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Reviews in pulmonary medicine 2023

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Reviews in: pulmonary medicine 2023

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Editorial: Reviews in: pulmonary medicine 2023

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KEYWORDS

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Editorial on the Research Topic
Reviews in: pulmonary medicine 2023

Pulmonary disease is an ever-growing field. Recent research focuses on basic and clinical advances in interstitial lung disease (ILD) such as idiopathic pulmonary fibrosis (IPF) and the IPF genome, chronic obstructive pulmonary disease (COPD), epigenetics, pulmonary hypertension (PH), sarcoidosis, and eosinophilic pneumonia.

Autophagy plays a vital role in the maintenance of homeostasis and recent studies have explored the connection between autophagy and the development of different lung diseases. Autophagy appears to play a protective role in the development of IPF and a pathogenetic role in the progression of COPD. There are conflicting results on the role of autophagy in PH and asthma (1).

Epigenetic mechanisms include post-translational methylation and acetylation of histone proteins and DNA, and modulation of miRNA production. Up- or down-regulation of methylation in various genes have been demonstrated in COPD, and a variety of epigenetic alterations that include histone modification, DNA methylation, and non-coding RNA have been reported in IPF, and DNA methylation, histone modifications, and noncoding RNA have been shown in PAH (2). Additionally, epigenetics may improve early diagnosis and treatment of ILDs avoiding several biases, especially in the treatment of ILDs and in IPF the most common ILD with a poor survival rate.

A major current problem is the search for accurate vasodilator treatment in patients with pulmonary hypertension (PH) associated with IPF. The latter when combined with PH is regrouped in Group 3 of the ERS/ESC Guidelines (3). Nathan et al. (4) suggested treprostinil as an accurate vasodilator therapy in IPF. However, further clinical trials are needed to establish the efficacy of this treatment because the results of this study appear to be still inconclusive (5).

Multiplex immunolabeling and *in situ* sequencing transcriptomic analysis of lung tissue sections provided new insights into the immunopathogenesis of granulomas in sarcoidosis. Sarcoidosis lesions contain T-cell infiltrates that surround the granuloma core and B-cell clusters that are morphologically and molecularly suggestive of tertiary lymphoid structures (6). New perspectives on sarcoidosis have identified fatigue as an extremely significant symptom of the disease distinguishing it from other chronic diseases (7).

In terms of imaging [18F]-fluorodeoxyglucose positron emission tomography ([18F] FDG PET) is performed in suspected pulmonary and cardiac sarcoidosis. Recent data suggest that the association of [18F] FDG PET with late gadolinium tracer enhancement and cardiac magnetic resonance may help to differentiate cardiac sarcoidosis from other causes of myocardial inflammation (8).

Acute and chronic eosinophilic diseases are rare interstitial lung conditions. Pathological findings and high-resolution computed tomography (HRCT) imaging patterns may improve diagnostic accuracy and facilitate differential diagnosis with other eosinophilic lung diseases (9).

An international group of radiologists and pulmonologists (10) proposed a deep learning algorithm, based on the ATS/ERS/JRS/ALAT IPF guidelines criteria (SOFIA), to classify HRCT patterns for IPF diagnosis. The study included 203 patients with suspected IPF and concluded that artificial intelligence (AI) improves the accuracy of imaging evaluation and clinical diagnosis of ILD. Algorithms including clinical features, radiological patterns, and specific autoantibodies have been developed to improve the accuracy of diagnosis and management of ILD patients suffering from connective tissue diseases such as systemic sclerosis, rheumatoid arthritis, and polymyositis/dermatomyositis (11).

Patients affected by systemic sclerosis frequently develop interstitial lung disease (SSc-ILD). Patients with SSc-ILD have a significantly higher survival rate than patients with IPF-usual interstitial pneumonia (UIP). The survival rate of patients with SSc-ILD is negatively associated with the New York Heart Association (NYHA) class and pulmonary arterial pressure value (12).

There are still some limitations to the incidence and prevalence of ILDs reported in regional Registries. In fact, data from the Asian Pacific Registry have only recently been published allowing comparison with data from European Registries (13). ILD and IPF progression and survival remain uncertain and are currently associated with the number of exacerbations per year.

An association has been found between ILD and lung cancer in the same patients. These patients are affected by IPF and non-small cell lung cancer (NSCL); their prevalence is approximately 10% and they have a very poor prognosis. Of note, Uhlenbruch et al. (14) reported a 48% association between ILD and NSCLC at autopsy.

Last but not least, great progress has been made in IPF genomic analysis with the detection of well-established common and rare variants within the TERT and RTEL1 genes that, in combination with environmental factors, contribute significantly to IPF risk (15).

In conclusion, this annual review summarizes interesting advances in all forms of ILD and COPD; however, further clinical research in large multicenter clinical trials is needed in the near future to improve our understanding of these topics.

Author contributions

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Conflict of interest

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Sarcoidosis-related autoimmune inflammation in COVID-19 convalescent patients

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Currently, there are a large number of reports about the development of autoimmune conditions after COVID-19. Also, there have been cases of sarcoid-like granulomas in convalescents as a part of the post-COVID-19 syndrome. Since one of the etiological theories of sarcoidosis considers it to be an autoimmune disease, we decided to study changes in the adaptive humoral immune response in sarcoidosis and SARS-CoV-2 infection and to find out whether COVID-19 can provoke the development of sarcoidosis. This review discusses histological changes in lymphoid organs in sarcoidosis and COVID-19, changes in B cell subpopulations, T-follicular helper cells (Tfh), and T-follicular regulatory cells (Tfr), and analyzes various autoantibodies detected in these pathologies. Based on the data studied, we concluded that SARS-CoV-2 infection may cause the development of autoimmune pathologies, in particular contributing to the onset of sarcoidosis in convalescents.

KEYWORDS

autoimmunity, sarcoidosis, COVID-19, post-COVID-19 syndrome, B-cell, follicular Th, follicular Treg, autoantibodies

1 Introduction

Sarcoidosis remains to be recognized as one of the granulomatous diseases of unknown etiology (1). Multiple conducted studies confirm one of the most common theories regarding autoimmune pathogenesis behind the emergence of granulomatous inflammation that might result from bacterial and viral agents, inorganic and organic substances, vaccines, etc. (Figure 1) (2, 3). The current concept implies that caseous necrosis-free granuloma arises due to the aforementioned cues in genetically predisposed subjects, followed by the development of self-recovery or chronicity of clinical and multi-organ alterations (4–6).

Granuloma formation occurs in intrathoracic lymph nodes, lungs, skin, heart, and other organs upon contact with antigen-presenting cells (macrophages, dendritic cells, activated epithelial cells) by a triggering agent, followed by the development of unregulated autoimmune inflammation, additionally characterized by an imbalance between pro- and anti-inflammatory acquired immune cell subsets (T- and B lymphocytes) as well as regulatory T cells (7–9). Moreover, a tight link between sarcoidosis and COVID-19 caused by SARS-CoV-2 has been hypothesized, which may be another new trigger agent related to sarcoidosis, capable of either provoking or exacerbating it (10–12).

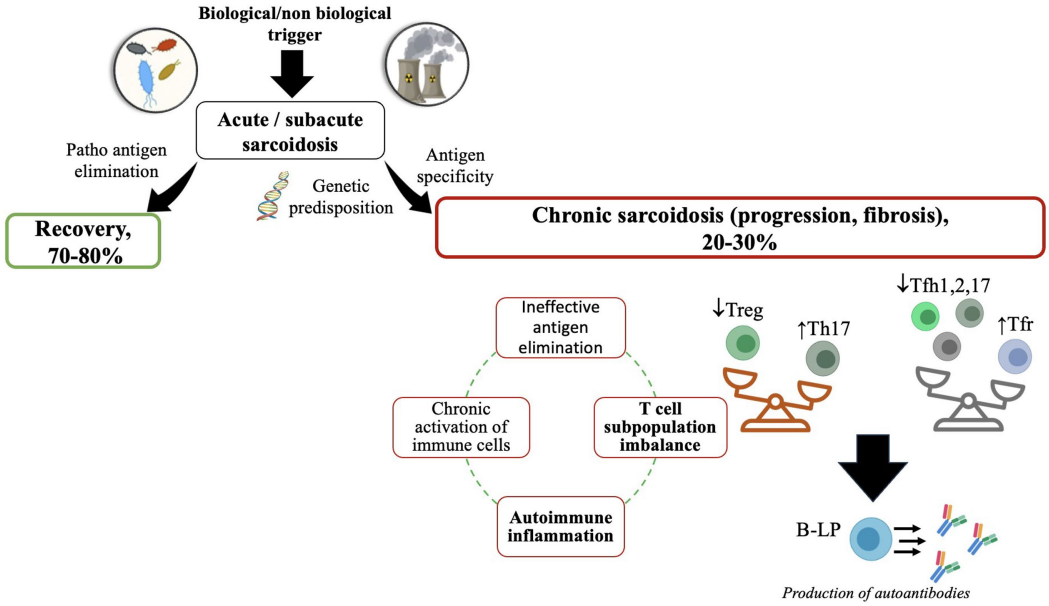

FIGURE 1
A putative scheme of the development of sarcoidosis. ↑—high level; ↓—low level. The figure was drawn by the authors.

In early 2023, based on the analysis of the medical records of approximately 6 million subjects, it was shown that prior SARS-CoV-2 infection elevated the risk of developing a wide range of autoimmune diseases, including rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, dermatopolymyositis, systemic sclerosis, Sjögren's syndrome, mixed connective tissue disease, Behçet's disease, rheumatic polymyalgia, vasculitis, psoriasis, inflammatory bowel disease, celiac disease, and type 1 diabetes (13). It is believed that genetic and environmental factors act as the major causes contributing to the development of autoimmune diseases, whereas infectious events coupled with viral, bacterial, and fungal infections may serve as one of the most crucial triggers in the emergence of immune system impairment resulting in autoimmunity (14). Moreover, mechanisms such as molecular mimicry, recognition of similar epitopes derived from protein molecules, and polyclonal activation of T- and B cells may affect virus-induced autoimmune diseases. Similarly, an important cue resulting in the development of autoimmune pathologies may be an uncontrolled inflammatory response related to the overproduction of pro-inflammatory cytokines (15), which may be closely related to a cytokine storm in severe COVID-19 and long-COVID-19 sequelae, including autoimmune reactions (16–18). In this regard, it has been reported that psoriatic arthritis (19, 20), systemic lupus erythematosus (21, 22), and other organ-specific and systemic autoimmune manifestations (23, 24) can be observed after COVID-19 infection. Moreover, 33 aberrantly expressed genes common to COVID-19 and sarcoidosis were discovered and functionally analyzed to reveal that such genes are associated with the production of cytokines involved in the immune response and T cell cytokine production (25). In addition, inflammatory aggregates consisting of macrophages, multinucleated epithelioid cells, and CD4+ T cells that histologically resembled sarcoidosis-related granulomatous events were detected during postmortem examination of lung biopsies from COVID-19 patients (26–28).

The aim of the review was to determine autoimmune features in patients with sarcoidosis and to assess immune disorders as predictors of activation and progression post-COVID-19.

2 Review analysis methods

We analyzed original papers and reviews covering the period from December 2019 to May 2023, published in accessible international databases ("Medline," "PubMed," and "Scopus"), with queries for the keywords "COVID-19," "SARS-CoV-2," "sarcoidosis," "Treg," "follicular Treg," and "Treg subsets." Inclusion criteria were as follows: original research with observation of patients with sarcoidosis and COVID-19, meta-analysis, reviews, and research articles; exclusion criteria: books, clinical trials, and clinical cases.

The analysis was carried out in accordance with the PRISMA protocol[1] used for this type of study.

3 Onset of sarcoidosis during or after COVID-19

Granuloma formation associated with clinical cases in post-COVID-19 patients is one of the most crucial confirmations of this event after a coronavirus infection. Clinical cases accompanied by the emergence of symptoms and manifestations of sarcoidosis during or after COVID-19, in addition to post-vaccination after the SARS-CoV-2 infection, are shown in Table 1.

Hence, patients of different sexes and ages during or 2–3 weeks after the onset of COVID-19 had various manifestations of sarcoidosis,

1 http://www.prisma-statement.org

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TABLE 1 Clinical cases of sarcoidosis onset during or after COVID-19.

Authors, year of publication	Patients (sex, age)	Onset of symptoms	Symptoms	Treatment and outcome
Behbahani et al. (29)	Woman, 72 years old	2 weeks after recovery from COVID-19 pneumonia	Cutaneous, painful, firm nodules representing noncaseating sarcoid-like granulomas	Clobetasol ointment: granulomas gradually reduced within 25 days.
Polat Ekinci (30)	Woman, 55 years old	2–3 weeks after COVID-19	Sarcoid-like granulomas mimicking cicatricial syndrome. 1–2 cm round, mobile and tender subcutaneous nodules on both arms, 3–4 mm size three subcutaneous papules in the periorbital area	No treatment was administered to the female patient due to the lack of any evidence of systemic sarcoidosis, and the lesions began to regress spontaneously within one month.
Somboonviboon (31)	Man, 35 years old	10 weeks after COVID-19	Bilaterally enlarged hilar, paratracheal, and subcarinal lymph nodes revealed by CT. Panuveitis and papillitis found during an eye examination	One-month of prednisolone therapy resulted in reduced intrathoracic lymph nodes, improved vision, and reduced hyperemia of the optic nerve head.
Capaccione (32)	Man, 61 years old	14 months after severe COVID-19	Lymphadenopathy of mediastinal and intrathoracic lymph nodes	Systemic prednisolone therapy
Rodrigues (33)	Woman, 57 years old	After COVID-19	Erythematous, symmetrical, non-pruritic papules and plaques	Systemically administered prednisolone together with Azathioprine. Clinical improvement.
Palones (34)	Woman, 45 years old	2 weeks after COVID-19 onset	Cough and 2–3 cm erythematous skin rashes, painful on palpation. CT showed lung infiltrates with granulomatous changes.	Inhaled corticosteroids: six-month follow-up X-ray improvement
Rabufetti (35)	Man, 31 years old	2 weeks after COVID-19 onset	Erythematous skin lesions and mediastinal lymphadenopathy found by CT	Systemically administered prednisolone: regression of skin lesions
Pokhriyal (36)	Man, 64 years old	1 week after COVID-19 onset, using PCR (+)	Shortness of breath and symptoms of pneumonia concomitant with a large 6.3 × 4.7 cm size lung mass detected in the right upper lobe along with enlarged bilateral lymph nodes with signs of granulomatous inflammation	Simultaneously administered inhaled corticosteroids together with systemic prednisolone therapy: clinical and X-ray improvement.

ranging from cutaneous erythematous manifestations to pulmonary infiltrative changes. For example, a 72-year-old woman was found to have cutaneous painful, firm nodules representing noncaseating sarcoid-like granulomas, presented 2 weeks after recovery from COVID-19 pneumonia (29).

Another female patient was found to have swelling over old scars and *de novo* papules and vesicles 1 month after being diagnosed with COVID-19. Dense subcutaneous nodules appeared on the elbows. A needle biopsy obtained from an old scar-infiltrated plaque revealed during histopathological examination non-necrotic exposed granulomas in the superficial and deep dermis, suggestive of sarcoid granuloma. Similar data were obtained after an excisional biopsy of the subcutaneous nodule. However, no SARS-CoV-2 RNA was detected in the affected areas (30). Similar symmetrical erythematous non-pruritic papules and plaques were observed in a 57-year-old COVID-19 convalescent woman who was found to have sarcoid granulomas after histological examination of a skin biopsy (33).

Some patients were noted to have bilateral lymphadenopathy affecting hilar, paratracheal, and subcarinal lymph nodes based on chest CT scans performed 10 weeks after COVID-19. At the same time, panuveitis and papillitis were simultaneously found. Histological examination of transbronchial biopsy samples from intrathoracic lymph nodes revealed pathological sarcoid granulomas (31). Such data were recapitulated when examining the patient 14 months after severe COVID-19 (32). The development of cardiac sarcoidosis after acute COVID-19 has been rarely described (37). One of the recently published cases described an infiltrative process based on respiratory CT data paralleled with a severe cough. The patient was also found to have painful 2–3 cm cutaneous erythematous changes after COVID-19 infection (34). In addition, histochemical examination of a similar clinical case revealed a large number of specifically stained CD4+ T cells along the periphery of the granuloma (35).

Thus, it can be concluded that SARS-CoV-2 may be one of the cues resulting in the development of sarcoidosis-related inflammatory changes, ranging from affected skin to lymphadenopathy and pulmonary infiltrative foci, which may be paralleled by profoundly altered T and B cell immune responses.

4 B cell subset alteration in sarcoidosis during COVID-19

The phenotypic profile of B cells may indirectly mirror the functions of some B cell subsets and, therefore, their relevant role in the pathogenesis of sarcoidosis and COVID-19.

The role of the adaptive humoral arm in the pathogenesis of sarcoidosis is additionally evidenced by data showing that one of the signs of this disease is coupled to polyclonal hypergammaglobulinemia (38). Despite this, several reports noted that patients with sarcoidosis have normal serum immunoglobulin levels (39), but molecular biological analysis of IgA and IgG transcripts revealed a high frequency of somatic hypermutations suggesting persistent antigenic B cell stimulation (40). In addition, the latter study using histological methods showed B cell accumulation in pulmonary foci, which agrees with previous observations (41).

Recent studies described that patients with sarcoidosis had reduced levels of peripheral blood "naïve" IgD + CD38– and memory IgD–CD38+ and IgD–CD38– B cell subsets, while activated IgD + CD38+ and IgD + CD38++ were increased (42). This may be due to the migration of such cells to the lymph nodes and, possibly, to the foci of inflammation (43). Further investigation allowed to identify that the peripheral blood memory B cell population was altered in sarcoidosis patients compared to healthy subjects due to the decreased levels of "unswitched" (IgD + CD27+) and "class-switched" (IgD − CD27+) memory B cells, whereas the levels of CD19 + CD24+++CD38+++ and CD19 + CD5 + CD27– regulatory B cells were increased (42). The latter B cell phenotype is characterized by a stronger anti-inflammatory potential due to IL-10 production (44). Saussine et al. also found a higher count of IL-10-producing regulatory B cells in the peripheral blood of active chronic sarcoidosis patients (43). Classically, it is recognized that the CD5+ B cells could be found in various human tissues being capable of autoantibody production (including rheumatoid factor and anti-ssDNA antibodies) and that the count of CD5+ B cells is expanded in autoimmune diseases such as rheumatoid arthritis and Sjögren's syndrome (45, 46). Unfortunately, little is known about the functional potential of CD5+ B cells and the role they may play in the pathophysiologic mechanisms of human autoimmune diseases. In mouse models, CD5+ B cells have been shown to belong to a B1a subset that is typically located in the peritoneum and produces low-affinity autoreactive IgM antibodies (47). Furthermore, IL-10 is produced by CD5+ B cells and is involved in the regulation of autoimmunity during experimental autoimmune encephalomyelitis in mice (48). In humans, CD5 expression could be found on the cell surface of CD24+++CD38++ T1 transitional B cells (49), but recent data suggest that these cells are capable of producing low levels of IL-10 compared with other transitional B cell subsets (50). Intriguingly, some reports show that CD5 can be considered an activation marker for human B cells. Hence, human CD5-negative B cells may be suggestive of an *in vitro* activated population after exposure to phorbol-myristic acetate (PMA) or EL4 thymoma cells, which turn into CD5-positive cells (51). Finally, human CD5+ B cells have not been clearly characterized, although they may act as additional diagnostic and therapeutic targets in several autoimmune diseases.

In addition, high-frequency CD19+/–CD20–CD27++ plasmablasts in peripheral blood have been demonstrated in sarcoidosis (52). A special role in the development of inflammation has been attributed to IgA+ plasmablasts, which are found in substantial numbers in the peribronchial infiltrates of sarcoidosis patients (53). To assess B cell activation, serum B cell activating factor (BAFF), belonging to the TNF family, was also analyzed and found to be elevated in sarcoidosis, paralleling the activated inflammatory process (43, 54). BAFF levels were correlated with severe disease course and clinical manifestations (55). Moreover, elevated vitreous BAFF levels have been also noted in patients with sarcoidosis uveitis (56, 57) and granulomas in skin lesions of sarcoidosis (58). Hence, activated B cells are involved in granuloma formation and contribute to the development of not only systemic but also local inflammatory events.

Thus, B cells in sarcoidosis predominantly bear an "activated" phenotype, likely as a compensatory response due to the hyperactivation of pro-inflammatory immune cells and their migration into affected tissues. An increased count of CD19 + CD5 + CD27– cells in bronchoalveolar lavage has been previously reported in sarcoidosis (59), thereby confirming the assumption that Breg cells counteract to suppress inflammatory reactions. However, Breg cells may also contribute to disease progression. In this regard, Mengmeng et al. uncovered an elevated CD19 + CD24 + CD38+ Breg cell count in peripheral blood in active sarcoidosis. Moreover, the level of peripheral blood IL-35-producing Bregs was elevated and correlated with disease activity, while anti-IL-35 antibodies provided better control of sarcoid granuloma development in mice (60). Hence, Breg function in sarcoidosis remains underinvestigated, while recent studies suggest an ambiguous role such cells may play in disease pathogenesis.

B cells also play an important role in the pathogenesis of COVID-19 (61–63). The quality of the B cell response, including the development of high-affinity antibodies and memory B cells, is necessary to prevent the spread of infection and rapid virus elimination (64). In this regard, patients with COVID-19 were found to have decreased peripheral blood "naive" B cell levels along with elevated plasmablast counts (65). Moreover, Kudryavtsev et al. discovered a decline in peripheral blood memory B cell levels along with increased plasmablast counts during acute vs. convalescent COVID-19 in healthy volunteers [I. V. (66)]. Further investigation allowed to find that the peripheral blood levels of "class-switched" (IgD-CD27+) and "unswitched" (IgD + CD27+) memory B cells were significantly reduced during acute disease, while the percentage of double-negative (DN) memory B cells (CD27-IgD-) was markedly increased (67).

Based on the surface expression of CD21 and CD11c, DN memory B cells can be divided into four subsets: DN1 (CD21 + CD11c–), DN2 (CD21–CD11c+), DN3 (CD21–CD11c–), and DN4 (CD21 + CD11c+). DN1 B cells (CD21 + CD11c-) were significantly reduced in severe and critical cases, but not in mild/moderate ones, compared with healthy subjects; DN2 B cells (CD21–CD11c+) were significantly increased in severe, mild/moderate, and critical cases; the DN3 (CD21–CD11c–) subset increased along with escalating disease severity; and the DN4 subset was not determined in peripheral blood samples from either COVID-19 or healthy subjects (68, 69). In COVID-19, the DN3 B cell subset may migrate to the site of inflammation to further contribute to developing formation (68). Moreover, this cell type can also contact CD4+ T cells in the lungs, thereby accounting for local antibody production (68). The presence of the DN3 subset may be related to a dominant extrafollicular B cell response, implying earlier production of antibodies with low-affinity maturation, a lack of memory cell formation, or the emergence of "short-lived memory B cells" unable to produce high-affinity antibodies upon repeated antigen encounters (64, 69). Indeed, it has been shown that peripheral blood IgM-positive DN2 and DN3 B cell subsets dominate in patients with severe

COVID-19 (70). Moreover, some studies have reported high levels of "extra-follicular" B cell development and low efficiency of somatic mutagenesis during B cell maturation in peripheral lymphoid organs (71, 72), which may also be paralleled with the emergence of low affinity antibodies that can, among other effects, elicit autoreactivity. A recent study demonstrated a positive correlation between peripheral blood DN3 B cell subset levels and autoreactive antibodies such as anticardiolipin IgG, antichromatin IgG, and Smith antigen IgG in COVID-19 patients (70). In addition, the increased count of peripheral blood DN B cells in COVID-19 may suggest the prevalence of the "extra-follicular" pathway for B cell development during the antigen-specific humoral response that may be predominant in the severe disease course (73, 74). Furthermore, the prevalence of "extra-follicular" mechanisms in antigen-dependent B cell maturation has been observed in a typical autoimmune disease such as systemic lupus erythematosus (75, 76).

Such alterations in developing B cells are also suggested by the high serum BAFF levels observed in severe acute COVID-19 (77, 78). COVID-19 non-survivors vs. survivors demonstrated higher serum BAFF levels (79). Moreover, upregulated lung BAFF expression was observed in COVID-19 infection (80), while Alturaiki et al. found higher blood BAFF levels in mild SARS-CoV-2 (81). Elevated BAFF levels may underlie the maintenance of autoreactive B cell clones because this cytokine promotes the survival of CD38high B cells (82, 83), which are able to secrete autoantibodies, therefore suggesting the risk of developing autoimmune pathologies during the long COVID-19 syndrome. On the other hand, anti-BAFF monoclonal antibodies can be effective in the treatment of autoimmune pathologies (84), which could be a crucial component in lowering the risk of developing autoimmune reactions in severe COVID-19 cases.

B cell hyperactivation was also observed after COVID-19 recovery, which can be considered part of the post-COVID-19 syndrome, resulting in autoimmune reactions. It is known that both the percentage and the absolute count of activated B cells bearing a CD19 + CD80 + /CD86 + phenotype remain at a high level after recovery (85). Moreover, COVID-19 convalescents have also been observed to have high peripheral blood levels of upregulated surface PD1-positive plasmablasts and plasma cells (85). In addition to high CD86 expression on B cells, Castleman et al. (86) found high levels of the activation molecule CD69 on CD19+ B cells in COVID-19 convalescents, who were also noted to have a greater percentage of memory B cells compared to acute COVID-19 [I. V. (66)]. However, such cells may be involved in autoreactive effects post-infection, as was found by Vijayakumar et al., who showed that patients who experienced acute respiratory distress syndrome (ARDS) as part of the post-COVID-19 respiratory syndrome had an increased number of airway IgD–CD27+ memory B cells that correlated with CT scan-detected respiratory abnormalities (87). Overall, there is evidence of impaired B cell function after SARS-CoV-2 infection and aberrant expression of major B cell markers, e.g., in patients after severe COVID-19 who experienced downregulated B cell CD19 expression 1 year later (88), which may affect B cell activation upon antigen recognition. Furthermore, after severe COVID-19, patients were noted to lack surface CD21 (involved in the transduction of the surface B cell receptor-linked activating signal) typical of activated self-reactive B cells (86). The levels of the surface inhibitory molecules CD22 and CD72 on B cells were also found to be downregulated. BCR-linked stimulation of B cells with a similar phenotype resulted in hyperactivation of BCR-coupled effector molecules such as pSYK, pBLNK, and pPLCγ2 (86).

5 Autoantibodies in sarcoidosis and COVID-19

As mentioned above, the adaptive humoral arm is of particular importance in the pathogenesis of sarcoidosis. In addition to antibody production, some B cell subsets may also play a regulatory role by suppressing activated immune cells through the secretion of anti-inflammatory cytokines such as IL-10 and IL-35 (89).

Recent studies assessing the autoantibody profile demonstrate that class M (IgM) and class G (IgG) immunoglobulins are produced (90), which are able to specifically recognize proteins expressed in different human tissues targeted by sarcoidosis. For instance, uveitis in sarcoidosis patients was noted to be associated with elevated levels of anti-retinal autoantibodies (91). Caforio et al. found that cardiomyocyte-specific and anti-intercalated disc autoantibodies are produced in cardiac sarcoidosis (92). Hence, such findings were mainly observed in cardiac sarcoidosis (92). In addition, other studies have reported autoantibodies against cytoskeletal components and lysosomal trafficking proteins, regardless of the organ affected (93). Moreover, patients with sarcoidosis often had high antinuclear antibody (ANA) titers (58), anti-dsDNA antibodies (94), and those recognizing cyclic citrullinated peptides (95). Analyzing samples collected from 154 sarcoidosis patients uncovered elevated levels of anti-mitochondrial antibody-M2, anti-Ro52, anti-Ro60, anti-SSB, anti-P0, anti-CCP, anti-β2-GP, anti-Sm antibodies, and rheumatoid factor (RF) (96). Bronchoalveolar lavage fluid and sera from patients with sarcoidosis have been found to contain large amounts of IgG capable of specifically recognizing a wide range of different autoantigens (97).

Recently, the theory describing the development of autoantibodies against vimentin has become widespread. Bagavant et al. revealed an increased anti-vimentin IgG titer in patients with sarcoidosis vs. healthy subjects (98). However, despite the discovery of anti-vimentin autoantibodies, other studies refuted that they could have a profound impact on the overall pathogenesis of the disease (99). Therefore, the question regarding the role of autoantibodies in the pathogenesis of sarcoidosis remains open. In this context, an experimental model of granulomatous inflammation has been proposed after inoculating mice with vimentin-rich patient-derived blood samples (98).

Both during and after acute COVID-19, phenotypical and functional impairment of B cells was noted when they acquired the potential to produce autoreactive antibodies. B cells are mainly known to produce antibodies as a determining arm of adaptive humoral immunity in both infectious events and autoinflammation. There are emerging data regarding the activation of autoreactive B cell clones in patients with COVID-19 (100). Moreover, COVID-19 convalescents were noted to contain peripheral blood autoantibodies against various cytokines (IFN-α, IFN-ω, IFN-γ, IL-1β, IL-6, IL-10, IL-17, IL-21, and GM-CSF) and chemokines (CCL2, CXCL1, CXCL7, CXCL13, and CXCL16) (101, 102). In addition, elevated titers of autoantibodies specific for chromatin, cardiolipin, and Smith antigen have been observed (86). The latter was found in systemic lupus erythematosus (SLE) (103). At the same time, Chang et al. uncovered anti-cytokine autoantibodies in acute COVID-19 [S. E. (104)], which were found in

approximately 50% of 147 COVID-19 convalescent patients. Another study showed that 101 out of 987 patients during acute SARS-CoV-2 infection had type I interferon-neutralizing antibodies, including those targeting IFN-ω (13 patients), 13 different types of IFN-α (36 patients), or both (52 patients) (105). It should be noted that the appearance of anti-type I IFN antibodies has also been observed in classic autoimmune diseases such as systemic lupus erythematosus (106) and systemic sclerosis (107). Furthermore, that study also identified three patients bearing blocking antibodies against IL-6, IL-22, and IL-12p70 (105). Another study obtained similar data (108), demonstrating that COVID-19 patients had elevated levels of autoantibodies recognizing various immunomodulating cues, including cytokines, chemokines, complement components, and cell surface proteins. Hence, it has been suggested that such autoantibodies interfere with the effective functioning of the human immune system and affect immune control of viral infection by inhibiting cell-to-cell signaling and altering the composition of circulating immune cells, ultimately exacerbating the severity of SARS-CoV-2 infection.

Interestingly, Woodruff et al. showed that virtually no antibodies against Sm/RNP, Ro, La, and dsDNA were detected in severe COVID-19 cases, whereas antinuclear antibodies were detected in approximately 40% of these patients (109). Moreover, approximately 40% of COVID-19 patients had antibodies against carbamylated vimentin (anti-CarP), which plays an important role in the destruction of connective tissue in SLE and rheumatoid arthritis (110, 111).

On the other hand, the majority of patients with ARDS were found to have elevated antinuclear antibody levels (112), which raises the question of the existence of similar mechanisms underlying lung damage in SARS-CoV-2 infection and exacerbation of some autoimmune diseases, including SLE and rheumatoid arthritis (113). Similar data have been obtained by several independent groups describing elevated antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) titers after acute COVID-19 (112, 114, 115). Moreover, ANAs may be closely related to hair loss as a part of the long COVID-19 syndrome (116). On the other hand, detected rheumatoid factor may be another example of emerging autoantibodies after COVID-19, whose increase during acute disease was closely associated with its severe and critical course (117). Other studies described anti-platelet autoantibodies as able to markedly impact the severity of acute coronavirus disease (118). Gagiannis et al. also observed an elevated titer of anti-PM-Scl−/anti-Scl-70 antibodies in patients who developed pulmonary fibrosis, which raises the question of long-term consequences related to severe COVID-19. In addition, the detection of increased autoantibody titers specific to phospholipids (anticardiolipin, anti-β2-glycoprotein I, anti-phosphatidylserine/prothrombin) in acute COVID-19 has also been reported (119–121).

Furthermore, anti-cytokine autoantibodies associated with human inborn genetic defects mimic primary immunodeficiencies. Such pathologies are called "phenocopies of inborn errors of immunity" (122) and are often found in adults (123). Due to the appearance of autoantibodies specific for various kinds of cytokines, such as autoantibodies against type I IFN, IFNγ, GM-CSF, IL-17A, IL-17F, IL-22, IL-23, and IL-6, patients are predisposed to various infectious diseases, as well as bacterial, fungal, or viral infections (124). Patients with inborn defects in the IFNAR1 and IFNAR2 genes encoding type I IFN have a severe course of acute respiratory viral infections such as influenza and COVID-19 (105, 124). Neutralizing autoantibodies related to SARS-CoV-2 or phenocopy of inborn errors of immunity leads to severe infection and contributes to autoimmune disease.

An autoantibody spectrum detected in sarcoidosis and COVID-19 is shown in Table 2.

6 Alterations in Th subsets in patients with sarcoidosis and acute COVID-19.

It should be noted that the pathogenesis of sarcoidosis has long been associated with Th1 cell hyperactivation (125); sometime later, the key role in its development was considered to be due to altered Th1/Th17 cell ratios in the foci of granuloma formation (126). Currently, it is also common to pay attention to Th2 cells as a potential player in granuloma formation (127). This assumption is confirmed by clinical observations pointing to increased levels of peripheral blood CCR4 + CD4+ cells in sarcoidosis, as well as elevated concentrations of CCL17 chemokines both in the blood serum and at the site of granuloma formation (128). Moreover, underlying *in vivo* experimental models of pulmonary fibrosis demonstrated the key role of CCR4 ligands (primarily CCL17, but also CCL22) in tissue fibrosis, where blockade of CCL17 effects in mice resulted in lesion reduction (129). Excessive Th2 cell activation in patients with sarcoidosis is also confirmed by upregulated expression levels of IL-13 mRNA (one of the key Th2 cytokines) in peripheral blood mononuclear cells (130). Moreover, animal models (131) and tissue specimens obtained from patients with sarcoidosis (132) showed that hyperproduction of Th2 cytokines is accompanied by tissue macrophage activation and differentiation toward the M2 phenotype, which contributes to the development and maintenance of tissue foci of chronic inflammation, the formation of granulomas, and foci of fibrosis.

Apart from analyzing the balance between Th1 and Th2 cells, studies investigating the pathogenesis of sarcoidosis have paid special attention to the role of Th17 cells and their specific subpopulations. Data on temporal changes in peripheral blood Th17 cells are very conflicting, because some studies indicate an increased level of CCR6+ effector T helper cells (CD45RA-CD45R0+) in patients vs. controls (133), whereas others evidence that, for example, the level of IL-17A-producing cells in patients' peripheral blood was markedly below the control range (134). We found no significant differences in the level of CCR6-expressing Th cells not only between acute or chronic onset sarcoidosis but also when compared with the control group. At the same time, elevated blood serum levels of cytokines and chemokines such as IL-17, IL-22, IFN-γ, and CCL20 produced by patient Th17 cells are noted in the majority of studies (135). Subsequently, higher levels of these cytokines have been shown to be contained not only in bronchoalveolar lavage fluid (BALF) and granulomatous tissue but also in the cell types involved in their production (136). In parallel, the discovery of a fundamentally novel T helper cell population, T helper 17 (Th17) cells, in addition to a unique highly specialized subtype, Th17.1 cells, capable of producing both Th1 and Th17 cytokines, including IFNγ and IL-17A, suggested that sarcoidosis might be autoimmune in nature (137, 138). A series of studies have detected higher levels of Th17.1 cells and related proinflammatory cytokines in the peripheral blood and BAL fluid in sarcoidosis (133, 139). Moreover, the level of total CCR6+ Th cells, including Th17.1 cells, was significantly increased in lung-related lymph nodes of patients compared to controls (140).

TABLE 2 Autoantibody spectrum in sarcoidosis and COVID-19.

Autoantibody type	COVID-19	Sarcoidosis	Functions
Antinuclear antibodies (ANA), including anti-dsDNA antibodies, anti-Ro52 antibodies, anti-Ro60 antibodies, anti-SSB antibodies, anti-P0 antibodies, anti-chromatin antibodies, anti-Sm antibodies, anti-PM-Scl—/anti-Scl-70 antibodies	↑ Basic-Jukic et al. (114), Castleman et al. (86), Gagiannis et al. (112), Manav et al. ((116), Pascolini, et al. (115), and Woodruff (109))	↑ Shi et al. (96), Ueda-Hayakawa (58), and Weinberg et al. (94)	Destroy cell nuclear material; immune complex-mediated damaging effect on host tissues
Anti-cyclic citrullinated peptide antibodies (anti-CCP)	↑ Woodruff (109)	↑ Kobak et al. (95) and Shi et al. (96)	Induce bone erosion via osteoclast activation
Anti-mitochondrial antibody-M2, anti-ribosomal-P0-antibodies	Not significant Woodruff (109)	↑ Shi et al. (96)	Directed against lipoproteins on the inner mitochondrial membrane and ribosomes; contribute to biliary cirrhosis and SLE, respectively
Rheumatoid factor (RF)	↑ Jeong et al. (117)	↑ Shi et al. (96)	Contribute to chronic inflammation of the synovial membrane; promote cartilage destruction
Anti-vimentin antibodies	↑ Woodruff et al. (109)	↑ Bagavant et al. (98) and Hanoudi et al. (93)	Disorganization of cytoskeleton components
Antineutrophil cytoplasmic antibodies (ANCAs)	↑ Basic-Jukic et al. (114)		Attack neutrophils, leading to their degranulation and destruction
Antiphospholipid antibodies (Anticardiolipin, anti–β2-glycoprotein I, anti-phosphatidylserine/prothrombin)	↑ Castleman et al. (86), Xiao et al. (119), Zhang et al. (120), and Zuo et al. (121)	↑ Shi et al. (96)	Damage to the endothelium and hemostatic system; contributes to thrombosis
Anti-cytokine autoantibodies, including anti-type I IFN antibodies	↑ Acosta-Ampudia et al. (101), Bastard et al. (105), Chang et al. (104), Garmendia et al. (102), and Wang et al. (108)		Block cytokine signaling pathways, leading to the spread of infectious agents
Organ-specific autoantibodies (anti-retinal autoantibodies, anti-glomerular basement membrane (GBM) antibodies, anti-cardiomyocyte antibodies)	↑ Woodruff et al. (109)	↑ Avendaño-Monje et al. ((91) and Caforio et al. (92))	Damage to various tissues

Regarding the pathogenesis of COVID-19, the role of the Th1 cell subset, which plays a key role in the immune response against intracellular pathogens, is quite controversial. For instance, some studies suggest that IFNγ-producing Th1 cells may play a positive role in COVID-19, and their higher activity may be associated with a milder disease course (141, 142). On the other hand, older patients, who are usually characterized by severe COVID-19, were noted to have decreased levels of IFNγ-producing virus-specific cells, which also indirectly indicates an important role of Th1 cells in the development of an effective immune response (143). However, Th1 cell-induced IFNγ and TNFa overproduction in response to SARS-CoV-2 infection, as well as the massive death of virus-infected cells, can result in damaged lung tissue and trigger acute respiratory distress syndrome. In particular, during acute COVID-19 infection, the migration of Th1 cells into inflamed tissues has been indirectly evidenced by their slightly decreased percentage in the peripheral blood, which has been observed in several studies (144–146). However, some studies have revealed an accumulation of "atypical" peripheral blood Th1 cells expressing surface markers such as CD161 and IL-1RI (146), which are more typical of Th17 cells (or "non-classical" Th17.1 cells) in patients with severe COVID-19 pneumonia. Th2 cells primarily target multicellular pathogens, but virus-specific Th2 cells are detected in COVID-19 (147), while high levels of Th2 cell cytokines are found in the blood serum of patients during the acute phase of the infection (144). Patients also had an increased percentage of peripheral blood T helper cells expressing surface CCR4 along with nuclear GATA3 (148). A rise in peripheral blood Th2 cells bearing the CXCR3–CCR6– phenotype was closely related to unfavorable outcomes in severe COVID-19, which allowed for it to be considered as an independent prognostic marker (149). Elevated peripheral blood Th2 cell levels and hyperactivation may be closely related to associated symptoms such as intestinal hypermotility, gastric acidification, and dyspnea, which accordingly could be considered typical defense mechanisms to remove parasites via Th2 cytokines (150). With regard to inflamed lung tissues, BALF cells obtained from patients with severe COVID-19 were shown to have upregulated expression of not only the genes encoding crucial cues accounting for Th2 cell "polarization" (*GATA3*, *IL4R*, and *MAF*) but also did not differ in production levels of key Th2 cytokines when assessing patients with varying degrees of COVID-19 severity (151). Moreover, COVID-19 convalescent patients were found to have additionally high peripheral blood Th2 cell levels that persisted for several months, while the concentrations of IL-4, IL-5, and IL-13 did not differ significantly from those in the control groups [F. (152)].

