also at an increased risk for developing MTX-related lymphoproliferative disorder (LPD) (15). Interestingly, LPD regresses in many cases after the withdrawal of MTX (15, 16). Recent studies investigating the clinical and histopathologic characteristics of these patients have shown that in half of these cases this is linked to Epstein-Barr virus infection (15, 17) with p38 MAP kinase, PI3 kinase, and MEK pathways being implicated (18). The lung can also be involved in the context of MTX-related LPD (15, 16, 19, 20): Cases of lung lymphomatoid granulomatosis, a rare entity characterized histologically by multiple nodular lesions and vessel wall infiltration by lymphoid cells, have been described (16, 19, 20).

Several risk factors have been identified (**Table 1**), but it is remains uncertain to what extent they contribute to the occurrence of M-pneu. These factors include: age more than 60 years, diabetes mellitus, hypoalbuminemia, previous use of DMARDs), renal dysfunction, male gender, increased Health Assessment Questionnaire (HAQ) score, decreased pain Visual Analog Scale (VAS) score and pre-existing lung disease (6, 12, 21–23). However, these have not been replicated in other studies (24). Genetic factors might also play a role. In a Japanese population, an association between M-pneu and the HLA-A31:01 haplotype has been described (25). However, in a Genome Wide Association Study in a United Kingdom population, these results were not reproduced, but three Single Nucleotide Polymorphisms (SNPs) have been found to be associated with M-pneu occurrence with borderline significance (26). Environmental factors also possibly contribute. It has been suggested that increased latitude is related to an increased risk for M-pneu development. In fact, Jordan et al. using data from the New Zealand ministry of health showed that

TABLE 1 | Proposed risk factors for the development of methotrexate-associated pneumonitis (M-pneu) and rheumatoid-arthritis-interstitial lung disease (RA-ILD).

Risk factors	
M-pneu	**RA-ILD**
Pre-existing lung disease	Disease activity
Age > 60 years	Age
Male sex	Male gender
Diabetes mellitus	Smoking
High HAQ score, low pain VAS score	Positive rheumatoid factor
Chronic kidney disease	Positive anti-citrullinated peptide antibody
Hypoalbuminemia	MUC5B promoter variant rs35705950
Previous use of DMARDs	
Genetic factors (e.g., HLA-A31:01)*	
Environmental factors (e.g., latitude)	

DMARDs, disease-modifying antirheumatic drugs; HAQ, health assessment questionnaire; HLA, human leukocyte antigen; VAS, visual analog scale.
**Not confirmed in all populations.*

the incidence rate ratio for M-pneu was increased by 16% per one degree of increasing latitude (27).

Diagnosis

A diagnosis of M-pneu is based on the clinical and radiologic findings. Other diagnostic modalities like pulmonary function tests (PFTs) and bronchoalveolar lavage (BAL) might prove to be helpful as well. However, the differential diagnosis, which includes infections, like *Pneumocystis jirovecii* pneumonia (PJP), viral and atypical pneumonias, and ILD due to RA (RA-ILD), is difficult to be made (11).

Performance of PFTs routinely for diagnostic or prognostic purposes is still under debate (12). Although some studies have demonstrated only a minor effect of MTX on PFTs (28), two prospective studies have found that there are some alterations: Khadadah et al. (29), describe that after 2 years of treatment of low-dose MTX, patients may develop a restrictive pattern with significant decline in total lung capacity (TLC), functional residual capacity (FRC), forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and an increase in the FEV1/FVC ratio. Similarly, Cottin et al. (30), examining 124 patients treated with MTX, described a reduction of FVC, FEV1, and diffusing capacity of the lung for carbon monoxide (DLCO)/alveolar volume (VA). However, these changes could not predict the 3.2% of patients who developed M-pneu in their study (30). On the other hand, Saravanan et al. (8), have suggested that PFT abnormalities [low FEV1, vital capacity (VC) and diffusing transfer of the lung for carbon monoxide (TLCO)] might have a prognostic role, carrying a higher risk for M-pneu development in RA patients.

Of note, in published guidelines for MTX treatment in RA, based on literature review and expert opinion it is stated that PFTs with DLCO should be performed in patients with pre-existing lung disease or current symptoms (low strength of recommendation [D]) (6). In pediatric populations, some studies do not describe any abnormalities in children with juvenile idiopathic arthritis (JIA) treated with MTX (31, 32), while others conclude that there are some alterations in PFTs, like decrease of the mid-mean expiratory flow (MMEF) and DLCO (33, 34) or an increase in the TLC, FRC and residual volume (RV) (35). However, these are not affected by MTX and they were rather attributed to JIA *per se.* Besides, none of these patients developed clinically significant lung disease in these studies (33).

BAL examination is often performed in these patients. Most investigators agree that a lymphocytic pattern is observed (36), although cases of with BAL neutrophilia have been also reported (10, 37). Lymphocytosis in BAL is not specific for M-pneu as it is also seen in interstitial pneumonitis due to RA (36, 38) and in RA patients treated with MTX without respiratory symptoms (39). A recent systematic literature review examining characteristics of BAL in M-pneu has shown that lymphocytosis was present in the majority (89%) of BAL samples, while high levels of neutrophils were present in only 17% (40). In fact, six cytological patterns were identified (four with predominant lymphocytosis and two in which neutrophilia was the principal finding (40). It has been also suggested that predominance of $CD4^+$ T cells in BAL is suggestive of M-pneu (36) but there is some evidence that an increased CD4/CD8 ratio can also be found in other RA patients, usually those with pulmonary involvement (40). Also, the CD4/CD8 ratio can be found low or normal in about half of the M-pneu patients. Chikura et al. suggested that neutrophils are increased in the BAL of patients with M-pneu having received treatment for <6 months and with a cumulative dose of <300 mg, while the opposite was the case for lymphocyte numbers (41). These results were independent of the indication for which MTX was given (i.e., RA, Primary biliary cholangitis, Psoriatic arthritis, and others). Finally, serum levels of KL-6, a glycoprotein antigen, and surfactant protein D, both expressed mainly by type II pneumocytes, have been proposed as biomarkers for diagnosing and monitoring M-pneu (42). However, they are found to be increased in other lung diseases as well (43), therefore their utility, if any, in the setting of M-pneu remains to be defined.

Transbronchial lung biopsy (TBLB) might also be a useful diagnostic adjunct. In a study evaluating 44 patients with drug-induced lung injury, 75% underwent TBLB (44). TBLB was diagnostically helpful in 75%. Although histopathology alone cannot diagnose M-pneu, it may provide useful supplemental information that can be incorporated with clinical, radiologic, laboratory, and other features in the final diagnosis (44).

Imaging Features

Radiological findings reflect the underlying histopathologic process and include mostly non-specific interstitial pneumonia (NSIP), more so than bronchiolitis obliterans organizing pneumonia (BOOP) (45): on chest radiography, M-pneu gives rise to diffuse heterogeneous opacities in NSIP or bilateral scattered heterogeneous or homogeneous opacities with a peripheral distribution in the upper and lower lobes in BOOP. On CT scanning, scattered or diffuse ground-glass opacities are seen in early NSIP and basal fibrosis in the later stages of the disease. In BOOP, poorly defined nodular consolidations, centrilobular nodules, bronchiolitic (tree-in-bud) changes and

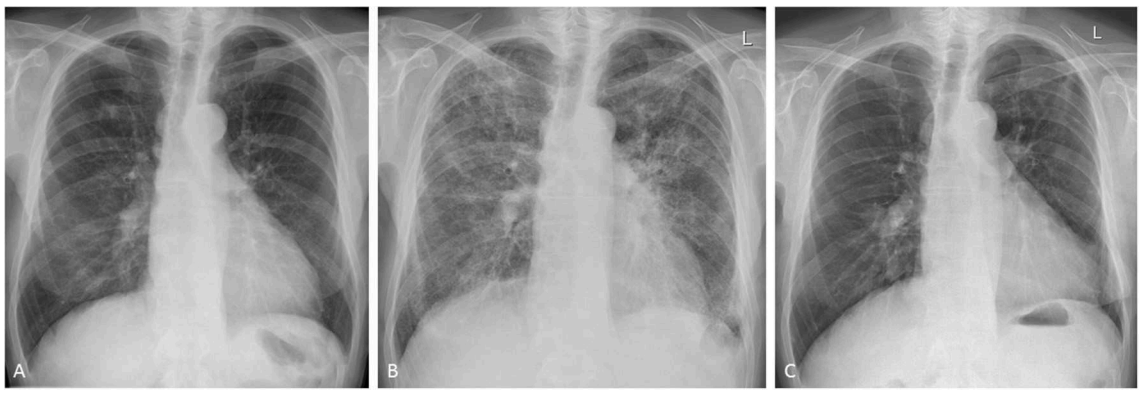

FIGURE 1 | Methotrexate-induced pneumonitis in a 77-year-old man with rheumatoid arthritis. **(A)** Posterior-anterior chest radiograph immediately before the initiation of treatment. Following 10 days of methotrexate, the patient experienced progressive dyspnea and fever. Follow-up chest radiography showed bilateral heterogeneous opacities in all lung zones. **(B)** The patient was transferred to the intensive care unit for supportive treatment. High-dose glucocorticoids were administered and gradually withdrawn following clinical and radiological improvement. Initial high-resolution CT scanning showed diffuse infiltrates and bilateral patchy consolidations with only very limited ground-glass opacities (images not shown). **(C)** Seven months after stopping methotrexate, the changes of pulmonary toxicity had fully resolved.

bronchial dilatation are the dominant features (**Figures 1A–C**) (6, 46). In a study examining CT findings in M-pneu, it was found that in the majority of the patients, these lesions subsided during a mean follow-up period of 31 days (46).

Histologic Findings

The most common histopathological pattern observed includes interstitial infiltrates by lymphocytes, histiocytes, and eosinophils with or without granulomas (36). Granulomas, usually non-caseating, are also identified in some patients, while hyperplastic type II pneumocytes and perivascular inflammation are also commonly seen (47). Other patterns have also been described and often coexist with interstitial pneumonitis, such as diffuse and organized alveolar damage (3, 12, 47). The latter seems to be more frequent in acute cases of M-pneu (47).

Treatment

In suspected M-pneu MTX should be discontinued immediately. Often, treatment with steroids is required (8). Other immunosuppressive drugs, such as cyclophosphamide (CYC), have also been administered successfully (48). Tocilizumab (TCZ), given its efficacy as monotherapy in RA, is also an attractive therapeutic option, since its use has been reported to be beneficial (38).

Prognosis

The prognosis of M-pneu is generally good and most patients recover fully (8), however, mortality is reported to be relatively high reaching 17.6% (6, 11). Other smaller studies have reported even higher figures up to 30% (49). Besides, in a review assessing patients (including individuals with RA) who developed M-pneu, the percentage was 13% (47). Furthermore, a study by Chikura et al. examining 56 RA patients with M-pneu suggested that mortality was more increased in patients who developed pneumonitis after treated with MTX for <6 months compared to those treated for a longer time period (41). It is suggested that this difference in mortality is accompanied by specific histopathologic features and characteristics in the BAL examination (41). Re-introduction of MTX in patients who have developed M-pneu has led to recurrence of lung injury and in many cases to death (11, 49). There are single cases, however, in which the drug has been re-introduced successfully (50).

Rheumatoid Arthritis Related Interstitial Lung Disease

RA is not merely a disease of the joints. It is a true systemic inflammatory disease with effects on many organs and organ systems. A variety of pulmonary manifestations can be seen in RA including pulmonary nodules, pleural effusions, bronchiectasis, and, most importantly, ILD (2).

Epidemiology

ILD is a frequently under-recognized complication of RA. The estimated prevalence is heavily dependent on the ascertainment method used. Bongartz et al. reported a lifetime risk of 7.7%, a 9-fold increase over the general population (51). Studies using the ERAS and ERAN early arthritis cohorts as well as the ILD specific BRILL study in the UK reported a prevalence of RA-ILD of 3–5% (52, 53) (**Table 2**). All of these studies identified clinical RA-ILD; if screening of asymptomatic individuals with RA is utilized, the prevalence of ILD increases depending on the performance characteristics of the screening methodology used. High resolution CT scanning identifies ILD in 19–67% of RA patients depending on the thresholds for diagnosis employed (54, 55). A study performing unselected histological assessment of pulmonary tissue in RA patients revealed evidence of ILD in 80% of patients (69). For these studies in which ILD was diagnosed based on radiologic and histological data, it should be noted that they probably overestimate clinically relevant RA-ILD. Patients were included irrespective of pulmonary symptoms and many of them had normal PFTs.

TABLE 2 | Comparison of clinical and imaging features in M-pneu *vs.* RA-ILD.

	MTX-pneu	RA-ILD	References
Frequency in RA	0.3–11.6%	3–5% (clinical diagnosis) 19–67% (radiological diagnosis)	(3–6, 52–55)
Course	Usually acute or sub-acute, within the first year of treatment	Usually chronic*	(8, 10, 38)
Clinical symptoms	Fever, dry cough, dyspnoea	Fever, dry cough, dyspnoea	(3, 11, 12)
Imaging findings	Mostly NSIP No specific predilection New or evolving diffuse interstitial or mixed interstitial and alveolar infiltrates Diffuse and patchy bilateral ground glass opacity with or without reticulation Cellular interstitial infiltrates, granulomas, diffuse alveolar damage	UIP > NSIP Basal and peripheral distribution CXR: punctate and reticulonodular densities and coarse reticulations CT: basal cystic changes (honeycombing, peripherheal reticular opacities, bronchioloectasis Lower lobe volume loss in the course of disease	(45–47, 56–58)
Bronchoalveolar lavage	Lymphocytic more common that neutrophilic pattern	Neutrophilic or lymphocytic pattern#	(36, 40, 41, 59)
Histopathology	Interstitial infiltrates by lymphocytes, histiocytes and eosinophils sometimes with non-caseating granulomas	UIP, NSIP > OP and other patterns	(12, 38, 47, 53, 60)
Treatment options	Discontinuation of MTX Glucocorticoids Rarely cyclophosphamide, TCZ	Glucocorticoids MTX or LEF possibly beneficial anti-TNF, ATC, TCZ: inconclusive data rituximab: possibly beneficial	(3, 7, 8, 12, 48, 61–68)

*ATC, abatacept; CT; computed tomography; CXR, chest x-ray; LEF, leflunomide; MTX, methotrexate; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; TCZ, tocilizumab; TNF, tumor necrosis factor; UIP, usual interstitial pneumonia. *Cases of fulminant RA-ILD have been described. #It has been suggested that RA patients with clinical/radiologic findings of lung involvement have neutrophilic pattern and those without a lymphocytic pattern.*

Pathogenesis and Risk Factors

Increasing evidence supports a primary role for the lung in initiating RA pathogenesis and RA-ILD may occur prior to the onset of the joint disease (70–72). Known predictors of RA-ILD include RA severity, age, male sex, smoking, and seropositivity for rheumatoid factor or anti-citrullinated peptide antibodies anti-citrullinated peptide antibodies (51, 71) (**Table 1**). In the past several years, biomarkers for RA-ILD have been suggested: Citrullinated isoforms of heat shock protein 90 (hsp90) have been shown to be potentially useful as a biomarker of RA-ILD (73). Hsp90 could also be identified in BAL specimens (74). Recently, the gain-of-function MUC5B promoter variant rs35705950, has been found to be associated with the development of ILD in RA patients with an Odds Ratio of 3.1 (75). This is especially interesting given that the same MUC5B variant is the strongest known risk factor for idiopathic pulmonary fibrosis (IPF), which shares many similarities with RA-ILD (76).

Clinical Symptomatology and Laboratory Findings

The clinical findings in RA-ILD are similar to those previously described for M-pneu with dyspnoea and non-productive cough with or without fever predominating (7). Most typically, RA-ILD develops insidiously over time and may be present and asymptomatic for a significant period. This diagnostic delay may be further exacerbated by the fact that patient's rheumatoid joint disease may limit their ability to exercise sufficiently to precipitate exertional dyspnea. Clinical examination findings may be absent in early disease but ultimately the majority of patients will have fine bibasal crepitations (77). The majority of those with an usual interstitial pneumonia (UIP) pattern RA-ILD will also develop clubbing, similar to IPF patients (77). Radiologic findings are of little help in distinguishing the two disorders with a significant degree of overlapping features (46). However, a key distinguishing feature can be chronicity. MTX-pneu is typically a fulminant acute process (11) (**Table 2**). A more indolent subacute or chronic development of radiologic findings strongly favors RA-ILD. In this scenario, historic radiologic imaging demonstrating evidence of similar but early ILD changes argues against MTX-pneu. However, RA-ILD may present as a fulminant and potentially fatal process, including early in the disease process (2, 78, 79).

Diagnosis

The diagnosis of RA-ILD can generally be made by a combination of clinical features as described above and congruent findings on chest imaging. It is important to remember that RA patients are, at least equally, and in often cases more likely, to develop other causes of dyspnea and cough than the general population. For example, the risk of infection, including atypical infections, pulmonary emboli, and lung cancer, are all increased in RA patients (80–82). PFTs may provide evidence of restrictive lung disease with a reduced TLCO/DCLO generally being the first manifestation.

Bronchoscopy and BAL may be performed to rule out other diagnoses. BAL is frequently abnormal in RA-ILD, but the findings are non-specific and rarely diagnostically useful. In rare cases open lung biopsy may be needed to confirm a diagnosis, in general when an alternative diagnosis is suspected.

Imaging Features

Apart from treatment-related complications, the thoracic manifestations of RA are plentiful (56) and include pleural changes, large airway involvement and, more so than with other collagen vascular diseases, a usual interstitial pneumonia (UIP) pattern of interstitial lung disease as distinct from a non-specific interstitial pneumonia (NSIP) or other patterns (71, 83) (**Table 2**). Clinically relevant ILD is less common, comprising basal cystic changes (honey combing), peripheral reticular

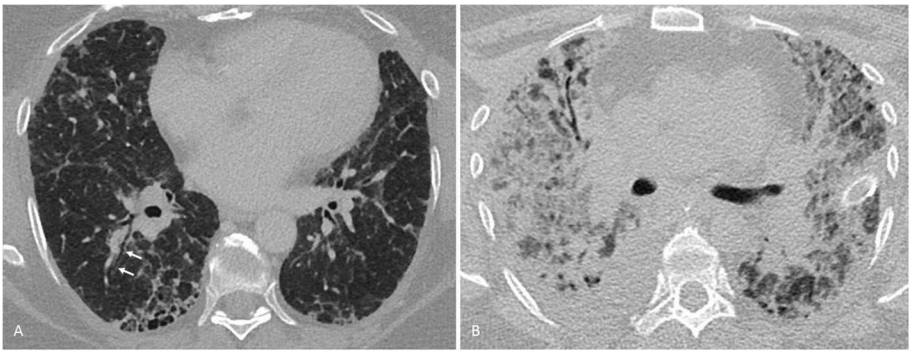

FIGURE 2 | Interstitial lung disease in a 56-year-old woman with rheumatoid arthritis. **(A)** One millimeter transverse axial CT-section through the lung bases show subpleural honeycombing and early traction bronchiectasis (arrows), consistent with a usual interstitial pneumonia pattern. **(B)** Nine months later, the patient developed severe dyspnea at rest and required mechanical ventilation. On bronchoalveolar lavage, influenza A virus was found to be present. A follow-up CT now showed a small right-sided pleural effusion and multifocally confluent consolidation, partially obscuring equally patchy bilateral ground-glass opacification. A few thickened septae (crazy-paving pattern) could be delineated (not shown). These findings were consistent with a viral pneumonia. Despite extracorporeal membrane oxygenation therapy, the patient deceased.

opacities and bronchioloectasis, best seen on CT scanning, and lower lobe volume loss which may advance in the chronic stage (**Figure 2**). Bronchiolitis obliterans has been described in RA, while follicular bronchiolitis is more common, showing small nodular changes on CT. Rheumatoid nodules as large as 5 cm are more likely in men, typically occur in smokers and may be seen prior to the articular manifestation of the disease. Nodules may cavitate, occasionally calcify and rarely rupture.

Histologic Findings

Findings on BAL are generally abnormal but non-specific in RA-ILD. Common findings include some form of neutrophil or lymphocytic predominant leucocytosis, or alterations in T-lymphocyte ratios (36, 41, 59, 84–86). Histologic findings are congruent with those seen with the underlying ILD phenotype, including neutrophilic or lymphocytic infiltrates, and fibrotic changes. A number of histopathological findings have been suggested to aid in the differentiation of MTX-pneu from RA-ILD including type II pneumocyte hyperplasia and fibroblast proliferation (11). However, these features have also been reported in RA-ILD.

Treatment

Glucocorticoids remain an important part of the acute management of RA-ILD. The optimum longer-term management of RA-ILD is uncertain, however, given the known factors predictive of RA-ILD described above it is logical that good RA disease control should be the cornerstone of any strategy (61). This is supported by the significant decline in the reported frequency of RA-ILD as RA treatment options have advanced (87). Given its proven efficacy in RA joint disease there is good reason to expect that MTX may be a justified part of any treatment strategy in an RA patient with ILD; evidence to support this strategy is beginning to emerge (60, 88). Despite previous concerns over potential pulmonary toxicity with leflunomide, this agent also appears to be potentially beneficial for RA-ILD (62). In the setting of RA-ILD, the choice of biological therapy is not clear: A recent review of the literature identified seven studies and 28 case reports, which showed an increased mortality with the use of tumor necrosis factor-inhibitors (TNF-i) (63). In this analysis, female sex and longer disease duration were associated with ILD onset or worsening (63). The heterogeneity in the reported outcome measures was too large to draw any firm conclusions. Other agents, such as Abatacept (ATC) have been investigated in few studies: In a Japanese study, deterioration of RA-ILD was described in 11 of 131 patients (8.4%) and was associated with concomitant MTX use (Odds Ratio of 12.75) (89). By contrast, a multicentric analysis from Spain concluded that ATC was associated with stable ILD in about two thirds of the patients (64). The role of TCZ in RA-ILD is less clear. A retrospective study in Japan showed worsening of ILD with TCZ in only six of 78 patients (7.7%) (65) or even improvement (38). These findings are in line with data from clinical trials in Systemic sclerosis (90), where it has been shown to preserve lung function, although this was not the primary endpoint.

Preliminary evidence of a particular role for Rituximab (RTX) is beginning to emerge (66, 67, 91, 92). An observational study of 56 patients with RA-ILD treated with RTX showed that 16% improved and 52% remained stable; a particularly impressive response given the aggressive natural history of RA-ILD (11, 66). This is logical given the association of RA-ILD with other known predictors of Rituximab response, in particular seropositivity (68).

Other agents are currently under investigation in the treatment of RA-ILD: The anti-fibrotic tyrosine kinase inhibitor nintedanib has been shown to be effective in an animal model of RA-ILD; the same agent has demonstrable efficacy in RCTs in IPF and, recently, also in systemic sclerosis (93–95). Another anti-fibrotic agent, pirfenidone, has been shown to downregulate profibrotic pathways in a bleomycin-induced mouse model and lung biopsy specimens from RA-ILD patients (96). **Figure 3**

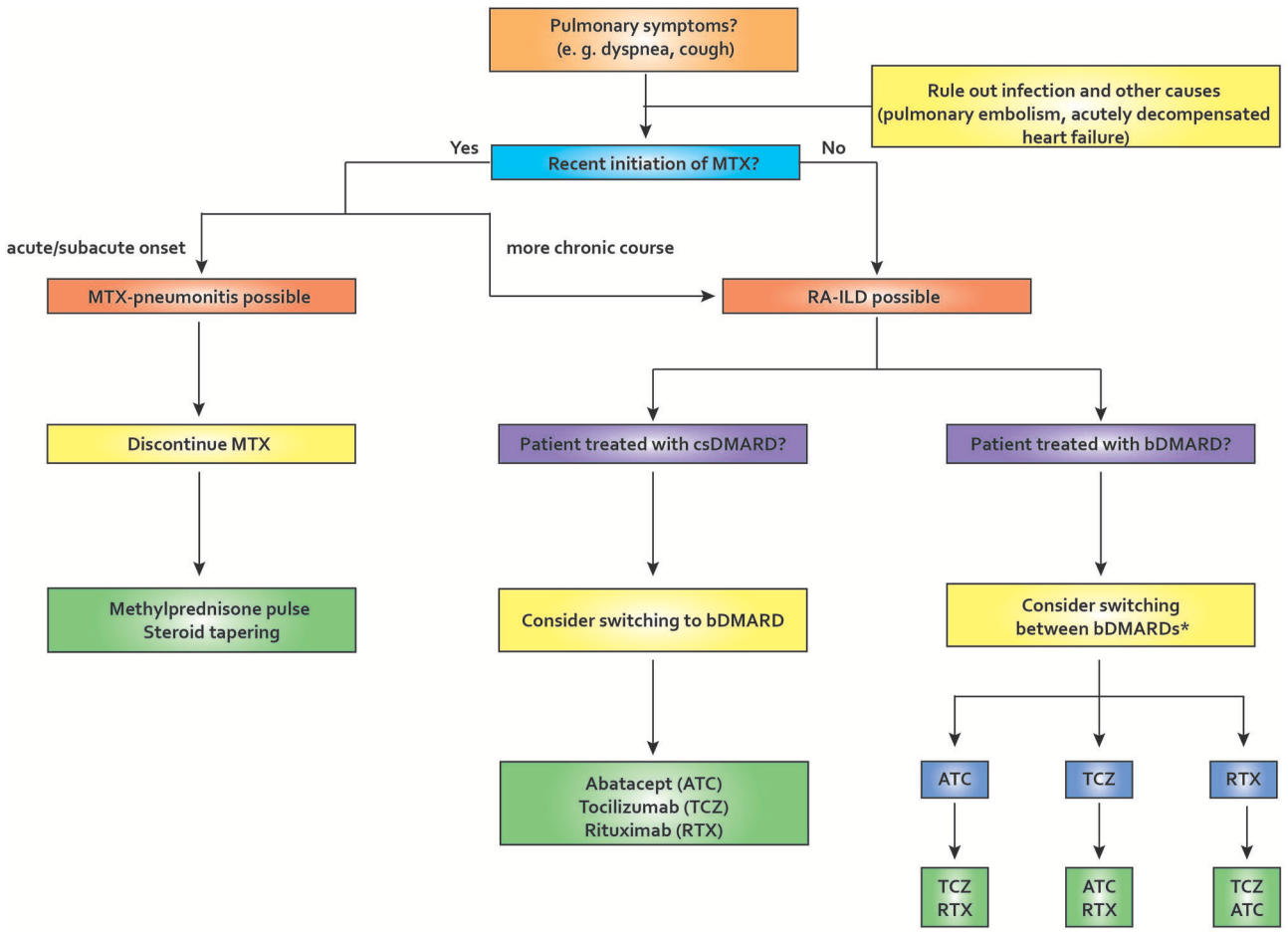

FIGURE 3 | Proposed algorithm for pulmonary symptoms in rheumatoid arthritis. In the setting of recent MTX initiation, MTX-pneu is always a concern, especially if the onset of symptoms is acute or sub-acute. In this case, MTX needs to be stopped and usually glucocorticoid therapy and supportive care in an intensive care unit is required. If the onset is more insidious, RA-ILD is a possibility. After ruling out other causes of pulmonary symptoms, management should depend on various factors, including comorbities, age, disease activity, and others. If a patient is diagnosed as having RA-ILD and receives a csDMARD, switching to a bDMARD may be appropriate. If a patient is already on bDMARD therapy, switching therapies may be required. Many authors tend to avoid TNF-inhibitors in this situation, but the evidence is weak. ATC, abatacept; bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ILD, interstitial lung disease; MTX, methotrexate; MTX-pneu, MTX-pneumonitis; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab. *TNF-inhibitors have been reported to be associated with worsening lung function in RA-ILD (weak evidence level).

depicts our proposed treatment approach to the treatment of pulmonary manifestations in RA.

Prognosis

ILD in general has a poor prognosis, however, this is even more true of RA-ILD, which has an ominous prognosis with a Hazard Ratio (HR) for death of 2.86 (51). Overall, respiratory causes are the second most common cause of death in patients with RA; symptomatic RA-ILD contributes 13% of the excess mortality associated with RA (51, 53, 97). Median survival following a diagnosis of RA-ILD is <3 years (2, 97). Acute fulminant RA-ILD occurring rapidly following disease onset is well-documented and frequently fatal (2, 78, 79). RA-ILD patients with a UIP pattern on imaging have increased mortality compared to other patterns, with a relative risk of 2.39 for UIP compared to NSIP (98). As well as the inherent mortality associated with RA-ILD itself, these patients are also at significantly increased risk of pulmonary infection (71, **Figure 2**).

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Methotrexate pneumonitis usually presents acutely but its incidence has been decreasing over time. Suspension of MTX and administration of glucocorticoid pulse therapy are usually required. In the long term, MTX therapy may associate with a lower incidence of RA-ILD, thus questioning the fear of progressive pulmonary fibrosis associated with this agent. Regarding bDMARDs, ATC, TCZ, or RTX appear more promising than TNF-i in patients requiring more

intense immunosuppression although the evidence base for this remains weak.

Future studies should aim at determining the exact prevalence of RA-ILD in early stage RA patients and will certainly rely on PFTs and imaging with CT at baseline and during the disease course to help identify patients at high risk for progression.

AUTHOR CONTRIBUTIONS

GF, EN, and RC wrote the first draft of the manuscript. PK edited and revised the manuscript and drafted the figures. JL edited the manuscript and contributed figures. All authors revised the manuscript critically and approved the final version of the manuscript.

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REVIEW
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Systemic Sclerosis Associated Interstitial Lung Disease: New Directions in Disease Management

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A subgroup of patients with systemic sclerosis (SSc) develop interstitial lung disease (ILD), characterized by inflammation and progressive scarring of the lungs that can lead to respiratory failure. Although ILD remains the major cause of death in these individuals, there is no consensus statement regarding the classification and characterization of SSc-related ILD (SSc-ILD). Recent clinical trials address the treatment of SSc-ILD and the results may lead to new disease-altering therapies. In this review, we provide an update to the diagnosis, management and treatment of SSc-ILD.

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Keywords: scleroderma, interstitial lung disease, systemic sclerosis, cyclophosphamide, nintedanib, pirfenidone

INTRODUCTION

Scleroderma or systemic sclerosis (SSc) is a systemic multi-organ disorder characterized by autoimmunity, systemic inflammation, vascular injury, and tissue fibrosis (1). Hippocrates provided the first description of their "thickened" skin texture around 400 BCE followed by labeling of the skin as "wood-like" by Curzio (2). In 1836, Fantonetti applied the term "scleroderma," derived from the Greek words skleros (hard or indurated) and derma (skin), to describe the human skin and joint disease presenting with tightened dark leathered skin leading to impaired joint mobility (2).

Classification of patients with SSc is based on the extent of skin involvement- diffuse cutaneous sclerosis (dcSSc) or limited cutaneous sclerosis (lcSSc), the latter characterized by skin sclerosis restricted to the hands, face, neck and distal extremities (3). Although SSc mainly affects the skin, pulmonary manifestations have an unpredictable course and remain the main cause of morbidity and mortality (4).

EPIDEMIOLOGY

The overall incidence rate of SSc in the adult population of the United States is approximately 20 per million per year (5) and approximately one in 10,000 individuals worldwide (1). Incidence and prevalence rates are fairly similar for Europe, the United States, Australia, and Argentina suggesting a prevalence of 150–300 cases per million; Scandinavia, Japan, the UK, Taiwan, and India report lower prevalence (6). The European League Against Rheumatism (EULAR) study showed a median disease duration of 7.1 years for patients with dcSSc and 15.0 years for lcSSc (7). The ratio of women to men developing SSc is 4:1 with an age of 45–55 at presentation (8). Cigarette smoking contributes to disease severity, but is not associated with risk of developing SSc-ILD (9).

In a review of patients with SSc-ILD, pulmonary fibrosis accounted for 19% of deaths and pulmonary hypertension (PH) in 14% (4). In an Italian cohort, the survival of SSc-ILD patients was reported to be 29–69% at 10 years from diagnosis with a female to male ratio of 9.7:1 (10).

African-American scleroderma patients have an earlier onset and more severe pulmonary disease. However, African American race is not a significant risk factor for mortality after adjustment for socioeconomic factors (11). Al-Sheikh reported that European-descent white subjects (55%, 95% CI 51–60) have poorer survival compared to Hispanic subjects (81.3%, 95% CI 63–100). East Asians have the longest median survival time (43.3 years) and Arabs the shortest median survival time (15 years) (12). Independent of race, lower median household income predicted increased mortality (11).

MECHANISM OF FIBROSIS IN SSC-ILD

Similar to other fibrotic lung diseases, injury to epithelial cells, activation of innate and adaptive immunity, and fibroblast recruitment and activation may lead to excessive extracellular matrix production and scarring in SSc-ILD (13). The factors that promote the activation and increased matrix production of fibrogenic fibroblasts in SSc-ILD are not well studied. However, recent data suggest that myofibroblast differentiation and proliferation are key pathological mechanisms driving fibrosis in SSc-ILD (14).

In bronchoalveolar lavage (BAL) fluid from patients with SSc-ILD, the pro- inflammatory cytokines interleukin (IL)-8, tumor necrosis factor-a (TNF), and macrophage inflammatory protein−1a are increased (15). Lung biopsies from patients with SSc-ILD demonstrate increased expression of Toll-like receptor (TLR) 4 in fibroblasts (11, 16). TLR4 is widely recognized as central to the innate response to gram-negative bacteria, but it can also be activated by endogenous ligands generated by cellular injury, autoimmune response, and oxidative stress. TLR4 activation potentiates TGF–β signaling and suppresses antifibrotic microRNAs (miR-101, miR 18a5p, miR-1343, miR-153, miR-326, miR-27b, miR-489, miR26a) (11, 17). TGF-β, through indirect influence on cytokines, primarily platelet derived growth factor (PDGF), promotes fibrogenesis (18). Elevated levels of IL-33 have been correlated with the severity of skin and lung fibrosis (19).

OTHER PULMONARY MANIFESTIONS IN SSC

Lung involvement including ILD, PH, or a combination of ILD and PH, occurs in more than 70% of patients with SSc. Pulmonary vascular disease, primarily pulmonary arterial hypertension, occurs in 10–40% of patients with SSc. Recently, coexisting PH was reported in a large SSc-ILD cohort often occurring early after diagnosis of SSc-ILD (20).

CLINICAL DIAGNOSIS OF SSC-ILD

The diagnosis of SSc-ILD is based on finding ILD on HRCT of the chest in a patient with known SSc accompanied by normal or abnormal pulmonary function tests showing restriction. Approximately one third of patients with SSc have positive anti-topoisomerase (Scl-70) antibodies; these patients have a greater likelihood of developing ILD, compared to those with lcSSc or those with positive anti-centromere antibodies (21). In the EULAR analysis, 53% of cases with dcSSc and 35% of cases with lcSSc had SSc-ILD (22). Historically, African American ethnicity, higher Rodman skin score (a measure of skin thickness), high creatinine and serum CPK levels, hypothyroidism, and cardiac involvement are associated with increased risk for the development of ILD (23, 24). Current risk factors for progression include diffuse vs. limited disease, a disease duration of >5 years, extent of parenchymal disease on HRCT of >20%, a forced vital capacity (FVC) of <70%, and the detection of anti-topoisomerase antibody (25).

DIAGNOSIS OF SSC-ILD

The most common symptoms of SSc-ILD are dyspnea, fatigue, and non-productive cough (26). Early ILD is frequently asymptomatic. As part of the diagnostic evaluation for a patient with SSc-ILD, auscultation of bibasilar fine inspiratory crackles at the lung bases should warrant a HRCT of the chest (27). The most common radiological finding is a non-specific interstitial pneumonia pattern with peripheral, bibasilar distribution of ground glass opacities (28, 29) (**Figure 2**). A pattern of usual interstitial pneumonia, characterized by honeycomb cysts and traction bronchiectasis may also be seen in up to a third of patients with SSc-ILD (29). The presence of ground glass opacities may herald the development of pulmonary fibrosis (30).

The most common histopathologic finding on lung biopsy is fibrotic NSIP (31) (**Figure 3**). A usual interstitial pneumonia (UIP) pattern can also be seen. When compared to lung biopsies of patients with idiopathic pulmonary fibrosis, SSc-ILD patients have more germinal centers and fewer fibroblast foci (32).

Almost all patients with SSc-ILD have positive antinuclear antibodies; this can be accompanied by anti-topoisomerase I (anti-Scl-70), anti- Th/To, anti-U3 ribonucleoprotein (RNP), anti- U11/U12 RNP, and rarely anti-centromere antibodies (33). The sensitivity and specificity of these autoantibodies varies in SSc depending on ethnicity, geographic region of origin, and method of detection (34).

Pulmonary function tests may be normal at presentation, but can be helpful in the follow up of SSc-ILD (35). Forced vital capacity below 80%, low diffusing capacity of the lungs for carbon monoxide (DLCO), and older age are predictors for mortality in SSc-ILD (15, 36). A rapid decline in DLCO may be the single most significant predictor of poor outcome and extent of ILD (37–39).

Analysis of BAL from patients with SSc-ILD typically shows increased number of granulocytes, especially neutrophils and eosinophils, and sometimes an increased level of lymphocytes and mast cells (40). In a series of 156 patients with SSc-ILD, a high percentage of neutrophils in BAL was associated with a 30% increase in risk of mortality (41).

The diagnosis of SSc-ILD is based on finding ILD on the HRCT of the chest in a patient with known SSc, and with exclusion of other etiologies of pulmonary parenchymal disease such as drug induced lung toxicity, heart failure, or recurrent

aspiration. A lung biopsy may be considered if there is suspicion for malignancy or granulomatous disease (40).

BIOMARKERS IN THE DIAGNOSIS OF SSC-ILD

There are no biomarkers that are part of a standard of care diagnostic work-up. In two study cohorts that included 427 individuals with SSc, lung-epithelial-derived surfactant protein (SP-D) was identified as a potential biomarker of SSc-ILD. It is suggested that elevated serum levels of SP-D would increase the risk of finding pulmonary fibrosis on chest images 3-fold (OR: 3.15 [1.81–5.48], $p < 0.001$) (42). Chemokine (C-C motif) ligand 18 (CCL18) is another biomarker that may predict the progression of ILD. The CCL18 is a pro-fibrotic factor and is found elevated in serum, BAL and lung tissue from patients with IPF or SSc-ILD (43). CCL18 is secreted predominantly by alveolar macrophages and is reflective of active lung injury (44).

The levels of Krebs von den Lungen-6 (KL-6), a glycoprotein found predominantly on type II pneumocytes and alveolar macrophages, are elevated in the serum of patients with SSc-ILD and may correlate with the presence of pneumonitis and the radiological fibrosis score in patients with SSc (45). KL-6 has been used as a marker for acuteness of lung fibrosis and the presence of pneumonitis (42). In a study of lung biopsies from 112 patients, the KL-6 level was significantly higher in patients with clinically active pneumonitis (1,497 +/- 560 U/ml) compared with inactive pneumonitis (441 ± 276 U/ml ($p < 0.001$) (46).

CLINICAL MANAGEMENT OF PATIENTS WITH SSC-ILD

The importance of a decline in lung function and survival in patients with SSc was noted by Ferri (47). SSc-ILD is classified as limited or extensive based on the findings of high-resolution computed tomography (HRCT) and lung function FVC (15). Patients with >20% HRCT abnormalities are considered to have extensive lung disease and those with <20% HRCT changes as limited disease. If the FVC is <70%, patients have extensive lung disease, and if the FVC is >70%, patients have limited disease (15). Patients with extensive disease have higher mortality and risk of lung function deterioration (15).

The treatment for SSc-ILD has focused on immunosuppressive therapies, particularly cyclophosphamide (CYC) and mycophenylate mofetil (MMF) based on the results of two pivotal clinical trials. Results from the Scleroderma Lung Study 1 showed a 1% change in FVC in the placebo group compared to a 2.6% change in FVC in the treated SSc subjects at 12 and 18 months (31). After 24 months, there were no differences between groups (48, 49). The results of the Scleroderma Lung Study I supported CYC as a standard of care until smaller studies reported beneficial effects of MMF in SSc-ILD. This led to the Scleroderma Lung Study II comparing

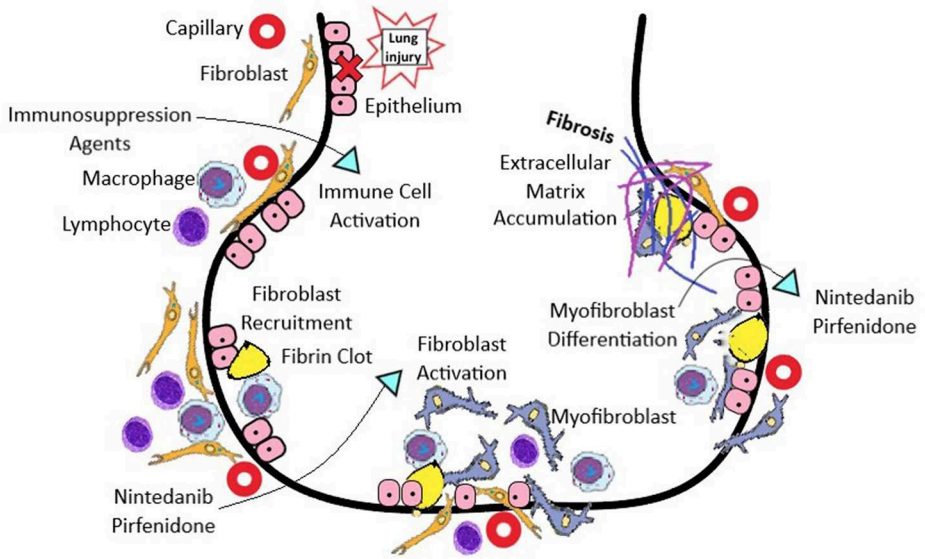

FIGURE 1 | The pathogenesis of SSc-ILD involves vascular, immunological, and fibrotic processes. The initial injury begins with endothelial and alveolar cell injury, which upregulates adhesion molecules and chemokines to attract leukocytes, which enable both innate and adaptive immune responses. Anti-topoisomerase 1 antibodies form immune complexes, and are taken up via Fc receptors, and activate endosomal Toll-like receptors in immune cells, which leads to type I interferon production. IFN release can induce TLR 3 expression on the surface of fibroblasts, causing pro-collagen production. Ligands for Toll-like receptors (TLRs) stimulate dendritic cells to produce IFN-α and interleukin (IL)-6, which in turn activate Th2 cells, produce IL-4 and IL-13, and stimulate pro-fibrotic macrophages. Macrophages produce multiple profibrotic factors including: TGFβ, connective tissue growth factor (CTGF), and PDGF, which promote fibroblast recruitment, invasion and proliferation. Fibroblast activation then occurs, and differentiation to a contractile myofibroblast phenotype result in overproduction and accumulation of extracellular matrix, resulting in progressive fibrosis. *Immunosuppression agents: mycophenolate mofetil, cyclophosphamide, tacrolimus, cyclosporine, tocilizumab, rituximab.

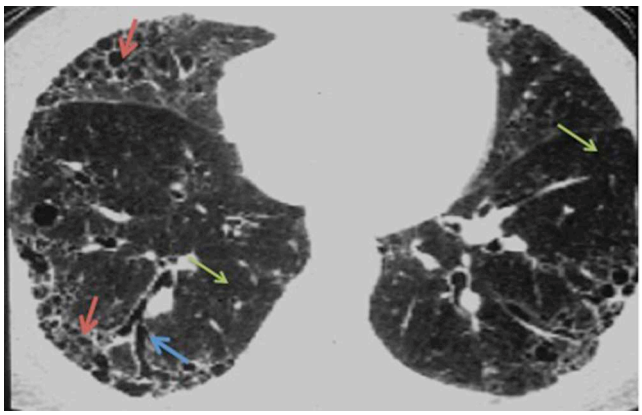

FIGURE 2 | HRCT of a usual interstitial pneumonia (UIP) pattern, characterized by honeycombing (red arrows), and traction bronchiectasis (blue arrow). Normal lung tissue is signaled with green arrows.

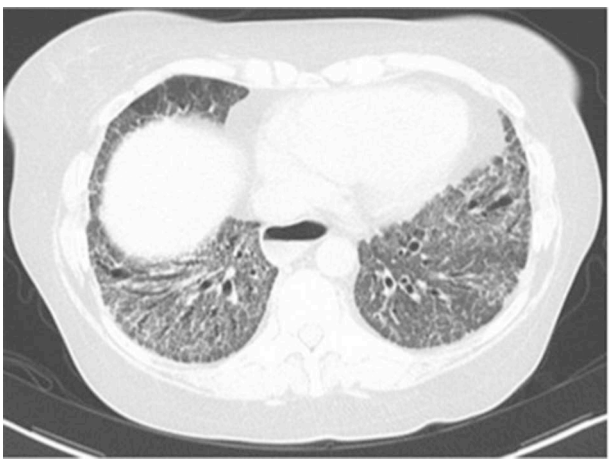

FIGURE 3 | Fibrotic nonspecific interstitial pneumonia (NSIP).

CYC vs. MMF showing that MMF was as effective and safer than CYC over a 24-month time period (54). Although this trial had a large dropout rate and lacked a placebo arm, MMF fell into a standard of care for SSc-ILD (54). Goldin et al. recently reported that changes in quantitative fibrosis scoring of the HRCT in SLS II correlated with FVC and the transition dyspnea index (50).Despite a previously negative trial with a tyrosine kinase inhibitor, imatinib (51), the recently completed SENSCIS trial in which 50% of the subjects were on a stable dose of MMF demonstrated an improvement in FVC with the addition of nintedanib (52). Of note, 50% had diffuse SSc and 60% of the participants were anti-topoisomerase positive.

The optimal treatment of SSc-ILD is not known. Developing treatments that would prevent SSc-ILD disease progression rather than disease regression is a research goal (39). Current management includes initiation of immunosuppressive treatment for SSc-ILD with ongoing evidence of disease progression based on PFT decline or radiographic deterioration. Initial therapy does not include steroids in light of the risk of renal crisis especially in dsSSc patients. Patients are more likely to benefit from immunosuppressant therapy during the early course of the disease, before substantial loss of lung function occurs (53). The most rapid decline in FVC occurs within the initial 3 years of disease onset (54). When therapy is initiated, exercise tolerance and PFTs should be monitored at 6-month intervals (55). Frequent HRCT images are not recommended and can be repeated when a change in clinical symptoms occur. (56) Most physicians seem to treat patients with extensive lung disease (presentation in HRCT and lung biopsy with UIP pattern, and evidence of ground glass opacities occupying more than 10% of lungs (**Figures 1**, **2**). With the completion of more randomized clinical trials, newer treatments with or without the adopted immunosuppressive agents may demonstrate efficacy in SSc-ILD.

Mycophenolate Mofetil (MMF)

Mycophenolate mofetil (MMF)is an inhibitor of lymphocyte proliferation and is often used as first line treatment in patients with SSc-ILD who are at risk for progressive ILD (57). The role of MMF in SSc-ILD was studied in the Scleroderma Lung Study II that evaluated 142 patients with SSc-ILD with FVC of <80%, and ground glass opacities on HRCT. Participants were given either 1,500 mg MMF twice daily for 24 months or oral cyclophosphamide (CYC) titrated up to a maximum dose of 1.8–2.3 mg/kg for 12 months. MMF was better tolerated than CYC and had a lower incidence of leukopenia and thrombocytopenia (57). Bone marrow suppression and gastrointestinal (GI) symptoms were the most commonly observed adverse effects of MMF. A complete blood count should be performed before starting therapy and during treatment. The target dose of MMF is generally between 1.5 and 3 g daily usually in two divided doses to avoid GI side effects.

In an observational study, 13 patients received anti-thymocyte globulin plus prednisolone for 5 days, followed by MMF maintenance therapy for 12 months. Long-term MMF was well tolerated, but there was no change in mean FVC or diffusion capacity after receiving this combined therapy (58).

Cyclophosphamide (CYC)

Cyclophosphamide (CYC) is considered an alternative to MMF based on the results of the Scleroderma Lung Study II. The unfavorable adverse effect profile includes infertility, opportunistic infections, hemorrhagic cystitis, bladder cancer, and neutropenia (59). Monthly intravenous administration of CYC is preferred over oral administration, due to a lower cumulative dose effect, less frequent adverse effects, and the ability to ensure adequate hydration before administration (28). Six CYC monthly intravenous infusions are recommended (60), with monthly monitoring of white blood cell count, renal function, and urinalysis. Corticosteroid pulses have been used with CYC with favorable results, but not as monotherapy (61). After completing a course of CYC, the treatment is commonly switched to a less toxic maintenance agent such as MMF or Azathioprine. Improvement in lung function after CYC treatment tends to decrease after discontinuation (62). For this reason, maintenance therapy is recommended, preferably with MMF (57).

Azathioprine

Azathioprine is a less efficacious initial therapy for SSc-ILD than CYC. In a randomized, double-blind trial, 60 patients with early SSc-ILD received either Azathioprine or CYC. During the first 6 months of therapy, patients also received prednisone, which was tapered subsequently. After 18 months FVC ($-11.1 \pm 1\%$), and DLCO ($-11.6 \pm 1.3\%$) were significantly worse ($p < 0.001$) in the Azathioprine group. In the CYC group, DLCO and FVC remained unchanged (63).

Cyclosporine and Tacrolimus

Cyclosporine and tacrolimus selectively inhibit calcineurin, thereby impairing the transcription of IL-2 and several other cytokines in T lymphocytes. Cyclosporine is an immunosuppressive agent mainly used to treat organ rejection post- transplant. Cyclosporine is a highly nephrotoxic agent that causes a decrease in the glomerular filtration rate (GFR) and a decrease in creatinine clearance (64). In a retrospective, observational study, tacrolimus may have some benefits for SSc-ILD. Twenty patients with SSc-ILD treated with CYC were divided into two groups: one treated with tacrolimus and low-dose corticosteroids following CYC and the other treated with low-dose corticosteroids after CYC. No difference was observed in PFTs at baseline in each group (%VC: $79.5 \pm 16.1\%$ vs. $87.4 \pm 18.8\%$, %DLCO: $59.5 \pm 11.5\%$ vs. $63.7 \pm 14.6\%$). In 3 years follow up; subjects treated with tacrolimus did not demonstrate disease progression (65). Neither CYC or tacrolimus is considered standard of care management for SSc-ILD.