Analysis of the Th cell subset profile in COVID-19 revealed a decline in the percentage of Th17.1 and Th1 lymphocytes capable of producing IFN-γ (145). Moreover, T helper cells from SARS-CoV-2-infected patients contained more IL-17A and IL-2 in response to *in vitro* stimulation, compared to healthy volunteers (148). At the same time, the aforementioned work showed a lower percentage of T helper cells bearing surface key Th17 antigens (CD161 and CCR6) whereas the level of Th2-positive (CCR4 and GATA3) cells was significantly elevated compared to the control group. Similar data were obtained using molecular biology methods, which revealed that peripheral blood CD4+ T cells from patients with severe COVID-19 had downmodulated expression of Th17-associated genes, e.g., *RORC*, *IL17A*, *IL17F*, and *CCR6* (151). However, another study showed that in the peripheral blood specimens of COVID-19 patients, the percentage of Th17 and follicular T cells was higher, paralleled by moderately decreased Th1 cell levels, whereas that for Th2 and Th17.1 cell subsets did not differ compared with the control group (146).

It is possible that Th17 cells migrate to the site of inflammation with varying efficiency at different stages of the infection process. This explains why the BALF data are so important because they point to an accumulation of Th17 cells bearing a "pro-inflammatory" phenotype in the affected lung tissue (153). For instance, lung tissue specimens obtained from COVID-19 patients were enriched for cells co-expressing CCR6 and IL17A and also had high levels of IL-6, IL-17A, GM-CSF, and IFNγ found in BALF. The crucial role of Th17 cells in the pathogenesis of COVID-19 is suggested by the data showing that after successful completion of the infection process and pathogen elimination, memory Th17 cells remain persistently in circulation. In this regard, some studies have uncovered the emergence of virus-specific memory Th17 cells capable of producing IL-17A, IL-17F, and IL-22 in response to *in vitro* stimulation with the SARS-CoV-2 S protein-derived peptide pool (147).

Thus, the pathogenesis of sarcoidosis and COVID-19 is closely related to profound alterations in the major T helper cell profile coupled to the regulation of the three types of inflammatory reactions, such as the type 1 response aimed at eliminating intracellular pathogens, the type 2 response associated with control over multicellular pathogens and relevant toxins, and the type 3 response necessary for effective elimination of pathogens (bacteria and fungi) localized in the intercellular space of various host tissues. These alterations may directly impact the activation of the humoral immune response, which is controlled by follicular T helper cells.

7 Follicular helper T cell subset alterations

Cross-talk between follicular helper T cells (Tfh) and B cells at the border of T cell and B cell areas in the lymphoid follicle is necessary for the development of an effective humoral immune response (154). Tfh cells are characterized by surface expression of the chemokine receptor CXCR5, which is necessary for migration to the B cell zone (154). Tfh plays a pivotal role in B cell maturation and differentiation during the germinal center reaction that occurs in peripheral lymphoid organs (155–157). Tfh cells also control antibody class switching in B cell-produced immunoglobulins, eliciting somatic hypermutation and clonal selection of high-affinity B cells that further differentiate into plasma cells and memory B cells. Thus, this CD4+ T cell is required for the production of both high-affinity pathogen- and self-antigen-specific antibodies and autoantibodies, respectively. The detection of CD4 + CXCR5+ T cells is crucial in both infectious and autoimmune diseases to assess the quality of the adaptive humoral immune response. At the same time, the half-life of Tfh cells in peripheral blood is highly heterogeneous. For instance, circulating Tfh cells can be divided into four major subsets based on CXCR3 and CCR6 coexpression: CXCR3 + CCR6 − Tfh1, CXCR3 − CCR6 − Tfh2, CXCR3 − CCR6+ Tfh17, and CXCR3 + CCR6+ Tfh17.1 cells. Moreover, these cell types mimic Th1, Th2, classic Th17, and pro-inflammatory Th17.1 cells, respectively, in terms of functional activity and phenotype (158–160). Altered Tfh cell function, as well as an altered balance between their individual circulating subsets, is closely related to pathological effects on the activity of the overall antigen-specific humoral immunity. This may potentially account for the fact that an imbalance between the proportion of Tfh1 cells, on the one hand, and Tfh2 cells, along with Tfh17 cells, on the other hand, is observed in rheumatoid arthritis, SLE, Sjogren's syndrome, multiple sclerosis, type 1 diabetes mellitus, and other conditions (161).

Regarding sarcoidosis, the profile of Tfh cells has only recently been investigated. In particular, Kudryavtsev et al. assessed Tfh subset composition by assessing the expression of differentiation molecules and chemokine receptors (42). It was revealed that in chronic sarcoidosis, upregulated CXCR5 expression was observed on central memory CCR7 + CD45RA− CD4+ T cells along with an elevated percentage of peripheral blood CXCR3−CCR6− Tfh2-like cells. While evaluating the surface chemokine receptor expression on central memory Tfh cells, it was found that in pulmonary sarcoidosis peripheral blood samples contained an elevated percentage of Tfh2 (CXCR3 − CCR6 − CCR4+), Tfh17 (CXCR3 − CCR6 + CCR4+), and dual-positive Tfh17 (CXCR3 + CCR6 + CCR4+) paralleled with significantly reduced Tfh1 (CXCR3 + CCR6 − CCR4−) and Tfh17.1 (CXCR3 + CCR6 + CCR4−) levels [I. (42)]. A decline in peripheral blood Tfh1 and Tfh17.1 cell levels in sarcoidosis seems to be related to their migration to organs and tissues affected by sarcoid granulomas. Zhou et al. (9) also noted an altered Tfh cell subset composition associated with increased levels of Tfh2 and Tfh17 cells but decreased levels of Tfh1 and Tfh17.1 cells. Notably, Tfh2 and Tfh17 cells contributed to the survival of activated "naive" B cells, their transformation into plasma cells, and antibody class switching, whereas Tfh1 cells performed regulatory functions related to the emerging humoral immune response (159). It is possible that an imbalance between pro- and anti-inflammatory Tfh cell subsets may play a paramount role in abrogating the overall development of autoimmune reactions.

Indeed, other studies have reported elevated bronchoalveolar lavage fluid (BALF) levels of CXCR3 chemokine receptor-expressing follicular T cells (53) found on both Tfh1 and Tfh17.1 cells. Furthermore, d'Alessandro et al. (162) showed upregulated expression of the integrin molecule CD103 on peripheral blood, BALF, and intrathoracic lymph node biopsy specimens in patients with sarcoidosis, indirectly confirming a theory of migration of such cells into inflammatory foci. Ly et al. verified the presence of CD4 + CXCR5+ T cells in sarcoidosis-related skin lesions (163). However, other reports, on the contrary, revealed an increased level of peripheral blood Tfh1 cells along with decreased levels of BALF Tfh1 and Tfh2 cells in chronic sarcoidosis (59). Hence, ambiguous data regarding the role of

follicular T cells and B cells in this pathology implies a need for their more thorough study.

Follicular T helper cells are responsible for the quality of the antiviral B cell response in COVID-19, owing to the fact that Tfh cell-mediated stimulation of B-lymphocytes enables more fine-tuned differentiation, resulting in the emergence of long-lived memory B cells and plasmacytes that produce virus-specific high-affinity antibodies (64). In particular, circulating Tfh cells from COVID-19 patients support *in vitro* B-cell differentiation into antibody-secreting plasma cells and antibody production, whereas altered differentiation of SARS-CoV-2-specific Tfh cells at early stages of infection was closely related to severe COVID-19, accompanied by delayed production of high-affinity antibodies and disease progression (164). Subsequently, the level of SARS-CoV-2-specific cTfh cells in COVID-19 convalescent patients correlated with SARS-CoV-2-neutralizing antibody titers, which evidenced a crucial function of this cell type in maintaining protective immunity [J. (165)].

However, data regarding circulating Tfh cell levels in acute COVID-19 as well as in the post-infection period have been rather ambiguous. For instance, one study noted a decline in CD4 + CXCR5+ T cell frequency, particularly in severe disease (144). In contrast, other studies have reported an increase in peripheral blood Tfh cell levels (146), especially for those cell subsets expressing activation markers such as PD-1 (166), HLA-DR and CD38 (67), and ICOS (167). Importantly, such cell types are highlighted by high expression of the proliferation marker Ki67 (67), suggesting the emergence of post-clonal expansion Tfh cells in an overactivated state that have entered the circulation in severe COVID-19. However, upon SARS-CoV-2 infection, Tfh cell differentiation becomes altered (151). By examining lymphoid organ autopsy samples, Kaneko et al. detected atrophy of the lymph node germinal center (B-dependent zones) (73), which may be due to a heightened cytokine storm wherein TNF-α blocks Bcl-6+ Tfh cell differentiation. This may be related to an enhanced local Th1 cell response. It has been shown that Th1/Tfh1 alters the differentiation of follicular T helper cells, promoting antibody production (73, 168). However, even CD4 + CXCR5+ Tfh cells lacking Bcl-6 expression can interact with and induce the proliferation of naive extrafollicular B cells. Thus, patients with acute COVID-19 infection were found to have enhanced functional and proliferative Tfh cell potential, but impaired differentiation negatively affected the B cell immune response. Importantly, such an impaired adaptive humoral response is often observed in severe COVID-19 and testifies to its inability to result in fully-fledged pathogen-specific humoral immunity (73).

When the CD45RA- memory Tfh cell population was subdivided into Tfh1, Tfh2, and Tfh17 subsets based on surface chemokine receptor expression, it was found that acute COVID-19 was associated with a decreased percentage of Tfh1 paralleled with elevated Tfh17 levels (169). Juno et al. unraveled that among all Tfh cell subsets, the SARS-CoV-2-specific antiviral response peaked in Tfh17 cells, whereas Tfh1 and Tfh2 cells were most closely related to blood plasma SARS-CoV-2-specific antibody neutralizing activity (170). COVID-19 convalescent patients continued to carry an altered profile of circulating Tfh cell cells. Although the total Tfh population did not differ between healthy and convalescent subjects, the level of CXCR3-expressing Tfh1 cells was reduced. Interestingly, in a cohort of recovered patients, the percentage of Tfh1 cells that correlated with the antibody-neutralizing activity peaked in those who had a more severe infection (165). On the other hand, high levels of circulating Tfh1 and Tfh2 were paralleled by markedly reduced levels of Tfh17 (152). COVID-19 convalescents vs. healthy subjects showed a higher frequency of circulating effector memory CCR7loPD-1+ Tfh-em cells and a low level of central memory CCR7hiPD-1+ Tfh-cm cells [F. (152)]. In addition, some studies reported enhanced Tfh cell activity in COVID-19 convalescents [F. (152, 171)], which may contribute to the emergence of autoimmune and allergic reactions during post-COVID-19 syndrome. Furthermore, Tfh cell activity depends on the severity of SARS-CoV-2 infection, such that the level of effector memory Tfh-em cells promoting class switching to IgG antibodies remains high for a long time in patients recovering from severe COVID-19 (152). Kudryavtsev et al. found that Tfh1, Tfh2, and Tfh17 levels remained high in COVID-19 convalescent patients compared with healthy subjects (66). Hence, it may serve as a basis for the development of an autoimmune process with altered immune tolerance often observed in post-COVID-19 syndrome.

A comparison of circulating Tfh cell subpopulations in sarcoidosis and COVID-19 is presented in Table 3.

8 Follicular regulatory helper T cells – Crucial players in the antigen-specific humoral response

It is believed that Tfr represents one of the regulatory T cell subsets that may originate from both thymic Tregs via thymic selection and emerging antigen TCR specificity, or from CXCR5 and BCL-6-co-expressing FoxP3+ cells arising *de novo* in peripheral lymphoid organs (175–177). Follicular regulatory helper T cells play a rather ambiguous role in regulating the humoral immune response. On the one hand, they contribute to the survival and proliferation of B cells specific for some environmental foreign antigens, while on the other hand, they are able to suppress the proliferation and differentiation of foreign antigen-nonspecific B cells by creating a proper environment that mainly promotes the development of antigen-specific germinal center B cell clones in peripheral lymphoid organs (175, 178). Moreover, Tfr cells suppresed Tfh activity, leading to a restrained germinal center response at the stage of Tfh cell-mediated B cell costimulation, which appears to be the key function of this Treg population (175). On the other hand, Tfr cells act to suppress not only Tfh but also B cells, resulting in downregulated antibody production (179). It has also been hypothesized that during germinal center formation, Tfrs regulate the production of antigen-specific antibodies during the primary immune response, and with repeated antigen encounters, their role in regulating the humoral response becomes less prominent (180). On the contrary, Tfrs are thought to play a key role in the later stages of the germinal center response (181).

In the context of the development of autoimmune pathologies, a suppressive role of Tfr has been demonstrated, contributing to the limitation of the autoimmune humoral response (179, 180). Potentially, it may explain why a key role in the development of efficiently functioning Tfr cells is related to their thymic differentiation. Analyzing circulating Tfr cells in patients with sarcoidosis showed that within the total CD45RA–CCR7+ central memory Treg population, the proportion of CXCR5+ Tregs was increased, whereas the percentage of thymic CXCR5+ Tregs did not significantly differ from that in the control group (174). Moreover, d'Alessandro et al. (162)

TABLE 3 Patterns of circulating follicular helper T cell fluctuations in sarcoidosis and COVID-19.

Cell subsets	COVID-19	Sarcoidosis	Functions
Tfh1	↑ (Golovkin et al. (169) and Kudryavtsev et al. (66)) ↓ Zhang et al. (165)	↑ d'Alessandro et al. (162) ↓ Zhou and Arce (9)	Suppress Tfh2-dependent antibody induction, regulate humoral immune response
Tfh2	↑ Kudryavtsev et al. (66)	↑ Kudryavtsev et al. (42) and Zhou and Arce (9)	Contribute to the differentiation and proliferation of activated "naive" B cells, primarily eliciting antibody class switching to IgA and IgG
Tfh17	↑ Golovkin et al. (169), Kudryavtsev et al. (66)	↑ Zhou and Arce (9)	Contribute to the differentiation and proliferation of activated "naive" B cells, primarily eliciting antibody class switching to IgE and IgG
Tfr	↓ Søndergaard et al. (172) and Zahran et al. (173)	↑ d'Alessandro et al. (162) and Igor Kudryavtsev et al. (174)	For antigen-specific vs. antigen-nonspecific B cell clones, it promotes the formation and survival of the former along with the inhibition of the latter, suppressing Tfh cells

showed that the level of peripheral blood CD4highCD25highCXCR5high Tfr cells was increased in sarcoidosis, while the level of alveolar Tfr cells correlated with the Scadding stages. Furthermore, the level of this Tfr cell subset was shown to be higher in bronchoalveolar lavage fluid (BALF) than in peripheral blood in patients with pulmonary sarcoidosis (59). Based on such data, it can be assumed that in sarcoidosis, Tfr functions may be impaired both at the systemic level (e.g., at thymic Tfr differentiation or impaired function in peripheral lymphoid organs) and during their migration to inflammatory foci, where their regulatory functions may also be altered. It is likely that the peripheral blood Tfr subpopulation declines during novel coronavirus infection because Tfr differentiation, acted upon by pro-inflammatory cytokines, is aimed at creating effector Tfh subsets that promote sustained inflammation to eliminate the pathogen in the acute period. Of note, sarcoidosis is a chronic process often accompanied by fibrosis and a marked autoimmune reaction. Therefore, a rise in Tfr cell levels in both peripheral blood and BALF in sarcoidosis may be a compensatory response necessary to curb inflammation at the site of the tissue lesion, where Tfr cell functional activity may not be as effective, which could contribute to pulmonary fibrosis.

Very few clinical cases are available that describe thymoma formation in sarcoidosis. For instance, Hato et al. reported a clinical case in which calcified thymoma and sarcoid granuloma were localized in the lung parenchyma and intrathoracic lymph nodes (182). A clinical case has also been described in which a patient with existing sarcoidosis developed a thymoma (183). In addition, a malignant thymoma has also been reported, and it has been suggested that it provoked the development of autoimmune sarcoid due to impaired T cell tolerance (184). Moreover, Esendagli et al. clearly demonstrated the thymus-related role in the development of sarcoidosis (185). For example, in their reported clinical case, a 53-year-old female patient presented with sarcoid granulomas in the lung parenchyma, intrathoracic lymph nodes, and skin. A thymectomy resulted in the resolution of the sarcoidosis manifestations. In addition, impaired thymic T-cell differentiation in sarcoidosis was also suggested by high expression of non-TCR-mediated cell activation markers in total peripheral blood "naive" Th cells, apoptosis-related proteins, and profoundly dysregulated CD4+ T-cell differentiation (186).

Profoundly altered thymic function and lowered thymic development of various "naive" T cell subsets in acute COVID-19 are evidenced by lowered TREC (T cell receptor excision circles) levels in the peripheral blood in severe and critical COVID-19 (187, 188). Moreover, this may be related to SARS-CoV-2 infection of the thymic epithelial cells, resulting in altered T cell maturation and differentiation (189). Also, impaired thymocyte selection may be accompanied not only by a decreased percentage of functionally active Treg subsets but also with the release of autoreactive T cell clones into the periphery, capable of mounting a response to host self-antigens and eliciting the development of autoimmune pathologies. This may potentially account for a decline in peripheral blood T regulatory follicular cell levels that was noted in acute SARS-CoV-2 infection compared to the control group (172). Moreover, Zahran et al. obtained similar data showing that hospitalized patients with a severe form of COVID-19 had decreased counts of circulating CD4 + CXCR5 + ICOS+Foxp3+ Tfr cells (173). It should be noted that the level of circulating CD45RA–CD127–CD25 + CXCR5hiPD-1hi Tfr also tended to decrease steadily in COVID-19 convalescent patients (152). In addition, a negative correlation between the frequency of circulating Tfr and virus-specific IgM, IgG, and IgA antibodies was observed in the latter cohort of patients. Follicular T regulatory cells may play an important role in controlling the development of the humoral memory response and antibody specificity, as well as interfering with autoantibody formation. Thus, lowered Tfr levels along with increased Tfh levels in acute COVID-19 may contribute to the development of humoral autoimmune reactions and the emergence of autoimmune pathologies during the post-COVID-19 syndrome. While analyzing the role of B cells and diverse Tfh cell subsets in the development of autoimmune events in sarcoidosis along with COVID-19, it is necessary to consider the issue of the disturbed structure of peripheral lymphoid organs, where an interaction between T and B cells occurs and arises under such pathological conditions. For instance, a non-infectious, non-caseating T and B cell-containing granuloma emerges (190, 191). Such lymphocyte cell types mainly reside in the periphery of the granuloma and exert a high proliferative potential as assessed by Ki-67 expression (192). A granuloma *per se* represents a focus of limited granulomatous inflammation primarily involving macrophages, epithelioid cells, lymphocytes, and plasma cells (191). Epithelioid cells may fuse to form giant cells, both along the periphery of the granuloma and in its center (191). A biopsy of intrathoracic lymph nodes collected from patients with chronic sarcoidosis revealed high levels of B cells and follicular T helper cells (162). When comparing B and Tfh cell counts in patients with sarcoidosis, it was found that the level of B cells and CD4 + CXCR5+ T cells was significantly higher in lymph node biopsy compared to BALF and peripheral blood sample (162). Thus, the adaptive humoral response in this pathology plays an important role not only in the systemic but also in the local inflammatory response.

Multiple studies have noted disturbances primarily in the organization of B cell-dependent zones in acute COVID-19, most often being associated with a decreased volume of germinal centers or their full disappearance, apparently resulting in a mild humoral response in patients with severe disease course (73, 193, 194). The number of lymph node follicular dendritic cells, Bcl-6+ Tfh, and B cells is reduced, whereas AID+ B cells, which are usually kept at an intact level (73, 194), are aberrantly located in subcapsular and paracortical lymph node zones (195). On the other hand, extrafollicular plasmablasts, whose development is not tightly controlled by Tfh and Tfr cells, predominantly display an IgM+ phenotype. They can sometimes be found at high levels in the paracortical and medullary zones of lymph nodes (193, 194, 196). However, along with the loss of follicles, some studies reported lymphoid hyperplasia and the mosaic structure of lymphoid tissue (197). Moreover, splenic white pulp was also noted to contain a lowered relative number and volume of lymphoid follicles, and a decreased number of Bcl-6+ B cell-containing germinal centers (73). Hence, severe acute COVID-19 infection was often found to have an inconsistent adaptive immune response due to depletion of the T helper arm and B-dependent zones in the lymphoid organs. However, it is primarily the increased activity of the above cell types that may underlie an allergic or autoimmune pathology in convalescent subjects.

9 Conclusion

Analyzing the available publications allowed us to uncover that SARS-CoV-2 elicits the development of symptoms typical of sarcoidosis a few weeks after COVID-19. The appearance of bilateral lymphadenopathy and eye and skin lesions related to a triggering factor is rather characteristic of an autoimmune process, accompanied by hyperactivation of specific B cell subsets observed after COVID-19, which are also observed in autoimmune inflammation (Figure 2). B cell phenotypic and functional impairments lead to the development of autoreactive potential and autoantibody production. In SARS-CoV-2 infection, follicular helper T cells determine the quality of the virus-specific B cell response. At the same time, Tfh-mediated B cell stimulation may be more finely tuned, resulting in the emergence of long-lived memory B cells and plasmacytes that produce high-affinity antibodies. On the other hand, expanding our understanding of the essential rules of Tfh and Tfr function may allow the development of

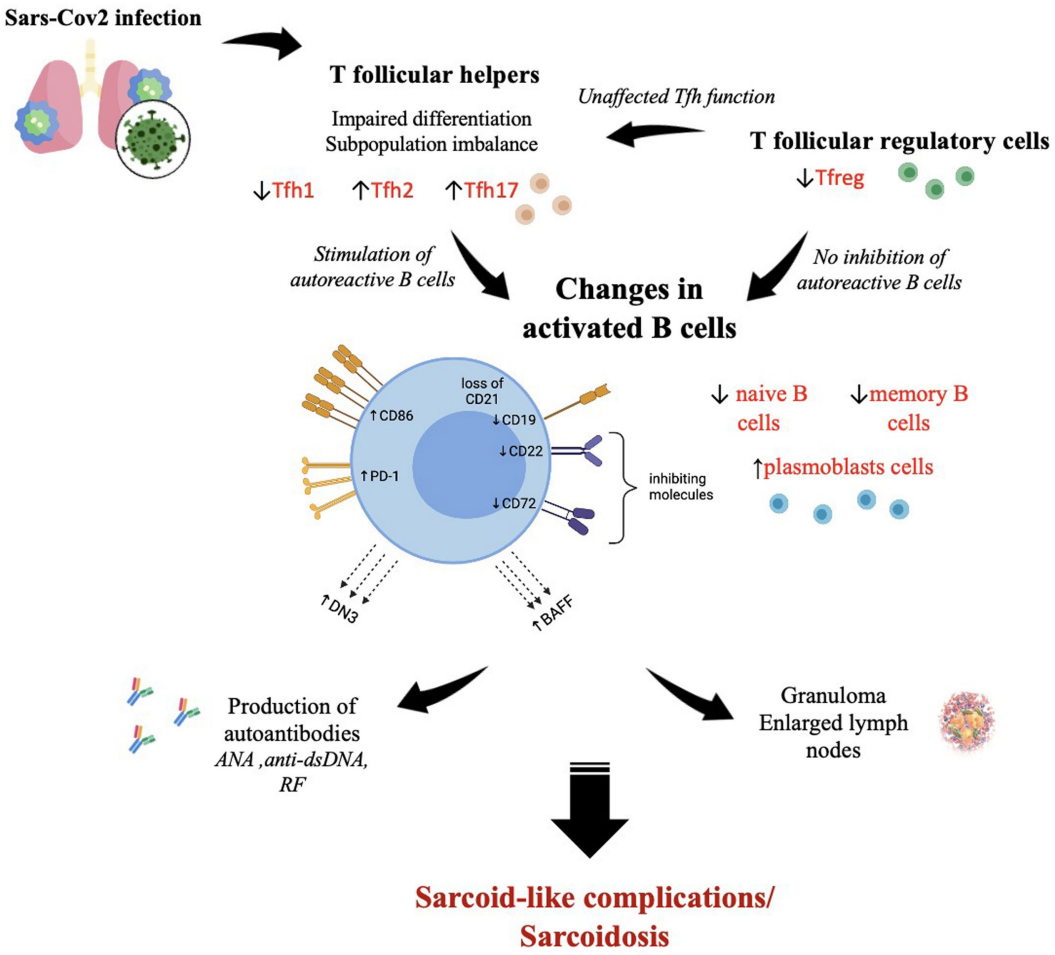

FIGURE 2
The SARS-CoV-2-induced immunological changes in T follicular helper cells, T follicular regulatory cells, and B cells, which contribute to the development of autoimmune reactions with sarcoid granuloma formation and autoantibody production. ↑—high level; ↓—low level. The figure was drawn by the authors.

new approaches to restore the functions and balance between individual subsets of these cell types in the prevention and treatment of autoimmune and inflammatory diseases. The data obtained not only reflect the specific features of sarcoidosis-related autoimmune inflammation associated with SARS-CoV-2 infection but also the need to shed light on the further management strategy of such patients, taking into account the changes identified. At present, the existing concept allows for the monitoring of sarcoidosis patients without therapy. On the other hand, patients with a history of sarcoidosis are required to be prepared for its activation and chronicity. However, the question of establishing immunological criteria accounting for the need for immunotherapy and drug administration remains open.

Author contributions

AR: Writing – original draft, Conceptualization, Formal analysis. IK: Writing – original draft, Project administration, Writing – review & editing. AM: Writing – original draft. JM: Writing – original draft. DI: Writing – review & editing, Methodology, Writing – original draft. II-S: Formal analysis, Writing – original draft. DK: Funding acquisition, Project administration, Writing – review & editing. AS: Writing – original draft, Project administration.

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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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Progress in the treatment of lung adenocarcinoma by integrated traditional Chinese and Western medicine

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Non-small cell lung cancer (NSCLC) overwhelmingly represents the predominant histological subtype of lung cancer, with lung adenocarcinoma emerging as the most prevalent form. Conventional Western medical treatments encompass a spectrum of modalities, including surgical interventions, cytotoxic chemotherapy, radiotherapy, targeted pharmacotherapy, and immunotherapy. In contrast, Traditional Chinese Medicine (TCM) methodologies encompass traditional Chinese medicine treatments, acupuncture therapies, and tuina treatments. While conventional Western medicine has made remarkable strides in the treatment of lung cancer, it is important to acknowledge the limitations inherent in singular treatment approaches. Consequently, the quest for a more comprehensive and integrative therapeutic paradigm becomes imperative. A deficiency of evaluation criteria specific to lung adenocarcinoma treatment in the realm of TCM represents an outstanding challenge in need of resolution. Nonetheless, in the backdrop of the continuous evolution of lung adenocarcinoma treatment modalities, the amalgamation of Chinese and Western medical approaches for treating this condition has exhibited a promising trajectory. It not only contributes to mitigating toxicity and augmenting efficacy but also serves to reduce a spectrum of postoperative complications, thereby enhancing the quality of patients' survival and extending life expectancy. This article furnishes a comprehensive survey of the research advancements in the integration of Chinese and Western medical approaches for treating lung adenocarcinoma. It elucidates the merits and demerits of individual and combined therapeutic strategies, surmounts current limitations, underscores the virtues of amalgamating Chinese and Western medical paradigms, and offers a more holistic, integrated, and efficacious treatment blueprint.

KEYWORDS

combined Chinese and Western medicine treatment, lung adenocarcinoma, review, Western medicine, Chinese medicine

1 Causes of lung adenocarcinoma

Lung cancer stands as the predominant malignant ailment in China, with a staggering annual incidence of 789,000 new cases and approximately 631 deaths (1). Non-small cell lung cancer, chiefly represented by lung adenocarcinoma, encompasses a spectrum of clinicopathological types, including invasive adenocarcinoma (IAC), invasive adenocarcinoma variants, micro-invasive adenocarcinoma (MIA), and pre-infiltrative lesions; the latter category

further bifurcates into adenocarcinoma *in situ* (AIS) and Atypical adenoma hyperplasia (AAH) (2). Notably, early-stage lung adenocarcinoma patients typically remain asymptomatic and are often incidentally diagnosed during routine physical examinations. However, the highly infiltrative and metastatic nature of lung adenocarcinoma occasionally results in distant metastases upon diagnosis. Patients in the intermediate and advanced stages of the disease frequently manifest conspicuous symptoms, primarily characterized by hemoptysis, chest tightness, dyspnea, and bone pain, among others (2).The therapeutic management of lung adenocarcinoma in Western medicine varies based on disease staging. In the early stages, surgical resection assumes a pivotal role, achieving a curative effect through tumor excision. In contrast, late-stage patients typically undergo conventional chemotherapy, radiotherapy, targeted pharmacotherapy, and immunomodulation to gain control over the disease, alleviate symptoms, and extend survival (3).

Chinese medicine's approach to lung adenocarcinoma centers on the modification and regulation of the body's internal milieu using traditional Chinese medicine components. This approach aims to bolster immunity, reduce adverse reactions, and enhance clinical efficacy. Modalities include traditional Chinese medicine treatments, acupuncture, and tuina therapy, among others (4). While Western medicine has made substantial strides in treating lung adenocarcinoma in recent years, improving patient survival rates, the associated adverse reactions and toxic side effects detrimentally impact patients' quality of life (5).

In contrast, Traditional Chinese Medicine (TCM) boasts several advantages in the treatment of lung adenocarcinoma. It emphasizes evidence-based and individualized treatment plans tailored to patients' specific conditions (6). However, standardized diagnostic and therapeutic criteria for TCM treatment of lung adenocarcinoma have not been universally established, representing an ongoing challenge in this field (7).

To address the need for a more comprehensive and integrated approach, the combination of Chinese and Western medicine has emerged as a compelling research focus (8). This integrated approach capitalizes on Western medicine's direct targeting of tumors and Chinese medicine's role in enhancing immune function, thereby improving treatment compliance and efficacy. This synergistic approach not only reduces toxicity and enhances efficiency but also mitigates post-surgery complications, enhances the quality of life, and extends survival (9). The combination of Traditional Chinese Medicine and Western medicine in the management of lung adenocarcinoma represents a holistic and synergistic treatment strategy, harnessing the strengths of both paradigms. It takes into account patients' specific conditions and physical status, facilitating the formulation of scientifically grounded treatment plans (10). Consequently, the combination of Chinese and Western medicine emerges as a superior approach to lung cancer treatment. This article offers a comprehensive review of the utilization of Chinese medicine, and Western medicine, and their synergistic combination in the recent treatment of lung adenocarcinoma.

1.1 Western medicine to the etiology of lung adenocarcinoma

Within the purview of Western medicine, the precise etiology of lung adenocarcinoma remains enigmatic, and its pathogenesis is postulated to stem from a myriad of factors, as gleaned from clinical observations (11). These contributory factors encompass an array of determinants, such as long-term tobacco smoking, environmental pollution, occupational exposures, genetic predisposition, and concomitant chronic respiratory ailments (12). Notably, while chronic tobacco smoke exposure ranks as the most prevalent cause, lung adenocarcinoma manifests in approximately 15–20% of non-smokers, often attributed to a complex interplay of environmental and genetic influences (9). Literature within the field has reported that variances in the germline ancestry of lung adenocarcinoma may also exert an influence on the subsequent selection of somatic mutations, thereby contributing to the development of diverse subtypes of this cancer (13).

Furthermore, obesity, recognized as a risk factor for various malignancies, has been posited to exert differential effects on the idiosyncratic incidence patterns among lung adenocarcinoma patients (14). Clinical presentations among individuals afflicted by lung adenocarcinoma predominantly encompass persistent cough, chest pain, hemoptysis, dyspnea, chest constriction, and fever.

1.2 Understanding of etiology and pathogenesis of lung adenocarcinoma in traditional Chinese medicine

From a TCM perspective, lung adenocarcinoma is perceived as a manifestation of the body's internal imbalance, reflecting disturbances not only within the body but also in the intricate interplay with the external environment. This pathological state is characterized by the depletion of vital qi, internal deficiencies, external pathogenic factors, and a profound disruption in the harmonious equilibrium between yin and yang.

Under these conditions, malignancy can take root as malevolent influences exploit the body's weakened state, infiltrating the lungs and precipitating dysfunctional pulmonary processes (15). Consequently, the disease primarily emerges as a consequence of deficiency and is considered a "real" ailment. The underlying root of this ailment lies in the deficiency of vital qi, with associated symptoms marked by the accumulation of phlegm, stagnation of qi, blood stasis, and the accumulation of toxic elements within the pulmonary system, all contributing to the pathogenesis of lung adenocarcinoma (16).

By the principles of Chinese medicine, the lung is associated with the emotion of sadness and is intrinsically linked to the water element, the source of phlegm. Women, often more susceptible to emotional distress and prone to stagnation, may experience deficiencies in vital qi, ultimately fostering the formation of pulmonary "rocks." Notably, lung adenocarcinoma is typified by coldness, fluid coagulation, and a propensity toward qi stagnation and blood stasis, rendering it prone to metastasis. These factors collectively contribute to the higher incidence of lung adenocarcinoma among the female population (17).

2 Overview of lung adenocarcinoma treated by Western medicine

Lung adenocarcinoma, originating from lung epithelial cells, is generally less aggressive than small-cell lung cancer. Its development is typically gradual, often remaining asymptomatic in its early stages

(18). The international TNM staging system classifies lung adenocarcinoma into four stages: stage I for early-stage disease and stages II, III, and IV for intermediate and advanced stages (19). Each stage and subtype of lung adenocarcinoma warrants specific treatment approaches.

2.1 Surgical treatment

In the early stages, radical surgical resection stands as the optimal treatment approach for tumors. For stage I lung adenocarcinoma with high-risk factors, the gold standard of treatment is lobectomy combined with mediastinal lymph node dissection (20). Older patients typically undergo wedge resection or lobectomy as the standard treatment. In cases of local and regional advancement, combining surgical intervention with drug therapy and radiotherapy has shown promise in enhancing patient survival (21). Surgical treatment offers the advantage of directly excising tumors and affected organs comprehensively, irrespective of cell proliferative status or treatment sensitivity. This approach aims to completely remove the tumor and associated local tissues while preserving healthy lung tissue, it can also better understand the situation of regional lymph node metastasis and effectively control the further enlargement and spread of lung cancer, thereby achieving a radical therapeutic outcome and enhancing the patient's quality of survival.

2.2 Chemotherapy

Early-stage lung adenocarcinoma often presents with subtle or no clinical symptoms, and symptoms typically become evident in the middle or advanced stages of the disease. This necessitates systemic treatments, which can limit the applicability of surgical methods. Depending on disease type and stage, appropriate radiotherapy methods can be selected, and conventional chemotherapy is employed in various contexts, including neoadjuvant chemotherapy, postoperative chemotherapy, and combined radiotherapy and chemotherapy (22). Research has demonstrated that platinum-based adjuvant chemotherapy significantly enhances the survival rates of patients with completely resected stage II or stage III lung adenocarcinoma, particularly when tailored to individual patients through biomarker screening (23). Previous experiments have indicated that for stage IV lung adenocarcinoma patients, a radiotherapy regimen followed by a combination of cisplatin and other chemotherapy agents can enhance the efficacy of radiotherapy while mitigating its side effects (24). Postoperative chemotherapy plays a pivotal role in reducing the incidence of lung adenocarcinoma and extending patient survival. Systemic chemotherapy not only controls tumor growth, reduces symptoms, and improves quality of life, but also delays metastasis to other organs. Paclitaxel as a natural compound is widely used as a chemotherapeutic drug, by inhibiting mitosis and triggering apoptosis of cancer cells, thus effectively preventing the proliferation of cancer cells, with good anti-tumor effects and few side effects (25). Camptothecin is a quinoline alkaloid, as a natural antitumor drug, mainly sensitive to proliferating cells, blocking cell division of cell cycle-specific antitumor drugs, in combination with cisplatin can enhance the sensitivity of lung cancer cells to cisplatin (26).

2.3 Targeted drug therapy

Targeted drugs represent a potent therapeutic avenue for lung adenocarcinoma, precisely honing in on specific molecules within the cancer cells, including EGFR, ALK, KRAS, ROS1, BRAF, and more. This precision inhibits the growth and dissemination of cancerous cells effectively (27). However, drug resistance remains a challenge in the targeted treatment of lung adenocarcinoma, necessitating the exploration of new mutant genes to catalyze breakthroughs in this therapeutic approach (28). Emerging studies have identified three genes, namely CDCA8, MCM6, and TTK, as potential novel drug targets, harboring pivotal roles in restraining lung cancer cell proliferation, exerting anti-tumor activities, and potentially enhancing patient survival (29). Targeted drug therapy is a purposive treatment with the advantages of less damage to normal cells, less harm to the body, and better therapeutic effects.

2.4 Radiotherapy

Radiotherapy stands as an effective approach for alleviating symptoms and bolstering local lesion control in patients grappling with advanced lung adenocarcinoma. It achieves this by employing high-energy rays to eliminate tumor cells, thereby restraining tumor growth (30). Research has highlighted that, alongside induction systemic therapy and maintenance therapy, stereotactic radiotherapy substantially extends progression-free survival from 3.5 months to an impressive 9.7 months in lung adenocarcinoma patients (31). Additionally, the application of stereotactic radiotherapy in patients with low metastatic burden significantly enhances survival rates. This reflects not only a breakthrough in augmenting the survival prospects of advanced lung adenocarcinoma patients but also demonstrates the benefits of local consolidation interventions (32).

Previous investigations have demonstrated that employing moderate radiation therapy doses in lung adenocarcinoma patients can enhance overall survival without elevating the incidence of radiation pneumonitis (33). Radiation therapy is uniquely suited to treating multiple lesions throughout the body and having a low impact on the entire body due to its lack of site restriction as well as its lesser vascular restriction.

2.5 Immunotherapy

Amid the ongoing progress in molecular and immune research along with the development of related drugs, immunotherapy has swiftly emerged as a linchpin in the management of operable and metastatic lung adenocarcinoma. This represents a pivotal advancement in lung adenocarcinoma treatment in recent years, primarily due to its capacity to engage the body's immune system to combat tumor cells through activation or enhancemen (34).

Immunotherapy can be delineated into two distinct modalities. Monotherapy acts to impede the interaction between tumor cells and the immune system, thereby triggering the immune system's assault on tumor cells. In contrast, employing a combined approach involving chemotherapy and immunotherapy serves to ameliorate the side effects stemming from chemotherapy (35). Ginsenoside is a natural steroid that enhances and regulates the immune function, which not only inhibits the proliferation of lung adenocarcinoma, induces

apoptosis of cancer cells, inhibits the inflammatory response of the body, but also plays a role in lung protection (36). Resveratrol is a natural polyphenolic compound with anti-free radical and antioxidant properties, which exerts anti-lung adenocarcinoma effects by modulating anti-inflammatory and hormonal effects (37). Therefore, the advantage of immunotherapy is that it allows tumors to achieve sustained remission and the adverse effects produced are relatively mild; as a popular treatment modality, immunotherapy, especially combination therapy, is widely used in the treatment of patients with lung adenocarcinoma, which creates more possibilities for the improvement of patients' quality of survival.