Bosentan

Bosentan, is a nonselective endothelin receptor antagonist, used in the treatment of pulmonary hypertension. It is known that the endothelin system participates in the pathogenesis of SSc, and that it could delay the progression of SSc-ILD. A prospective, double-blind, randomized, placebo-controlled, parallel group study was conducted to evaluate changes in 6 min walk test distance, FVC and DLCO changes. 163 patients were enrolled, 77 were randomized to receive Bosentan, and 86 were randomized to receive placebo for 12 months. No significant difference between treatment groups was observed for change in the 6-min walk distance. No deaths occurred in this study group. FVC and DLCO remained stable. In Conclusion, these data do not support the use of endothelin receptor antagonists as therapy for SSc-ILD (66).

BIOLOGICAL IMMUNOTHERAPIES

Rituximab

Rituximab, a monoclonal antibody that targets CD20 positive B-lymphocytes, is suggested for patients with refractory SSC-ILD (67). In a pilot study, rituximab plus standard therapy (prednisone, CYC, and/or MMF) compared to standard therapy alone showed that the 8 patients in the rituximab group had a significantly better FVC, and DLCO (median percentage of improvement of 10.25 and 19.46%, respectively) at 1 year, than the other 6 patients receiving standard therapy alone (68). Further studies are need to assess the efficacy of rituximab in SSc-ILD (69).

Tocilizumab

TociIizumab, a humanized monoclonal antibody against the human IL-6 receptor *a* chain, is approved for treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and Castleman's disease (70). In patients with SSc-ILD, higher levels of serum IL-6 appear to be predictive of early disease progression in patients with mild ILD, this could be used to target treatment in this group of patients (71). In a randomized 48-week trial of 87 patients with dcSSc, FVC was significantly improved after 24 weeks in the Tocilizumab group (-34 vs. -171 ml respectively, $p = 0.0368$). However, no significant difference in FVC was found between the treated and control groups at 48 weeks (72).

Pomalidomide (POM)

Pomalidomide (POM), is an immunomodulator with antiangiogenic properties, and cytotoxic activity. Approved for the treatment of relapsed and refractory multiple myeloma (73). A 52 week randomized, double blind clinical trial of 23 patients with SSc-ILD was conducted to evaluate the safety and efficacy of POM on FVC and mRSS. Twenty-three patients were enrolled and randomized to receive POM or placebo. FVC deteriorated in both treatments (POM -5.2%, placebo -2.7%), mRSS (POM -2.7, placebo -3.7). Since very few subjects were enrolled the results were inconclusive (74).

Bortezomib

Bortezomib, is a FDA approved medication for the treatment of multiple myeloma. Bortezomib inhibits TGF- signaling *in vitro*, promotes normal repair and prevents lung fibrosis. The objective of the trial is to establish the safety and tolerability of bortezomib in SSc patients as well as exploratory effects on FVC. Participants receive MMF (1.5 g twice a day orally) and Bortezomib(1.3 mg/m^2) subcutaneously once per week for the first 2 weeks vs. MMF plus placebo (normal saline) for 24 weeks. The trial is planned for completion in June 2019.

ANTI-FIBROTIC AGENTS

Nintedanib and pirfenidone have anti-fibrotic effects and are approved for use in patients with idiopathic pulmonary fibrosis (IPF). In a case series of five patients with SSc-ILD, pirfenidone (1,200–1,800 mg/day) was associated with a reduction in dyspnea and an increase in VC (10%) from baseline (75). LOTUSS, a 16-week open label phase II trial of the safety and tolerability of pirfenidone on patients with SSc-ILD, pirfenidone was generally well tolerated, but there were no significant changes in FVC (76). SLS III, a double-blind, parallel group, randomized and placebo-controlled clinical trial is currently being conducted in patients with SSc-ILD. Participants must be treatment naive. The objective of this study is to determine the efficacy and safety of the combination of MMF with Pirfenidone. Subjects will be randomized 1:1 to receive MMF plus Pirfenidone or MMF plus placebo. The trial is scheduled for completion on May 2021.

Nintedanib, is a tyrosine kinase inhibitor (77) for vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), and colony stimulating factor 1 receptor (CSF1R) (78), slows disease progression and improves survival in patients with IPF. The SENCSIS trial, a double blind, randomized, placebo-controlled trial evaluated the efficacy and safety of oral nintenadib (150 mg bid) treatment for at least 52 weeks in patients with SSc-ILD (79). In the SENSCIS trial, 50% of the subjects had dsSSc and were on a stable dose of MMF. Subjects had a diagnosis of SSc with an onset of the first non-Raynaud's symptom within the past 7 years before entry and a HRCT that showed fibrosis affecting at least 10% of the lungs. The primary end point was the annual rate of decline in FVC. Key secondary end points were absolute changes from baseline in the modified Rodnan skin score (MRSS) and in the total score on the St. George's Respiratory Questionnaire (SGRQ). Neither of the two secondary endpoints achieved statistical significance highlighting the variability and poor reproducibility of the MRSS and the questionable applicability of the SGRQ for understanding dyspnea in SSc-ILD. The adjusted annual rate of change in FVC was −52.4 ml per year in the nintedanib group and −93.3 ml per year in the placebo group (difference, 41.0 ml per year; 95% [CI], 2.9–79.0; $P = 0.04$). Patients on a stable MMF dose did not elicit further improvement with add-on therapy with nintenadib.

Diarrhea, the most common adverse event, was reported in 75.7% of the patients in the nintedanib group and in 31.6% of those in the placebo group (52). An extension trial, SENSCIS-ON will assess long-term safety of treatment with oral Nintedanib in 450 subjects who completed the SENSCIS trial. This trial should be completed by July 2021.

OTHER TREATMENT MODALITIES

Lung Transplantation

Lung transplantation should be considered in the early stage of respiratory failure for all patients with chronic lung disease. However, gastrointestinal comorbidities that are often seen in patients with SSc-ILD may complicate the transplant evaluation (80). A systematic review by Khan et al. was performed to identify studies of the survival outcome post lung transplantation between patients with SSc vs. patients with no Ssc (ILD patients requiring lung transplantation) (81). SSc post-transplantation survival ranged 69–91% at 30-days, 69–85% at 6-months, 59–93% at 1-year, 49–80% at 2-years, and 46–79% at 3-years (82–85). The short-term and intermediate-term survival post-lung transplantation are similar to ILD patients requiring lung transplantation.

TABLE 1 | Completed clinical trials for patients with SSc-ILD.

Drug and study design	Name of study	Indications	Adverse effects
Mycophenolate mofetil (MMF). 2-year randomized, double-blind, active comparator/placebo-controlled trial	SLSII (57) NCT00883129	-First line treatment in patients who are at risk of progressive ILD. -Maintenance therapy	-Bone marrow suppression -Gastrointestinal (nausea, diarrhea, abdominal cramping) -Pancytopenia -Hypertension -Hyperglycemia
Cyclophosphamide (CYC) 1-year, randomized, double-blind, placebo-controlled trial plus 1 additional year of follow-up without study medication	SLS I (28, 59) NCT00004563	Second line treatment	-Infertility -Opportunistic infections -Hemorrhagic cystitis -Bladder cancer -Leukopenia -Thrombocytopenia
Bosentan 12-month randomized, double-blind, placebo-controlled trial	BUILD-2 (66) NCT00070590	Investigational approach	-Gastrointestinal (weight gain, nausea, vomiting) -Fatigue, Dizziness -Edema
Pirfenidone 16-week randomized, open-label comparison of two titration schedules	LOTUSS (76) NCT01933334	Investigational approach	-Gastrointestinal -Skin(sun sensitivity and rash) - Elevated liver enzymes
Pomalidomide 52 week randomized, double-blind, placebo-controlled, parallel-group study	CC-4047 (1, 74) NCT01559129	Investigational approach	-Gastrointestinal -Leuokopenia
Nintedanib 52 week, double blind, randomized, placebo-controlled trial evaluating FVC changes, efficacy and safety	SENCSIS trial (52, 79) NCT02597933	Investigational approach	-Gastrointestinal, mainly diarrhea -High blood pressure
Hematopoietic bone marrow stem cell transplant Randomized, open-label, phase II multicenter study of high-dose immunosuppressive Therapy	Scleroderma: cyclophosphamide or transplantation (SCOT) NCT00114530	Investigational approach	-Immunosuppression

TABLE 2 | Ongoing clinical trials for SSc-ILD patients.

Drug and study design	Name of study	Clinical trial identifier	Phase trial
Nintedanib An open-label extension trial of the long term safety of Nintedanib.	SENCSIS trial	NCT03313180	III
Bortezomib	Comparing and combining Bortezomib and Mycophenolate in SSc pulmonary fibrosis	NCT02370693	II, recruiting
Pirfenidone plus MMF vs. MMF plus placebo.	Scleroderma Lung Study III	NCT03221257	II, recruiting

Autologous Hematopoietic Stem Cell Transplantation (AHSCT)

Autologous hematopoietic stem cell transplantation (AHSCT) has been proposed as a potential therapy for severe SSc disease (86). In a meta-analysis study including patients with SSc-ILD on cyclophosphamide who underwent AHSCT, AHSCT reduced all-cause mortality (risk ratio [RR], 0.5 [95% confidence interval, 0.33–0.75]) and improved FVC (mean difference [M] 9.58% [95% CI, 3.89–15.18]), total lung capacity (M, 6.36% [95% CI, 1.23–11.49]), and assessment of quality of life (QOL) using a Short Form Health Survey showed improvement (M, 6.99% [95% CI, 2.79–11.18]) (87). Treatment-related mortality considerably varied between trials, but was overall higher with AHSCT (RR, 9.00 [95% CI, 1.57–51.69]). In the ASSIST trial, HSCT and antithymocyte globulin therapy preceded by CYC and filgrastim was superior to CYC with regards to skin score and lung volumes, although no difference was observed in DLco No deaths occurred in either group over 24 months of follow up (88). Recently, the SCOT (Scleroderma: CYC or transplantation) trial in patients with severe dcSSc with renal or pulmonary involvement, which goal was to determine the safety and effectiveness of high dose immunosuppressive therapy followed by AHSCT compared to CYC alone. The study demonstrated that myeloablative CD34+ selected AHSCT promoted greater event-free survival (survival without significant organ damage or death) than 12 months of CYC. The survival benefit was also noted at 54 months (79 vs. 50%) and at 72 months (74 vs. 47%) (89). **Tables 1**, **2** show a summary of ongoing and completed clinical trials on Ssc-ILD treatment.

CONCLUSIONS

Although there is no consensus statement that defines the criteria for SSc-ILD, HRCT, and PFTs serve as the primary diagnostic and staging parameters for establishing a diagnosis. Although MMF has been the initial treatment choice for SSc-ILD due to safer toxicity profiles and outcomes, more recent trials raise the option of antifibrotics or combination immunomodulatory/antifibrotic therapy as potential new treatments for patients with SSc-ILD. Lung transplant should be considered as an option, but the significant comorbidities associated with SSc including GI comorbidities should be addressed with medical and surgical evaluations prior to referring for transplant.

Many questions remain unanswered. When should treatment be initiated for SSc-ILD? What treatment regimen is most efficacious? How long should the patient be treated with SSc-ILD? With the development of more sophisticated classification criteria and assessment of HRCT, availability of reliable and reproducible biomarkers and molecular profiling, answers for these questions will impact treatment strategies for patients with SSc-ILD.

AUTHOR CONTRIBUTIONS

PB conducted literature review, conducted exploratory analysis, and helped to develop the first draft of the manuscript. MG helped in developing the first draft of the manuscript. MM conducted literature review, conducted exploratory analysis, and developed the final version of the manuscript.

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SYSTEMATIC REVIEW
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The Role of the Multidisciplinary Evaluation of Interstitial Lung Diseases: Systematic Literature Review of the Current Evidence and Future Perspectives

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The opportunity of a multidisciplinary evaluation for the diagnosis of interstitial pneumonias highlighted a major change in the diagnostic approach to diffuse lung disease. The new American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society guidelines for the diagnosis of idiopathic pulmonary fibrosis have reinforced this assumption and have underlined that the exclusion of connective tissue disease related lung involvement is mandatory, with obvious clinical and therapeutic impact. The multidisciplinary team discussion consists in a moment of interaction among the radiologist, pathologist and pulmonologist, also including the rheumatologist when considered necessary, to improve diagnostic agreement and optimize the definition of those cases in which pulmonary involvement may represent the first or prominent manifestation of an autoimmune systemic disease. Moreover, the proposal of classification criteria for interstitial lung disease with autoimmune features (IPAF) represents an effort to define lung involvement in clinically undefined autoimmune conditions. The complexity of autoimmune diseases, and in particular the lack of classification criteria defined for pathologies such as anti-synthetase syndrome, makes the involvement of the rheumatologist essential for the correct interpretation of the autoimmune element and for the application of classification criteria, that could replace clinical pictures initially interpreted as IPAF in defined autoimmune disease, minimizing the risk of misdiagnosis. The aim of this review was to evaluate the available evidence about the efficiency and efficacy of different multidisciplinary team approaches, in order to standardize the professional figures and the core set procedures that should be necessary for a correct approach in diagnosing patients with interstitial lung disease.

Keywords: interstitial lung disease (ILD), connective tissue disease (CTD), multidisciplinary team (MDT), rheumatologist, interstitial pneumonia with autoimmune features (IPAF)

INTRODUCTION

Multidisciplinary discussion (MDD) is currently recommended during the diagnostic process of interstitial lung diseases (ILD) in particular when idiopathic pulmonary fibrosis (IPF) is suspected (1, 2). IPF has the worst prognosis among the different forms of ILD, with a median survival of 3–5 years from the diagnosis. It can generally be suspected in male subjects over the age of 60 who present an usual interstitial pneumonia pattern (UIP) at radiology and histology. In subjects with a radiological pattern compatible with UIP and in the absence of a detectable etiology, surgical lung biopsy (SLB) is not necessary, whereas it should be considered in patients with probable or indeterminate radiological patterns for UIP especially when an alternative diagnosis is not achievable (1). MDD is currently replacing the histological evaluation, due to its limited reliability and intrinsic risks particularly in elderly or highly comorbid patients (3). Given the poor prognosis of IPF and the availability of new anti-fibrotic drugs such as pirfenidone and nintedanib, the diagnosis formulated via MDD is currently considered the gold standard (4–6). Despite this guideline for IPF diagnosis, there are no available studies that clearly assess the impact of multidisciplinary team (MDT) in the approach to patients with ILD and we do not know if the evaluation by experts can actually be better than MDD. Nonetheless, the participation by clinicians, radiologists, and when applicable histopathologists, could be considered useful to share clinical cases between physicians with different points of view in order to establish a "common language" and improve the knowledge of the singles (7).

Applying the guidelines of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society and Latin American Thoracic Association (ATS/ERS/JRS/ALAT), the recommended MDT is generally composed by a clinician (often a pulmonologist), a thoracic radiologist and pathologist with experience in ILD. Other physicians as rheumatologist should be considered only in selected cases (8). Current clinical practice guidelines for IPF recommend to perform a battery of serological test as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA) by immunofluorescence, rheumatoid factor (RF), myositis panel, and anti–cyclic citrullinated peptide (ACPA) without a previous consultation with rheumatologist, reserving this possibility in case of positivity of serological tests or presence of clinical manifestations suggesting an underling rheumatological disease (especially in women <60 years old) (8).

Hence ILD could be related to rheumatoid arthritis (RA), systemic vasculitis (especially antineutrophil Cytoplasmic Antibodies (ANCA)-associated Vasculitis) (9) and different connective tissue disease (CTD) especially systemic sclerosis (SSc), myositis spectrum disorders comprising overlap myositis and antisynthetase syndrome (ASSD) but also systemic lupus erythematosus, primary Sjoġren's syndrome, and mixed CTD (10, 11). Specific classification criteria are available for most CTDs, while classification criteria currently lack for diseases such as ASSD, making the correct diagnosis very challenging (12).

The recent introduction of criteria defining interstitial pneumonias with autoimmune features (IPAF) has allowed to reclassify those ILD that did not meet any CTD criteria, creating a growing interest in research concerning these new entities, especially on their possible evolution in CTD and overall prognosis (13).

The primary objective of this study was to perform a systematic review of literature to explore the evidence on the organization and outcome of MDT for the diagnosis and management of ILD, and to evaluate the role of rheumatologist. A secondary objective is to elaborate a definite proposal of ILD multidisciplinary evaluation.

MATERIALS AND METHODS

A systematic literature review was performed using electronic databases Pubmed (1999–2019) and Embase (1999–2019). The search strategy was elaborated to include the greatest number of references dealing with the populations and the interventions object of the study by using the following keywords in combination with the Boolean operators OR and AND: "*interstitial," "pneumonia," "multidisciplinary," "lung disease, interstitial," "pulmonary fibrosis," "interstitial pneumonias," "multidisciplinary team,"* and "*multidisciplinary approach."* Three reviewers (FF, GG, and AC) independently screened the titles and abstracts of all retrieved papers and selected the studies to be included in this review, after removing duplicates. All the articles selected by at least one of the reviewers were retrieved for full text evaluation. Article were selected according *a priori* inclusion criteria according to PICO methodology: (a) population: subjects aged>18 years with a suspected or established diagnosis of ILD; (b) intervention: multidisciplinary approach involving at least two different physicians of two different specialties; (c) type of study: metanalysis, randomized controlled trial (RCT), cohort, case control and case series (>5 patients) in English language. Other languages and other study designs (narrative review, case reports and meeting abstracts) were excluded. In case of disagreement between the reviewers, a further author (CS) was consulted to achieve a consensus. Primary outcome of this systematic review was the definition of the organization and physicians involved in the MDT with particular attention to clinical data collected and instrumental exams performed. A secondary objective was to evaluate the outcome of multidisciplinary approach (e.g., diagnosis or management) and to evaluate the role of rheumatologist. Selected articles were reviewed independently by three reviewers (FF, GG, and AC) and all data were extracted using an extraction form designed to respond to primary and secondary objectives of the review. The following data were extracted: authors, journal, year of publication, study design, inclusion and exclusion criteria, number of participants, population (ILD onset or established ILD, IPF, CTD related ILD, or both), interventions (physicians involved, instrumental examinations considered during the MDD) and outcomes evaluated (diagnosis, prognosis, efficacy of a treatment and other).

RESULTS

The search provided a total number of 333 citations from Pubmed and 955 from Embase. After excluding duplicates, a total

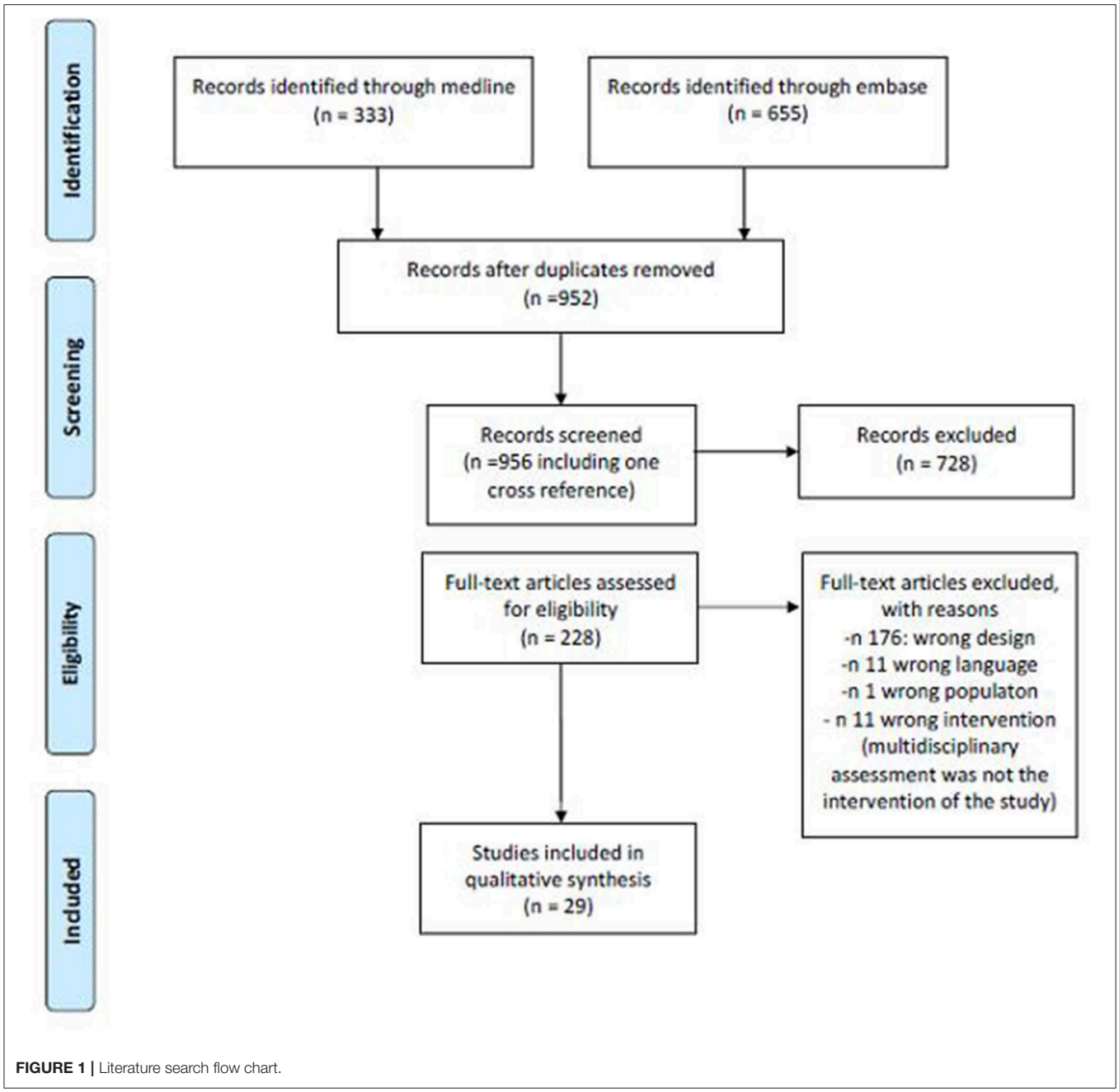

FIGURE 1 | Literature search flow chart.

of 952 references were screened for title and abstract and a total of 228 (including one cross reference) for full text analysis. A total of 29 papers were finally included for data extraction. **Figure 1** summarizes the number of papers excluded and the reason for exclusion. **Table 1** summarizes the main characteristics of the included studies.

Physician Involved in the MDT

In the included studies, the professional figures most frequently involved in MDT were: pulmonologist (29/29), thoracic radiologist (26/29), and thoracic pathologist (23/29). The rheumatologist role was described in 7 studies. Other professional figures were reported in 7 studies, including: clinical nurse specialist, cardiothoracic surgeon and lung transplantation team, occupational therapists, cardiologist, immunologist, palliative care expert, respiratory therapist, physiotherapist, and dietitian.

Some studies compared different compositions of MDT. Lok performed a comparison between a general respiratory clinic composed only by a pneumologist and a nurse (84 patients) and an ILD clinic setting including a specialist with interest in ILD with the support of radiologist, pathologist, and access to transplant and cardiothoracic program (54 patients). A multidisciplinary approach-based follow-up seemed

TABLE 1 | Characteristics and results of selected studies.

References	Study design	Population	Number of participants	Mean age(years) mean ± SD or (IQR)	Female %	Mean follow-up (months)
Burge et al. (14)	Retrospective cohort	ILD onset	71	/	/	/
Chartrand et al. (15)	Retrospective cohort	ILD established, myositis spectrum of disease, and/or SynS	33	55	22 (66.7%)	/
Castelino et al. (16)	Retrospective cohort	ILD onset	50	64 (32–80)	27 (54%)	12
De Sadeleer et al. (17)	Retrospective cohort	ILD onset	938	60.8 (14–90)	34.8%	
Ferri et al. (18)	Retrospective case-control	UCTD, IPAF, U-ILD	52 UCTD vs. 50 (35 IPAF-15 U-ILD)	UCTD 55 ± 13, IPAF 63 ± 12, U-ILD 68 ± 8.9	UCTD 44 (86%) IPAF 24(69%) U-ILD 9(60%)	/
Flaherty et al. (19)	Retrospective cohort	ILD onset (CTD excluded)	58	/	/	/
Fujisawa et al. (20)	Retrospective cohort	ILD onset (subjected to Surgical Lung Biopsy)	465	65	35%	7
Han et al. (21)	Retrospective cohort	Idiopathic ILD	56	56.9 ± 12.6	32 (57.1%)	7
Jeong et al. (22)	Prospective cohort	ILD related to CTD Idiopathic ILD	44 (23 CTD-ILD vs. 21 IPF)	CTD-ILD: 58.5, Idiopathic ILD: 70	CTD-ILD: 69.6%, Idiopathic ILD: 23.8%	
Jo et al. (23)	Retrospective cohort	Idiopathic ILD	417		31	26.16
Jo et al. (24)	Retrospective cohort	Idiopathic ILD, ILD related to CTD, unclassifiable ILD	90	67 ± 11	36 (40%)	/
Kalluri et al. (25)	Retrospective case-control/retrospective cohort	Idiopathic ILD	32	MDC group: 22, no MDC group: 10	MDC group: 36%, no MDC group: 40%	No MDC group: 17.4; MDC group: 14.4
Kohashi et al. (26)	Retrospective cohort	Idiopathic ILD that underwent to SLB	47	62 (56–67)	14 (29.8%)	1,582 (1,213–1,935) days
Kondoh et al. (27)	Retrospective cohort	Idiopathic ILD, Unclassifiable ILD, NSIP, hypersensitivity Pneumonia, ILD related to CTD	179	65 (60–70)	56 (31.3%)	/
Levi et al. (28)	Prospective cohort	New onset: ILD related CTD, Idiopathic ILD, IPAF	60	67.3 ± 12	27(45%)	/
Lok (29)	Retrospective cohort	/	138	General respiratory clinic: 64.6 vs. Patients of ILD clinic: 55.9	General respiratory clinic 31 (37%) ILD clinic: 28 (52%)	General respiratory clinic 31.9 vs. ILD clinic 22.3
Chaudhuri et al. (30)	Retrospective cohort	ILD established: ILD related to CTD, Idiopathic ILD	318	/	/	/
Nakamura et al. (31)	Retrospective cohort	U-ILD	33	64.4 ± 8.8	17(51.5%)	60.5
Newton et al. (32)	Retrospective cohort	familial pulmonary fibrosis	115	58 ± 10	57 (49.6%)	180
Patterson et al. (3)	Case control study	ILD onset	327 (80 of age>70)	54 ± 12 non-elderly vs. 76 ± 4 elderly	115(47%) non-elderly, 54 (68%) elderly	/
Pezzuto et al. (33)	Retrospective cohort	ILD onset	124	69 ± 7.9	37 (29.8%)	/

(Continued)

TABLE 1 | Continued

References	Study design	Population	Number of participants	Mean age(years) mean ± SD or (IQR)	Female %	Mean follow-up (months)
Tanizawa et al. (34)	Retrospective cohort	ILD established (UIP pattern at histology) CTD-ILD related are excluded	252.215 IPF, 19 U-ILD, 13 hypersensitivity pneumonitis	68.1 (62.1–72.6) with BCF vs. 67.7 (62.5–73.8) without BCF	32 (33.3%) in with BCF vs. 43(27.6%) without BCF	/
Thomeer et al. (35)	RCT	ILD established	182	18–75	NA	12
Tomassetti et al. (36)	Cross sectional	ILD established (without define UIP pattern on HRCT)	117 (59 BLC vs. 59 SLB)	59 (29–77) BLC vs. 59 (34–74) SLB	31 (53.4%) in BLC vs. 31 (52.5%) in SLB	
Tominaga et al. (37)	Retrospective cohort	Idiopathic ILD	95	63 (40–79)	17 (10.7%)	/
Oltmanns et al. (38)	Retrospective cohort	ILD established	63	68 ± 7	16. (25%)	11±7
Ussavarungsi et al. (39)	Retrospective cohort	U-ILD	74	63 (20–89)	33(45%)	/
Walsh et al. (40)	Retrospective cohort	ILD onset	70	60.9 ± 15.5	46(66%)	67
Yamauchi et al. (41)	Prospective cohort	Idiopathic ILD	30	64.5 ± 6.3	8(26.7%)	/

SD, standard deviation; IQR, interquartile range; MDT, multidisciplinary team; ILD, interstitial lung disease; HRCT, high resolution computer tomography; PFT, pulmonary function test; CT, computed tomography; ASSD/Syns, antisynthetase; UCTD, undifferentiated connective tissue disease; IPAF, Interstitial pneumonia with autoimmune features; U-ILD, undifferentiated connective tissue disease; CTD, connective tissue diseases; CTD-ILD, interstitial lung disease related to connective tissue diseases; MDC, multidisciplinary collaborative; SLB, surgical lung biopsy; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia; BLC, bronchoscopic lung biopsy; /, not reported.

to give an advantage in terms of survival in patients aged <60 years, being age an important negative prognostic factors in this population (29). In the study by Burge et al., the MDT was composed by a clinical nurse specialist as well as the classical organization which included specialist radiologist, histopathologist, and clinician. The authors highlighted the importance of MDD in the diagnosis of ILD compared to histology. The 71 patients in the study had in fact undergone video-assisted thoracoscopic surgery (VATS), and a retrospective analysis by MDT of the histological, clinical and radiological data was performed. In 30% of cases after MDD the diagnosis differed significantly from the histology report, and in a further 12% MDD changed the diagnosis from probable to confident (14).

Not all cases must necessarily be submitted to MDD. Chaudhuri et al. applied the MDD in the retrospective evaluation of 318 patients. The MDT of this study met weekly, and only patients sent by ILD expert clinicians were evaluated. The authors emphasized that after the multidisciplinary analysis the diagnosis could change, and that in doubtful cases, where biopsy was not possible due to comorbidities, the diagnosis could be reconsidered and reviewed over time based on the evolution and any response to therapy (30). Flaherty et al. highlighted how in the evaluation of patients with suspected IPF the review of the case by the radiologist, pathologist and clinician is fundamental, and that the sharing of clinical, radiological and possibly histopathological information can modify the diagnosis and/or increase diagnostics confidence and interobserver agreement. The diagnostic process described in this study was in fact organized through 4 different steps during which more information were progressively shared and the progressive interaction between the MDT members was permitted. The agreement between clinicians and radiologists was thus increased from the beginning to the end of the diagnostic process (0.39 vs. 0.88) (19).

The multidisciplinary approach, while representing the gold standard in the diagnosis of ILD, is not always practicable in normal clinical routine since local structures may not have experts in this field or meetings may be difficult to organize due to the geographical distance between the participants or time-related limits. A solution to overcome these limits could be provided by digital platforms. Fujisawa et al. validated a digital platform for the organization of MDD. The clinical data and radiological and histological images of 465 patients with suspected ILD (all therefore subjected to SLB) were included in an electronic database accessible via the web. Each patient was given a numerical identification code. The members of the MDT (clinicians, radiologists, and pathologists) could then separately access the various information and then a web conference to discuss with the other two members of the MDT. Also in this study, the MDD made possible to reformulate the initial diagnosis in a conspicuous number of cases (49%), and from the analysis of the survival curves it was shown that also this MDD modality is able to identify those diagnoses with the worse prognosis (like IPF) [(20); **Table 2**].

TABLE 2 | Physicians involved in the MDT.

References	Pulmonologist	Radiologist	Pathologist	Rheumatologist
Burge et al. (14)	1	1	1	0
Chartrand et al. (15)	1	1	1	1
De Sadeleer et al. (17)	1	1	1	1
Ferri et al. (18)	1	1	1	1
Kondoh et al. (27)	1	1	1	0
Levi et al. (28)	1	1	1	1
Jo et al. (24) 10/1/2019 9:37:00 p.m.	1	1	1	1
Flaherty et al. (19)	1	1	1	0
Fujisawa et al. (20)	1	1	1	0
Han et al. (21)	1	1	1	0
Jo et al. (42)	1	1	1	0
Kohashi et al. (26)	1	1	1	0
Lok (29)	1	1	1	0
Chaudhuri et al. (30)	1	1	1	0
Nakamura et al. (31)	1	1	1	0
Patterson et al. (3)	1	1	1	0
Pezzuto et al. (33)	1	1	1	0
Tanizawa et al. (34)	1	1	1	0
Thomeer et al. (35)	1	1	1	0
Tomassetti et al. (36)	1	1	1	0
Tominaga et al. (37)	1	1	1	0
Oltmanns et al. (38)	1	1	1	0
Walsh et al. (40)	1	1	1	0
Yamauchi et al. (41)	1	1	1	0
Jeong et al. (22)	1	1	0	1
Newton et al. (32)	1	1	0	0
Ussavarungsi et al. (39)	1	1	0	0
Castelino et al. (16)	1	0	0	1
Kalluri et al. (25)	1	0	0	0

Variables Evaluated During MDD

Clinical history assessment is reported in 24 of the 29 included studies. In addition to demographics (age and sex), the most frequently collected data concerned smoke (17/29) and environmental exposure (11/29). The evaluation of symptoms related to the possible presence of CTD and physical examination were reported in 7 studies.

High resolution computed tomography (HRCT) was evaluated in all studies except two: one dealing with a multidisciplinary approach not for the diagnosis, but for palliative care of ILD patients (25), and one focused on transbronchial lung cryobiopsy (39). HRCT was usually acquired only at baseline during the diagnostic process (24/27 studies). In 3 studies including longitudinal information, HRCT was repeated after 3–6 months in two studies (22, 31), and not specified in one study (35). Baseline chest X-ray was described in only one study (37).

Pulmonary function tests (PFT) were part of the core set of parameters analyzed during multidisciplinary evaluation in almost all studies (27/29). PFT were not performed in the same two previously described studies, in which even HRCT was not performed (25, 39). In 21 studies, PFTs were performed only at the baseline while in 6 studies repetition was described during follow-up with different timing: 1–3 months (38), 3 months (22), 3–6 months (31), annually (27), and not specified (32). The parameters considered were in most cases the forced vital capacity (FVC), the ability to spread carbon monoxide (DLCO) and forced expiratory volume in the 1st second (FEV1); less frequently, total lung capacity (TLC); and residual volume (RV).

Pulmonary histology was evaluated in 21 studies. The role in the MDD of biopsy and especially of two different techniques (namely surgical lung biopsy SLB, and bronchoscopic lung biopsy BLC) was evaluated in a cross-sectional study involving 171 patients (58 BLC vs. 59 SLB). Both the modalities of biopsy increased the diagnostic accuracy of IPF (36). Ussavarungsi evaluated the role of Transbronchial Cryobiopsy (TBC) in the MDD; in this series of 74 patients, TBC failed to obtain histological samples demonstrating a specific UIP or NSIP pattern (39). In a retrospective cohort of 124 patients with suspected IPF, authors suggested to perform HRCT at baseline together with PFT (FVC, TLC; RV and DLCO), laboratory test for CTD and vasculitis, and bronchoalveolar

lavage (BAL) for cytological and microbiological tests. HRCT results were then reviewed by MDT and classified according to the ATS/ERS/JRS/ALAT guidelines in UIP pattern, probable UIP and inconsistent with UIP patterns. Only in the last two and in presence of clinical, immunological, microbiological, and cytological abnormalities suggestive for IPF, the authors recommended biopsy. 15/124 patients could not be classified in neither of proposed definitions of HRCT patterns, but they were subsequently diagnosed with IPF after MDD and biopsy (33).

Serological data were reported in 17/29 studies, and 14 included autoantibody profile tests, especially RF, ACPA, ANA, antibodies against extractable nuclear antigens (ENA), myositis specific antibodies (including anti-synthetase) and myositis associated. Two studies reported genetic evaluation. Newton correlated traditional parameters evaluated during MDD (demographic data, physical examination, PFT, and HRCT) with four telomere-related genes mutations (TERT, TERC, RTEL1, and PARN). These genetic investigations were not usually performed during the traditional MDD for ILD, but this study focused on the evaluation of hereditary forms of pulmonary fibrosis (32). Another genetic test relating the MUC5B gene (rs35705950), associated with susceptibility to IPF, was obtained in a study cohort involving 252 ILD patients considered through MDD for diagnosis. In this study, the presence of bronchiolocentric fibrosis seemed not to correlated with MUC5B gene, telomere length, and IPF diagnosis formulated through MDD (34).

Further instrumental investigations evaluated during MDD were described in 15 studies, including BAL, doppler echocardiography, and 6-min walking test (**Table 3**).

Outcome Evaluated by MDT

Fifteen studies had as outcome a reference standard diagnosis, 7 prognostic evaluation, 5 both diagnosis and prognosis, 1 evaluated efficacy of pirfenidone treatment, and 1 the effect of multidisciplinary approach on patient perception of the disease.

Evaluating in detail the studies in which the outcome was the diagnosis, after the assessment by the MDT of a large cohort of 417 patients collected in the Australian IPF Registry (AIPFR), it was shown that in 23% of cases the guidelines for IPF were not applied by referring physicians (42). Despite this observation, in another study by the same authors the MDD showed to be relevant not only for the diagnosis, but also for the investigations prescribed and therapeutic behavior. After multidisciplinary evaluation of 93 patients, in fact, ILD diagnosis was changed in 53% of patients referred, and 71% of unclassifiable disease were re-classified under a specific diagnosis with obvious implication on therapeutic approach including an increased recommendation for anti-fibrotic therapy and referral for clinical trials (24). In a larger study by De Sadeleer involving 938 patients sent for multidisciplinary evaluation, the diagnosis was reached in 79.5% and modified in 41.9% of cases after MDD, while a diagnostic conclusion was not achieved only in 19.5% of the patients; however, in this case further investigations (16% of the total court) were at least suggested. This study demonstrated that a correct diagnosis also correlated with better prognosis, and that MDT could be helpful for the identification of those patients with worse prognosis. Indeed patients who were diagnosed as IPF demonstrated a worse prognosis than those classified as not-IPF after MDD [Hazard ratio (HR) 4.31, $p < 0.001$], while patients initially classified as IPF who reported a change in their diagnosis after MDD showed a better prognosis compared to patients definitely diagnosed with IPF (HR 0.37, $p = 0.094$) (17). In another study of 33 patients with previous diagnosis of unclassifiable-ILD (U-ILD), clinical, radiological and histological data were retrospectively evaluated by MDT. After MDD, the initial diagnosis was confirmed in 18 (54.5%) patients, but changed to collagen vascular disease-related interstitial pneumonia in 9 (27.3%), to chronic hypersensitivity pneumonitis in 3 (9.1%), to idiopathic pleuro-parenchymal fibroelastosis in 2 (6.1%), and IPF with emphysema in 1 (3.0%) patient (31).

The importance of cooperation between clinicians, radiologists and pathologists was reinforced by the analysis of patients enrolled in the IFIGENIA trial, a randomized placebo-controlled trial conducted on patients with IPF in which N-Acetylcysteine was associated referred to standard therapy (azathioprine plus steroid). Patients diagnosed as IPF by the clinician were subjected to a commission of thoracic radiology experts who evaluated chest HRCT images and by expert pathologists who evaluated the results of biopsies if performed. The diagnosis of IPF was rejected in 12.8% of cases formulated by the expert clinician after reviewing the histology and HRCT images thus demonstrating the importance of the multidisciplinary collaboration between clinicians, expert radiologists, and pathologists for a correct diagnosis of IPF (35). The reliability of MDD composed by these professional figures was also assessed. Seven different MDTs assessed 70 cases, for a total of 490 diagnoses [CTD-related ILD ($n = 146$), IPF ($n = 88$), idiopathic NSIP ($n = 50$), hypersensitivity pneumonitis ($n = 46$), and others ($n = 160$)]. Inter-MDT agreement for a first-choice diagnosis of IPF was good ($\kappa = 0.60$), good for CTD-related ILD ($\kappa = 0.64$), but fair for idiopathic NSIP ($\kappa = 0.25$), and hypersensitivity pneumonitis ($\kappa = 0.24$). The authors therefore recognized the excellent performance of the MDT in diagnosing IPF for which better defined classification criteria are available than for other conditions, i.e., hypersensitivity pneumonitis. Furthermore, the highest frequency of CTD-ILD, demonstrated the importance of including a rheumatologist in the multidisciplinary evaluation of ILD (40).

Besides the diagnostic process, MDD could be performed to evaluate the prognosis of particular populations of ILD patients. In a prospective cohort study involving 327 subjects, multidisciplinary approach was employed to evaluate the role of age onset to determine both diagnosis and prognosis of ILD patients (3). MDT can also be used not only in the diagnosis of IPF but also to identify sub-populations of patients with a worse prognosis. In a study conducted on 47 patients with IPF confirmed after SLB and MDD, the multidisciplinary evaluation allowed to identify the presence of emphysema and its extent as negative prognostic factors for survival (26). In the evaluation of the patient's suitability for starting pirfenidone therapy, the multidisciplinary meeting, where clinicians, radiologists and pathologists discussed clinical and instrumental data, was essential to identify IPF patients (38).

TABLE 3 | Variables evaluated during MDD.

References	Clinical evaluation	HRCT	PFT	Lung biopsy	Laboratory test	Other
Burge et al. (14)	History (brief clinical history, the duration of breathlessness, exposure, and smoking histories) Physical examination (crackles and clubbing)	Yes, pre-operative lung CT	Full lung function tests before biopsy (not described)	Yes	Immunological tests to identify collagen-vascular diseases, antibodies associated with hypersensitivity pneumonitis, and angiotensin converting enzyme levels	/
Chartrand et al. (15)	History (smoke, family history) BMI	Yes at baseline	Yes, FVC, DLCO	No	5 myositis-specific (Jo1, PL12, PL7, OJ, EJ, Mi2, SRP) and myositis-associated antibodies (Ro52, Ku, PM-Scl) antibodies (Jo1, PL-7, PL-12, EJ, OJ), 2 other myositis-specific antibodies (Mi-2, SRP), and 3 myositis-associated antibodies (Ku, PM-Scl, Ro-52)	/
Castelino et al. (16)	History (occupational and environmental exposures, medication history, family history) Physical examination (skin, mucus membranes, musculoskeletal, oropharyngeal, and gastrointestinal system)	Yes at baseline	Yes, FVC, DLCO	Yes	Anti-nuclear antibody (performed using HEp2 cell lines at BWH), ENAs, RF, inflammatory markers (ESR and CRP)	-Nailfold capillaroscopy -Echocardiography -Esophageal testing for pH or manometric studies
De Sadeleer et al. (17)	History (familial history, exposures, comorbidities, and medication use) -Physical examination	Yes at baseline	Yes not specified	Yes	Serological data (not specified)	BAL
Ferri et al. (18)	- History (demographic, occupational, smoking, medication, environmental, occupational, autoimmune manifestation)	Yes at baseline	Yes, including DLCO	Surgical lung biopsy Skin biopsy	ANA, anti-ENA, ESR, CRP, routine blood chemistry, urinalysis, infections, RF (first line), antiCCP, complement, ASMA, AMA, ANCA, antiphospholipid, organ specific antibodies, 24 h proteinuria (second line)	Doppler echocardiography, Joint echography, Nailfold capillaroscopy, Schirmer's test, Salivary gland echography, Minor salivary gland biopsy, Muscle biopsy, Electromyography
Flaherty et al. (19)	History (symptoms, environmental exposures, comorbid illnesses, medication use, smoking history, family history) -Physical examination findings	Yes at baseline	Yes, lung volumes and DLCO	No	Serological data (not specified)	/
Fujisawa et al. (20)	History (symptoms, environmental exposures, smoking history, family history, comorbid illnesses) -Physical examination	Yes, within 3 months from SLB	Yes, FVC, FEV1, DLCO	Yes	Blood test results, arterial blood gas analysis (or SpO2)	6-MWT, bronchoscopy, including bronchoalveolar lavage
Han et al. (21)	- History [smoking history; environmental, occupational and drug exposure; history of established connective tissue disease (CTD)]	Yes at baseline	Yes not specified	Yes	No	/

(Continued)

TABLE 3 | Continued

References	Clinical evaluation	HRCT	PFT	Lung biopsy	Laboratory test	Other
Jeong et al. (22)	- History (exercise status, Educational status, underlying rheumatic diseases)	Yes, repeat at 6 months	Yes, lung volumes, and DLCO, repeat at 3 months	No	No	The Brief Illness Perception Questionnaire (IPQ), Beliefs about Medicines Questionnaire (BMQ), Patient Health Questionnaire-2 (PHQ-2), Adherence measures
Jo et al. (42)	History (smoke, presence of underlying rheumatic diseases) -Physical examination(BMI)	Yes at baseline	Yes, FVC, FEV1/FVC, and DLCO	Yes	No	/
Jo et al. (24)	-History smokers (pack/years)	Yes at baseline	Yes, FVC, TLC, DLCO	Yes	Extended myositis screen and hypersensitivity precipitins and BNP	6-MWT, Resting SpO2, Nadir SpO2, Transthoracic echocardiogram, right heart catheterization
Kalluri et al. (25)	-Charlson Comorbidity Index -Pharmacotherapy (anti fibrotics, PPI, opioids, benzodiazepines)	No	Yes, FVC, DLCO	No	No	/
Kohashi et al. (26)	-History (smoke) - BMI	Yes at baseline	Yes, FVC, FEV1, FEV1/FVC, DLCO	No	BNP, LDH, KL-6, SP-D, ANA, RF, other autoantibodies	echocardiography
Kondoh et al. (27)	-History (smoke)	Yes at baseline	Yes, FVC, DLCO, FEV1/FVC repeated every year	Yes	No	BAL, PaO2
Levi et al. (28)	-History (smoke, family history of ILD, medications and environmental risk factors)	Yes at baseline	Yes, FVC%, DLCO%, and TLC%	Yes	Complete blood count, chemistry, renal and liver function tests, antinuclear antibody, rheumatoid factor (RF), C-reactive protein (CRP), anti-dsDNA, Scl70, anti-SSA, and anti-SSB were done. A cyclic citrullinated peptide (CCP) antibodies test was done in the case of a positive RF result, anti-Jo1, anti-RNP, anti-Smith, anticentromere, antimyeloperoxidase, antiproteinase−3, and anticardiolipin antibodies, erythrocyte sedimentation rate, various IgG subclasses including IgG4, and vitamin D (level)	Echocardiogram (Pulmonary hypertension, right heart failure), O2 saturation, Bronchoscopy (BAL only, TBB, Cryobiopsy, EBUS), 6-min walking distance (6MWD) test,
Lok (29)	-Evaluation of ongoing pharmacologic therapy	Yes at baseline	Yes, FEV1,FVC,TLC, DLCO	Yes	No	/
Chaudhuri et al. (30)	No	Yes at baseline	Yes, lung volumes, and DLCO	No	No	/
Nakamura et al. (31)	-Evaluation of Smoking index -GAP (Gender, Age, and Physiology) score	Yes, every 3–6 months	Yes, FVC, FEV1, DLCO, DLCO/VA every 3–6 months	Yes	Krebs von der Lungen-6, surfactant protein D, antinuclear antibody, auto-antibodies related to connective tissue diseases	Echocardiography

(Continued)

TABLE 3 | Continued

References	Clinical evaluation	HRCT	PFT	Lung biopsy	Laboratory test	Other
Newton et al. (32)	History (ethnicity, clinical manifestations: dyspnea, cough, smoking status) -Physical examination (crackles, clubbing)	Yes at baseline	Yes, FVC DLCO at baseline and during follow up without a established timing	No	No	/
Patterson et al. (3)	-History (race, smoking habits, clinical features of sarcoidosis, hypersensitivity pneumonitis, and CTD related ILD)	Yes at baseline	Yes, FVC, and DLCO at baseline and yearly	Yes	No	Walking distance, Hypoxemia
Pezzuto et al. (33)	No	Yes at baseline	Yes, at the time of evaluation FVC, TV, TLC, DLCO	Yes	For exclusion of CTD and vasculitis but not specified	BAL
Tanizawa et al. (34)	-History (ethnicity/race, smoking status, selected comorbidities) (asthma; congestive heart failure; gastroesophageal reflux; sleep apnea; diabetes), exposure history	Yes closed to biopsy. Categorized as definite UIP, possible UIP, or inconsistent with UIP pattern	Yes, close to biopsy FVC, FEV1, TLC, DLCO	Yes	No	MUC5B genotyping and telomere length measurement
Thomeer et al. (35)	No	Yes within 12 months before biopsy and during follow up	No	Yes	No	/
Tomassetti et al. (36)	-History: onset, symptoms, detailed history of exposure, family history, past medical history, and medications	Yes at baseline	Yes, at the time of evaluation FVC, RV, TLC, DLCO	No	Blood cell count, LDH, CRP, ESR, liver and kidney function profile, autoimmunity—ANA ENA ANCA	/
Tominaga et al. (37)	-History: onset, symptoms, detailed history of exposure, family history, past medical history, and medications	Yes, baseline	Yes VC, DLCO	Yes	Rheumatoid arthritis test, rheumatoid arthritis particle agglutination (RAPA) and ANA, serum biomarkers (Krebs von der Lungen-6 and surfactant protein-D)	/
Oltmanns et al. (38)	-History (comorbidities, smoking history)	Yes at baseline	/	Yes	Blood gas analysis, liver function test	/
Ussavarungsi et al. (39)	No	No	/	Yes	No	/
Walsh et al. (40)	-History (smoking habits, rheumatological disease, and rheumatological manifestation)	Yes at baseline	/	Yes	Autoantibodies	/
Yamauchi et al. (41)	-History (smoke)	Yes at baseline	/	No	KL-6, SP-D	/

CT, computer tomography; BMI, body mass index; FVC, forced vital capacity; DLCO, the ability to spread carbon monoxide; FEV1, forced expiratory volume in the 1st second; less frequently, TLC, total lung capacity; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide; ENA antibodies against extractable nuclear antigens; BAL, bronchoalveolar lavage; ASMA, antibodies against smooth muscle; ANCAs, anti-neutrophil cytoplasmic antibodies; CTD, connective tissue disease; SLB, surgical lung biopsy; 6mwt, six minute walking test; ILD-CTD, interstitial lung disease related to connective tissue disease; IPF, idiopathic pulmonary fibrosis; SpO2, saturation of peripheral oxygene; BNP, natriuretic peptide B; LDH, lactic dehydrogenase; KL-6, Krebs von den Lungen 6; SP-D, surfactant protein-D; NSIP, idiopathic non-specific interstitial pneumonia; IPAF, interstitial pneumonia with autoimmune features; TBB, transbronchial biopsy; Scl70, anti-topoisomerase1; EBUS, endobronchial ultrasound; PaO2, Partial Pressure of Oxygen in Arterial Blood; U-ILD, undifferentiated interstitial lung disease; BCF, bronchiolocentric fibrosis; MUC5B, mucin 5B; /, not reported.