2.6 Microbial gut flora therapy

The gut microbiota plays a pivotal role as an immunomodulator, exerting influence over the therapeutic response and effectiveness of certain immunotherapeutic agents. It has been established that the composition of the gut microbiota can correlate with both positive and negative treatment outcomes (38). Consequently, research into the tumor gut microbiome has been a topic of fervent discussion in recent years.

Several studies have illuminated the potential of interventions like Bifidus tetra punctate tablets to enhance the gut microbiota of lung adenocarcinoma patients. These interventions have shown significant promise, not only in regulating the patient's intestinal microecology and augmenting immunity but also as adjunctive antitumor therapies when combined with conventional chemotherapy, with minimal drug toxicity (39). Subsequent research has revealed notable disparities in the gut flora of lung cancer patients compared to individuals with benign lung lesions, further substantiating the existence of specific intestinal microorganisms within the tumor population (40). These findings not only underscore the significance of the gut microbiota in lung adenocarcinoma but also open up new avenues for its treatment.

2.7 Summary

In recent years, Western medical approaches to lung adenocarcinoma have indeed achieved significant breakthroughs. This progress encompasses not only a diverse array of treatment modalities but also notable enhancements in the overall survival rates of patients. Nevertheless, it is essential not to overlook the associated challenges. Western medical treatment may give rise to issues such as toxic side effects, adverse reactions, drug resistance, and immune evasion. These phenomena consistently impact the quality of life of patients, and addressing these challenges represents a crucial imperative for the medical community moving forward. The advantages and disadvantages of Western medicine in the treatment of lung adenocarcinoma are shown in Table 1.

3 Status of traditional Chinese medicine treatment of lung adenocarcinoma

The most significant departure from Western medicine lies in its emphasis on holistic regulation. Chinese medicine perceives a close interconnection between tumor development and the status of other internal organs such as the spleen, stomach, liver, and kidneys (16). Consequently, traditional Chinese medicine aims to harmonize these organs, fostering the revitalization of vital qi, with the overarching goal of bolstering the body's resilience, combating cancer, and dispersing nodules through a comprehensive and synergistic approach. The principle of "supporting the positive and dispelling the evil" constitutes a fundamental tenet in the treatment of malignant tumors, aiming to enhance the patient's overall immunity (41). This approach aligns closely with the core concept of immunotherapy in Western medicine, which seeks to mitigate drug resistance and prevent tumor immunity evasion. In both traditional Chinese medicine and Western medicine, the shared objective is to eliminate cancer cells within the body by stimulating the regrowth of immune cells and enhancing immune function. Additionally, these therapies work toward regulating the tumor microenvironment, thereby contributing to the treatment of lung adenocarcinoma. In the context of traditional Chinese medicine, lung adenocarcinoma is categorized as a syndrome associated with "plaque" and "lung accumulation." It is often attributed to deficiencies in positive qi and insufficient spleen qi. Treatment approaches typically revolve around nurturing the earth element and generating gold, fortifying the Middle Earth, and bolstering qi. One notable example is the "soup from the Discussion of Internal and External Injuries," which epitomizes this methodology (42). Given the intricate and varied disease presentations among lung adenocarcinoma patients, traditional Chinese medicine adopts a dialectical treatment approach that underscores the importance of "when the positive qi is in memory, the evil can not be interfered with." This involves focusing on the sonification of the spleen and kidney, strengthening and safeguarding the positive qi while concurrently addressing detoxification and the dispersal of nodules. The treatment strategy further encompasses activating blood circulation, dispelling blood stasis to counteract the toxicity of cancer, and is marked by an individualized and flexible use of herbal medicines (43).

3.1 Herbal medicine for the treatment of lung adenocarcinoma

Traditional Chinese medicine (TCM) often categorizes lung adenocarcinoma into four distinct types based on the disease's different stages and characteristics: deficiency of lung spleen and qi, deficiency of qi and yin, internal obstruction of blood stasis and toxicity, dampness and phlegm obstruction. Treatment is then tailored to these specific types and stages, with a primary focus on supporting the positive qi as the initial step, followed by attacking the pathogenic factors and ultimately complementing treatment with tonification (44). The primary objective of traditional Chinese medicine in the treatment of lung adenocarcinoma is to regulate the body's immune function, induce apoptosis in tumor cells, and inhibit tumor cell proliferation. There are many compounds with medicinal value in flavonoids, which not only have cough suppressant, expectorant, asthma, and antibacterial activities but also have anti-free radical and antioxidant effects. In clinical flavonoids practice, certain herbs like Lobelia and Mulberry leaf have been noted for their ability to clear heat, remove toxins, reduce swelling, and alleviate pain, making them valuable in the treatment of lung cancer (45). Scutellaria barbata, for

TABLE 1 Advantages and disadvantages of western medicine in the treatment of lung adenocarcinoma.

Treatment mode	Categorization	Methodologies	Advantages	Disadvantages
Western medicine treatments	Surgical interventions	Resection	Radical resection	Wound pain, shortness of breath, fatigue and loss of appetite
	Cytotoxic chemotherapy	Platinum, paclitaxel and other chemotherapeutic agents	Improves survival and delays metastasis to other organs	Adverse reactions such as malignant vomiting and myelosuppression
	Targeted pharmacotherapy	Specific molecules: EGFR, ALK, KRAS, ROS1, and BRAF, etc.	Inhibition of lung cancer cell growth, antitumor activity and enhancement of survival rate	Drug resistance, immune escape and toxic side effects
	Radiotherapy	High-energy rays	Improvement of survival rate Localized consolidation interventions	Fatigue, loss of appetite and mood swings
	Immunotherapy	Activation and enhancement of the immune system	Improvement of survival rates	Toxic side effect
	Microbial gut flora therapy	Regulates intestinal microecology and improves immunity	Lower drug toxicity	Fatigue and loss of appetite

example, is employed for dispersing blood stasis, halting bleeding, promoting diuresis, and reducing swelling, making it suitable for addressing conditions like lung carbuncle, pulmonary tuberculosis with hemoptysis, and various types of bruises and injuries (46).

Recent reports have also highlighted the anticancer efficacy of active ingredients found in herbs that promote blood circulation and alleviate blood stasis. These components significantly enhance hemodynamics and the microenvironment, reduce thrombosis, boost blood flow, and subsequently inhibit lung cancer invasion and metastasis (47). The advantage of traditional Chinese medicine in treating lung adenocarcinoma is that it can provide evidence-based treatment according to the cause and development of the patient's disease, enhance the immunity of the patient's body, improve the quality of life, and prolong the growth period.

3.2 Acupuncture for lung adenocarcinoma

Acupuncture and moxibustion represent traditional Chinese medicine therapies rooted in the principles of yin and yang, the five elements, qi, blood, bodily fluids, internal organs, meridians, and the dynamics of the five movements and six qi (48). In the context of treating lung adenocarcinoma, acupuncture, and moxibustion primarily aim to enhance the circulation of qi and blood, promote the smooth flow of qi, and mobilize qi. It's crucial to note that while acupuncture and moxibustion can provide valuable support, they cannot cure lung adenocarcinoma and should be considered as complementary therapies.

The selection of specific acupuncture points and needling techniques is tailored to the individual patient's condition, with the objective of either tonifying deficiencies or promoting detoxification through various approaches. If the patient exhibits weakness in positive qi, tonification methods are employed; conversely, if pathogenic factors are dominant, detoxification methods are applied, or a combination of both strategies may be utilized. Ultimately, the goal is to strengthen the positive qi and dispel pathogenic influences (49).

Studies have demonstrated the benefits of acupuncture in alleviating lung cancer-related symptoms such as cough and phlegm, facilitating phlegm expectoration, and reducing the frequency of coughing (50). When used in conjunction with pharmacological interventions, it can yield significant analgesic effects (51). Acupuncture treatment has shown promising benefits in reducing patients' adverse effects, relieving pain, and controlling tumor persistence.

3.3 Acupressure therapy for lung adenocarcinoma

Tui na practitioners employ a variety of techniques, including massage, manual acupoint stimulation, and structural adjustments, to rebalance the body's state based on the specific needs of their patients. In the context of treating lung adenocarcinoma, tui na serves to promote blood circulation and alleviate pain (52). The primary techniques utilized in tui na include kneading, pinching, pushing, holding, and pressing, with a focus on areas related to the lungs and the back.

Research has indicated that daily kneading and pressing along the lung meridian represents an effective tui na method that can stimulate the functioning of internal organs, thus contributing to the equilibrium of yin and yang within the body (53). Appropriate massage techniques help facilitate phlegm discharge, enhance blood circulation, and alleviate symptoms like chest tightness, thereby ensuring the patient's respiratory tract remains clear and relieving lung cancer-related symptoms such as cough, chest tightness, and shoulder and back pain (54). The most significant advantage of Tui Na treatment for lung adenocarcinoma is that it relieves the patient's pain and can also be used as an adjunct to acupuncture as a way to increase the range of motion in the joints.

3.4 Summary

Chinese medicine treatment of lung adenocarcinoma exhibits several distinctive characteristics, including a multifaceted approach, consideration of multiple perspectives, and targeting

various facets of the condition. Currently, Chinese medicine treatment for lung adenocarcinoma has evolved and is demonstrating promising results, whether used independently or in conjunction with Western medicine. However, it's essential to acknowledge that traditional Chinese medicine's effectiveness in treating lung adenocarcinoma is not universally precise. While these therapies primarily focus on safeguarding lung function, they may not consistently inhibit cancer cell growth or exhibit potent cytotoxic effects on lung cancer cells. Furthermore, there remains a lack of standardized diagnostic and treatment criteria within traditional Chinese medicine for lung adenocarcinoma. The absence of unified typing standards and evaluation criteria contributes to the complexity of treatment. Consequently, relying solely on Chinese medicine for the treatment of lung adenocarcinoma may not guarantee a complete cure. Instead, it is often advisable to incorporate Chinese medicine as a complementary therapy alongside Western medical approaches to optimize the chances of success and enhance the overall therapeutic outcome. The advantages and disadvantages of Chinese medicine in the treatment of lung adenocarcinoma are shown in Table 2.

4 Treatment of lung adenocarcinoma with the combination of traditional Chinese and Western medicine

4.1 Combined operation of traditional Chinese medicine

Surgical treatment is often considered the best approach for patients in the early stages of lung adenocarcinoma to achieve a radical cure. However, some patients may experience various uncomfortable symptoms post-surgery, including mood disorders, wound pain, asthma, fatigue, and loss of appetite. These symptoms can significantly impact the patient's quality of life and hinder their postoperative recovery (55). Some patients are also intolerant to surgical treatment, and there are also problems such as large postoperative trauma, susceptibility to complications, and recurrence rates. Western medical treatments may have limitations in addressing these specific aspects of postoperative discomfort. Chinese medicine, rooted in a "people-oriented" treatment philosophy, offers a holistic approach that can provide valuable support for patients during their recovery (56). Research has indicated that the use of flavonoids in Chinese medicine as an adjuvant therapy following radical surgery can have several benefits for non-small cell lung cancer (NSCLC) patients. This approach has been shown to extend the survival period and enhance the quality of life for these patients. Additionally, Chinese medicine adjuvant therapy may reduce the rate of tumor recurrence and metastasis in lung cancer patients (57). Studies conducted by Li TM and others, employing Chinese herbal medicine (CHM) from Taiwan as a postoperative treatment for lung cancer patients, demonstrated a significant improvement in patient survival. The results indicated a lower mortality risk ratio in the group receiving CHM, highlighting the potential of Chinese medicine as an adjuvant therapy in reducing mortality rates among lung cancer patients (58).

4.2 Chinese medicine combined with Western medicine chemical treatment

For patients with intermediate and advanced lung adenocarcinoma, conventional treatment typically revolves around chemotherapy, with a common regimen involving platinum-containing double drugs. This chemotherapy approach is versatile and can be applied as a standalone treatment or in combination with other modalities, allowing for tailored treatment plans based on the patient's specific condition. These plans may encompass preoperative treatment, postoperative adjuvant therapy, or late-stage treatment. However, chemotherapy, especially when used in combination, can come with side effects that some patients may find challenging to tolerate. Common adverse reactions include malignant vomiting and myelosuppression, which can lead to a reduced capacity for chemotherapy (59). For neoadjuvant chemotherapy, although it can control the growth of tumor cells, the disadvantages of adverse effects and reduced patient tolerance to surgery should not be ignored. Traditional Chinese medicine, grounded in the principle of maintaining the dynamic balance of the body, offers an alternative approach.

Song et al. (60) found that triptolide, as a world-recognized natural antitumor drug, can specifically target different cell signaling pathways associated with lung cancer progression; when co-administered with cisplatin, it can inhibit the expression of the nuclear factor κB (NFκB) signaling pathway and NFκB-regulated drug-resistance genes, and thus play a role in drug-resistant retroviral processes. Research conducted by Guo et al. (61) divided patients with stage IV lung adenocarcinoma into two groups: one receiving platinum-based chemotherapy alone and the other receiving a combination of traditional Chinese medicine alongside chemotherapy. The results indicated a noteworthy difference in survival outcomes.

TABLE 2 Advantages and disadvantages of Chinese medicine in treating lung adenocarcinoma.

Treatment mode	Categorization	Methodologies	Advantages	Disadvantages
Chinese medicine treatments	Chinese medicine	Regulates the immune function of the body	Clear heat, remove toxins, reduce swelling and alleviate pain, improving hemoptysis and microenvironment	As an adjunctive therapy only
	Acupuncture	Enhance the circulation of qi and blood, promote the smooth flow of qi, and mobilize qi	Analgesic	As an adjunctive therapy only
	Acupressure therapy	Regulates the body's homeostasis	Promotes blood circulation and relieves chest tightness	As an adjunctive therapy only

Patients who received only chemotherapy had a one-year survival rate of just 27%, which fell short of the average survival period (with an average survival time of 5 months). In contrast, patients who received traditional Chinese medicine alongside chemotherapy achieved a one-year survival rate of 88%, with an average survival time of 27 months. This difference was statistically significant ($p < 0.0001$), highlighting the potential of traditional Chinese medicine to enhance the survival rate of stage IV lung adenocarcinoma patients undergoing second-line chemotherapy.

In a study conducted by Lu et al. (62), 60 patients with advanced lung adenocarcinoma were randomly divided into two groups: the control group consisting of 27 patients, and the observation group consisting of 33 patients. The control group received pemetrexed combined with cisplatin regimen chemotherapy, while the observation group received Shengmai capsules in addition to the control group's treatment. The study's results revealed that the effective rate was 60.61% in the observation group and 62.96% in the control group. Importantly, the difference between the two groups was not statistically significant ($p>0.05$). Additionally, when comparing serum carcinoembryonic antigen (CEA) levels between the two groups before treatment (22.36 + 5.35 μg/L in the control group, 21.19 + 4.69 μg/L in the observation group), there was no statistically significant difference ($p>0.05$). However, after treatment, both groups exhibited lower CEA levels compared to before treatment (18.77 + 5.92 μg/L in the control group, 13.57 + 5.59 μg/L in the observation group), with the CEA level in the observation group being lower than that in the control group ($p<0.05$). This outcome suggests that the combination of traditional Chinese medicine with a chemotherapy regimen can mitigate the toxic effects of chemotherapy.

In light of these findings, it is evident that tailoring treatment approaches to individual patient differences in clinical practice, such as combining chemotherapy with traditional Chinese medicine treatment, can effectively reduce toxicity while improving patients' survival prognosis and overall clinical outcomes.

4.3 Chinese medicine combined with targeted drug therapy

Targeted drug therapy is primarily designed to inhibit the proliferation of tumor cells and induce apoptosis by acting on specific targets that play a role in tumor cell growth and metastasis. While targeted drug therapy has revolutionized personalized cancer treatment in modern oncology, it also comes with challenges such as drug resistance, immune evasion, and various toxic side effects, including skin rashes, diarrhea, and liver function impairment (63). These adverse reactions can be severe enough to cause some patients to discontinue treatment, ultimately limiting the clinical utility of targeted drugs and the potential societal benefits they offer. In traditional Chinese medicine, the adverse reactions associated with targeted drug therapy are often attributed to pathogenic factors such as heat and toxicity. For these types of adverse reactions, the treatment approach typically involves clearing heat, detoxifying, and dispersing wind to expel the pathogenic factors from the body.

Jiao et al. (64) conducted a study to investigate the combination of traditional Chinese and Western medicine in lung adenocarcinoma patients to delay acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). Patients were randomly assigned to two groups: the experimental group received EGFR-TKI along with traditional Chinese medicine, while the control group received EGFR-TKI alone. The results revealed that the survival period of the EGFR-TKI + traditional Chinese medicine group was 13.50 months, whereas the EGFR-TKI group had a survival period of 10.94 months. This difference was statistically significant ($p < 0.05$), indicating a significant extension in overall survival for the experimental group. Additionally, the experimental group exhibited a significantly higher overall quality of life improvement rate (20.54%) compared to the control group (15.98%). This difference was statistically significant ($p = 0.0160$). These findings demonstrate that the combined treatment of traditional Chinese medicine with targeted drugs can effectively delay resistance to EGFR-TKI, enhance the quality of life for patients, and broaden the application of targeted drugs.

4.4 TCM combined with radiation therapy

Radiotherapy is a crucial approach in cancer treatment, utilizing radiation to target and treat tumor lesions. It is known for its localized application and wide range of therapeutic applications, offering targeted treatment options (22). However, the side effects of radiotherapy should not be ignored. After radiotherapy, patients with mild symptoms will experience fatigue, loss of appetite, and emotional uncertainty; some patients who have received radiotherapy for a long period will experience skin damage, esophageal damage, and lung damage, and in severe cases, they will experience radiation pneumonitis, radiation esophagitis, and bone marrow suppression, etc. (65). Incorporating Chinese medicine as an adjunct to radiotherapy can effectively mitigate the toxic side effects experienced by patients following radiotherapy. It helps alleviate post-radiotherapy discomfort, enhances patient compliance, and improves treatment efficacy (66).

In a study led by Du et al. (67), gefitinib and three-dimensional conformal radiotherapy were employed for treating 60 patients with advanced lung adenocarcinoma presenting with symptoms of breath and yin deficiency. Additionally, traditional Chinese medicine was integrated into the treatment protocol by administering Guiqi Yiyuan Cream orally to another 60 patients in the control group. The study outcomes revealed significant differences in favor of the treatment group. After 7 weeks of continuous treatment, the treatment group exhibited a higher total effective rate (70.00% vs. 51.57%) and total control rate (86.67% vs. 80.00%) compared to the control group, with these differences being statistically significant ($p < 0.05$). Moreover, the incidence rates of malignancy, diarrhea, and rash in the control group were notably higher (65.00, 20.00, and 13.33%, respectively) than those in the treatment group (28.33, 6.67, and 3.33%, respectively), and these differences were statistically significant ($p < 0.05$ or $p < 0.01$). These findings underscore the remarkable clinical efficacy of combining Guiqi Yiyuan Cream with gefitinib and radiotherapy in treating advanced lung adenocarcinoma with breath and yin deficiency syndrome. This combined approach significantly improves patient prognosis and extends their survival. Traditional

TABLE 3 Case and efficacy of combined Chinese and Western medicine in the treatment of lung adenocarcinoma.

Treatment mode	Categorization	Examples	Healing effect
Combine traditional Chinese and Western medicine	Combined operation of traditional Chinese medicine	Chinese herbal medicine care after surgical treatment	Reducing mortality
	Chinese medicine Combined with Western medicine chemical treatment	Shengmai capsule was given on the basis of pemetrexed combined with cisplatin	Reduce chemotherapy toxicity Improve survival prognosis
	Chinese medicine combined with targeted drug therapy	Targeting EGFR-TKI drugs in combination with traditional Chinese medicine	Delaying EGFR-TKI resistance Improving patients' quality of life Expanding the scope of targeted drugs
	TCM combined with radiation therapy	Combination of Gefitinib and three-dimensional conformal radiotherapy with Guiqi Yiyuan Cream	Significantly improves patient prognosis Reduces toxicity and increases sensitivity Prolongs patient survival
	TCM combined with immunotherapy	Immune checkpoint inhibitor combined with Qingzao Lung Rescue Soup	Enhances the host's immune response Improves the overall survival of patients

Chinese medicine offers unique advantages in reducing the adverse effects of radiotherapy while enhancing tumor tissue sensitivity to radiation and thereby improving treatment effectiveness. Some studies have demonstrated that traditional Chinese medicine's heat-clearing and detoxification properties, as well as its ability to promote blood circulation and eliminate blood stasis, can sensitize tumor tissues to radiotherapy (68).

4.5 TCM combined with immunotherapy

The introduction of immune checkpoint inhibitors marked a significant advancement in the treatment of early-stage tumors, offering the potential for personalized cancer treatment by harnessing the body's natural tumor-fighting mechanisms (69). While targeted therapies like immunotherapy have shown great promise in treating cancer, they also come with the challenge of identifying and managing their toxic side effects. These side effects can include conditions like rash, itching, diarrhea, thyroid dysfunction, colitis, and pneumonia. Western medicine approaches immunotherapy with careful consideration of each patient's variability and sensitivity to these toxicities. Tailored dosing is often necessary to optimize the benefits while minimizing adverse effects (70).

Here, traditional Chinese medicine can play a valuable role as an adjuvant therapy following immunotherapy. For instance, Qingzao Lung Rescue Soup has been found to effectively extend the survival period of non-small cell lung cancer patients, enhance the host's immune response, and improve overall survival rates (71). Acupuncture, too, offers advantages in immunotherapy for non-small cell lung cancer. Scholars like Mao Jinfeng and colleagues have discovered that wheat grain moxibustion at the foot-sanli point can complement Western medicine treatments for advanced non-small cell lung cancer, boosting the immune function of patients who are tumor-free post-surgery. This combination treatment approach is well-received, well-tolerated, and safe, making it a promising option for clinical use (72). The cases and efficacy of combined Chinese and Western medicine in the treatment of lung adenocarcinoma are shown in Table 3.

5 Summary

Over the years, a range of treatment modalities, including surgery, chemotherapy, targeted drugs, radiation therapy, immunotherapy, and interventions in the intestinal flora, have played pivotal roles in managing lung adenocarcinoma across its different stages. These treatments are continually evolving with advancements in society and medical science. However, it's important to acknowledge that these Western treatments often come with varying degrees of adverse effects for patients. Chinese medicine, with its emphasis on the holistic balance of the body and a "patient-centric" treatment approach, presents a significant advantage when combined with Western medicine. The integration of Chinese medicine into Western medicine regimens helps mitigate the drawbacks of Western treatments (73). This combined approach can contribute to improved patient well-being by reducing toxic side effects, preventing tumor recurrence and metastasis, stabilizing the patient's emotional state, alleviating clinical symptoms, and extending the patient's survival period.

The effectiveness of combined Chinese and Western medicine treatment compared to individual medication still lacks robust multi-center, randomized controlled, large-sample clinical data for confirmation. Additionally, the field of Chinese medicine lacks standardized criteria for the dialectical classification of lung adenocarcinoma and evaluation criteria for the disease. Further, there is limited experimental validation of the interactions between Chinese and Western medicine treatments for lung adenocarcinoma and how these interactions affect the internal environment of the body. Research into the mechanisms underlying the reduction of toxicity in combined Chinese and Western medicine treatment is also a promising future direction that requires rigorous investigation through high-quality clinical studies.

In conclusion, the integration of Chinese and Western medicines in cancer treatment remains a major area of interest and will continue to advance based on a solid and innovative theoretical foundation. We anticipate breakthroughs in this field that will bring hope to patients with cancer. Natural compounds mentioned in this article are shown in Figure 1. The comparison between Western medicine and Chinese medicine in the treatment of lung adenocarcinoma is shown in Figure 2.

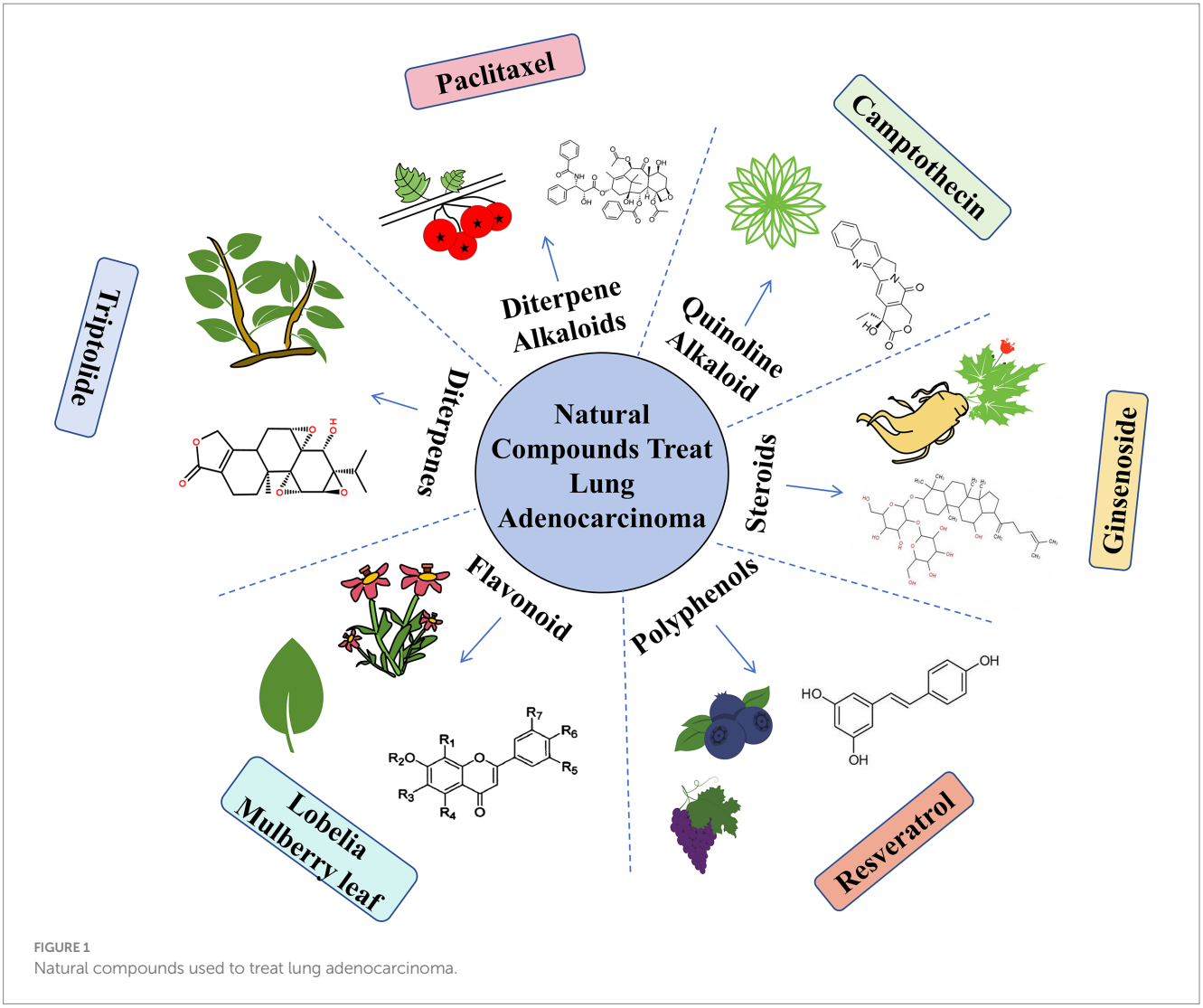

FIGURE 1
Natural compounds used to treat lung adenocarcinoma.

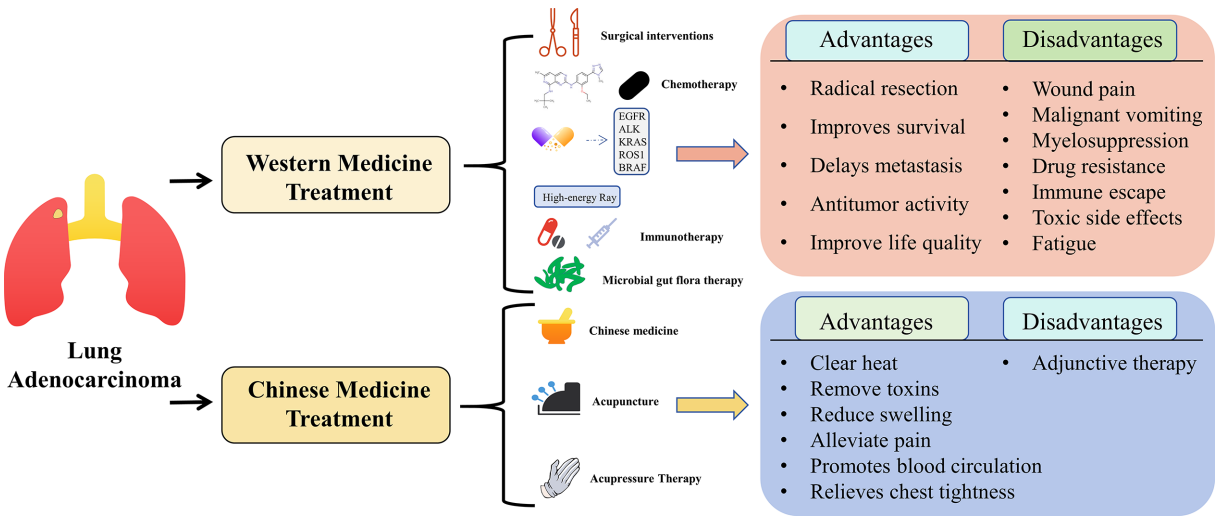

FIGURE 2
Western medicine compared with Chinese medicine in treating lung adenocarcinoma.

Author contributions

HJ: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. LB: Project administration, Supervision, Writing – review & editing.

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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.

Publisher's note

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Neutrophil extracellular traps and their implications in airway inflammatory diseases

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Neutrophil extracellular traps (NETs) are essential for immune defense and have been increasingly recognized for their role in infection and inflammation. In the context of airway inflammatory diseases, there is growing evidence suggesting the involvement and significance of NETs. This review aims to provide an overview of the formation mechanisms and components of NETs and their impact on various airway inflammatory diseases, including acute lung injury/ARDS, asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis. By understanding the role of NETs in airway inflammation, we can gain valuable insights into the underlying pathogenesis of these diseases and identify potential targets for future therapeutic strategies that either target NETs formation or modulate their harmful effects. Further research is warranted to elucidate the complex interactions between NETs and airway inflammation and to develop targeted therapies that can effectively mitigate their detrimental effects while preserving their beneficial functions in host defense.

KEYWORDS

neutrophil extracellular traps, airway inflammation, ARDS, asthma, COPD, cystic fibrosis, targeted therapy

1 Introduction

Neutrophils, the most common type of white blood cells in mammalian blood, play a crucial role as the first line for defensing against infection and the non-specific immune response. They are activated and rapidly migrating to the site of infection through the blood vessel wall, guided by the cytokines and chemotactic factors. Upon activation, neutrophils not only phagocytose pathogens but also undergo a form of programmed cell death called NETosis, releasing a fibrous network known as neutrophil extracellular traps (NETs) (1, 2). NETs consist of genomic DNA as a scaffold, along with various proteins such as histones, myeloperoxidase (MPO), neutrophil elastase (NE), citrullinated histone 3 (CitH3), and cathepsin G (CG) (3). The web-like structure of NETs helps localize bacteria, fungi, viruses, and other pathogens to a specific area, slowing down the further spread of inflammation, however, research has shown that neutrophil extracellular traps are involved in the pathophysiology of various diseases. These include microbial infections, autoimmune diseases, inflammation, tumors, atherosclerosis, intracerebral hemorrhage, and thrombosis (4–13). Besides, age may also be associated with the formation of NETs. It has been reported that neutrophils from elderly patients respond to the presence of mitochondria, enhancing the formation of extracellular traps. It has also been found that these NETs formed by neutrophils

in the elderly exhibit higher levels of oxidation and increased resistance to degradation by DNase I. Additionally, higher concentrations of residual NETs have been detected in the plasma of older individuals (14). However, the exact mechanisms through which age regulates NET formation are not fully understood, but the increased risk may be related to lower degradation of NETs in elderly patients.

It is important to note that NETs themselves can also damage respiratory epithelial cells and endothelial cells, and excessive production of NETs can worsen inflammatory lung injury (15–17). For example, neutrophils from patients with ARDS exhibit enhanced activity and an increased ability to release NETs, leading to severe pathological changes such as alveolar wall damage, pulmonary interstitial edema, and congestion. Due to the unique potential of NETs components to cause tissue injury and regulate immune responses, researchers have recognized that targeting the components of NETs or the related pathway could be a potential approach for treating various diseases including airway inflammatory diseases. By analyzing recent research on NETs, particularly in the context of respiratory diseases, we can gain insights into the progress and controversies surrounding NETs. This understanding will help us further comprehend the role of NETs in the pathophysiology of respiratory diseases, unravel disease mechanisms, and explore new therapeutic targets and strategies.

2 Mechanisms of NETs formation

2.1 Suicidal/lytic NETosis

It has been shown that various stimulating factors can initiate or trigger the process of neutrophil extracellular traps formation (18–20). These factors include mitogen phorbol 12-myristate 13-acetate (PMA), cholesterol crystal, calcium ionophore A23187, nigericin, immune complexes, and pathogens such as fungi, bacteria, viruses. Neutrophils are stimulated by PMA, resulting in the release of calcium ions from the endoplasmic reticulum into the cytoplasm. This stimulation activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which in turn leads to the activation of protein kinase C (PKC) and the downstream Ras/Raf/MEK/ERK signaling pathway. As a result, reactive oxygen species (ROS) are generated through NADPH oxidase. ROS can directly facilitate the translocation of peptidylarginine deiminase 4 (PAD4) into the nucleus, where it modifies histones through citrullination, ultimately leading to chromatin dispersion (21–23). Besides, upon activation and ROS production, NE translocates from granules to the nucleus and cleaves histones, promoting chromatin decondensation. Subsequently, MPO binds to chromatin, further promoting chromatin decondensation. The synergistic action of NE and MPO enhances chromatin decondensation, leading to cell membrane rupture and release of NETs (24, 25). NE can also cleave gasdermin D (GSDMD) in the cytoplasm, activating it to form pores on the plasma membrane, nuclear membrane, and granule membrane. As a result, antimicrobial proteins attach to the decondensed chromatin, forming a mesh-like structure (26). Additionally, during NETosis, the cytoskeletal systems, including microtubules, microfilaments, and intermediate filaments, rapidly disassemble, leading to cell membrane rupture, cell lysis, and the release of NETs into the extracellular space (27).

However, in reality, there are still different viewpoints regarding the NADPH oxidase-dependent NETs formation pathway. According to the research by Kenny et al. (28), the production of ROS is a hallmark of NETosis induced by PMA, *Candida albicans*, and Group B streptococcus. However, nigericin and A23187, in contrast, does not induce the production of ROS during the process of inducing NETs. Additionally, the ROS generated by NADPH oxidase is only partially required for the induction of NETosis by *C. albicans* and Group B streptococcus. During SARS-CoV-2 lung infection, the formation of NETosis is a key feature of severe COVID-19 (29, 30). Similarly, it is yet to be determined whether ROS directly participate in this process (31). Besides, the activation of neutrophil extracellular traps using the ionophores A23187 or nigericin does not depend on MPO or NE (28). Which provided the different opinions regarding the essential components of NETs during NETosis process. Although GSDMD was initially thought to be required for NET formation, studies have shown that GSDMD-deficient mouse neutrophils are as competent as wild-type mouse neutrophils in producing NETs. Furthermore, the process of generating NETs through both noncanonical and canonical inflammasome signaling pathways also does not require GSDMD (32). There is still much controversy and conflicting conclusions regarding the requirements of PAD4 activity for the formation of NETs (28, 33–35). Neutrophils from PAD4 knockout mice are unable to citrullinate histone H3 and fail to release NETs upon stimulation or infection by PMA, LPS, calcium ionophores, *Shigella flexneri*, or methicillin-resistant *Staphylococcus aureus* (MRSA). This study demonstrated the necessity of PAD4 in the formation process of NETs (36). However, there are also some different conclusions. For example, PAD4 is not necessary for the process of NETosis induced by *C. albicans* or group B Streptococcus infections (27). Additionally, PAD4 release and histone arginine citrullination can exist independently of NET formation (37). Overall, it should be recognized that there has been continuous debate regarding the process of neutrophil extracellular traps formation. This controversy arises from various stimuli including bacteria, viruses, fungi, or chemicals, as well as variations in neutrophil types and detection techniques. It could be valuable to investigate this subject under specific circumstances (Figure 1).

2.2 Vital/non-lytic NETosis

In addition to lytic NETosis, neutrophils can also release NETs through vesicular secretion, known as non-lytic NETosis. This process has been observed in neutrophils that come into contact with activated platelets, as well as in response to *S. aureus* and *C. albicans* infections. In non-lytic NETosis, neutrophils encapsulate NETs complexes in vesicles and transport them to the extracellular space for release, while the cells themselves remain viable and functional, maintaining the integrity of the cell membrane.

Various pathogens activate neutrophils to release NETs through distinct mechanisms. For example, *S. aureus* and *C. albicans* activate Toll-like receptor 2 (TLR2), whereas the LPS in Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*)-induced Toll-like receptor 4 (TLR4) to initiate NETs release (38–40). What is different from the above process is that, platelet-induced NETs formation during infection is LFA1-reliable process and which also depends on the direct interaction of neutrophils and platelets (41). In

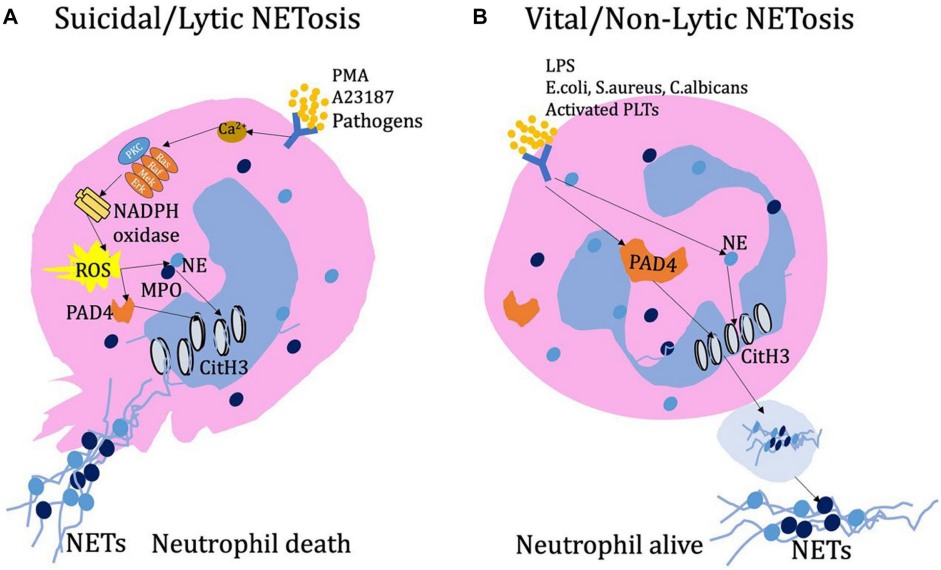

FIGURE 1
(A) Lytic NETs have been observed to form in response to various stimuli, including PMA, calcium ion carriers, and pathogens. When stimulated, neutrophils release Ca^{2+} ions and activate NADPH oxidase on the cell membrane. This activation can occur through the PKC or Ras-Raf-Mek-Erk signaling pathway, leading to the production of ROS. Subsequently, ROS promotes the entry of PAD4 into the nucleus, where it modifies histones through deamination, ultimately resulting in chromatin decondensation. Additionally, during activation and ROS production, the combined action of NE and MPO enhances chromatin decondensation. As NETosis progresses, the cell's cytoskeleton system, including microtubules, microfilaments, and intermediate filaments, undergoes rapid disassembly. This disassembly ultimately leads to cell membrane rupture, cell dissolution, and the release of NETs into the extracellular space. **(B)** Early non-lytic NET formation occurs without causing cell lysis or death. This process is induced by various stimuli such as LPS, *E. coli*, *S. aureus*, *C. albicans*, or activated platelets. Simultaneously, the activation of PAD4 and the translocation of NE to the nucleus result in chromatin decondensation. The resulting protein-decorated chromatin is expelled via vesicles without disrupting the plasma membrane. Once released into the extracellular environment, NETs do not compromise the structural and functional integrity of neutrophils.

non-lytic NETs release, similar to lytic NETosis, peptidylarginine deiminase 4 (PAD4) and neutrophil elastase (NE) also play roles in chromatin decondensation within the nucleus (3). Non-lytic NETs release represents a non-self-sacrificing anti-inflammatory mechanism of neutrophils, occurring more rapidly (within 5–60 min) compared to lytic NETsosis (3–4 h), resembling the initial response of neutrophils to infection (26). Many aspects of the pathological and physiological mechanisms of non-lytic NETs release remain unclear including vesicle formation for NETs transport, the process of NETs release, and the involved signaling pathways (Figure 1).