Possible applications of MDD could encompass the management of ILD patients. In a study by Kalluri, subjects with ILD secondary to rheumatic diseases referred to the MDT (composed of pneumologist and rheumatologist), were compared with patients suffering from IPF followed according to a normal care setting. While the disease progression assessed through the worsening of the HRCT and PFT parameters was comparable, patients evaluated by MDD experienced greater satisfaction and more participation in their care path (22). A multidisciplinary approach in palliative care involving the participation of ILD experts, a palliative respiratory care expert, nurse, respiratory therapist, physiotherapist, and a dietitian, compared to the standard approach (namely ILD experts and a nurse) proved efficacy in improving the management of a small series of 32 patient, in terms of reduced number of emergency visits and hospital admissions (25).

There is little evidence concerning the role of MDT activity in the follow up. The diagnosis of ILD can change over time in light of new clinical or serological elements that may emerge in the course of the disease, as well as the progress and response to therapy. In a retrospective study of 56 patients evaluated during a 7-month average follow-up, it was shown how the re-evaluation of new clinical elements and a second HRCT by the pulmonologist and radiologist can modify the diagnosis of a first multidisciplinary discussion (10.7%), as well as the level of agreement (25% of cases). The multidisciplinary evaluation should therefore be a dynamic process not limited to the initial phase of the diagnostic process but also considered during the follow up (21). In a retrospective cohort study, 30 patients with a probable UIP pattern on HRCT and histology compatible or probable for UIP were identified by MDD. The evolution of the radiological data and the prognostic implications of patients who evolved radiologically were therefore evaluated against a specific HRCT pattern. In this case, the MDT and in particular the interaction between the radiologist and pathologist was fundamental to identify the target population of this study (41).

Role of Rheumatologist

The rheumatologist was included in MDT in 7 studies. The retrospective study by Chartrand highlighted the role of the rheumatologist in the MDT while evaluating patients with ILD. From the National Jewish Health Metical database, the authors identified patients initially referred as IPF. After the multidisciplinary evaluation, the diagnosis was modified in 33 patients in ASSD (27/33) or a myositis spectrum disease (6/33). In these patients the identification of specific myositis antibodies (in particular anti-synthetase) or myositis associated were fundamental. The authors underlined that about a third of the patients was ANA negative, and so the research of the autoimmune profile should be extended to these antibodies that often recognize cytoplasmic antigens. Moreover, in 85% of cases at least one manifestation attributable to CTD was present, such as Raynaud's phenomenon, mechanic's hand, Gottron's papules, capillaroscopic alterations. Among these, the muscular manifestations were present only in a third of patients (15). A retrospective observational study of 50 patients, the MDD led to a final diagnosis of CTD-ILD in 25 patients, IPF in 15 and other forms of ILD in 10. In particular, in 7 of the 25 patients with CTD-ILD the pre-MDD diagnosis was IPF with completely different prognostic and therapeutic implications. Therapy therefore changed in 20 of 25 patients with CTD-ILD and in 4 of 15 patients with IPF after MDT evaluation (16). In the study by Ferri et al., the MDD was performed by a rheumatologist and a pneumologist. Other professional figures such as the thoracic radiologist, surgeon and pathologist were considered only in selected cases. Given the type of setting, the authors described a more detailed clinical and laboratory assessment set with particular attention to the evaluation of autoimmune clinical manifestations and serological investigations. In the evaluation of the patient, specific instrumental investigations were also included, such as nailfold capillaroscopy, joint and salivary glands ultrasound, suggesting an application based on clinical suspicion (18). In a prospective study of 60 patients the role of the rheumatologist in the classification of patients with ILD at the onset is again emphasized. The diagnostic process was divided into three phases: a first phase in which the traditional MDT was involved, consisting of pulmonologist, radiologist and pathologist, and a second one where a rheumatologist evaluated the cases independently. In the course of traditional MDD clinical information, PFT, HRCT, biopsy, and BAL when available were evaluated. Serological investigations routinely performed included ANA, anti-dsDNA, anti-topoisomerase-1(Scl70), anti-SSA, and anti-SSB, ACPA (done in the case of a positive RF result). To these tests, the following could be added after the rheumatologic evaluation: anti-Jo1, anti-RNP, anti-Smith, anticentromere, ANCA, and anticardiolipin antibodies, various IgG subclasses including IgG4. Also anti-synthetase antibodies were tested if deemed necessary by the rheumatologist. Finally, there was a third phase of comparison between MDT and rheumatologist, in which some diagnoses formulated by the MDT were modified. In particular 21.9% of IPF cases and 28.5% of hypersensitivity pneumonia cases (HP) the diagnosis was modified in favor of pathologies of rheumatological interest such as Sjogren's syndrome, associated ANCA-associated vasculitis, RA, ASSD, SSc, and related IgG4 pathology. The authors also argued that the rheumatological evaluation could have avoided 7 bronchoscopies and 1 lung biopsy (28).

DISCUSSION

Before the publication of the 2002 ATS guidelines, the diagnosis of ILD was based on histopathology. However, the interobserver agreement between expert histopathologists was reported low, especially in the presence of non-specific interstitial pneumonia (NSIP) pattern (43). The level of diagnostic accuracy and interobserver agreement between radiologists was better than between pathologists, and HRCT is currently the most used diagnostic tool in the evaluation of patients with ILD, being less invasive than lung biopsy. Furthermore, different histopathological findings may be present in different lobes of the same patient. Already before the publication of ATS/ERS/JRS/ALAT guidelines, the importance of a multidisciplinary evaluation of IPF patients was proposed

(29). Current clinical practice guidelines suggest that in patients with suspected IPF a definite UIP pattern at HRCT could be considered a sufficient criterion for making the diagnosis. About half of the patients, however, presents a probable or inconsistent UIP pattern. In this group of patients the MDT is fundamental (44), especially for the identification of IPF which is the form of ILD with the worst prognosis with an average survival of 2–3 years from diagnosis. Given the current availability of effective anti-fibrotic drugs such as nintedanib and pirfenidone, a correct and early diagnosis of IPF is crucial (5).

SLB is generally considered in cases where imaging is inconsistent with UIP and in case of conflicting clinical data. Nevertheless, an UIP patter at histology is not necessarily indicative of IPF as demonstrated in the study by Tominaga, where the clinical information and HRCT images of 95 patients diagnosed as IPF and confirmed by a histological pattern compatible with UIP, were first re-evaluated separately and later on the course of MDD by a group of radiologists and pulmonologists. The two groups were progressively provided with more clinical data and radiological images. With the increase of clinical and radiological information, the degree of certainty in the diagnosis was reduced to a low or to an intermediate level in 41% of cases (37).

Multidisciplinary evaluation is essential in patients who do not have a definite UIP pattern at HRCT. Especially for probable UIP pattern, different studies have reported a variable frequency of IPF from 90 to 60%. Given the prognostic importance of a correct diagnosis, integration of imaging with clinical and histological data is fundamental, as demonstrated in a cohort of 179 patients with probable UIP pattern at HRCT in which the 50% of cases were diagnosed by MDD as IPF presenting worse prognosis compared to patients without IPF (27).

MDT classically include a pulmonologist, a radiologist and pathologist expert in ILD, but other professional figures including specialists in rheumatology, thoracic surgery, lung transplantation, and occupational medicine are often involved on demand (17). Despite the importance of MDD and available recommendations, there are no indications on the optimal composition of the MDT, on the timing or how to organize these meetings. Although in most cases the MDD aims to make an accurate diagnosis of ILD, the multidisciplinary approach can be used in patient care or for follow-up. Depending on the aims and degree of experience of the MDT itself, the organization may be different. For example, members of a recently established MDT could meet more frequently while in the case of clinicians with more experience in multidisciplinary discussion, the assessment could only be performed in selected cases. Depending on the purpose of the MDD, the members could be different, for example in the diagnostic evaluation the thoracic surgeon might not be useful (44).

Despite the recommendations and the available studies, it is currently not known whether the multidisciplinary approach is better than the single expert's clinical judgment in the diagnosis of patients with ILD. Moreover, the strict application of the guidelines for IPF is not always feasible; for example it is not always possible to perform SLB for safety reasons, and in the definition of the UIP pattern (both radiological and pathological) often the agreement between the observers is only moderate. Finally, the guidelines do not indicate how some clinical aspects, which may help to increase diagnostic confidence, should be included in MDD. This means that the multidisciplinary approach is not always applicable, and often the diagnosis is left to the opinion of the expert. The concept of "working diagnosis" recently proposed by the Fleischner Society allows to justify a disease-specific therapy despite a non-definite diagnosis (45). The lack of a standardized ontological framework can also determine heterogeneity in diagnosis for patients with ILD. Ryerson et al. made a proposal to standardize the terminology, by subdividing according to the degree of diagnostic confidence (> 90%, between 89 and 50% and <50%) the wording in the diagnosis of ILD in "confident," "provisional," and "unclassifiable ILD" (46). An international study involving 404 physicians that evaluated 60 cases of suspected IPF employed these standardized definitions to evaluate the impact of diagnostic likelihood on physician's decision to performed biopsy and on which treatment prescribe. This study showed that in presence of a provisional high confidence IPF diagnosis only a minority of patients (29.6%) would be addressed to SLB. Furthermore, most physicians prescribed anti-fibrotic therapy without performing histological evaluation in 63% of patients with a diagnostic likelihood of 70%, and in 63.0 and 41.5% of provisional high confidence and low confidence IPF diagnoses, respectively. The behavior of experts participating to this study was in most cases different from the guidelines; for instance, especially university hospital physicians tended not to require biopsy and to choose therapy according to a "working diagnosis" instead of a certain diagnosis as defined by the current guidelines. Therefore, the MDD would have a role in training physicians especially when they work in isolation (47).

The ATS guidelines emphasize the need to exclude the presence of a CTD during the evaluation of a patient with ILD. Despite this recommendation, rheumatologists are not considered mandatory among professional figures involved in the MDD, reserving the rheumatological evaluation only to patients with positive autoantibody serology, suspicious clinical manifestations for CTD and other rheumatological diseases, or in case with demographic characteristics atypical for IPF (e.g., female, age younger than 60 years, not smokers). The presence of a rheumatologist could therefore be fundamental in identifying specific non-pulmonary clinical manifestations that could not be easily recognized by traditional members of MDT, especially in patients with demographic, clinical and histopathological features inconsistent with IPF (15). For example, in female patients younger than 50 years, a diagnosis of IPF is unlikely compared to a male smoker over 60. Furthermore, some radiological patterns such as NSIP or organizing pneumonia (OP) are more characteristic of ILD associated with CTD. The presence of a definite UIP pattern, however, does not exclude the presence of an underlying autoimmune disease especially RA and some cases of SSc (48). Histological UIP pattern is indistinguishable between IPF and CTD-ILD, but some characteristics such as increased expression of lymphoid hyperplasia with germinal centers, more plasmatic infiltration, and less severe honeycombing are typical for CTD.

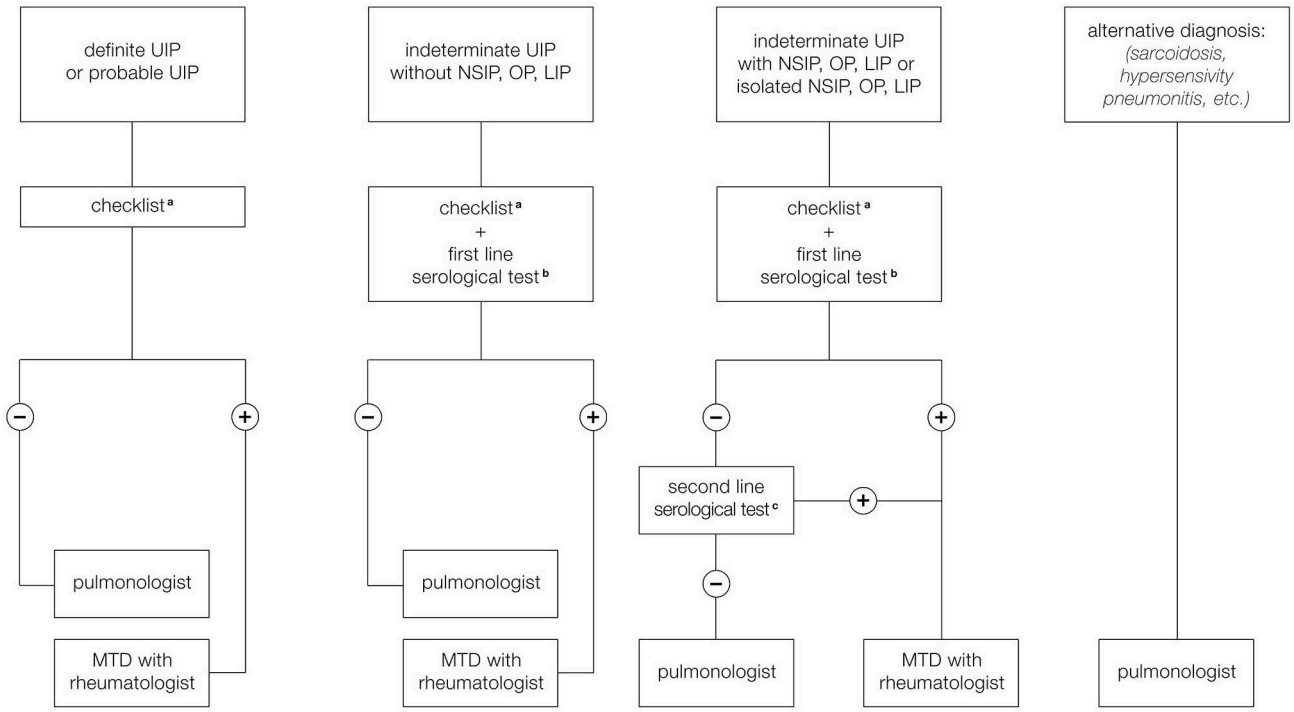

FIGURE 2 | Proposal for a multidisciplinary team (MDT) involving the rheumatologist. (a) Checklist regarding signs and symptoms compatible with CTD or arthritis. (b) First line serological test: RF, ACPA, ANA, CPK. (c) Second line serological test: Anti-ds DNA, Anti-Ro (SS-A), Anti-La (SS-B), Anti-ribonucleoprotein, Anti-topoisomerase (Scl-70) Anti-tRNA synthetase, Anti-PM-Scl, Anti-MDA5.

ILD can be a manifestation developed during an established CTD, so the diagnostic approach, therapy, and follow-up are better defined, and the rheumatologist is naturally involved in patient management. In other contexts, ILD may be the first manifestation at the onset of a not recognized CTD and the other typical clinical features may appear after the pulmonary involvement. This is known for example, especially in myositis spectrum disorders where in 10–30% of cases ILD may be the predominant manifestation (10), in particular in case of ASSD where the classical triad arthritis, myositis and ILD may develop during the follow up (49). The lack of specific classification criteria for ASSD makes the correct diagnosis for these patients more difficult, and an expert rheumatologist would be essential during the evaluation of these patients (12). Moreover, very few patients affected by SSc or RA may present as ILD at the onset, so in these cases the diagnostic process could be very challenging. In these pathological contexts the rheumatologist is crucial to identify the signs and symptoms more nuanced and less clear that cannot be recognized by other professional figures traditionally involved in the MDT.

The evaluation of the patient with ILD cannot be independent of the execution of blood tests, in particular autoimmunity, and different guidelines have proposed the execution of different biochemical test. The French guidelines recommends to evaluate complete blood cell count, CRP, serum creatinine, transaminases, γ-glutamyltransferase, and alkaline phosphatases, ANA, ACPA, and RF, reserving the search of other more specific antibodies (anti-SSA, anti-SSB, anti-centromeres, Scl70, anti-U3RNP, anti-synthetase antibodies, anti-thyroid antibodies) in case of positivity of first line antibodies or in presence of clinical manifestation compatible with CTD (50). The ATS/ERS/JRS/ALAT guideline recommends CRP, ESR, ANA (by immunofluorescence), RF, myositis panel and ACPA performing other test according to symptoms and signs (8). In the last few years, the diffusion of laboratory kits able to identify specific and associated myositis antibodies has made possible to reclassify patients with doubtful clinical pictures especially in the presence of negative ANA or with cytoplasmatic patterns. In particular antibodies such as MDA-5 and specific anti-synthetase antibodies such as PL2 and PL7 identify myositis with prevalent pulmonary expression that could be the first clinical manifestation up to 10–30% of cases of myositis spectrum disease (10).

The studies included in this review show that there is not a common behavior in serological evaluation, and only in 17 studies biochemical tests were evaluated during MDD. Fourteen studies reported the evaluation of autoantibodies without a clear suggestion of which test should be performed, and in 5 studies is not reported which serological test was chosen.

Another diagnostic challenge is represented by IPAF, a clinical entity of more recent characterization and of which classification criteria have been formulated (13). IPAF could be considered an ILD in which clinical or serological abnormalities typical of CTD are present but insufficient to satisfy classification criteria of a defined autoimmune disease. These classification criteria share

many characteristics with undifferentiated connective tissues and allow to identify as IPAF very different clinical entities including patients with very early SSc or other CTD such as myositis spectrum diseases with a predominant pulmonary manifestation at onset. This could result in a mis-classification of patients especially without a rheumatologic evaluation (51).

Despite these considerations, no clear indications are available about the rheumatologist involvement in MDT. Only 7/29 studies included in this review described a rheumatological evaluation during MDD paying attention to the correct re-classification of patients who were initially classified as IPF (15, 16), and to the possibility of avoiding not necessary diagnostic procedures (28). From the available studies it is not possible to identify a univocal attitude on the modalities and timing of involvement of the rheumatologist in such a context.

For these reasons we have formulated a proposal for the organization of the MDT that provides different scenarios to suggest when and how the rheumatologist should be included in MDD, especially to help to identify CTD-ILD and IPAF (**Figure 2**). A first scenario includes ILD patients with HRCT pattern typical for UIP which is less frequent in cases of ILD associated with autoimmune diseases and more typical of IPF. However, it is still possible that a UIP pattern could be found, even if less frequently, in course of rheumatological disorders, especially RA and SSc. We have therefore proposed that the pulmonologist participating to MDT should be trained to identify clinical manifestations compatible with CTD or RA belonging to the checklist reported in **Table 4**. This core set includes main signs and symptoms typical of rheumatologic diseases that can be more frequently complicated with ILD: SSc, RA, Sjogren syndrome, and myositis spectrum disorder. For joint involvement, we have decided to include patients presenting at least one swollen or tender joint on examination excluding distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal in agreement with the definition reported in 2010 classification criteria for RA (54). For myositis spectrum disorders we have included the search for weakness of proximal musculature of the upper and lower limbs and for the presence of typical cutaneous manifestations (Gottron's papules and sign) described in the classification criteria of 2017 for idiopathic inflammatory myopathies (53). To identify patients affected by ASSD, fever, mechanic's hands, Raynaud's phenomenon and dysphagia have been included in the checklist. In particular, the last two manifestations together with puffy fingers, sclerodactyly, and telangiectasias, belong to scleroderma spectrum manifestations and so they should be considered as part of the coreset of clinical manifestations to be evaluated during diagnostic approach of patients with ILD. Finally, the sicca syndrome has been described according to the 2002 classification criteria for Sjogren's syndrome as a sensation of daily dryness, ocular or oral duration longer than 3 months (52). In case of positivity of at least one of these clinical criteria, we have proposed to involve the rheumatologist for a second evaluation in order to confirm the first clinical impression and therefore to perform further instrumental examinations, such as biochemical tests (including autoantibodies), capillaroscopy or echography suggested by the rheumatologist based on his clinical suspicion, thus avoiding useless and expensive investigations. Furthermore, this approach makes it possible to identify IPAF. According to the ATS classification criteria, in fact, being absent the morphological domain [HRCT pattern compatible with NSIP, OP or LIP (lymphoid interstitial pneumonia)], both the serological and the clinical domain are required. Therefore, our checklist including all the manifestations present in the clinical domain of these criteria, allows to identify patients with suspected IPAF and to confirm the suspicion after performing serological investigations.

Another scenario includes ILD patients with probable UIP pattern, indeterminate UIP pattern on HRCT. In this case, patterns frequently observed during CTD as NSIP, OP,

TABLE 4 | Signs and symptoms to be assessed in the suspicion of a rheumatological disease.

Clinical manifestation of autoimmune disease	Description
Joint involvement	Any swollen or tender joint on examination excluding distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Synovitis could be confirmed by imaging (Definition according 2010 Rheumatoid Arthritis Classification Criteria)
Raynaud syndrome	A vascular disorder especially of the fingers and toes, that is characterized by pallor, cyanosis, and redness in succession usually upon exposure to cold
Puffy fingers or sclerodactyly	Swelling or thickening of fingers
Distal digital tip ulceration	Loss of epithelialization and tissues involving, in different degrees, the epidermis, the dermis, the subcutaneous tissue, and sometimes also involving the bone
Telangiectasia	Small dilated-blood vessels near the surface of the skin or mucous membranes, measuring between 0.5 and 1 ml in diameter, especially localized on finger or face
Mechanics hand	Rough, cracked, hyperkeratotic, aspect of palmar areas of the fingers with fissures of the skin
Sicca syndrome	Sensation of dryness of eyes and/or mouth daily and persistent for 3 months (52)
Gottron signs	Fixed rash or patches on the extensor surfaces of the joints (especially elbows and/or knees)
Gottron papules	Erythematous to violaceous papules and plaques over the extensor surfaces of the metacarpophalangeal and interphalangeal joints
Eliotrophic rash	Violaceous erythema of the upper eyelids often with associated edema and telangiectasia
Fever	Unexplained by other causes
Muscle weakness	Weakness of proximal upper and lower extremities as Distal muscles are less involved. Weakness of neck flexors is usually more severe than of neck extensors (53)
Dysphagia	Difficulty in swallowing

and LIP would be included so the probability to observe an ILD secondary to an autoimmune disease is greater than in case of typical UIP pattern. For this reason, we have added to the clinical domain a biochemical screening test including ANA, RF, ACPA, and creatine phosphokinase (CPK). In case of negativity of both clinical and serological domain, patients presenting NSIP, OP, or LIP pattern are subjected to further serological evaluation in order to exclude IPAF or myositis spectrum disorders, and evaluated by a rheumatologist. In case of positivity of at least one of clinical or serological parameters during the screening, patients would be referred to rheumatologist that would suggest to perform further instrumental investigations such as biochemical tests (including autoantibodies), capillaroscopy, or echography based on clinical suspicion in order to avoid unnecessary investigations and to accurately diagnose patients with CTD-ILD (**Figure 2**).

CONCLUSION

The role of the rheumatologist in MDD for the evaluation of patients with ILD is still not defined but could be fundamental for the correct diagnosis of CTD-ILD and IPAF. From the literature review, it emerges that in most cases the MDT is composed by the pulmonologist, radiologist and pathologist. The first being an essential member of the MDT, could be trained to be able to identify patients with suspected CTD-ILD and IPAF in order to select them for rheumatological evaluation. This organization could simplify the multidisciplinary meeting, reducing the times in which all professions are required for MDD. Our proposal for the organization of the MDT also provides a minimum core set of blood tests for screening, reserving the execution of second-level investigations only after a rheumatological indication and targeted according to the clinical suspicion, thus avoiding unnecessary and confounding tests.

AUTHOR CONTRIBUTIONS

FF and CS formulated the concept and design the paper. FF, GG, and AC performed SRL. FF wrote the manuscript. CS, GC, LC, and MG revised the manuscript critically, approved the final manuscript, and agreed to be accountable for all aspects of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficiency of Therapeutic Plasma-Exchange in Acute Interstitial Lung Disease, Associated With Polymyositis/Dermatomyositis Resistant to Glucocorticoids and Immunosuppressive Drugs: A Retrospective Study

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Interstitial lung disease (ILD) is a life-threating complication, commonly associated with polymyositis (PM), and dermatomyositis (DM). A subset of acute ILD associated with PM/DM patients are refractory to conventional treatment, and leads to a high rate of mortality. The efficacy of therapeutic plasma-exchange (TPE) as a PM/DM treatment to improve muscle involvement is controversial due to a lack of evidence. However, in recent reports, TPE has been effective in improving lung involvement. To evaluate the efficacy of this therapy, we retrospectively studied TPE treatment outcomes for in 18 acute PM/DM-ILD patients who were resistant to conventional therapies. Five patients were diagnosed with DM (27.8%), 11 with CADM (61.1%), and two with PM (11.1%). Among 18 patients, 11 (61.1%) achieved satisfactory improvement after four or more rounds of TPE, whereas seven died due to respiratory failure. We also analyzed risk factors to predict unresponsiveness to TPE in these patients. Notably, the prevalence of subcutaneous/mediastinal emphysema was significantly higher in the non-responsive group (6/7, 85.7%) than in the responsive group (2/11, 18.2%; $P = 0.013$); moreover, patients with this complication were mainly in the CADM subgroup (6/8, 75%). Subcutaneous/mediastinal emphysema and increased serum ferritin levels were shown to be poor prognostic factors, predictive of unresponsiveness to TPE, in PM/DM patients. No autoantibodies were found to be associated with TPE outcome, although we only investigated anti-Jo-1 and anti-Ro antibodies; the clinical significance of other myositis-specific autoantibodies, especially anti-melanoma differentiation-associated gene 5 (MDA5) antibody, is not known. Our results indicate that TPE might be an alternative treatment for acute PM/DM-ILD patients resistant to conventional therapies, except for those with subcutaneous/mediastinal emphysema and high serum ferritin levels.

Keywords: therapeutic plasma exchange, interstitial lung disease, dermatomyositis, polymyositis, efficiency

INTRODUCTION

Idiopathic inflammatory myopathy (IIM) is a group of heterogeneous inflammatory muscle disorders, which includes subacute, chronic, and acute IIM. IIM is characterized by low muscle strength and endurance, as well as inflammatory cell infiltration into the skeletal muscles (1). Based on distinct clinical features, IIM can be subdivided into dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). Clinically amyopathic dermatomyositis (CADM) is also defined in recent years and classified as a subgroup of DM. DM and PM are the most common forms of IIM and are also life-threating in rheumatic diseases. Besides the muscle and skin, other vital organs such as the lung and heart can also be involved in PM/DM, and complications in these organs contribute to the high rate of mortality associated with these conditions. Interstitial lung disease (ILD) is one of the most common and life-threating complications of PM/DM, with a prevalence up to 86% (2–6). The survival rate of patients with PM/DM-ILD is 56.7% during the first year, and even lower in those with acute ILD (7). Further, patients with rapidly progressive ILD are often resistant to high-dose glucocorticoids and immunosuppressive agents (8), thereby resulting in acute fatal respiratory failure with a 6-months survival rate of 40.8–45.0% (9, 10). The lack of effective treatment strategies for PM/DM-ILD patients who are resistant to glucocorticoids and immunosuppressive agents is the main contributor to high mortality rates.

Therapeutic plasma exchange (TPE) is a blood purification method that removes circulating cytokines, immune complexes, immunoglobulins, and complement components. Since the 1980s, it has been used to manage autoimmune diseases (11). However, the efficiency of TPE as a treatment for IIM remains controversial, due to a lack of evidence regarding its significant effects on improving muscle involvement (12–15). TPE is still not considered a standard treatment procedure for IIM. However, in recent years, it has shown promise. A patient with acute ILD associated with PM/DM was successfully treated and several case studies reported significant improvements in lung involvement after TPE treatment (16–20). Although evidence for TPE efficacy in PM/DM-ILD is limited, its potential as an effective treatment strategy for this disease is worth exploring, especially for patients who are resistant to glucocorticoids, and immunosuppressive agents. For a better understanding of the benefits of this treatment, we retrospectively studied the efficacy of this therapy based on 18 patients with acute PM/DM-ILD who were resistant to conventional therapies and specifically focused on the clinical characteristics of those who benefited from TPE.

METHODS

Subjects

In this study, patients who were diagnosed with PM/DM-ILD resistant to conventional therapies and treated with TPE from January 2011 to May 2018 at the First Affiliated Hospital of Xiamen University were included. The conventional therapies included glucocorticoids and immunosuppressive agents. A total of 18 patients met the following inclusion criteria: (1) patients admitted into the intensive care unit (ICU) for ILD aggravation after failure of intensive treatment; (2) patients treated with TPE for more than four rounds. Patients with malignancy-associated disease, inclusion body myositis, and overlapping cases were excluded. The diagnosis of PM/DM was based on the Bohan and Peter diagnostic criteria, and diagnosis of clinically amyopathic dermatomyositis (CADM) was based on the diagnostic criteria of the European Neuromuscular Center international workshop (21), and the diagnosis of CADM, as a subtype of DM characterized by typical skin manifestations with little or no myositis, was based on the diagnostic criteria of the European Neuromuscular Center international workshop (22). CADM included both amyopathic dermatomyositis and hypomyopathic dermatomyositis. Amyopathic dermatomyositis is characterized by heliotrope rash, Gottron's papules, or Gottron's sign, and with normal creatine kinase (CK) and muscle biopsy results and no muscle weakness. Hypomyopathic dermatomyositis bears similar characteristic skin findings mentioned with no clinical evidence of muscle disease but mild changes in CK, magnetic resonance imaging (MRI), EMG, or muscle biopsy. Patients classified as having premyopathic dermatomyositis for whom fatal ILD developed within the first 6 months of their disease course were also included as CADM. All patients underwent muscle biopsies in the quadriceps. A chest high-resolution computed tomography (HRCT) was performed on each patient. ILD was diagnosed using HRCT imaging with the following qualitative criteria: signs of ground glass opacities, reticular abnormalities, traction bronchiectasis, irregular linear opacities, subpleural curvilinear shadows, and honeycombing. This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University, in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from either the patient or their authorized relative.

Data Collection

The electronic medical record of each patient was retrospectively reviewed. The following data were collected: information of patients' characteristics, such as age, sex, and disease course of PM/DM; clinical symptoms including IIM-related and pulmonary symptoms; occurrence of subcutaneous/mediastinal emphysema; Acute Physiology and Chronic Health Evaluation (APACHE) II score (23) during the first 24 h after admission to the ICU; type of immunosuppressive therapy administered; use of ventilator assistance; laboratory findings.

TPE Procedures

TPE procedures were performed every day for 3 days, and every other day after that, using the AQUARIUS multifiltrate machine (Edwards Lifesciences AG, Irvine, CA, USA). Intravenous methylprednisolone (40–80 mg/days) and oral immunosuppressive agents were administered as a combined maintenance therapy. For vascular access, a double coaxial lumen 14-Fr catheter was inserted percutaneously, either through the right or left femoral vein, using the Seldinger technique. The blood flow rate was 80 mL/min for TPE. Plasma (40–60 mL plasma/kg) was exchanged for the same volume of normal fresh frozen plasma each time. The duration of TPE was 3–4 h. The

procedures were performed by trained nurses and supervised by senior physicians at the ICU. Treatment was suspended when a significant improvement in CT or death occurred.

Statistical Analysis

All statistical calculations were conducted using SPSS 23.0 software. Data are presented as the mean ± standard error of mean (SEM), or median (range) for continuous variables, and numbers (percentages) for qualitative variables. For comparisons between two groups, the chi-squared, or Fisher's exact tests were used for binary data and the Student's *t*- or Mann-Whitney *U*-tests were used for continuous data. Results of the logistic regression models are shown as the odds ratio (OR) and 95% confidence interval (CI). A $p < 0.05$ indicated statistical significance.

RESULTS

Efficacy of TPE for Acute PM/DM-ILD Patients Resistant to Conventional Therapies

This retrospective study included 18 patients who received TPE for the aggravation of ILD after treatment with a combination of high-dose glucocorticoids, cyclophosphamide, a calcineurin inhibitor, or intravenous immunoglobulin G. Five patients were diagnosed with DM (27.8%), 11 with CADM (61.1%), and two with PM (11.1%). The main respiratory symptom was dyspnea on exertion. Fine crackles were also observed in these patients. Although seven patients (38.9%) died from respiratory failure after TPE, the other 11 patients (61.1%) showed great improvement in lung involvement, reduced HRCT scores (24, 25), and their conditions were not life-threatening after treatment (**Figure 1**). These data suggested that TPE might be an alternative treatment strategy for acute PM/DM-ILD patients resistant to conventional therapies.

Clinical Characteristics of PM/DM-ILD Patients Responsive to TPE

We analyzed the characteristics and clinical profiles of the PM/DM-ILD patients whose conditions were improved by TPE. We divided PM/DM-ILD patients into responsive ($n = 11$) and non-responsive ($n = 7$) groups. Responsiveness was defined as improved or controlled lung involvement and rescue from life-threating complications, whereas non-responsiveness was defined as aggressive lung involvement and death. The clinical characteristics of the patients are summarized in **Table 1**.

No significant differences were observed between the responsive and non-responsive groups in terms of other clinical parameters such as age, types of IIM, and disease duration (**Table 1**). In the two groups, the most common IIM type was CADM (54.5 and 71.4%, respectively). Skin lesions were observed in nine cases in the responsive group (81.8%) and six in the non-responsive group (85.7%), including skin ulceration (three and three, respectively), palmar papules (four and three), oral erosions (one and zero), heliotrope rash (four and two), and Gottron papules (six and five). Skin ulceration, palmar papules, and oral erosions are unique cutaneous phenotypes associated with the anti-melanoma differentiation associated protein 5 (MDA5) antibody (26); regarding these rashes, there were no significant differences between the two groups.

Notably, six patients (five CADM and one DM) of seven patients in the non-responsive group suffered from mediastinal emphysema; only two (one CADM and one DM) of 11 patients in the responsive-group had this complication. Patients with SP were mainly in the CADM subgroup (6/8, 75%). Three cases in the non-responsive group had SP concomitant subcutaneous emphysema. The prevalence of subcutaneous/mediastinal emphysema was significantly higher in the non-responsive group (85.7%) than in the responsive group (18.2%), suggesting that subcutaneous/mediastinal emphysema might be a treatment response predictor for TPE.

Laboratory Characteristics of PM/DM-ILD Patients Responsive to TPE

Laboratory findings of PM/DM-ILD patients receiving TPE are shown in **Table 2**. Antinuclear antibodies (≥1: 100) were detected in three patients (16.7%). The myositis-specific autoantibody, anti-Jo-1, was present in only one patient (5.6%). Regarding myositis-associated autoantibodies, anti-SSA/Ro antibodies were identified in 12 patients (66.7%). In four patients (22.2%), no antibodies were detected. The CD4+/CD8+ T ratio was significantly higher in the responsive group than in the non-responsive group ($p = 0.049$), implying that TPE might have exerted little effects on PM/DM-ILD patients whose pathogeneses were mainly attributed to CD8+ T cells. Levels of C-reactive protein and serum ferritin were significantly lower in the responsive group than in the non-responsive group ($p = 0.031$ and $p = 0.002$, respectively). Besides the three mentioned parameters, no other significant differences between the groups were identified.

HRCT Findings in PM/DM-ILD Patients Responsive to TPE

HRCT imaging characteristics of all patients are shown in **Table 3**. Ground glass opacities, irregular linear opacities, and consolidation were the main image findings in these patients. No significant differences in HRCT features of PM/DM-ILD were observed between the responsive and non-responsive groups. The condition of most patients was too serious for them to undergo pulmonary function tests. **Figure 1** shows improvements in the CT scores of survivors before and after TPE treatment (2.414 ± 0.1379 and 1.073 ± 0.1236, respectively, $p < 0.0001$).

Risk Factors to Predict TPE Efficiency

We next evaluated the risk factors that could predict the unresponsiveness of PM/DM-ILD patients to TPE treatment. The results of univariate analysis revealed that four parameters, namely subcutaneous/mediastinal emphysema, CD4+/8+ ratio, and CRP and serum ferritin levels, were significantly different between the responsive and non-responsive groups. A multivariable logistic model was then established to predict the risk factors related to patient unresponsiveness to TPE

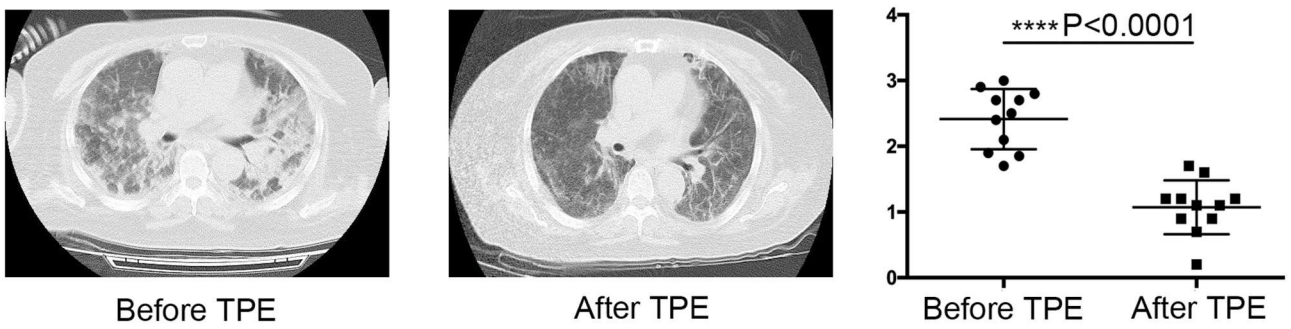

FIGURE 1 | Effect of therapeutic plasma exchange (TPE) on polymyositis (PM) and dermatomyositis interstitial lung disease (PM/DM-ILD) improvement. **(A)** Representative CT images of the lung before and after TPE. Lung CT scans of one patient before and after TPE. Interstitial opacities with multifocal ground glass opacities and consolidations (left panel). Follow-up CT scan indicating the frank regression of interstitial pneumonia (right panel). **(B)** CT score before and after TPE treatment in the responsive group ($n = 11$), $^{****}p < 0.0001$.

(**Table 4**). The results of logistic regression analyses showed that subcutaneous/mediastinal emphysema and serum ferritin levels were significantly associated with this in acute PM/DM-ILD patients who were resistant to conventional therapies. CRP levels and the CD4+/8+ ratio were found to be risk factors for death.

DISCUSSION

ILD is very common in PM/DM patients and can cause life-threatening complications even after standard treatments. A large proportion of patients with acute PM/DM-ILD show no response to conventional therapies including glucocorticoids and immunosuppressive agents, leading to uncontrolled and aggressive lung involvement and finally death due to respiratory failure. This is the first and largest retrospective study to analyze the efficacy of TPE therapy for acute PM/DM-ILD patients who were resistant to conventional therapies and to evaluate the risk factors that can predict unresponsiveness to this treatment. Our study showed that TPE might be an alternative treatment for acute PM/DM-ILD patients who are resistant to conventional therapies.

TPE was initially developed to treat liver failure and immune diseases. The use of TPE against PM/DM has been controversial for years. The American Society for Apheresis' indication category for TPE use in PM/DM was IV in the latest 2016 Therapeutic Apheresis guideline (27). To date, this recommendation is based on the results of a unique randomized controlled trial comprising 39 PM/DM patients by Miller et al. (12). In that study, there was no significant difference in final muscle strength or functional capacity following plasma exchange, leukapheresis, or sham apheresis. No concomitant immunosuppressants except glucocorticoids were administered to all patients. In 1981, Dau, in an uncontrolled trial, treated 35 inflammatory myopathy patients with TPE combined with immunosuppressants (cyclophosphamide or chlorambucil), and found improvement in muscle strength without significant side effects in 32 of them (13). Other retrospective multicenter studies have also demonstrated the efficiency of TPE in PM/DM. Herson examined 38 PM/DM patients who were treated with TPE as a rescue therapy when conventional treatment failed, and observed improvements in muscle strength in 24 (63%) patients (14). Cherin investigated 27 patients who suffered from severe pharyngeal muscle weakness and were resistant to conventional therapy; eight (30%) reported the disappearance of symptoms, whereas the other 19 (70%) reported the stabilization of dysphagia after receiving TPE (15). Some case reports have also showed that TPE in association with immunosuppressant agents could play a relevant role in severe pharyngo-esophageal muscle weakness (28).

The effects of TPE on acute respiratory failure during ILD have not been fully established. In 2015, Omotoso published a report in which TPE was found to be beneficial for the treatment of a patient with ILD-associated antisynthetase syndrome who was refractory to glucocorticoids and other immunosuppressive therapeutics (17). Bozkirli also reported a case of antisynthetase syndrome with ILD who benefited from double-filtration plasmapheresis (16). The therapeutic effects of TPE also include the removal of pathological substances from the blood, such as autoantibodies, cytokines, complement components, and paraproteins. Further, other possible mechanisms include alterations to lymphocyte proliferation, the immune system, and cell sensitivity to immunosuppressants or chemotherapeutic agents (29–31). Although more data are necessary, TPE might be an immediate treatment option for acute PM/DM-ILD patients who are resistant to conventional therapies. Moreover, because TPE substitutes fresh frozen plasma components such as anti-idiotypic antibodies and immunoglobulins, which target host antigens, this therapy might provide additional therapeutic benefits (29). Clearly, TPE is only a short-term solution, because immune cells that secrete antibodies, complement components, and cytokines will continue to function in response to repeated antigenic stimulation after TPE. Moreover, the transient effects of TPE require additional long-term immunosuppression treatment. Another disadvantage of this therapy is risks associated with the use of blood products, including sexually transmitted diseases. Despite these drawbacks,

TABLE 1 | Comparison of clinical characteristics between PM/DM-ILD patients who were responsive and non-responsive to TPE.

Variables	Responsive group ($n = 11$)	Non-responsive group ($n = 7$)	*P*-value
Sex, male/female, *n* (%)	3/8 (27.3/72.7)	3/4 (42.9/57.1)	0.627
Age, years, mean ± SEM	55.70 ± 11.08	52.71 ± 11.46	0.540
DISEASE DURATION, WEEKS, MEDIAN (RANGE)			
at ILD diagnosis	3.0 (1–4)	3.2 (1.57–5.71)	0.328
at PM/DM/CADM diagnosis	13 (2.43–96)	6.86 (4–528)	0.536
IIM TYPE, *n* (%)			
PM/DM	2/3 (18.2/27.3)	0/2 (0/28.6)	0.952
CADM	6 (54.5)	5 (71.4)	0.637
CLINICAL SYMPTOM, *n* (%)			
Arthritis/arthralgia	4 (36.4)	1 (14.3)	0.596
Skin rash	9 (81.8)	6 (85.7)	1.000
Fever	3 (27.3)	2 (28.6)	1.000
Cough	4 (36.4)	3 (42.9)	1.000
Dyspnea on exertion	9 (81.8)	6 (85.7)	1.000
Dysphagia	3 (27.3)	1 (14.3)	1.000
Muscle weakness/myalgia	5 (45.5)	1 (14.3)	0.316
Subcutaneous/mediastinal emphysema *n* (%)	2 (18.2)*	6 (85.7)	0.013
APACHE II Score, median (range)	17 (11–24)	18.5 (15–31)	0.126
P/F ratio	218.8 ± 13.38	173.3 ± 21.38	0.074
THERAPY, *n* (%)			
High-dose steroids	11 (100)	7 (100)	NA
Cyclosporine A	8 (72.7)	5 (71.4)	1.000
Cyclophosphamide	6 (54.5)	2 (28.6)	0.367
Intravenous immunoglobulin G	6 (54.5)	5 (71.4)	0.637
Hydroxychloroquine	1 (9.1)	1 (14.3)	1.000
Methotrexate	1 (9.1)	0	0.611
Thalidomide	2 (18.2)	0	0.137
Total dosage of MP before TPE, mg (mean ± SEM)	460.9 ± 49.88	341.4 ± 61.81	0.153
Duration of MP use before TPE, days (mean ± SEM)	6.6 ± 0.3	6.4 ± 0.4	0.676
PLASMA EXCHANGE			
Times, median (range)	5 (4–24)	6 (4–10)	0.724
Plasma amount, mL, median (range)	3,000 (2,500–3,000)	3,000 (2,500–3,000)	0.724
Use of ventilator, *n* (%)	4 (36.4)	6 (85.7)	0.066

*ILD, Interstitial lung disease; PM, polymyositis; DM, dermatomyositis; CADM, clinically amyopathic dermatomyositis; IIM, idiopathic inflammatory myopathy; SEM, standard error of mean; TPE, therapeutic plasma-exchange; APACHE II, Acute Physiology and Chronic Health Evaluation; MP, methylprednisolone; P/F, arterial partial pressure of oxygen /fraction of inspired oxygen. *$p < 0.05$.*

no plasma-related adverse events were observed in patients after short-term treatment in the current study.

In the present study, a multivariable logistic model showed that subcutaneous/mediastinal emphysema and serum ferritin levels were significantly associated with unresponsiveness to TPE. A previous study showed that serum ferritin level is the most significant prognostic factor for PM/DM (32). Moreover, serum ferritin was found to predict the disease severity and prognosis for anti-MDA5 antibody-associated ILD with DM; a serum ferritin concentration cut-off value of 1,600 μg/L was suggested to be the best indicator of survival in this subgroup (33). In the present study, the average ferritin level in the unresponsiveness group was 1518.6 μg/L, almost equal to that value. However, the lack of an anti-MDA5 antibody test did not allow us to conclude whether patients in the unresponsiveness group had anti-MDA5 antibody-associated ILD. In addition, PM/DM-ILD patients with hyperferritinemia might be unresponsive to TPE when resistant to conventional therapies.

Subcutaneous/mediastinal emphysema was found to be another potential prognostic factor associated with TPE outcome in our study. DM/PM patients are mostly predisposed to develop spontaneous pneumomediastinum with a prevalence ranging from 2.2 to 8.6% (10, 34–36). Spontaneous pneumomediastinum can be fatal if unrecognized and can lead to death within 2 months in approximately 25% of patients (34, 35); further, it is more prevalent in patients with CADM (34). In this retrospective study, six patients with spontaneous pneumomediastinum (6/8, 75%) were diagnosed with CADM. CADM patients should be carefully screened for spontaneous pneumomediastinum since the latter is a prognostic factor. A previous study also

TABLE 2 | Comparison of laboratory characteristics between responsive and non-responsive groups of PM/DM-ILD patients.

Clinical parameters	Responsive group ($n = 11$)	Non-responsive group ($n = 7$)	P-value
Lymphocytes, $\times 10^9$/L, median (range)	0.69 (0.38–9.50)	0.60 (0.12–1.16)	0.285
CD4+/8+ T ratio, mean ± SEM	2.01 ± 0.58*	1.29 ± 0.87	0.049
Platelet count, $\times 10^9$/L, mean ± SEM	224.819 ± 85.427	203.571 ± 91.874	0.894
Erythrocyte sedimentation rate, mm/h, median (range)	29 (2–105)	30 (1–64)	0.660
C-reactive protein, mg/L, mean ± SEM	6.506 ± 5.056*	15.281 ± 8.170	0.031
Serum ferritin, μg/L, median (range)	414.6 (78.1–3659.4)*	1518.6 (984.2–3819.2)	0.002
IL-6, pg/mL, median (range)	3.58 (0.07–35.50)	19.77 (5.99–832)	0.247
Procalcitonin (PCT), ng/mL, median (range)	0.710 (0.037–0.655)	0.125 (0.036–7.520)	0.151
Serum albumin (ALB), mg/L, mean ± SEM	31.960 ± 3.289	32.486 ± 3.023	0.204
Alanine aminotransferase (ALT), IU/L, median (range)	99 (20–142)	60 (26–439)	0.659
Aspartate aminotransferase (AST), IU/L, median (range)	64 (20–100.5)	60 (24–467)	0.860
Creatine kinase, IU/L, median (range)	80 (10–3,794)	83 (46–770)	0.930
Lactate dehydrogenase (LDH), IU/L, median (range)	412 (58–1,337)	491 (312–2,032)	0.375
Creatine, IU/L, mean ± SEM	54.82 ± 21.10	107.14 ± 128.4	0.325
Positive antinuclear antibody, *n* (%)	3(27.3)	0	0.245
Positive anti-Jo-1 antibody, *n* (%)	1(9.1)	0	0.611
Anti-SSA antibody, positivity, *n* (%)	7 (63.5)	5 (71.4)	1.000
Anti Ro-52 antibody, *n* (%)	7 (63.5)	4 (57.1)	1.000
Immunoglobulin A, mg/dL, median (range)	1.78 (1.39–3.55)	1.91 (0.72–3.65)	1.000
Immunoglobulin M, mg/dL, median (range)	1.45 (0.765–2.05)	1.100 (0.245–8.900)	0.425
Immunoglobulin G, mg/dL, mean ± SEM	14.84 ± 5.97	8.75 ± 6.15	0.894

$p < 0.05$. SEM, standard error of mean; ILD, interstitial lung disease; PM, polymyositis; DM, dermatomyositis.

TABLE 3 | Comparison of HRCT findings between responsive and non-responsive groups of PM/DM-ILD patients.

CT findings	Responsive group ($n = 11$)	Non-responsive group ($n = 7$)	*P*-value
Consolidation, *n* (%)	9 (81.8)	6 (85.7)	1.000
Ground glass opacities, *n* (%)	5 (45.5)	5 (71.4)	0.367
Irregular linear opacities, *n* (%)	8 (72.7)	5 (71.4)	1.000
Traction bronchiectasis, *n* (%)	0	2 (28.6)	0.137
Honeycombing, *n* (%)	1 (9.1)	1 (14.3)	1.000
Subpleural curvilinear shadows, *n* (%)	0	1 (14.3)	0.389

ILD, interstitial lung disease; PM, polymyositis; DM, dermatomyositis; HRCT, high-resolution computed tomography.

TABLE 4 | Adjusted odds ratios (ORs) with associated 95% confidence interval (95%CI) for death.

Variables	Death		
	OR	95%CI	*P*-value
CD4+/8+ T cell ratio	0.188	0.030–1.164	0.072
C-reactive protein (mg/L)	1.351	0.972–1.878	0.073
Subcutaneous/mediastinal emphysema	15.185	1.233–186.983	0.034*
Serum ferritin (μg/L)†	5.683	1.110–29.101	0.037*

$p < 0.05$. Model was adjusted for sex and age.
†OR and 95% CI are expressed by standard deviation increases in serum ferritin.

demonstrated that anti-MDA5 antibodies are associated with spontaneous pneumomediastinum (35). Spontaneous pneumomediastinum increases the risk of death in DM patients with anti-MDA5 antibody-associated ILD (37). These findings again indicate that anti-MDA5 antibodies might be associated with TPE outcome. However, anti-MDA5 and other myositis-specific autoantibodies were not investigated in the present study. In the responsive group, two patients suffered from spontaneous pneumomediastinum and one patient died due to respiratory failure several months after discharge from the hospital. Taken together, these results suggest that spontaneous pneumomediastinum is a poor prognostic factor for TPE and that patients who suffer from this could comprise a population that should be excluded from TPE treatment.