3 NETs in airway inflammatory diseases

3.1 Acute lung injury/acute respiratory distress syndrome

3.1.1 Sepsis-associated ALI/ARDS

Sepsis is a syndrome characterized by a systemic inflammatory response caused by invading pathogenic microorganisms, such as bacteria. It has a high incidence and mortality rate among critically ill individuals. Acute respiratory distress syndrome (ARDS) or its early stage, acute lung injury (ALI), is a common complication of sepsis and one of the most critical prognostic factors for mortality in septic patients. ARDS/ALI is characterized by lung inflammation, increased microvascular permeability, lung edema, membrane formation, and interstitial fibrosis (42, 43). These pathological changes result in reduced lung compliance, increased intrapulmonary shunting, and ventilation-perfusion mismatch, ultimately leading to respiratory distress and severe hypoxemia. The migration and infiltration of activated neutrophils in lung tissue play a crucial role in the development of ARDS/ALI, causing damage to epithelial and endothelial cells, among other effects. Neutrophils are considered as critical inflammatory cells in the pathogenesis of ARDS. The emerging research evidence suggests that neutrophil extracellular traps released by neutrophils are involved in the pathological process of ALI/ARDS. This discovery provides important clues for further understanding the development mechanism and treatment strategies of ARDS, offering hope for improved care and treatment for patients.

NETs are an innate defense mechanism responsible for clearing pathogens during early infection and inflammation. However, excessive NETs can cause damage to host cells and tissues, making it crucial to regulate their balance (1). PAD4 plays a crucial role in the process of neutrophil releasing NETs by modifying histones and causing chromatin decondensation. Lefrançais et al. (44) constructed a mouse model of lung injury by intratracheal instillation of methicillin-resistant *S. aureus* (MRSA). The severity of lung injury is reduced in PAD homozygous knockout mice ($PAD^{-/-}$), but bacterial load and levels of inflammatory cytokines increase. Ultimately, compared to wild-type mice, the survival rate of $PAD^{-/-}$ mice does not show a significant improvement. However, the survival rate is obviously improved in PAD heterozygous knockout mice ($PAD^{+/-}$), which have a phenotype intermediate between $PAD^{-/-}$ and wild-type mice. Moreover, elevated levels of plasma NETs have been associated with the severity and mortality of sepsis-related ARDS, while lower

levels of plasma DNase I have been associated with the development of sepsis-induced ARDS. Inhibitors of PAD2/PAD4, such as YW3-56, have demonstrated the ability to inhibit LPS-induced lung vascular leakage, decrease acute lung injury, and improve survival rates in mouse models of endotoxemia (45). Interestingly, it has been reported that in sepsis-related acute lung injury, the PAD2 inhibitor AFM32a can reduce the production of inflammatory factors, alleviate lung injury, and inhibit the generation of NETs. As a result, it improves survival rates (46). These findings suggest that both of PAD2 and PAD4 may play a significant role in the pathological process of sepsis-related lung injury. NE is one of the main components of NETs. Sivelestat is a selective NE inhibitor and the only specific therapy available for ARDS. A systematic review and meta-analysis revealed that sivelestat not only reduces the mortality rate and incidence of adverse events in ALI/ARDS patients, but also shortens mechanical ventilation time and ICU stay, increases non-ventilated days, and improves patient's oxygenation index (47). However, the efficacy of sivelestat sodium in treating ARDS is still controversial in clinical research (48, 49). The use of DNase to degrade NETs related DNA is a therapeutic approach for treating lung injury mediated by NETs. Research with animal models has found that treatment with DNase I can alleviate inflammatory damage in the airways (15, 44).

Zhang et al. (50) reported that NETs induce ferroptosis in alveolar epithelial cells through the activation of METTL3-mediated m6A modification. Additionally, inhibiting NETs formation by knocking out peptidylarginine deiminase 4 (PAD4) can alleviate ferroptosis and sepsis-related lung injury in mice. There might be an association between NETs and pyroptosis. In a mouse model of ALI induced by LPS attack, the levels of NETs and the proportion of necrotic alveolar macrophages were significantly increased. The NETs-DNA degrading agent DNase I can alleviate alveolar macrophage necrosis, and the pyroptosis inhibitor Ac-YVAD-cmk can also alleviate the levels of NETs in BALF and neutrophil infiltration in the alveoli. Poly I:C can induce the production of NETs and the occurrence of lung injury. Inhibiting the receptor TLR3 of Poly I:C can suppress the aforementioned response. Additionally, Poly I:C induces the activation of p38 MAPK, and p38 inhibitor can inhibit the generation of NETs (51). Therefore, the TLR3-P38-MAPK pathway may become a potential target for regulating the production of NETs. IRF-1 is a transcription factor involved in regulating immune and inflammatory responses. It plays an important role in physiological and pathological states such as infection, tumor formation, and autoimmunity. In the LPS-induced ALI model, IRF-1 gene knockout mice showed significantly reduced lung injury and decreased release of NETs. In addition, IRF-1 plays a crucial role in regulating the classical ROS-dependent NETosis process (52). This provides another perspective for us to further understand the mechanism of NETs production and study their clinical application value. Our team has also previously discovered that NETs regulate LPS-induced acute lung injury through the cGAS-STING pathway, and that DNase or inhibitors of the cGAS-STING pathway can alleviate lung injury (53). In a mouse model of acute lung injury induced by mitochondria, neutrophils from older mice showed impaired chemotactic activity, but trended towards higher formation of extracellular traps (14). This may be related to age-related immune regulation.

Du et al. (54) have successfully developed a novel biomimetic DNase I delivery system called DCNV (genetically and bio-orthogonally engineered cell-derived nanovesicles). This innovative system demonstrates high efficiency in targeting the lungs during LPS-induced acute lung injury and effectively clears pulmonary NETs. This study suggests that we can enhance the therapeutic efficacy of drugs through materials engineering modifications. However, the safety of drugs or drug delivery systems needs further confirmation. Recently, research has reported the therapeutic effects of traditional Chinese medicine in this aspect. Lianhua Qingke (LHQK) can effectively ameliorates lung inflammatory response and lung injury partially by inhibiting cf-DNA, CitH3-DNA levels, the components of NETs (55). Xuebijing injection is a traditional Chinese medicine compound formulation that includes components such as safflor yellow A (SYA), hydroxysafflor yellow A (HSYA), and anhydrosafflor yellow B (AHSYB). Research has found that these components can inhibit the production of NETs *in vitro* or *in vivo*, and alleviate LPS-induced airway injury (56). However, the specific molecular mechanism is still not clear, and further research is needed to explore the interaction between Xuebijing injection and NETs, as well as its potential impact on the treatment of sepsis. In addition, Xuanfei Baidu decoction (XFBD) remarkably inhibit NETs markers MPO and H3Cit expression in LPS induced acute lung injury in mice, and meanwhile alleviate inflammatory lung injury (57). It is undeniable that further research is needed to clarify the efficacy, mechanisms of action, and specific active ingredients of traditional Chinese herbal medicines in the treatment of acute lung injury. In recent years, studies have shown that stem cell therapy has demonstrated certain potential value in research on various disease models, and some have even shown clinical applications (58). For example, mesenchymal stem cells from bone marrow can regulate lung inflammation, reduce oxidative damage, and decrease NETs release in mice with LPS-induced acute lung injury models, offering a promising therapeutic approach (59). An iron-chelating agent, deferasirox (DFS), can inhibit the generation of dsDNA or NETs in BALF induced by LPS, thereby alleviating lung injury, this may be partially attributed to the inhibition of ROS generation (60).

In summary, NETs represent the promising therapeutic targets in sepsis or endotoxin-related acute lung injury/ARDS and can be approached from various directions, such as increasing NETs clearance, reducing NETs production, or selectively inhibiting NETs and their components. While there is growing evidence suggesting the involvement and significance of NETs in airway inflammatory diseases, most research is still in the preclinical stage, involving cell and animal experiments. Further basic and clinical research is needed to fully understand the process of NETs formation, their biological characteristics, and regulatory role in the inflammatory micro-environment. This will help us identify potential therapeutic targets and develop targeted therapies that can effectively modulate their harmful effects while preserving their beneficial functions in host defense. It is crucial to transfer our comprehension regarding NETs from laboratory experiments to practical applications. Additionally, there is a need for further clinical research to assess the effectiveness and safety of therapies focusing on NETs in the treatment of ALI/ARDS and other respiratory disorders.

3.1.2 Transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) is a cause of death in critically ill patients following blood therapy, whether it involves whole blood or blood components. TRALI usually manifests within 6 h of transfusion and is clinically characterized by hypoxemia and

respiratory distress. Pathologically, TRALI is characterized by pulmonary edema, congested capillary leukocytes, and diffuse infiltration of neutrophils in lung tissue (61, 62). Patients with TRALI have been found to have elevated levels of neutrophil extracellular traps in their lungs and plasma (63, 64). Caudrillier et al. (64) established a mouse model of neutrophil and platelet dependent TRALI, in which they observed a significant increase in NETs in both the pulmonary microcirculation and plasma. Pulmonary microthrombi in the lung vasculature are a key pathological feature of ARDS/ALI. Platelet activation can promote the release of NETs, and the histones expressed on NETs may, in turn, activate platelets, leading to further release of NETs and promoting pulmonary coagulation and thrombus formation, thus creating a vicious cycle. Furthermore, targeted inhibition of platelet activation using aspirin or glycoprotein IIb/IIIa inhibitors, or directly targeting components of NETs with histone-blocking antibodies and DNase I, has shown improved outcomes in terms of pulmonary edema, vascular permeability, and even mortality. Additionally, studies have investigated the use of small molecules like β-nitrostyrene derivatives (BNSDs), such as compound C7, which have demonstrated protective effects against LPS-induced acute lung injury. These compounds inhibit neutrophil aggregation, release of inflammatory mediators, platelet aggregation, myeloperoxidase activity, and release of NETs (65). The interactions between neutrophils and platelets in the pathophysiology of TRALI present a potentially modifiable target for drug interventions. Furthermore, studies have explored the mechanisms of NETs-mediated TRALI in mouse models. It has been discovered that increased expression of miR-144 promotes NETs-induced TRALI by down-regulating KLF2 (Krüppel-like factor 2) and activating the NF-kappaB/CXCR1 (C-X-C motif receptor 1) signaling pathway (66). We casually speculate these findings shed light on the molecular pathways involved in TRALI and provide potential targets for therapeutic interventions. Additionally, studies have reported the activation of the complement system in TRALI patients, which is associated with an increase in NETs. In an *in vitro* "two-hit model" of TRALI simulated by LPS and C5a, the formation of NETs was also observed (67). These findings suggest that the complement system may also be involved in the pathological process of TRALI.

In summary, although there is currently limited research on NETs-mediated TRALI, NETs have been implicated in the pathogenesis of TRALI, and understanding their role in this condition may help develop targeted therapies to prevent or treat TRALI in the future. However, it is important to note that further research is still needed to fully elucidate the mechanisms underlying NETs-mediated TRALI and evaluate the efficacy of potential interventions.

3.1.3 Ventilator-associated lung injury

Mechanical ventilation is a commonly used supportive treatment in the ICU to assist patients with their breathing. Its primary goals are to ensure airway patency, enhance ventilation and oxygenation, and prevent hypoxia and hypercapnia. However, it is important to note that mechanical ventilation can also lead to lung injury, which is referred to as ventilator-associated lung injury (VALI). VALI can occur due to multiple factors, such as high tidal volumes, excessive airway pressure, repetitive alveolar collapse and recruitment, and the release of pro-inflammatory mediators. These factors can cause inflammation, oxidative stress, alveolar damage, and disruption of the lung's physiological balance. Additionally, mechanical ventilation can contribute to lung overdistension and shear stress, further exacerbating lung injury (68–70). During mechanical ventilation, a significant release of inflammatory cytokines and chemokines occurs, leading to the recruitment of numerous neutrophils into lung tissues, where neutrophils are the primary effector cells in VALI (71–73). Studies have shown that in ventilator-induced lung injury models, the accumulation of neutrophils in the lungs can be observed early, even before physiological signs of lung injury become apparent. Additionally, in VILI models, the expression of chemokines like CXCL1 (KC) and CXCL2/3 (MIP-2) significantly increases, and their interaction with CXCR2 plays a crucial role in recruiting neutrophils and contributing to lung inflammation (74). These inflammatory factors such as IL-8, IL-1β, and TNF-α can also induce the release of neutrophil extracellular traps from neutrophils (75, 76). It has been proved the NETosis occurs in the pathogenesis of ventilator-associated lung injury, certainly, the specific mechanism is not clear.

In a mouse model of neutrophil and platelet-dependent VILI, increased of circulating NETs component MPO-DNA and the formation of NETs is required the simultaneous stimulation of integrins and G-protein-coupled receptors on neutrophils. Additionally, the heterodimerization of platelet-derived CCL5 and CXCL4 enhances their ability to activate and recruit inflammatory cells. Therefore, the study showed that blocking the heterodimerization of CCL5 and CXCL4, regulating NETs formation by DNase I, or inhibiting integrins/G-protein-coupled receptors could alleviated ALI (77). In a VILI model, the components of pulmonary NETs, including DNA, Cit-H3, and NE, were found to increase. Pre-treatment with DNase I to degrade NETs could alleviate previous lung injury. Furthermore, in a TLR4 knockout acute lung injury mouse model, NETs formation was reduced and lung injury was relieved. Therefore, the authors believe that TLR4 partially mediates the process of NETs promoting VILI (78). However, the authors believe that it is difficult to determine whether the above changes have a direct causal relationship with TLR4 or are just accompanying changes. These findings suggest that NETs may play an important role in VILI. Further research on the role of NETs in VILI and related pharmacological interventions may help us better understand the pathogenesis of VILI and provide new insights into its prevention and treatment. Although the mechanism by which NETs participate in ventilator-associated lung injury is unclear, it is undeniable that NETs and their components, or the pathways they generate, may become targets for the treatment of lung injury.

3.2 NETs in asthma

Bronchial asthma is a chronic inflammatory disease characterized by heterogeneous inflammation involving multiple cell types, such as eosinophils, mast cells, T lymphocytes, neutrophils, and airway epithelial cells. Asthma patients experience variable and reversible airflow obstruction, often presenting with recurrent wheezing, shortness of breath, chest tightness, and/or cough (79–81). The traditional view recognizes eosinophilic inflammation as a characteristic feature of the pathogenesis of asthma. However, current evidence confirms the importance of neutrophilic inflammation in asthma, and in certain cases, eosinophils and neutrophils can coexist, with neutrophils even playing a predominant role. Asthma phenotypes are commonly classified based on the cellular profile obtained from

induced sputum. Additionally, methods such as nasal lavage or nasal irrigation are also used for assessing asthma subtypes.

Neutrophil-mediated asthma airway inflammation differs from Th2 cell-mediated eosinophilic airway inflammation, and is referred to as Th2-low asthma (82, 83). The active involvement of neutrophils can lead to airway inflammation and pathological changes. Compared to Th2 cell-mediated asthma, Th2-low asthma patients have lower levels of IgE and fewer eosinophil, and may not be responsive to traditional asthma treatments such as corticosteroids. It should be noted that Th2-low asthma and Th2-high asthma are not strictly mutually exclusive, and some patients may have both types of airway inflammation (84). Currently, there is much debate regarding the existence of neutrophilic asthma. For example, it has been argued that the elevated levels of neutrophils in the airways of asthmatic patients could be a result of corticosteroid treatment, as glucocorticoids can enhance neutrophil survival and neutrophils express glucocorticoid receptor β (GRβ) (85). However, increased neutrophil levels have also been observed in asthma patients who have not received steroid treatment (86). Therefore, in addition to the traditional eosinophilic inflammation, neutrophilic inflammation also plays an important role in asthma, and there are instances where neutrophils may even surpass eosinophils in quantity.

The high expression of NETs has been found in bronchial biopsy specimens, sputum, and plasma samples from asthma patients (87–89). Particularly, there is a correlation between high levels of extracellular DNA (eDNA) in sputum and severe asthma (87). In neutrophilic asthma patients, there is an elevation in extracellular DNA levels in sputum, and it is negatively correlated with FEV1% (90). The increase in eDNA in sputum of asthma patients is associated with disease severity, as well as the increased frequency of oral corticosteroid use. And there is a correlation between the increased presence of eDNA and NETs components NE-DNA and H3Cit-DNA (91). The plasma levels of CitH3 are elevated in asthma patients, and the concentration is negatively correlated with the percentage decrease in FEV1/FVC in asthma patients (92). Furthermore, in models of asthma induced by viral infection, LPS, HDM, and air pollutants, the involvement of NETs has been observed (93–95). One of the components of NETs Double-stranded DNA (dsDNA) promote rhinovirus-induced type-2 allergic immune responses and asthma exacerbation (93). These studies suggest that NETs are involved in the pathogenesis of asthma and may even be associated with the severity or acute exacerbation of asthma.

Unlike with the Th2-dominated eosinophilic asthma, neutrophilic asthma is more obviously associated with the presence of Th17 cells and their related cytokines such as IL-17 (91, 96–98). In children with exacerbation of asthma, there is a significant increase in IL-17A levels in their sera. *In vitro* studies using stimulated neutrophils from children with asthma exacerbation have shown that it can induce the formation of IL-17A-enriched NETs. These IL-17A-enriched NETs, in turn, promote fibrotic changes *in vitro* (99). This suggests a potential role of IL-17A/NETs in the pathogenesis of asthma exacerbation and associated fibrosis. In patients of severe asthma, particularly in patients with a neutrophil proportion of ≥5%, BALF DNA is significantly increased, and high expression of H3Cit-is also observed in severe asthma with a higher proportion of neutrophils, and NETosis is associated with IL-17 levels. Meanwhile, in animal models, exposure of allergen-sensitized mice to LPS can lead to NETosis in lung tissue and mediastinal lymph nodes. In PAD4 knockout mice, NETosis is reduced and Th17 inflammatory responses are decreased (97). Which indicate that NETosis may play an immunomodulatory role in Th17/IL-17-mediated severe asthma. Recent clinical studies have shown that blocking the IL-33 receptor chain ST2 can reduce the frequency of uncontrolled acute exacerbations in type 2 low asthma patients who have fewer eosinophils in their peripheral blood (100). In addition, anti-IL-33 has been shown to inhibit neutrophilic inflammation in animal models of asthma. These findings suggest that IL-33 may be involved in non-type 2 inflammation (101). As previously mentioned, rhinovirus can cause acute exacerbation of asthma, and a team of researchers explored its mechanism and found that blocking IL-33 can reduce the aggregation of neutrophils and the formation of NETs, ultimately alleviating acute exacerbations in asthma (102). Recently, Tsai et al. (103) reported the association between NETs and the asthmatics who was nonresponse to inhaled corticosteroids, or termed uncontrolled asthma. Furthermore, they found the DNase I could significantly inhibited airway hyperreactivity and inflammation, even in the murine model of steroid resistant neutrophilic airway inflammation. CCL4L2 was observed associated with the insensitive effect of steroids treatment in asthmatics and mouse model. Interestingly, NE-deficient mice showed impaired NETosis in asthma models induced by OVA and LPS, accompanied by decreased levels of dsDNA and expression of inflammatory factors such as IL-1β, IL-6, and IL-17. Collectively, these results indicate the involvement of NETs in neutrophil-mediated airway inflammation and may also suggest the potential therapeutic target of CCL4L2 for asthmatics refractory to steroids. These results suggest that NETs may be involved in steroid-resistant asthma. In the neutrophilic asthma model induced by OVA/CFA/LPS, researchers have found that NETs are involved in the pathological process of asthma (104). In the neutrophilic asthma model, treatment with DNase I or CI-amidine can reduce the expression of MPO and CitH3, decrease airway hyperresponsiveness, alleviate the accumulation of inflammatory cells and mucus obstruction, and mitigate inflammation-induced damage. In Th17-mediated severe asthma models induced by OVA/HDM/LPS, characterized by neutrophilic aggregation, the expression of Th2 cells, Th17 cells, and their associated inflammatory factors increases. The expression of NETs-associated dsDNA, MPO-DNA, CitH3, and PAD4 also increases. Treatment with Simvastatin can suppress the inflammatory response and reduce NETs generation. Mechanistic studies suggest that this therapeutic effect of Simvastatin may be achieved through the inhibition of PAD4 (105).

During the inflammatory process, damaged or infected tissues release chemokines, such as interleukin-8 (IL-8), which are CXC chemokines. These chemokines can bind to specific receptors on the surface of neutrophils, such as CXCR1 and CXCR2, activating the movement and chemotactic response of neutrophils (106). CXCR2 antagonist AZD5069 is being studied for reducing the number of neutrophils in the sputum of severe asthma patients, however there is no reduction in the frequency of severe exacerbations (107–109). However, the clinical effectiveness of CXCR2 antagonists in the treatment of asthma is currently uncertain. For instance, in patients receiving SCH527123 treatment, there may be a reduction in mild exacerbations ($p = 0.05$) and improvement in ACQ scores ($p = 0.053$), and there is no statistically significant difference in FEV1 changes (109). This could be attributed to the complexity of asthma, which involves interactions among multiple inflammatory cells and mediators. Targeting solely neutrophils may not fully address the

intricate pathological mechanisms of asthma. Although the relationship with NETosis remains unclear, these findings offer a potential indication of whether CXCR2 antagonists can be utilized to inhibit neutrophils and modulate NETosis for therapeutic benefits.

Recombinant human deoxyribonuclease I (rhDNase) intervention in the OVA-induced eosinophilic asthma model also reduces reactive oxygen species, increases the superoxide dismutase/catalase ratio, enhances glutathione peroxidase activity, and increases thiol content, thus significantly improving lung tissue oxidative stress (110). In a toluene diisocyanate induced animal model of asthma, Th2-related inflammatory factors and NETs levels increase. These can be suppressed by DNase I, but not by dexamethasone. In addition, inhibiting the expression of NETs can promote repair of damaged epithelium (111). Therefore, NETs may play a role in both eosinophil-and neutrophil-mediated asthma as they have been observed in models and clinical samples of both types of asthma. However, there is a lack of clear research evidence regarding the specific mechanisms of NETs in Th2-dominant allergic airway inflammation.

3.3 NETs in chronic obstructive pulmonary disease

Components related to NETs, such as cf-DNA, MPO, NE, LL-37 and a-defensins have been found to be elevated in the airways of chronic obstructive pulmonary disease (COPD) patients, suggesting their possible involvement in airway inflammation and tissue damage. COPD is a common and treatable inflammatory disease characterized by progressive airflow limitation and tissue destruction (112, 113). Stimuli such as cigarette smoke, environmental pollutants, bacteria, viruses, and oxidative stress induce the secretion of chemokines and inflammatory mediators by lung epithelial cells and macrophages, which in turn attract neutrophils and monocytes from the circulation to infiltrate the lung tissue, causing sustained inflammation (114–117).

It is suggesting that NETs formation is not limited to COPD exacerbations but also exists in stable COPD and is associated with the severity of airflow limitation (118). In a study based on COPD patients, it was found that the content of histone-elastase complex concentration in sputum is significantly correlated with severity indicators of COPD such as GOLD score, COPD assessment test (CAT) score, exacerbation frequency, and percent predicted FEV1. Other NET markers, such as cf-DNA, were not associated with exacerbation frequency or GOLD scores, while elastase, MPO, and EN-RAGE were associated with exacerbation frequency, percent predicted FEV1, and GOLD scores (119). The key component NE of NETs is associated with bacterial infection-induced acute exacerbations in COPD, and NE may become an accurate predictor of a bacteria-associated exacerbation (120). As described earlier, IL-8 can promote the process of NETosis through its receptors, CXCR1 and CXCR2, on neutrophils. Peripheral blood neutrophils from COPD patients do not spontaneously form NETs *in vitro*, but can form NETs upon stimulation with autologous sputum supernatant, the NETs formation could be reduced by CXCR2 antagonist AZD5069 (121). These results indicate the importance of the inflammatory environment in the process of NETosis, and suggest that CXCR2 may regulate the production of NETs. Besides, there is generation of NETs in the subacute airway inflammation mouse model induced by CS (cigarette smoke), and *in vitro* cigarette smoke extract (CSE) can stimulate the production of NETs in airway epithelial cells in an NADPH oxidase-dependent manner (122). When used in combination with tiotropium, neutrophil elastase inhibitor AZD9668 did not show any clinical benefits in COPD patients and had no impact on inflammatory biomarkers (123).

Under physiological conditions, NETs are degraded by endogenous nucleases and cleared by alveolar macrophages (124, 125). It has been suggested a significant reduction in the number of macrophages in sputum samples from COPD patients compared to normal controls, and the phagocytic function of surviving macrophages is also defective (87, 126). Therefore, we speculate that, the decreased ability of COPD patients to naturally clear NETs results in their accumulation in lung tissues, promoting inflammation and exacerbating lung injury. NETs are associated with the worsening of COPD, and selective inhibition of NETs formation or targeting components may become potential therapeutic approaches for alleviating COPD. The specific mechanisms of how NETs are involved in the pathophysiology of COPD are still unclear and further basic experiments and clinical trials are needed for in-depth research.

3.4 NETs in COVID-19 related ARDS

In COVID-19, ARDS occurs as a result of an excessive immune response to the viral infection. The release of pro-inflammatory cytokines and the recruitment of immune cells, including neutrophils, contribute to the formation of NETs. The presence of a neutrophil activation signature is a prominent characteristic observed in the transcriptomes of circulating leukocytes in severe cases of COVID-19. NETs released during COVID-19 can cause direct damage to lung tissue and induce further inflammation. They can also contribute to the formation of microthrombi, impairing blood flow and oxygenation in the lungs. Additionally, the excessive presence of NETs can activate immune cells and amplify the immune response, leading to a cytokine storm and worsening lung injury.

The findings of the prospective cohort study indicate a significant increase in CitH3 and MPO in COVID-19 patients who require endotracheal intubation. The ratio of Pao_2/FiO_2 inversely correlates with the levels of NETs. Additionally, there is a direct correlation between plasma NETs and the Sequential Organ Failure Assessment (SOFA) score, which is a clinical marker used to assess the severity of illness. The increased levels of CitH3 and MPO, which are associated with NETs, further support the involvement of NETs in the pathogenesis of COVID-19 related ARDS (127). The levels of cf-DNA, MPO-DNA, and CitH3 are elevated in the serum of COVID-19 patients. Besides, hospitalized patients who require mechanical ventilation exhibit higher levels of cf-DNA and MPO-DNA (128). These findings suggest that the presence and abundance of NETs in the plasma of COVID-19 patients may serve as indicators of disease severity and organ dysfunction. There have been studies investigating the underlying mechanisms of NETs in mediating COVID-19 related ARDS. Indeed, SARS-CoV-2 has the ability to directly stimulate human neutrophils to release NETs. This stimulation occurs through the interaction of the viral spike glycoprotein (S) with angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) (29). ACE2 is known to facilitate viral entry into host cells and is expressed in various cell types, including lung pneumocytes,

epithelial cells, and endothelial cells (129). The activation of ACE2 by SARS-CoV-2 plays a critical role in triggering the release of NETs by neutrophils. NETs-based immunothrombosis is another critical mechanism for disease severity or organ damage (130). Autopsies of the lungs of COVID-19 patients have shown diffuse neutrophil infiltration accompanied by extensive NET deposition, often associated with platelet aggregation and microvascular thrombosis (131). This finding suggests that the formation of microthrombi may be associated with the severity of COVID-19 in patients. The formation of microthrombi can lead to impaired pulmonary circulation, exacerbate lung injury, and further worsen the condition of COVID-19. Studies have shown that NETs can promote thrombus formation through various mechanisms, including platelet adhesion and activation, binding to cells and fibrinogen, and interaction with von Willebrand factor (vWF). NETs-driven thrombosis is primarily platelet-dependent, and have been suggested as a crucial contributor to neutrophil-related thrombo-inflammation (132). NETs also contribute to the generation of local clotting enzymes, increasing the likelihood of clot formation. They can activate the extrinsic pathway through the production of tissue factor (TF) and initiate thrombus formation by activating the contact pathway via the activation of coagulation factor XII (FXII) (133). Certainly, the formation of pulmonary microthrombi mediated by NETs is a complex cascade reaction involving the interaction of various factors, including cytokines, chemokines, platelets, hemostatic and coagulation systems (134). Given the prominent role of immune thrombosis in the pathogenesis of COVID-19-associated ALI/ARDS, pharmacological inhibition or degradation of NETs may be a promising approach to alleviate disease severity and improve survival rates. In the treatment of COVID-19 ARDS, specific strategies targeting NETs have not been widely adopted. Although NETs play a role in inflammation and thrombus formation, there are currently no specific drugs or treatment methods available to specifically target NETs.

3.5 NETs in pulmonary cystic fibrosis

Pulmonary cystic fibrosis (PCF) is a commonly inherited disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. PCF is a recessive genetic disorder. CFTR gene mutations result in the dysfunction of chloride ion transport across the respiratory epithelium, which plays a crucial role in the formation of thin, freely flowing mucus. Therefore, patients with PCF will produce a large amount of thick mucus in their lungs, blocking the airways and bronchioles at various levels, leading to bacterial colonization. Pathophysiological studies have confirmed that cystic fibrosis is primarily driven by neutrophils (135–138). Mutations in the CFTR gene in individuals with cystic fibrosis make them more susceptible to respiratory infections, such as *P. aeruginosa*. The recurring infection process leads to a significant infiltration of neutrophils in the lungs, triggering the occurrence of chronic inflammation. Meanwhile, once infected, neutrophils are attracted to the airways, resulting in the formation of NETs that worsen the disease. The sputum of PCF patients contains NETs-related proteins such as NE and MPO, as well as neutrophil-associated proteins. Additionally, it contains a high concentration of extracellular DNA, which originates from necrotic neutrophils (139–141). NETs contribute to the thickening of mucus in the airways of CF patients, and enzymes like NE and MPO cause damage to the respiratory epithelium and connective tissue (140, 142–144). In the key components of NETs, MPO is believed to be associated with the severity of diseases and decline in lung function, while NE is considered a biomarker for the severity of CF disease and also promotes disease progression (145, 146). Calcium-binding protein S100A8/A9 has recently received significant attention as a NET protein, which has been found in the sputum, serum, and bronchoalveolar lavage of CF patients (147–149). Its expression levels can serve as biomarkers for CF patients and are associated with lung function decline (150). Our previous research has confirmed that neutrophils in the inflammatory environment of the airways have an extended lifespan, which sustains the persistent presence of inflammation (151). Similarly, in patients with cystic fibrosis, the longer lifespan of neutrophils leads to an increased production of NETs (152). This may, at least partially, explain how NETs contribute to the progression of CF disease. These studies all indicate that NET and component proteins play a crucial role in lung CF, and targeted treatment against NET may have potential clinical benefits for pulmonary CF patients. Nebulized inhalation of rh-DNase I (pulmozyme) is a clinical method for treating patients with cystic fibrosis. rh-DNase I can break down excessive DNA in the respiratory secretions of CF patients, thereby reducing the amounts of respiratory secretions and the risk of respiratory tract infection, and improving lung function in patients. In addition, studies have shown that the use of rh-DNase I not only rapidly improves FEV1, but also correlates with improvement in the rate of FEV1 decline within 2 years of long-term use (136, 153, 154). Not all drugs are effective, for example, CXCR2 antagonists named SB-656933 did not provide clinical benefits for CF patients (155). CF patients received neutrophil elastase inhibitor AZD9668 suggested no impact on sputum neutrophil count, neutrophil elastase activity and lung function. However, there is a decreasing trend in inflammatory biomarkers in sputum (156). Similar to other respiratory diseases, further research is still needed to understand the specific molecular mechanisms through which NETs mediate diseases and explore the feasibility of targeting them for treatment due to the complex composition of NETs.

4 Crosslinking between macrophage and NETs

Macrophages play a crucial role in the pathogenesis of inflammation by participating in inflammation, immune regulation, and post-injury repair processes. Macrophages are highly plastic cells that can polarize into several distinct subtypes and exert different functions under different stimuli (157, 158). It has been reported that NETs can promote the polarization of macrophages towards the M1 phenotype, thereby facilitating acute-phase inflammation in ARDS (159). Indeed, we also know that excessive polarization of M2 macrophages can lead to the progression of pulmonary tissue fibrosis in the late stage of ARDS. Therefore, it is worthwhile to explore the targeting of NETs levels and macrophage polarization status in conducting ARDS/ALI-related research. A large amount of NETs has direct cytotoxicity on epithelial cells and is engulfed by alveolar macrophages, leading to AIM2 inflammasome activation and caspase-1 dependent cell pyroptosis in alveolar macrophages, followed by the release of more

TABLE 1 NETs as the target for treatment of airway inflammatory disease.

Inhibitor	Target	Effect	Disease/animal model
DNase	NETs-DNA	Decrease protein leakage/pulmonary edema, reduce accumulation of inflammatory cells, alleviate inflammatory damage	ALI model
DNase	NETs-DNA	Alleviate lung injury	VILI model
DNase	NETs-DNA	Reduce NETs, inhibit airway hyperreactivity and inflammation, even in the steroid resistant neutrophilic airway inflammation	Asthma model
rhDNase	NETs-DNA	Reduce ROS, increase superoxide dismutase/catalase ratio, enhance glutathione peroxidase activity, increase thiol content, improve lung tissue oxidative stress, promote repair of damaged epithelium	Asthma model
rhDNase	NETs-DNA	Break down excessive DNA in the respiratory secretions, reduce the amounts of respiratory secretions and the risk of respiratory tract infection, and improve lung function	CF patient
Sivelestat	NE	Reduce the mortality rate and incidence of adverse events, shorten mechanical ventilation time and ICU stay, increase non-ventilated days, improve oxygenation index	ALI/ARDS patient
AZD9668	NE	No impact on sputum neutrophil count, neutrophil elastase activity and lung function, a decreasing trend in inflammatory biomarkers in sputum	CF patient
AZD9668	NE	No clinical benefits and no impact on inflammatory biomarkers	COPD patient
YW3-56	PAD2/PAD4	Inhibit lung vascular leakage, decrease acute lung injury, improve survival rates	LPS induced ALI
AFM32a	PAD2	Reduce the production of inflammatory factors, alleviate lung injury, inhibit the generation of NETs, improves survival rates	Sepsis-related ALI
Simvastatin	PAD4	Suppress the Th17-mediated neutrophilic inflammation, reduce NETs generation	Severe asthma model
Cl-amidine	Nonselective PAD inhibitor	Decrease citrullinated histone-DNA conjugates in BALF and NETs in plasma, fail to decrease NE-DNA complexes in lung, no effect on lung injury or inflammatory cell recruitment	Severe bacterial pneumonia/acute lung injury model
Cl-amidine	Nonselective PAD inhibitor	Decrease expression of MPO and CitH3, reduce airway hyperresponsiveness, alleviate cellular accumulation and mucus obstruction in airway inflammation, and mitigate inflammatory damage	Neutrophilic asthma model
Ac-YVAD-cmk	Pyroptosis	Alleviate levels of NETs in BALF and neutrophil infiltration in alveoli	LPS induced ALI
Deferasirox	Iron-chelating	Inhibit the generation of dsDNA and ROS, alleviate lung injury	LPS induced ALI
Compound C7	Neutrophil function of superoxide generation and elastase release	Inhibit neutrophil/platelet aggregation, inflammatory mediators, reduce release of MPO and NETs	LPS induced ALI
AZD5069	CXCR2	Reduce sputum neutrophil counts, no effect associated with improvement in clinical outcomes	Asthma patient
SCH527123	CXCR2	Reduce mild exacerbations and improve ACQ scores, no statistically significant difference in FEV1 changes	Asthma patient
AZD5069	CXCR2	Reduce the NETs formation	Peripheral blood neutrophils from COPD patient
SB-656933	CXCR2	No effect	CF patient
Metformin	AMPK	Enhance BALF macrophage ability to uptake apoptotic neutrophils and NETs	ARDS patient
LHQK	Uncertain	Reduce cf-DNA, CitH3-DNA levels, ameliorate inflammatory response	LPS induced ALI
Xuebijing	Uncertain	Inhibit the production of NETs, alleviate airway injury	LPS induced ALI
XFBD	Uncertain	Inhibit MPO and H3Cit expression, alleviate inflammatory lung injury	LPS induced ALI
MSC	Uncertain	Reduce oxidative damage, decrease NETs release	LPS induced ALI

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ACQ, asthma control questionnaire; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; LPS, lipopolysaccharide; LHQK, Lianhua Qingke; MSC, mesenchymal stem cells; NETs, neutrophil extracellular traps; NE, neutrophil elastase; VILI, ventilator-induced lung injury; XFBD, Xuanfei Baidu decoction.

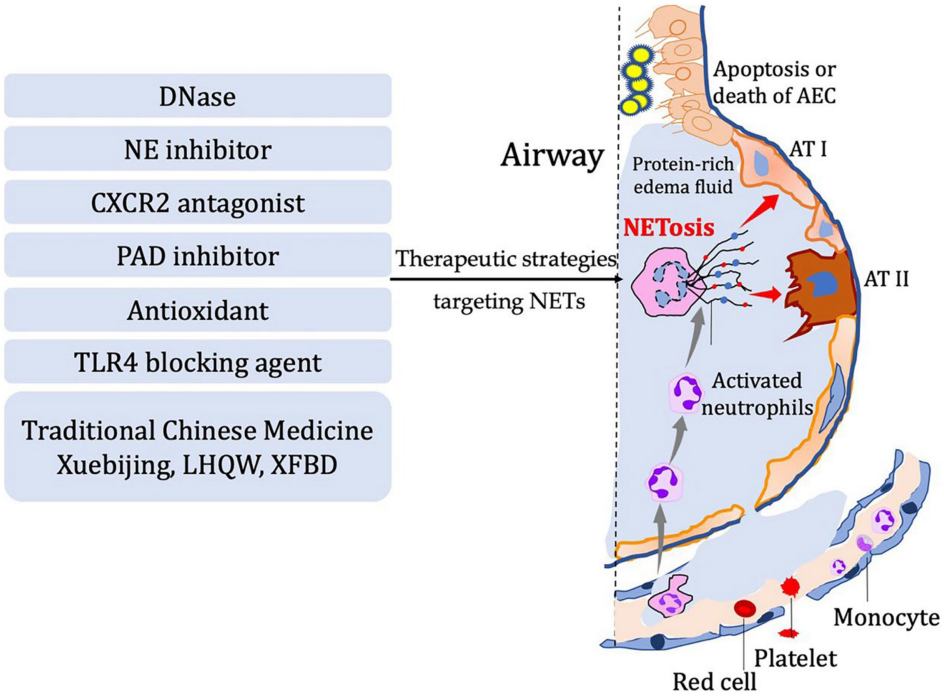

FIGURE 2
In diseases characterized by airway inflammation and injury, the activation of NETosis and the production of corresponding components mediate the inflammatory pathological processes in the lungs. Several potential therapeutic strategies have been developed based on the process of NETosis. These include DNase, NE inhibitor, CXCR2 antagonist, PAD inhibitor, antioxidants, TLR4 blocking agents, and even traditional Chinese herbal medicine.

inflammatory factors, inducing more neutrophil infiltration (160). In a sepsis-induced lung injury model, researchers found that increased NETs can promote the assembly of NLRP3 inflammasome, activate caspase-1, and ultimately lead to alveolar macrophage pyroptosis. However, this phenomenon was not observed after degradation of the NETs. Besides, NETs induce an increase in ROS, which promotes the activation of NLRP3 NLRP3 deubiquitination, leading to subsequent pyroptosis in alveolar macrophages. Inhibition of ROS can inhibit the NLRP3 pathway and further alleviate inflammation-induced lung injury (161).