There are some limitations to the present retrospective study. The high cost of TPE imposed restrictions on its application, thus limiting the size of our patient sample size. Further, the lack of data on most myositis-specific antibodies, and especially anti-MDA5 antibody testing, in these patients did not allow us to conclude whether the anti-MDA5 antibody was a predictive factor of TPE outcome. It was reported that forced vital capacity is a poor predictive factor for survival with ILD (38). In this retrospective study, pulmonary function tests including carbon monoxide-diffusing capacity were unavailable due to the patients' severe disease states. Moreover, measurements of Krebs von den Lungen-6 levels were not performed; therefore, the severity of

ILD could not be assessed. Those limitations resulted in these important parameters being excluded from predictive evaluation.

In conclusion, this retrospective study shows promise regarding the use of TPE in addition to glucocorticoids and immunosuppressants for early-stage PM/DM-ILD. Further, subcutaneous/mediastinal emphysema and serum ferritin levels might serve as poor prognostic factors of responsiveness to TPE. More controlled trials and long-term observations are required in the future.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Ethics Committee of the First Affiliated Hospital of Xiamen University with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

YN, SC, and GS conceived and designed this study. YN and YL were responsible for the integrity of the study, interpretation of data, and drafting of the manuscript. YN, GY, and YS participated in medical record collection. All authors reviewed and approved the manuscript for submission.

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REVIEW
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Inflammatory Myopathy-Related Interstitial Lung Disease: From Pathophysiology to Treatment

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Inflammatory myopathies (IM) are auto-immune connective tissue diseases characterized by muscle involvement and by extramuscular manifestations. As such, pulmonary manifestations, which mainly include interstitial lung disease (ILD), often darken two out of four distinct IM, namely dermatomyositis and overlapping myositis. Being the initiation site of the disease and being the leading cause of morbidity and mortality, ILD is of major importance in this context. ILD has a heterogeneous expression among the patients, with various onset mode, various radiological pattern, various severity and finally with different prognoses, which are particularly difficult to predict at the time of IM diagnosis. Therefore, ILD is a challenging issue. Treatments are based on steroids and immunosuppressive or targeted therapies. Their respective place is yet poorly codified however and remains often based on clinician expertise. Dedicated clinical trials are lacking to date and are also difficult to build, due to difficulty of constituting large and homogeneous patient groups and to rigorously evaluate disease outcomes. Indeed, pulmonary function tests alone are being regularly defeated in IM, in which respiratory muscles are often involved. Composite scores, bringing together several lung parameters, should thus be developed and validated in the future, to better assess the disease response to treatment. This review aims to describe the current knowledge of IM immuno-pathogenesis, the clinical features associated with IM related-ILD, focusing of both severity and prognosis, and the actual therapeutic approaches.

Keywords: inflammatory myopathy, myositis, interstitial lung disease, auto-immunity, antisynthetase, anti-MDA-5 autoantibody

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INTRODUCTION

Interstitial lung disease (ILD) and inflammatory myopathy (IM) are intimately (1). Diagnosing ILD in patients with IM is associated with worse morbidity and higher mortality than in patients without and therefore conditions the strength of the treatments (2).

In contrast, diagnosing autoimmune features in patients with ILD is of importance, as it confers a better prognosis than idiopathic forms: ILD with autoimmune features but without classification criteria for connective tissue diseases (CTD) as well as connective tissue disease (CTD)-related ILD have a better prognosis than idiopathic ILD (3–5).

The description of IMs has largely evolved over the past decades (6, 7). Based on clinical, immunological and histological features, five groups can be distinguished to date (**Figure 1**): (i) overlap myositis, which is the most common (ii) dermatomyositis, which often associates a specific skin involvement, (iii) immune mediated necrotizing myopathy (iv) sporadic inclusion body myositis and (v) polymyositis (8–11). These three latter are most of the time restricted to the muscles. The occurrence of ILD is more strongly associated with two out of five IM subtypes (**Figure 1**). As such, ILD commonly occurs in overlap myositis, among which the anti-synthetase syndrome (aSyS) is the most frequent and can be individualized in many ways (10–14). Other overlap disorders, with myositis-associated autoantibodies (anti-PM-Scl, anti-RNP, anti-Ku etc.) also belongs to this IM subgroup. It is considered that ¾ of the patients with aSyS present with an ILD, whereas this proportion is nearly 1/3 for the other overlap disorders (**Table 1**). Importantly, ILD may be associated with some phenotype of DM, especially the hypo- or amyopathic forms that are associated with anti-MDA-5 (melanoma differentiation-associated protein 5) auto-antibodies, in which its prevalence reaches up to 90% (15, 24, 25) especially in Asian populations. In association with anti-MDA-5, two distinct types of ILD may be distinguished: the rapidly progressive ILD *vs.* the chronic ILD. In all other cases, ILD occurs more seldom (<10% of the cases) and is most of the time non-severe (26–30).

However, classifying the patients as IM-related ILD is still difficult do date. Indeed, the EULAR-ACR classification criteria for adult and juvenile IM has just been validated, but has many limitations (8, 31, 32). Hence, these classification criteria do not take into account lung involvement and many myositis specific antibodies (MSA). Some patients could thus be misclassified, especially those that are hypo- or amyopathic. Hence, some could classify the patients with ILD, MSA and an hypo- or amyopathic disease as interstitial pneumonia with auto-immune features (IPAF) (33). Obviously, IPAF must not yet be considered as a diagnosis at all, and IPAF classification criteria remain controversial and need to be better defined (34). For instance, some series reported MSA in more than 30% of patients with ILD (35). It is however worth noting that considering IM-related-ILD diagnosis is in fact very important to drive pulmonary and extra-pulmonary management of the patients. Indeed, IM-related ILD has a heterogeneous spectrum, regarding the clinical and radiological features. In the absence of robust markers, prognosis is difficult to predict at diagnosis. Treatments are not standardized, as they have not yet been evaluated rigorously.

By focusing on the two main entities, aSyS and anti-MDA-5 dermatomyositis, the purpose of this review is to describe their immunopathogenesis, the means of assessing ILD activity and progression, as well as severity and prognosis, in order to provide insight into current and future treatments.

IMMUNOPATHOGENESIS

Autoimmune diseases are multifactorial diseases, tolerance breakdown being the results of various genetic susceptibilities, endocrinal and environmental factors that affect both the innate and adaptive immune system. As one of the largest areas of exchange of the individual with the elements of the environment,

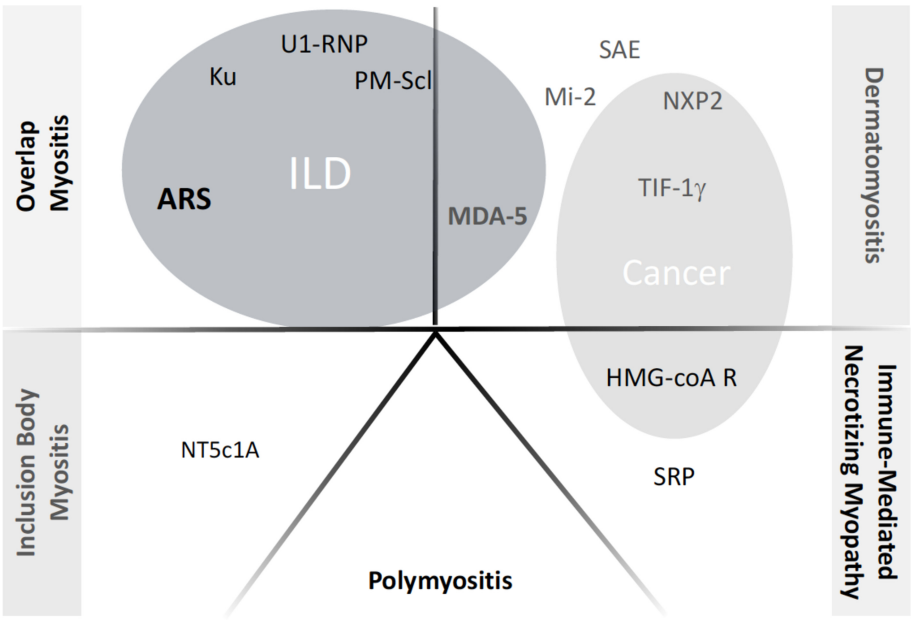

FIGURE 1 | Current classification of inflammatory myopathies and the respective autoantibodies. ILD, Interstitial Lung Disease; ARS, anti-tRNA-antisynthetase autoantidodies, including anti-Jo-1, PL7, PL12, OJ, EJ, Zo, KS, YRS. NXP2: example of myositis specific autoantibody or myositis associated autoantibody; when appearing inside gray circles, the autoantibodies have been shown to correlate with occurrence of either ILD or Cancer, respectively.

TABLE 1 | Prevalence of ILD in the context of Inflammatory-myopathy.

Diseases	Autoantibodies	Prevalence of the ILD	References
	Myositis-specific autoantibodies		
Dermatomyositis	MDA-5	90%	(15–17)
Antisynthetase syndrome	All ARS	80%	(18, 19)
	Jo-1	70%	
	Non-Jo-1	85%	
	Myositis-associated autoantibodies		
Overlap myositis	RNP	50%	(20)
	PM-Scl	25%	(21, 22)
	Ku	35%	(23)

ARS, anti-ARNt synthetase auto-antibodies; ILD, Interstitial Lung Disease.

some hypothesize that the lungs could be the initiation site of different IMs.

MDA-5 is a protein which functions as an intracellular pattern recognition receptor, recognizing double-strand RNA as danger signals. Upon activation, MDA-5 drives the production of large amounts of type I interferons (36). Anti-MDA-5 dermatomyositis is indeed associated with large amounts of type I interferons and mimics some monogenic interferonopathies (37, 38). However, the reasons leading to type I interferon pathway activation remains unknown to date and anti-MDA-5 autoantibodies have not been demonstrated as being pathogenic. Very little is known regarding the causes and consequences of such direct activation on lung parenchyma and on innate and adaptative immunity, but different data argue for the involvement of macrophages, as it has been reported in various autoimmune diseases (39). These cells may play important roles in immune-regulation and tissue-repair. As such, recent data have revealed that non-inflammatory macrophages (previously called M2 macrophages, which produce IL-10 and TGFβ) are involved in the progression of lung fibrosis (40, 41). Interestingly, soluble macrophage-mannose receptor, sCD206, a serum marker for M2 polarization, is increased in MDA-5 DM-associated ILD and its titer correlated with a poor outcome (42). Interleukin(IL)-18 (43), a potent macrophage activating molecule could be involved in the development of ILD. In addition, several macrophage activation markers, including ferritin (44), NOS2 or neopterin are increased in the patients with anti-MDA-5 dermatomyositis.

ASyS is a heterogeneous disease, immunologically characterized by MSA directed against different ARNt-synthetases, among which anti-hystidyl-tRNA-synthetase (also called anti-Jo-1) is the most common (18, 45). To date, seven auto-antibodies directed against other tRNAsynthetases, including anti-Alanyl (PL-12), anti Threonyl (PL-7), anti-Glycyl (EJ) -t-RNA-synthetases have been described. Although dark areas persist, the immunopathogenesis of Jo-1 positive aSyS is best described and could nowadays be drawn as follows: following environmental exposure to tabacco smoke (46), airborne contaminants (47) including mineral particles (such as asbestiform amphiboles) or respiratory tract infections (48), the lung tissue is aggressed. This leads to cellular stress, danger signal pathway activation and cell death with microparticle release. Innate immune cells–such as NK cells- are unspecifically activated and release proteolytic enzymes, including Granzyme B (49). The antigen, Histidyl-tRNA-synthetase, which is expressed into a specific conformation within the lungs, is then released in the extracellular milieu and has many immune properties, including activity in inflammatory response with its cytokine like domains, chemoattractant properties with $CCR5^+$ cell recruitment and capacity to activate other immune cells (50, 51). All the immune cells are present within the lungs of patients with aSyS (52). Tolerance breakdown may occur when the different adaptive immune cells are successively activated. The cascade of events is efficiently favored by a certain genetic background, like HLA-B*08.01 (53), and includes antigen presentation, CD8-T cell priming and CD4-T cell-B-cell crosstalk. As a witness of these processes, type I/II interferons, B lymphocyte stimulator and other cytokines are increased in the sera of aSyS patients. Finally, anti-Histidyl-tRNA-synthetase autoantibodies are produced. The way the disease propagates to other organs remains largely unexplained: although histydyl-tRNA-synthetase could be abnormally expressed in various tissues, the pathogenicity of anti-Jo-1 is still matter of controversies and the presence of Jo-1 specific T cells within extra-pulmonary target tissues has to be further determined.

INITIAL EVALUATION

Clinical Evaluation of the ILD

Patients with IM-related ILD may present with clinical symptoms, including fever (1/4), cough (1/3) or dyspnea (>1/2), which could be either related to ILD or not, especially when gastro-esophageal reflux or respiratory muscle involvement also occurs as part of the aSyS (18, 19). Regarding the shortness of breath, it is immediately important to evaluate (i) the rapidity of onset, as the (sub)acute forms settling within 3 months –defining rapidly-progressive (RP)-ILD are of worse prognosis (54, 55) and (ii) the severity, as some patients require intensive care support (56). In contrast, the patients with mild ILD or in which ILD will develop later in the follow-up (1/5) can be asymptomatic, justifying careful explorations.

Explorations of the ILD

The severity of ILD can also be assessed by oximetry and blood gases to evaluate hypoxemia and/or hypercapnia.

CT-Scan is the major tool of the evaluation (**Figure 2**), revealing different types of lesions and helping in classifying ILD into different patterns, as defined by the ATS/ERS consensus for idiopathic interstitial pneumonias (**Table 2**) (61). As such, bi-basal ground glass opacities and linear reticulations are associated with non-specific interstitial pneumonia (NSIP) and are the most common, as found in other connective tissue disorders like systemic sclerosis. Alveolar condensations -willingly bilateral- also occur, especially in the RP-ILD subset and define organizing

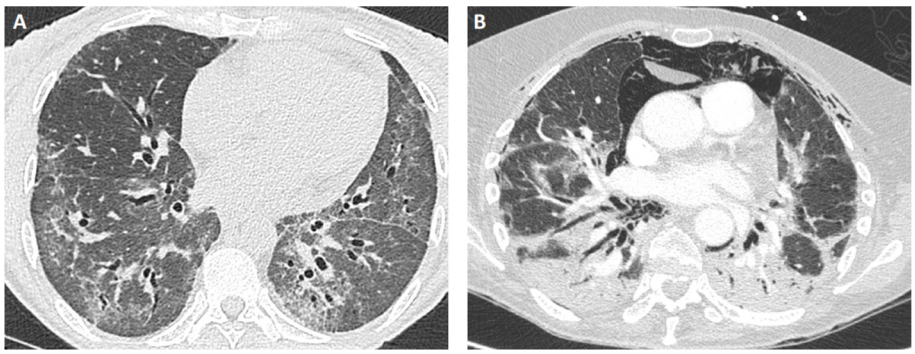

FIGURE 2 | Examples of lung CT findings in patients with IM-related ILD. **(A)** NSIP pattern in a patient with PL12+ antisynthetase syndrome: ground glass opacities with bilateral proximal bronchiectasis. **(B)** OP pattern in a patient with MDA5+ dermatomyositis: extensive parenchymal consolidation and pneumomediastinum.

pneumonia (OP). Both patterns may also mix together (NSIP-OP). Usual interstitial pneumonia (UIP), with sub-pleural honey combing lesions, is less frequent and dramatically more seldom in IM-related ILD than in rheumatoid arthritis-related ILD. In the worse cases with acute lung injury, often leading to acute respiratory distress syndrome (ARDS), CT-scan may show features of acute interstitial pneumonia with consolidations and extensive ground glass opacities.

CT-scan is also important to evaluate (i) the presence of fibrosing lesions, including traction bronchiectasis and reticulations, which are present at first evaluation in high proportion (57, 62), and (ii) the extension of the lesions (63) -usually bilateral and starting in posterior and basal regions- within all the lung parenchyma.

The distribution of these patterns partially depends on the IM subtype, NSIP predominating in aSyS and OP in MDA-5-dermatomyositis (**Table 2**) (58).

At diagnosis (as well as in any case of worsening during follow-up), endoscopy and broncho-alveolar lavage (BAL) could be discussed. It might help in distinguishing specific deterioration from intercurrent factors that may have caused respiratory decline, including aspiration pneumonia in newly diagnosed patients, or opportunistic infections, which occur mostly in patients under immunosuppressive therapy. In addition, rare cases of bronchiolo-alveolar cancer can be thus detected. BAL fluid discloses aspecific alveolitis with high counts of lymphocytes, neutrophils, eosinophils or with mixed cellularity.

Lung histology is no longer recommended due to the low benefit/risk ratio of the biopsy procedure, and ILD subtype could be almost easily determined on CT-scan rather than on histological features.

When possible, pulmonary function tests help in evaluating ILD severity, as well as detecting a possible respiratory muscle involvement. Restrictive syndrome, defined by a total lung capacity (TLC) <80% with a more or less severe decrease of forced vital capacity (FVC), is almost constantly observed. Severity of restriction may be appreciated by TLC impairment on plethysmography. However, the FVC impairment is more routinely followed as it is more easily measured on spirometry. Muscle impairment and especially diaphragmatic involvement may worsen this parameter and is suggested when FVC is dramatically lower than expected as compared to CT-scan lesions or when decubitus FVC is significantly lower than conventional FVC. Diffusing capacity of the lung for carbon monoxide (DLCO) impairment often precede TLC and FVC decrease. DLCO is also useful to evaluate the ILD severity at any time of the disease course and/or to suspect pulmonary hypertension when excessively reduced in comparison to FVC deterioration. In this context, the screening for pulmonary hypertension by trans-thoracic echocardiography is recommended (64).

Exploring diaphragmatic involvement might be useful. Measurement of maximal static inspiratory pressure (PI max)

TABLE 2 | ILD-patterns on lung CT-scan: lesion types and prevalence in IM-related ILD.

ILD pattern		Predominant lesions on CT-scan	Prevalence in ASyS	Prevalence in MDA5*
Non-Specific Interstitial Pneumonia	NSIP	Basal ground glass opacities, linear reticulations	50%	20%
Organizing Pneumonia	OP	Alveolar consolidations	20%	50%**
	NSIP-OP	Associations of NSIP & OP lesions	25%	30%
Usual Interstitial Pneumonia	UIP	Basal subpleural reticulations with bronchectasis and honeycombing lesions	10%	<5%
Acute Interstitial Pneumonia	AIP	Consolidations and extensive ground-glass opacities	<5%	30%**
Other associated anomalies				
Signs of Fibrosis		Reticulations, Traction Bronchectasis	>75%	40%
Non-significant adenopathies			30%	30%

**To be confirmed in larger series, ** OP and AIP are often difficult to distinguish. Adapted from (56–60).*

and of maximal static expiratory pressure (PE max) are low invasive parameters that could be combined with radioscopic assessment of diaphragmatic course and electromyography of the diaphragm to explore significant diaphragmatic dysfunction (65, 66).

Six-minutes walk test (6MWT) may be useful to estimate ILD severity in the absence of significant muscle involvement. Dyspnea, nadir of oxygen saturation and walking distance are the main parameters evaluated during the test.

FVC, DLCO and in a lesser extend 6MWT are therefore main physiologic parameters for assessing respiratory severity at diagnosis and also to evaluate response to therapy during the disease course.

Extra-Pulmonary Evaluation

Besides pulmonary evaluation, muscle, skin, heart, joint, and vessel involvement must be carefully assessed. Above all, severe myositis with dysphagia and respiratory muscle involvement may complicate the management of ILD and biased the ILD evaluation.

A particular attention should be paid for skin manifestations, as ulcerations are found especially in MDA-5+ dermatomyositis (16).

In all patients with newly identified ILD, the last ATS/ERS/ALAT/JRS recommendations indicated an overwhelming agreement to perform serological testing to achieve a diagnosis rigorously. The majority of panelists acknowledged routine testing for C-reactive protein, antinuclear antibodies, myositis linear-dot panel or immunoprecipitation, as well as rheumatoid factor and anti–cyclic citrullinated peptide for Rheumatoid arthritis (67). Other detailed tests, such as creatine kinase, have to be performed on a case-by-case basis according to the associated clinical signs.

EVOLUTION

Short-Term Prognosis

Three factors, that are linked together, could be identified as short-term prognosis factors: (i) the severity of the ILD itself, (ii) the rapidity of onset (RP-ILD) (54, 55) and (iii) the presence of anti-MDA-5 auto-antibodies (15). Even in the absence of any comparative study, it is admitted that the most severe patients with either aSyS or anti-MDA-5 dermatomyositis, notably those requiring intensive care, are of worse prognosis. In these patients, the severity is evaluated clinically or with the CT-scan (showing extended OP or acute interstitial pneumonia lesions), but rarely with the pulmonary function tests, often impossible to perform. In intensive care unit, the mortality ratio reaches 50% (56). Most of the severe patients presented a RP-ILD, which is itself associated with a high mortality risk ratio, as compared to patients with chronic onset of ILD, both during aSyS and anti-MDA-5 dermatomyositis. When comparing patients according to the nature of the myositis specific autoantibodies, it has been clearly shown that the presence of MDA-5 autoantibodies is by itself a risk factor of early mortality, as compared to anti-ARNt-synthetases (15).

Long-Term Prognosis

General Outcome

Despite early mortality in the severe forms, the 5-year survival ratio is >85% in IM-ILD (18, 19, 59). Although some patients could worsen during the first year of treatment, the time to disease progression usually counts in years (57, 58). As examples, in long-term follow-up series, 20% of the patients with IM-related ILD (not including patients with anti-MDA-5) worsen despite immunosuppressive treatments, with the risk of developing respiratory failure. The remaining patients being stable (35–55%) or improved (25–45%) (59, 68, 69). It is thus important to find factors predictive of ILD progression over time, especially during the first months of treatment. However, the heterogeneity of IM-related ILD makes assessment of prognosis particularly difficult, not allowing us to clearly stratify the patient and adjust the treatment to the potential of aggravation. Such attitude is still a real challenge and should be the subject of future studies.

Evaluations

The severity of the ILD on pulmonary functions tests is probably not sufficient to predict long-term evolution. Some retrospective studies suggested a correlation between the PFTs at onset (such as low DLCO or FVC) and the long-term ILD prognosis (59, 70). However, in a prospective cohort, the first value of either FVC or DLCO did not correlate with improvement or worsening over time (71). This was at least partly due to the existence of respiratory muscle involvement, which is a confusing factor to interpret FVC as a marker of lung involvement only. It could be thus more relevant to evaluate the kinetic of FVC variations between two early time points, as a predictive factor of long-term response to treatment. However, such option has not been validated prospectively in large cohorts.

It has been demonstrated in studies dedicated to IPF, that serial decline in the FVC over 6–12 months is a powerful predictor of mortality (72). An absolute change in the FVC of 10% of the predicted normal value is a predictor of mortality but this large amplitude of change is less prevalent than relative change in a given time period, which has been shown to be also predictive of mortality in the majority of IPF studies. More recently, Goh et al. (73) have examined correlations between short-term pulmonary function trends and long-term outcome in ILD associated with systemic sclerosis, which is very close to chronical forms of IM-related ILD. Disease severity at baseline and subsequent pulmonary function trends were independent prognostic determinants. At 1 year, categorical FVC trends provide the most accurate prognostic information, especially when integrated with DLCO trends. Thus, the optimal definition of categorical decline in FVC for trial purposes may consist of either a $\geq$10% decline in the FVC or a 5–9% marginal decline in the FVC in association with a $\geq$15% decline in the DLCO for systemic sclerosis. However, such studies are lacking in IM-related ILD (74).

Thus, as suggested by these studies, it would be probably more accurate in IM-related ILD also to at least consider these parameters as qualitative variable, taking into account the proportion of patients improving/worsening FVC and/or DLCO for at least 10 and 15%, respectively.

Furthermore, defining time to ILD progression or event-free survival could be relevant and should be rigorously evaluated in the future as end-points. Composite scores including dyspnea score, muscle and physiologic parameters would probably be of great interest for evaluating disease progression and treatment response in IM-related ILD. Defining and validating such scores will be a challenge in the future.

Valuable information coming from CT-scan analyses is also insufficiently robust to date. Regarding the ILD radiologic pattern, some suggested UIP was worse than NSIP, especially in terms of disease progression (68). Although histology of UIP is more frequent than expected in the autopsy series, the corresponding radiologic pattern has however a better prognosis than IPF (75). A recent large study showed that the UIP pattern on lung-CT-scan is significantly associated with mortality. As opposed to acute interstitial pneumonia, the OP pattern was associated with the lowest mortality on long-term follow-up (76). No study has demonstrated yet a worse prognosis according to either fibrosing scores and/or extension scores assessed on CT-scan in IM-related ILD, as it has been for example reported in systemic sclerosis (63). At least, anti-rheumatic drug modifications (DMARDs) overtime correlated with the initial extension of the ILD within the lung parenchyma (60).

Different biomarkers could correlate with ILD prognosis. However, further studies are required to validate on a large scale the promising interest of KL-6 (77), Ferritin (44), C-RP or IL-18 serum dosage (43) alone or mixed together, to perform them routinely and stratify the patient with IM-related ILD early, according to their potential prognosis value. In ASyS patients, it has been shown that patients with non-Jo-1 had a worse prognosis in terms of mortality as compared to Jo-1 patients (18, 19). Although not rigorously demonstrated, these data could be at least due to higher proportions of hypo- or amyopathic patients in the non-Jo1 group, in which the ILD could therefore be more severe upon diagnosis. The concomitant positivity of anti-Ro 52 kilo-daltons, which is quite common in IM and especially in ASyS (78) might worsens the ILD prognosis (79). Using unsupervised analyses, three distinct subgroups with different prognoses can be observed on a large French multicentric cohort of MDA-5 dermatomyositis (Allenbach et al. unpublished data). The first cluster with severe lung involvement and a dramatically poor prognosis corresponded to the well-recognized "anti-MDA5+ RP-ILD." In addition, two other overlapping forms were isolated: the "anti-MDA5+ arthro-DM," with a good prognosis, and the "anti-MDA5+ vasculo-DM," with an intermediate prognosis. The decisional algorithm showed that only three variables (Raynaud phenomenon, arthralgia/arthritis and gender) are good predictors for cluster appurtenance and their related outcome.

ILD Complications

Besides progression of fibrosing ILD, aspiration or opportunistic pneumonia, IM-related ILD has two major complications.

Although rare (<8% of the cases) and often associated with pneumothorax, pneumomediastinum is non-fortuitously associated with IM-related ILD, as it occurs more commonly than in other connective tissue-related ILD (80). Association with MDA-5 auto-antibodies, long suspected from various reports (81–83) has been rigorously demonstrated only recently (84). Pneumomediastinum is an aggravating factor, that usually occurs early (<24 months) in the course of the disease. Its underlying mechanism remains unknown to date.

Pulmonary hypertension is the second feared ILD complication. In contrast to pneumomediastinum, pulmonary hypertension occurs lately in the course of ILD and witnesses its severity. Indeed, during aSyS and conversely to other connective tissue diseases, pulmonary hypertension belongs to group III only and is diagnosed in almost 8% of the cases (64). However, in the severe forms, a contribution of a vascular component is not excluded. Even though there is no recommendation for pulmonary hypertension specific treatments in this context, its screening with repeated echocardiography is recommended. When necessary, right heart catheterization will confirm the diagnosis. In a French series, patients with pulmonary hypertension had a significantly lower survival rate.

Thus, finding efficient prognosis factors (or prognosis scores pooling the different parameters), correlating with long-term disease severity is of major importance, and should be the prospect of future studies. Indeed, the development of patient stratification according to the risk of progression, in order to manage therapeutic strategies for each patient. Such personalized medicine remains a challenge in the field of IM-related ILD.

TREATMENTS

Adjuvant Therapies

Besides different possibilities of medical treatment, patients with IM-related ILD must benefit from the update of the vaccines, like annual vaccination against flu, anti- pneumococcal vaccination. Such attitude is indeed justified by a recent study showing that antibody response rates in the connective tissue-related ILD patients (including those receiving immunosuppressants) were comparable with those of a control group without ILD (85). In addition, no acute exacerbation was observed after pneumococcal immunization, indicating pneumococcal vaccines in ILD patients are efficient and safe (85).

Occurrence of opportunistic infections in IM-related ILD is significant and could be at least associated with the disease itself and its treatments (86). Thus, preventive treatment of *pneumocystis jirovecii* with trimethoprime + sulfamethoxazole or in case of contraindication with atovaquone, should be prescribed as soon as patients received steroids >20 mg/d during >4 weeks and especially for the most severe patients (87).

Pulmonary rehabilitation as well as muscle physiotherapy may also be beneficial (88). Since nutrition-related factors have been noticed as a prognostic factor for patients with chronic respiratory diseases, including patients with ILD, particular attention should also be paid to this aspect of the patients' care (89). When clearly implicated and if possible, exposure to cigarette smoke and other airborne contaminants should be avoided.

All patients should benefit from this personalized treatment approach. Therapeutic education programs should address symptom management, oxygen therapy and medications. Patients emphasized the importance of understanding what the

future might hold and were generally supportive of discussing advance care planning and end-of-life care.

Steroids and Classical Immunosuppressive Drugs

In the absence of randomized clinical trials, treatments of IM-related LD are based on small retrospective studies. Treatment efficacy is difficult to evaluate in this context and requires sufficiently long evaluation period. In most of the studies, the outcome measures are improvement of pulmonary function tests between two time points (FVC and/or DCLO being considered as quantitative variables). However, FVC also depends on respiratory muscle involvement and make respiratory evaluations difficult when the IM is severe.

Even though we noticed the absence of dedicated trial, treatment of IM-related ILD is based on steroids. Intravenous high doses are initially given in the most severe forms or RP-ILD.

Addition of an immunosuppressive drug as a first line treatment progressively became consensual, being now a cornerstone of the treatment, as ¾ of the patients could develop steroid resistance or relapse when tapering the doses (90), irrespectively of the initial severity. As such, cyclophosphamide and tacrolimus have been reported in retrospective studies to improve FVC and/or DLCO in almost all patients (91–93). Although less commonly reported, azathioprine and methotrexate could also be efficient (94, 95). Interestingly, tacrolimus and mycophenolate mophetil have shown interest in reducing steroid doses. Recently, one study has compared aztioprine vs. mycophenolate mophetil: both improved PFTs in similar proportions (96). Azathioprine allowed a greater decrease in the dose of steroids as compared to mycophenolate mophetil, while being associated with more side effects. Among these immunosupressants, intravenous cyclophosphamide, mycophenolate mofetil, and azathioprine have been reported to be efficient in similar proportions (97).

Some reports emphasize the interest of immunosuppressive treatment associations (98), especially when ILD is severe. However, such attitude exposes the patients to higher infectious risks.

IM-related ILD is a chronical disease and requires prolonged treatment duration, often exceeding several years. There is however no clear information to date regarding the most appropriate time and modalities to stop the treatments.

Single case reports indicated some benefit from plasma exchange for IM associated severe ILD, especially those with anti-MDA-5 autoantibodies, but no conclusion could be drawn to date. While some reported its use as an initial treatment in severe ASyS patients (99), no data support the long-term efficacy of intravenous immunoglobulin treatment for ILD in the context of IM.

Biologics

Over the past decades, the relative place of biologics to treat IM-related ILD has increased a lot. Among them, the anti-CD20 targeting B-cell therapy has become the most documented. In one of the few prospective studies, 50% of refractory AsyS patients receiving rituximab as a third line therapy improved their FVC at 1 year (100). Several retrospective studies (101–103) and a meta-analysis (104) reported promising results of rituximab on pulmonary function tests. On the other hand, efficacy of rituximab based on the improvement of CT-score was less clear. However, the cost in terms of risk of infections, with sometimes fatal complications, is high (101). In these retrospective series, rituximab was most of the time used as at least a second line treatment and there was no comparison with other treatments. Thus, the place of anti-CD20 monoclonal antibodies in the therapeutic arsenal needs further clarifications, which will emerge from prospective trials currently in progress.

Other targeted therapies have been tried in severe RP-ILD associated with anti-MDA5 dermatomyositis. On the faith of a small case series of four patients, basiliximab, a monoclonal antibody targeting CD25+ activated T cells, could improve patients' survival (105). Similarly, JAK-inhibitors (in this case tofacitinib), which blocks interferon pathways and other pro-inflammatory cytokine pathways, has shown a promising survival rate improvement (17, 106).

Of note, anti-TNFα targeting therapies are usually not recommended in the context of IM (107), partly due to the occurrence of muscular aggravations under treatment.

Future Directions

Depending on a better understanding of the immune mechanisms leading to ASyS and MDA-5 dermatomyositis, new immune-based therapeutic strategies could emerge in the future. As such, different existing biologics could find a place to treat IM-related ILD, including anti-IL12/23, anti-IFNα and anti-IFNα receptors antibodies, anti-IL-6 or other anti-B cell therapy like ibrutinib etc. However, the rational to use these treatments lack translational data to date showing a clear involvement of these pathways in ILD pathogenesis. New directions could also be developed in the future according to these immunological researches and help in developing new treatments. As examples, blocking pattern recognition receptor-dependent immune cell activation or macrophage activation pathways, which seems specifically involved in ILD associated with MDA-5 positivity might become real and might open a new era in the future. Future immunotherapies have to integrate innovative approaches based on selective and oriented immunomodulations as well as on concomitant therapies promoting tissue repair. Anti-fibrotic agents could be a new treatment option: (i) fibrotic mechanisms are at work in the lung of patients with IM-related ILD, (ii) the recent results obtained in patients treated with nintedanib for systemic sclerosis-related ILD, another connective tissue disease associated with fibrosing ILD, are promising (108). Although such clinical trials required a large number of patients to be informative, efforts should be done to define eligible patients and to build international and randomized prospective trials, at least in ASyS-related ILD.

Lung Transplantation

Few cases of lung transplantation have been reported in patients with IM-related ILD (109). Of note, comorbidities as well

as immune fragility of the patients, related to the previous immunosuppressive treatment they received, negatively impact the prognosis of the procedure. In addition, involvement of respiratory muscles, especially in ASyS, and/or skin vascular sequelae in MDA-5 positive patients are probably factors of transplantation failure. However, in patients carefully selected the reported risk of IM-related ILD recurrence is not higher than that of other connective tissue disorders, including systemic sclerosis, and a 5-year survival rate of 75% has been described in a small case series (110). Thus, lung transplantation is possible in IM-related ILD and its prognosis factors for success should be more largely studied worldwide. Extracorporeal membrane oxygenation (ECMO) may be interesting as a bridge to lung transplantation in selected patients already considered as candidates for lung transplantation. Thus, referring severe patients to transplantation centers early in the course of the disease is important.

CONCLUSION

Although the knowledge of IM-related ILD has tremendously progressed over the past decades, its management remains a challenge to date. Based on basic and clinical research, the future objectives will need to focus on the IM-related ILD definition of classification criteria, the development of reliable disease activity and progression scores that can be used as robust end-point for the future clinical trials and the finding of early prognosis biomarkers. The aims will be to adapt therapeutic strategies to individual risk factors (patients' stratification) and to find new efficient immune-based biologics as well as to prospectively study the relevance of innovative anti-fibrotic agents.

AUTHOR CONTRIBUTIONS

BH and YU wrote the manuscript and built the tables and figures, which are original.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Acute Exacerbation of Interstitial Lung Disease in Adult Patients With Idiopathic Inflammatory Myopathies: A Retrospective Case-Control Study

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Objective: This study aimed at clarifying the prevalence, risk factors, outcome, and outcome-related factors of acute exacerbation of interstitial lung disease (AE-ILD) in patients with idiopathic inflammatory myopathy (IIM).

Methods: Data of IIM patients who were admitted to the First Affiliated Hospital of Zhejiang University (FAHZJU) from September 2007 to September 2019 were retrospectively collected. And the IIM patients with AE-ILD formed the case group. In addition, age and sex matched IIM patients without AE-ILD were randomly selected to constitute the control group. A 1:2 case-control study and intragroup analysis were performed to identify risk factors for development of AE-ILD in IIM patients and unfavorable short-term outcome in AE-ILD patients through comparison, univariate and multivariate logistic regression analysis.

Results: AE-ILD occurred in 64 out of 665 IIM patients (9.6%) with a short-term mortality rate of 39.1%. And the 64 IIM patients with AE-ILD formed the case group. Besides, 128 age and sex matched IIM patients without AE-ILD were randomly selected to constitute the control group. The retrospective case-control study revealed that elevated on-admission disease activity ($P < 0.001$), lower percent-predicted diffusing capacity of the lung for carbon monoxide (DLCO%, $P = 0.013$) and diagnosis of clinically amyopathic dermatomyositis (CADM, $P = 0.007$) were risk factors for development of AE-ILD in IIM patients. The following intragroup analysis indicated that elevated on-admission disease activity ($P = 0.008$) and bacterial infection ($P = 0.003$) were significantly correlated with the unfavorable short-term outcome of patients complicated with AE-ILD. In addition, combined use of steroid and disease modifying antirheumatic drugs (DMARDs, $P = 0.006$) was found to significantly reduce the short-term mortality in IIM patients with AE-ILD.

Conclusion: AE-ILD is a less frequent but fatal complication in IIM patients with elevated on-admission disease activity, lower DLCO% and diagnosis of CADM working as risk factors, indicating the potential roles of autoimmune abnormality and hypoxia in development of AE-ILD. Elevated on-admission disease activity and bacterial infection could predict unfavorable short-term outcome of IIM patients with AE-ILD. A therapeutic regimen of steroid and DMARDs was found to reduce short-term death in these patients.

Keywords: interstitial lung disease, dermatomyositis, polymyositis, complication, outcome

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INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a group of autoimmune diseases that primarily target the skeleton muscles (1, 2). Dermatomyositis (DM) and polymyositis (PM) are two conventional subtypes of IIM, while clinically amyopathic dermatomyositis (CADM) is a newly recognized subset of DM with typical skin rash of DM and slight muscular damage. Although the incidence of DM, PM, and CADM was considerably low in common people, the high mortality rate, the various clinical manifestations, and multiple complications have drawn much attention from clinicians and researchers. In published studies, the 10-year survival rate for patients with DM, PM, or CADM ranged from 51 to 91% (3). An ∼4.5% in-hospital mortality rate was seen in two retrospective studies (3, 4).

Multiple organs apart from muscle are often affected as well, leading to critical worsening of the life quality and outcome of these patients (5). Among the multiple extramuscular complications of IIM, interstitial lung disease (ILD) was identified as both the most frequent and severe involvement, leading to a significant elevation in mortality rate (6). Moreover, acute exacerbation of ILD (AE-ILD), which used to be mainly studied in patients with idiopathic pulmonary fibrosis, has also been noticed in patients with connective tissue disease (CTD). In CTD patients, AE-ILD was reported to occur at a 1-year frequency of 1.25–3.3%, at a lifetime incidence of 7.2% in CTD patients, and contributed to a high mortality rate within these patients (7, 8). In the past few years, there existed a few reports and small-sample studies of AE-ILD, or rapid progression of ILD, in IIM patients. However, systemic understandings including the incidence of AE-ILD, its risk factors and outcome in IIM patients remained unclear. It is thus necessary to uncover the enigma by figuring out factors correlated with AE-ILD in patients with DM, PM, or CADM, and factors associated with outcome of patients with AE-ILD.

In this study, we retrospectively reviewed the medical records of 424 patients with DM, PM, and CADM who were admitted to our center from February 2011 to February 2019, and performed a case-control analysis to identify potential related risk factors for AE-ILD among these patients. Besides, factors affecting the short-term outcome of patients with AE-ILD were as well-probed into via subgroup analysis.

MATERIALS AND METHODS

Patients

Medical records of adult patients who were admitted to the inpatient department of the Qingchun division of the First Affiliated Hospital of Zhejiang University (FAHZJU) with the diagnosis of DM, PM, or CADM from September 2007 to September 2019 was reviewed and collected. The approval (Reference Number: 2019-646) of the Institutional Review Board (IRB) of the FAHZJU was acquired before the initiation of the study, and written informed consent from each patient involved was acquired as well. The inclusion criteria of this study were: (1) age over 18 years old; (2) the diagnosis of DM or PM fulfilled the diagnostic criteria of Bohan and Peter (9), and the diagnosis of CADM met the criteria developed by Sontheimer (10). Exclusion criteria were: (1) overlap syndromes with other connective tissue diseases; (2) hospitalization for causes unrelated to myositis and its complications, such as fracture, pregnancy, cataract, and appendicitis etc.; (3) myopathies that might be related to thyroid dysfunction, excessive exercises, inherited, or metabolic disorders, recent use of muscle-impairment drugs including statins, chloroquine, colchicine, entecavir, traditional Chinese medicine, etc.; (4) loss to follow-up within 2 weeks after discharge.

Methods

Medical records of all patients enrolled were retrospectively collected by reviewing the electronic medical record (EMR) system. Data including demographic information, course of disease, duration of diagnosis delay, clinical manifestations, or complications, on-admission disease activity, results of pulmonary function test, preceding comorbidities, harmful hobbies, imaging reports, laboratory findings, medications, as well as short-term outcome were acquired and analyzed. ILD, subtype of ILD and AE-ILD were evaluated by radiologists using high-resolution computed tomography (HRCT). In absence of diagnostic criteria dedicated to AE-ILD in patients with CTD, an updated criteria of acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) was adopted based on the experience of published studies on AE-ILD in CTD patients. The updated criteria included previous or concurrent diagnosis of ILD, acute worsening or development of dyspnea typically <1 month duration, computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia (UIP) pattern, and deterioration not fully explained by cardiac failure or fluid overload (11). Compared with the previous diagnostic criteria for AE-ILD proposed in 2007 (12), the new criteria does not demand thorough exclusion of infection. And infection has been found to participate in the pathogenesis and progression of idiopathic pulmonary fibrosis (IPF) (13). As previously suggested, the occurrence of this clinical and radiological manifestation in a background of possible or inconsistent with UIP pattern was also considered diagnostic for AE in CTD patients (14, 15). Cases manifested as UIP pattern were identified based on their radiologic appearance on HRCT: the presence of basal-dominant reticular opacities and predominantly basal and subpleural distribution of honeycomb lesions, with multiple equal-sized cystic lesions of 2–10 mm diameter with a thick wall (16). Diagnosis of bacterial, fungal, or tuberculosis infection was a comprehensive decision based on the essential positive result of etiological detection, HRCT manifestation, clinical symptoms, infection-related laboratory abnormalities, treatment of intravenous antibiotics, and antifungal drugs, positive response after treatment, etc. The etiological detection was defined as the culture of bronchoalveolar lavage fluid (BALF) and sputum. Sputum culture result counted only if >25 squamous epithelial cells per low-power field were observed (17). In bacterial infections, the thresholds for positivity of quantitative cultures were applied: 10^5 cfu/ml for sputum culture (17), 10^4 cfu/mL for bronchoalveolar lavage (18). For patients with

infection of *Candida albican* or *Candida glabrata*, the BALF or sputum culture should show a visually medium to large amount of *C. albicans* or *C. glabrata* in the sample. The repeated cultures of BALF or sputum were routinely initiated before intravenous use of antibiotics or anti-fungal medications. Meanwhile diagnosis of virus infection, to be specific, Epstein-Barr virus (EBV) or Cytomegalo virus (CMV) infection, relied on the screening of serum antibody and DNA of these two viruses. Identification of gastrointestinal hemorrhage was based on repeated positive results of fecal occult blood test. To minimize omission of lymphadenectasis, hepatomegaly, and splenomegaly, the identification was based on records of physical examination together with reports of ultrasound examination, computed tomography and positron emission tomography. On-admission disease activity was routinely assessed by the Myositis Disease Activity Assessment Visual Analog Scales (MYOACT) within the first week of admission (19). Immunosuppressive regimens used during hospitalization were categorized into four groups: (1) steroid monotherapy; (2) steroid + disease-modifying antirheumatic drugs (DMARDs); (3) steroid + intravenous immunoglobulin (IVIG); (4) steroid + DMARDs +IVIG. In this study, usage of DMARDs included usage of mycophenolate mofetil (MMF), thalidomide, hydroxychloroquine, cyclosporine, azathioprine, methotrexate, cyclophosphamide, etc. Short-term mortality, or unfavorable short-term outcome, referred to in-hospital mortality or death within 2 weeks of hospital discharge.

To probe into factors exerting significant influence on development of AE-ILD within patients with DM, PM, or CADM, a case-control study was performed. Patients diagnosed with AE-ILD constituted the case group. And ILD patients without AE-ILD were selected using a systematic sampling method by matching age and sex with cases with AE-ILD at a proportion of 1:2. Comparisons, univariate and multivariate logistic regression analysis were performed between the case group and the control group. To clarify the time axis of risk factors and results, only clinical manifestations or complications that happened before the diagnosis of AE-ILD would be taken into account for patients with AE-ILD. In order to identity potential factors affecting the short-term outcome of the AE-ILD patients involved, the AE-ILD patients were further divided into two groups: patients who died in hospital or within 2 weeks of hospital discharge were defined as the mortality group, and those who survived after 2 weeks of hospital discharge were categorized as the survival group. Comparisons and logistic regression analysis were made between the two groups of patients regarding age, sex, clinical features, disease activity, laboratory findings, etc.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (Chicago, IL, USA) and R 3.6.1. The normality of continuous variables was tested by the Kolmogorov-Smirnov goodness-of-fit model. Continuous variables were expressed as mean ± SD if normally distributed and median (quartiles) if skewed. Ordinal categorical variables were as well shown as median (quartiles). Unordered categorical variables were presented as numbers and percentages. Independent sample *t*-test was used to compare normally distributed continuous variables. And Mann-Whitney *U*-test was applied to compare skewed continuous variables or ordinal categorical variables. Chi-square test and Fisher's exact test were used to compare unordered categorical variables. All tests were two-sided and a $P < 0.05$ was considered statistically significant. Univariate and multivariate logistic regression analyses were subsequently adopted to identify risk factors for AE-ILD in patients with PM, DM or CADM as well as risk factors for unfavorable short-term outcome in AE-ILD. In the study of risk factors for AE-ILD, explanatory factors with $P < 0.1$ in the univariate logistic regression analysis were entered into the multivariate logistic regression analysis. In the process of figuring out risk factors for unfavorable short-term outcome, however, factors with $P < 0.05$ in univariate analysis were enrolled into the multivariate logistic regression analysis owing to the limited number of AE-ILD patients. For normally distributed continuous variables with missing values, inputation using expectation maximization (EM) algorithm was performed for those that passed univariate screening. Multivariate logistic regression analysis with a stepwise forward likelihood ratio (LR) method was used to determine the statistically significant factors. Results from the multivariate logistic regression were presented as an odds ratio (OR) with 95% confidence interval (CI). A two-sided $P < 0.05$ was considered to be statistically significant. If there existed any positive result in serum biomarkers or disease activity in multivariate logistic regression analysis, a receiver operating characteristic (ROC) curve analysis would be performed to evaluate its predictive value for development and outcome of AE-ILD.

RESULTS

A total of 665 patients treated at FAHZJU with a diagnosis of DM, PM, or CADM between September 2007 and September 2019 were enrolled into this study, including 334 with DM, 264 with PM, and 67 with CADM. Four hundred and eighty-three patients (72.6%) were identified to be complicated with ILD. Sixty-four out of 665 patients were diagnosed with AE-ILD during their stay in hospital (**Figure 1**). The incidence of AE-ILD was 9.6% in patients with DM, PM, or CADM, and 13.3% in patients who were complicated with ILD at the same time. To be specific, the incidence of AE-ILD in patient with DM, PM, and CADM were 10.8, 5.7, and 19.4%, respectively. In the 665 patients, the average age for AE-ILD patients was 57.7 ± 11.9 years, which was significantly higher than that of the patients without AE-ILD (53.1 ± 13.7 years, $P = 0.011$). Among the 64 AE-ILD patients, 25 were males and 39 were females. The proportion of males in AE-ILD patients was not significantly different from that in non-AE-ILD patients (39.1 vs. 32.3%, $P = 0.272$). Short-term mortality rate for AE-ILD and non-AE-ILD patients were 39.1 vs. 5.7% ($P < 0.001$).

In total, 64 AE-ILD patients and 128 ILD patients without occurrence of AE-ILD were included in the case-control analysis to identify risk factors for AE-ILD in patients with DM, PM, or CADM. Due to the retrospective nature of this study, only 137 patients (54 of AE-ILD patients and 83 of patients without

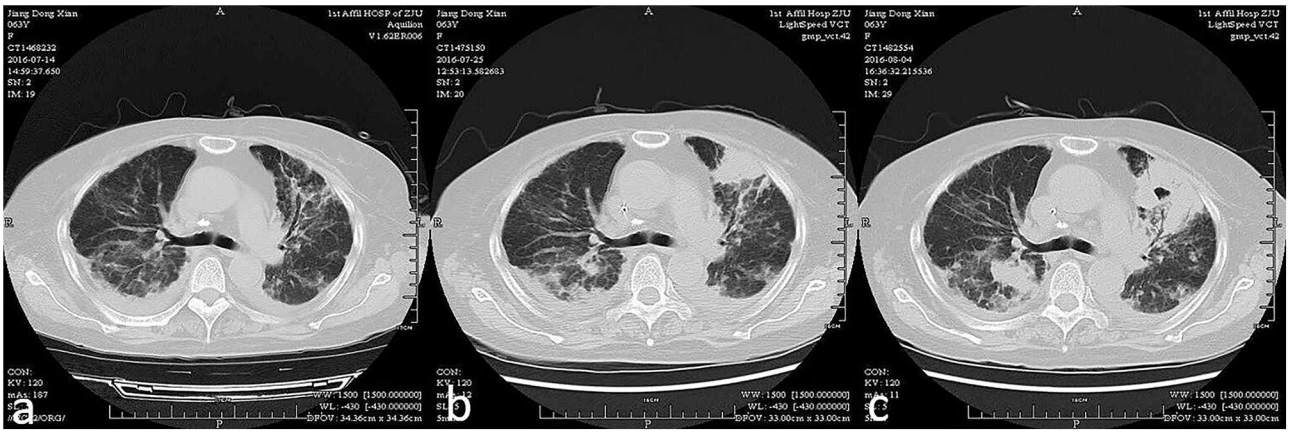

FIGURE 1 | Acute exacerbation of interstitial lung disease of a patient within 3 weeks (from **a–c** chronologically).