In ARDS patients, the ability of macrophages to phagocytose NETs and apoptotic neutrophils is diminished. These NETs further activate inflammatory responses and induce fibrosis and lung atelectasis, thereby exacerbating lung injury (162). These effects may be due to abnormal macrophage function or inhibition by inflammatory factors. In addition, metformin can activate AMPK activity in bronchoalveolar lavage (BAL) macrophages of ARDS patients, enhancing their ability to uptake apoptotic neutrophils and NETs. This enhanced uptake capacity of macrophages may help alleviate lung injury caused by ARDS (162). In a study on endotoxemia-induced acute lung injury, it was found that metformin alleviates acute lung injury caused by endotoxemia by restoring AMPK-dependent mTOR inhibition (163). Therefore, metformin may have the potential as a therapeutic agent for treating ARDS. However, further research is needed to validate its efficacy and ensure its safety. *In vitro* experiments have found that human granulocytes can produce NETs upon cytokines stimulation, and co-culture with different immune cells revealed that macrophages can reduce the formation of NETs while NK cells or Treg cells have no effect (164). This further suggests that macrophages may be involved in the dynamic changes of NETs.

Currently, there is still much to be explored regarding the association between macrophages and NETs. Moreover, further investigation and research are needed to fully understand the role of NETs and potential therapeutic targets in other diseases.

5 Conclusion

Inflammation response is the body's primary reaction to injury in order to restore internal homeostasis. However, excessive inflammation can actually lead to tissue damage. The role of NETs in the pathological processes of diseases effectively illustrates this viewpoint (Figure 2). Indeed, neutrophil extracellular traps (NETs) play a critical role in the inflammatory response by capturing and eliminating pathogens such as bacteria and viruses. These structures consist of proteins and other cellular components released by neutrophils, forming a mesh-like substance that can trap and kill pathogens. Additionally, NETs can release chemokines, cytokines, and other inflammatory mediators to attract and activate immune cells, thereby amplifying the inflammatory response. However, it is important to note that NETs can also contribute to tissue damage and exacerbate inflammation. They have the potential to induce cell death and disrupt cell membranes, leading to increased inflammation and tissue injury. Therefore, maintaining a balance and regulating the release and function of NETs is crucial for immune and inflammatory homeostasis. Neutrophil extracellular traps, have been found to play a crucial role in respiratory system inflammatory diseases, including

acute lung injury/acute respiratory distress syndrome, chronic obstructive pulmonary disease, asthma, and cystic fibrosis. By examining recent research advancements, we can gain a better understanding of the development and mechanisms behind these diseases. This understanding opens up possibilities for the identification of novel therapeutic targets, offering potential avenues for managing these respiratory conditions (Table 1).

Author contributions

NX: Validation, Writing – original draft, Writing – review & editing. JZ: Validation, Writing – original draft, Writing – review & editing. ZK: Writing – original draft. WC: Validation, Writing – review & editing. B-pT: Conceptualization, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing.

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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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Chronic obstructive pulmonary disease (COPD) and COPD-like phenotypes

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Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease. Historically, two COPD phenotypes have been described: chronic bronchitis and emphysema. Although these phenotypes may provide additional characterization of the pathophysiology of the disease, they are not extensive enough to reflect the heterogeneity of COPD and do not provide granular categorization that indicates specific treatment, perhaps with the exception of adding inhaled glucocorticoids (ICS) in patients with chronic bronchitis. In this review, we describe COPD phenotypes that provide prognostication and/or indicate specific treatment. We also describe COPD-like phenotypes that do not necessarily meet the current diagnostic criteria for COPD but provide additional prognostication and may be the targets for future clinical trials.

KEYWORDS

chronic obstructive pulmonary disease, phenotypes text word count: 2, chronic hypercapnic respiratory failure, chronic hypoxemic respiratory failure, preserved ratio impaired spirometry (PRISm), hyperinflation, preserved spirometry at risk for COPD, frequent respiratory exacerbations

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by noxious particles or gases and influenced by host factors (1). COPD diagnosis requires not only a consistent history but also the presence of airflow limitation via spirometry. Historically, two phenotypes have been described to further characterize the disease: *chronic bronchitis*, which is associated with airway inflammation with the main characteristic being chronic productive cough, and *emphysema*, which is associated with alveolar destruction and presents with dyspnea. Although these phenotypes provide some additional characterization of the pathophysiology of the disease, they are not extensive enough to reflect the heterogeneity of COPD and do not provide granular categorization that indicates specific treatment, perhaps with the exception of adding

inhaled glucocorticoids (ICS) in patients with chronic bronchitis (2). Moreover, the current definition of COPD does not include individuals with high respiratory burden, e.g., high mortality and frequent respiratory hospitalizations, that do not have airflow limitation (3–5). The first objective of this review is to describe clinically relevant COPD phenotypes that provide prognostication and/or indicate specific treatment (**Figure 1**). The second objective is to describe COPD-like phenotypes that do not necessary meet the current diagnostic criteria for COPD but provide additional prognostication and may indicate response to certain treatments that can be tested in future clinical trials. **Table 1** provides a summary of all phenotypes.

Asthma-COPD overlap and COPD with eosinophilia

Asthma-COPD overlap is a relatively new term that describes the coexistence of asthma and COPD (6). Definitions have been proposed by scientific groups including the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the Global Initiative for Asthma (GINA) but none offer prognostication and do not indicate specific treatment (7). Because bronchodilator responsiveness (BDR) is one of several criteria to confirm lung function variability, (8) BDR presence is often and erroneously considered equivalent to asthma diagnosis. Although BDR is more common and greater in patients with asthma than those with COPD, BDR cannot distinguish asthma and COPD (9–11). Further, the association of BDR with clinical outcomes in patients with COPD has been extensively studied with conflicting findings (12–14). Early studies showed that BDR cannot predict response to treatment (12–14). The only outcome which is consistently associated with BDR is FEV_1 decline over time (15–17). The inconsistent findings regarding the association of BDR and clinical outcomes may be related to various BDR definitions and protocols. In COPD, an increase in both FEV_1 and FVC by 12% and 200 ml after bronchodilator administration was associated with a phenotype that is characterized by less emphysema but reduced mortality (15). BDR in FVC is typically associated with greater degree of emphysema (18, 19) and functional small airway disease (20). A drawback of BDR is its instability over time (14, 15). Nevertheless, the hallmark of asthma is lung variability, and it is not surprising that BDR is not stable over time. A recent study showed that consistent BDR in individuals with former or current smoking exposure is associated with prior asthma diagnosis, lung function decline, and functional small airway disease (20).

Eosinophils are strongly tied with Th2-mediated inflammation, historically considered the type of inflammation that occurs in asthma, as opposed to Th1-mediated inflammation, typically present in COPD (6). Increased sputum and blood eosinophil counts indicate response to ICS and patients with COPD who have blood eosinophil counts $\geq$ 300 cells/μL should consider adding ICS combined with bronchodilator treatment (**Figure 1**) (1). Biologic agents that target interleukin-5, interleukin-5 receptor and interleukin-4/interleukin-13 receptor in patients with COPD and elevated blood eosinophil counts reduce exacerbations (**Figure 1**) (21, 22). A post-hoc analysis of two randomized placebo controlled trials in COPD determined that the anti-IL5 agent benralizumab had greater response in patients with BDR in FEV_1 (23). This is the first study showing that BDR can indicate response to a specific pharmacological agent.

> *Summary: High eosinophils in patients with COPD indicate obstructive lung disease that responds to ICS and biologics, and BDR may indicate disease with greater response to biological therapy.*

COPD with static hyperinflation

Hyperinflation often occurs in COPD as the disease progresses and is well known to be associated with poor prognosis (24–27). The landmark study by Casanova et al. (25) showed that hyperinflation, defined as decreased inspiratory capacity to total lung capacity (TLC) ratio, is associated with increased mortality. More recently, studies confirm those findings using other definitions of hyperinflation (26, 27). Several definitions exist which refer to whether measurements of hyperinflation occur during rest (static) or exercise (dynamic) and the measurement themselves, e.g., functional residual capacity, residual volume (RV) (28).

Lung volume reduction surgery can alleviate static and dynamic hyperinflation and improve outcomes, including mortality (**Figure 1**) (29, 30). In one study, patients with upper-predominant emphysema, low post-rehabilitation exercise capacity who underwent lung volume reduction surgery had a long-term survival benefit (29). Nevertheless, lung volume reduction surgery is associated with high perioperative mortality, limiting the enthusiasm for the procedure (31). Recently, endobronchial valves placed bronchoscopically, a significantly less invasive procedure than lung resection, have been used as an alternative method to reduce hyperinflation. Endobronchial valves decrease the size of hyperinflated areas of the lung by allowing air to exit the hyperinflated areas but not to re-enter it. By reducing hyperinflation, endobronchial valves have been shown to improve lung function, exercise capacity, quality of life, and may reduce mortality (24, 32, 33). Patients with COPD should not only have severe lung function impairment (FEV1% predicted $<$ 45%) and static hyperinflation (TLC $>$ 100% and RV $>$ 175%) but also need to have significantly reduced exercise capacity (6-min walk distance $<$ 450 m or 1,476 feet) to benefit from endobronchial valves (34). Moreover, these patients should not have severe alveolar gas exchange impairment (PaO_2 $<$ 45 mmHg, and $PaCO_2$ $>$ 50 mmHg) and significantly impaired exercised capacity which can increase the periprocedural risk. Chronic bronchitis is one of the exclusion criteria as it can be associated with difficultly clearing airways of the treated areas and risk of respiratory infections. Insertion of endobronchial valves are associated with 25–30% risk for pneumothorax and for that reason requires inpatient observation for 3 days (32).

> *Summary: Lung volume reduction in selected patients with severe lung function impairment and static hyperinflation is associated with improvement in lung function, exercise capacity, and quality of life.*

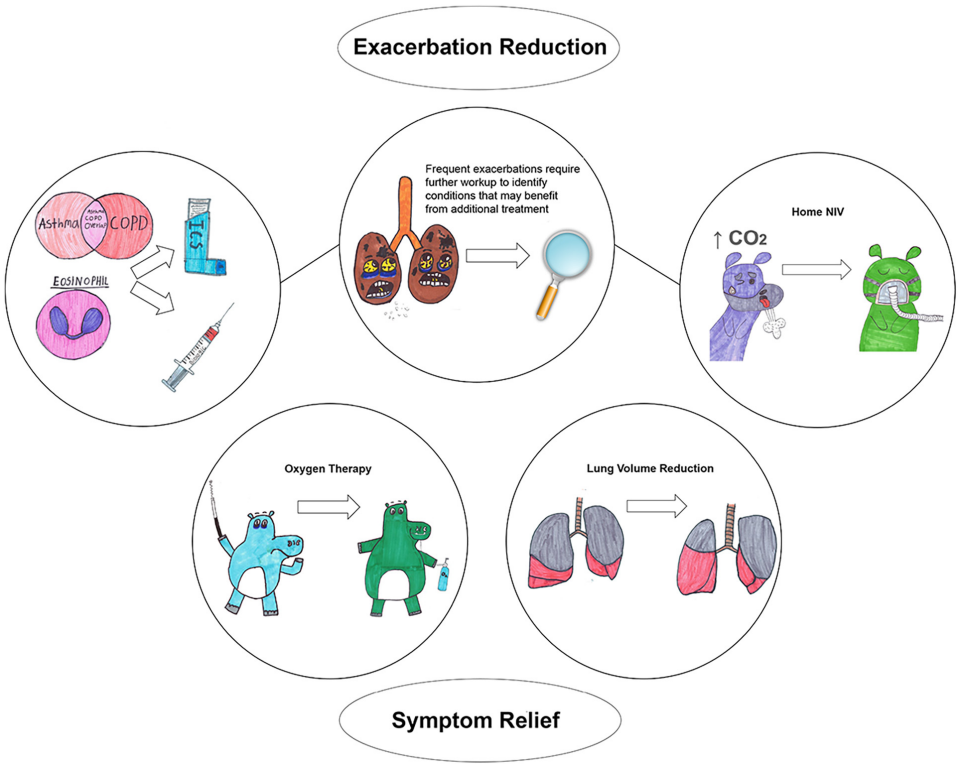

FIGURE 1
Clinically relevant COPD phenotypes and corresponding treatments.

TABLE 1 **Summary of chronic obstructive pulmonary disease (COPD) and COPD-like phenotypes.**

Phenotypes	
Asthma-COPD overlap and COPD with eosinophilia	High eosinophils in patients with COPD indicate obstructive lung disease that responds to ICS, and high eosinophils and BDR may indicate disease that responds to biological therapy.
COPD with static hyperinflation	Lung volume reduction in selected patients with severe lung function impairment and static hyperinflation is associated with improvement in lung function, exercise capacity, and quality of life.
COPD with chronic hypoxemic respiratory failure	Oxygen supplementation in patients with COPD and resting chronic hypoxemic respiratory failure improves survival but is not beneficial in those with isolated exertional or nocturnal hypoxemia.
COPD with chronic hypercapnic respiratory failure	Home nocturnal non-invasive ventilation in patients with COPD and chronic hypercapnic respiratory failure improves survival and reduces hospitalizations.
COPD with frequent respiratory exacerbations	Frequent respiratory exacerbations may indicate escalation of treatment (ICS, azithromycin, roflumilast, home NIV) and further investigation is required to identify other conditions, e.g., antibody deficiency syndrome, that may benefit from additional treatment.
Preserved spirometry at risk for COPD	Individuals with normal spirometry and history of smoking who have chronic bronchitis or respiratory exacerbations have increased respiratory-related hospitalizations and mortality. Further research is needed to assess preventive treatment for individuals with normal spirometry but who are at risk of progressing to COPD.
Preserved ratio impaired spirometry (PRISm)	PRISm is a volatile spirometric pattern associated with respiratory symptoms and mortality. Further research is needed to confirm whether individuals with PRISm benefit from existing treatment for COPD.

COPD with chronic hypoxemic respiratory failure

In the advanced stages of COPD, hypoxemia, defined as oxygen saturation below 89%, may develop. Oxygen supplementation in patients with COPD and chronic hypoxemic respiratory failure at rest has shown remarkable long-term mortality benefit with more than 50% increase in survival (Figure 1) (35, 36). However, the benefit of oxygen supplementation in isolated hypoxemia on exertion (absence of hypoxemia at rest) is either minimal or absent (37–39). Emtner et al. (38) showed that oxygen supplementation increased exercise capacity in patients undergoing exercise training. Patients who received oxygen supplementation while exercising

were able to train 4 min longer than those who did not receive oxygen. Nonoyama et al. (37) showed that oxygen supplementation improved a 5-min walk test by just 15 steps relative to air supplementation (control) (37). A large meta-analysis showed that oxygen supplementation in patients with COPD and isolated exertional hypoxemia does not improve any clinical outcome (40). Supplemental oxygen in those with moderate hypoxemia is also not beneficial (39, 40). Oxygen supplementation in those with isolated nocturnal hypoxemia has no benefit despite that these patients may be hypoxemic more than half of the duration of their sleep (41, 42).

> *Summary: Oxygen supplementation in patients with COPD and resting chronic hypoxemic respiratory failure improves survival but it is not beneficial in those with isolated exertional or nocturnal hypoxemia.*

COPD with chronic hypercapnic respiratory failure

Chronic hypercapnic respiratory failure is another consequence of COPD that occurs in advanced stages of the disease and is associated with increased mortality (43–45). The pathophysiological mechanism of chronic hypercapnic respiratory failure is complex and not entirely understood but hypoventilation seems to play the primary role (46, 47). During sleep, hypoventilation is more pronounced and nocturnal home non-invasive ventilation (NIV) has been used in these patients (48). Early studies of home nocturnal NIV in those patients showed no benefit (49, 50) but recent randomized controlled trials (RCTs) showed improvement in clinical outcomes, including reduction in hospitalizations and mortality benefit (**Figure 1**) (51, 52). Recent meta-analyses found an improvement in mortality, hospitalizations, dyspnea, exercise capacity, and health-related quality of life relative to standard treatment (53, 54). It seems that the benefit is related to a particular ventilator strategy, known as high intensity, that includes large inspiratory to expiratory airway pressure difference, high minute ventilation, and reducing baseline CO_2 levels by 25%, as well as with selection of patients with severe disease, those with FEV_1% predicted < 50% and $PaCO_2$ > 52 mmHg (51, 52, 55). RCTs with favorable outcomes recruited patients with severe lung function impairment and hypercapnia who had a recent COPD-related hospitalization or chronic hypoxemic respiratory failure (51, 52, 56). A recent metanalysis showed that both higher baseline arterial CO_2 levels and greater magnitude of the CO_2 reduction from NIV are associated with greater improvement in clinical outcomes (53). Nevertheless, this may merely reflect that these patients are sicker and benefit more from treatment. Despite the significant benefits from home nocturnal NIV, it is underutilized among those with COPD-related hospitalizations, with less than 3% of those patients using bilevel positive airway pressure/home NIV (57, 58).

> *Summary: Home nocturnal non-invasive ventilation in patients with COPD and chronic hypercapnic respiratory failure improves survival and reduces hospitalizations.*

COPD with frequent respiratory exacerbations

This phenotype of COPD has attracted a lot of attention despite the small proportion of patients with this phenotype, due to fact that this group of patients consume the largest proportion of healthcare resources and have poor prognosis (59, 60). Beeh et al. (59), in a sample of patients with moderate or severe COPD, showed that 14% of the patients accounted for 57% of the total COPD-related hospitalizations. In our previous work, among patients with COPD and mild-to-moderate lung function impairment, the top 5% in exacerbation frequency accounted for 34% of the total exacerbations in the cohort (60). Those with frequent exacerbations have increased mortality relative to those with no exacerbations (60). Although a formal definition for this phenotype does not exist, at least two moderate exacerbations or one hospitalization has been used as a cutoff to identify patients with COPD who require escalation of treatment according to GOLD guidelines (1). Patients with frequent exacerbations may benefit from addition of ICS on bronchodilator therapy, azithromycin, and roflumilast.

This phenotype is heterogenous and likely includes patients with chronic bronchitis, asthma-COPD overlap, and chronic hypercapnic respiratory failure (**Figure 1**). Thus, patients with frequent exacerbations and asthma-COPD overlap may benefit from the addition of ICS and/or biological therapy (1, 21, 23). Patients with frequent exacerbations and chronic hypercapnic respiratory failure may see a reduction in hospitalizations with home NIV use (61). Another comorbidity should be considered with this phenotype, e.g., antibody deficiency syndrome, which may increase respiratory exacerbations (62, 63). A retrospective study of patients with COPD and antibody deficiency syndrome with frequent exacerbations showed that appropriate treatment including cycling antibiotics or IgG supplementations reduced respiratory exacerbations from median of four to one exacerbation every year (64).

> *Summary: Frequent respiratory exacerbations may indicate escalation of treatment (ICS, biologics, azithromycin, roflumilast, home NIV) and further investigation is required to identify other conditions*, e.g., antibody deficiency syndrome, *that may benefit from additional treatment.*

Preserved spirometry at risk for COPD

Recently, this phenotype has been the focus of several investigations because it may reflect a state or condition that precedes COPD and may benefit from early treatment. Woodruff

et al. (4) showed that among individuals with at least 20-pack year of current or former smoking exposure, CAT score > 10 (highly symptomatic) was associated with increased respiratory exacerbations and hospitalizations (4). Pooling individual data of 5 prospective cohorts, Balte et al. (65) showed that non-obstructive chronic bronchitis (chronic bronchitis with normal spirometry) was associated with respiratory-related hospitalizations and mortality (65). A metanalysis confirmed that non-obstructive chronic bronchitis was associated with increased all-cause mortality in individuals with current or former smoking exposure but not in people without history of smoking exposure (5). Air trapping in individuals with current or former smoking exposure is associated with increased medication use, respiratory hospitalizations, progression to COPD, and mortality (5, 66). Regan et al. (67) showed that among people with at least 10 pack-years of current or former smoking exposure, 42% have features consistent with obstructive lung disease in the chest CT (67). Respiratory exacerbations in individuals with normal lung function and current or former smoking exposure are associated with lung function decline and increased all-cause mortality (60). It is possible that progression to COPD is mediated by lung function decline that results from respiratory exacerbations in individuals with normal lung function. COPDGene investigators have led an effort to expand the definition of COPD to include individuals without spirometric obstruction who are at risk for lung function decline or death (3).

A recent RCT showed that dual bronchodilator treatment in individuals with smoking history and respiratory symptoms but relative normal spirometry defined as post-bronchodilator $FEV_1/FVC \geq 0.7$ and FVC % predicted $\geq 70\%$ did not improve respiratory symptoms (68). However, the lack of efficacy could be due to the fact that bronchodilators have minimal effect on individuals with near normal lung function. It is possible that other types of pharmacotherapy in a different group of individuals should be tested, e.g., inhaled corticosteroids in individuals with non-obstructive chronic bronchitis or respiratory exacerbations. Identifying individuals with normal lung function at risk for COPD and lung function decline may be the focus of future therapeutic trials that will test pharmacological agents which can prevent progression to COPD.

> *Summary: Individuals with normal spirometry and history of smoking who have chronic bronchitis or respiratory exacerbations have increased respiratory-related hospitalizations and mortality. Further research is needed to assess preventive treatment of individuals with normal spirometry but who are at risk of progressing to COPD.*

Preserved ratio impaired spirometry (PRISm)

Preserved ratio impaired spirometry (PRISm), also known as restrictive or unclassified spirometry, is a common spirometric pattern which occurs in 10–20% of spirometries (69–72). PRISm is usually defined as reduced FEV_1 with a normal FEV_1/FVC (69) but other definitions applied also refer to a non-obstructive abnormal spirometry (70). General population studies have reported that it is associated with increased all-cause mortality (70, 73). Studies in individuals with current or former smoking exposure have shown that PRISm is a heterogenous group with significant symptoms and reduced exercise capacity that includes patients with an FEV_1% predicted that can range from 44 to 79%, a body mass index (BMI) between 17.2 and 53.8 kg/m^2, and radiographic emphysema on chest CT that can range from < 1% to up to 11% (69). Individuals with PRISm have higher BMI relative to patients with normal spirometry or obstruction and it has been postulated that PRISm merely is the result of high BMI. However, a landmark study by Jones and Nzekwu (74) showed that although BMI is inversely associated with FVC and total lung capacity (TLC), obesity in individuals with no respiratory disease is unlikely to reduce FVC below the lower limit of normal (LLN). One study demonstrated that among patients undergoing preoperative evaluation for bariatric surgery with a BMI of $\geq$ 35 Kg/m^2, only 3% had an FVC < LLN (75). Although a proportion of PRISm could be related only to obesity, it is unlikely that obesity is the sole cause of PRISm in the majority of the cases. Other diseases such as interstitial lung diseases (ILD) can cause PRISm (72) but the prevalence of ILD is extremely low and thus it is unlikely that ILD accounts for the majority of PRISm cases. Cohorts such as COPDGene, with a PRISm prevalence of 12–15%, exclude ILDs (69, 76).

Most individuals with PRISm likely have obstructive lung disease. Approximately half of individuals with PRISm have TLC on chest CT and < 80% predicted or LLN, which likely results from obesity (69). Obesity is associated with increased FEV_1/FVC in patients with COPD (77). Lower TLC secondary to obesity may result in pseudo-normalization of FEV_1/FVC ratio and underdiagnosis of obstructive lung disease. Our previous work has shown that air trapping in PRISm is associated with increased respiratory exacerbations, progression to COPD, and increased mortality (78). Unfortunately, no clinical trials have assessed the effect of existing pharmacotherapies on PRISm. Conducting clinical trials in PRISm is a difficult task as PRISm is an unstable phenotype (76, 79). It has been reported that 25% of individuals with PRISm have COPD on future spirometries, and 16% of those with PRISm had COPD in prior spirometries (76).

> *Summary: PRISm is a unstable spirometric pattern associated with respiratory symptoms and mortality. Further research is needed to confirm whether individuals with PRISm benefit from existing treatment for COPD.*

Conclusion

More granular phenotyping of COPD (asthma-COPD overlap, hyperinflation, chronic hypercapnic respiratory failure, frequent respiratory exacerbations) can help to identify patients that respond well to existing treatments, e.g., ICS, home nocturnal NIV. Further research is needed in those individuals at risk for COPD who do not yet have obstructive spirometry (normal spirometry or PRISm) to assess

whether treatment can improve outcomes including preventing progression to COPD.

Author contributions

SF: Conceptualization, Writing – original draft, Writing – review & editing. DG: Supervision, Writing – review & editing. NT: Supervision, Writing – review & editing. FS: Writing – review & editing. JZ: Supervision, Writing – review & editing. AC: Supervision, Writing – review & editing.

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Conflict of interest

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Interstitial lung disease: a review of classification, etiology, epidemiology, clinical diagnosis, pharmacological and non-pharmacological treatment

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Interstitial lung diseases (ILDs) refer to a heterogeneous and complex group of conditions characterized by inflammation, fibrosis, or both, in the interstitium of the lungs. This results in impaired gas exchange, leading to a worsening of respiratory symptoms and a decline in lung function. While the etiology of some ILDs is unclear, most cases can be traced back to factors such as genetic predispositions, environmental exposures (including allergens, toxins, and air pollution), underlying autoimmune diseases, or the use of certain medications. There has been an increase in research and evidence aimed at identifying etiology, understanding epidemiology, improving clinical diagnosis, and developing both pharmacological and non-pharmacological treatments. This review provides a comprehensive overview of the current state of knowledge in the field of interstitial lung diseases.

KEYWORDS

interstitial lung disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia

Interstitial lung disease

Interstitial lung disease (ILD) is an umbrella term for ~200 different diseases that may result in inflammation and scarring of the lung tissue (Figure 1) (2). ILD is characterized by progressive dyspnoea, cough, hypoxia, impaired lung function, diffuse bilateral infiltrates on imaging, inflammation, fibrosis, limited patient mobility and reduced quality-of-life (QOL) (3). Most ILD cases result from an etiological factor, such as exposure to allergens, hazardous material,

asbestos, drugs or an underlying autoimmune disease (2–5). The development of these cases is a complex process that is influenced by a variety of factors, including the individual's genetic traits, and exposure to environmental pollutants (6). Idiopathic Pulmonary Fibrosis is the most aggressive form of ILD, causing progressive and permanent lung scarring. It causes a chronic and irreversible lung disease with a poor prognostic outcome with a median survival rate of 3–5 years post-diagnosis if left untreated (5, 7, 8). Although two antifibrotic medications demonstrated a significant reduction in the rate of disease progression, it remains difficult to predict disease behavior for individual patients (5, 7, 8). The purpose of this review is to provide up-to-date information on interstitial lung disease (ILD), with a particular emphasis on definition, classifications, etiology, epidemiology, diagnosis, pharmacological, and non-pharmacological management.

ILD has been classified into the following categories based on a recent publication by the American Thoracic Society Consensus Statements (Figure 2) (2–5, 10–12).

Classification

Idiopathic

Idiopathic interstitial pneumonias (IIPs), represent a broad spectrum of diseases, each demonstrating distinct clinical features and rates of progression (3, 6). These diseases can be classified into several types, including:

- Idiopathic pulmonary fibrosis which is chronic and has a high risk of developing a progressive-fibrosing phenotype.
- Chronic IIPs: these can further be divided into various forms such as desquamative interstitial pneumonia, or pleuroparenchymal fibroelastosis, idiopathic nonspecific interstitial pneumonia.
- Acute IIPs: a prime example of this category is acute interstitial pneumonia.
- Subacute IIPs: an example of this type is a cryptogenic organizing pneumonia.
- Unclassifiable interstitial lung disease: these are IPPs that cannot be accurately categorized due to their unique and mixed characteristics.

The cause of these idiopathic conditions remains elusive, but their progression tends to be characterized by persistent and often worsening fibrosis, functional lung impairment, and a declining prognosis (13). The most severe and common idiopathic form is idiopathic pulmonary fibrosis (IPF), accounting for ∼50% of all reported IIPs for which there is no cure (2–5, 11, 14). The considerable variability seen among patients makes individual outcome prediction difficult (3–5). Some IPF patients experience rapid progression and others experience slow progression. A systematic review suggested that gastro esophageal reflux disease (GERD) is associated with IPF (15). There is also a higher incidence among individuals who actively smoking cigarettes at the time of diagnosis or have a history of smoking (2, 13). Pharmacological treatments for IPF have historically included triple therapy [prednisolone, azathioprine, and N-acetyl cysteine (NAC)] and NAC monotherapy which were proven to be ineffective (16–19). The last decade has seen introduction and widespread use of two anifibrotic agents (Pirfenidone and Nintedanib) which have been shown to slow the rate of forced vital capacity decline (16–19).

Autoimmune-related

- Acute conditions, rapid progressive interstitial lung disease such as diffuse alveolar hemorrhage in ANCA-associated vasculitis or in systemic lupus erythematosus and anti-MDA5-antibody-associated amyopathic dermatomyositis.
- Chronic disease includes connective tissue disease-associated interstitial lung disease (CTD-ILD). Diseases such as systemic sclerosis and rheumatoid arthritis are CTD-ILD conditions that can cause inflammation and damage to various body tissues, including the lungs (20). CTDs are also associated with other less common types such as idiopathic inflammatory myopathy (dermatomyositis, polymyositis), systemic lupus erythematosus, and Sjögren's syndrome (21). Connective tissue disease is systemic immune diseases where T- and B-cells attack the lung tissue, causing inflammation. Although specific causes are unknown, environmental factors, toxins and genetics contribute to CTD-ILD (21, 22). ILD is prevalent in an estimated 15% of patients with CTDs, and slightly higher in patients with SSc and RA. The risk of CTD-ILDs is associated with women younger than 50 years of age (21) and other comorbidities (23).

Exposure-related ILD diseases

Some exposure-related diseases are chronic and have a high risk of developing a progressive-fibrosing phenotype, such as hypersensitivity pneumonitis, which is mostly related to the inhalation of organic particles (e.g., domestic, or occupational exposure to mold, birds or other exposures).

- Chronic such as pneumoconiosis due to inhalation of inorganic substances, respiratory bronchiolitis-interstitial lung disease and postinfectious interstitial lung disease. Environmental and occupational exposures represent a significant cause of certain ILDs (24). Long-term exposure to airborne irritants such as silica dust, asbestos fibers, and specific animal droppings can lead to inflammation and fibrosis in the lung tissue, resulting in conditions such as silicosis, asbestosis, or hypersensitivity pneumonitis. These harmful substances can cause direct damage to the lungs, triggering an inflammatory response that can lead to fibrotic scarring (20, 24).
- Acute, such as drug or radiation-induced lung injury, may occur due to chemotherapy drugs, antibiotics, anti-inflammatory medications, and certain heart drugs can cause lung tissue damage, leading to drug-induced ILDs. The mechanism may involve direct toxicity to lung tissue, allergic reaction, or initiation of an autoimmune response (25).

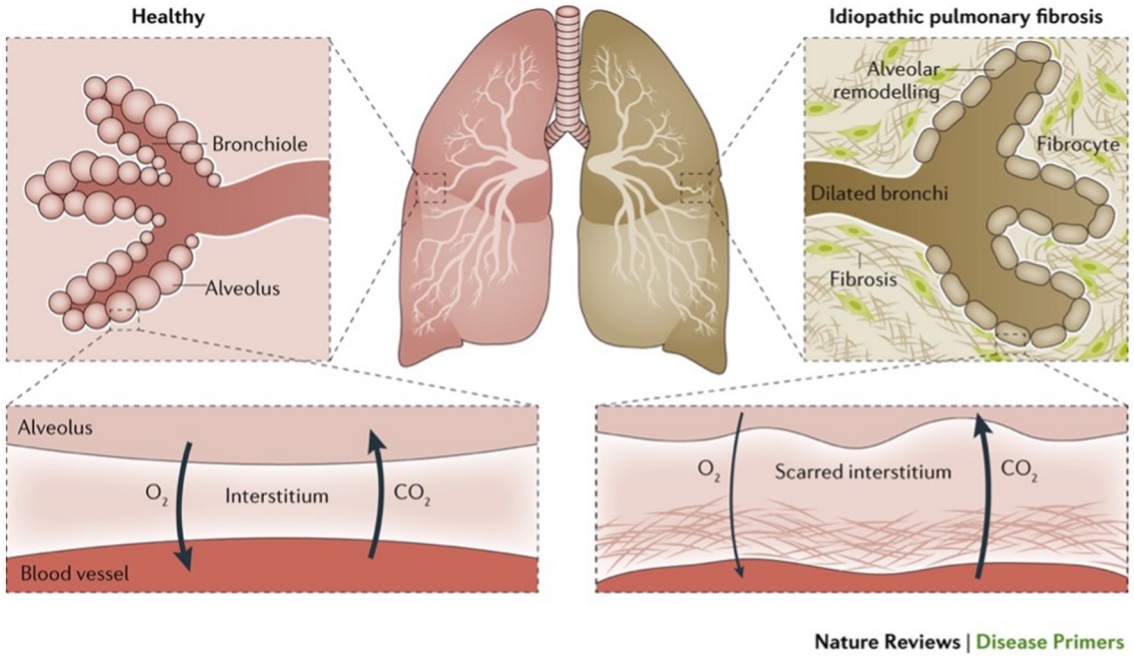

FIGURE 1
Illustrates normal lungs and lungs with a type of ILD (idiopathic pulmonary fibrosis) (1).

Interstitial lung diseases with cysts or airspace filling

- Langerhans cell histiocytosis.
- Lymphangioleiomyomatosis (LAM).
- Pulmonary alveolar proteinosis.

Lymphangioleiomyomatosis which is characterized by abnormal growth of smooth muscle cells primarily in women of childbearing age (26, 27). Pulmonary Langerhans cell histiocytosis, which involves accumulation of a specific type of immune cell in the lungs (27). Pulmonary alveolar proteinosis and pulmonary alveolar microlithiasis, both characterized by abnormal accumulation of substances in the alveoli.

ILDs related to distinct primary diseases

These are more likely to show a progressive-fibrosing phenotype such as in sarcoidosis. Sarcoidosis is a multisystem chronic inflammatory disease that affects multiple organs in the body, including lymph nodes, eyes, skin, and, most commonly (28), the lungs. It leads to abnormal macrophages and T-lymphocyte activation that targets body organs (29). It was first described in 1889 by Besnier (30) and characterized by the non-malignant formation of non-caseating epithelioid granulomas in the pulmonary alveolus. The most commonly reported symptoms include cough, fever, breathlessness, night sweats, weight loss and bilateral hilar lymphadenopathy. The causes are unknown, but a growing body of research has investigated the mechanism of granuloma formation, including genetic and environmental factors (31). The most commonly reported genetic factor linked to sarcoidosis is HLA-DRBI (32, 33). The role of interactions at the major histocompatibility complex (MHC) binding site is also significant (34). Environmental factors, including exposure to insecticides, clay, pine tree pollen, talc, zirconium, and aluminum, can influence both the prognosis and susceptibility of sarcoidosis (35). Sarcoidosis is more common in African Americans with a reported incident rate of 17–35 per 100,000 population and in people aged between 20 and 39 years (32, 36). Severity of the disease is also greater in black populations (37). Hispanics and Asians have been reported to have the lowest incidence rate of 1–3 per 100,00 population. Diagnosing sarcoidosis depends on clinical, radiological, and histological evidence of the formation of non-caseating granulomas (38). Phenotypic impairments in pulmonary function vary by race, gender, disease duration, and tobacco use (39). The differential diagnoses include viral and bacterial infections, autoimmune disease, hematological malignancy, and mycobacterium infection (38, 40). Although flexible bronchoscopy has demonstrated accurate results for sarcoidosis diagnosis, endobronchial ultrasound-guided transbronchial needle aspiration is the recommended sampling method in patients suspected of having sarcoidosis (41, 42).

Other ILD diseases

Examples include chronic eosinophilic pneumonia, malignant diseases with associated interstitial lung disease (e.g., lymphangitis carcinomatosis), and acute eosinophilic pneumonia (43).

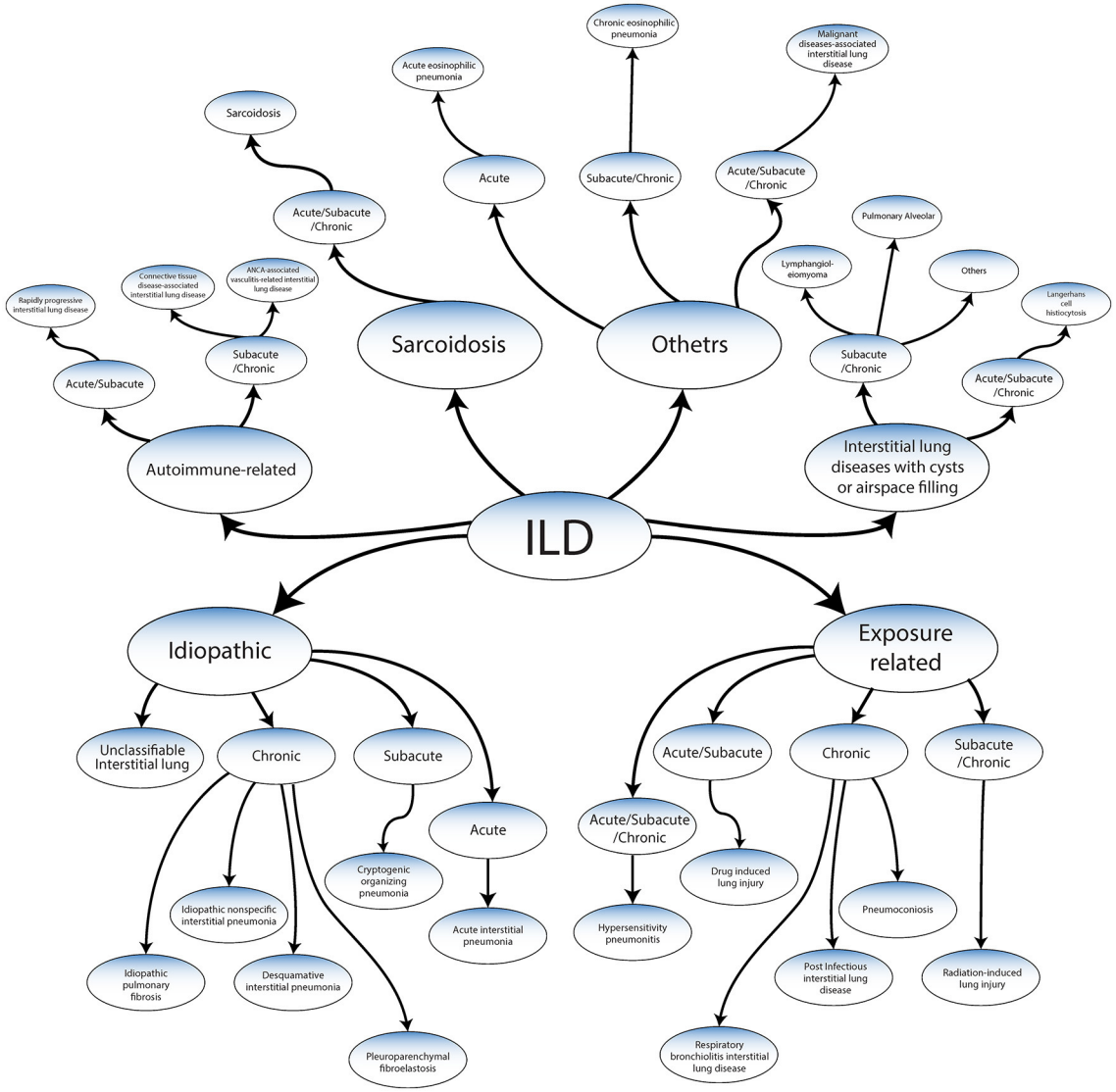

FIGURE 2
Classification of ILDs adapted from ATS/ERS 2013 guidelines and Wijsenbeek et al. (9).

Etiology

While the pathophysiological mechanisms are not entirely understood, ILD is categorized as a restrictive lung disease that reduces lung expansion and total lung capacity (TLC) (44). It causes scars and damage to alveoli leading to changes in lung function and decreased lung capacity and gas exchange (1). Scarring and lung damage are linked to the creation of fibroblastic foci, where fibroblasts proliferate in response to alveolar cell injury. Triggered by transforming growth factor beta (TGF-β), this process transforms fibroblasts into myofibroblasts, which secrete collagen, leading to fibrosis (45). Understanding the functionality of the lung and how ILD specifically changes lung structure and function helps to differentiate it from other lung diseases (2). Although the impact of socioeconomic factors on clinical outcomes in patients with interstitial lung disease is not well characterized, they may also play a role (46). A range of causes contribute to the development of ILD. These causes can be categorized into known and unknown origin (3).

Inflammation

Several factors can trigger inflammation in interstitial lung disease, with autoimmune disease being the most common. Autoimmune disease (AD) is defined as "a clinical syndrome caused by the activation of T cells or B cells, or both, in the absence of an ongoing infection or other discernible cause" (47). Previous research has identified differences in the blood cells' genetic expression between healthy individuals and those with fibrotic lung diseases, suggesting that blood markers could help in understanding these conditions better (48). Monocytes have been correlated with disease severity in IPF and have been associated with abnormalities in various blood cell types, including

macrophages and lymphocytes. In the single-cell resolution analysis of immune cells in IPF and FHP, it was found that there are common changes in monocyte populations across both IPF and FHP, while lymphocytes exhibit disease-specific differences (48). The inflammatory response is a complex cascade of events involving various immune cells, such as lymphocytes and macrophages, as well as the release of inflammatory mediators like cytokines and chemokines. This response is usually beneficial for dealing with acute injuries or infections (10). However, in the case of interstitial lung disease (ILD), the inflammatory process becomes dysregulated and can lead to progressive lung damage (9). In addition, the role of Autotaxin (ATX), an enzyme responsible for producing lysophosphatidic acid (LPA), significantly contributes to the inflammation and fibrosis observed in interstitial lung diseases (49). The persistent inflammation leads to further tissue damage, creating a vicious cycle. Abnormal multiplication and excessive protein secretion by fibroblasts, including collagen, contribute to the process of fibrosis (10). These proteins accumulate and harden, leading to fibrosis, which stiffens the lung tissue and impairs its ability to exchange oxygen and carbon dioxide effectively (10). Scarring and lung damage are linked to the creation of fibroblastic foci, where fibroblasts proliferate in response to alveolar cell injury. Triggered by transforming growth factor beta (TGF-β), this process transforms fibroblasts into myofibroblasts, which secrete collagen, leading to fibrosis (50).

Risk factors

Recent advancements in single-cell RNA sequencing (scRNA-seq) technologies have provided novel insights into the pathogenesis of IPF (51). Study by Unterman et al. (51) has revealed reveals that certain immune aberrations, like the increase in classical monocytes, are observed in both stable and progressive forms of IPF. However, significant distinctions are evident, particularly regarding regulatory T cells (Tregs). An increase in Tregs, alongside the formation of a specific lung-blood immune recruitment axis, is more prominently associated with or specific to progressive IPF (51).

Smoking

Cigarette smoking is a notable contributing cause of ILD and a significant contributor to numerous diseases and deaths (52). Cigarettes contain an estimated 5,000 chemicals (53), most of which have been contributed to deaths and a large number of diseases (54, 55). Smoking has been associated with a million deaths in the previous century, and could result in over 1 billion deaths in the current century (56). These include acute eosinophilic pneumonia and pulmonary hemorrhage syndrome, where smoking plays a crucial role in their pathogenesis. Among chronic lung diseases, desquamative interstitial pneumonia (DIP), respiratory bronchiolitis associated interstitial lung disease (RB-ILD), pulmonary Langerhans cell granulomatosis (PLCH) demonstrated associated with smoking (57). Despite the clear linkage between smoking and these diseases, the relationship with other lung conditions like Idiopathic Pulmonary Fibrosis (IPF) and Rheumatoid Arthritis-related ILD (RA-ILD) is more complex. While there is a high prevalence of smoking amongst patients with these conditions, smoking has not been definitively established as their cause. Interestingly, conditions such as sarcoidosis and hypersensitivity pneumonitis show no etiological association with smoking, despite similar prevalence rates (58).

Desquamative interstitial pneumonia

Desquamative interstitial pneumonia (DIP) was first described in 1965 by Liebow et al. (59) and was later described as alveolar macrophage pneumonia due to its nature of diffuse filling of alveolar spaces (3). The most commonly presented symptoms are dyspnoea and cough. Less common symptoms are fever, chest pain, and fatigue (60). Radiographs typically show fine reticulation and bilateral ground-glass opacities in the basal part of the lung, widespread build-up of pigmented macrophages within the alveoli, an increase in numbers of type II alveolar epithelial cells and commonly diffuse thickening of alveolar septa, septal fibrosis and mild interstitial inflammation (60).

DIP is a restrictive disease that results in a reduced diffusing capacity of carbon monoxide, and it can be accurately diagnosed with a surgical lung biopsy. Although mostly found among smokers (60), 20% of DIP cases are associated with non-smokers and linked to etiological causes, including environmental exposures (molds, dust), occupational exposures to inorganic particles (solder fumes, flock-workers, diesel fumes, tungsten carbide), viral infections (hepatitis C virus, cytomegalovirus), medications (sirolimus, nitrofurantoin), and connective tissue disease (rheumatoid arthritis, systemic sclerosis, rarely systemic erythematosus lupus) (57).

Treatment should initial focus on removing the exposure, such as smoking cessation, in conjunction with medical intervention (60). A recent systematic review by Hellemons et al. found that corticosteroids, specifically prednisolone, were used to treat 91% of patients; with less commonly used treatments being primarily methylprednisolone and antibiotics such as clarithromycin, azathioprine, ribavirin, chloroquine and cyclophosphamide (60).

Respiratory bronchiolitis-associated interstitial lung disease

Respiratory bronchiolitis associated interstitial lung disease (RB-ILD) is a type of interstitial pneumonia commonly linked to smoking; and it is associated with accumulation of pigmented macrophages in the peribronchiolar alveolar spaces and distal bronchioles. Respiratory bronchiolitis is characterized by shortness of breath (61).

Air pollution

The air we inhale contains 78% nitrogen, 21% oxygen, 0.9% argon, 0.04% carbon dioxide, and other trace gases (62). However, it also carries pollutants, oxidants, and other harmful particles that damage the tiny thin alveolar epithelium, which leads to abnormal lung functionality. Inhaling these toxins trigger an immune system response which, as a result, can lead to a variety of different disorders (63).

Several studies have established air pollution as a risk factor for the development and progression of ILD (64, 65). A study conducted in Northern Italy demonstrated that an increase in nitrogen dioxide (NO_2) exposure during the cold season was associated with an increased incidence of IPF (66). Another study in India revealed a significant correlation between increased city-wide concentrations of particulate matter with a diameter $\leq 2.5\,\mu m$ (PM2.5) and the percentage of hypersensitivity pneumonitis cases registered in that center's ILD registry (67). A study of 25 patients with IPF using weekly spirometry found that higher weekly mean concentrations of nitrogen dioxide (NO_2), particulate matter 2.5 (PM2.5), and particulate matter 10 (PM10) contributed to lower mean forced vital (64) capacities (FVCs) over the study period (68, 69).

Occupational exposure

Occupational exposure to certain substances has been shown to contribute to various types of ILD (70, 71), although the majority of occupational exposure takes time to show symptoms for example, coal mine dust, asbestos fibers, crystalline silica, mold, and cobalt-tungsten carbide alloy are commonly reported as the causes of ILD. Occupational exposure to asbestos, silica, and coal dust was estimated to have caused 125,000 deaths according to the Global Burden of Disease Study in 2010 (72). The prevalence of this disease has been increasing among workers exposed to occupational dust. In the Jiangsu Province of China, for example, 9,243 cases were reported from 2006 to 2017, and in the United Kingdom, the most common type of pneumoconiosis is asbestosis (73). Furthermore, a systematic review demonstrated that gases, fumes, and vapors (71) may account for 26% of IPF (71).

Genetic

A growing body of evidence shows that genetic factors play a role in some of ILD onset (74, 75). It is now understood that certain inherited traits, such as rare pathogenic variants in genes associated with telomere maintenance and surfactant production (76), common single nucleotide polymorphisms (77), and reduced leukocyte telomere length can contribute to an increased risk of ILD (78). An estimated fifth of IPF cases can be traced back to familial origins, leading to the term familial pulmonary fibrosis when two or more blood relatives are diagnosed with ILD (79, 80).

Understanding these genetic variants has the potential to aid predicting the prognosis of ILD. Specifically, single nucleotide polymorphisms (SNPs), which are single base pair changes in the DNA sequence are among the DNA variations polymorphisms can affect the function of a gene and the activity of the encoded protein (81). In patients IPF, MUC5B promoter polymorphism (rs35705950) MUC5B, which is a mucin protein, has been linked to an increased risk of developing the disease (82). In particular, IPF susceptibility has been linked to polymorphisms in the promoter of the gene encoding salivary mucin, 5b (MUC5B), and the Toll-interacting protein (rs5743890; TOLLIP). These genetic variants, despite their association with a fairly mild phenotype, serve as promising targets for precision medicine in IPF (83).

Age and gender

Recent research highlights the importance of considering both gender and age in understanding the epidemiology, pathophysiology, and treatment responses of ILDs (26, 84). For instance, studies on non-IPF ILDs, such as hypersensitivity pneumonitis and connective tissue disease-associated ILDs, indicate gender and age-related differences in incidence, disease progression, and outcomes (85).

Male sex and older age are associated with a higher incidence rate of IPF (5). Specifically, the risk of developing IPF is 1.5–2 times more in men than women (86). This is because telomeres shorten with age, and IPF is associated with telomere shortening. It has been observed that the risk of developing hypersensitivity pneumonitis is more pronounced in men than in women (87). The development of interstitial lung disease linked to connective tissue disease (CTD-ILD) is more commonly observed in younger women who are nonsmokers (88). The prevalence of systemic lupus erythematosus is significantly higher in women than in men, with the ratio of affected individuals ranging from 7:1 to 10:1 (89). This disparity is also evident in other forms of interstitial lung disease, such as lymphangioleiomyomatosis (LAM), which primarily affects white women (26).

Similar trends are observed in other ILDs, indicating a potential underlying biological mechanism linked to that influences susceptibility to lung fibrosis (85, 89). Research suggests that hormonal differences, especially the protective role of estrogen against lung tissue damage, may contribute to these disparities. Moreover, lifestyle, including smoking habits which are historically more prevalent among men, could further exacerbate the risk of developing ILDs (89, 90).

Aging is a risk factor for ILDs, with a significant increase in incidence observed among older adults. This trend is particularly evident in IPF, where the disease predominantly affects individuals over the age of 65 (26). The association between aging and ILDs can be partially attributed to the biological process of telomere shortening (75, 78). Telomeres, protective caps at the end of chromosomes, naturally shorten as individuals age, contributing to cellular senescence and reduced regenerative capacity (75, 78). In IPF and possibly other ILDs, accelerated telomere shortening due to genetic factors or environmental exposures can lead to premature lung aging and increased vulnerability to fibrotic processes. Studies have found that men over 65 exhibit the most significant telomere shortening, correlating with the highest risk for developing IPF (75, 78). However, it's essential to consider that aging affects lung physiology and immune responses in both genders, contributing to a general increase in ILD susceptibility among older adult (91).

Epidemiology

ILD is a growing global health issue, with an increase of 86% in ILD-related mortality (92, 93) and predicted to account for 0.26% of all-cause mortality in 2027 in the world A recent study found that the prevalence of ILD ranged from 6.3 to 71 per 100,000 people, and the incidence rate of ILD ranged from 1 to 31.5 per 100,000 people per year (94). Another study from France reported a prevalence rate of 97.9 per 100,000 and incidence of 19.4 per 100,000 for individual per year (95). Specifically, this study reported Sarcoidosis

and IPF as the most commonly reported ILDs in Europe and North America (93). In addition, hypersensitivity pneumonitis was commonly reported condition in Asia, with reported rates of ranging from 10.7 to 47.3% of all ILDs in India and 12.6% in Pakistan. On the other hand, connective tissue disease-associated interstitial lung disease (CTD-ILD) was commonly reported in Canada (33.3%). In Belgium, the incidence of CTD-ILD was estimated to be around 7.5% cases per 100,000 population per year (96). The British Lung Foundation estimated the incidence rate of IPF is about 50 per 100,000 population per year in the UK (97). There are limited studies regarding the prevalence and incidence rate of ILD in Saudi Arabia. However, a recently, a study by Kaul et al. (93) reported variability in the global prevalence of ILD. This epidemiologic study presented findings on the prevalence of connective tissue disease cases in Saudi Arabia, reporting a rate of (34.8%) (93). In addition, one study by Alhamad (98) recruited 330 patients with ILD from a single tertiary care center. Included patients were native Saudis with a mean age of 55.4 years and were mainly female (61.2%). As above, 34.8% of cases of ILD were CTD-ILD, followed by IPF (23.3%), Sarcoidosis (20%), and HP (6.3%) (98).

Diagnosis

Importance of accurate diagnosis in ILD

Accurate diagnosis is essential to ensuring the most favorable disease prognosis for patients (99). Thus, following the international guidelines and the evidence-based diagnostic pathways may save lives (5). The updated guidelines have changed how ILD is diagnosed, from depending primarily on a histopathological investigation to a new gold standard multidisciplinary team (MDT) approach that uses various methods and tools (4, 5, 9). Previous studies have demonstrated that a multidisciplinary approach enhances the accuracy in the final decision among ILD specialists (100, 101) (Figure 3).

Composition and process of MDT

Conducting a thorough investigation and detailed assessment that takes into account various factors is essential to facilitate these processes (5, 100). These include a comprehensive investigation and a detailed assessment of medical history, onset and clinical course, family history, occupational and environmental exposure, toxic response, medications (chemotherapy) exposure, and comorbidities (10, 101). It also includes physical examinations, blood tests, pulmonary function tests and radiological assessments (101). High-resolution chest computed tomography (HRCT) can help identify any structural abnormalities or interstitial lung disease that may contribute to the patient's symptoms (5). It is also paramount to ensure the MDT is available for reassessment of treatment when the patient is not following the anticipated disease course (9). If no specific interstitial disease diagnosis is made, a more invasive investigation may be considered, such as bronchoscopy, bronchoalveolar lavage, transbronchial lung cryobiopsy (BLC), or surgical lung biopsy (5, 11). If the ILD does not fit a pattern or is a rare type, such as lymphangioleiomyomatosis (LAM) or Langerhans cell histiocytosis (LCH), the case is referred to a specialist center, where the condition is reviewed using advanced diagnostic methods and tools (10, 102). Furthermore, advancements in genetic testing, serum biomarkers, and artificial intelligence technologies for radiologic and histopathological assessment are revolutionizing the diagnostic approach (103).

Factors to consider in diagnosis

Once a diagnosis is made, the next step involves assessing the severity of the disease, typically by disease-specific investigations (104). These tests help identify the ILD subtype and its associated severity. Patient-reported outcomes are also collected to understand the impacts of the disease from the patient's perspective (105). These insights offer a holistic understanding of the patient's condition and guide subsequent management strategy steps (99). In addition to these measures, identifying and managing complications and comorbidities are crucial (105). This multidisciplinary approach guarantees that not only is the primary ILD treated but also that other existing conditions or complications are addressed; hence minimizing the potential negative impacts of any comorbidities on the patient's overall health status. The MDT has a responsibility to refer to the wider interdisciplinary team to ensure holistic care and follow up (5).

Disease-specific investigations

The monitoring of core outcome measures like forced vital capacity, diffusing capacity of the lung for carbon monoxide, chest radiographs and high-resolution CT scans enables the tracking of the course and progression of the disease (99). Also monitoring symptoms that are most commonly reported, such as breathlessness, cough, and fatigue, which cause physical and emotional distress and, in addition, low quality of life (5, 106).

Importance of identifying and addressing comorbidities

Interstitial lung diseases are commonly associated with several comorbidities influencing their course, progression, and overall patient outcomes (107). These comorbidities include both acute and chronic infections, gastro-oesophageal reflux, pulmonary hypertension, cardiac disease, pulmonary embolism, lung cancer, obstructive sleep apnoea, and depression (108). Gastro-oesophageal reflux is observed in up to 94% of IPF patients. Pulmonary hypertension is also common, with prevalence rates ranging from 32 to 85% in IPF, 5%−74% in Sarcoidosis, and 5%−12% in systemic sclerosis (SSc). Cardiac diseases are found in about 60% of IPF and 20% of sarcoidosis cases. Lung cancer is seen in ~4.4%−10% of IPF cases. Obstructive sleep apnoea is highly prevalent in ILDs, with rates of 60%−90% in IPF, 50% in SSc-ILD,

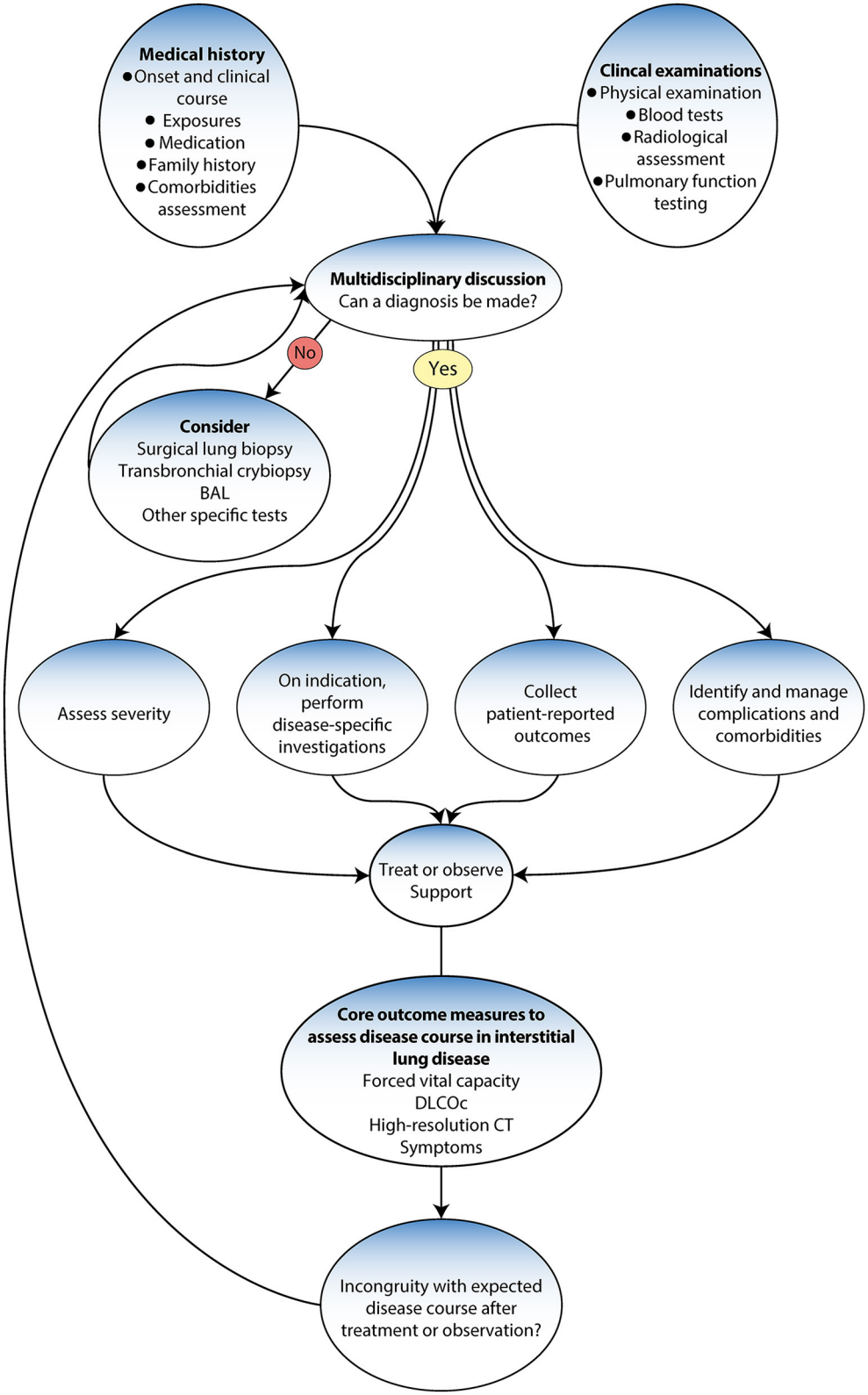

FIGURE 3
Diagnostic algorithm adapted from Wijsenbeek et al. (9).

and 65% in Sarcoidosis. Depression is also a common comorbidity in ILDs, with a prevalence >20% in ILDs overall and 11%−50% in IPF.

For patients diagnosed with definite or probable idiopathic pulmonary fibrosis (IPF), the patient may be suitable for antifibrotic treatment or considered for clinical trials. In these

cases, the specialist center reviews the condition and recommends suitable treatment paths. The shared care approach is again employed to ensure ongoing monitoring and management (5, 9).

Evaluating disease severity and risk-benefit profiles

In patients with a definite or possible diagnosis of nonspecific interstitial pneumonitis (NSIP) or connective tissue disease (CTD) or if further diagnostic review is necessary—which may include a biopsy—the specialist center's MDT takes the lead (24). After the review, the specialist center provides feedback, and the suggested course of action is initiated at the local level. Regular reviews at the specialist center ensure ongoing patient monitoring and care plan adaptability. Ongoing monitoring helps identify any inconsistency in the expected disease course after treatment or observation and allows for necessary adjustments in the management plan. Throughout this process, the key role of multidisciplinary discussion is reiterated, ensuring a comprehensive, patient-centerd approach to managing ILD (101).

Pulmonary function testing

A lung function test is crucial for diagnosing obstructive vs. restrictive lung function. ILD is a restrictive disease that shows a low total lung capacity, residual volume, and lower forced vital capacity and causes a low (DLCO; Figure 4) (109). Spirometer is regularly used in patients with ILD to assess treatment response and monitor disease progression (5). The gold standard for assessing the clinical endpoint in IPF has been hospital-based spirometer measurements of forced vital capacity (FVC) every 3 months. Unfortunately, obtaining lung function tests can be challenging, and delays are common. For example, it was not possible to conduct lung function tests during the COVID-19 pandemic lockdown, and many patients with ILD were unable to monitor their conditions (110, 111). Moreover, the cost and burden on the national healthcare system further add to the difficulties faced in obtaining these essential tests (4).

Radiological investigation and other specialist investigations

A comprehensive investigation of radiological imaging should be provided by a specialized thoracic radiologist who is part of the multidisciplinary team of ILD diagnosis (100). Basal predominant traction bronchiectasis or honeycombing in the absence of features suggesting alternative diagnoses suggest a usual interstitial pneumonia pattern on CT. In the presence of no identifiable cause of disease, these cases can be diagnosed as idiopathic pulmonary fibrosis by a multidisciplinary team (Figure 5) (99).

Invasive testing

Healthcare providers have access to a range of invasive options, such as bronchoscopy lavage (BAL), transbronchial biopsy (TBBX), and surgical lung biopsy (SLB) to obtain definitive histopathologic evidence for various lung diseases (4). Bronchoscopy is an endoscopic procedure designed to visualize the airways. It has both diagnostic and therapeutic applications. For instance, during bronchoscopy, bronchoalveolar lavage (BAL), biopsies, cytology, transbronchial needle aspiration, and endobronchial ultrasound can be performed for diagnostic purposes. On the therapeutic front, it allows interventions such as balloon dilatation, ablation, brachytherapy, and stent placement (4). Bronchoalveolar lavage (BAL) plays an especially significant role in diagnosing diffuse lung diseases (112). The procedure involves instilling a saline solution into a segment of the lung and then collecting the fluid for analysis. The BAL fluid's differential cell counts, microbiologic studies, and cytology contribute to diagnosing various diseases. Particularly in the context of Interstitial Lung Disease (ILD), cellular analysis of the BAL fluid can aid in identifying the underlying cause and potentially excluding IPF (9). If the diagnosis remains elusive even after the bronchoscopy with BAL, a surgical lung biopsy may then be deemed appropriate. This procedure involves the removal of a small piece of lung tissue for laboratory examination and testing. This can provide definitive histopathologic evidence of the disease process (9). However, latest guidelines suggest transbronchial lung cryobiopsy (TBLC) could be a preferable option to surgical lung biopsy in well-equipped centers, due to its association with fewer adverse events (5, 103, 113, 114). Biopsies can be obtained via several methods, such as video-assisted thoracoscopic surgery (VATS) or open lung biopsy. However, these are more invasive procedures with inherent risks, usually reserved for cases where non-invasive techniques and bronchoscopy with BAL fail to yield a definitive diagnosis. These procedures may have complications, including pneumothorax and postoperative pneumonia. A biopsy would aid in diagnosis, but it might be impractical due to patient comorbidities or refusal. In these scenarios, multidisciplinary team discussions play a crucial role in establishing the most probable "working diagnosis," integrating all available information, including demographic data, disease behavior pre and post-treatment, and bronchoalveolar lavage findings.

Interstitial lung disease management

The management of ILD often follows a series of evaluation steps and treatment pathways (Figure 6) (99, 115). Efforts should be made to provide symptom relief, which could involve various strategies, such as pulmonary rehabilitation (PR) and psychological support, to alleviate symptoms and improve the overall wellbeing of the patient. After providing symptom relief, the next crucial step involves assessing the patient's tolerance to and the effectiveness of any medication being used (116). In severe cases where medications are not effective, a lung transplant referral may be considered. Disease education and peer support can be crucial. Patients should be made aware of their condition, its potential implications, and how to manage it effectively. Peer support can also help the patient cope better with the disease. The

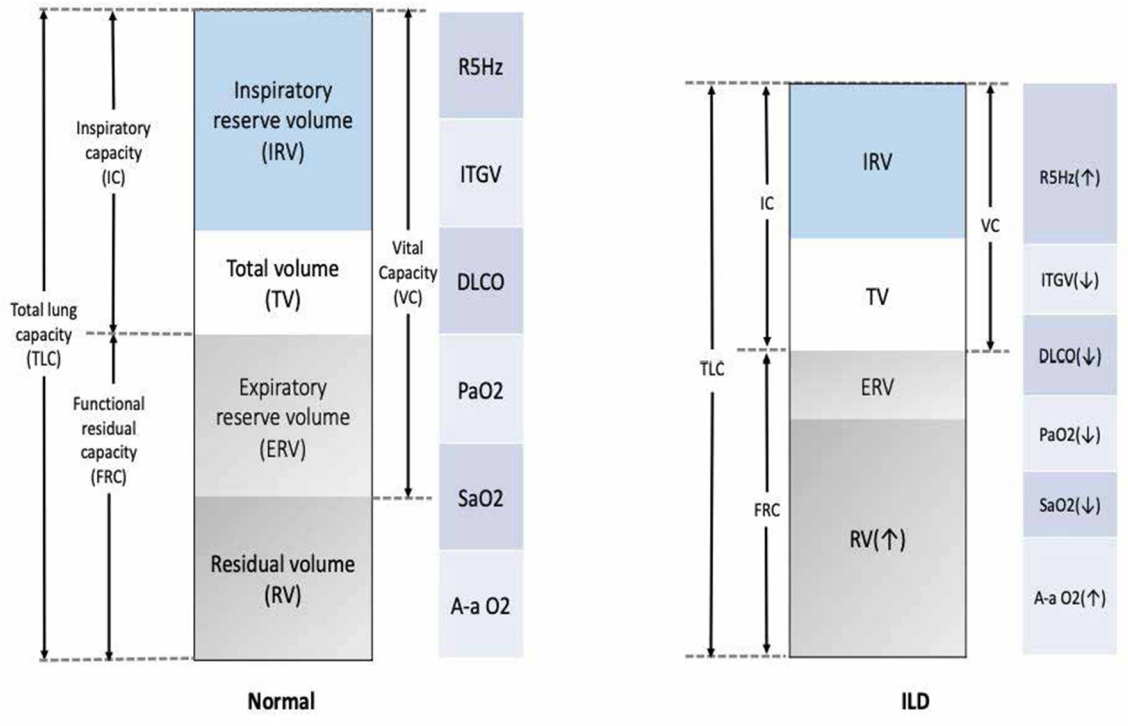

FIGURE 4
Common functional abnormalities in patients with ILD. VC, vital capacity; FRC, functional residual capacity; ITGV, intrathoracic gas volume; TLC, total lung capacity; R5Hz, resistance measured at 5 Hertz; DLCO, diffusion capacity; PaO_2, partial pressure for oxygen; SaO_2, arterial saturation of oxygen; A-a O_2 gradient, alveolar-arterial oxygen gradient; VO_2, oxygen uptake.

management of ILD includes pharmacological treatment approved by the FDA, such as nintedanib and pirfenidone, management drugs such as oral corticosteroids (including prednisone), and others, such as mycophenolate mofetil (CellCept®), azathioprine (Imuran®), and cyclophosphamide (Cytoxan®) (117, 118). Non-pharmacological management includes ceasing medications known to cause ILD; avoiding occupational and environmental exposure to toxins and antigens; having vaccinations (including annual influenza vaccination); quitting smoking; and receiving treatment with PR, supplemental oxygen, and lung transplantation (10).

Pharmacological management

ILDs are a complex group of diseases with diverse causes, meaning the most effective treatments will vary from patient to patient and depend on the specifics of their condition (119). For instance, sarcoidosis is managed primarily through immunosuppression (120, 121). Systemic sclerosis-associated (SSc) ILD is treated with mycophenolate mofetil, tocilizumab, and cyclophosphamide. In the case of ANCA-associated ILD, the main treatments are rituximab and cyclophosphamide. Lymphangioleiomyomatosis (LAM) is treated using an inhibitor of the mechanistic target of rapamycin mTOR inhibitor. Pulmonary alveolar proteinosis (PAP) is managed with whole lung lavage (WLL) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Finally, IPF is treated with antifibrotic medications (19).

Immune suppression therapies

Drugs that suppress the immune system employ a broad range of mechanisms to reduce the body's immune responses, critical for preventing organ rejection after transplantation or treating autoimmune conditions, such as lupus, psoriasis, and rheumatoid arthritis (117, 122). Widely used immunosuppressants include cyclosporine A, tacrolimus, glucocorticoids, methotrexate, and biological agents (e.g. rituximab). Unfortunately, these drugs can lead to an increased risk of infections and the development of malignancies (117).

Corticosteroids, such as prednisolone, are one of the most commonly used immunosuppressive therapies for ILD (123). They have broad anti-inflammatory and immunosuppressive effects. However, they are associated with significant side effects, such as weight gain, indigestion problems, restlessness, sweating, and mood changes (120). These side effects are particularly notable when the substances are used in high doses or for prolonged periods. Thus, corticosteroids often are employed in conjunction with other drugs to reduce the dose needed and mitigate side effects. Other immunosuppressants that have been used in the treatment of ILD include mycophenolate mofetil and azathioprine (124). These drugs are typically prescribed to organ transplant patients, but they have also shown some efficacy in treating ILD. Rituximab, a monoclonal antibody that depletes B cells, is another agent which

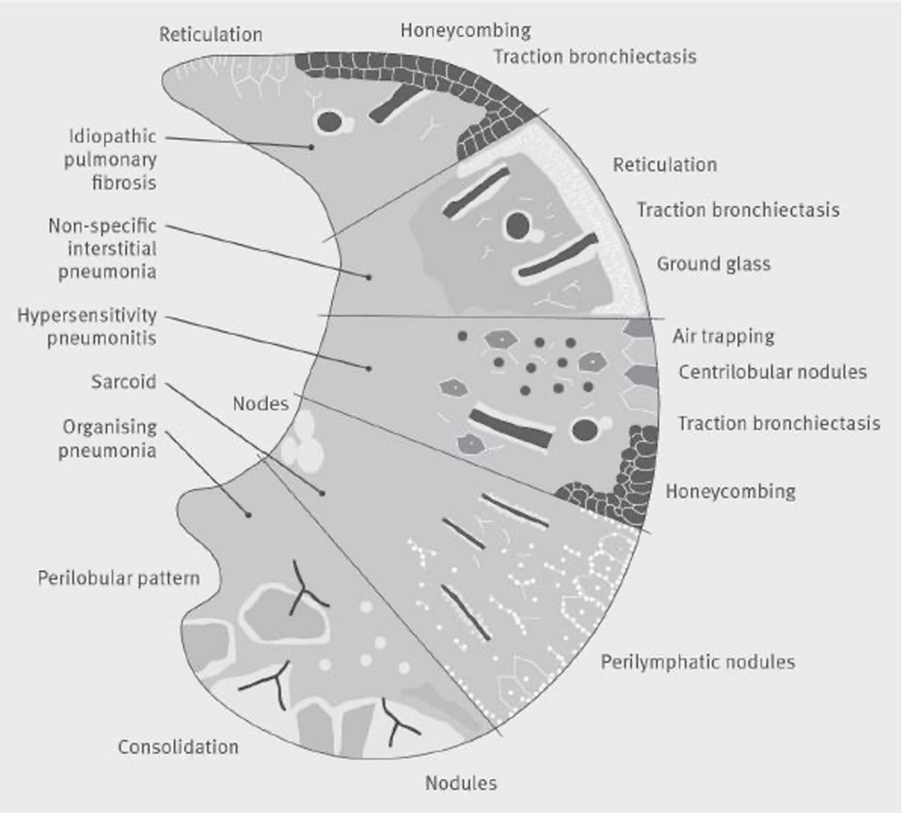

FIGURE 5
A visual representation of patterns of damage that could be seen on a CT scan in several common interstitial lung diseases. The lower section of the figure represents organizing pneumonia, where a CT may show consolidaiton, a perilobular pattern and nodules. The second section shows Sarcoidosis, where a CT often shows bilateral symmetrical hilar lymph nodal enlargment, fibrosis in the posterior segments of the upper lobes and perilymphatic nodules. The middle section represents hypersensitivity pneumonitis, where focal ground-glass opacity, air trapping, increased attenuation lung in the lung forming the three-density sign can be seen with or without reticulation, traction bronchiectasis and honeycomb cysts. The section second from top illustrates nonspecific interstitial pneumonia, whilst the top section shows a usual interstitial pneumonia pattern which if basal and lower zone predominant in the absence of an identifiable cause of disease could be diagnosed by a multidisciplinary team as idiopathic pulmonary fibrosis.

has been studied for use in ILD, especially in patients who fail to respond to traditional immunosuppressive therapies (117, 125).

Patients historically relied on either antifibrotic medication for IPF or immunosuppressive treatments for non-IPF ILD. Antifibrotic agents, including pirfenidone and nintedanib, have been approved for use in IPF, with nintedanib also approved for fibrotic ILDs with progressive phenotypes, such as progressive pulmonary fibrosis (PFF) (7, 8). Preclinical investigations suggest such antifibrotic drugs could be effective in managing pulmonary fibrosis resulting from a variety of causes. Moreover, they are reported to possess anti-inflammatory properties (7, 8).

Nintedanib is an intracellular tyrosine kinase inhibitor (TKI) demonstrated to have antifibrotic properties (7, 8). The SENSCIS trial (126) was the first phase III study to evaluate the efficacy and safety of nintedanib in patients with non-IPF ILD. Following the results of this trial, the FDA granted approval for nintedanib to be used for the treatment of systemic sclerosis (SSc) ILD (7, 126). The INBUILD trial (127) that led to the approval of this drugs for treatment of any progressive pulmonary fibrosis (PFF) documented an ~50% decrease in the rate of forced vital capacity (FVC) decline in the treated group relative to the placebo group. Such treatment can also potentially mitigate the risk of exacerbation and death. Finally, the INPULSIS-1 and INPULSIS-2 studies were 52-week, randomized, and double-blind phase 3 trials designed to examine the efficacy and safety of nintedanib in patients with IPF (7, 128). These trials found a significant FVC rate decline in those who received a placebo compared to those who received nintedanib.

Several studies of pirfenidone (17, 129–131) that included patients with a variety of ILD subtypes, who had not responded to traditional treatment, also showed encouraging safety profiles and the potential efficacy of this drug. Antifibrotic medications, such as nintedanib, have shown considerable potential in treating both IPF and non-IPF ILDs. Their safety profiles, along with the potential they show in slowing FVC decline and reducing other complications, make them an important area of study for further clinical trials.

Non-pharmacological management

A range of non-pharmacological methods can be employed to address various aspects of fibrotic ILD regardless of disease stage

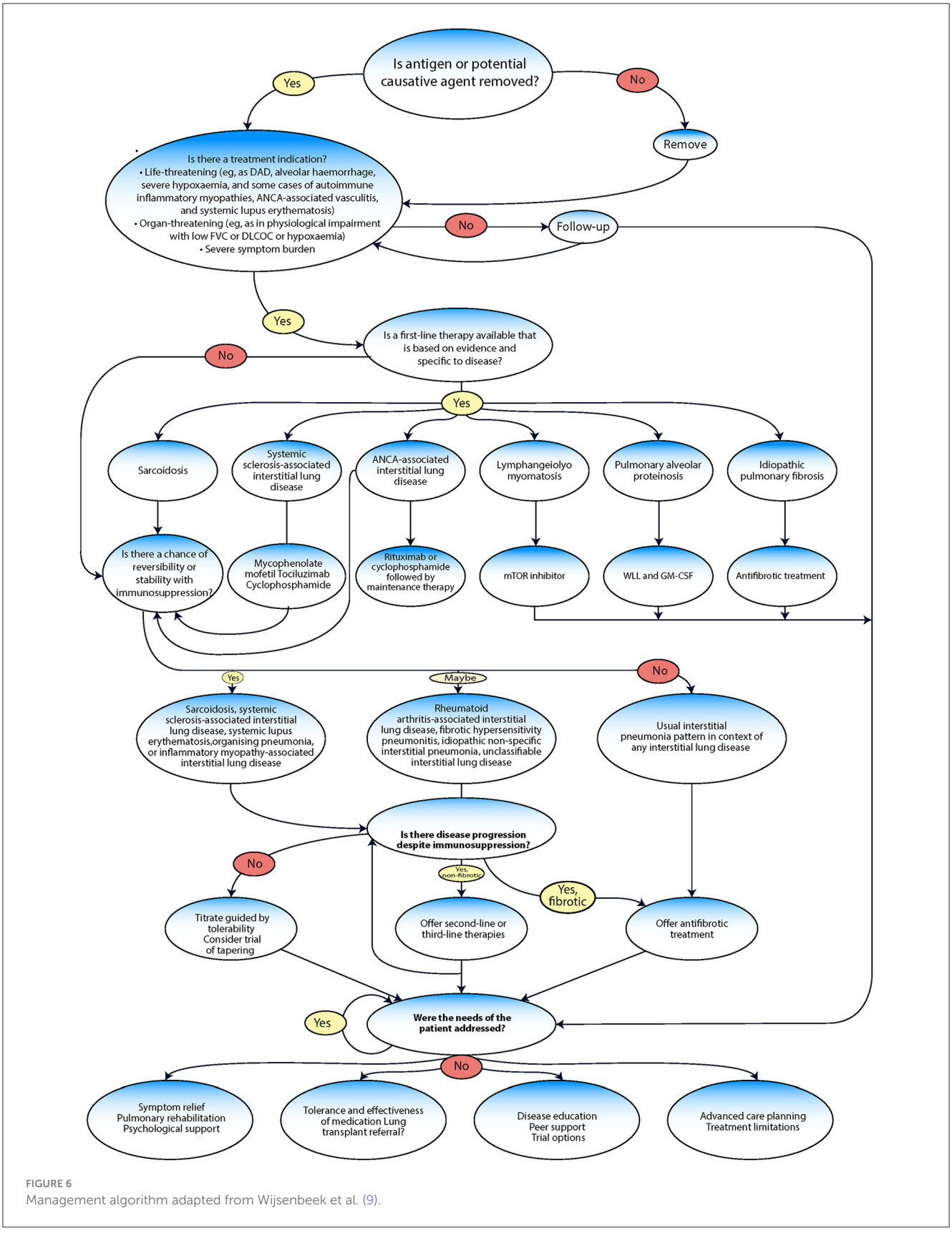

FIGURE 6
Management algorithm adapted from Wijsenbeek et al. (9).

or cause. Patients with ILD should receive regular influenza and pneumonia vaccines with their treatments as a preventive measure for seasonal infections (4). It is also important for patients to stop smoking, avoid harmful substances, protect themselves from harmful work conditions, and discontinue any drugs that might lead to ILD. Due to frequent physical deterioration in severe cases,

a pulmonary rehabilitation program designed for lung patients could potentially reduce their symptoms and improve their physical abilities (14, 132). Similarly, long-term oxygen therapy (133) can be helpful for some. Comorbid conditions and overall physical frailty can significantly decrease quality of life; however, addressing these through screenings and appropriate management can improve a patient's situation (133). Those with a severe form of ILD, known as PF ILD, may be eligible for a lung transplant. For severe ILD patients who cannot undergo transplantation due to age >65 years, class I obesity (BMI 30–34.9 kg/m^2), severe malnutrition, or other factors, managing symptoms and improving comfort should be the main goal (134, 135).