AE-ILD) received pulmonary function test within the first week of hospitalization. The case group presented more frequently with treatment of steroid + IVIG ($P = 0.034$), diagnosis of CADM ($P = 0.034$) and less frequently with allergic history ($P = 0.049$). Higher levels of serum ferritin ($P = 0.027$) and C reactive protein (CRP, $P = 0.004$) were seen in patients with AE-ILD. On-admission disease activity, which was evaluated by MYOACT score, was as well-significantly higher for patients in the case group ($P < 0.001$). In addition, AE-ILD patients were found to present with lower level of percent-predicted diffusing capacity of the lung for carbon monoxide (DLCO%, $P = 0.009$; **Table 1**, **Supplementary Data 1**).

Univariate analysis showed that there were eight factors associated with AE-ILD at the level of $P < 0.1$. These factors included elevated on-admission disease activity ($P < 0.001$), lower DLCO% ($P = 0.010$), serum ferritin ($P = 0.058$), CRP ($P = 0.037$), hypertension ($P = 0.065$), allergic history ($P = 0.058$), treatment of steroid + IVIG ($P = 0.038$), and diagnosis of CADM ($P = 0.038$) (**Supplementary Table 1**). Inputation was performed for DLCO% before multivariate logistic regression analysis. Using Kolmogorov-Smirnov test, DLCO% was found a continuous variable that was subject to normal distribution. EM inputation was hereby performed to handle the impact of missing values more appropriately. Afterwards, all variables with $P < 0.1$ were entered into the multivariate logistic regression analysis, and elevated on-admission disease activity ($P < 0.001$), lower DLCO% ($P = 0.013$), and diagnosis of CADM ($P = 0.007$) were found to be significantly different between the case group and the control group. The results were found similar to those without EM imputation (**Table 2**). As presented in **Figure 2**, the optimal cut-off value of the on-admission disease activity for AE-ILD was >7.5, with a sensitivity of 76.6% and a specificity of 57.0%. The area under the curve (AUC) was 0.705.

Of the 64 AE-ILD patients identified in the study, 25 (39.1%) died in hospital or within 2 weeks of hospital discharge. In addition to 36 AE-ILD patients with DM, we also found 15 PM patients and 13 CADM patients who as well-suffered from AE-ILD. And 15 of them (23.4%) manifested as UIP pattern in HRCT. Infection happened to 30 out of 64 adult AE-ILD patients. Ten had bacterial infection, 12 had fungal infection, three were diagnosed with tuberculosis, one was found to have EBV infection. Three suffered from both bacterial and fungal infection, and one had both bacterial and EBV infection. Bacterial (21.9%) and fungal (23.4%) infections were hereby recognized as the two most common infections in AE-ILD patients. Only eight patients with infections (five in bacterial infection, two in fungal infection, and one in tuberculosis infection) were identified based on positive result of BALF smear or culture. To be specific, bacterial infection included four cases of *Acinetobacter baumannii*, four cases with *Stenotrophomonas maltophilia*, three case with *Klebsiella pneumonia*, onc case with *Pseudomonas* aeruginosa, one case with *Staphylococcus haemolyticus*, and one case with *Staphylococcus aureus*. And fungal infection included 10 cases with medium to large amount of *C. albicans*, three cases with *Aspergillus fumigatus*, one case with *Pneumocystis carinii* and one case with *C. glabrata*. Therefore, infections in patients with AE-ILD were mostly opportunistic infections. Details on infections in the matched control group was provided in **Supplementary Data 2**. In addition, the most commonly used therapy was a combined application of steroid and DMARDs (45.3%). And MMF (48.3%) was the most frequently used DMARD in this regimen. Patients with unfavorable short-term outcome presented more frequently with dysphagia ($P = 0.030$), bacterial infection ($P = 0.001$), hypertension ($P = 0.017$), treatment of steroid + IVIG ($P = 0.013$), and less frequently with treatment of steroid + DMARDs ($P = 0.001$). Higher on-admission disease activity ($P = 0.014$) was as well-seen in patients with unfavorable outcome (**Table 3**).

Univariate analysis showed that there were six factors associated with unfavorable short-term outcome in AE-ILD patients at the level of $P < 0.05$. These factors included dysphagia ($P = 0.019$) bacterial infection ($P = 0.002$), on-admission disease activity ($P = 0.012$), hypertension ($P = 0.020$), treatment of steroid + DMARDs ($P = 0.002$) and steroid + IVIG ($P = 0.018$) (**Supplementary Table 2**). The following multivariate logistic regression analysis revealed that higher on-admission

TABLE 1 | Comparison of clinical characteristics between case group and control group.

Factors	AE-ILD (64)	Non-AE-ILD (128)	*P*-value
Age (y)	60.5 (48.0, 66.0)	60.0 (48.3, 65.0)	0.726
Sex (male/female)	25/39	50/78	1.000
Course of disease (m)	3.0 (1.0, 6.8)	4.0 (2.0, 8.8)	0.122
Duration of diagnosis delay (m)	2.0 (1.0, 4.5)	3.0 (1.0, 6.0)	0.113
Clinical manifestations or complications			
Fever	27 (42.2%)	40 (31.3%)	0.134
Lymphadenectasis	26 (40.6%)	47 (36.7%)	0.599
Hepatomegaly	1 (1.6%)	1 (0.8%)	1.000
Splenomegaly	14 (21.9%)	21 (16.4%)	0.355
Heliotrope rash	33 (51.6%)	63 (49.2%)	0.759
Gottron's sign	36 (56.3%)	65 (50.8%)	0.474
Periungual erythema	13 (20.3%)	21 (16.4%)	0.504
Mechanic's hands	9 (14.1%)	17 (13.3%)	0.881
Raynaud's phenomenon	4 (9.5%)	8 (9.5%)	1.000
Muscle pain	22 (34.4%)	53 (41.4%)	0.347
Muscle weakness	50 (78.1%)	111 (86.7%)	0.127
Joint pain	17 (26.6%)	24 (18.8%)	0.213
Joint swelling	8 (12.5%)	21 (16.4%)	0.476
Dysphagia	11 (17.2%)	27 (21.1%)	0.522
Dysarthria	5 (7.8%)	8 (6.3%)	0.919
Respiratory muscle involvement	2 (3.1%)	7 (5.5%)	0.717
Cardiac involvement	4 (6.3%)	10 (7.8%)	0.922
Gastrointestinal hemorrhage	9 (14.1%)	15 (11.7%)	0.643
Bacterial infection	14 (21.9%)	21 (16.4%)	0.355
Fungal infection	15 (23.4%)	22 (17.2%)	0.301
Tuberculosis infection	3 (4.7%)	3 (2.3%)	0.402
EBV or CMV infection	2 (3.1%)	6 (4.7%)	0.890
Carcinoma	6 (9.4%)	11 (8.6%)	0.857
UIP pattern	15 (23.4%)	23 (18.0%)	0.370
Pneumomediastinum	4 (6.3%)	6 (4.7%)	0.909
On-admission disease activity			
MYOACT score	10.0 (8.0,12.0)	7.0 (5.0,9.0)	<0.001
Pulmonary function test			
FVC% (%)	66.1 ± 17.9	67.4 ± 19.2	0.684
TLC (L)	3.1 (2.6,4.3)	3.6 (2.9,4.2)	0.107
FEV1% (%)	66.8 ± 15.8	70.4 ± 21.3	0.288
FEV1/FVC	0.8 (0.7,0.9)	0.8 (0.8,0.9)	0.335
DLCO% (%)	53.6 ± 15.4	62.3 ± 20.5	0.009
On-admission laboratory findings			
ALT (U/L)	49.0 (22.8,122.3)	50.0 (27.0,134.0)	0.710
AST (U/L)	48.0 (29.5,105.8)	61.5 (31.5,163.3)	0.283
Cr (μmol/L)	52.0 (43.0,69.0)	49.5 (43.0,59.0)	0.129
LDH (U/L)	421.0 (330.8,619.3)	401.0 (300.5,820.8)	0.844
CK (U/L)	179.0 (54.3,958.5)	484.5 (58.0,2465.5)	0.113
CK-MB (U/L)	31.5 (18.3,55.5)	32.0 (19.0,110.0)	0.210
CRP (mg/L)	10.1 (4.5,43.7)	6.1 (2.3,18.8)	0.004
Ferritin (ng/ml)	821.7 (342.9,2034.5)	532.7 (247.4,1205.9)	0.027
ANA	40 (62.5%)	75 (58.6%)	0.603
Comorbidities/Harmful hobbies			
Smoking	14 (21.9%)	26 (20.3%)	0.802
Alcohol abuse	10 (15.6%)	24 (18.8%)	0.593
Hypertension	22 (34.4%)	28 (21.9%)	0.063
Diabetes	8 (12.5%)	12 (9.4%)	0.504
Hepatitis	4 (6.3%)	15 (11.7%)	0.232
Allergic History	4 (6.3%)	21 (16.4%)	0.049
Immunosuppressive therapy			
Steroid monotherapy	19 (29.7%)	37 (28.9%)	0.911
Steroid + DMARDs	29 (45.3%)	71 (55.5%)	0.184
Steroid + IVIG	13 (20.3%)	12 (9.4%)	0.034
Steroid + DMARDs + IVIG	3 (4.7%)	8 (6.3%)	0.913
IIM subtypes			
DM	36 (56.3%)	72 (56.3%)	1.000
PM	15 (23.4%)	44 (34.4%)	0.122
CADM	13 (20.3%)	12 (9.4%)	0.034

AE-ILD, Acute exacerbation of interstitial lung disease; y, years; m, months; EBV, Epstein-Barr virus; CMV, Cytomegalo virus; UIP pattern, Usual interstitial pneumonia pattern; MYOACT, Myositis Disease Activity Assessment Visual Analog Scales; FVC%, Percent-predicted forced vital capacity; TLC, Total lung capacity; FEV1%, Percent-predicted forced expiratory volume in 1 s; FEV1/FVC, Ratio of FEV1 over FVC; DLCO%, Percent-predicted diffusing capacity of the lung for carbon monoxide; ALT, Glutamic pyruvic transaminase; AST, Glutamic oxaloacetic transaminase; Cr, Serum creatinine; LDH, Lactate dehydrogenase; CK, Creatine kinase; CK-MB, Creatine kinase isoenzymes; ANA, Antinuclear antibody; DMARDs, Disease-modifying anti-rheumatic drugs; IVIG, Intravenous immunoglobulin; IIM, Idiopathic inflammatory myopathies; DM, dermatomyositis; PM, Polymyositis; CADM, Clinically amyopathic dermatomyositis.

TABLE 2 | Multivariate logistic regression analysis of risk factors for AE-ILD in patients with DM, PM, or CADM.

Factors	*P*-value	OR value	95% CI
On-admission disease activity (MYOACT score)	<0.001	1.243	1.127–1.371
DLCO%	0.013	0.972	0.950–0.994
CADM	0.007	3.781	1.444–9.903

DM, dermatomyositis; PM, Polymyositis; CADM, Clinically amyopathic dermatomyositis; OR value, Odds ratio value; 95%CI, 95% Confidence interval; MYOACT, Myositis Disease Activity Assessment Visual Analog Scales, DLCO%, Percent-predicted diffusing capacity of the lung for carbon monoxide.

disease activity ($P = 0.008$), bacterial infection ($P = 0.003$), and treatment of steroid+DMARDs ($P = 0.006$) were significantly correlated with unfavorable short-term outcome in AE-ILD patients (**Table 4**). As presented in **Figure 3**, the best cut-off value of the on-admission disease activity for unfavorable short-term outcome in patients with AE-ILD was >8.5, with a sensitivity of 84.0% and a specificity of 43.6%. The AUC was 0.682.

DISCUSSION

To date, this is the first study to systematically probe into the risk factors for development of AE-ILD in patients with

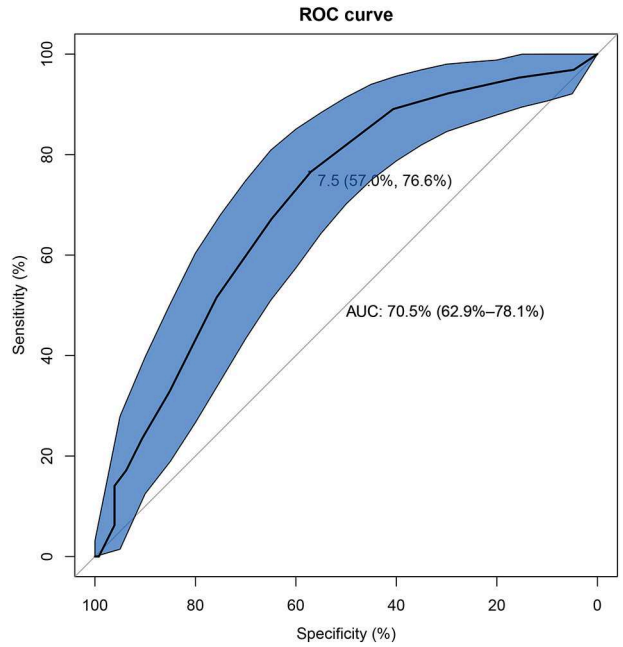

FIGURE 2 | The receiver operating characteristic curve of on-admission disease activity for development of AE-ILD in IIM patients. AE-ILD, Acute exacerbation of interstitial lung disease; IIM, Idiopathic inflammatory myopathies.

DM, PM, or CADM, and potential factors affecting the short-term outcome of the AE-ILD patients. Preceding studies on acute exacerbation mainly focused on AE-IPF. And the annual incidence of AE-IPF ranged from 7 to 19.1% in different clinical trials and retrospective studies (20–25). Knowledge on AE-ILD in non-IPF patients, namely connective-tissue-disease-related ILD (CTD-ILD), was limited. The reported incidence of AE-ILD in rheumatoid arthritis (RA) patients with ILD was 7.7–22% (26, 27). Tomiyama et al. revealed an AE-ILD incidence of 9.4% in systemic sclerosis (28). In this study, the incidence of AE-ILD was 9.6% in patients with DM, PM, or CADM, and 13.3% in patients complicated with ILD. And the mortality rate of AE-ILD was significantly higher than that in non-AE-ILD patients (39.1 vs. 5.7% $P < 0.001$). Besides, the average age for AE-ILD patients was as well-higher than that of the patients without AE-ILD (57.7 ± 11.9 vs. 53.1 ± 13.7 years, $P = 0.011$). Elevated on-admission disease activity, lower DLCO% and diagnosis of CADM were found to be risk factors for development of AE-ILD in patients with DM, PM, or CADM. Moreover, bacterial infection, elevated on-admission disease activity and treatment of steroid + DMARDs were significantly correlated with short-term outcome in AE-ILD patients.

Previous studies revealed that declined forced vital capacity (FVC), low diffusing capacity of the lung for carbon monoxide (DLCO), pulmonary hypertension, comorbid coronary artery disease, surgical resection of lung cancers and various infections etc. were found to be risk factors for AE-ILD (29–31). However, the results were not homogeneous in different studies. In

TABLE 3 | Comparison of clinical characteristics between mortality group and survival group.

Factors	Mortality group (25)	Survival group (39)	*P*-value
Age (y)	62.0 (47.0,67.0)	60.0 (51.0,65.0)	0.967
Sex (male/female)	12/13	13/26	0.241
Course of disease (m)	2.0 (1.0,4.5)	3.0 (1.0,9.0)	0.235
Duration of diagnosis delay (m)	2.0 (1.0,3.0)	3.0 (1.0,6.0)	0.332
Clinical manifestations or complications			
Fever	14 (56.0%)	13 (33.3%)	0.073
Lymphadenectasis	8 (32.0%)	18 (46.2%)	0.261
Hepatomegaly	1 (4.0%)	0 (0.0%)	0.391
Splenomegaly	6 (24.0%)	8 (20.5%)	0.742
Heliotrope rash	12 (48.0%)	21 (53.8%)	0.648
Gottron's sign	12 (48.0%)	24 (61.5%)	0.287
Periungual erythema	4 (16.0%)	9 (23.1%)	0.492
Mechanic's hands	4 (16.0%)	5 (12.8%)	1.000
Raynaud's phenomenon	0 (0.0%)	4 (10.3%)	0.149
Muscle pain	11 (44.0%)	11 (28.2%)	0.194
Muscle weakness	20 (80.0%)	30 (76.9%)	0.771
Joint pain	7 (28.0%)	10 (25.6%)	0.835
Joint swelling	3 (12.0%)	5 (12.8%)	1.000
Dysphagia	8 (32.0%)	3 (7.7%)	0.030
Dysarthria	4 (16.0%)	1 (2.6%)	0.072
Respiratory muscle involvement	1 (4.0%)	1 (2.6%)	1.000
Cardiac involvement	3 (12.0%)	1 (2.6%)	0.291
Gastrointestinal hemorrhage	5 (20.0%)	4 (10.3%)	0.468
Bacterial infection	11 (44.0%)	3 (7.7%)	0.001
Fungal infection	9 (36.0%)	6 (15.4%)	0.057
Tuberculosis infection	0 (0.0%)	3 (7.7%)	0.275
EBV or CMV infection	0 (0.0%)	2 (5.1%)	0.516
Carcinoma	0 (0.0%)	6 (15.4%)	0.074
UIP pattern	5 (20.0%)	10 (25.6%)	0.603
Pneumomediastinum	3 (12.0%)	1 (2.6%)	0.291
On-admission disease activity			
MYOACT score	10.0 (9.0, 14.5)	9.0 (7.0, 12.0)	0.014
Pulmonary function test			
FVC% (%)	61.7 (36.7, 85.1)	69.0 (58.8, 79.3)	0.248
TLC (L)	3.2 (2.6, 4.3)	3.1 (2.4, 4.4)	0.787
FEV1% (%)	64.0 (42.7, 77.2)	69.4 (60.9, 78.6)	0.205
FEV1/FVC	0.8 (0.7,0.9)	0.8 (0.7,0.9)	0.615
DLCO% (%)	51.1 (44.9, 61.8)	58.2 (42.8, 63.2)	0.533
On-admission laboratory findings			
ALT (U/L)	63.0 (29.5, 120.5)	39.0 (21.0, 139.0)	0.559
AST (U/L)	60.0 (34.5, 97.0)	44.0 (24.0, 215.0)	0.461
Cr (μmol/L)	67.0 (41.0, 98.0)	52.0 (43.0, 63.0)	0.198
LDH (U/L)	439.0 (369.0, 609.5)	403.0 (317.0, 625.0)	0.518
CK (U/L)	151.0 (38.0, 312.0)	193.0 (93.0, 1667.0)	0.128
CK-MB (U/L)	25.0 (17.0, 58.5)	37.0 (20.0, 54.0)	0.405
CRP (mg/L)	18.7 (5.4, 53.2)	9.5 (4.4, 27.2)	0.259
Ferritin (ng/ml)	834.9 (611.0, 2757.4)	811.6 (186.4, 1690.2)	0.139

(Continued)

TABLE 3 | Continued

Factors	Mortality group (25)	Survival group (39)	*P*-value
ANA	12 (48.0%)	28 (71.8%)	0.055
Comorbidities/Harmful hobbies			
Smoking	6 (24.0%)	8 (20.5%)	0.742
Alcohol abuse	4 (16.0%)	6 (15.4%)	1.000
Hypertension	13 (52.0%)	9 (23.1%)	0.017
Diabetes	4 (16.0%)	4 (10.3%)	0.701
Hepatitis	2 (8.0%)	2 (5.1%)	0.640
Allergic History	2 (8.0%)	2 (5.1%)	0.640
Immunosuppressive therapy			
Steroid monotherapy	8 (32.0%)	11 (28.2%)	0.746
Steroid + DMARDs	5 (20.0%)	24 (61.5%)	0.001
Steroid + IVIG	9 (36.0%)	4 (10.3%)	0.013
Steroid + DMARDs + IVIG	3 (12.0%)	0 (0.0%)	0.055
IIM subtypes			
DM	14 (56.0%)	22 (56.4%)	0.974
PM	7 (28.0%)	8 (20.5%)	0.490
CADM	4 (16.0%)	9 (23.1%)	0.960

y, years; m, months; EBV, Epstein-Barr virus; CMV, Cytomegalo virus; UIP pattern, Usual interstitial pneumonia pattern; MYOACT, Myositis Disease Activity Assessment Visual Analog Scales; FVC%, Percent-predicted forced vital capacity; TLC, Total lung capacity; FEV1%, Percent-predicted forced expiratory volume in 1 s; FEV1/FVC, Ratio of FEV1 over FVC; DLCO%, Percent-predicted diffusing capacity of the lung for carbon monoxide; ALT, Glutamic pyruvic transaminase; AST, Glutamic oxaloacetic transaminase; Cr, Serum creatinine; LDH, Lactate dehydrogenase; CK, Creatine kinase; CK-MB, Creatine kinase isoenzymes; ANA, Antinuclear antibody; DMARDs, Disease-modifying anti-rheumatic drugs; IVIG, Intravenous immunoglobulin; IIM, Idiopathic inflammatory myopathies; DM, dermatomyositis; PM, Polymyositis; CADM, Clinically amyopathic dermatomyositis.

TABLE 4 | Multivariate logistic regression analysis of risk factors for unfavorable short-term outcome in patients complicated with AE-ILD.

Factors	*P*-value	OR value	95% CI
On-admission disease activity (MYOACT score)	0.008	1.346	1.082–1.674
Bacterial infection	0.003	13.494	2.398–75.945
Steroid+DMARDs	0.006	0.137	0.033–0.565

AE-ILD, Acute exacerbation of interstitial lung disease; MYOACT, Myositis Disease Activity Assessment Visual Analog Scales; DMARDs, Disease-modifying anti-rheumatic drugs.

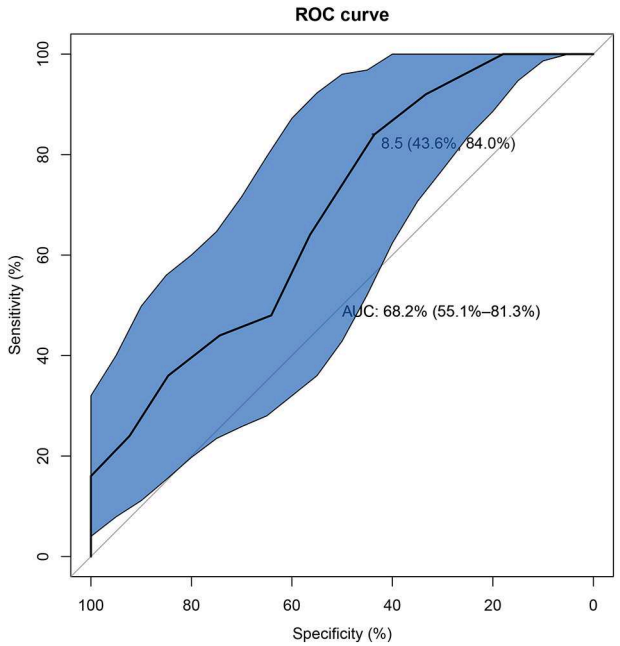

FIGURE 3 | The receiver operating characteristic curve of on-admission disease activity for unfavorable short-term outcome in IIM patients with AE-ILD. IIM, Idiopathic inflammatory myopathies; AE-ILD, Acute exacerbation of interstitial lung disease.

this study, decreased DLCO%, which reflected lower diffusing capacity, was found to be a risk factor for AE-ILD in patients with DM, PM, or CADM. The role of lower DLCO% in AE-ILD was not clear. On the one hand, lower DLCO% reflected decreased gas-exchanging function of lung. With no significant alteration in pulmonary ventilation function etc., decreased gas-exchanging function would lead to hypoxia, which could subsequently contribute to progress of ILD. Hypoxia have been recognized to induce progress of interstitial lung disease through augmenting oxidative and inflammatory pathways, increasing the total lung collagen content and heterogeneous structural alterations (32–34). On the other hand, decreased DLCO% could be an early-stage manifestation of AE-ILD since ILD and its progression could result in impaired diffuse capacity via alveolar structural alteration, thickening of alveolar capillary wall, etc. Lower DLCO% seemed to be both initiating factor and consequence of AE-ILD.

MYOACT score works as a systemic evaluation of disease activity of IIM (19, 35). After adjusting for other factors, elevated on-admission MYOACT score was found to be related to development of AE-ILD in IIM patients. The role of CTD disease activity in AE-ILD was disputable in published studies. In a retrospective study concerning RA patients receiving tocilizumab treatment, AE-ILD was found to be positively related to disease activity of RA (36). However, no similar association was seen in RA patients treated by corticosteroids and immunosuppressants. The predictive role of MYOACT score in this study might lie in the partially overlapped pathological mechanism between AE-ILD and IIM. Elevated levels of several cytokines and chemokines, namely IL-6, IL-8, IL-17, IL-23, etc., were seen in peripheral blood, muscle or skin of IIM patients, and were consistent with disease activity (37). Meanwhile several studies also observed significant elevation of cytokines and chemokines including IL-6, IL-8 in patients with ILD exacerbation, and the elevation was found to be related to worse outcome (38, 39). The partially overlapped pathological mechanism made baseline disease activity a valuable predictor of AE-ILD. Besides, after adjusting for factors including infections, medication, pulmonary function, etc., the significance of on-admission disease activity could, to some extent, demonstrated the role of autoimmune abnormality in development of AE-ILD. In 2011, Shu etc. found

that initial disease activity, which was evaluated by MYOACT score, was not significantly correlated with long-term outcome of IIM patients (40). And no linkage between initial disease activity and short-term outcome of hospitalized IIM patients was reported previously. By narrowing down to DM, PM, or CADM patients complicated with AE-ILD, on-admission disease activity, which was evaluated by MYOACT score, was found to herald unfavorable short-term outcome in this study.

However, the evaluation of disease activity demands ability for communication, which would be difficult in patients with mental retardation or disturbed behavior. It would thus be of great significance to identify serum biomarkers for development and outcome of AE-ILD in IIM patients. Researchers in Hamamatsu University found that higher levels of ferritin predicted development of AE-IPF and unfavorable outcome (41). However, in this study, serum ferritin was not found to be significantly related to development of AE-ILD after adjusting for other clinical features. Nor was it identified to predict short-term outcome of IIM patients with AE-ILD. Preceding study also revealed that CRP could be used to predict development of AE-ILD in patients receiving non-pulmonary surgery (42). Nevertheless, no statistical significance for CRP was seen in IIM patients with regard to development and outcome of AE-ILD. Further studies would be demanded to identify serum biomarkers for development and outcome of AE-ILD in CTD patients.

In addition to the high prevalence of ILD in CADM patients, preceding studies proposed that rapidly progressive pattern of ILD was more frequently seen in CADM patients compared with patients with DM or PM (43, 44). After multivariate logistic regression analysis, diagnosis of CADM was found to be a risk factor for AE-ILD in patients with DM, PM or CADM, which was consistent with the past clinical findings. Although CD8+ T cells were found to play a key role in development of IIM-related ILD, high proportion of CD4+ T cells seemed to play a greater role in acute exacerbation of ILD. Suda and his colleagues focused on CADM patients and found that the CD4/CD8 ratio in bronchoalveolar lavage fluid (BALF) was higher in patients with rapidly progressive ILD in comparison to that in chronic ILD patients (45). Ito et al. demonstrated similar results in BALF and peripheral blood of patients with DM (46). Moreover, Mukae et al. uncovered a higher CD4/CD8 ratio in BALF of CADM-related ILD patients compared with that in ILD patients with classic DM (43). Taken together, the higher proportion of CD4+ T cells in BALF seem to link diagnosis of CADM with higher incidence of AE-ILD. Confirmation of the role of higher proportion of CD4+ T cells and exploration of its detailed mechanism in immune abnormality of AE-ILD in IIM patients demands further exploration.

In-hospital IIM patients regularly received immunosuppressive therapy, which greatly increased their vulnerability to bacterial, fungal, or viral infection. More infections, opportunistic bacterial and fungal infections in particular, were hereby identified in this study. Although infectious triggers were found in 10–30% of patients with AE in preceding study (47), no significant association was found between infections and development of AE-ILD after adjusting for disease activity, pulmonary function, medication, etc. In the following intragroup analysis, bacterial infection was found to be associated with unfavorable short-term outcome in DM, PM, or CADM patients complicated with AE-ILD. Similar linkage between infection and short-term outcome was seen in IIM patients (3, 4). And opportunistic infection was as well-recognized as a major cause of mortality in patients with IIM-related ILD (48). However, this is the first study identifying infection as risk factor for unfavorable short-term outcome in patients complicated with AE-ILD.

The mortality rate of patients with AE-ILD was relatively high. For patients with IPF, 46% of deaths are secondary to AE and median survival period after AE is 3-4 months (49). And a high mortality rate (55.6%) was as well-seen in CTD patients with AE-ILD (14). In this study, the short-term mortality rate of AE-ILD group was 39.1%. The relatively high mortality rate of AE-ILD patients indicated much room for improvement in therapeutic regimens. In IIM patients with AE-ILD, a combined use of steroid and DMARDs was found to reduce the short-term mortality rate of these patients. Meanwhile no significant effect was identified in the application of intravenous immunoglobulin. Preceding study revealed a favorable response of exacerbation of ILD in RA patients after receiving a combined therapy of steroid and DMARDs (50). And cyclosporine, tacrolimus, and cyclophosphamide were the major DMARDs used in this study. However, the mostly commonly used DMARD in our study was MMF, the use of which has been proved effective in myositis-related ILD (51). The combined use of steroid and MMF in CTD patients with AE-ILD deserved further exploration in the future. Intravenous immunoglobulin, which was as well-frequently used in patients with ILD or AE-ILD, still played a disputable role in treatment of AE-ILD, especially CTD-related AE-ILD (29, 52). Biologics could be viewed as a two-edge sword in AE-ILD. On the one hand, rituximab, etc. have shown optimistic result in therapy of several AE-ILD cases (52, 53). On the other hand, biologics have also been reported to induce AE-ILD (54, 55). Apart from immunosuppressant treatment, empirical antibiotic therapy is also considered for all patients (56). Application of azithromycin and prophylactic use of co-trimoxazole were found effective in several clinical trials (57–59). Besides, antifibrotic medication, anti-acid therapy, plasma exchange, Polymyxin-B-immobilized fiber column (PMX) and fluid management were as well-found to have potential, yet disputable effect on outcome of AE-ILD patients (29–31).

The most significant limitations of this study are the retrospective and observational nature of the study and the small sample size. Furthermore, absence of records of pulmonary hypertension and several myositis-associated antibodies in over half of the patients also restrained us from figuring out their roles in development of AE-ILD among IIM patients. A large prospective cohort study is essential to confirm our findings and fill in the gaps. In spite of all the limitations, we intended to shed some light on the future study of AE-ILD in patients with DM, PM, or CADM.

CONCLUSIONS

AE-ILD is a fatal complication in IIM patients. Elevated on-admission disease activity, lower DLCO% and diagnosis of CADM were found to be risk factor for development of AE-ILD in patients with DM, PM, or CADM. Speculations on the roles of autoimmune abnormality and hypoxia in development of AE-ILD were hereby brought up. In addition, elevated on-admission disease activity, bacterial infection could be used to predict unfavorable short-term outcome in AE-ILD patients. A therapeutic regimen of steroid and DMARDs was found to reduce short-term death in IIM patients with AE-ILD.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board (IRB) of the First Affiliated Hospital of Zhejiang University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors met the criteria for authorship established by the International Committee of Medical Journal Editors. Specifically, JLia and HC were responsible for substantial contributions to the conception, design, analysis, drafting the work, revising the work, and reviewing of the manuscript. YK, CS, WC, and JLin assisted with the data gathering, revising the work, and reviewing of the manuscript. All the authors listed have approved for publication of the content and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.00012/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Multidisciplinary Approach in the Early Detection of Undiagnosed Connective Tissue Diseases in Patients With Interstitial Lung Disease: A Retrospective Cohort Study

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Interstitial lung disease (ILD) encompasses a wide range of parenchymal lung pathologies with different clinical, histological, radiological, and serological features. Follow-up, treatment, and prognosis are strongly influenced by the underlying pathogenesis. Considering that an ILD may complicate the course of any connective tissue disease (CTD) and that CTD's signs are not always easily identifiable, it could be useful to screen every ILD patient for a possible CTD. The recent definition of interstitial pneumonia with autoimmune features is a further confirmation of the close relationship between CTD and ILD. In this context, the multidisciplinary approach is assuming a growing and accepted role in the correct diagnosis and follow-up, to as early as possible define the best therapeutic strategy. However, despite clinical advantages, until now, the pathways of the multidisciplinary approach in ILD patients are largely heterogeneous across different centers and the best strategy to apply is still to be established and validated. Aims of this article are to describe the organization of our multidisciplinary group for ILD, which is mainly focused on the early identification and management of CTD in patients with ILD and to show our results in a 1 year period of observation. We found that 15% of patients referred for ILD had an underlying CTD, 33% had interstitial pneumonia with autoimmune feature, and 52% had ILD without detectable CTD. Furthermore, we demonstrated that the adoption of a standardized strategy consisting of a screening questionnaire, specific laboratory tests, and nailfold videocapillaroscopy in all incident ILD proved useful in making the right diagnosis.

Keywords: interstitial lung disease, connective tissue diseases, multidisciplinary team, early diagnosis, rheumatology, pulmonology, radiology

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INTRODUCTION

Interstitial lung disease (ILD) includes a heterogeneous group of parenchymal lung pathologies with different clinical, histological, radiological, and serological features (1). To correctly classify ILD is crucial, since follow-up, treatment, and prognosis are strongly dependent on ILD subtype (2, 3). Considering that ILD may complicate the course of any connective tissue disease (CTD) and that signs of CTD are frequently not easy to identify (4–7), an underlying CTD should be ruled out in every ILD, even when the suspect is low or even absent. The recent definition of interstitial pneumonia with autoimmune features (IPAF) is a further confirmation of the close relationship between CTDs and ILD and of how the borders between the rheumatology and pulmonology practices are day by day less defined (8). In a similar context, the multidisciplinary approach is assuming a growing and accepted role, as the discussion of such cases may help to identify the sometime subtle signs or symptoms of CTD in ILD (9–14). However, despite the clinical advantages, the pathways of the multidisciplinary approach in ILD are largely heterogeneous across different centers and countries, and the best strategy to apply is still to be established and validated, as well as the composition of the multidisciplinary team (i.e., the rheumatologist is not included in many of the described multidisciplinary teams) (15). Furthermore, until now, no screening tools for the early identification of CTD signs and symptoms have been applied in ILD, although previous reports in other settings showed their potential usefulness (16). The inclusion of the rheumatology assessment is an added value for patients (9, 17, 18), and the possibility to start the multidisciplinary pathway from a screening tool seems to be effective in terms of health-care resources optimization. Despite these observations, the best strategy to apply in the multidisciplinary evaluation still has to be defined and validated (19). In this article, we want to describe the organization, and share the first results, of our Multidisciplinary Group for Interstitial Lung Disease (GI-ILD), focusing on the early identification of CTDs in ILD patients referring to our clinics.

MATERIALS AND METHODS

The Pavia Multidisciplinary Group for Interstitial Lung Disease

The GI-ILD is a multidisciplinary group first established in 2015 as a shared initiative between the Rheumatology, Pulmonology, and Radiology Divisions of the University and IRCCS Policlinico San Matteo Foundation of Pavia, a tertiary center of referral in the diagnosis and treatment of CTDs, ILD, and rare pulmonary diseases (4, 5, 20–32). The GI-ILD has been first created for the collegial discussion and revision of the most complex or intriguing cases of ILD through a multidisciplinary discussion (MDD). From 2015 to 2018 the selection of cases to be discussed was on individual basis, as every clinician identified independently the patients. To improve the GI-ILD diagnostic performance at the meantime reducing the risk of missed CTDs diagnosis, from 2018, we established a multistep assessment pathway for newly referred (incident) ILD patients in our hospital. Actually, the process of selection is preliminary to MDD, and it is addressed to focus on patients at increased risk of CTDs, to facilitate the admission to our Multidisciplinary Rheumatology–Pulmonology outpatient clinic for the final assessment.

GI-ILD General Organization

The organization of the GI-ILD is represented in **Figure 1**. Our multidisciplinary group includes a team of six Pulmonology, three Rheumatology, two Radiology, and one Pathology specialists supported by their respective fellows. The group's meetings are regularly scheduled every 2 weeks. The GI-ILD is mainly focused on ILD patients first referred to the Pulmonology Unit and without a previous diagnosis of any CTD, to rule out the occurrence of an underlying autoimmune disorder. Patients with a previous diagnosis of CTD have a direct access to the Rheumatology CTD outpatient clinic for diagnosis confirmation. During the first pulmonology assessment, patients are asked to perform or repeat pulmonary function tests (PFT) with diffusion capacity test (DLCO) and to fill in a 12-item questionnaire addressed to identify CTDs features. A previous version of this questionnaire has been applied in another setting with good results (16). When available, all the high-resolution computed tomographies (HRCT) of the chest are evaluated and, if not performed in our center, a copy of the DICOM images are stored for future MDD. Further steps include nailfold videocapillaroscopy (NVC), which is performed independently of Raynaud's Phenomenon (RP) occurrence (25), and a locally established autoimmune and laboratory panel of tests (**Figure 2**). To avoid possible selection bias, NVC and laboratory tests are, respectively, performed in the Rheumatology and in the Laboratory Division of the IRCCS Policlinico S. Matteo Foundation, a tertiary structure with high skills in the analysis of autoimmune and laboratory tests (33–36). Patients with either a positive questionnaire, NVC, or autoimmune and laboratory panel enter the MDD. During the MDD, the baseline screening results are presented, and the clinical case is discussed, together with the evaluation of chest HRCT images, PFT, and DLCO results. At the end of the discussion, patients without the suspect of an underlying CTD are planned for the regular pulmonology follow-up and treatment according to the suspected or established diagnosis. In case of CTD/IPAF, the patients are referred to the Multidisciplinary Rheumatology–Pulmonology outpatient clinic (RP-OC) for the final diagnostic steps, treatment, and follow-up definition. According to guidelines or expert recommendations, every patient is treated following the best therapeutic option established for the specific diagnosis.

First Step

Baseline screening questionnaire

The baseline screening questionnaire consists of 12 questions, focusing on 11 CTD manifestations such as RP (question 1), mechanic's hands and pitting scars (question 2), cutaneous sclerosis or puffy fingers (question 3), skin lesions such as heliotrope rash, Gottron's papules, malar rash (question 4), arthritis/inflammatory arthralgias (questions 5 and 6), dry eyes

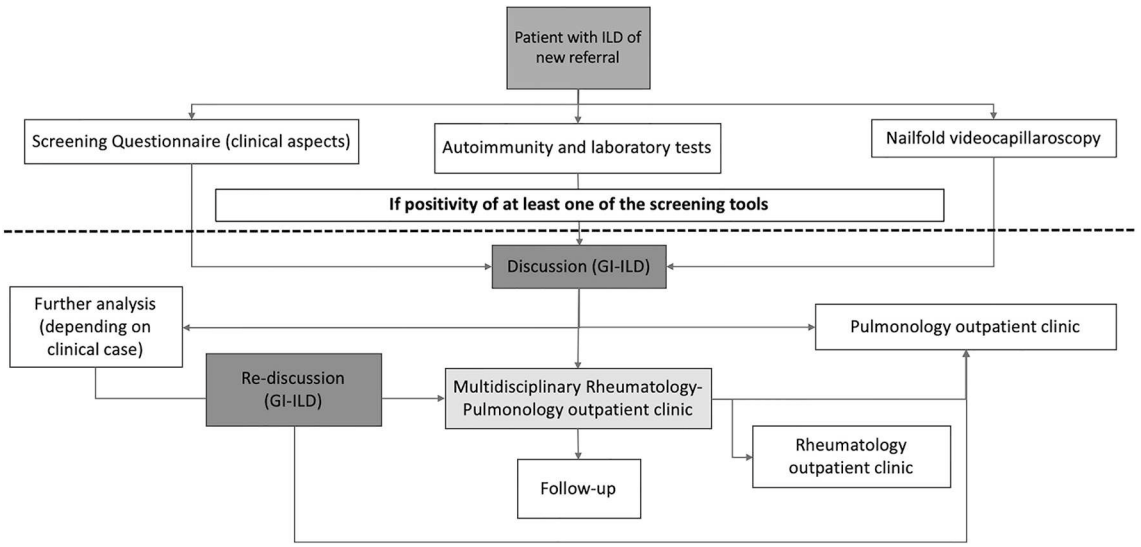

FIGURE 1 | Flow chart of the multidisciplinary discussion we applied in our cohort of newly referring ILD. ILD, interstitial lung disease; GI-ILD, Multidisciplinary Group for Interstitial Lung Disease.

Laboratory questionnaire

- ☐ ANA Centromere pattern positivity
- ☐ ANA Nucleolar pattern positivity
- ☐ ANA > 1/160 titer
  Specify the pattern of ANA test: .....
- ☐ ANA Cytoplasmic pattern positivity
- ☐ Rheumatoid Factor
  Titer and laboratory reference values: .....
- ☐ Anti-CCP positivity
  Titer and laboratory reference values: .....
- ☐ Anti-ENA positivity
  Specify which Anti-ENA are positive: .....
- ☐ Myositis specific/associated antibodies positivity
  Specify which Myositis specific/associated antibodies are positive: .....
- ☐ Systemic sclerosis rare antibodies positivity (test only if history of Raynaud's phenomenon)
  Specify which Systemic sclerosis rare antibodies are positive: .....
- ☐ p-ANCA positivity (anti-myeloperoxidase antibody)
- ☐ c-ANCA positivity (anti-proteinase 3 antibody)
- ☐ Lymphopenia (lymphocytes < 1500/mmc)
- ☐ Hyperferritinemia
  Value and reference levels: .....
- ☐ High Creatine-phosphokinase
  Value and reference levels: .....
- ☐ High aldolase
  Value and reference levels: .....
- ☐ Nailfold videocapillaroscopy with severe alterations (scleroderma or borderline pattern)

FIGURE 2 | Laboratory tests assessed as a screening tool in newly referring patients with interstitial lung disease.

and dry mouth (question 7), oral ulcers (question 8), dysphagia (question 9), proximal muscle weakness (question 10), cutaneous telangiectasias (question 11), and other CTD (and also vasculitis) features such as deep venous thrombosis, sinusitis, and adult-onset asthma (question 12). As pointed-out, every item explores a single manifestation, except for questions 5 and 6, which

should be considered as a single item. The positivity of a single item of the baseline questionnaire is sufficient to enter the MDD.

Autoimmune and laboratory tests

Laboratory tests (**Figure 2**) include the antinuclear antibody (ANA) test (for both classic and cytoplasmic positivity) (HEp-2000®; Immunoconcepts), an extractable nuclear antigen screen test (EliA SymphonyS; Phadia 250), rheumatoid factor (Rheumatoid factor Flex reagent cartridge Dimension Vista; Siemens), anticyclic citrullinated peptide antibodies (EliA CCP; Phadia 250), antineutrophil cytoplasmic antibodies (ANCA) tests (EliA PR3 S and EliA MPO S: Phadia 250), creatine-phosphokinase, aldolase, erythrocyte sedimentation rate and C-reactive protein, and myositis-specific/myositis-associated antibodies (anti-Jo1, anti-PL7, anti-PL12, anti-OJ, anti-EJ, anti-Pm-Scl 75 and 100, anti-SRP, anti-Mi2, anti-MDA5, anti-NXP2, anti-TIF1gamma, anti-Ku, and anti-Ro52) (EUROLINE, Autoimmune Inflammatory Myopathies 16 Ag; EUROIMMUN). Systemic sclerosis rare antibodies (e.g., anti-PDGFR, anti-Ku, anti-Th/T0, anti-NOR90, anti-fibrillarin, anti-RNA polymerase I and III) [EUROLINE: Systemic Sclerosis (Nucleoli) Profile; Immunoblot EUROIMMUN] are tested only in patients with RP and after the negative result of myositis-specific/myositis-associated antibodies. As a reference value for autoimmune tests, we used the IPAF criteria (8), although for ANA without the nucleolar and anticentromere positivity, we considered as significant every pattern with titers higher than 1/160. Among the positive laboratory findings, we considered also hyperferritinemia and lymphopenia because of some reports as negative prognostic factor in patients with anti-MDA5 syndrome and thus potentially linked to the occurrence of CTD-ILD (37–39). Furthermore, on the basis of previous reports, we included also ANCA antibodies, ANA cytoplasmic positivity, and muscle enzymes assessment (15, 23, 40, 41). In case of a single positive result in autoimmune or laboratory tests, the patient is considered eligible for discussion during the GI-ILD.

Nailfold videocapillaroscopy

NVC is performed by the Rheumatology team generally within 10 days from the first pulmonology assessment. A single experienced operator (LC) performs NVC on a VideoCap 13 microscope with 200× magnification. Each exam includes the storage of pictures (three per finger) on a dedicated computer. A second rheumatologist reviews all the stored NVC images and formulates a comment (see Contribution). NVC is systematically performed in all patients according to the consolidated methodology described by Cutolo et al. (42) on each finger of both hands excluding thumbs. Patterns are described as "normal," "aspecific abnormalities," and "scleroderma pattern" (25). Scleroderma anomalies include megacapillaries, specific microhemorrhages, neoangiogenesis, or avascular areas (42). Patients with scleroderma anomalies are discussed during the GI-ILD.

Second Step

Multidisciplinary discussion

The results of the first step are presented during the GI-ILD by the clinician in charge of the patient. HRCT scans are collegially reviewed and discussed, to identify the radiological pattern of lung involvement (43). CT findings are qualitatively analyzed by two radiologists with great expertise on ILD. Similarly, PFTs results are presented, together with other clinically relevant information. In some cases, according to clinical suspicion, further analysis could be asked: muscle magnetic resonance, or muscle biopsy in suspected inflammatory myositis; plan X-rays or Doppler ultrasound of hands and feet in the suspect of arthritis; bronchoscopy with bronchoalveolar lavage fluid examination and cytogram to better characterize alveolitis; and surgical or cryo-biopsies in case of suspected IPF or other forms of fibrosing ILD not otherwise characterizable. Cases for which further analysis are needed enter a rediscussion in the subsequent GI-ILD. After the multidisciplinary discussion, patients diagnosed with a CTD-ILD or IPAF are followed up in the multidisciplinary Rheumatology–Pulmonology outpatient clinic, whereas all the other ILD patients without any rheumatologic involvement continue a regular pulmonology follow-up in a dedicated ILD outpatient clinic. According to the diagnosis, when clinically indicated, specific anti-fibrotic or immunosuppressant therapy is started.

Multidisciplinary rheumatology–pulmonology outpatient clinic

The Rheumatology–Pulmonology outpatient clinic is in charge to FMe (Pulmonologist) and to LC (Rheumatologist). At first assessment, patients generally repeat PFT with DLCO. A pulmonology and rheumatology medical examination is then performed, and all the data from the screening phase and of previous tests are reviewed. If a diagnosis is obtained, the appropriate treatment is started according to international guidelines or expert recommendations, and follow-up is planned. PFT + DLCO are repeated every 6 months. Annual HRCT is performed in patients with fibrotic ILD (with or without CTD) or IPF to follow up the stability/progression of fibrotic lung disease, as well as surveillance for possible neoplastic evolution on fibrotic scars or parenchyma. Timing for HRCT follow-up in non-fibrotic CTD-ILD depends largely on clinical and functional aspects. ILD patients diagnosed with established CTDs are subsequently followed in the CTD outpatient clinic and in the Rheumatology–Pulmonology outpatient clinic, while IPAF patients are followed up only in the Rheumatology–Pulmonology outpatient clinic, to identify patients who will develop an established CTD during follow-up. For every definite diagnosis, we adopt well-established classification criteria (8, 44–49), except for the antisynthetase syndrome, because of the lack of shared definitions (8, 50). In fact, in our cohort, every patient testing positive for antisynthetase antibodies is diagnosed with antisynthetase syndrome, in line with our previous reports (5). In case of ILD patients with clinical or laboratory findings suggestive for CTD but without fulfilling any of the existing classification criteria, the final attributed diagnosis is undifferentiated connective tissue disease (45).

Data collection

Patient's data from January to December 2018 were collected from electronic health records and medical records of GI-ILD. Every patient signed an informed consent during the first clinical evaluation. The screening questionnaire, autoimmune and laboratory tests, and NVC are collected from patient's medical records, while HRCT and PFT performed at the IRCCS Policlinico S. Matteo Foundation are stored in electronic health records. Copies of outside-performed HRCT DICOM files and PFT are recorded during GI-ILD evaluation and stored locally on a dedicated computer. All patient's medical records are stored in the multidisciplinary Rheumatology–Pulmonology outpatient clinic.

Statistical Analysis

Patients' characteristics at screening visit have been reported using median and interquartile range for the quantitative variables and absolute/relative frequency values for the qualitative ones. The population study has been divided in three different groups: *connective tissue disease* (CTD), which includes patients diagnosed with established autoimmune rheumatic diseases; *interstitial pneumonia with autoimmune features* (IPAF); and finally, the "other ILD" group, including all the remaining patients. Overall comparison among groups was performed by the one-way ANOVA or by non-parametric Kruskal–Wallis test for quantitative variables and by the chi-square or Fisher's exact test for categorical variables. Statistical significance was set at $p < 0.05$. Significant differences between groups were further evaluated in a *post-hoc* analysis (head-to-head comparison) with a statistical significance set at $p < 0.025$ (Bonferroni correction). Analyses were performed using STATA software package (2018, release 15.1; StataCorp, College Station, TX).

RESULTS

We retrospectively analyzed the performance of the GI-ILD group from January to December 2018 (**Table 1**). A total of 142 patients were referred to the Pulmonology outpatient clinic for a suspected ILD. Fifteen of them were excluded from the multidisciplinary approach after the first screening visit because an alternative diagnosis out of ILD was reached (five idiopathic pulmonary arterial hypertension, one pulmonary veno-occlusive disease; eight chronic obstructive pulmonary disease with paraseptal emphysema mimicking lung cysts or fibrotic air space enlargements; one lung cancer with carcinomatous lymphangitis). Eight patients entered the GI-ILD multidisciplinary discussion, but a definite diagnosis was not yet established at the end of the period considered for the present study, so they were excluded from analysis (STROBE diagram, **Figure 3**). We thus enrolled 119 patients (59 female and 60 male, 50% each), with a median age at first referral of 70 years (interquartile range, 64–77 years). A CTD was diagnosed in 18 cases (15%: 11 male, 60%; 7 female, 40%) and an IPAF in 39 (33%: 10 male, 26%; 29 female, 74%), together representing 48% of the evaluated cases. The remaining 62 patients (52% of cases: 23 female, 37%; 39 male, 63%) had other forms of ILD (idiopathic, sarcoidosis, exposure related, rare ILD, other origin, i.e., Langerhans cell histiocytosis and lymphangioleiomyomatosis). Sex prevalence was different across the three groups ($p = 0.036$). In a *post-hoc* analysis, we observed that female patients were more commonly classified as IPAF ($p = 0.010$). The age at first referral was not different between patients with (70 years; interquartile range, 64–77) and without CTD/IPAF (70 years; interquartile range, 63–77) ($p = 0.665$). In addition, when considering the referral age of CTD (median, 69 years; interquartile range, 61–73) vs. IPAF (median, 70 years; interquartile range, 64–78 years), we did not find statistically significant differences ($p = 0.508$). The CTD patients were classified as rheumatoid arthritis in four (3%), systemic sclerosis in three (3%), undifferentiated connective tissue disease in three (2%), and antisynthetase syndrome in two (2%) cases, whereas six patients (5%) were classified one each as polymyositis, dermatomyositis, Sjogren syndrome, scleromyositis, amyopathic dermatomyositis, and granulomatosis with polyangiitis. Although granulomatosis with polyangiitis is not a CTD but a vasculitis, we included this patient in the analysis because identified thanks to screening steps. Patients in the "other ILD" group ($n = 62$) were mainly classified as idiopathic pulmonary fibrosis ($n = 30$, 48%). Interestingly, three of these patients (10%) were also diagnosed with polymyalgia rheumatica. The remaining 32 patients were diagnosed as idiopathic non-specific interstitial pneumonia (NSIP) ($n = 2$; 2%), respiratory bronchiolitis–ILD ($n = 5$; 4%), cryptogenic organizing pneumonia ($n = 2$; 2%), lymphoid interstitial pneumonia ($n = 2$; 2%), hypersensitivity pneumonitis ($n = 5$; 4%), secondary organizing pneumonia (OP) ($n = 3$; 2%), postactinic fibrosis ($n = 1$; 1%), sarcoidosis ($n = 3$; 2%), Langerhans cell histiocytosis ($n = 1$; 1%), lymphangioleiomyomatosis ($n = 1$; 1%), combined pulmonary fibrosis and emphysema ($n = 5$; 4%), pleuroparenchymal fibroelastosis ($n = 2$; 2%).

The results of the first screening step have been reported in **Figure 4**, stratified according to the diagnosis. The screening questionnaire discriminated well between CTD and other groups (CTD vs. IPAF, $p = 0.001$; CTD vs. other ILD, $p < 0.001$). Laboratory screening was less significantly positive in other ILD ($p = 0.002$ vs. CTD and $p < 0.001$ vs. IPAF). ANA test positivity was more common in CTD group ($p = 0.016$ vs. IPAF and $p < 0.001$ vs. other ILD) and in IPAF group (with respect to other ILD, $p = 0.016$), whereas cytoplasmic positivity of ANA test was more common in CTD and IPAF group with respect to other ILD ($p = 0.012$ and $p = 0.003$, respectively). A similar trend was observed for antiextractable nuclear antigen screen ($p < 0.001$ between IPAF and other ILD) and for myositis-specific and myositis-associated antibodies positivity (for both CTD vs. other ILD and for IPAF vs. other ILD, $p < 0.001$). Rheumatoid factor positivity was not different across the groups ($p = 0.791$), anticyclic citrullinated peptide antibodies were more common in CTD patients with respect to other ILD ($p = 0.008$). Finally, NVC was more frequently positive in CTDs ($p = 0.003$) with respect to IPAF and ($p < 0.001$) with respect to other ILD and in IPAF patients ($p = 0.010$) with respect to other ILD.

Regarding the HRCT pattern observed (**Figure 5**), the most prevalent was usual interstitial pneumonia (usual interstitial

TABLE 1 | Results of the GI-ILD multidisciplinary approach in the cohort of patients analyzed (from January to December 2018), see text for details.

ILD category		Specific diagnosis (no of patients and %)		No ILD patients (tot 119)	Median Age (y) and IQR	Male ($n = 60$; 50%)	Female ($n = 59$; 50%)	Preliminary screening phase								HRCT pattern				
								Questionnaire (≥1 item pos)	Scleroderma pattern at NVC	Laboratory screening						NSIP	NSIP + OP	UIP (def/prob)	OP	Other patterns
										ANA	Cytoplasmic ANA	Anti-ENA	MSA/MAA	RF	anti-CCP					
CTD-ILD		SSc	4 (3%)	18 (15%)	69 (61–73)	11 (57%)	7 (43%)	100%	44%	89%	28%	28%	28%	17%	11%	34%	22%	17%	11%	17%
		RA	3 (3%)																	
		ASSD	2 (2%)																	
		UCTD	3 (2%)																	
		Other CTD	6 (5%)																	
IPAF		IPAF	39 (33%)	39 (33%)	70 (64–78)	10 (26%)	29 (74%)	56%	10%	56%	28%	51%	56%	10%	3%	61%	8%	15%	13%	3%
Other ILD	Idiopathic	IPF	30 (25%)	62 (52%)	70 (63–77)	39 (63%)	23 (37%)	52%	0%	32%	6%	10%	0%	3%	0%	10%	2%	61%	6%	21%
		RB-ILD	5 (4%)																	
		idiopathic NSIP	2 (2%)																	
		idiopathic LIP	2 (2%)																	
		COP	2 (2%)																	
	Sarcoidosis	Sarcoidosis	2 (2%)																	
	Exposure-related	SOP	2 (2%)																	
		Post actinic Fibrosis	1 (1%)																	
	Rare ILD	CPFE	5 (4%)																	
		PPFE	2 (2%)																	
	Myscellanea	HP	5 (4%)																	
		LAM	1 (1%)																	
		LCH	1 (1%)																	
		p-value			=0.665	=0.036		<0.001	<0.001	<0.001	=0.007	<0.001	<0.001	=0.791	=0.003	<0.001	=0.008	<0.001	=0.005	=0.035

ILD, interstitial lung disease; CTD-ILD, connective tissue disease associated ILD; IPAF, interstitial pneumonia with autoimmune features; SSc, systemic sclerosis; RA, rheumatoid arthritis; ASSD, antisynthetase syndrome; UCTD, undifferentiated connective tissue disease; IPF, idiopathic pulmonary fibrosis; RB-ILD, respiratory bronchiolitis-ILD; NSIP, non-specific interstitial pneumonia; LIP, lymphoid interstitial pneumonia; COP, cryptogenic organizing pneumonia; SOP, secondary organizing pneumonia; CPFE, combined pulmonary fibrosis and emphysema; PPFE, pleuroparenchymal fibroelastosis; HP, hypersensitivity pneumonitis; LAM, lymphangioleiomyomatosis; LCH, Langerhans cell histiocytosis. MSA/MAA, myositis specific antibodies/myositis associated antibodies; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibodies; NVC, nailfold videocapillaroscopy; NSIP, non-specific interstitial pneumonia; NSIP + OP, non-specific interstitial pneumonia + organizing pneumonia; UIP, usual interstitial pneumonia.

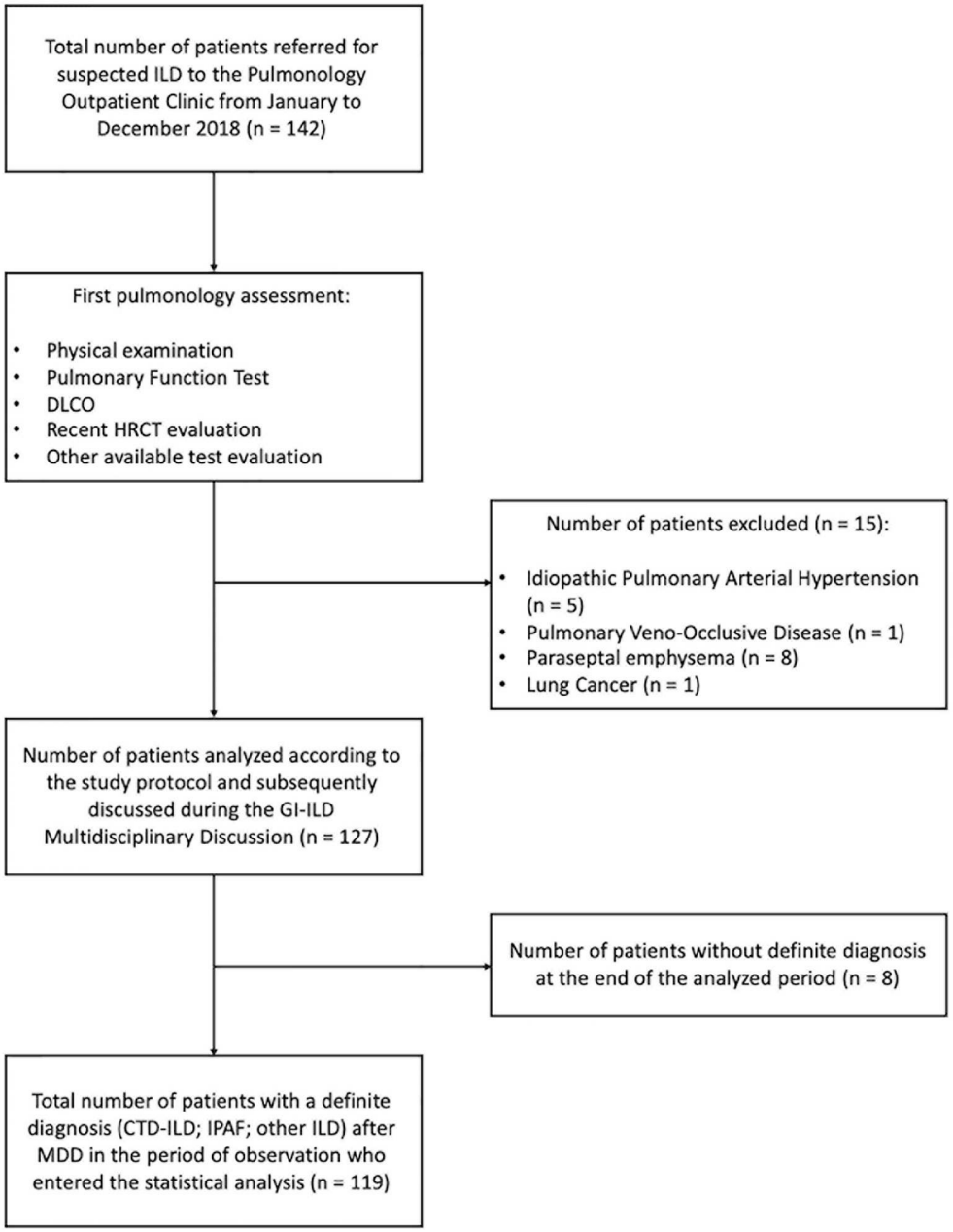

FIGURE 3 | STROBE diagram of the principal selection and analytical phase of the study (STROBE: Strengthening the reporting of observational studies in epidemiology following the EQUATOR network).

pneumonia probable, $n = 47$, 44%) followed by NSIP ($n = 24$, 20%), fibrosing NSIP ($n = 12$, 10%) and OP ($n = 11$, 8%). Some patients had superimposed NSIP and OP ($n = 8$, 7%). The distribution of different patterns across the established groups (CTD, IPAF, and other ILD) was statistically different ($p < 0.001$). In particular (**Figure 5**), NSIP pattern was less common in "other ILD" ($p = 0.013$ vs. CTD and $p < 0.001$ vs. IPAF), the mixed pattern NSIP + OP was more common in CTD than in other ILD ($p < 0.001$), and usual interstitial pneumonia was more common in other ILD ($p \leq 0.001$ with respect to other groups).

DISCUSSION

The multidisciplinary collaborative model we applied in the assessment of newly referred ILD seems to be effective in the *de novo* diagnosis of CTD/IPAF. In fact, we correctly classified more than 45% of patients within the spectrum of autoimmune connective tissue disorders. Interestingly, we did not include three patients with polymyalgia rheumatica in the CTD group, although this exclusion could be discussed, in particular if we

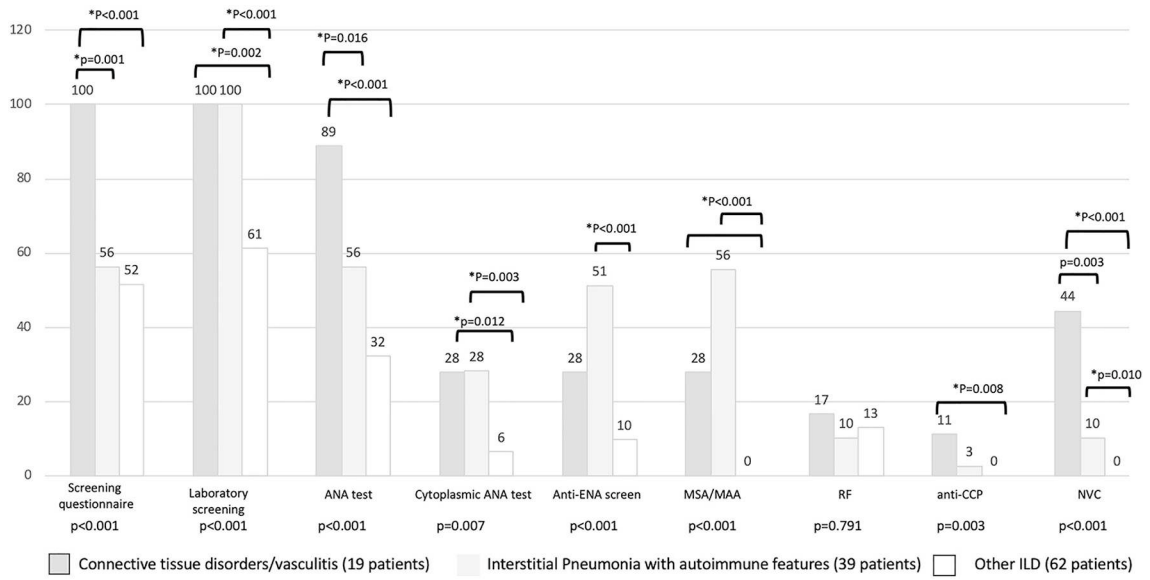

FIGURE 4 | Results (in percentage) of different screening steps according to final patients' classification. *Statistical significance <0.025 for *post-hoc* analysis. MSA/MAA, myositis specific antibodies/myositis associated antibodies; RF, rheumatoid factor; anti-CPP, anti-cyclic citrullinated peptide antibodies; NVC, nailfold videocapillaroscopy.

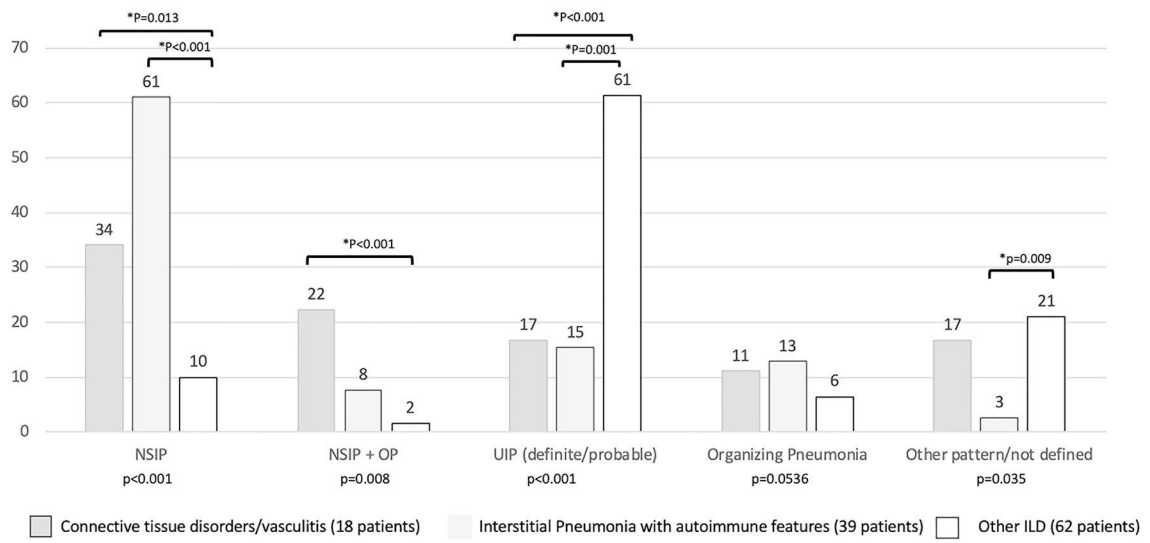

FIGURE 5 | Prevalence (in percentage) of high resolution computed tomography pattern according to final patients' classification. *Statistical significance <0.025 for *post-hoc* analysis. NSIP, non-specific interstitial pneumonia; NSIP + OP, non-specific interstitial pneumonia + organizing pneumonia.

consider the recently described case series of Sambataro et al. (51).

The results we obtained are relevant, even because our model is reproducible and potentially applicable in other centers after an external validation of the entry questionnaire. The model described seems to improve the overall ILD management, increasing the capability to perform a preliminary differential diagnosis of possible rheumatic disorders underlying an ILD. In fact, the identification of subtle CTD signs is not always easy (52), with the risk to underdiagnose rheumatologic disorders, as we recently showed in a cohort of patients first referring to our hospital with a diagnosis of idiopathic pulmonary arterial hypertension (6). Furthermore, several patients we screened were at the end diagnosed with established CTDs, as a further confirmation that the definition of CTD signs is not rarely troublesome also in ILD patients. The adoption of a self-administered questionnaire seems to represent an added value, allowing the homogeneous evaluation of CTD symptoms in a

non-rheumatology setting before the MDD. Moreover, thanks to a well-established collaboration between the Gynecology and the Rheumatology Division of our hospital, a similar approach has been previously applied to a cohort of pregnant women, showing that in patients with positive results, a final diagnosis of CTD was performed in the 25% of cases (16). This is a preliminary confirmation of the potential efficacy of a similar approach in patients referred for ILD, not suspected for but at risk to have a CTD. It is true that continuous clinical exchange within the multidisciplinary team may increase the sensibility of pulmonologist to rheumatology conditions and vice versa, but a standardized preliminary screening for ILD patients may surely reduce the interoperator variability in the assessment of CTD signs. This may be useful, in particular, in smaller secondary centers, were an MDD is not established or feasible. Obviously, as previously suggested, this approach should be validated in other contexts, and support from the National Health Systems and of respective national scientific societies will be necessary for its further application. If the questionnaire is important and generally positive in patients diagnosed with established CTD, in IPAF patients, it is possible to have only laboratory signs of autoimmunity and not clinically relevant features (8). On this basis, during the screening of ILD patients, it is mandatory not only to evaluate the autoimmune profile indicated in the IPAF criteria but also to consider other laboratory tests (15, 23) that have been associated to ILD occurrence, such as the panel we selected. The prototypical example is the cytoplasmic positivity of ANA, which has been linked to the occurrence of antisynthetase syndrome (41). Furthermore, we also enlarged the spectrum of potential rheumatology conditions identified by considering ANCA-associated vasculitis because these conditions are not rarely complicated by the occurrence of ILD (40) and are of primarily interest for both rheumatologists and pulmonologists. One of the patients discussed in the GI-ILD was diagnosed with granulomatosis with polyangiitis, having reported the occurrence of sinusitis together with ANCA positivity at baseline assessment. However, the most useful screening tool we identified was nailfold videocapillaroscopy, which was positive only in case of CTD or IPAF diagnosis, independent to the occurrence of RP, as recently shown in antisynthetase syndrome (25). Although nailfold capillaroscopy should surely enter the routine assessment of every ILD patient, the overall rate of positivity of the test we found in our cohort was quite low.

From the combination of these different domains, during the MDD, we can obtain a series of information that could be helpful in patient's classification, at the same time reducing the number of referral visits before a CTD diagnosis is established. When an ILD occurs, the early identification of CTD or IPAF is crucial and should be carefully considered for the best therapeutic strategy to apply. In fact, an ILD with an autoimmune origin could benefit from immunosuppressant drugs such as cyclophosphamide, cyclosporine, mycophenolate mofetil, azathioprine, and rituximab (20, 53, 54), whereas until now, these patients were simply excluded from the access to anti-fibrotic drugs, such as Nintedanib and Pirfenidone (55). However, the exclusion of these patients from CTD group could be discussed, in particular, if we consider the recently described case series of Sambataro et al. (51) or the promising results of the INBUILD study (56).

In conclusion, with our study, we confirmed that the multidisciplinary approach we applied may be really useful in the identification of CTD-ILD/IPAF in ILD patients without previous rheumatology diagnosis. We suggest that a rheumatologist is necessary in every ILD multidisciplinary team and that, to optimize the diagnostic pathway, a preliminary screening phase with a dedicated questionnaire could be useful. In our opinion, a targeted autoimmune and laboratory profile evaluation and nailfold capillaroscopy should be part of the routine assessment of ILD patients.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

The GI-ILD is approved and recognized by our Foundation. In line with the Declaration of Helsinki, with our national and institutional regulations, and according to our local Institutional Review Board, we obtained from all patients the signed informed consent for the retrospective use of clinical data collected.

AUTHOR CONTRIBUTIONS

TO, RD, AV, FMe, FMa, ZK, PM, and VC organized the GI-ILD. VC, CM, FMe, CS, and LC drafted the screening questionnaire. CA, LC, ZK, CS, FMa, and FMe defined the laboratory test to be searched for in the preliminary phase. LC performed the nailfold videocapillaroscopies, which were reviewed by EM and, in case of conflict, by VC and GZ. AV, RD, and AF performed, analyzed, and discussed CT scans. CT and CL for the pulmonology counterpart. SG, LD, EM, GZ, and VM for the rheumatology counterpart filled the database. LC performed statistical analysis. All Pavia's authors participated to GI-ILD meetings. The paper was mainly drafted by CT, VM, LC, and FMe. CM revised the first draft, and other authors contributed to paper improvement with respect to first version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Lung Involvement in Primary Sjögren's Syndrome—An Under-Diagnosed Entity

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Interstitial lung disease (ILD) represents a frequent extra-glandular manifestation of primary Sjögren's Syndrome (pSS). Limited published data regarding phenotyping and treatment exists. Advances in managing specific ILD phenotypes have not been comprehensively explored in patients with coexisting pSS. This retrospective study aimed to phenotype lung diseases occurring in a well-described pSS-ILD cohort and describe treatment course and outcomes. Between April 2018 and February 2020, all pSS patients attending our Outpatient clinic were screened for possible lung involvement. Clinical, laboratory and high-resolution computed tomography (HRCT) findings were analyzed. Patients were classified according to HRCT findings into five groups: usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), combined pulmonary fibrosis and emphysema (CPFE), and non-specific-ILD. Lung involvement was confirmed in 31/268 pSS patients (13%). One-third (10/31) of pSS-ILD patients were Ro/SSA antibody negative. ILD at pSS diagnosis was present in 19/31 (61%) patients. The commonest phenotype was UIP $n = 13$ (43%), followed by NSIP $n = 9$ (29%), DIP $n = 2$ (6 %), CPFE $n = 2$ (6 %), and non-specific-ILD $n = 5$ (16%). Forced vital capacity (FVC) and carbon monoxide diffusion capacity (D_{LCO}) appeared lower in UIP and DIP, without reaching a significant difference. Treatment focused universally on intensified immunosuppression, with 13/31 patients (42%) receiving cyclophosphamide. No anti-fibrotic treatments were used. Median follow-up was 38.2 [12.4–119.6] months. Lung involvement in pSS is heterogeneous. Better phenotyping and tailored treatment may improve outcomes and requires further evaluation in larger prospective studies.

Keywords: interstitial lung disease (ILD), lung fibrosis, sicca syndrome, ESSDAI—EULAR Sjögren's Syndrome Disease Activity Index, Sjögren's Syndrome (SS)

INTRODUCTION

Primary Sjögren's Syndrome (pSS) is an increasingly recognized autoimmune disease, primarily affecting secretory gland tissue. Its prevalence is estimated at ∼60 cases per 1,00,000 population. The clinical hallmarks are xerophthalmia and xerostomia, however ∼30–50% of patients will develop extra-glandular manifestations in a variety of organ systems (1, 2). Lung involvement is

relatively common, affecting 9–22% and confers major adverse effects on both life quality and mortality, resulting in a 4-fold increase in 10 years mortality (3, 4).

Lung involvement typically presents with exertional dyspnea and a persisting dry cough. Pulmonary function testing (PFT) is recommended, commonly revealing a reduced carbon monoxide lung diffusion capacity (D_{LCO}), and a disproportional loss in forced vital capacity (FVC) (5–7). Abnormalities may be apparent on a standard chest x-ray (CXR), but their absence should not discourage further evaluation for interstitial lung disease (ILD). Pulmonary symptoms can be the first manifestation of pSS. Nannini et al. reported on 105 pSS patients, 10% of whom displayed respiratory manifestations at diagnosis or within the 1st year. At 5 years, prevalence had risen to 20% (+/– 4%) (8). Dry cough was the predominating symptom, affecting 41–61% of patients, with higher than anticipated rates for respiratory infections and pneumonia at 10–35% (3, 9).

Efforts have been made to characterize the relationship between various pSS and interstitial lung diseases, with emphasis upon idiopathic pulmonary fibrosis (IPF). HRCT has been advocated, with a recent systematic evaluation in 527 unselected pSS patients confirming significant interstitial lung changes in 39%. By far the commonest pattern of involvement was non-specific interstitial pneumonia (NSIP), which was observed in 42% of those affected. Usual interstitial pneumonia (UIP), similar in character to IPF, occurred in 11%. Organizing pneumonia (OP) and lymphocytic interstitial pneumonia (LIP) both accounted for <4% of cases. In 82 patients (40%), mixed disease patterns were observed on HRCT (4). The commonest recognized entity is combined pulmonary fibrosis and emphysema (CPFE), which typically consists of upper lobe pan-lobular lung emphysema and basal interstitial features similar to UIP. Usually occurring in smokers, it has also been observed in never smokers (5). LIP has been reported in 10–15% of pSS ILD cases. HRCT imaging reveals thickening of broncho-vascular bundles and interlobular septa, as well as interstitial nodules, ground-glass opacities, and cysts in up to 82% (6, 7, 10).

Within pSS cohorts, ILD has traditionally been linked to smoking, older age, hypergammaglobulinemia, increased rheumatoid factor (RF), or antinuclear antibody titers, anti-SSA or -SSB antibody positivity, elevated C-reactive protein (CRP), and reduced serum C3 levels (10–13). Regarding treatment for pSS ILD, few studies have considered the nature of lung involvement when evaluating efficacy of immunosuppressive drugs, with most being derived from case studies. Corticosteroids together with azathioprine or cyclophosphamide are common in treating pSS-ILD. Many patients, particularly those with UIP, do not appear to benefit from this approach (14–16). Rituximab has been suggested as a universal agent to control pSS-ILD irrespective of form, but data from large studies remains elusive (17).

There is little published information regarding ILD and the typical pSS serological markers and disease activity. No data exists for correlations between biomarkers and the ILD response to immunosuppressive regiments. The primary aim of this study was to systematically evaluate the incidence and characterize ILD phenotype in a well-defined pSS-ILD cohort and summarize outcomes in terms of survival, pulmonary function, serial HRCT scans and response to treatment.

METHODS

Study Design

A retrospective observational cohort study at a single tertiary care institution was performed.

Setting

Patients were recruited *a priori* from attendances at both the Rheumatology or Pulmonology outpatient departments of Hannover Medical School between April 2018 and February 2020. Preliminary clinical screening involved identifying patients with new-onset persisting cough and/or exertional dyspnoea New York Heart Association (NYHA) ≥2 associated with any combination of sicca symptoms, myalgia and/or arthralgia or already known patients with pSS and ILD. Patients fulfilling clinical criteria underwent PFT and assessment of various serum markers for autoimmune disease. Based upon these findings, patients suspected of having ILD were referred for HRCT chest imaging in keeping with EULAR Sjögren's syndrome disease activity score (ESSDAI) recommendations (11). Patients fulfilling diagnostic criteria for pSS without pathological lung function and/or imaging formed the control group (**Figure S1**). All study participants provided written informed consent and the study received Institutional Review Board approval by Hannover Medical School (8179_BO_S_2018).

Participants

Diagnosis of pulmonary involvement in pSS reflected American College Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria (12), with a minimum score of 10, which includes shortness of breath or dry cough accompanying abnormal PFT or pathological findings on HRCT scans. pSS classification criteria were applied to all patients reporting either dry eyes or mouth, or those fulfilling at least one positive domain of the ESSDAI with suspected pSS (ESSDAI) (11).

ESSDAI score was calculated for all patients with lung involvement. pSS criteria were met if the combined score for the following items was ≥4: focal lymphocytic sialadenitis and focus score ≥1 (three points) in the labial minor salivary gland biopsy (13), positive anti-SSA (Ro) antibodies (three points), Schirmer test ≤ 5 mm/5 min in at least one eye, or stimulated whole saliva flow rate increase in weight <2.75 g/2 min (one point). In our institute the Saxon test continues to be used to measure xerostomy. It is defined as a stimulated salivary flow test, an increase in weight <2.75 g/2 min is defined as pathological (14). Stimulated and unstimulated salivary flow tests seem to be comparable (15) and the stimulated salivary flow test is still recommended by EULAR in their latest pSS management recommendations (16). Patients presenting with secondary Sjögren's syndrome or possible secondary Sjögren's syndrome with overlap to dermatomyositis or scleroderma were excluded of the study.

Regarding peripheral neuropathy, the same criteria as in a recently published pSS cohort were used (2). All patients

underwent Saxon and Schirmer tests, as well as testing for Ro52 and Ro60 antibodies, which were measured quantitatively using EliA by Thermo Fisher (Freiburg, device Phadia250). Patients with one positive test and suspected pSS, underwent a labial minor salivary gland biopsy. Biopsies exhibiting focal lymphocytic sialadenitis with a focus score $\geq$1, were considered diagnostic of pSS. Patients with biopsies revealing a focus score of <1 did not meet the classification criteria for pSS, and were excluded from the study.

Variables

Analyses of PFT, HRCT, ESSDAI score, and diagnostic criteria were collated. Furthermore, all treatments for pSS-ILD was documented.

Data Collection

Non-contrast, HRCT scans were performed using volumetric acquisition, with thin-section reconstruction using maximum 1.5 mm slices, as recommended in the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (17). Images were reviewed by a blinded thoracic radiologist, and classified according to Fleischner Society criteria for interstitial lung disease (18, 19).

PFTs were performed on all patients in a dedicated laboratory, consisting of either standard spirometry or body plethysmography in cases with FVC loss suspected of having restrictive ventilatory defects. Diffusion capacity was measured using single-breath determination of carbon monoxide uptake. All tests were performed according to ATS/ERS guidelines (20–22) and results interpreted by blinded pulmonologists. In case of abnormal FVC and or low diffusion capacity (DLCO) chest X-ray (CXR) and in 36 cases HRCT of the chest were performed. Only patients with pathological HRCT scans were included into the analyses.

Follow up PFTs were considered improved if they increased $\geq$10% of level at treatment initiation, or progressive disease if they decreased $\geq$10% over treatment baseline. Values remaining between $\pm$10% corridor of baseline were considered stable.

Participants completed a structured questionnaire regarding symptoms, including EULAR Sjögren's syndrome patient reported index (ESSPRI). Furthermore, Saxon and Schirmer tests, salivatory gland biopsy, if necessary, as well as diagnostic work up for ESSDAI scoring were performed (11). In keeping with routine departmental protocols, all clinical and diagnostic data were prospectively archived in a customized Microsoft® Access database (Microsoft Corporation, Redmond, WA, USA).

Statistical Analysis

Descriptive statistics were calculated using R version 3.6.0 (Foundation for Statistical Computing, Vienna, Austria) in conjunction with "Hmisc" (Frank E. Harrell Jr. (2020). Hmisc: Harrell Miscellaneous. R package version 4.3-1.), "dplyr" (Hadley Wickeam, Romain Fracois, Lionel Henry, and Kirill Müller (2020). Dplyr: A Grammar of Data Manipulation. R package version 0.8.5.) and "ggplot2" (H. Wickam. ggplot2: Elegant graphics for data analysis. Springer-Verlag New York, 2016) packages. To compare age of pSS onset between ILD and non-ILD controls, a non-parametric age distribution was assumed and a two-sided Wilcoxon signed-rank test was used, $p < 0.05$ were considered statistically significant. Values reported are median [inter-quartile range] unless otherwise reported.

RESULTS

Two-hundred and sixty-eight patients with pSS were identified, of whom 51/268 had clinical symptoms like dry cough or shortness of breath. All symptomatic patients underwent PFT, 36/51 had pathological findings defined as FVC $\leq$ 80% predicted and/or DLCO $\leq$ 70% predicted. HRCTs were performed on all 36 patients. Of these, 31/36 (86%) exhibited pathological findings possibly related to pSS. Five patients had no changes suggestive of ILD and were excluded from the analysis. In total 31/268 (13%) pSS patients had ILD. Demographics for pSS-ILD patients are summarized in **Table 1**. The majority of patients were never-smoking females, presenting in their seventh decade. All were Caucasian. Compared to non-ILD patients ($n = 237$), pSS-ILD patients were significantly older (59.0 [50.4–68.5] vs. 53.3 [40.9–63.9] years; Wilcoxon Rank Sum $p = 0.0044$, **Figure 1**) at time of pSS diagnoses. Median follow-up was 38.2 [12.4–119.6] months.

At ILD diagnosis, the median ESSDAI was 19.0 [14.3–24.8]. After lung involvement, the most common domains of disease activity were hematological (15/31, 48%), joints (12/31, 39%), and biological (9/31, 29%). The latter derived from hypergammaglobulinemia and or hypocomplementemia or presence of cryoglobulinemia. In nine patients (29%), both the Saxon and Schirmer tests were pathological, with one or other being positive in 22/31 patients (71%). Of the 10 SSA (Ro)-antibody negative patients (31%), whilst half were also Saxon test negative all had salivary gland biopsies $\geq$ Chisholm Mason grade 3. Four patients without objective xeropthalmia and xerostomia were diagnosed with pSS due to positive anti-SSA(Ro) antibodies and focal sialadenitis.

At ILD diagnosis PFTs demonstrated impaired ventilation and diffusion in almost all patients, with median forced vital capacity (FVC) being 65 [52–88]% predicted and median DLCO of 48 [41–80]% predicted. Patients demonstrating UIP and in particular desquamative interstitial pneumonia (DIP) were most severely affected with FVC of 60 [−46-65]% predicted and 50 [45–55]% predicted at diagnosis, along with DLCO of 53 [36–71]% predicted, and 35 [29–41]% predicted respectively (**Table 2**).

Analysis of the CT imaging revealed that UIP was the predominating pattern of disease ($n = 13$, 42%), with NSIP also proving common ($n = 9$, 29%). Similar numbers of the much more aggressive DIP and multi-factorial CPFE were observed (both $n = 2$, 6%).

The remaining five patients exhibited various different patterns of lung involvement including bronchiectasis, tree in bud phenomena suggestive of bronchiolitis, and in one patient cystic changes suggestive of LIP. Due to the small numbers these cases were amalgamated into non-specific disease for the purposes of analysis (**Figure 2**).

TABLE 1 | Summary of patient demographics.

Cohort demographics ($n = 31$)		
Female, *n* (%)	22	(71)
Never smoking, *n* (%)	23	(74)
Initial manifestation (ILD), *n* (%)	17	(71)
Age 1st manifestation, years	58.9	[49.6–68.4]
– ILD as 1st manifestation, *n* (%)	19	(61)
– Time to pSS diagnosis in ILD first, months	6.2	[3.1–44.1]
– Time to ILD diagnosis in pSS first, months	3.1	[0.0–38.8]
Follow up, months	38.2	[12.4–119.6]
EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)		
Constitutional Symptoms, *n* (%)	1	(3)
Lymphadenopathy, *n* (%)	1	(3)
Glandular involvement, *n* (%)	2	(7)
Articular involvement, *n* (%)	12	(39)
Cutaneous involvement, *n* (%)	3	(10)
Pulmonary involvement, *n* (%)	31	(100)
Renal involvement, *n* (%)	1	(3)
Muscular involvement, *n* (%)	1	(3)
Peripheral nervous system involvement, *n* (%)	6	(19)
Central nervous system involvement, *n* (%)	1	(3)
Hematological involvement, *n* (%)	15	(48)
Biological involvement, *n* (%)	9	(29)
Laboratory values at ILD diagnosis		
CRP >10 mg/l, *n* (%)	13	(42)
Rheumatoid factor positive, *n* (%)	16	(52)
ANA >1:160, *n* (%)	28	(90)
Presence of SSA (Ro) antibody, *n* (%)	21	(68)
Presence of SSB (La) antibody, *n* (%)	7	(23)
xANCA positive, *n* (%)	3	(10)
Xerostomia tests		
Saxon test pathological, *n* (%)	12[a]	(41)
Schirmer test pathological, *n* (%)	27[a]	(87)
Salivary gland biopsy		
Chisholm Mason- grade ≥3, *n* (%)	11[b]	(85)
Lung function at ILD diagnosis		
% Predicted forced vital capacity (FVC)	65	[52–88]
% Predicted diffusing capacity (D_{LCO})	48	[41–80]
CT patterns of lung disease		
Usual interstitial pneumonia, *n* (%)	13	(42)
Non-specific interstitial pneumonia, *n* (%)	9	(29)
Desquamative interstitial pneumonia, *n* (%)	2	(7)
Combined pulmonary fibrosis and emphysema, *n* (%)	2	(7)
Unspecific interstitial change, *n* (%)	5	(16)
Treatment		
1st line DMARD		
– Cyclophosphamide, n (%)	13	(42)
– Azathioprine, n (%)	8	(26)
– Methotrexate, n (%)	5	(16)
– Hydroxychloroquine, n (%)	2	(7)
– Rituximab, n (%)	1	(3)
– Mycophenolate mofetil, n (%)	1	(3)
Number of treatment modalities attempted per patient	3	[2–3]

Clinical, laboratory, pulmonary function, and computer tomography findings at the time of original diagnosis have been included.

[a] *Results available for 29/31 patients included in the cohort.*

[b] *Results available for 13/31 patients included in the cohort.*

Values represent median [inter-quartile range] unless otherwise stated.

ILD, interstitial lung disease; pSS, primary Sjögren's Syndrome; CRP, C reactive protein; ANA, antinuclear antibody; xANCA, atypical anti-neutrophil cytoplasmatic antibodies; DMARD, disease modifying anti-rheumatic drug.

Subgroup analysis revealed a persisting female predominance across all forms of lung involvement. Patients exhibiting a DIP pattern presented much earlier. Lung function revealed more profound ventilatory impairment in UIP and DIP compared to other phenotypes. A similar, albeit less obvious, pattern was observed in diffusion coefficients. Regarding 1st line treatment, no clear patterns reflecting pulmonary phenotype were identified and again the small numbers prevented statistical appraisal. During the 29.0 [8.9–80.5] months of follow-up after ILD diagnosis, 24/31 patients achieved stabilized or improved FVC after commencing treatment (**Figure 3**). One patient died during follow-up due to an unrelated cancer. It should be noted however, that follow-up in the predominant pulmonary phenotypes remains limited (UIP 18.0 [9.5–97.8] months; NSIP 12.0 [8.9–49.7] months).

In general terms, 1st line treatment consisted of systemic corticosteroids in conjunction with disease modifying anti-rheumatic drugs (DMARDs). Cyclophosphamide was most commonly used ($n = 13$, 42%), followed by azathioprine and methotrexate ($n = 8$, 26% and $n = 5$, 16%). In 26/31 patients (84%) the 1st line DMARD was changed. The median numbers of different DMARDs used was 3 [2–3], with the maximum used in an individual patient being seven.

Evaluating 1st line treatment choice, patients commenced on cyclophosphamide tended to be younger at median 58.4 [47.6–67.2] years and have poorer lung function (median FVC 64 [44–88]% predicted) compared to the other DMARDs used. Given the limited data available no statistical analysis has been performed.

In terms of initial treatment response, across all groups and independent of treatment received, a gradual slowing in FVC loss was observed, with a suggestion of some recovery among those patients with the longest follow-up. These trends were more apparent in the larger NSIP and UIP subgroups but the limited follow-up prevents meaningful interpretation of these preliminary findings (**Figure S2**). Follow-up HRCT Thorax has to date been performed in 13/31 patients (42%) at a median 7.0 [4.1–17.8] months after the first scans. A small minority of patients (6/13, 46%) demonstrated radiological progression. This included both DIP patients who had received cyclophosphamide, as well as 2/9 (22%) NSIP patients who received hydroxychloroquine or cyclophosphamide respectively, a CPFE patient (1/2, 50%) who received methotrexate and a single UIP patient (1/13, 8%) who initially received mycophenolate. Nonetheless none of the patients have died due to their lung disease or required lung transplantation during ongoing follow-up, or have been commenced on additional anti-fibrotic therapies, such as pirfenidone or nintedanib.

DISCUSSION

Our data raises a number of important aspects regarding ILD and pSS despite small cohort size and limited follow-up. Firstly, symptomatic lung involvement was identified in 13% of pSS patients attending our institution. This corroborates previously reported prevalence ranging from 9–22% (23, 24) and supports initiating structured screening for lung disease in pSS patients.

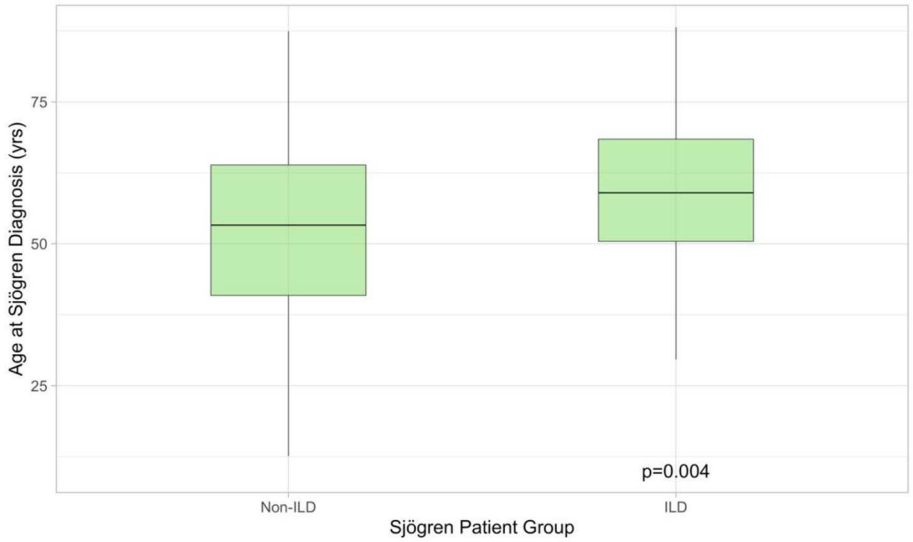

FIGURE 1 | Boxplot illustrating age at which Sjögren's syndrome was diagnosed in patients with ($n = 31$) and without ($n = 268$) lung involvement. The former were older at presentation. ILD, interstitial lung disease.

Normal lung physiology features inherent functional reserves and inevitably significant pathology exists before patients become symptomatic. This is common in many lung diseases, partially accounting for disappointing outcomes in chronic respiratory conditions including ILD.

The second important implication is the need for effective pSS screening in patients presenting with apparently idiopathic ILD. Reliance upon antibody testing for anti-SSA (Ro) and anti-SSB (La) appears inadequate for screening, with our results suggesting that up to one-third of patients could be missed. Potential advantages of augmenting screening with testing for dry eyes and mouth and in equivocal cases proceeding to salivary gland biopsy requires further careful evaluation.

Rheumatologists regularly evaluate ILD patients on respiratory wards or as outpatient pulmonology referrals. Interdisciplinary cooperation may explain the high percentage of ILD patients, in whom pSS was subsequently diagnosed on routine screening (9/31, 29%) compared to previous reports. of 10% (8). This raises the possibility that significant numbers of ILD patients with undetected pSS may be missed or managed as IPF instead. Recently, interstitial pneumonia with autoimmune features (IPAF) was defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) as an interstitial pneumonia with clinical, serological, or morphological features of an autoimmune disease without fulfilling criteria for a specific connective tissue disease (CTD) (25). In such cases, we would advocate additional diagnostic work up for pSS-ILD given the heterogeneity of the latter, which lies well within the IPAF criteria.

Compounding this further, is the diversity of ILD observed in the cohort. A persisting misconception remains, that NSIP is the predominating HRCT phenotype occurring in autoimmune connective tissue diseases (4, 26). Our data could not corroborate this, with UIP actually being the most common manifestation. Unquestionably, the data presented is circumstantial and no causality can be inferred. It remains possible that our results merely reflect different conditions occurring in the same patient. Contradicting this however is the predominance of never-smoking females with UIP. Nevertheless, the data reiterates the need for critical appraisal of ILD phenotypes as a catalyst for further research and potentially, individualized treatment. Current data for UIP in pSS is limited, with case reports suggesting a poor response to augmented immunosuppression (1). Although our data does not support these results, it should be reiterated that our experiences are greatly limited, in terms of both numbers and duration of follow-up. It should be noted however that reports suggesting more favorable outcomes in CTD-associated UIP compared to idiopathic UIP (27).

Contradictory data exists regarding the age of diagnosis in pSS with ILD and without. Whilst Dong et al. report a significant age difference 57.44 (+/− 14.08) years in pSS patients without ILD vs. 61.00 (+/− 11.23) years in patients with ILD, Palm et al. did not see a difference (4, 23, 28). In our cohort pSS patients with ILD were older than patients without ILD at time of diagnosis.

The choice of treatment in our cohort was based on severity of lung involvement and HRCT findings. If alveolitis was detected and severe impairment of lung function was present, glucocorticoids in combination with intravenous cyclophosphamide was used as first line treatment. If possible six courses of cyclophosphamide (15 mg/kg) were given monthly followed by a maintenance therapy of mycophenolate mofetil or azathioprine.

TABLE 2 | Subgroup demographics with respect to interstitial lung disease patterns, as determined in the original CT Thorax.

	UIP		NSIP		DIP		CPFE		Unspecific	
Patient, *n* (%)	13	(43)	9	(29)	2	(6)	2	(6)	5	(16)
Female, *n* (%)	9	(69)	5	(56)	2	(100)	1	(50)	3	(60)
Age Onset, years	58.9	[50.6–68.8]	57.3	[50.0–64.3]	36.8	[36.2–37.4]	60.6	[43.5–77.8]	67.8	[63.9–68.3]
Age SS, years	59.0	[50.7–68.8]	57.7	[50.2–68.4]	45.7	[37.5–53.9]	60.7	[43.6–77.9]	67.9	[64.0–68.4]
Age ILD, years	61.9	[54.9–69.3]	57.4	[51.1–64.4]	36.9	[36.2–37.5]	62.7	[47.6–77.9]	68.4	[65.9–70.8]
Never smoker, *n* (%)	10	(77)	6	(67)	1	(50)	1	(50)	5	(100)
– Pack years	2		9		3		18		-	
ESSDAI score	18	[14–25]	17	[15–22]	19	[13–25]	12	[10–14]	22	[21–25]
Lung function at ILD diagnosis										
FVC, % pred	60	[46–65]	70	[54–76]	50	[45–55]	98	[93–102]	79	[78–98]
D_{LCO}, % pred	53	[36–71]	47	[41–68]	35	[29–41]	70	[55–84]	79	[63–84]
Treatment										
1st line treatment										
CYC, n (%)	6	(45)	5	(56)	2	(100)	0	-	0	-
AZA, n (%)	4	(31)	1	(11)	0	-	1	(50)	2	(40)
MTX, n (%)	1	(8)	1	(11)	0	-	1	(50)	2	(40)
HCQ, n (%)	0	-	1	(11)	0	-	0	-	1	(20)
RTX, n (%)	1	(8)	0	-	0	-	0	-	0	-
MMF, n (%)	1	(8)	0	-	0	-	0	-	0	-
Number treatments	3	[2–4]	3	[2–3]	2	[1–3]	3	[1–4]	2	[2–3]
Treatment outcomes										
FVC										
Improved, *n* (%)	2	(15)	1	(12)	2	(100)	0	-	0	-
Stabilized, *n* (%)	8	(62)	4	(44)	0	-	2	(100)	3	(100)
Declined, *N* (%)	3	(23)	4	(44)	0	-	0	-	0	-
D_{LCO}										
Improved, *n* (%)	3	(23)	1	(11)	2	(100)	0	-	1	(20)
Stabilized, *n* (%)	9	(69)	5	(56)	0	-	2	(100)	4	(80)
Declined, *N* (%)	1	(8)	3	(33)	0	-	0	-	0	-
Follow up, months	37	[12–96]	17	[13–50]	113	[9–218]	65	[10–120]	170	[81–182]
Deaths, *n* (%)	1	(8)	0		0		0		0	

Lung function outcomes based upon ±1% per month change over baseline values at original diagnosis.
UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; DIP, desquamative interstitial pneumonia; CPFE, combined pulmonary fibrosis and emphysema; SS, Sjögren's Syndrome; ILD, interstitial lung disease; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; FVC, forced vital capacity; D_{LCO}, Carbon monoxide lung diffusion capacity; CYC, cyclophosphamide; AZA, azathioprine; MTX, methotrexate; HCQ, hydroxychloroquine; RTX, rituximab; MMF, mycophenolate mofetil.
Values represent median [inter-quartile range] unless otherwise stated.

In January 2020 EULAR recommendations for the management of pSS have been published, as first line treatment for moderate and high ESSDAI score glucocorticoids 0.5–1 mg/kg are recommended regarding to severity. As second line immunosuppressive agents are suggested, and as a rescue therapy cyclophosphamide and rituximab are recommended. But the task force points out that there are no controlled studies or head to head comparisons of any immunosuppressive agents allowing support of a differentiated organ-guided therapeutic approach (16). Which highlights the necessity of therapy studies in pSS patients with extra-glandular manifestations.

Research into UIP treatments in non-pSS populations has received a great deal of attention in the past decade. Traditional treatments with steroids, azathioprine, and n-acetyl-cysteine, based on IFIGENIA study (29) were called into question by the extended PANTHER-IPF study (30) which suggested that immunosuppression was actually worsening prognosis in UIP-ILD. This combined with the early results from the CAPACITY (31) and ASCEND (32) trials led to a paradigm shift away from immunosuppression and toward novel anti-fibrotic agents. Beyond idiopathic pulmonary fibrosis, recent data from the SENSCIS study (33) examined the effects of nintedanib in systemic sclerosis associated lung disease. This prospective, randomized, placebo controlled study included over 570 patients and demonstrated clinical benefit. Current publications from this cohort have not yet attempted to describe or phenotype ILD in these patients.