Symptom management

Patients with ILD have different symptoms prognoses. Some can live many years with a disease that responds well to treatment, but others, particularly those with progressive idiopathic fibrotic ILD (PIF-ILD), have a shorter life expectancy similar to that of lung cancer patients (136). Regardless of their specific condition, ILD patients usually have common symptoms that significantly affect their quality of life, including breathlessness, cough, heartburn, and depression (2, 118). These patients often also have sleep issues, feel fatigued, lose weight, and suffer from a loss of appetite. Managing these symptoms can be challenging due to the psychological stress of living with a chronic, life-limiting disease. Hence, a combined approach that includes patient education and self-management is crucial. Several drug and non-drug therapies are available to alleviate symptoms in patients with IPF. These include mild narcotics, respiratory rehabilitation exercises (e.g. pursed-lip breathing), and supplemental oxygen.

Pulmonary rehabilitation

Pulmonary rehabilitation (PR) is a comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities, as recently defined by the European Respiratory Society (ERS) and American Thoracic Society (ATS) (137). The first official definition of PR was published by ATS, which described it as the "an art of medical practice wherein an individually tailored, multidisciplinary program is formulated which through accurate diagnosis, therapy, emotional support and education, stabilizes or reverses both the physio-and psychopathology of pulmonary diseases and attempts to return the patient to the highest possible capacity allowed by his pulmonary handicap and overall life situation" (138). PR offers many benefits for patients with ILD, including improved physiological condition, symptom relief, better psychological health, and cost savings. Past studies have shown positive outcomes for those undergoing PR, such as an improvement in both the 6-min walking test (6 MW) distance, exercise capacity, and overall quality of life (137).

ILD patients may also benefit from supplemental oxygen therapy being a common treatment for ILD (139). It addresses low oxygen levels in the blood and can stop or slow down the development of problems such as high blood pressure in the lungs, heart-related issues, or cognitive dysfunction. How much and how often oxygen is prescribed can vary greatly among ILD patients. Nevertheless, being able to move around, work, exercise, and even travel while using oxygen can significantly improve a patient's life (140).

Lung transplantation

Lung transplantation remains the best option for patients with advanced IPF, with ~66% of transplant recipients living for more than 3 years after the surgery and 53% surviving for over 5 years (139). The criteria for lung transplantation in ILD patients encompass UIP or NSIP evidence, a 10% FVC or 15% DLCO decrease over 6 months, an oxygen saturation <88%, a 6-min walk of fewer than 250 m, a 50-m decrease in 6MWD within 6 months, or pulmonary hypertension. The evaluation and waiting period for lung transplantation can last for years, making it a challenging and difficult time for patients and their families (141). While post-transplantation survival rates in IPF patients are around 66% beyond 3 years and 53% beyond 5 years (142), lung transplantation can be a life-saving procedure that significantly improves life expectancy and enhances quality of life for some patients with IPF (135, 143). When lung transplantation is being considered, it is crucial to review the patient at a specialist center. Transplant medicine experts can thoroughly assess the patient's suitability for this major surgical procedure, help prepare the patient, and manage their post-transplant care. The shared care approach is continued in these cases to ensure the best possible patient outcome (100).

Palliative care

ILDs can greatly affect a patient's functional abilities, which can cause physical and psychological distress as the disease worsens (144). The WHO defines such care as "an approach that improves the quality of life of patients and their families through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" (145). Palliative care, which focuses on managing the discomfort, symptoms, and stress of severe illness, should be started as soon as ILD is diagnosed. The main objective of palliative care is to relieve suffering and help the patient and their caregivers live as well as possible. It should be provided in conjunction with other treatments and should involve both primary caregivers and specialist teams (146). Although palliative care is an essential part of a good healthcare approach for patients with organ failure, end-stage chronic illness, issues related to aging, cancer, and cardiovascular diseases, only 14% of patients receive it, according to the World Health Organization (WHO) (145).

Palliative care has been found, for example, to improve survival in patients with cancer (147). Although a poor understanding of palliative care services had previously been reported among clinicians (148), palliative care teams are now available with well-trained and specialized providers (149). Palliative care takes a holistic view of patient care, focusing on these key areas to provide comprehensive support, specifically, relieving discomfort and other challenging symptoms considering both the psychological and spiritual aspects of patient care, improving the overall quality of life and illness progression. Care can be implemented at any stage of illness, alongside other life-prolonging treatments, such as chemotherapy or radiation therapy, and includes necessary

diagnostic procedures to manage symptoms effectively. It offers support to help patients live as fully as possible until death, acknowledges death as a natural part of life; employs a team-based approach to meet the needs of both patients and their families, and includes grief counseling when necessary.

New guidelines (146) emphasize the importance of palliative care for patients with ILD. However, palliative care services are still limited and not well implemented. A recent systematic review reported that only about 38% of ILD patients were referred to palliative care. Barriers included fear of discussing the disease trajectory (150, 151) and limited awareness about the actual role of palliative care among patients (148, 152). Hospice care should be considered when a patient is not expected to live more than 6 months. Given the unpredictable nature of ILD, especially IPF.

Prognosis

The prognosis and severity of ILD depend on the type of ILD and factors such as comorbidities, rate of lung function decline, smoking status, age and the individual's overall health (153). The outcome and course of interstitial lung diseases, including recovery, potential complications, and duration, vary greatly among patients. The classification of the disease, severity, and demographic play a crucial role in predicting its future. It is also necessary to manage comorbid diseases, which can significantly affect survival rates in patients with ILD (154). For example, in patients with IPF, death for non-respiratory reasons was associated mainly with cancer, heart failure, stroke, and coronary artery disease. Recently, a systematic review with a meta-analysis examining the prognosis of IPF reported survival rates of 88% at 1–2 years and 31% at >5 years among patients diagnosed with IPF (155).

To better understand the outcome and course of ILDs, it is essential to assess key physiological parameters and functional indicators. For idiopathic lung disease patients, multiple factors have been shown to be indicators of a poor prognosis and negatively impact the quality of life. These include:

- A decrease in 6-min walk (6 MW) distance by more than 150 m within 4 year.
- A decline in forced vital capacity (FVC) by more than 10% within 6 months.
- A reduction in diffusing capacity for carbon monoxide (DLCO) by more than 15% within 6 months.

Progression

Understanding disease progression is crucial in progressive pulmonary fibrosis (PPF) and fibrosing ILD as it impacts patient management and treatment strategies (124). PFF refers to a specific form of ILD (5). It applies to a patient with an ILD of known or unknown etiology who exhibits radiological evidence of pulmonary fibrosis, but they do not meet the criteria for idiopathic pulmonary fibrosis (IPF) (5, 124).

Progressive fibrosing ILDs affect 2.2–20.0 out of every 100,000 people in Europe and 28.0 out of 100,000 in the USA (156). Furthermore, a range of 18%−32% of ILDs are estimated to develop into this progressive fibrosing state (116).

The definition of disease progression in patients with fibrosing ILD lacks uniformity (9, 13, 17, 124). Clinical trials have attempted to establish criteria for the identification of individuals whose non-idiopathic pulmonary fibrosis is progressing.

Clinical trials, such as the INBUILD trial, often provide more specific criteria for defining disease progression (127). The criteria used in the INBUILD trial include a relative decline in FVC of 10% or more, a relative decline in FVC of between 5 and 10% coupled with increased fibrosis on high-resolution computed tomography (HRCT), a relative decline in FVC of between 5% and <10% coupled with worsening respiratory symptoms or worsened respiratory symptoms and increased fibrosis on HRCT only. This and similar trials provide an empirical framework for assessing disease progression, which can influence both patient management and the development of new therapeutic strategies.

Another notable study is the ILD trial, which evaluates unclassifiable ILDs. This trial defines disease progression as an absolute decline in FVC of more than 5% or significant symptomatic worsening which is not as a result of cardiac, pulmonary (except worsening of underlying uILD), vascular or other causes. The uILD trial highlights the importance of distinguishing disease progression from other comorbid conditions or secondary complications, especially when the ILD is unclassifiable (157).

The RELIEF study offers another criterion for assessing progression in fibrosing ILDs. This trial uses a slope calculation based on at least three values, documenting an annualized decline in FVC of 5% (absolute) or more despite appropriate conventional therapy. This approach stresses the progressive nature of these diseases as it demonstrates how patients may still experience a significant deterioration of their lung function, notwithstanding optimal standard treatment (158).

Kreuter et al. described disease progression as a composite of at least a 10% decline in FVC, a 50-m decline in the 6-min walk distance (6MWD), or death (159). In addition, ILD progression has been defined as a decline in lung function, worsened respiratory symptoms, and unresponsiveness to anti-inflammatory or immunomodulatory treatments (24).

The outcomes of these trials have helped lead to the development of a universally accepted definition for PPF, which is outlined below. These parameters provide clinicians with a structured approach to identifying and managing disease progression in patients with fibrosing ILDs, despite the inherent challenges associated due to the diverse nature of these conditions (124). The criteria for identifying PPF requires at least two of the following three symptoms within the past year, given that no other explanation for these symptoms is found (5, 9):

1. Worsening respiratory symptoms: these could include increased shortness of breath, worsening cough, or other symptoms associated with deteriorating lung function.
2. Physiological evidence of disease progression can be determined by either of the following: (a) An absolute decline in forced vital capacity (FVC) >5% predicted within a year of follow-up. (b) An absolute decline in the diffusing capacity

of the lung for carbon monoxide (DLCO, corrected for hemoglobin) >10% predicted within a year of follow-up.

3. Radiological evidence of disease progression, as indicated by one or more of the following: (a) Increased extent or severity of traction bronchiectasis and bronchiectasis. (b) New ground-glass opacity with traction bronchiectasis. (c) Emergence of fine reticulation. (d) The increased extent or increased coarseness of reticular abnormality. (e) New or increased honeycombing. Increased lobar volume loss (5).

While these criteria offer a structured approach to defining disease progression in fibrosing ILDs, it is important to note that predicting the course of disease for an individual patient remains a significant challenge. Factors such as decline in FVC, lower DLCO, honeycombing on HRCT and scoring systems used can be indicative of disease progression in ILDs characterized by PPF (5). Despite current limitations, these evolving approaches represent significant progress toward personalized medicine in the management of PF-ILDs.

In summary, research has established a significant association between FVC decline in IPF patients and increased mortality rates, particularly in cases with an absolute FVC decline of 10%−15% (160). However, validated biomarkers for disease progression are still lacking (56), and the irregular measurement of Forced Vital Capacity (FVC) remains a common practice (161).

Acute exacerbation in ILD

Acute exacerbation in patients with ILD was first defined by Kondoh: "(1) exacerbation of dyspnea within a few weeks; (2) newly developing diffuse pulmonary infiltrates on chest x-ray films; (3) deterioration of hypoxemia (PaO_2/fractional concentration of oxygen in inspired gas FIO_2 <225); and (4) absence of apparent infectious agents" (162). Collard et al. (163) defined an exacerbation as "acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality, typically less than 1-mo's duration with the exclusion of alternative etiologies." It was also defined by Raghu et al. (5) as an acute clinically significant deterioration of respiratory symptoms without an identified cause sudden worsening of respiratory symptoms that lasts less than a month. Computed tomography scans typically show the presence of a new ground-glass opacity and/or consolidation and the absence of heart failure or fluid overload.

The National Institutes of Health-sponsored IPF Clinical Trials Network (IPFnet) proposed the diagnostic criteria of acute exacerbation and described the clinical, radiological and histopathological presentation of patients with IPF (163). The following criteria were proposed for diagnosing an acute exacerbation in IPF:

- A worsening of clinical symptoms lasting <30 days.
- The appearance of new bilateral ground-glass opacification and/or consolidation on high-resolution computed tomography (CT).
- Deterioration not fully explained by cardiac failure or fluid overload the absence of alternative etiologies, such as heart failure, or pulmonary embolism.

The incidence of acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) varies depending on the study cohort, with a range from 2% to 15% per year (164, 165). However, the prevalence of AEs is lower in non-IPF ILD (166), with an average of 2% per year. This difference in incidence is likely due to the different underlying pathologies of AE-IPF and non-IPF ILD. AE-IPF is characterized by progressive fibrosis of the lung tissue, while non-IPF ILD is characterized by a variety of other pathologies, such as inflammation, infection, and autoimmune disorders.

The diagnosis process for acute exacerbation in ILD commences with a thorough history and physical examination. If this initial step identifies an extra-pulmonary diagnosis, then it is not an acute exacerbation. Conversely, when no extra-pulmonary condition is detected, the timeframe of respiratory deterioration is assessed. If the worsening lasts beyond a month, it is not an acute exacerbation. However, if the respiratory decline has occurred within a month, the subsequent step is a CT scan of the chest. If this scan reveals alternative conditions such as pneumothorax, pleural effusion, or pulmonary embolism, the diagnosis would again rule out acute exacerbation. In the absence of these alternatives, the existence of new bilateral ground-glass opacities (GGO) or consolidation becomes the critical element. If such features are missing, acute exacerbation is ruled out. Should the CT scan indicate new bilateral GGO or consolidation, then possible causes such as cardiac failure or fluid overload are considered. If such conditions can account for the CT findings, it is not an acute exacerbation. However, if these findings remain unexplained, the diagnosis is an acute exacerbation of ILD. The final determination involves identifying possible triggers for the exacerbation, such as infection or post-procedural/operative complications. If a trigger is found, it qualifies as a triggered acute exacerbation, whereas the lack of a recognizable trigger would lead to a diagnosis of idiopathic acute exacerbation (163).

Acute exacerbation of interstitial lung disease (AE-ILD) can arise from various forms of ILD, but a higher risk is associated with usual interstitial pneumonia (UIP)-like lesions in chronic hypersensitivity pneumonitis (HP) and in patients with connective tissue disease-interstitial lung disease (CTD-ILD). Other risk factors include male gender, concurrent pulmonary hypertension, coronary artery disease, increased body mass index, and increased exposure to ozone and nitrogen dioxide. Inconsistencies exist regarding former smoking and age as risk factors. A retrospective study revealed that ∼22% of ILD and lung cancer patients undergoing chemotherapy experienced AE-ILD, suggesting certain chemotherapy agents as safer options. Surgical biopsy is another significant risk factor for AE-ILD, with incidence rates varying from <2.5% after ILD diagnosis biopsy to 3%−32% post-pulmonary resection for lung cancer. Lower FVC and diffusing capacity for carbon monoxide serve as additional risk factors for respiratory decline post-surgery. AE-ILD incidence has also been reported in non-pulmonary major surgeries, and a potential association between AE-ILD and bronchoalveolar lavage (BAL) is observed in IPF. Future research needs to explore the risk of AE-ILD post-cryobiopsy, given the currently limited data (159).

AE-ILD is a severe condition, leading to high mortality rates; between 35 and 46% of IPF-related deaths arise from AE-IPF. Mortality rates during the hospital stay for AE-IPF patients can exceed 50%, and the median survival period ranges from 1 to 4 months post-AE-IPF. One-month mortality varies from 37 to 53%, while 3-month mortality is between 63.8% and 73.7%. IPF patients have worse survival rates than other ILD sufferers, but AE-ILD is fatal across all ILD types. Prognostic factors include diminished baseline pulmonary function and oxygenation, advanced fibrosis or disease on HRCT, >15% lymphocytosis in BAL, and several blood markers.

Treatment of acute exacerbations of interstitial lung disease (AE-ILD) typically involves high-dose corticosteroids and antibiotics, but their efficacy is not supported by solid evidence. Guidelines recommend supportive care such a symptom palliation and oxygen supply and discourage mechanical ventilation due to the high mortality. Various treatment regimens, including steroid therapy with tacrolimus or cyclosporine, rituximab with plasma exchange and intravenous immunoglobulin, and intra-venous thrombomodulin, have shown potential benefits. Anti-acid therapy and antifibrotic drugs could potentially prevent AE-IPF, though further data is needed. A non-steroid approach with the best supportive care and broad-spectrum antibiotics shows varying survival outcomes, depending on previous treatments.

Obtaining bronchoalveolar lavage (BAL) biomarkers and conducting HRCT can prove to be a significant challenge. However, the advent of daily remote monitoring, especially home spirometry, offers a potential, non-invasive solution (167). These tools provide the means to safely identify patients who are at increased risk for developing AE-ILD, promote a deeper understanding of AE-PF clinical progression, and potentially enable early detection of AE-IPF. Given the supportive evidence that shows how home spirometry can enhance clinical trial outcomes for IPF therapeutics, we should direct our focus toward studies assessing the benefits of daily home spirometry for ILD patients (168). This focus leads us seamlessly into the broader application of remote monitoring. Using questionnaire responses to monitor symptoms like fatigue, cough, anxiety, depression, and quality of life, as well as tracking vital physiological parameters such as heart rate, oxygen saturation, respiratory rate, and FVC; we can gain a comprehensive view of a patient's state which sustains a practical approach to disease management.

Author contributions

MA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. A-MR: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JJ: Conceptualization, Project administration, Supervision, Validation, Visualization, Writing – review & editing. YR: Conceptualization, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AF: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JH: Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. JP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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Advancements in the study of acute lung injury resulting from intestinal ischemia/reperfusion

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Intestinal ischemia/reperfusion is a prevalent pathological process that can result in intestinal dysfunction, bacterial translocation, energy metabolism disturbances, and subsequent harm to distal tissues and organs via the circulatory system. Acute lung injury frequently arises as a complication of intestinal ischemia/reperfusion, exhibiting early onset and a grim prognosis. Without appropriate preventative measures and efficacious interventions, this condition may progress to acute respiratory distress syndrome and elevate mortality rates. Nonetheless, the precise mechanisms and efficacious treatments remain elusive. This paper synthesizes recent research models and pertinent injury evaluation criteria within the realm of acute lung injury induced by intestinal ischemia/reperfusion. The objective is to investigate the roles of pathophysiological mechanisms like oxidative stress, inflammatory response, apoptosis, ferroptosis, and pyroptosis; and to assess the strengths and limitations of current therapeutic approaches for acute lung injury stemming from intestinal ischemia/reperfusion. The goal is to elucidate potential targets for enhancing recovery rates, identify suitable treatment modalities, and offer insights for translating fundamental research into clinical applications.

KEYWORDS

intestinal ischemia/reperfusion, acute lung injury, animal models and evaluation indicators, pathophysiological mechanism, treatment strategy

1 Introduction

Intestinal ischemia/reperfusion (II/R) commonly occurs in the context of severe shock, infection, traumatic injury, mesenteric artery embolism, intestinal volvulus, intestinal obstruction, small bowel transplantation, liver transplantation, cardiopulmonary bypass surgery, and abdominal aortic aneurysm surgery. The associated morbidity and mortality remain significant (1). This is closely linked to the anatomical structure of the intestine and the body's prioritization of ensuring blood supply to vital organs such as the heart and brain during acute ischemic stress (2). Following the relief of the cause of intestinal ischemia through surgery or other means, although the intestinal tissue can restore blood perfusion, the body undergoes a series of pathophysiological changes during II/R. These changes include ischemic injury due to hypoxia and lack of essential energy substances, resulting in damage to the intestinal tissue and increased vascular permeability. Subsequent reperfusion injury leads to metabolic disorders, activation of inflammatory signaling pathways and oxidative stress pathways, intracellular

calcium overload, mitochondrial damage, and cell death (3). Oxygen and nitrogen free radicals, as well as inflammatory factors produced during II/R, are released into the blood, rapidly activating immune cells and triggering systemic inflammatory response syndrome (SIRS) (4). Additionally, the integrity of the intestinal mucosal barrier is compromised, allowing intestinal bacteria, endotoxin, and other substances to enter the circulatory system, causing distal tissue and organ damage, and potentially leading to multiple organ dysfunction syndrome (MODS) (5), posing a threat to patients' lives.

Among the various distal organs, the lung, being the sole recipient of all cardiac output, is highly sensitive to II/R and is particularly vulnerable. It exhibits early and severe characteristics of injury (6). Pathological manifestations of lung injury include alveolar epithelial and pulmonary capillary endothelial destruction, alveolar edema, neutrophil infiltration, and hyaline membrane formation (7), involving various interrelated pathophysiological mechanisms such as inflammatory response, oxidative stress, apoptosis, autophagy, and ferroptosis. Figure 1 summarizes the main processes and related mechanisms of acute lung injury induced by intestinal ischemia/reperfusion (Figure 1). Failure to adequately manage patients with acute lung injury caused by intestinal ischemia/reperfusion may lead to disease progression and subsequent development of acute respiratory distress syndrome (ARDS), characterized by a significantly high mortality rate of approximately 40% (8). However, the underlying mechanism of II/R-induced ALI (II/R-ALI) and effective methods to alleviate lung injury after II/R are not well-defined.

This article seeks to examine the animal models utilized in recent preclinical investigations of II/R-ALI, focusing on diagnostic criteria for acute lung injury, signal transduction pathways, injury-associated cytokines, treatment modalities, and existing challenges within this domain. The objective is to elucidate potential pathogenic mechanisms, identify relevant biomarkers, investigate novel targeted therapeutic approaches, and offer insights for both fundamental research and clinical translation.

2 Animal models and indicators for lung injury assessment

2.1 Animal models

Numerous studies on II/R-ALI lack standardized animal models and diagnostic criteria for lung injury. Researchers have employed various animal species to establish II/R models in order to fulfil the requirements for detecting corresponding indicators. For example, Li et al. (9) utilized C57BL/6J mice, Chen et al. (10) employed Sprague-Dawley rats, Bian et al. (11) utilized pigs, and Anderson et al. (12) utilized horses. Moreover, the timing of sample collection for intestinal tissue ischemia and reperfusion varies. The duration of intestinal ischemia induced by clamping the superior mesenteric artery ranged from 30 min to 2 h. The shortest duration for removing the artery clip to restore blood perfusion of the superior mesenteric artery was 60 min, while the longest was seven days.

2.2 Assessment of lung injury

In animal studies, the assessment of II/R-ALI primarily encompasses the following dimensions. Physiological impairment, such as reduced arterial partial pressure of oxygen (PaO_2) in blood gas analysis; diminished lung compliance: decreased static compliance of lung tissue, elevated airway resistance; heightened permeability of the alveolar capillary membrane: increased total protein concentration in alveolar lavage fluid, augmented extravasation of FITC fluorescent dye, elevated extravascular lung water content, and increased wet/dry weight ratio of lung tissue; escalated pathological damage score of lung tissue: accumulation of neutrophils in alveoli or pulmonary interstitium; formation of hyaline membrane, presence of protein fragments in the alveolar space, thickening of alveolar walls; inflammatory response in lung tissue: increased absolute number of neutrophils in bronchoalveolar lavage fluid, heightened activity of myeloperoxidase (MPO) in lung tissue, and increased concentrations of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-18) and chemokines (CXCL1, CXCL2, CXCL8) in lung tissue or bronchoalveolar lavage fluid (13); exacerbated oxidative stress: elevated concentrations of malondialdehyde (MDA) and reactive oxygen species (ROS) in lung tissue and blood, and decreased concentration of glutathione (GSH) and superoxide dismutase (SOD); apoptosis of lung tissue: increased number of TUNEL-positive cells in lung tissue, decreased ratio of Bcl-2/Bax, and increased expression of pro-apoptotic factors caspase-3, caspase-8, and caspase-9. Table 1 summarized recent animal models of II/R-induced lung injury and associated assessment indicators (Table 1).

3 The mechanism of intestinal ischemia/reperfusion-induced acute lung injury

3.1 Oxidative stress

Oxidative stress is a pathological process characterized by excessive production of oxidizing substances and an imbalance in the body's antioxidant defence system. This leads to the infiltration of inflammatory cells, increased secretion of proteases, and the generation of a large number of intermediate products, such as reactive oxygen species and active nitrogen, which the body is unable to neutralize. This process has detrimental effects on the body and is considered a crucial factor in ageing and disease (31). The classical mechanism of oxidative stress is crucial in II/R-ALI.

3.1.1 Production of reactive oxygen species

ROS, primarily produced by mitochondria, are the metabolites of oxygen molecules and the highly reactive chemicals derived from them. They are direct participants and important biomarkers of oxidative stress (32). Under normal physiological conditions, cells produce a small amount of ROS as part of physiological processes such as pathogen inactivation, wound healing, and tissue repair (33). During intestinal ischemia, tissue cell metabolism slows down or stops, leading to the inability of mitochondrial metabolism to recover coenzymes (NADH, H^+, and $FADH_2$). Upon reperfusion, the release of a large number of electrons from the coenzymes exceeds the transfer capacity of the respiratory chain, producing a large amount of ROS. Additionally, the change in respiratory chain compounds caused by ROS exacerbates mitochondrial dysfunction and disrupts mitochondrial ROS production. Furthermore, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase uses NADPH and H^+ as substrates to catalyze the reduction of O_2 to ROS (34). Calcium

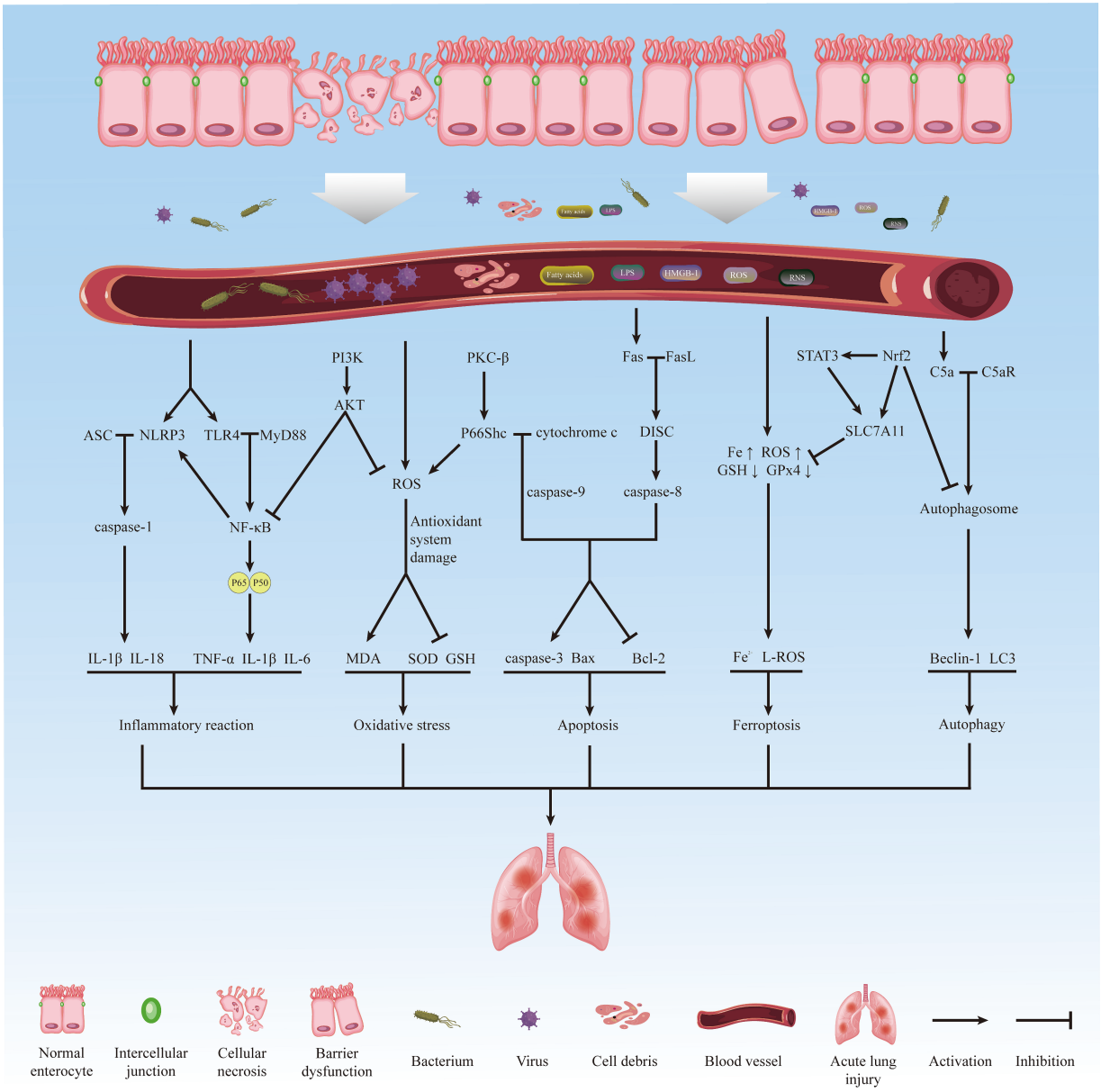

FIGURE 1
The main process and related mechanisms of acute lung injury induced by intestinal ischemia/reperfusion.

overload and reduced ATP synthesis lead to the activation of xanthine oxidase (XO) and the production of ROS. Nitric oxide synthase (NOS) exists as a homodimer under physiological conditions, while it exists as a monomer that contributes to the production of ROS during II/R, which is involved in producing ROS (35). A large amount of ROS produced by the body through the above pathways enters the blood circulation, accelerating ischemia/reperfusion injury. The excessive production of ROS overwhelms the body's processing capacity of antioxidant substances, such as SOD, glutathione peroxidase (GSH-Px), and catalase (CAT), triggering systemic oxidative stress and tissue damage (36).

3.1.2 Oxidative stress-induced lung injury

Studies have confirmed that oxidative stress can reduce the oligomerization of tight junctions (TJs) in the alveolar barrier, recruit neutrophils to cross the alveolar barrier, secrete cytotoxic substances, and increase pulmonary capillary permeability (37). Increased ROS production also leads to the decomposition of TJs in lung tissue, up-regulation of pro-inflammatory cytokines and chemokines, amplifying tissue damage and pulmonary edema, and accelerating the destruction of the alveolar barrier (38). In a model of II/R, the content of MDA in lung tissue increased. At the same time, the total antioxidant capacity (TAC) decreased, and the expression of inducible nitric oxide synthase (iNOS) and its product NOx in lung tissue increased by 5.5 times and 2.1 times, respectively. The total score of pathological injury of lung tissue was also increased significantly. This led to robust inflammatory reactions, alveolar edema, hemorrhage, and alveolar emphysema. However, treatment with the antioxidant cilostazol restored the balance between MDA and TAC, significantly alleviating lung injury. Furthermore, enhancing NADPH oxidase

TABLE 1 Animal models and lung injury assessment indicators for II/R-ALI.

Species	II/R model		Assessment of lung injury	References
	Ischemia time	Reperfusion time		
Mice	30 min	4 h	HE, MPO, MDA, FITC, occludin	(14)
	30 min	6 h	HE, water weight of lung, TNF-α, IL-6, IL-1β, MPO, IL-8, IL-18	(15)
	40 min	7 days	HE, BALF, TPC, TNF-α, IL-6, IL-1β, MPO, TUNEL	(16)
	45 min	2 h	HE, SOD, MPO, MDA, GSH, TNF-α, IL-1β, lung water, LDH, NLRP3, Bax, Bcl-2, caspase-3, CXCL-1	(17) (18)
	45 min	3 h	HE, TEM, water weight of lung, MDA	(19)
	45 min	2 h/24 h	MPO, EPO, iNOS, IL-6, IL-10, W/D, neutrophil and eosinophil number in lung tissue, SaO_2	(20)
	45 min	5 h	MDA, MPO, water weight of lung	(21)
	1 h	1 h	HE, BALF, TPC, water weight of lung, GSH, MDA, HMGB1, TNF-α, IL-6, PaO_2, HE, Masson, IL-1β	(7, 22)
	1 h	3 h	HE, MPO, caspase-3, TUNEL, TNF-α, IL-6	(23)
	1 h	4 h/20 h	HE, LDH, TUNEL, IL-6, MPO	(24)
	1 h	2 h/4 h/6 h/12 h	HE, NETs, HMGB1, CXCL1, CXCL2, TLR4, BALF, MPO	(6)
	90 min	30 min/1 h/90 min	HE, Masson, BALF, TPC, GSH, MDA, PaO_2, water weight of lung, TUNEL, TLR-4, TEM, TNF-α, IL-6, Bax, Blc-2	(9, 25)
Rats	30 min	1 h/4 h/24 h	HE, MPO, MCs, neutrophil	(26)
	30 min	2 h	HE, NF-κB, MDA, iNOS, NOx, p65, TNF-α, IL-6, MPO, ICAM-1, Bcl-2	(27)
	40 min	8 h/16 h/24 h	HE, TNF-α, IL-10	(28)
	45 min	2 h	Pulmonary artery reactivity, circulating leukocytes number, ROS, SOD, IL-6, NF-κB, eNOS, IL-1β	(29)
	1 h	2 h	Caspase-1, mTOR, p70S6K, p65, NLRP3, TLR4, W/D, MPO, MDA, SOD, TNF-α, IL-6	(10, 30)
Pig	2 h	4 h	HE, MDA, SOD, MPO, W/D, Cst, Raw, PaO_2, $D_{A\text{-}a}O_2$, PPI, BALF	(11)
Horse	2 h	2 h/6 h/12 h/18 h	HE, RR, total WBC count, total neutrophil count, IL-β, TNF-α, IL-10, TGF-β, caspase-3, caspase-8, caspase-9	(12)

HE, hematoxylin-eosin; MPO, myeloperoxidase; MDA, malondialdehyde; FITC, fluorescein isothiocyanate; BALF, bronchoalveolar lavage fluid; TPC, total protein concentration; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick-end Labeling; SOD, superoxide dismutase; GSH, glutathione; LDH, lactate dehydrogenase; TEM, transmission electron microscope; EPO, erythropoietin; NOS, nitric oxide synthase; W/D, wet/dry weight ratio; SaO_2, arterial oxygen saturation; PaO_2, arterial blood partial pressure of oxygen; NETs, neutrophil extracellular traps; MCs, mast cells; NO, nitrogen oxides; ROS, reactive oxygen species; Cst, static compliance; Raw, airway resistance; $D_{A\text{-}a}O_2$, alveolar-arterial oxygen pressure difference; PPI, pulmonary permeability index; RR, respiratory rate; WBC, white blood cell.

activity and mast cell activation were found to be related to II/R-ALI. Inhibition of mast cell degranulation can protect lung endothelial cells from oxidative stress and improve lung function (39).

3.1.3 Oxidative stress-related signaling pathways

Studies have indicated that the PI3K/Akt signaling pathway is closely associated with oxidative stress, and its activation can effectively inhibit oxidative stress-induced apoptosis (40). PTEN, a negative regulator of the PI3K/Akt pathway, is enhanced in ischemia/reperfusion injury, leading to reduced Nrf2 activity, oxidative stress, and impaired intestinal and lung functions (41). Research has shown that bone marrow mesenchymal stem cell derived-exosomes (BMSC-exos) significantly regulate the PTEN/AKT/Nrf2 signaling pathway, reducing apoptosis and oxidative stress and improving intestinal injury (42). Additionally, miR-144-3p, which can inhibit the synthesis of target gene proteins, was found to target PTEN expression. Regulating BMSC-exos on the PTEN/AKT/Nrf2 pathway and oxidative stress is achieved by regulating miR-144-3p, providing evidence for the potential application of BMSC-exos in the treatment of ischemia/reperfusion injury (43).

3.2 Inflammatory response

As a crucial digestive organ, the intestine harbors a diverse microbial flora. During II/R, the release of intestinal flora into the bloodstream triggers SIRS (44). The activation of the NF-κB signaling pathway, Toll-like receptor 4 (TLR4) signaling pathway, and NOD-like receptor protein 3 (NLRP3) inflammasome are identified as the primary cause of ALI in this context.

3.2.1 NF-κB signaling pathway

NF-κB is a rapid-acting nuclear transcription factor that governs essential cellular signal transduction pathways. Following I/R, the disruption of the intestinal mucosal barrier and compromised immune function led to the influx of bacteria, endotoxins,

inflammatory mediators, and oxidative stress-related factors into the circulation. These substances bind to cell surface receptors and activate the IκB kinase (IKK) complex through various adaptors and signal kinases. The activation of IKK complex phosphorylates IκBα, an inhibitor of NF-κB, resulting in the release and translocation of NF-κB dimer to the nucleus. This process regulates the transcription of target genes, leading to the production and release of inflammatory mediators (45). Previous research has demonstrated that the activation of the NF-κB signaling pathway significantly upregulates the expression of inflammatory cytokines such as IL-1, IL-6, and TNF-α in lung tissue. This activation also increases neutrophil infiltration in lung tissue. It reduces the expression of intercellular adhesion molecule-1 (ICAM-1), resulting in lung tissue congestion, edema, and widespread infiltration of inflammatory cells in the alveoli and interstitial lung tissue. Additionally, it damages the integrity of the alveolar barrier (46). TNF-α, in particular, not only directly causes lung tissue damage but also forms a positive feedback loop with NF-κB, inducing endothelial cells to produce IL-1β, IL-6, and other inflammatory factors, thereby triggering a cascade effect of inflammatory factors and exacerbating secondary lung injury (15). In animal experiments, overexpression of miR-146 reduced the secretion of pro-inflammatory cytokines by inhibiting the TNF receptor-associated factor 6 (TRAF6)/NFκB signaling pathway, inhibited the apoptotic response in the intestine and lung tissues of mice with II/R-ALI, and protected mice from II/R-ALI (47).

3.2.2 TLR4 signaling pathway

Toll-like receptors (TLRs) are a class of type I transmembrane protein receptors that identify pathogen-associated molecular patterns (PAMPs) on microorganisms and damage-associated molecular patterns (DAMPs) from host's damaged cells and are crucial for innate immunity (48). TLR4 is a pattern recognition receptor within the TLRs family, primarily recognizing exogenous ligands such as lipopolysaccharide, as well as specific endogenous ligands including free fatty acids, heat shock proteins, and high mobility group protein B1 (HMGB1). Upon ligand binding, the TLR4 receptor domain interacts with cytoplasmic adaptor proteins (MyD88, TIRAP/MAL, and TRIF) to activate various signal transduction pathways, including extracellular signal-regulated kinase (ERK), c-Jun NH2 terminal kinase (JNK), mitogen-activated protein kinase (MAPK), and nuclear factor kappa B (NF-κB) pathways, resulting in the production of pro-inflammatory cytokines and chemokines (49). During II/R, intestinal wall permeability decreases, leading to increased circulating blood lipopolysaccharide levels. This triggers the TLR4 signal transduction pathway, inducing a cascade reaction through the myeloid differentiation factor 88-dependent factor, resulting in excessive activation of the mononuclear macrophage system, immune response, cytokine storm, and ultimately ALI (50).