Our cohort included only one patient with HRCT features suggestive of LIP, which may just reflect the small size of our

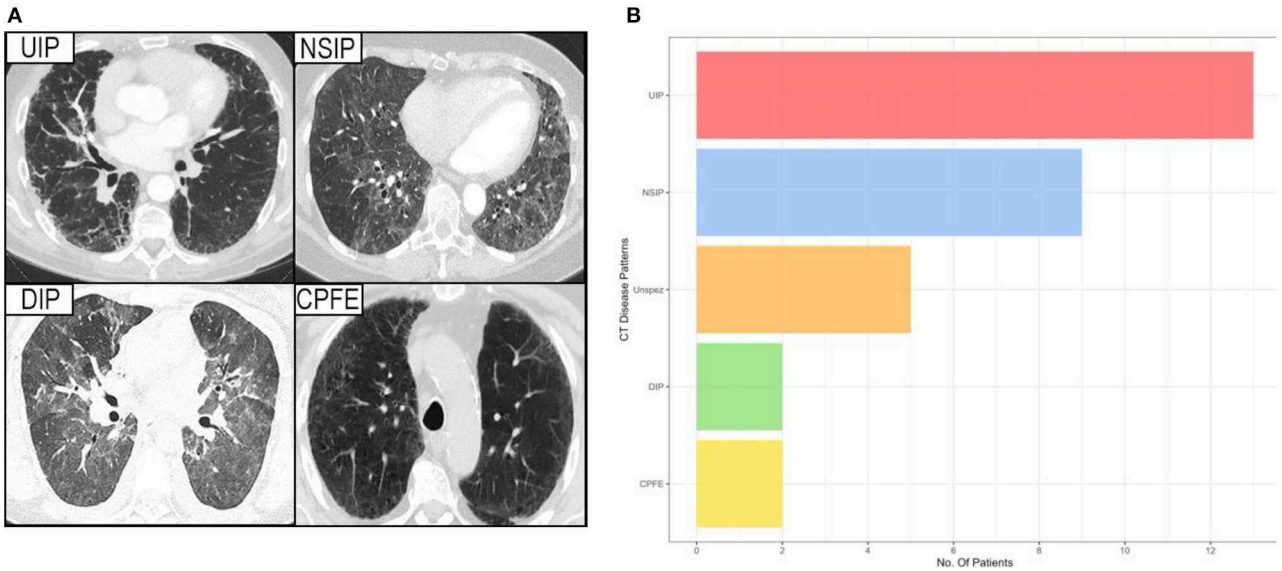

FIGURE 2 | (A) Showing the HRCT pattern of the various interstitial lung diseases. **(B)** Showing the prevalence of different forms of interstitial lung disease among patients with a proven Sjögren's syndrome, considered contributory to their lung disease. UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; DIP, desquamative interstitial pneumonia; CPFE, combined pulmonary fibrosis and emphysema; Unspez, unspecific interstitial changes.

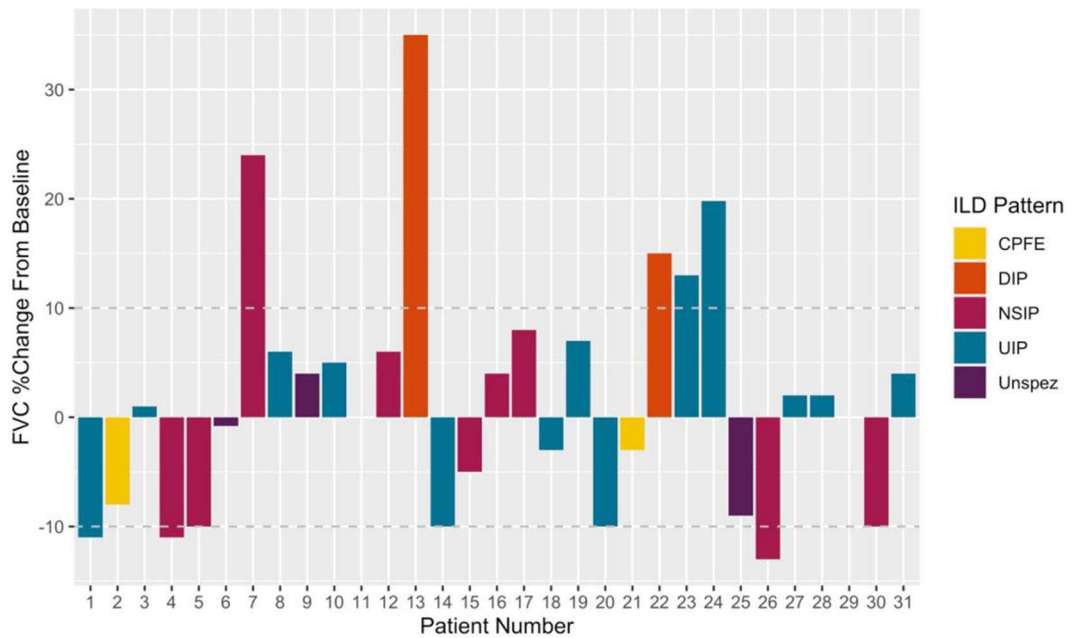

FIGURE 3 | Illustrating %changes in FVC following treatment initiation. Deltas calculated using last available measurement. Disease progression (treatment failure) was defined as a 10% fall in FVC from that recorded at treatment initiation. A 10% improvement symbolized Improved on treatment. Patients within ± 10% baseline were classed as stable.

cohort. Furthermore, LIP is a histological diagnosis, biopsies were performed only in 4/31 patients, so that no meaningful statistical analyses was possible.

Nevertheless, our cumulative findings reinforce the need for continued refinement of disease phenotypes and evaluation of tailored treatment approaches. Due to its limitations, the data presented here is at best preliminary and serves principally as a basis for focusing future research. Our cohort is small, the data collection was entirely retrospective and both evaluation—in terms of lung function and HRCT scanning—contains inevitable

selection bias. In certain populations, HRCT in asymptomatic patients have confirmed pathological interstitial findings (4). In our institution performance of HRCT in asymptomatic patients is ethically difficult. To compensate for this, the PFT criteria are intended to allow very early detection, to minimize the number of potential missed cases. Crucially, no reliable screening has been performed in asymptomatic patients. Compounding this further, was the reliance on lung function and HRCT imaging rather than histological confirmation. Regarding PFT, analysis was based on FVC values, rather than lung volumes such as total lung capacity (TLC). FVC has been almost universally employed in large multi-center IPF studies due to logistical concerns. TLC measurements on body plethysmography offer clear advantages in identifying and monitoring ILD, but is both time consuming and expensive. Similar issues exist with transbronchial and open-lung biopsies, notwithstanding the additional patient risk such procedures entail.

In conclusion, our results reveal that pulmonary disease is commonly associated with pSS, manifesting in a variety of different clinical entities. Screening for pSS in patients with unclear lung disease should be performed regardless of subjective sicca symptoms via screening for xeropththalmy or xerostomy and in case of unremarkable antibodies a salivary gland lip biopsy should be performed. Based upon existing data from other disease groups, potential exists for improving outcomes by refining disease recognition strategies and designing appropriate studies with aim of structured surveillance and tailored treatment strategies.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethics committee of Hannover Medical Highschool. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DE, AJ, GS, and SH: conception and design of the study, acquisition and interpretation of data, drafting the article, and final approval of the version to be submitted. TSk, TW, and RS: interpretation of data, revising critically for important intellectual content, and final approval of the version to be submitted. JH: acquisition of data, analyzing all CT reports, revising critically for important intellectual content, and final approval of the version to be submitted. TT and TSe: acquisition and interpretation of data and final approval of the version to be submitted. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.00332/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Predictors and Mortality of Rapidly Progressive Interstitial Lung Disease in Patients With Idiopathic Inflammatory Myopathy: A Series of 474 Patients

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Objective: This study was conducted to identify the characteristics and prognosis of rapidly progressive interstitial lung disease (RP-ILD) in idiopathic inflammatory myopathy (IIM) and to assess the predictors for poor survival of RP-ILD in IIM.

Methods: A total of 474 patients with IIM were enrolled retrospectively according to medical records from Peking University People's Hospital. Clinical and laboratory characteristics recorded at the diagnosis of patients with RP-ILD and chronic ILD (C-ILD) were compared. The Kaplan–Meier estimator and univariate and multivariate analyses were used for data analysis.

Results: ILD was identified in 65% (308/474) of patients with IIM. Patients with ILD were classified into two groups based on lung features: RP-ILD (38%, 117/308) and C-ILD (62%, 191/308). RP-ILD resulted in significantly higher mortality in IIM compared with C-ILD (27.4 vs. 7.9%, $P < 0.05$). In this study, by comparing IIM patients with and without RP-ILD, a list of initial predictors for RP-ILD development were identified, which included older age at onset, decreased peripheral lymphocytes, skin involvement (periungual erythema, skin ulceration, and subcutaneous/mediastinal emphysema), presence of anti-MDA5 antibody, serum tumor markers, etc. Further multivariate Cox proportional hazards model analysis identified that anti-MDA5 positivity was an independent risk factor for mortality due to RP-ILD ($P < 0.05$), and lymphocytes <30% in BALF might also be associated with poor survival of myositis-associated RP-ILD ($P < 0.05$).

Conclusion: Our study shows that RP-ILD results in increased mortality in IIM. Anti-MDA5 positivity and a lower lymphocyte ratio in BALF might be the predictive factor of mortality due to RP-ILD.

Keywords: myositis, interstitial lung disease, MSAs, rapidly progressive, survival

INTRODUCTION

Idiopathic inflammatory myopathy (IIM) is a group of systemic autoimmune diseases characterized by skin rash, proximal muscle weakness, and extramuscular manifestations, such as arthralgia, fever, and interstitial lung disease (ILD). Dermatomyositis (DM), polymyositis (PM), and clinically amyopathic dermatomyositis (CADM) are the three main subtypes of IIM (1, 2). Myositis-associated ILD is one of the leading extramuscular features, occurring in 20–80% of all PM/DM/CADM patients (3, 4). Rapidly progressive ILD (RP-ILD) in IIM is a life-threatening subtype of myositis-associated ILD, which tends to be resistant to high-dose glucocorticoid treatment and immunosuppressants (4–6). Recently, a study in a European myositis cohort reported that 40–60% of patients with RP-ILD were admitted to the ICU, and hospital mortality was 45–51% (7). Some patients with RP-ILD decline within weeks, but for other patients, the time to ILD-induced deterioration is on the order of years (8), and the 5-year survival rate is more than 85% in myositis-associated ILD (9, 10). However, it is difficult to predict whether patients with myositis-associated ILD will develop fatal disease progression at the early stage of the disease. Therefore, it is necessary to identify potential factors to predict survival of patients with myositis-associated RP-ILD in the early stage of disease development.

The pathogenesis of lung injury in myositis is unclear. Although anti-aminoacyl tRNA synthetase (ARS) and anti-melanoma differentiation-associated 5 (MDA5) antibodies have been described as associated with RP-ILD (11), the exact pathophysiology and diagnostic value of these autoantibodies remain to be elucidated. Previous studies have reported the relationship between poor outcomes of RP-ILD with DM classification, older age, skin ulceration, lack of myositis, and positivity of anti-MDA5 antibody (12–14). Fever, elevated serum CRP, and ferritin levels and ground-glass attenuation on high-resolution CT (HRCT) have been suggested as risk factors for ILD in myositis (14–16). However, due to the heterogeneity of IIM, the prevalence, risk predictors, and survival rates of RP-ILD vary widely among different studies.

In this study, we investigated the clinical and laboratory characteristics at the time of diagnosis of ILD in DM/PM/CADM patients. Moreover, we compared serum biomarkers and pulmonary characteristics of RP-ILD and chronic-ILD (C-ILD) to exploit potential prognostic markers of myositis-associated RP-ILD in a large-scale patient cohort in China.

MATERIALS AND METHODS

Patients

Patients diagnosed with DM/PM/CADM in the department of rheumatology and immunology, Peking University People's Hospital between July 2000 and October 2019 were identified in this retrospective study. Cases satisfied diagnostic criteria suggested by the Bohan & Peter DM/PM classification or Sontheimer's definitions (2, 17). CADM is the combination of amyopathic DM (ADM) and hypomyopathic DM (HDM). Patients with other definite causes of interstitial lung disease, such as infectious pneumonia, chronic obstructive pulmonary disease (COPD), lung injury, and drug or occupational-environmental exposures were excluded at the initial diagnosis. Patients with complicating conditions, such as an active neoplasm and history of lung cancer, and other identifiable autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or systemic sclerosis (SSc), or that had been treated with systemic corticosteroids and immunosuppressants before referral to our hospital were also excluded. This study was approved by the ethics committee of Peking University People's Hospital.

Methods

Demographic, clinical, and laboratory data at the time of diagnosis and during follow-up were collected from hospital records. Demographic and clinical information, including age at onset, gender, disease duration at diagnosis, initial symptoms associated with the disease, Gottron's sign/papules, skin ulceration, periungual erythema, proximal muscle weakness, malignancy history, and ILD, were assessed. Laboratory data were recorded, including serum levels of creatine kinase (CK), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and ferritin. Myositis-specific autoantibodies (MSAs, antigens including Jo-1, PL-7, PL-12, EJ, OJ, KS, MDA5, NXP2, SAE, Mi-2, TIF-1γ) and myositis-associated autoantibodies (MAAs, antigens including Ro-52, PM-Scl, Ku) were identified in 207 patients by immunoblotting according to the manufacturers' instructions (Euroimmun, Germany).

Findings on arterial blood gas analysis, pulmonary function tests (PFT, including forced vital capacity, diffusing capacity for carbon monoxide and total lung capacity), chest high-resolution computed tomography (HRCT), and bronchoalveolar lavage fluid (BALF) were recorded at ILD diagnosis when available. Images of ILD on HRCT, including ground-glass attenuation (GGA), consolidations, nodular, reticulonodular, interlobular septal thickening, honeycombing, and traction bronchiectasis, were assessed. Based on the HRCT scan pattern, patients were classified into the following four groups: non-specific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia (LIP), usual interstitial pneumonia (UIP), and organizing pneumonia (OP). HRCT were reviewed by a panel of experienced radiologists according to 2013 ATS/ERS policies (18). The definition of RP-ILD was rapidly progressive dyspnea and hypoxemia with a worsening of radiologic interstitial lung changes within 3 months after the onset of respiratory symptoms. C-ILD was defined as an asymptomatic, slowly progressive ILD or as non-rapidly progressive over 3 months (19).

BALF was collected during bronchoscopy in clinic. Bronchoscopy was administrated with local anesthesia induced by lidocaine; 100 ml of sterile saline (0.9% NaCL) was instilled through the bronchoscope into the right lung field in two to four aliquots. BALF was collected after administration. Cellular components were separated from BALF by centrifugation (10 min, 1,200 rpm). Cytospin slides of cells in BALF were stained with hematoxylin-eosin for subsequent cell identification. The numbers of macrophages, lymphocytes, and neutrophils were recorded. The data of cytological analyses of BALF were collected from the standardized case record form in the clinical record.

The R Maximal Selected Rank (MaxStat) package was used to determine the optimal cutoff point in lymphocytes in BALF to predict poor survival of RP-ILD.

Statistical Analysis

Categorical variables were presented as frequency (percentages). Continuous data were expressed as the mean ± standard error or medians (interquartile range), and data on RP-ILD vs. C-ILD were compared using Student's *t*-test or the Mann–Whitney *U* test. Categorical variables were compared using Fisher's exact test or chi-square test. Outcomes were compared between RP-ILD patients and C-ILD patients. Survival between various groups was analyzed using a Kaplan–Meier curve with log rank test. Univariate and multivariate Cox regression analyses were used to identify predictors of poor survival due to RP-ILD.

RESULTS

Characteristics of ILD in Patients With PM/DM/CADM

The study cohort included 505 patients with myositis and 31 patients with other autoimmune diseases (11 patients overlapped with SLE, 9 patients overlapped with SSc, 9 patients overlapped with RA, 2 patients overlapped with SLE+SSc) were excluded. A total of 474 patients with PM/DM/CADM were enrolled in this study, including 87.6% (369/474) females with a mean age of 49.7 ± 14.0 years (**Table 1**). ILD was found in 65% (308/474) of patients with PM/DM/CADM. ILD was identified to precede IIM clinical manifestations in 10.7% (33/308) of patients; among these patients with isolated ILD, 57.6% (19/33) of them developed myositis within 1 year after ILD diagnosis, 36.4% (12/33) were diagnosed with myositis 1–3 years after ILD diagnosis, and 6.1% (2/33) had myositis after 3 years. ILD onset was identified concurrently with PM/DM/CADM in 57.1% (176/308) of patients and occurred after IIM onset in 32.1% (99/308) of patients. Patients with ILD were divided into two groups according to pulmonary manifestations: RP-ILD (38%, 117/308) and C-ILD (62%, 191/308). The most common pattern of chest HRCT in IIM with ILD was NSIP (67.2%, 207/308), followed by OP (26.0%, 80/308) and UIP (6.8%, 21/308).

TABLE 1 | Demographics and pulmonary characteristics of 474 patients with IIM.

Variables	*n* = 474
Female, no. (%)	369 (87.6)
Age at onset, years	49.7 ± 14.0
DIAGNOSIS	
DM, no. (%)	216 (45.6)
CADM, no. (%)	201 (42.4)
PM, no. (%)	57 (12.0)
ILD, no. (%)	308 (65)
Rapidly progressive ILD, no. (%)	117/308 (38.0)
Chronic ILD, no. (%)	191/308 (62.0)
ILD ONSET	
Before IIM onset, no. (%)	33/308 (10.7)
Concomitant with IIM, no. (%)	176/308 (57.1)
After IIM onset, no. (%)	99/308 (32.1)
HRCT PATTERN	
NSIP, no. (%)	207/308 (67.2)
OP, no. (%)	80/308 (26.0)
UIP, no. (%)	21/308 (6.8)

Continuous data are presented as M (mean) ± SEM (standard error of the mean). Binary data are presented as n/total number (percentage) of the patients. IIM, idiopathic inflammatory myositis; ILD, interstitial lung disease; DM, dermatomyositis; PM, polymyositis; CADM, clinically amyopathic dermatomyositis; HRCT, high resolution computerized tomography; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia.

Clinical and Laboratory Features in IIM Patients With RP-ILD Compared With C-ILD

Among 117 consecutive patients with RP-ILD, 41% (48/117) of patients had DM, 51.3% (60/117) of patients had CADM, and 7.7% (9/117) of patients had PM (**Table 2**). Patients with RP-ILD were older than those with C-ILD (54.1 ± 12.7 vs. 50.1 ± 12.9 years, $P = 0.009$). The mean disease duration in the RP-ILD group was significantly shorter than the C-ILD group (2.0 ± 0.9 vs. 31.6 ± 59.4 months, $P = 0.000$). Additionally, fever, periungual erythema, skin ulceration, and subcutaneous/mediastinal emphysema were significantly more common in patients with RP-ILD compared with C-ILD with incidence rates of 63.2 vs. 37.2%, 22.2 vs. 12.0%, 11.1 vs. 3.1%, and 6.0 vs. 0.0%, respectively. The levels of serum LDH ($P = 0.014$), AST ($P = 0.029$), CRP ($P = 0.019$), and ferritin ($P = 0.001$) were significantly higher in the RP-ILD group than in the C-ILD group. Muscle weakness and malignancy were less common in patients with RP-ILD than those with C-ILD with incidence rates of 47.9 vs. 64.9% ($P = 0.003$) and 3.4 vs. 9.4% ($P = 0.047$). Moreover, peripheral blood lymphocytes were significantly lower in patients with RP-ILD compared with C-ILD (1.1 ± 0.7 vs. 1.5 ± 0.9, $P = 0.000$).

In addition, increased CEA, NSE, and CYFRA21-1 in serum were significantly more common in the RP-ILD group than in the C-ILD group with incidence rates of 31.6 vs. 11.5%, 51.2 vs. 36.6%, and 66.7 vs. 38.2%, respectively. On the other hand, tumor markers including AFP, CA199, and CA125 were also screened for IIM patients, and there were no significant differences in these tumor markers between the RP-ILD and C-ILD groups. A total of 66.7% of patients with RP-ILD and 38.2% of patients with C-ILD had at least one of the tumor markers elevated in serum.

Comparison of MSAs/MAAs in IIM Patients With RP-ILD and C-ILD

MSAs/MAAs were detected in 207 patients with ILD in the present study. Prevalence of anti-MDA5 and anti-Ro-52 antibodies were significantly higher in IIM patients with RP-ILD than with C-ILD with respective incidence rates of 39.0 vs. 12.0% ($P = 0.000$) and 58.5 vs. 40.8% ($P = 0.012$) (**Table 3**). Anti-ARS antibodies, especially anti-Jo-1 antibody (13.4 vs. 32.0%, $P = 0.002$) were detected less commonly in patients with RP-ILD compared with patients with C-ILD. There were

TABLE 2 | Comparison of clinical and laboratory characteristics between DM/CADM/PM patients with RP-ILD and C-ILD.

Variables	RP-ILD $n = 117$	C-ILD $n = 191$	*P*-value
DIAGNOSIS			
DM, no. (%)	48 (41.0)	79 (41.4)	0.954
CADM, no. (%)	60 (51.3)	88 (46.1)	0.375
PM, no. (%)	9 (7.7)	24 (12.6)	0.180
DEMOGRAPHICS			
Female, no. (%)	87 (74.4)	145 (75.9)	0.758
Age at onset, years	54.1 ± 12.7	50.1 ± 12.9	0.009*
Duration of ILD, months	2.0 ± 0.9	31.6 ± 59.4	0.000*
CLINICAL VARIABLES			
Fever, no. (%)	74 (63.2)	71 (37.2)	0.000*
Gottron's sign/papules, no. (%)	81 (69.2)	137 (71.7)	0.640
Periungual erythema, no. (%)	26 (22.2)	23 (12.0)	0.018*
Skin ulceration, no. (%)	13 (11.1)	6 (3.1)	0.005*
Muscle weakness, no. (%)	56 (47.9)	124 (64.9)	0.003*
Subcutaneous/mediastinal emphysema, no. (%)	7 (6.0)	0 (0.0)	0.001*
Malignancy, no. (%)	4 (3.4)	18 (9.4)	0.047*
LABORATORY FEATURES			
Lymphocytes, $\times 10^9$/L	1.1 ± 0.7	1.5 ± 0.9	0.000*
CK, U/L	65 (30.5,274.5)	72 (34,563)	0.448
LDH, U/L	324 (221,501)	281 (193.8,395)	0.014*
AST, U/L	38 (21.5,84.5)	30 (20,60)	0.029*
CRP, mg/dL	7.6 (2.4,31.0)	5.0 (1.9,13.0)	0.019*
Ferritin (ng/mL)[a]	1,065 (584.1,2690)	307.9 (129.8,881.3)	0.001*
Elevated CEA, no. (%)	37 (31.6)	22 (11.5)	0.000*
Elevated NSE, no. (%)	60 (51.2)	70 (36.6)	0.012*
Elevated CYFRA21-1, no. (%)	78 (66.7)	73 (38.2)	0.000*

*Continuous data were expressed as the mean ± standard error or medians (interquartile range). Binary data were presented as n (percentage) of the patients. [a]49 patients of 117, 68 values missing in RP-ILD group; * <0.05. IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; RP-ILD, rapidly progressive ILD; C-ILD, Chronic ILD; CK, creatine kinase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; CRP, C-reactive protein, CEA, carcinoembryogenic antigen; NSE, neuron-specific enolase; CYFRA21-1, cytokeratin-19 fragment.*

TABLE 3 | Comparison of MSAs/MAAs between IIM patients with RP-ILD and C-ILD.

Variables	RP-ILD $n = 82$	C-ILD $n = 125$	*P*-value
MYOSITIS-SPECIFIC ANTIBODIES			
Anti-synthetase antibodies (+), no. (%)	35 (42.7)	71 (56.8)	0.047*
Anti-Jo-1, no. (%)	11 (13.4)	40 (32.0)	0.002*
Anti-MDA5, no. (%)	32 (39.0)	15 (12.0)	0.000*
Anti-Mi-2, no. (%)	2 (2.4)	3 (2.4)	1.000
Anti-TIF1-γ, no. (%)	3 (3.7)	4 (3.2)	1.000
Anti-NXP2, no. (%)	2 (2.4)	4 (3.2)	1.000
Anti-SAE, no. (%)	2 (2.4)	3 (2.4)	1.000
MYOSITIS-ASSOCIATED ANTIBODIES			
Anti-Ro-52, no. (%)	48 (58.5)	51 (40.8)	0.012*
Anti-PM/Scl-75/100, no. (%)	8 (9.8)	15 (12.0)	0.615
Anti-Ku, no. (%)	3 (3.7)	7 (5.6)	0.743

** <0.05. IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; RP-ILD, rapidly progressive ILD; C-ILD, Chronic ILD. ARS include EJ, OJ, PL-7, PL-12, KS. ARS, aminoacyl-tRNA synthetase; MDA5, melanoma differentiation-associated 5; TIF-1γ, translation initiation factor-1a; NXP2, nuclear matrix protein 2; SAE, small ubiquitin-like modifier enzyme; PM/Scl, polymyositis/scleroderma.*

no significant differences in prevalence of anti-Mi-2, anti-NXP2, anti-SAE, and other MAAs between the two groups. Out of 207 patients in which MSAs/MAAs were detected, 20 patients were identified without specific, associated myositis antibodies. Among these patients, ANA, RF, anti-SSA, anti-Sm, anti-Scl-70, anti-U1RNP, and ANCA were found in 35% (7/20), 20% (4/20), 5% (1/20), 0% (0/20), 0% (0/20), 5% (1/20), and 5% (1/20) of the patients, respectively.

Pulmonary Characteristics and Mortality of IIM Patients With RP-ILD and C-ILD

OP pattern on HRCT was more common in the RP-ILD group than in the C-ILD group at the initial assessment with incidence rates of 52.1 vs. 11.0% ($P = 0.000$) (**Table 4**). In contrast, NSIP and UIP patterns were associated with C-ILD as the incidence rates were 47.9 and 0.0% in RP-ILD subjects compared to 78.0 and 11% in C-ILD subjects, respectively. In total, 161 patients finished PFT and arterial blood gas analysis at initial evaluation, and these results were consistent with ILD in all patients. The results of decreased PaO_2 ($P = 0.000$) and PFTs, including lower FVC ($P = 0.000$), DL_{CO} ($P = 0.000$), and TLC ($P = 0.000$) verified severe lung impairment in patients with RP-ILD compared with those with C-ILD. Analysis of cell composition in BALF showed a significantly increased proportion of lymphocytes and decreased macrophage cells in the RP-ILD group compared with the C-ILD group with rates of 38.2 ± 23.2 vs. 20.4 ± 13.1 ($P = 0.000$) and 47.9 ± 22.5 vs. 68.8 ± 16.1 ($P = 0.000$). Out of 117 patients with RP-ILD, 78 received bronchoalveolar lavage immune cell tests, including 12 patients that did not survive and 66 that survived. Lymphocytes in BALF at <30% was found in 83.3% (10/12) of deceased patients compared with only 33.3% (22/66) of patients who survived ($P = 0.003$) (**Supplementary Table S1**). Out of 191 patients with C-ILD, 97 received bronchoalveolar lavage tests. Lymphocytes in BALF at <30% was found in 100% (7/7) of deceased patients with C-ILD compared with 81.1% (73/90) of C-ILD patients that survived, but the difference was not significant ($P = 0.348$) (**Supplementary Table S2**).

The mortality rates in patients with RP-ILD were significantly higher than those in the C-ILD group (27.4 vs. 7.9%, $P = 0.000$, respectively). The median time to death was 0.2 years in RP-ILD subjects compared to 5.7 years in C-ILD subjects. The main cause of death in the RP-ILD group was respiratory failure due to RP-ILD (62.5%, 20/32), and a quarter of patients died from complicating infections. We also compared therapeutic data between the two groups (**Table 4**). Patients in the RP-ILD group

TABLE 4 | Comparison of baseline pulmonary features and initial treatment between IIM patients with RP-ILD and C-ILD.

Variables	RP-ILD $n = 117$	C-ILD $n = 191$	*P*-value
PaO_2 < 80 (mmHg)[a]	59 (92.2)	22 (22.7)	0.000*
BASELINE PFTs (% PREDICTED)[a]			
FVC	65.7 ± 16.2	86.9 ± 15.1	0.000*
DLco	48.5 ± 16.0	72.3 ± 16.2	0.000*
TLC	70.6 ± 15.5	88.2 ± 14.4	0.000*
HRCT PATTERN			
NSIP, no. (%)	56 (47.9)	149 (78.0)	0.000*
OP, no. (%)	61 (52.1)	21 (11.0)	0.000*
UIP, no. (%)	0 (0.0)	21 (11.0)	0.000*
BRONCHOALVEOLAR LAVAGE[b]			
Total cell number ($\times 10^5$/ml)	3.0 ± 2.9	3.1 ± 3.2	0.137
Macrophage (%)	47.9 ± 22.5	68.8 ± 16.1	0.000*
Lymphocyte (%)	38.2 ± 23.2	20.4 ± 13.1	0.000*
Neutrophil (%)	12.6 ± 18.3	9.1 ± 10.0	0.084
Mortality, no. (%)	32 (27.4)	15 (7.9)	0.000*
Median time to death, years	0.2 (0.1, 1.5)	5.7 (1.0, 10.1)	0.012*
CAUSE OF DEATH			
Respiratory failure, no. (%)	20 (62.5)	2 (13.3)	0.002*
RF complicated with infection, no. (%)	8 (25.0)	1 (6.7)	0.236
Cancer, no. (%)	0 (0.0)	6 (40.0)	0.000*
Others, no. (%)	4 (12.5)	6 (40.0)	0.054
INITIAL TREATMENT			
CS pulse therapy (0.5 g/d IV 3 days)	103 (88.0)	15 (7.9)	0.000*
IMMUNOSUPPRESSANTS			
CsA	38 (32.5)	22 (11.5)	0.000*
MMF	1 (0.9)	12 (6.3)	0.020*
Tac	3 (2.6)	1 (0.5)	0.155
Intravenous CYC	74 (63.2)	90 (47.1)	0.007*
CsA+CYC	8 (7.3)	1 (0.5)	0.002*
Tofacitinib	4 (3.4)	0 (0.0)	0.020*
Rituximab	2 (1.7)	0 (0.0)	0.144

*Data are presented as n (percentage) of the patients. Data of pulmonary function test and bronchoalveolar lavage are presented as mean ± SEM. * <0.05. [a] 64 patients of 117, 53 values of baseline PaO_2, FVC, DLco, TLC missing in RP-ILD group; 97 patients of 191, 94 values of baseline PaO_2, FVC, DLco, TLC missing in C-ILD group. [b] 78 patients of 117, 39 values of bronchoalveolar lavage immune cell tests missing in RP-ILD group; 97 patients of 191, 94 values of bronchoalveolar lavage immune cell tests missing in C-ILD group. IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; RP-ILD, rapidly progressive ILD; C-ILD, chronic ILD; HRCT, high resolution computerized tomography; NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia; OP, organizing pneumonia; FVC, forced vital capacity; DLco, diffusion capacity for carbon monoxide; TLC, total lung capacity; RF: respiratory failure; IV, intravenous injection; CS, glucocorticoid; CsA, Cyclosporine; MMF, Mycophenolate mofetil; CYC, Cyclophosphamide; Tac, Tacrolimus.*

received more aggressive initial treatment regimes compared with patients in the C-ILD group. A total of 88% of patients with RP-ILD were treated with CS pulse therapy compared with 7.9% of patients with C-ILD at initial treatment ($P = 0.000$). Calcineurin inhibitors, especially cyclosporine, and intravenous cyclophosphamide (0.4–0.6 g every 2 weeks) were preferentially used in the RP-ILD group rather than mycophenolate mofetil; rituximab, tacrolimus, and tofacitinib were seldom used.

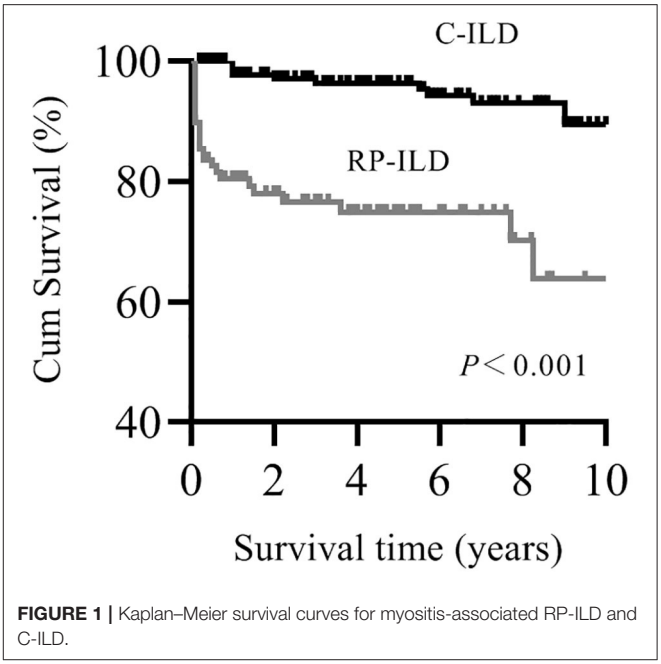

FIGURE 1 | Kaplan–Meier survival curves for myositis-associated RP-ILD and C-ILD.

Survival Analysis of IIM Patients With RP-ILD

Patients with myositis-associated RP-ILD had significantly lower survival rates than the C-ILD group (1-year survival, 76 vs. 98%; 5-year survival, 73 vs. 94%; $P = 0.000$) (**Figure 1**). Moreover, skin ulceration, LDH > 245 U/L, AST > 40 U/L, lymphocytes in BALF <30%, and anti-MDA5 antibody were associated with mortality on univariate analysis. Multivariate Cox proportional hazards model analysis identified that anti-MDA5 antibody (HR 11.639, [95% CI 1.338–101.240], $P = 0.026$) was an independent risk factor for mortality due to RP-ILD, and lymphocytes at <30% in BALF (HR 12.048, [95% CI 1.466–99.031], $P = 0.021$) might be associated with poor survival of RP-ILD (**Table 5**). Among patients with RP-ILD, anti-MDA5-positivity was significantly associated with poor survival (57% at both 5 and 10 years) compared to the anti-MDA5-negative group (89% at both 5 and 10 years, $P = 0.007$) (**Figure 2A**). Additionally, lymphocytes <30% in BALF might also be associated with poor survival of RP-ILD (87.3% at 5 years and 80.3% at 10 years) compared with lymphocytes at ≥30% in BALF (95.7% at both 5 and 10 years, $P = 0.031$) (**Figure 2B**). Notably, due to lack of data in BALF tests (33.3% in RP-ILD group and 49% in C-ILD group), the statistical power of analysis of the BALF lymphocyte ratio was insufficient, and a probable selection bias existed. Therefore, this result needs to be validated in future studies.

DISCUSSION

RP-ILD, a common complication of IIM, is a poor prognostic factor for patients with IIM (4, 5). Therefore, these patients need careful evaluation of clinical characteristics and radiological features during follow-up (20). The present study retrospectively reviewed 474 cases of IIM and identified initial predictors for myositis-associated RP-ILD from an inpatient rheumatology cohort in China.

TABLE 5 | Survival analysis in myositis-associated RP-ILD (Cox proportional hazards model).

Variables	Hazard ratio	95% CI	*P*-value
UNIVARIATE			
Fever	2.823	0.730–10.918	0.133
Skin ulceration	3.726	1.554–8.932	0.003*
Subcutaneous/mediastinal emphysema	2.999	0.721–12.475	0.131
LDH > 245 U/L	1.001	1–1.001	0.001*
AST > 40 U/L	1.005	1.002–1.008	0.002*
Anti-Jo-1 antibody	0.040	0–8.705	0.040*
Anti-MDA5 antibody	11.320	1.450–88.356	0.021*
Lymphocytes in BALF<30%	5.281	1.133–24.623	0.034*
MULTIVARIATE			
Anti-MDA5 antibody	11.639	1.338–101.240	0.026*
Lymphocytes in BALF<30%	12.048	1.466–99.031	0.021*
Skin ulceration	1.283	0.240–6.863	0.770

* *<0.05. Initial predictors for poor survival of myositis-associated RP-ILD due to respiratory failure were verified by multivariate analysis. MDA5, melanoma differentiation-associated 5; RP-ILD, rapidly progressive interstitial lung disease; BALF, bronchoalveolar lavage fluid.*

The prevalence of ILD was 65% in patients with DM/PM/CADM, and nearly 40% of them had RP-ILD in our center. The prevalence of ILD in our center is higher than other historical series (21). The possible reason is that our hospital is a well-known center for myositis and other rheumatic diseases in China, so increased frequency of severe patients with ILD were found in the in-patient clinical records. In addition, all patients received routine examination of HRCT to screen for potential ILD, which might lead to a higher prevalence of ILD in this cohort. However, differences might also exist in different countries. According to several other cohort studies, it seems that the prevalence of ILD in our study was similar with these previous studies and was not extraordinary (22, 23). The present study showed 10.7% of patients diagnosed with ILD before the diagnosis of IIM, so these patients required intensive evaluation during follow-up to reduce the rate of misdiagnosis. NSIP on chest HRCT of IIM patients was reported to be the most common pattern in our study, and this result was consistent with previous studies (24, 25).

Previous studies have identified that survival rates of patients with myositis-associated RP-ILD were lower than in C-ILD (26). Won et al. (27) report a 3-year survival rate for RP-ILD of 27.3%, and Fujisawa et al. (28) report a 5-year survival rate of 52% in the RP-ILD. However, the 5-year survival rate of the RP-ILD group in our study was 73%, which is higher than in previous reports. The potential reason may be the choice of different treatment regimens or different therapeutic effects among racial types. Rapid deterioration and infection secondary to over-immunosuppression were two main causes of death, so appropriate therapy regimens still need to be pursued by clinicians.

This study verified many clinical and laboratory prognostic factors previously reported to be associated with RP-ILD in IIM patients, such as age at onset, fever, periungual erythema, skin ulceration, and decreased peripheral blood lymphocyte cells as well as increased levels of AST, ferritin, LDH, and CRP (29).

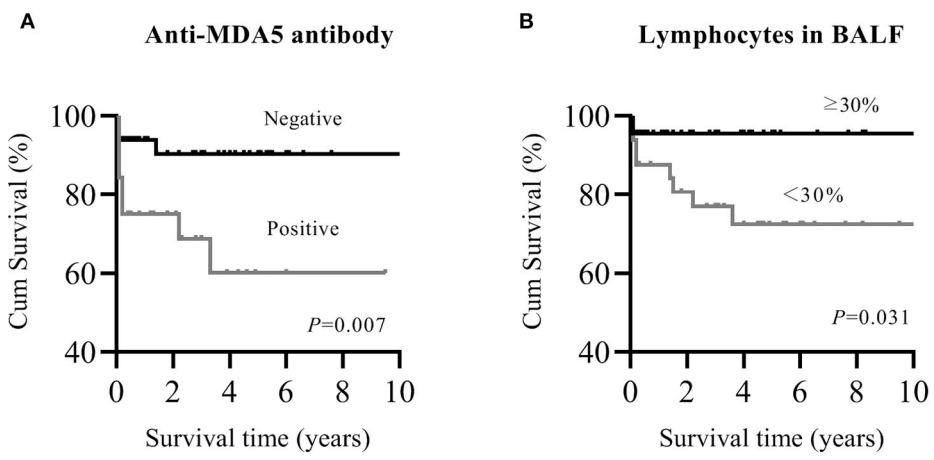

FIGURE 2 | Kaplan–Meier survival curves for myositis-associated RP-ILD. **(A)**, MDA5 positive and MDA5 negative; **(B)**, lymphocytes in BALF <30% and ≥30%. MDA5, melanoma differentiation-associated 5; RP-ILD, rapidly progressive interstitial lung disease; BALF, bronchoalveolar lavage fluid.

Additionally, serum tumor markers, such as CEA, NSE, and CYFRA21-1 were found to be associated with RP-ILD in our study. Although such tumor markers have been used to screen potential cancer in clinical practice, this result has not been reported before. The possible reason is that these tumor markers could be induced by intensive inflammation in lung.

Measurement of MSAs and MAAs are helpful in classifying different subtypes of IIM in clinical practice. Our study demonstrated that anti-MDA5 antibody was a specific biomarker for myositis-associated RP-ILD. Anti-Ro-52 antibody was also associated with RP-ILD in our study. These findings were consistent with previous studies (25, 30–32). In contrast, anti-ARS antibodies, especially anti-Jo-1 antibody, were related to myositis-associated C-ILD in our study, which indicated that anti-ARS antibodies may be a favorable predictor for RP-ILD. The multivariate Cox proportional hazards model analysis used in our study identified anti-MDA5 antibody as an independent predictor of poor outcome in patients with myositis-associated RP-ILD. The importance of anti-MDA5 antibody in the prognosis of myositis has been described by Tanizawa et al. (16), who showed that anti-MDA5 was an independent determinant of overall mortality in DM/PM patients with ILD.

Our analysis verified that low PaO_2, FVC, DL_{CO}, and TLC were associated with RP-ILD. This result confirmed that analyzing arterial blood gas and PFT were useful tests for myositis-associated RP-ILD. FVC and DL_{CO} values have been reported as predictive factors for poor prognosis of ILD in IIM (33, 34). Our study also found that initial low TLC was correlated with the onset of RP-ILD.

Currently, cellular profiles in BALF are used in patients with myositis to rule out infection in clinical practice. The relationship between cellular profiles of BALF and poor prognosis has not been supported by all studies (28, 35). Schnabel et al. (35) report the presence of neutrophils in BALF associated with progressive ILD. In contrast, Fujisawa et al. (28) indicate that a relatively high percentage of lymphocytes in BALF is correlated with myositis-associated ILD. However, our study demonstrates increased lymphocyte infiltration and decreased number of macrophage cells in BALF are associated with onset of RP-ILD in myositis patients. Our study further shows that lymphocytes at <30% in BALF is probably associated with poor survival of myositis-associated RP-ILD. The ATS guidelines (36) indicate that the presence of >15% lymphocytes in BALF represents a lymphocytic cellular pattern such as OP or NSIP.

Takei et al. (37) report that corticosteroids and other immunosuppressants are more effective in the patients with a lymphocyte differential count >15% than in patients with a lymphocyte differential count <15%. According to Takei et al., we speculate that the reason for this association is that patients with a lower lymphocyte ratio in BALF might respond poorly to treatment with corticosteroids or immunosuppressants, which might lead to poorer outcomes. However, due to the rather high percentage of missing data in BALF results (33.3% in RP-ILD group and 49% in C-ILD group), the statistical power of analysis of BALF lymphocyte ratio is insufficient. Only 10.3% (12/117) of patients died in the subgroup of RP-ILD patients with available BALF results compared to the overall mortality of 27.4% (32/117), which suggests a probable selection bias. Therefore, this result needs to be validated in future studies. It should be noted that the cutoff level of lymphocytes <30% in BALF should also be validated in future studies. Further research on lymphocyte subsets and function is also needed in future work to elucidate the immunological mechanism of different lymphocyte phenotypes and functions in myositis-associated RP-ILD.

There are several limitations in the present study. The retrospective nature and the selection of cases from a single center might have caused a selection bias. Because patients were selected from a center for myositis and other rheumatic diseases, more severe forms of disease were recorded. Because the study was retrospective, follow-up time was different among the cases, and some missing data could not be avoided. For example, MSAs, MAAs, lung function, and BALF test (including subsets of lymphocytes) were not performed in all the patients. On the other hand, the strength of the study is that it includes a large cohort of patients with myositis who have undergone HRCT. Further prospective and multicenter studies are needed to overcome these weaknesses.

CONCLUSIONS

Our study highlights that presence of RP-ILD results in an increased rate of mortality in DM/PM/CADM. IIM patients with predictive factors of RP-ILD, including anti-MDA5 antibody and lymphocytes <30% in BALF, should receive intensive follow-up.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YuL, JH, and XS conceived and designed the study and wrote the manuscript. XG, YiL, XJ, YG, YX, XZ, RC, and SL collected the data. YuL, XG, and YiL analyzed the data. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.00363/full#supplementary-material

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Lupus and the Lungs: The Assessment and Management of Pulmonary Manifestations of Systemic Lupus Erythematosus

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Pulmonary manifestations of systemic lupus erythematosus (SLE) are wide-ranging and debilitating in nature. Previous studies suggest that anywhere between 20 and 90% of patients with SLE will be troubled by some form of respiratory involvement throughout the course of their disease. This can include disorders of the lung parenchyma (such as interstitial lung disease and acute pneumonitis), pleura (resulting in pleurisy and pleural effusion), and pulmonary vasculature [including pulmonary arterial hypertension (PAH), pulmonary embolic disease, and pulmonary vasculitis], whilst shrinking lung syndrome is a rare complication of the disease. Furthermore, the risks of respiratory infection (which often mimic acute pulmonary manifestations of SLE) are increased by the immunosuppressive treatment that is routinely used in the management of lupus. Although these conditions commonly present with a combination of dyspnea, cough and chest pain, it is important to consider that some patients may be asymptomatic with the only suggestion of the respiratory disorder being found incidentally on thoracic imaging or pulmonary function tests. Treatment decisions are often based upon evidence from case reports or small cases series given the paucity of clinical trial data specifically focused on pulmonary manifestations of SLE. Many therapeutic options are often initiated based on studies in severe manifestations of SLE affecting other organ systems or from experience drawn from the use of these therapeutics in the pulmonary manifestations of other systemic autoimmune rheumatic diseases. In this review, we describe the key features of the pulmonary manifestations of SLE and approaches to investigation and management in clinical practice.

Keywords: systemic lupus erythematosus (SLE), interstitial lung disease (ILD), pleurisy, pleural effusion, shrinking lung syndrome, pulmonary arterial hypertension, acute lupus pneumonitis, pulmonary vasculitis

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disorder that can present with a wide array of clinical and immunological abnormalities (1). Pulmonary manifestations of the disease include disorders of the lung parenchyma, pleura, and pulmonary vasculature. Furthermore, some SLE therapies predispose to an increased risk of respiratory infections (2).

Clinical assessment of patients with SLE should routinely consider careful evaluation for respiratory involvement. Symptoms including dyspnea, pleuritic chest pain, reduced exercise tolerance, cough, and hemoptysis should prompt investigation for potential underlying lung disease (3, 4). However, it is important to consider that some asymptomatic patients may also present with incidental findings of abnormal chest imaging or lung function tests in the absence of overt respiratory symptoms (5). It is also important to consider whether these symptoms are occurring in the context of active SLE involving other organ systems. Serological evidence of increased disease activity including elevated erythrocyte sedimentation rate (ESR), low complement, and increased double-stranded DNA (dsDNA) antibody titers should also prompt the clinician to consider whether new respiratory symptoms are directly attributed to lupus.

The exact prevalence of SLE-related lung disease is unknown and previous studies have varied widely in their estimates. Most report that between 20 and 90% of SLE patients will experience some form of lung involvement during the course of their disease (6, 7). However, more recently it has been suggested that this figure lies between the range of 50–70% (8). Predictors for progression to earlier permanent lung damage, include older age and those positive for anti-RNP antibodies (9). Pulmonary manifestations of SLE are associated with a higher mortality rate (10) and this varies depending upon the exact type and extent of lung involvement seen. More chronic forms of lung disease relating to SLE can have a significant negative affect on patient wellbeing, physical performance status, and are detrimental to quality of life (11).

In this review, we discuss the latest understanding on the ways in which lupus can affect the respiratory system, highlight how these patients may present clinically, and outline current approaches for investigation and management.

DISEASES OF THE LUNG PARENCHYMA

Interstitial Lung Disease (ILD)

The estimated prevalence of SLE-associated interstitial lung diseases (ILD) is suggested to be between 3 and 9% (12, 13). Although ILD is highly prevalent in rheumatoid arthritis and other systemic autoimmune rheumatic diseases (such as scleroderma and anti-synthetase syndrome), it is relatively uncommon in SLE (8). A small study previously reported that clinical progression of ILD in SLE is slow and often stabilizes over time (12). Risk factors for developing SLE-associated ILD include longstanding disease, older age and overlapping clinical features with scleroderma such as Raynaud's phenomenon and sclerodactyly (14–17). Various forms of ILD have been described in SLE including non-specific interstitial pneumonia (NSIP), organizing pneumonia, lymphocytic interstitial pneumonia, follicular bronchitis, and usual interstitial pneumonia (18–21). Bronchiolitis obliterans has also been reported as an initial manifestation of SLE (19).

Patients present similarly in most types of ILD with symptoms such as cough and dyspnea although it is important to consider that some may be asymptomatic (22). Diagnosis of SLE-associated ILD can be made with high resolution computed tomography (HRCT) and excluding other potential causes of ILD (such as screening for overlap disorders by measuring rheumatoid factor, serum muscle enzymes, an extended myositis panel and anti-centromere autoantibodies) (23). Checking extractable nuclear antigens (ENA) should also be considered as previous studies have demonstrated that patients with anti-La, anti-Scl-70 and anti-U1RNP antibodies were more likely to develop ILD. Interestingly, anti-dsDNA antibody titer do no associate with the development of ILD (24). Lung function tests may show a restrictive pattern of disease and a decrease in diffusing capacity for carbon monoxide (DLCO) (8). Histological studies have reported the presence of lymphocytic and mononuclear interstitial and peribronchiolar infiltrates in biopsies taken from those with SLE-related NSIP (25).

There are a lack of clinical trials assessing the treatment of SLE-related ILD and in particular there are no head-to-head studies. Therefore, recommendations are predominantly based on case reports, small case series, physician expertise, and by applying findings from studies of ILD in other autoimmune rheumatic diseases. Intravenous cyclophosphamide was reported to show significant improvement vital capacity in two SLE patients with ILD in which both patients presented with pleuritic chest pain in the context of active SLE (26). Another case report noted that oral methotrexate resulted in a marked improvement in lung function in a patient with SLE-related ILD (27). An observational study of 14 patients with SLE-associated ILD reported that three patients showed significant improvement with high dose oral steroids (60 mg prednisolone daily for a minimum of 4 weeks). Six of the 14 patients had an improvement in respiratory symptoms and all were treated with systemic steroids (18). Three patients within the cohort died, two of pulmonary fibrosis, and one from infection thus highlighting the clinical challenge posed by immunosuppressive therapy in the context of SLE-related ILD. It is important to consider that this study was published in 1990 and thus predates a number of the newer treatments available for the management of SLE, such as mycophenolate mofetil (MMF), rituximab and belimumab.

Current treatment often includes the use of high dose corticosteroids along with agents such as cyclophosphamide and rituximab in severe cases (28, 29) to induce remission. Steroid-sparing agents such as MMF and azathioprine may be used in milder cases or in maintaining long-term control of the disease (30, 31).

Acute Lupus Pneumonitis

In some cases, chronic ILD may be the long-term sequelae of an acute process, for example acute lupus pneumonitis. This is a rare manifestation of SLE that has been reported to occur in 1–4% of patients (32). Clinically, acute lupus pneumonitis presents in the context of a systemic flare of SLE in addition to dyspnea, cough (including hemoptysis) and pleuritic chest pain. Fever is commonly associated with the acute presentation, thus making it a clinical challenge to differentiate from infection. There is limited data on lung histology in acute lupus pneumonitis, although reports of lymphocytic infiltrates and alveolar damage

with associated interstitial edema have been reported in both lung biopsy samples and at post-mortem assessment (24).

Acute lupus pneumonitis may also be the initial presenting symptom of SLE. A case series of five patients in which acute lupus pneumonitis was the first feature of SLE reported that all five were female, aged 14–26 years old. They were all ANA positive, whilst three were also positive for anti-dsDNA antibodies. Fever was present in all cases with cough as a presenting symptom in four of the five patients, with hypoxia noted in three. All patients received corticosteroids and four patients were treated with cyclophosphamide either as monotherapy or in combination with intravenous immunoglobulins (IVIg). The one patient who did not receive cyclophosphamide was treated with azathioprine. Three patients survived but two died as a result of infection (33). Others have also reported the use of IVIg in acute lupus pneumonitis (34, 35). Given that the differential diagnosis in this presentation often includes bacterial pneumonia, and as infection can commonly co-exist with acute lupus pneumonitis, IVIg represents a useful option as it does not convey the high risk of immunosuppression associated with other agents. It is also important to consider using broad spectrum antibiotics (in particular directed against encapsulated organisms) if there are concerns about intercurrent infection. Further, prompt initiation of systemic glucocorticoid therapy has been reported to be of benefit in reducing mortality rates. Additional treatments that have been used in the management of acute lupus pneumonitis are similar to those used in SLE-related ILD, such as high dose glucocorticoids in combination with either MMF, azathioprine, rituximab, or cyclophosphamide. However, in spite of this the outcomes are often poor with associated high mortality rates (33, 36).

PLEURAL DISEASE

Pleural involvement is the most common SLE-related lung disease (37). Clinically, patients often present with pleuritic chest pain, cough and dyspnea due to inflammation of the pleura (38). Patients may have an associated pleural effusion which is often bilateral and exudative in nature (39, 40). Estimates suggest that between 30 and 50% of SLE patients will develop a pleural effusion at some point during their disease course, although often these are small and may not result in obvious symptoms (39, 41).

Diagnosis of pleural involvement in SLE is usually clinical with typical features in the patient history. It is however important to exclude other causes of pleural inflammation that can occur in SLE including infection, pulmonary embolism, malignancy, congestive cardiac failure (37), or pericarditis, which may present in a similar manner. Drug-induced pleuritis from agents such as hydralazine, procainamide and anti-tumor necrosis factor-alpha medications should also be considered (42–44). In such cases, drug cessation is often sufficient to resolve symptoms.

Although not necessary for diagnosis, if there is clinical uncertainty as to the cause of a pleural effusion, aspiration can be performed. Pleural fluid in patients with SLE classically show elevated levels of protein, lactate dehydrogenase (LDH), leukocytes, and in some cases ANA positivity (37, 39).

The mainstay treatment of pleurisy in SLE has traditionally been non-steroidal anti-inflammatory drugs (NSAIDs) with some patients requiring corticosteroids (38). Rarely, other steroid-sparing agents such as azathioprine, methotrexate, cyclosporine, and cyclophosphamide may be indicated (37). In refractory disease, there have been cases showing effective use of pleurodesis (45, 46).

DISORDERS OF THE PULMONARY VASCULATURE

Pulmonary Arterial Hypertension (PAH)

Pulmonary arterial hypertension (PAH) is a progressive disorder characterized by a resting mean pulmonary artery pressure above 25 mmHg and a pulmonary wedge pressure below 15 mmHg (47). There are a number of possible underlying causes that may result in PAH in SLE, including left ventricular dysfunction or congestive cardiac failure that may be a result of the increased risk of atherosclerosis associated with SLE. It may also be a manifestation of the long-term sequelae of parenchymal lung diseases (such as ILD) or chronic thromboembolic disease (48). Studies estimate the prevalence of PAH in SLE to be in the range of 1–43% depending on the cohort (49–54). A recent comprehensive meta-analysis assessing the prevalence of PAH found an estimated pooled prevalence of 8% (55). Despite this, severe PAH is thought to be a rare manifestation in SLE and is not included in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) disease activity score (56).

Clinical symptoms of PAH in SLE are often non-specific and range from generalized fatigue and weakness to chest pain and dyspnea at rest (48). Initial investigations often include an electrocardiogram that may show right ventricular hypertrophy and right axis deviation. Radiographic imaging with computerized tomography may be used to exclude other diseases such as ILD and will often show enlarged pulmonary vessels (57). Echocardiography can estimate systolic pulmonary artery pressure and is therefore a vital non-invasive tool to assist in making a diagnosis. However, even with a suggestive echocardiogram result and high clinical suspicion, right heart catheterization remains the "gold standard" test to confirm the diagnosis (58).

Management of PAH in SLE is similar to that of idiopathic PAH. However, most randomized controlled trials that have specifically analyzed the management of PAH associated with connective tissue diseases often have not included a subgroup analysis of SLE patients (48). Drugs such as phosphodiesterase-5 inhibitors, endothelin receptor antagonists and prostacyclin pathway agonists have all shown to be effective in SLE associated PAH to varying degrees (59–64). More recently, the guanylate cyclase stimulator riociguat has shown to be effective in a small number of SLE-associated PAH cases (65, 66).

Numerous observational cohort studies have also noted benefit with corticosteroids and immunosuppressive therapy including cyclophosphamide, cyclosporine and MMF (67–70). One case report has also described effective use of rituximab in refractory SLE-associated PAH (71). Overall, it is generally

thought that a combination of both immunosuppression and traditional PAH treatment should be used together to enhance long-term outcomes (68).

Pulmonary Embolic Disease

Pulmonary embolism (PE) also needs to be considered in the acute setting in any patient with SLE who presents with pleuritic chest pain (especially if associated with acute hypoxia). In the more chronic setting, chronic pulmonary embolic disease can also lead to pulmonary hypertension (chronic thromboembolic pulmonary hypertension). It is particularly important to consider embolic disease in those patients who have secondary anti-phospholipid syndrome (APS), given the obvious increased risk of thrombosis associated with the disease. Previous studies have reported that one-third of patients with SLE will have positive anti-phospholipid antibodies and those with a positive lupus anticoagulant have previously been shown to have a six-fold increased risk of venous thrombosis. In comparison, a positive anti-cardiolipin antibody carried twice the risk when compared with SLE patients without positive anti-cardiolipin antibodies (72). Previous studies have also reported that patients with SLE, even in the absence of APS, are at an increased risk of unprovoked PE when compared with the general population and therefore the absence of positive anti-phospholipid serology should not be falsely reassuring.

The "gold standard" investigation for PE is computed topography pulmonary angiogram (CTPA), which can identify the presence of thrombosis within the pulmonary vasculature. However, it is important to consider that SLE patients presenting with pleuritic chest pain and hypoxia may instead be suffering from pleurisy (as described above). Results from the Michigan Lupus Cohort assessed the outcomes of 182 patients with SLE who had previously undergone a total of 357 CTPA scans. The authors found a significant decrease in the likelihood of confirming PE in patients who had previously had three or more scans, thus suggesting that repeated scanning of patients without a previously proven PE is unlikely to confirm a new diagnosis (73).

In the context of PE associated with APS, lifelong anticoagulation is likely to be recommended. Recent studies investigating direct oral anticoagulants have recommended against their use in arterial thrombosis, such as PE (74).

Pulmonary Vasculitis and Pulmonary Hemorrhage

Pulmonary vasculitis, or diffuse alveolar hemorrhage (DAH), is a rare but severe manifestation of SLE that is associated with a high mortality rate of up to 90% (75). This has been reported to affect <5% of patients with SLE and is more commonly seen concurrently in the context of active lupus nephritis (76). In addition, this manifestation has been reported to be the initial presentation of SLE in ∼20% of all cases, which means that it is important to consider lupus in any new case of pulmonary hemorrhage in which an alternate underlying cause is not present (77). It has also been reported that patients with secondary APS may be at increased risk of DAH and that this may also occur *de novo* in patients with SLE who are have anti-phospholipid antibodies without previous thrombotic events. This suggests that this is not entirely the result of anticoagulant therapy and may represent an as yet unclassified mechanism for pulmonary vasculitis (78). As with other acute pulmonary manifestations of SLE, the symptoms can often mimic infection thus making the diagnosis a challenge.

Findings from small cases series and cohort studies have highlighted that dyspnea and pulmonary infiltrates on thoracic imaging are almost universally in seen. Fever is reported in the majority of cases although occult hemoptysis is only seen in just over half of patients at presentation (79). Many patients will also present with extrapulmonary manifestations of SLE to suggest a generalized systemic flare of the disease. More subtle signs that suggest DAH include pleural effusions and anemia is seen in nearly all cases, and may be present before signs such as hemoptysis are observed (75, 80). Imaging studies often describe classical bilateral alveolar interstitial infiltrates. Many patients are deemed clinically unstable for further dedicated investigation however those that proceed to bronchoscopy are usually found to have high neutrophil count, low lymphocyte count and hemosiderin-laden macrophages within the lavage and occult blood often seen (79, 81). If the patient is able to tolerate pulmonary function tests then an elevated DLCO is usually indicative of alveolar hemorrhage.

Given a lack of clinical trial data from DAH in SLE, treatment recommendations are usually based upon other autoimmune conditions associated with pulmonary hemorrhage (such as ANCA-associated vasculitis) and often include pulsed intravenous steroids in combination with cyclophosphamide (79), rituximab, plasmapheresis, and IVIg (81, 82).

SHRINKING LUNG SYNDROME (SLS)

Shrinking lung syndrome (SLS) is an uncommon manifestation of SLE with an estimated prevalence of ∼1–2% (9, 83, 84). The exact cause of SLS is unclear, however it is believed to involve abnormal diaphragmatic strength and may be related to due to impaired phrenic nerve signaling (85).

Patients with SLS often present with symptoms of pleuritic chest pain and progressive dyspnea (86). Due to its rarity, there is no diagnostic criteria for SLS. Lung function tests often show a restrictive defect with a reduction in lung volume and DLCO (84). Radiographic imaging in SLS is often non-specific with occasional elevation of the diaphragm and basal atelectasis with usually no evidence of interstitial lung or pleural disease (87). It is also important to consider other conditions before a diagnosis of SLS is made including central nervous system disorders and diaphragmatic palsies (88).

Evidence for the optimal management of SLS is limited. Corticosteroids and immunosuppressive agents including azathioprine, MMF and rituximab have been used to varying degrees of efficacy (86, 89–92). Some have suggested the use of hematopoietic cell transplantation (93) and beta agonist therapy (94) in SLS. Others have reported some benefit in the use of theophylline thought to be helpful by improving diaphragmatic

TABLE 1 | A summary of the way in which pulmonary manifestations of systemic lupus erythematosus (SLE) may present in clinical practice, the underlying pathogenesis and relevant treatment options.

Diagnosis	Presentation	Pathogenesis	Relevant investigation findings	Histological features	Treatment
Interstitial lung disease	Chronic, often progressive dyspnea Cough (often non-productive) Possible evidence of scleroderma, anti-synthetase syndrome, or rheumatoid arthritis May be asymptomatic	Poorly understood/unclear Likely a result of the aberrant inflammatory response due to imbalance of pro- and anti-inflammatory cytokine release (96) Possibly the result of repeated alveolar injury resulting in a combination of both impaired apoptosis and abnormal fibroblast proliferation	Infiltrative changes on CXR or HRCT chest Restrictive pattern on pulmonary function tests with reduced DLCO Test for auto-antibodies suggestive of overlap disorder (e.g., RhF, anti-CCP, anti-centromere, anti-Scl-70, anti-RNP) and muscle enzymes (CK, LDH)	Mononuclear or lymphoplasmacytic interstitial and peribronchiolar infiltrates (particularly in NSIP pattern disease) Interstitial fibrosis present. Deposits of IgG, IgM, C1q, and C3 within alveolar septae previously reported (14)	Depends upon severity *Severe or rapidly progressive* Oral/IV corticosteroids followed by either Cyclophosphamide, Rituximab, MMF, Azathioprine
Acute lupus pneumonitis	Acute dyspnea Fever Cough (usually non-productive but occasional hemoptysis) Features of extrapulmonary SLE disease activity	Rapid systemic inflammatory response resulting in acute damage to the lung parenchyma. Alveolar injury resulting from direct immune-mediated inflammation	CXR – diffuse bilateral alveolar infiltrates CT thorax – previous reports of ground-glass changes Serological evidence of lupus activity (low complement and elevated anti-dsDNA antibody titers)	Often non-specific Features can include alveolar wall damage, necrosis, inflammatory infiltrate, oedema, hemorrhage, hyaline membranes (97) Capillary microangiitis, fibrin thrombi and necrotic neutrophils have also been described (98)	Systemic corticosteroids (either high dose oral or pulsed IV) plus either Cyclophosphamide, Rituximab, MMF, Azathioprine Possibly IVIg
Pleurisy	Chest pain (often pleuritic in nature) Cough Dyspnea Physical signs such as pleural rub may be present	Inflammatory infiltration into the pleura	Raised CRP Imaging usually normal CXR ± CT thorax or CTPA helpful to rule out other causes	Non-specific inflammatory changes associated with fibrin deposition along with pleural fibrosis (99)	*Mild* Oral NSAIDs *Moderate* Oral corticosteroids *Severe (rarely required)* IV corticosteroids, Azathioprine, Cyclophosphamide, Rituximab, MMF
Pleural effusion	Dyspnea Chest pain, usually associated with pleurisy May be asymptomatic Physical signs including reduce basal air entry and decreased resonance	*As per "Pleurisy"* Excessive inflammation results in exudative fluid secretion between pleural lining resulting in effusion	Effusion(s), usually bilateral, present on CXR or CT thorax Aspirate (if underlying diagnosis in doubt) – elevated protein, LDH, leukocytes, ANA positive in some cases	Predominantly based on cytological features Pleural fluid may show characteristic lupus erythematosus (LE) cells, e.g., neutrophils or macrophages containing intracellular evidence of phagocytosed lymphocyte nuclei (100)	Corticosteroids Drainage if large Pleurodesis in recurrent or refractory cases Cessation of any potential drug causes
Pulmonary arterial hypertension	Can be non-specific (such as fatigue and weakness) Progressive dyspnea Occasional chest pain Physical signs may show right ventricular heave	*Dependent upon underlying cause* Left ventricular dysfunction/congestive cardiac failure may result from direct myocardial inflammation from SLE (e.g., myocarditis) or as a result of enhanced atherosclerosis Chronic thromboembolic disease may result from pro-coagulant factors such as aPl antibodies Lung parenchymal disease as the result of direct inflammatory response in lung tissue Dysregulation between vasoconstrictive and vasodilatory mediators	EKG – RVH and right axis deviation Echocardiogram – elevated PASP, TR Right heart catheterization – mean arterial pressure ≥25 mm Hg confirms diagnosis CT thorax – useful to exclude other secondary causes CTPA – useful to rule out chronic embolic disease as a cause Check anti-centromere, anti-Scl-70, anti-U1RNP (to rule out scleroderma and other overlap syndromes)	Limited data Vascular lesions including eccentric and concentric intimal fibrosis and thrombotic lesions Venous occlusive lesions have been reported with pulmonary veins/venules Capillary congestion (101)	Phosphodiesterase-5 inhibitors Endothelin receptor antagonists Prostacyclin agonists Role for immunosuppression not clear
Pulmonary embolic disease	Usually acute onset Dyspnea Chest pain (often pleuritic) Hypoxia Occasionally hemoptysis	Thromboembolic disease usually as a result of pro-coagulant state This could include secondary antiphospholipid syndrome Severe proteinuria from lupus nephritis may result in anti-thrombin deficiency	Check aPl antibodies (LAC, aCL, anti-B2GPI) Elevated D-dimer CXR usually normal aside from potential wedge infarct CTPA	Evidence of thrombus within pulmonary arterial system	Anti-coagulation (low molecular weight heparin, oral vitamin K antagonist)
Pulmonary vasculitis	Acute dyspnea Commonly associated with fever and active extrapulmonary manifestations of SLE Hemoptysis May be initial presentation of SLE	Direct immune-mediated inflammatory response of the small vessels of the alveola resulting in increased permeability and eventually structural damage resulting in hemorrhage	CXR – bilateral alveolar interstitial infiltrates Pulmonary function tests – elevated DLCO Drop in Hb Important to check ANCA and urine dip for proteinuria/hematuria (to rule out intercurrent ANCA-associated vasculitis or pulmonary-renal syndrome)	Numerous intra-alveolar or interstitial aggregates that comprise of hemosiderin-laden macrophages Fresh hemorrhagic changes may be present in the context of DAH Capillaritis may be present (26)	IV corticosteroids Cyclophosphamide Rituximab IVIg Plasmapheresis May require mechanical ventilation
Shrinking lung syndrome	Progressive dyspnea Occasional pleuritic chest pain	Poorly understood Felt to be the result of marked diaphragmatic weakness or immobility. Possibly as a result of pleural adhesions Phrenic neuropathy also previously proposed as a possible mechanism	CXR – often non-specific, elevation of diaphragm and basal atelectasis may be seen Pulmonary function tests – restrictive pattern with reduced lung volume and DLCO	Extremely limited data from lung biopsy with features reported as alveolar microatelectasia and hyaline membrane formation (102) Post-mortem diaphragmatic tissue showing muscle atrophy (85)	Little evidence currently available to support treatment decisions Corticosteroids, Azathioprine, MMF, and Rituximab used with variable success in case reports

CXR, chest x-ray; HRCT, high resolution computerized tomography; NSIP, non-specific interstitial pneumonia; DLCO, diffusing capacity for carbon monoxide; RhF, rheumatoid factor; CCP, cyclic citrullinated peptide; RNP, ribonuclear protein; CK, creatinine kinase; LDH, lactate dehydrogenase; aPl, antiphospholipid; IV, intravenous; MMF, mycophenolate mofetil; CT, computerized tomography; IVIg, intravenous immunoglobulin; CRP, c-reactive protein; CTPA, computerized tomography pulmonary angiogram; NSAIDs, non-steroidal anti-inflammatory drugs; ANA, anti-nuclear antibody; EKG, electrocardiogram; RVH, right ventricular hypertrophy; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitation; LAC, lupus anticoagulant; aCL, anti-cardiolipin; B2GPI, beta-2-glyoprotein-I; Hb, hemoglobin; ANCA, anti-neutrophil cytoplasm antibody; DAH, diffuse alveolar hemorrhage.

strength (87, 95). Comprehensive studies have generally shown a good prognosis with treatment in most SLS patients (87, 88).

CONCLUSIONS

Pulmonary manifestations of SLE can present with a wide array of symptoms and can often be difficult to differentiate from other conditions, most notably infection. The key differences between these disorders are summarized in **Table 1**.

It is important to consider that SLE-related lung disorders are likely to be under-represented due to the fact that respiratory involvement may be asymptomatic. Furthermore, serositis (pleurisy/pleural effusion) is the only respiratory symptom included in the revised 1997 American College of Rheumatology (ACR) criteria for SLE (103) and no additional respiratory manifestations were included in the 2019 combined ACR/EULAR criteria (104). In terms of measuring disease activity from pulmonary manifestations of SLE, the British Isles Lupus Assessment Group (BILAG) index includes a subsection on (cardio)respiratory features of the disease, which considers pleurisy, pleural effusion, pulmonary hemorrhage/vasculitis, interstitial lung disease, and shrinking lung syndrome as possible pulmonary manifestations of the disease (105). In comparison, the SLEDAI-2K only accounts for pleurisy as a scorable item of lupus activity involving the lungs (106). In turn, this may result in a number of patients with respiratory complications of SLE (particularly those symptoms considered more mild) to be falsely considered as either in remission or a low disease activity state (107). In comparison, the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index for SLE does include a wide array of pulmonary manifestations although these are typically irreversible and thus may not be a useful measure in preventative studies (108). This has important implications for clinical trial design, which may exclude patients who have predominantly respiratory symptoms. As a result, evidence supporting therapeutic options in SLE-related lung disease are often extrapolated from other severe manifestations of the disease. Dedicated studies in the management of pulmonary disorders in SLE are greatly needed and represent a major unmet need.

AUTHOR CONTRIBUTIONS

RA conducted a literature review of relevant respiratory disorders. SAY, EKD, and CW expanded upon this. All authors agreed to the finalized version of this manuscript prior to submission.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Antisynthetase Syndrome-Associated Interstitial Lung Disease: Monitoring of Immunosuppressive Treatment Effects by Chest Computed Tomography

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Background: Antisynthetase syndrome (ASyS) is a rare autoimmune disease characterized by inflammatory myopathy, arthritis, fever, and interstitial lung disease (ILD). Pulmonary involvement in ASyS significantly increases morbidity and mortality and, therefore, requires prompt and effective immunosuppressive treatment. Owing to the rarity of ASyS, limited data exists on progression and prognosis of ILD under immunosuppression.

Objectives: The objective of the study was to evaluate the radiological progression and outcome measures of ILD with immunosuppressive therapy in patients with ASyS.

Methods: Twelve patients with ASyS-associated ILD (ASyS-ILD) were included. Demographic and clinical data, including organ involvement, pulmonary function tests (PFT), laboratory parameters, imaging studies, and treatment regimens were retrospectively analyzed from routinely collected data. The extent of ground glass opacities, fibrotic changes and honeycombing was analyzed and scored using high-resolution chest computed tomography (HRCT) scans. HRCT findings were compared between baseline and follow-up examinations. In addition, patients were stratified depending on whether they had received rituximab (RTX) or not.

Results: Pulmonary function tests revealed stable lung function and follow-up HRCT scans showed an improvement of radiological alterations in the majority of ASyS patients under immunosuppressive therapy. We did not detect significant differences between the RTX- and non-RTX-treated groups, but the RTX-treated patients more frequently had myositis and relapsing disease.

Conclusions: Radiographic alterations in ASyS-associated ILD respond to immunosuppressive treatment. RTX is a feasible treatment option with similar clinical and radiographic outcomes in patients with relapsing disease and clinically apparent myositis.

Keywords: antisynthetase syndrome, interstitial lung disease, immunosuppressive agents, inflammatory myopathies, myositis

INTRODUCTION

Antisynthetase syndrome (ASyS) is a rare autoimmune disease, belonging to the idiopathic inflammatory myopathies (IIM) (1). Due to frequent extramuscular manifestations, including fever, Raynaud's syndrome, arthritis, mechanic's hands and interstitial lung disease (ILD) (2, 3), ASyS is classified among the overlap myositis (4). Specific antibodies (abs) directed against different aminoacyl-tRNA synthetases (ARS) are the serological markers of ASyS. Anti-Jo1 abs are the most frequently detected ARS abs, and they are observed in up to 30% of patients with IIMs, whereas other ARS abs, such as anti-PL-7, anti-PL-12, anti-EJ, and anti-OJ, are less frequently detected (5). The classical clinical triad (arthritis, myositis, and ILD) can be observed in up to 90% of patients, but it is not always present in the early stages of the disease (6). The overall prognosis depends on the extent of organ involvement and on the occurrence of malignancies, which are, however, less common than in other IIMs subsets (7). ASyS-ILD is the most important prognostic factor in these patients and lung involvement is associated with an increased risk of mortality, thus requiring prompt immunosuppressive treatment (7, 8). To date, there is no standardized treatment for AsyS, and different therapeutic protocols have been adopted from other forms of inflammatory myositis (9). In most cases, glucocorticoids (GC) in combination with other immunosuppressive agents, such as cyclosporine (CsA) (10), methotrexate (MTX), azathioprine (AZA), or mycophenolate mofetil (MMF), cyclophosphamide (CYC), and rituximab (RTX) have been used in ASyS (9, 11).

In this single-center cohort study, we studied the effect of immunosuppression on high-resolution chest computed tomography (HRCT) findings in the course of ASyS-ILD, focusing particular on RTX.

PATIENTS AND METHODS

This retrospective observational study used routinely collected clinical data in patients with ASyS. The clinical care of patients with IIMs is organized in an interdisciplinary way among the Departments of Rheumatology, Neurology, Pulmonology, Dermatology, and Neuropathology, and relies on the use of standardized operating procedures. Management decisions are discussed and evaluated in multidisciplinary case conferences held on a monthly basis (12).

Patient Identification

All patients fulfilling at least two or more clinical findings consistent with ASyS (arthritis, myositis, ILD, Raynaud's phenomenon, mechanic's hands, or ARS abs) were recruited from the University Medical Center Goettingen and their medical records were independently reviewed by three investigators who extracted the data (PK, JGR and LR). Additional patients were identified by the analysis of positively detected ARS abs at our DIN:ISO 2001 certified autoimmune laboratory.

Tests for myositis-associated (MAA) and myositis-specific (MSA) antibodies including Mi-2 alpha, Mi-2 beta, TIF1 gamma, MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, and Ro-52 were performed using the 16 Ag EUROLINE Blot (Euroimmun AG, Lübeck, Germany). The presence of additional antibodies was examined using the Elia™ SymphonyS test assay (Thermo Fisher Scientific, Waltham, MA, USA), which screens for, among others, the presence of anti-SSA antibodies (60 and 52 kDa). Anti-SSA-antibodies have been reported in about 50% of patients with incomplete forms of ASyS (13). Patients were stratified according to treatment into two groups: patients which never received RTX and a second group which received RTX in the course of ASyS-ILD.

Data Assessment and Outcome Measures

Demographic data and clinical parameters were retrieved from patients' medical records. We evaluated the presence and spectrum of specific abs, organ involvement, laboratory parameters, pulmonary function tests (PFT), and imaging procedures in each patient. Histologic evidence of organ involvement was recorded, if available. As outcome measures for pulmonary involvement, we assessed the alteration of lung parenchyma on HRCT as well as PFTs before and during treatment. To assess the effect of immunosuppression, we recorded all patients' individual therapies used between the first and any subsequent follow-up HRCT scans. Progressive ILD was defined as worsening on imaging studies or worsening of PFT [at least a 10% decline of forced vital capacity (FVC) or at least a 15% decline of diffusion capacity for carbon monoxide (DLCO)].

HRCT Scanning and Interpretation

Baseline and follow-up HRCT scans were obtained with 4-, 16-, 64-, and 128-slice scanners from 2011–2019 at the same institute. The scans were interpreted and scored independently and blinded to patient identity and clinical details by a senior registrar-level radiology resident (EMS) and a board-certified thoracic radiologist (JL) with 4 and 22 years of experience, respectively.

The analysis of HRCT patterns was performed in line with the CT-evaluation used in the *Scleroderma Lung Study* by Goldin et al. (14): during the initial assessment, the presence or absence of other important comorbidities was noted. For comprehensive scoring, each lung was divided into three zones: upper (lung apex to carina), middle (carina to inferior pulmonary veins terminus)

and inferior (inferior pulmonary veins to lung bases), creating a total of six zones. The following lung findings were assessed and quantified: ground-glass opacities (GGO), fibrotic changes, interlobular changes and bronchiectasis (FIB), honey combing or subpleural cysts (HC). In baseline and follow-up data sets, the degree of abnormality in each lung zone was scored from 0to 4 (where 0 indicates absence, 1 = 1–25% involvement, 2 = 26–50%, 3 = 51–75% and 4 = 76–100%), as described previously (14). An example of the HRCT evaluation and terminology is presented in **Supplementary Figure 1**. For each study patient, baseline and follow-up measurements were determined using the overall mean of the entire lung for each abnormal parameter.

Statistical Methods

Demographic data of the study population were analyzed by descriptive statistics. The Shapiro-Wilk test was used for testing normal (Gaussian) distribution. Parametric between-group-comparisons were performed with either the Student's *t*-test for paired data (two groups) or mixed effects analysis with Tukey test as *post-hoc* analysis for multiple comparisons (more than two groups). Mixed effects analysis was used because repeated measures analysis of variance (ANOVA) cannot handle missing values. We analyzed the data instead by fitting a mixed model. This mixed model uses a compound symmetry covariance matrix and is fit using Restricted Maximum Likelihood (REML). In the absence of missing values, this method gives the same *P*-values and multiple comparisons tests as repeated measures ANOVA. In the presence of missing values (missing completely at random), the results can be interpreted like repeated measures ANOVA. Geisser-Greenhouse correction was used.

Non-parametric between-group-comparisons were performed with Fisher's exact test. The interrater agreement of HRCT scores between the two radiologists was assessed by the weighted kappa statistic. Values below 0.20 were considered as poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81–1.0 as very good agreement. $P < 0.05$ were considered statistically significant. Data analyses were performed with GraphPad Prism (version 8.4.0 for MacOS, GraphPad Software, San Diego, CA, USA) or STATA (STATA/MP version 16.1 for Windows, Stata Corp LLC, College Station, TX, USA).

RESULTS

Patient Cohort

We identified 22 patients with positive ARS abs. One additional patient met clinical criteria (ILD, arthritis, mechanic's hands, fever) for ASyS but tested positive for anti-RO52 abs only. Testing for antinuclear antibodies in this patient revealed a cytoplasmic fine-speckled staining pattern.

Of the 22 patients with positive ARS abs, nine were excluded because they did not have ILD; one patient was not eligible due to incomplete data. Therefore, a total number of 12 patients (eight female and four male patients) was included in the final analysis (**Supplementary Figure 2**). Of these, seven received RTX, five did not receive RTX.

Median follow-up time was 31 (6–156) months. Demographic and clinical characteristics are presented in **Table 1**. There were no differences between the RTX ever- vs. RTX never-groups with the exception of clinically significant myositis, which was only present in the RTX-treated patients.

Spectrum of Specific Antibodies in the Study Cohort

Anti-Jo-1 abs were present in 10 of 12 patients (83.3%). In addition, 10 of these 12 patients also tested positive for anti-SSA (detected either by ELiA, which recognizes anti-Ro52/Ro60, or anti-RO52 detected by Immunoblot; see Methods for details).

Organ Manifestations

Arthritis (joint pain and swelling) was clinically evident in 7 patients (58%), mainly involving the hands. Myositis [defined as myalgia accompanied by elevation of creatinine kinase (CK), consistent muscle biopsy, or compatible findings on magnetic resonance imaging] was present in five patients (5/12; 41.6%) and was the second most common manifestation.

Creatine kinase levels during follow-up remained stable or improved in all cases. Two of the patients had a remote history of breast cancer, one patient had received a diagnosis of ASyS during pregnancy related to ovarian cancer.

Immunosuppressive Treatment

Ten individuals received glucocorticoids (GC) while seven patients were treated with RTX during the study period. The reasons for RTX initiation were ILD progression in four patients (4/7, 57.1%), ILD at the time of ASyS diagnosis in two patients (2/7, 28.6%) and treatment of concomitant anti-CCP antibody positive rheumatoid arthritis in one patient (14.3%). Equally, relapsing disease with ILD flares and clinically apparent myositis in 5/12 (41.6%) patients led to RTX initiation. Six patients (6/12, 50%) received azathioprine (AZA). Less frequently used immunosuppressants were MTX in three and MMF in two patients. CYC (one patient), leflunomide (LEF; one patient), hydroxychloroquine (HCQ; one patient), and adalimumab (ADA; one patient) were used infrequently. The individual therapeutic regimens are presented in **Table 2**.

Pulmonary Function Testing

PFTs were obtained at baseline and throughout the course of the study. Forced vital capacity (FVC) and diffusion capacity for carbon monoxide (measured as single-breath carbon monoxide diffusion capacity; DLCO) are presented in **Figures 1A,B**. Baseline and follow-up PFTs were available for nine (FVC) and eight (DLCO SB) patients. Patients in the RTX group had worse baseline values for FVC and DLCO compared to the non-RTX group. However, the differences were not statistically significant.

High-Resolution Chest Computed Tomography Findings

HRCT of the chest was performed for each of the 12 patients at baseline (CT1). A second CT scan (CT2) was available in 10

TABLE 1 | Demographic and clinical characteristics of the patient cohort.

	RTX ever $N = 7$	RTX never $N = 5$	p-Value
Median age at diagnosis (range)	45 years (32–62)	39 years (22–53)	$p = 0.39$
Gender	5 females 2 males	3 females 2 males	$P > 0.99$
Median length of follow-up*	17 months (7–35)	32 months (1–156)	$p = 0.21$
Comorbidities	5 (71.4%)	4 (80%)	
Arterial hypertension	1 (20%)	1 (25%)	$p = 0.24$
Diabetes mellitus	0	0	–
Stroke	1 (20%)	1 (25%)	$p > 0.99$
Malignancy	2 (40%; 1 Ovarian-cancer, 1 Breast-cancer)	1 (25%; 1 Breast-cancer)	$p > 0.99$
Smoking status			
Never smoked	5 (71.4%)	0	$p > 0.99$
Past smoker	0	4 (100%)	$p = 0.42$
Current smoker	2 (28.6%)	1 (25%)	$p > 0.99$
Antisynthetase antibodies	6 (86.7%)	5 (100%)	
Anti-tRNA-synthetase (Jo1)	5 (83%)	5 (100%)	$p = 0.47$
Anti-hRNA-synthetase (PL7)	1 (17%%)	0	$p > 0.99$
Other antibodies			
Anti-RO52	2 (28.6%)	0	$p = 0.47$
Anti-SS-A (Ro60)	4 (57.2%)	4 (80%)	$p = 0.58$
Pulmonary function at baseline (% predicted and standard deviation)			
Mean FVC	76.3 ± 22.3	90 ± 5.66	$p = 0.44$
Mean DLCO SB	70.3 ± 10.6	99.5 ± 30.4	$p = 0.06$
Organ manifestations			
ILD	7 (100%)	5 (100%)	$p > 0.99$
Arthritis	5 (71.4%)	2 (40%)	$p = 0.56$
Mechanic's hands	2 (28.6%)	0	$p = 0.47$
Raynaud's phenomenon	3 (42.9%)	1 (20%)	$p = 0.58$
Fever	2 (28.6%)	1 (20%)	$p > 0.99$
Myositis	**5 (71.4%)**	**0**	$\mathbf{p < 0.05}$

DLCO, diffusion capacity for carbon monoxide; dsDNA, double-stranded deoxyribonucleic acid; FVC, forced vital capacity; ILD, interstitial lung disease; RTX, rituximab.
**Follow-up denotes interval between CT investigation CT1 and CT2. Bold values indicates statistically significant.*

patients after a median time span of 14.5 months (6–72). A third CT scan (CT3) was available in six patients, at a median time of 30 months (17–156) after the first scan.

The interrater agreement κ between the two radiologists was 0.82 for GGO, 0.54 for FIB and 0.05 for HC, corresponding to very good (GGO), moderate (FIB), and poor (HC) agreement, respectively.

Seven patients who received RTX during the study period were compared with five patients without RTX treatment. The total CT scores in the RTX vs. non-RTX groups are presented in **Figure 2A** and **Supplementary Table 1**. Overall, the mean CT scores declined over time in both groups, but there were no statistically significant differences neither between groups (RTX vs. no RTX) nor between CTs (CT 1 through CT 3).

Also, the CT scores for the specific findings of GGO, FIB, and HC showed a progressive decrease with treatment over time (**Figure 2B**). This was observed for patients in the RTX groups and in the non-RTX group from CT 1 through CT 3. However, there were no statistically significant differences between groups nor from CT 1 through CT 3.

Overall Outcome

No patient died during the study. Radiological findings improved in most patients, exemplified by a decrease of the GGO and FIB scores. We did not observe worsening of the low baseline scores for HC. PFTs were stable or improved in the majority of patients. One patient developed pneumonia and sepsis from a urological source under immunosuppression with the need for hospitalization. No other serious adverse events were documented.

DISCUSSION

We have shown that pulmonary outcomes, as assessed by PFT and HRCT, did not differ between the varying therapeutic regimens. Nevertheless, the use of RTX was employed in patients with more severe disease as demonstrated by a numerically (although not statistically significant) higher GGO score at baseline, more frequent relapses, and a higher prevalence of myositis.

The prevalence of anti-Jo1 abs in our patient cohort was 83.3%. Anti-SS-A abs can be detected in about half of the patients

TABLE 2 | Immunosuppressive treatments and outcomes of antisynthetase-associated interstitial lung disease.

Patient	Therapy				Outcome
	1st line	2nd/3rd line	GC	Reason for RTX	
RTX 1	RTX remission induction 2 × 1 g 4 w after Dx	MTX maintenance therapy 15 mg qw	5 mg qd	ILD at Dx, relapsing myositis	Improvement of ILD, stable lung function. Fatigue, no joint/muscle complaints
RTX 2	RTX remission induction 2 × 1 g 4 w after Dx, 2nd cycle after 8 m, + AZA maintenance therapy 150 mg qd	MTX maintenance therapy 15 mg qw 7 m after Dx	7.5 mg qd	Progression of ILD, relapsing myositis	Improvement of ILD and lung function
RTX 3	AZA maintenance therapy 150 mg qd	RTX remission induction 2 × 1 g 19 m after Dx	7.5 mg qd	Progression of ILD, relapsing myositis	Relapse and worsening of DLCO, stable FVC
RTX 4	MTX maintenance therapy 15 mg qw + ADA first 3 m	2nd: AZA maintenance therapy 150 mg qd 3rd: RTX remission induction 2 × 1 g 35 m	–	Progression of ILD	Progression of ILD, stable lung function
RTX 5	RTX remission induction 2 × 1 g (6 m) after CT2 (25 m after Dx)	AZA maintenance therapy 125 mg qd 28 m after Dx	10 mg qd	Progression of ILD, relapsing myositis	Stable ILD, persistent joint complaints and fatigue
RTX 6	AZA maintenance therapy 100 mg qd	RTX remission induction 2 × 1 g 7 m after Dx	2.5 mg qd	Relapsing arthritis, frequent GC pulses	Clinical and radiographic remission*
RTX 7	MMF maintenance therapy 2.5 g qd	RTX remission induction 2 × 1 g 8 m after Dx	5 mg qd	ILD at Dx	Improvement of ILD, remitting flares and bacterial infections
RTX never 1	CYC remission induction first 6 m after Dx	AZA maintenance therapy 150 mg qd	5 mg qd	–	Lost to follow-up
RTX never 2	Mitoxantrone (5 mg/m²) multiple sclerosis treatment	–	20 mg qd	–	Lost to follow-up
RTX never 3	GC monotherapy 5 mg first 35 m	MMF maintenance therapy after 41 m (CT2)	5 mg qd	–	Stable ILD
RTX never 4	LEF 20 mg qd + CsA mg/kg 12 m	LEF 20 mg qd + HCQ	5 mg qd	–	Clinical and radiographic remission*
RTX never 5	AZA maintenance therapy 100 mg qd	–	10 mg qd	–	Clinical and radiographic remission*

**Clinical remission describes the absence of extrathoracic complaints (e.g., myalgia and arthralgia), whereas radiographic remission is defined as the improvement of radiographic findings and stabilization/improvement of PFT.*

AZA, azathioprine; CsA, cyclosporine A; CYC, cyclophosphamide; DLCO, diffusion capacity for carbon monoxide; Dx, diagnosis; FVC, forced vital capacitiy; GC, glucocorticoids; HCQ, hydroxychloroquine; ILD, interstitial lung disease; LEF, leflunomide; m, month(s); MMF, mycophenolate mofetil; MTX, methotrexate; NA, not available; qd, daily; qw, weekly; RTX, rituximab.

with ASyS (13); in our cohort, 58.3% of patients tested positive for SS-A abs. Radiological signs of arthritis were present in 58% of the patients. According to the literature, arthritis is the presenting symptom in about 25% of cases of ASyS (15). At least 50–60% of patients with detectable anti-Jo1 and anti-PL-7 abs have clinically active arthritis defined by tenderness or joint swelling in the course of the disease (2, 16). Of these, two thirds have a rheumatoid arthritis-like symmetrical polyarthritis while one third presents with an asymmetrical oligoarthritis (13, 15). Radiographs in patients with ASyS may reveal erosive changes at the wrists, MCP- and PIP-joints, especially in a subset of ASyS patients with positive anti-CCP antibodies (11). Irrespective of the presence of rheumatoid factor or anti-CCP antibodies, ultrasonography can demonstrate severe inflammatory arthritis with erosive RA-like pattern in selected patients with ASyS (17).

Myositis was histologically proven in 41.7% of our patients. Most case series and registries include ASyS patients when myositis becomes clinically apparent or patients initially diagnosed with IIM are diagnosed as ASyS. For this reason, the reported frequency of 75% for myositis in ASyS may be lower early in the course of the disease (1, 13). Moreover, anti-PL7 ab positive patients frequently present an early-onset ILD accompanied by an amyopathic course compared to anti-Jo1 positive patients (18).

Given the rarity of ASyS, little is known about the long-term effects of immunosuppressive therapy on the course of ILD. Lung involvement represents the most serious and life-threatening complication of ASyS, and, therefore, early commencement of an adequate therapy is crucial. The therapeutic response of the disease to immunosuppression can be assessed by the course of the ILD. Normal PFTs at the initiation of treatment are associated with stable or even an improved course of ASyS-ILD, whereas dyspnea and decreasing FVC correlate with a poor prognosis and progression of ILD in ASyS (8). The majority of patients in our cohort had normal baseline PFTs and the data revealed stable lung function in most patients over time. GCs were the most common treatment used, but all except one patient received additional immunosuppressive

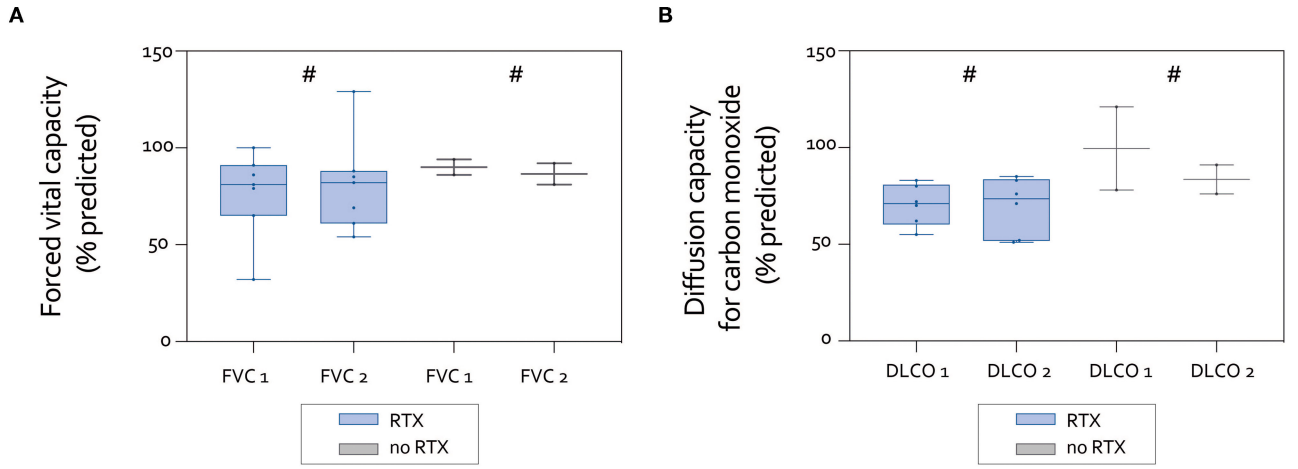

FIGURE 1 | Pulmonary function testing of patients with available data. **(A)** Forced vital capacity (FVC, % predicted) at baseline and follow-up. Spaghetti plots of individual patients (left) and Box-and-Whisker plots with median values (right) did not show statistically significant changes. **(B)** Diffusion capacity for carbon monoxide (DLCO, % predicted) at baseline and follow-up. Spaghetti plots of individual patients (left) and Box-and-Whisker plots with median values (right) did not show statistically significant changes (# not significant).

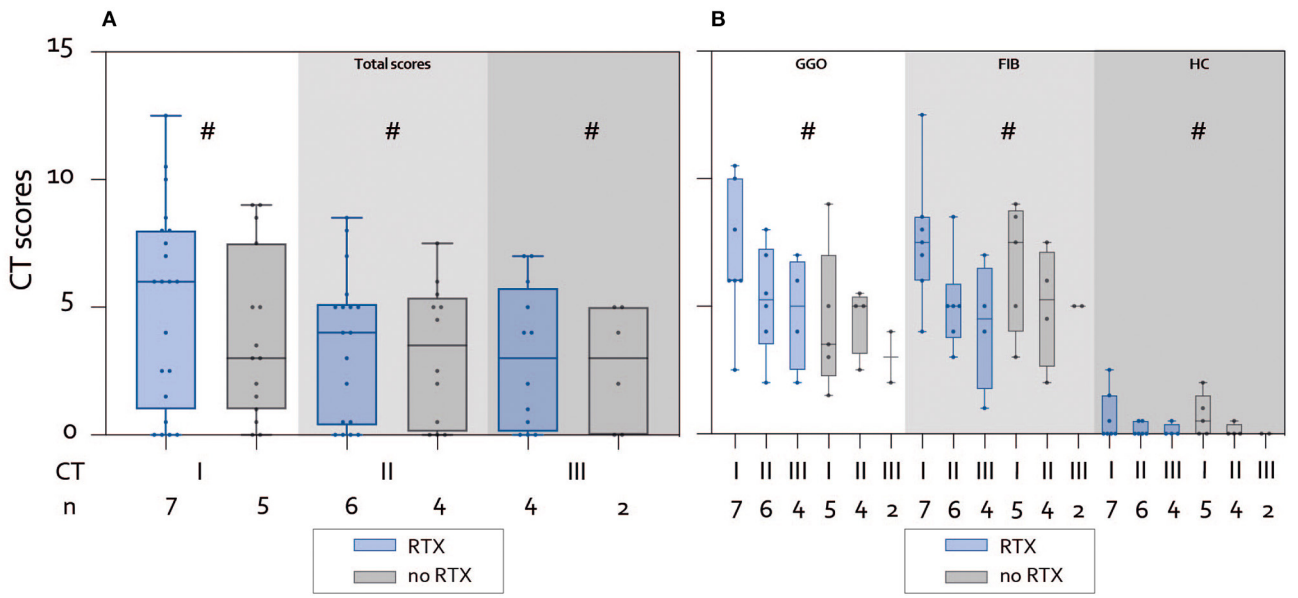

FIGURE 2 | Course of interstitial lung disease changes on chest computed tomography (CT) stratified according to treatment (Rituximab [RTX] vs. no RTX). **(A)** Total CT scores in the whole cohort. Mean CT scores with range for CT 1, 2, and 3 comparing the RTX vs. non-RTX group. There were no statistically significant differences (# not significant). **(B)** CT scores stratified according to type of change. Scores for ground glass opacities (GGO), lung fibrosis, interlobular changes and bronchiectasis (FIB), and honey combing (HC) decreased over time without reaching statistical significance (# not significant).

therapy. The improvement of lung HRCT scores observed in our study indicates a positive response of pulmonary parenchymal abnormalities to immunosuppression: fibrotic changes decreased in about 90% of patients, GGOs improved in about 60% of patients in the second available CT scan. Even if not universally present, HC also improved.

With respect to pulmonary function and overall outcome, RTX is a promising agent, especially early in the course of ASyS-ILD (19), findings which are supportive of our data. The majority of patients who received RTX in our study had clinically apparent myositis, more frequently had arthritis, or had relapsing disease with another immunosuppression.

In two of seven cases treated with RTX, the drug was started as a first-line therapy due to an early manifestation of ASyS-ILD. Additionally, our data demonstrate that other immunosuppressive agents also lead to improved HRCT imaging findings over time, but these patients differed in terms of disease severity and extrapulmonary manifestations.

The limitations of our study include its retrospective design and the small sample size lacking a control group. The intervals between follow-up HRCT scans varied considerably. Although we only examined patients with the presence of ILD at baseline (the first available HRCT), a clinically apparent lung disease may not have been evident in all patients at first presentation but may have developed over time. Abnormal radiology findings indicate an active underlying pulmonary disease which has not yet become apparent clinically. Consequently, the effect of immunosuppressive treatment must be interpreted with these limitations in mind. Also, we did not assess dyspnea scores, such as the St. George's respiratory questionnaire, in all patients since these are not consistently performed routinely in non-pulmonary clinics. The interrater agreement showed a moderate discrepancy in the assessment of HC. This has also been observed other studies, such as the Scleroderma Lung Study (14). However, as outlined above, HC was only rarely present. We, therefore, feel that this discrepancy does not severely affect our conclusions.

In conclusion, our results indicate a trend toward an improvement of ASyS-ILD outcome under treatment with RTX and other immunosuppressive therapies as well as a stabilization of PFT. RTX seems to be superior in patients with a higher number of clinical manifestations, including ASyS-ILD, myositis, arthritis, and in patients with relapsing disease. Nevertheless, prospective trials with pre-specified endpoints are required to further elucidate the impact of immunosuppression on progression and outcome of ASyS-ILD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the University Medical Center Goettingen (Protocol no. 4/8/19). All patients consented to the use of their routinely collected data for research purposes.

AUTHOR CONTRIBUTIONS

PK conceived the study, treated patients, abstracted and analyzed data, created the figures, and wrote the manuscript. JG-R abstracted and analyzed data, created the tables, and co-wrote the manuscript. LR abstracted data, reviewed and revised the manuscript critically. EM-S scored imaging data, contributed to the methodology, and revised the manuscript critically. UO analyzed data and revised the manuscript. CS and JS treated the patients, analyzed data, and critically revised the manuscript. JL scored imaging data, contributed figures, and revised the manuscript critically. RV conceived the study, analyzed data, co-wrote, and revised the manuscript critically. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.609595/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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