HMGB1, a primary DAMP released by necrotic intestinal cells following II/R, activates the TLR4/MyD88 signaling pathway, driving neutrophil recruitment to lung tissue. Activated neutrophils can release DNA and granular proteins, forming cytotoxic neutrophil extracellular traps (NETs), which damage the alveolar barrier and exacerbate lung tissue injury. Blocking HMGB1 reverses these effects, protecting lung tissue from inflammation (6). In a porcine II/R model, propofol pretreatment decreased inflammatory factor and oxidative stress-related substance levels in lung tissue, improved II/R-induced hypoxemia and acidemia, reduced airway resistance, and protected lung function by inhibiting the expression of the HMGB1/TLR4/PKR signaling pathway (11). In the oxygen and glucose deprivation/reoxygenation (OGD/R) model of mouse lung epithelial cells, silencing Nrf2 increased OGD/R-induced upregulation of TLR4 and MyD88, and exacerbated apoptosis and autophagy, revealing the role of the Nrf2/TLR4/MyD88 axis in inflammation-related lung injury (25). The TLR4/NF-κB signaling pathway is a classical mechanism triggering an inflammatory response in the ischemia/reperfusion model. Activation of TLR4 can promote NF-κB p65 activation, stimulate downstream inflammatory factor and chemokine production, and lead to ALI. BMSC-exos can inhibit TLR4/NF-κB signal transduction, control the inflammatory response, down-regulate the critical protease caspase-3 in the apoptotic cascade, reduce pulmonary microvascular epithelial cell apoptosis, and play a protective role in lung function (51).

3.2.3 NLRP3 inflammasome

NLRP3 is a receptor that contains NOD-, LRR-, and pyrin domain-containing 3. It has the ability to detect damage-associated molecular patterns (DAMPs) from pathogens and the host, thereby initiating the formation of NLRP3 inflammasome complex (52). As a major participant in II/R-ALI, NLRP3 becomes activated following II/R and aggregates with ASC (the adaptor protein in the NLRP3 inflammasome), which co-activate caspase-1 and promote the conversion of pro-IL-1β and pro-IL-18 into IL-1β and IL-18, causing acute inflammatory response and oxidative stress in lung tissue, leading to ALI (53). Furthermore, II/R stimulation can induce the production of intestinal lipid mediators, such as 12-HETE, 11-HETE, and 13-HODE, which have regulatory effects on both innate and adaptive immune responses. These mediators enhance the activation of NLRP3 inflammasome and the production of IL-1β in pulmonary vascular endothelial cells, contributing to ALI (54). It is now recognized that gut-derived lipid mediators hold the potential as regulators for treating and preventing II/R-related diseases. Over-activation of NLRP3 leads to the assembly of NLRP3 inflammasome complex and triggers pyroptosis through GSDMD-NT, resulting in plasma membrane rupture, production of inflammatory cytokines, and excessive release of LDH (55). Li et al. (17) observed increased expression levels of NLRP3 and NLRP3 inflammasome complex activation markers, such as caspase-1 and GSDMD, in *in vivo* mouse II/R models and cell experiments of OGD-R, along with elevated LDH activity.

3.3 Apoptosis

Apoptosis is a regulated cell death process characterized by cell shrinkage, plasma membrane protrusions, chromosome condensation, and nuclear fragmentation (56). Under normal physiological conditions, apoptosis occurs spontaneously in intestinal epithelial cells (IEC), maintaining the normal morphology and function of the intestine and ensuring intestinal homeostasis (57). However, under certain pathological conditions, apoptosis is the predominant outcome of inflammatory response and oxidative stress (58).

In the context of the II/R model, excessive apoptosis of IEC following ischemic stress leads to increased intestinal permeability,

secondary bacterial translocation, and apoptosis of distal lung tissue through a series of complex pathophysiological reactions. The acute inflammatory response in lung tissue induced by II/R triggers the binding of the death receptor Fas to its ligand FasL in lung epithelial cells (59). Additionally, the tumor necrosis factor receptor-1 (TNFR1) binds to its ligands TNF-α and TNF-related apoptosis-inducing ligand (TRAIL), initiating the mechanism of exogenous apoptosis. This leads to the recruitment of adaptor proteins, such as the Fas-associated death domain (FADD), to form a death-inducing signaling complex (DISC) that activates caspase-8 and its downstream apoptotic proteins. Simultaneously, cytochrome c is released into the cytoplasm, triggering the activation of caspase-9-dependent caspase-3 and initiating the downstream apoptotic cascade (60). Furthermore, the expression ratio of Bcl-2/Bax protein in lung tissue decreases (17), and the number of positive cells increases significantly, as indicated by TUNEL staining (16). Previous studies have demonstrated that in the II/R-ALI model, TNF-α and reactive oxygen species (ROS) can initiate endogenous or exogenous apoptotic pathways, increase the formation of caspase-3 and promote cell death (61).

As a member of the Shc A family, p66Shc is expressed in most cells except hematopoietic cell lines and plays a crucial role in apoptosis by inducing DNA fragmentation, cytoskeleton degradation, and the formation of apoptotic bodies (62). Studies have shown that after II/R, protein kinase C-β (PKC-β) is activated explicitly in lung tissue (63), leading to a significant up-regulation of p66Shc expression and increased sensitivity of lung tissue to oxidative stress (64). The phosphorylation and activation of Ser36 of p66Shc by PKC-β result in its translocation to mitochondria, leading to mitochondrial dysfunction and promoting apoptosis of lung tissue cells (65). The specific inhibitor of PKC-βII, LY333531, has been found to significantly inhibit the activation of p66Shc, mitochondrial translocation, and binding to cytochrome c, thereby reducing II/R-induced acute lung tissue injury, inflammatory cell infiltration, oxidative stress, and apoptosis (66). Additionally, Feng et al. (64) found that the upstream regulator of the p66Shc pathway, prolyl-isomerase Pin1, plays a similar role to PKC-β. II/R increased Pin1 protein expression and enzyme activity, promoting the translocation of p66Shc to mitochondria and accelerating apoptosis. Injection of the Pin1 inhibitor Juglone before II/R in rats effectively reduced secondary lung injury and improved the survival rate after II/R in rats. Functional analysis showed that p66Shc silencing significantly reduced OGD/R-induced human colonic adenocarcinoma cell line Caco-2 damage, increased cell viability, reduced mitochondrial superoxide levels, and reduced TUNEL-positive cells and caspase-3 activation.

3.4 Ferroptosis

The concept of ferroptosis was initially introduced by Dixon et al. (67) in 2012 as a novel form of regulated cell death distinct from traditional cell death programs. Ferroptosis is characterized as an iron-dependent and caspase-independent non-apoptotic cell demise. The underlying mechanism involves iron catalyzing the generation of lipid free radicals and glutathione deficiency or inactivation of the lipid repair enzyme GSH peroxidase 4 (GPx4) (68), leading to impairment of the intracellular antioxidant system. This is manifested by the accumulation of iron and lipid reactive oxygen species (L-ROS) in mitochondria, reduction or disappearance of mitochondrial cristae, increased mitochondrial membrane density, and rupture of the mitochondrial outer membrane, ultimately resulting in cellular dysfunction (69). Previous research has demonstrated that polyunsaturated fatty acids, oxygen, iron, and antioxidants are pivotal factors in inducing ferroptosis (70, 71). Current investigations have established a close association between ferroptosis and various human diseases, including cardiovascular and cerebrovascular diseases, tumors, respiratory diseases, and ischemia/reperfusion injury (72).

Scholars have identified ferroptosis as a critical factor in II/R-ALI, and the inhibition of ferroptosis has been shown to have a protective effect against II/R-induced organ damage (9). In the II/R-ALI model, the levels of endogenous iron, ferrous iron, ferritin, and MDA in lung tissue were significantly elevated, while the level of reduced glutathione was markedly reduced (73). Transmission electron microscopy results revealed characteristic structural changes of ferroptosis in the mitochondria of type II alveolar epithelial cells in II/R mice (74). Conversely, intervention with ferrostatin-1 in mice with II/R-ALI reduced lung tissue damage, improved lung epithelial cell viability, and restored epithelial barrier function (75). These findings indicate that ferroptosis is a crucial participant in II/R-ALI.

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a critical transcription factor that responds to intracellular oxidative stress and is closely associated with ferroptosis. It becomes activated in high oxidative stress conditions, leading to the transcription of target genes and binding to the antioxidant response element (ARE) in the nucleus. This activation promotes the translation of antioxidant and anti-inflammatory proteins (76), regulates the ferroptosis pathway by controlling glutathione, iron, and lipid metabolism, and influences mitochondrial function (77), ultimately playing a cytoprotective role. Studies have shown that Nrf2 activation in the nucleus can effectively prevent ALI (78). Additionally, the inhibitor of apoptosis-stimulating protein of p53 (iASPP) exerts p53-independent anti-ROS activity in the cytoplasm, promoting the accumulation and nuclear translocation of Nrf2, and increasing the expression of hypoxia-inducible factor-1α (Hif-1α). This process reduces the content of transferrin (TF) and ferritin-related proteins FTH1, NQO-1, and HO-1, thereby protecting cells from ferroptosis by regulating the Nrf2-dependent Nrf2/HIF-1/TF signaling pathway (9). Furthermore, Nrf2 silencing has been observed to exacerbate ferroptosis in lung epithelial cells and reduce the expression of telomerase reverse transcriptase (TERT) and SLC7A11. TERT has been reported to alleviate cell damage caused by ROS by going to mitochondria, while SLC7A11 is crucial in maintaining cell redox homeostasis (79, 80). The Nrf2/TERT/SLC7A11 axis has been shown to regulate ferroptosis, providing a potential new target for treating II/R-ALI (19). Additionally, signal transducer and activator of transcription 3 (STAT3) has been found to be involved in ferroptosis after II/R, being phosphorylated by Nrf2 to pSTAT3 and regulating SLC7A11 expression alongside Nrf2 (73). Further research is needed to explore the interaction between Nrf2 and STAT3 in ferroptosis. Activation of Nrf2 has also been shown to up-regulate the expression of heme oxygenase 1 (HO-1), another ROS detoxification enzyme (81). HO-1 content increases compensation with Nrf2 in II/R or OGD/R models, exerting an anti-iron ion effect (74). However, some studies have indicated that HO-1, in addition to acting as an antioxidant enzyme to prevent ferroptosis caused by oxidative stress after II/R, can induce ferroptosis under hypoxic conditions by releasing Fe^{2+} through its upstream regulator Hif-1α. Therefore,

further investigation is required to understand the dual role of HO-1 in II/R-induced ferroptosis in lung tissue cells (22).

3.5 Autophagy

Autophagy is a ubiquitous biological process found in eukaryotic cells. It involves the formation of autophagosomes, which are double-layered membranes that encapsulate cytoplasmic proteins or organelles. These autophagosomes are derived from the rough endoplasmic reticulum and subsequently fuse with lysosomes to form autolysosomes. Within these autolysosomes, the enclosed contents are degraded, contributing to the regulation of homeostasis and immune response (82). Autophagy is considered a highly conserved cellular self-protection mechanism in evolution and is also recognized as a mechanism of cell death juxtaposed with apoptosis and necrosis (83). Its involvement in physiological and pathological processes makes its role in various diseases intricate and contradictory. In the context of II/R, an inflammation-related illness, the relationship between autophagy and disease progression is closely intertwined (84). Researchers have proposed differing perspectives on the role of autophagy in this context.

3.5.1 Moderate autophagy

One potential mechanism is that following II/R, the body can effectively eliminate ectopic flora resulting from changes in intestinal mucosal permeability by activating autophagy. This process helps to maintain intestinal microecological balance, protect lung function, and regulate homeostasis (85, 86). For instance, using transmission electron microscopy, Yan et al. (25) observed a significant increase in the number of autophagosomes in lung tissue cells after II/R. Western blot results also confirmed the up-regulation of autophagosome markers LC3 and Beclin-1 in lung tissue. Further investigation into the mechanism revealed that Nrf2 could regulate the expression of p62, which is recruited into autophagosomes to participate in the degradation of target proteins through the autophagy-lysosomal pathway, thereby contributing to lung protection. Several studies have indicated that II/R can lead to autophagy dysfunction (87). Jiang et al. (88) also found autophagy dysfunction and abnormal activation of intestinal intraepithelial lymphocytes (IELs) in the II/R model. By promoting the expression of autophagy-related genes Beclin-1 and Atg16 and activating the NOD2/Beclin-1 pathway, the autophagy of IELs can be enhanced, the inflammatory response of intestinal mucosal epithelium can be reduced, and the energy balance and cell homeostasis of intestinal tissue during ischemia can be maintained, thereby improving ALI.

3.5.2 Excessive autophagy

Other researchers have suggested that abnormal and excessive autophagy of intestinal cells after intestinal ischemia can exacerbate intestinal mucosal barrier dysfunction and secondary lung injury (89). Previous studies have shown that II/R-ALI can generate significant complement C5a in lung tissue (90). Alveolar macrophages, as resident macrophages in lung tissue, exhibit up-regulated expression of their C5a receptor (C5aR) (91). Upon C5a binding to C5aR in alveolar macrophages, downstream signal transduction is initiated, promoting autophagy and activating macrophage autophagy. This eventually leads to apoptosis of alveolar macrophages and disrupts lung homeostasis. To investigate the specific mechanism, Hu et al. (92) established atg5-deficient mice (Mf-ATG5/mice) in macrophages to inhibit the occurrence of macrophage autophagy. The results showed that the production of inflammatory cytokines in bronchoalveolar lavage fluid (BALF) of Mf-ATG5/mice was significantly reduced, the expression of autophagosome-related proteins was decreased, and lung injury was alleviated. It was confirmed that C5a interacted with C5aR to induce autophagy and subsequent apoptosis of alveolar macrophages by promoting the degradation of Bcl-2 by Beclin-1, which aggravated ALI. Conversely, inhibition of autophagy can alleviate II/R-ALI.

Therefore, the role of autophagy in II/R-ALI remains controversial, and a critical threshold may exist between its protective and promoting effects, necessitating further research exploration.

3.6 Others

Other than the previously mentioned classic mechanisms of II/R-ALI, scholars have suggested that pyroptosis, formation of NETs, and alterations in intestinal flora and their metabolites may also play a role.

3.6.1 Pyroptosis

NLRP3-related pyroptosis has been shown to induce subsequent cell death by mediating the initial inflammatory response and plays an important role in various I/R injuries such as heart (93), liver (94), and kidney (95). Li et al. (17) found that in the intestine, like the above organs, when II/R leads to severe stress, NLRP3 inflammasome activates the caspase-1 pathway while causing an inflammatory response, promoting the maturation of IL-1β and GSDMD, and leads to pyroptosis of distal lung tissue cells. The same results were observed in the co-culture model of IEC-6 and MLE-12 cells induced by OGD/R. In the rat II/R model prepared by Yang et al. (96), immunofluorescence results showed that the expression level of pyroptosis marker GSDMD in lung tissue was significantly increased, and the application of inhibitors to block the formation of pyroptosis key factor NLRP3 complex can reverse the above phenomenon. It is suggested that pyroptosis is involved in the development of II/R-induced intestinal and distal lung injury, and inhibiting the occurrence of pyroptosis through appropriate pathways can effectively prevent organ damage.

3.6.2 Neutrophil extracellular traps

Studies have found that after intestinal ischemia, HMGB1 released by necrotic intestinal epithelial cells drives lung recruitment and excessive activation of neutrophils through the MyD88 signaling pathway to undergo morphological changes, nuclear membrane rupture, the release of DNA and granular proteins into the cytoplasm, and finally plasma membrane rupture, leading to the formation of extracellular NETs, thereby aggravating ALI. Lung cell death and new NETs formation exacerbated II/R-ALI (97). Zhan et al. (6) also confirmed that NETs degradation and HMGB1 pathway inhibition can be used as an effective targeted therapy strategy to reduce ALI caused by intestinal ischemia-reperfusion, and may be suitable for critically ill patients with acute intestinal ischemic diseases. However, some scholars have also proposed that appropriate NETs formation can prevent bacterial translocation caused by II/R, promote the repair of intestinal mucosal injury, and maintain the stability of intestinal epithelium (98). Therefore, like other immunomodulatory methods, it is particularly important to balance the advantages and disadvantages of NETs formation in some specific cases. Future

research should focus on the effects of NETs induction, inhibition, and degradation on pharmacological targets of diseases.

3.6.3 Intestinal flora and their metabolites

In recent years, the rapid development of microbial sequencing technology has provided a good platform for researchers to explore the mechanism of disease occurrence and development from a more microscopic perspective. Through sequencing technology, scholars have found that II/R inevitably causes changes in the intestinal microenvironment and habitat microorganisms. This ecological imbalance is characterized by the proliferation of Enterobacteriaceae bacteria and the reduction of beneficial symbiotic bacteria (such as Lactobacillus) (99). This gut microbiota pattern can amplify the damage to organs such as the intestine, kidney, and lungs caused by II/R (100, 101). Studies have shown that succinic acid produced by gut microbiota metabolism acts as an important mediator of the gut-lung axis during II/R. 16S rRNA sequencing showed that II/R could lead to the imbalance of bacteria producing succinic acid and bacteria consuming succinic acid in the intestine. The Simpson index and the ratio of Firmicutes/Bacteroidetes in the lung microbiota decreased significantly, resulting in the production and accumulation of succinic acid in the lung through the gut-lung axis, followed by SUCNR1-dependent macrophage polarization and promotion of alveolar epithelial cell apoptosis to aggravate lung injury. The laboratory test results of patients with cardiopulmonary bypass also confirmed the above phenomenon, indicating that succinic acid may become a new biomarker for II/R-ALI (102).

From this point of view, the mechanisms of II/R-ALI are complex and closely related, such as the interaction between inflammation, oxidative stress, and pyroptosis, the interaction between NETs formation and gut microbiota (103), which still need more research in the future to reveal.

4 Treatment approach

4.1 Pharmacological intervention

Numerous domestic and international researchers have conducted extensive investigations into drug therapies targeting the pathophysiological mechanisms of II/R-ALI, yielding significant advancements. In addition to the well-established anti-inflammatory, antioxidant, and anti-apoptotic medications, surprising findings have emerged regarding the protective effects of propofol (104), dexmedetomidine (105), and other anesthetic agents commonly utilized during surgical procedures. It is worth mentioning that a clinical case report published in 2023 mentioned that the use of propofol during intestinal transplantation in a 20-year-old male infant effectively reduced the secondary damage caused by II/R (106). These anesthetic drugs not only contribute to patient comfort but also demonstrate advantages in safeguarding perioperative organ function. However, more prospective and large-scale clinical trials in the future are still needed to provide strong evidence to support the reliability of laboratory-proven methods for the safe and effective clinical application of patients diseases.

With the increasing public attention to their health in recent years, people gradually realize the irreplaceable role of intestinal flora and its metabolites in the occurrence and development of diseases. Microbiota transplantation, oral probiotics and the use of gut microbiota-derived metabolites have been proven to be prospective methods for the prevention and treatment of II/R-ALI, which can be safely and effectively applied in clinical practice (107, 108).

Moreover, drug administration has evolved from traditional oral or intravenous routes to the utilization of extracellular vesicles, such as exosomes (109), to facilitate targeted drug delivery to specific sites for pharmacological effects. At present, the separation of intestinal-derived exosomes in mouse II/R models can be realized at the technical level, which will be very helpful for researchers to conduct follow-up clinical trials (110).

4.2 Surgical intervention

Operative treatments encompass ischemic preconditioning (IPC) and remote ischemic preconditioning (RIPC).

IPC involves subjecting organs or tissues to one or more transient ischemia/reperfusion cycles before prolonged ischemia and reperfusion (111). Wang et al. (112) confirmed that intestinal IPC enhances the tolerance of the intestine and distal organs to subsequent prolonged ischemia, significantly enhances the body's antioxidant capacity, suppresses the release of pro-inflammatory cytokines to mitigate SIRS, and reduces II/R-induced lung tissue apoptosis.

Remote ischemic preconditioning refers to the application of repeated transient non-lethal ischemia/reperfusion in organs or limbs to shield against subsequent distal organ ischemia/reperfusion injury. Hummitzsch et al. (113) demonstrated that subjecting Wistar rats to three bilateral hindlimb ischemic preconditioning sessions for 5 min each time significantly ameliorated local and distal intestinal damage caused by subsequent II/R. This may be due to the biologically active substances produced by the body after stimulation and released into the systemic circulation are transferred to the distal target organ or tissue for protection.

Although IPC has achieved good results in the prevention of II/R injury in animal experiments, it will bring side effects to patients in clinical practice. On the contrary, RIPC, an effective, simple and low-risk method, can be easily induced by transient blood flow obstruction using blood pressure cuffs (114), thereby enhancing its clinical translational potential. Other studies have corroborated that combined pretreatment with IPC and RIPC exerts a significantly more robust protective effect in the late stage of II/R (115). Future research can explore how to combine the two safely and effectively.

4.3 Stem cell therapy

Mesenchymal stem cells (MSCs) are pluripotent cells derived from the mesoderm, possessing self-renewal potential. As a prominent member of the stem cell family, MSCs find wide application in various clinical diseases (116). Research has demonstrated the protective effect of bone marrow-derived mesenchymal stem cells (BMSCs) on II/R-ALI (117). The mechanism primarily involves two categories: (1) exogenous MSCs migrate to locally damaged intestinal tissues and differentiate into IEC, thereby ensuring the integrity of the intestinal barrier, reducing bacterial translocation, and mitigating distal lung injury; (2) exogenous MSCs exert anti-inflammatory, anti-oxidative, anti-apoptotic effects, promote cell proliferation, and angiogenesis

through the release of cytokines. However, the protective effect of MSCs on II/R injury is limited to basic experiments such as cells and animals, and there is no relevant clinical study. Scholars are trying to make more MSCs reach the target tissue after intravenous injection to play a role and improve the efficiency of treatment. MSCs offer valuable insights for future research and clinical trials, representing a promising new treatment approach for II/R injury.

4.4 Traditional Chinese medicine therapy

With its extensive historical background, traditional Chinese medicine has witnessed significant growth in treatment approaches as an understanding of its theory has evolved. Currently, prominent traditional Chinese medicine treatments for II/R-induced systemic diseases include conventional Chinese medicine treatment and acupuncture treatment. The effectiveness of Artesunate (18), Corilagin (17, 118), and Nervilifordin F (30), active ingredients of *Artemisia annua*, ellagic tannin, and *Nervilia fordii*, has been confirmed in preclinical studies of II/R-related diseases. The potential mechanism aligns with the aspects mentioned above. Traditional Chinese medicine offers the advantages of multi-target, multi-channel, multi-level, and minimal adverse reactions, providing a crucial guarantee for its safe and practical application in clinical practice. Acupuncture is a traditional Chinese medicine therapy. However, acupoint electrical stimulation (119) is a novel treatment method combining modern electroacupuncture therapy with standard acupuncture, which has the advantages of being non-invasive, safe, and not limited by time and

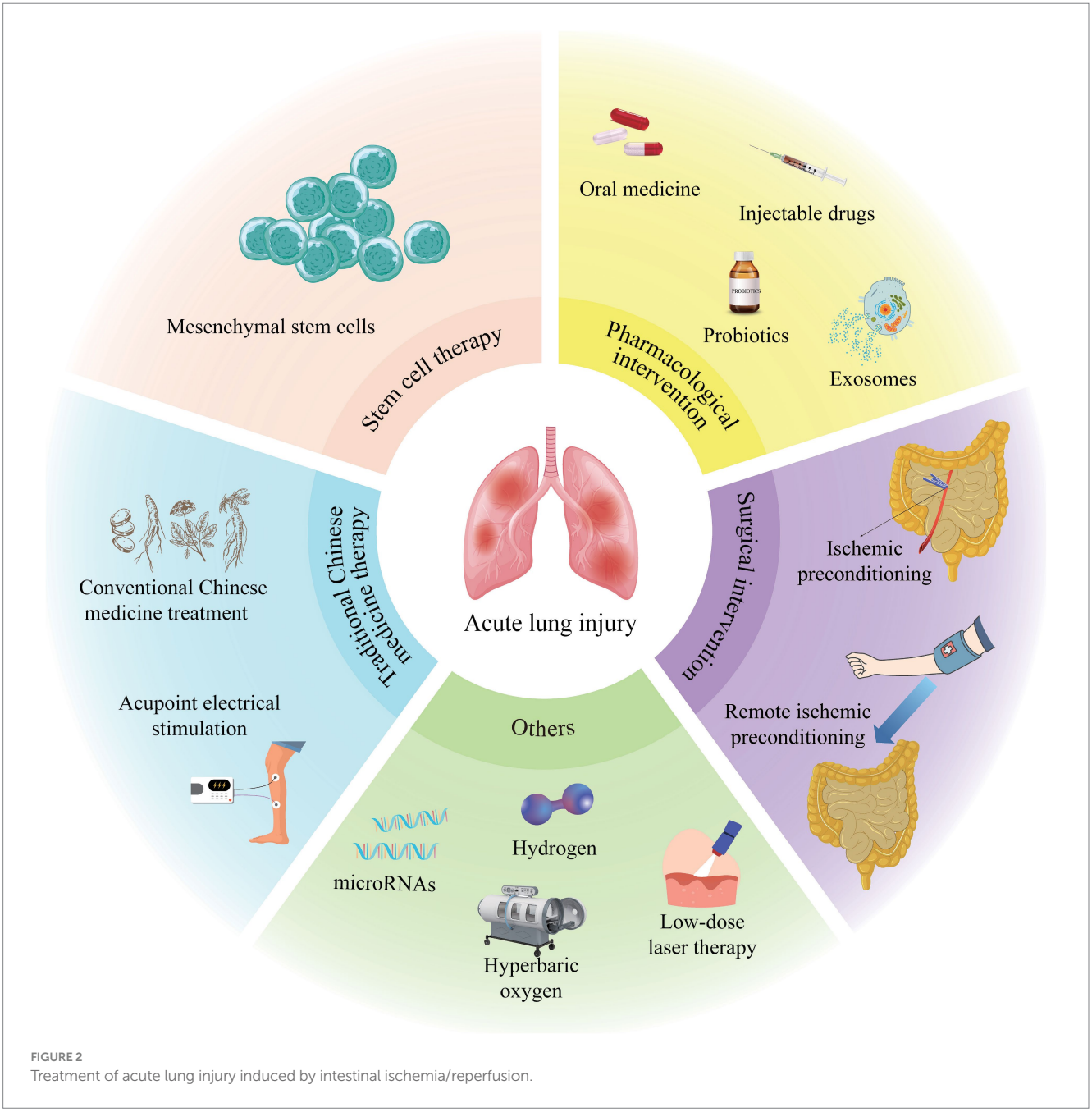

FIGURE 2
Treatment of acute lung injury induced by intestinal ischemia/reperfusion.

place. Acupoint electrical stimulation has been clinically utilized for many years to prevent and treat diseases caused by ischemia/reperfusion of various organs and gastrointestinal diseases (120), yielding satisfactory results. It achieves the effect of "Fuzheng Quxie" and balancing "Yin and Yang" by stimulating the conduction of meridians and collaterals of the whole body and adjusting "Gas-Blood and Zang-Fu." Geng et al. (121) confirmed that acupoint electrical stimulation therapy not only directly improves systemic inflammation caused by II/R but also indirectly promotes the differentiation of MSCs, playing a synergistic therapeutic role. Therefore, the combination of traditional Chinese and Western medicine holds broad application prospects, offering new hope for treating various II/R-induced diseases.

4.5 Others

In the process of exploring the treatment of II/R-ALI, scientists have also proposed that low-dose laser therapy (122), hyperbaric oxygen therapy (123), hydrogen inhalation therapy (124), and microRNA-targeted regulation strategies (125) have specific mitigating effects on II/R-ALI (Figure 2). However, the specific dosage, treatment time and appropriate administration method still need to be further studied, which will increase the challenge of clinical transformation of treatment methods.

5 Summarized and prospected

In recent years, domestic and international scholars have conducted extensive research and exploration into the pathogenesis and treatment of II/R-ALI animal models. They have elucidated the mechanisms of the inflammatory response, oxidative stress, apoptosis, ferroptosis, autophagy, and changes in the intestinal flora and their metabolites caused by II/R-ALI, leading to pathological changes in distal lung tissue. Significant progress has been made in strategies aimed at improving or treating ALI. However, current research on II/R-ALI faces several challenges that hinder the advancement of disease treatment. Firstly, most studies about II/R-ALI are still in the preclinical research stage, primarily involving animal models or cell experiments, and there is a need for more relevant clinical case studies. Secondly, the pathophysiological and molecular mechanisms of II/R-ALI are complex, interrelated, and mutually reinforcing, with diverse manifestations of damage, making it difficult to intervene accurately against a single mechanism or target. This significantly complicates the exploration of disease treatment methods. Finally, the timing of administration, dosage, adverse reactions, pharmacokinetics, and toxicological effects of existing therapeutic drugs still need to be determined. The treatment efficiency is low, as only a few MSCs reach the target tissue after intravenous injection. The use strategy of acupoint electrical stimulation therapy in treating cerebral ischemia/reperfusion and myocardial ischemia/reperfusion injury is relatively clear. Still, the exact mechanism of the therapeutic effect of II/R-ALI remains to be explored. Although many methods for the treatment of II/R-ALI have their advantages, they still have some limitations, which makes it impossible for scholars to reach a consensus on this, which will increase the challenge of clinical transformation of existing treatment methods. Therefore, actively seeking vital pathogenic mechanisms, proposing new research perspectives and treatment approaches, accelerating the development of clinical trials, and early intervention to halt the progress of II/R-ALI are expected to improve the cure rate of II/R-ALI.

Author contributions

SL: Writing – original draft, Methodology, Conceptualization. XZ: Writing – original draft, Visualization, Methodology. CM: Writing – original draft, Formal analysis. DZ: Writing – review & editing. TS: Writing – review & editing. WF: Writing – review & editing, Formal analysis. YW: Writing – review & editing. WL: Writing – review & editing, Supervision, Conceptualization.

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Conflict of interest

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Embolization coils in treating postoperative bronchopleural fistula: a systematic review

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Objective: This study aims to comprehensively evaluate embolization coils in treating postoperative bronchopleural fistula (BPF).

Methods: A systematic review based on PubMed, Embase, and The Cochrane Library studies was conducted. All cases receiving embolization coils in treating postoperative BPF were included. The primary outcome was the efficacy of embolization coils in achieving closure of postoperative BPF.

Results: 20 patients from 9 studies were included in this systematic review. A median number of 3 (range: 1–10) embolization coils with sealants obtained a complete closure rate of 80% in patients with postoperative BPF with sizes ranging from 2 to 3.1 mm. Three patients with BPF over 3 mm and one with multiple organ failure failed this treatment. Two cases of coil migration were reported without causing respiratory failure or fistula recurrence.

Conclusion: Embolization coils might be considered a safe and effective bronchoscopic treatment for small postoperative BPF of less than 3 mm in size. More extensive and rigorous studies are needed to further evaluate and confirm the optimal use of embolization coils in the context of an alternative to surgical repair.

KEYWORDS

bronchopleural fistula, embolization coil, bronchoscopic treatment, systematic review, interventional pulmonology

Introduction

Postoperative bronchopleural fistula (BPF) presents a significant challenge for both patients and physicians, with a prevalence ranging from 2.1 to 9.2% and a mortality rate between 16.4 and 71.2% (1). Postoperative BPF-related complications, such as infected pleural fluid regurgitation, severe pneumonia, and respiratory failure, contribute to the high mortality rate even after the standard surgical repair (1). Treating postoperative BPF remains a compelling challenge for thoracic surgeons and pulmonologists. Bronchoscopic treatments have emerged as complementary or adjuvant modalities in managing postoperative BPF (2). Sealants, embolization coils, and ventricular septal defect occluders have shown promise in cases where patients are unable or unwilling to undergo surgical repair, depending on the size and location of the BPF (3–5). Different embolization coils, originally designed for vessel occlusion, have demonstrated excellent efficacy with few complications in managing postoperative BPF since the 1990s (6). Typically made of platinum or other materials, these coils have proven to be cost-effective,

easy-to-perform, and minimally invasive bronchoscopic treatment options for small postoperative BPF (6–14). This study aims to evaluate the most recent clinical studies using embolization coils in treating postoperative BPF. These details can further contribute to our understanding of the efficacy and potential benefits of using embolization coils as a treatment option alternative to surgical repair for this challenging condition.

Methods

Literature search strategy

The search strategy to identify original studies on treating postoperative BPF with embolization coils was executed using the keywords "bronchopleural fistula" OR "air leak" OR "alveolar-pleural fistula" AND "coil" OR "coils." The search was conducted from July 1990 to December 2023 using PubMed, Embase, and The Cochrane Library databases. Additionally, bibliographies were manually searched for relevant articles.

The inclusion criteria were studies reporting the management of postpneumonectomy or postlobectomy BPF with embolization coils. The exclusion criteria were studies not referencing embolization coils in treating postoperative BPF, reviews, conference abstracts, studies lacking necessary information, and studies written in languages other than English.

Data extraction

Two independent reviewers (X.J.L. and K.Z.) utilized a standardized data abstraction form to collect detailed information on each patient's demographics, medical history, postoperative BPF features (location and size), embolization coil details (the brand, size, and number of coils inserted, the method of coil insertion, the sealants after coil insertion), and clinical outcomes in treating postoperative BPF with embolization coils. Treatment success refers to the complete closure of the postoperative BPF using embolization coils without any air leak via chest tube drainage. Treatment failure indicated partial or no closure of the BPF despite the use of embolization coils, even with additional coils, sealants, or both. Any disagreements between the two reviewers were resolved by consensus discussions.

Risk of bias in individual case reports

Some measures were implemented in this study to address potential biases inherent in individual case reports. The inclusion and exclusion criteria were clearly defined to reduce selection bias when including cases receiving embolization coils for the closure of postoperative BPF. The standardized data abstraction form was utilized by two independent reviewers to collect detailed information about each patient, minimizing bias and enhancing the reliability of data extraction. The disagreements in interpreting the data were resolved by consensus discussions, ensuring consistency and mitigating bias introduced by individual interpretations. The objective outcomes were evaluated by predetermined criteria, reducing subjective interpretation and potential bias in assessing the efficacy of the embolization coil.

Results

Study selection

The literature search strategy identified 97 studies, which were disregarded for the following reasons: duplicated cases ($n = 30$), records excluded by titles and abstracts ($n = 52$) studies not referencing postoperative BPF ($n = 3$), conference abstracts ($n = 1$), studies lacking necessary information ($n = 1$), and studies written in languages other than English ($n = 2$). Nine studies reporting the management of postoperative BPF with embolization coils were included in this systematic review (Figure 1) (6–14). Supplementary Table S1 contains all the data extracted from these studies, providing further insight into treating postoperative BPF with embolization coils.

Study characteristics

Table 1 summarizes the characteristics of the 20 patients for whom data were available from 9 studies. The median (range) age was 52 (33–80) years, and 64.3% of the population were male. The most prevalent cause for pneumonectomy or lobectomy was lung cancer (12/20, 60%), followed by tuberculosis-related lung diseases (3/20, 15%), other lung-related diseases (3/20, 15%) (such as sarcoidosis with massive hemoptysis, pulmonary sequestration, and breast cancer with lung metastasis), and cystic pulmonary hydatidosis (2/20, 10%). Postoperative BPF was found in the right upper lobe in 5 patients, the right lower lobe in 3 patients, the left upper lobe in 3 patients, the left lower lobe in 3 patients, the right main bronchus in 2 patients, the left main bronchus in 2 patients, and the bronchus intermedius in 2 patients, with a median size of 3.6 mm, ranging from 2 to 6 mm. In some cases, the initial attempts to close the postoperative BPF failed, including tube thoracostomy, surgical debridement, intercostal muscle flap, and other sealants such as fibrin glue and geofoam (Supplementary Table S1).

The median number of embolization coils inserted per patient was 3 (range: 1–10). There were four different types of commercially available embolization coils utilized in these studies: COOK Spring Medical Coils in 13 patients, Gianturco Stainless Steel Coils in 3, Boston Scientific Platinum Coils in 3, and TRUFILL Pushable Coils in 1. In the majority of these patients (13/20, 65%), embolization coils were inserted under bronchoscopic observation, followed by endoscopic and fluoroscopic surveillance (3/20, 15%), computer tomography guidance percutaneously (2/20, 10%), and fluoroscopic inspection (1/20, 5%). After the insertion of embolization coils, different sealants were used in all patients, including fibrin glue, N-butly-2-cyanoacrylate, lipiodol, and surgical cotton, either alone or in combination.

Efficacy and complications

The embolization coils with sealants achieved a complete closure rate of 80% (16/20) in patients with postoperative BPF, with sizes ranging

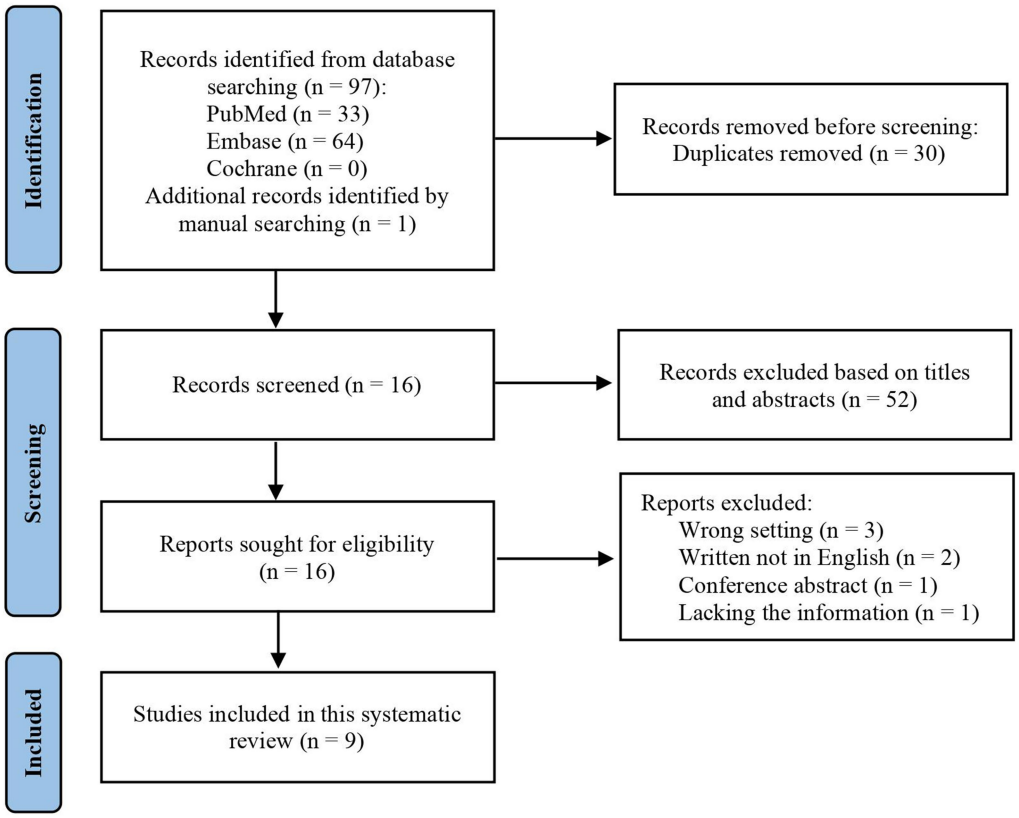

FIGURE 1
Literature flow diagram for embolization coils in treating postoperative bronchopleural fistula.

from 2 to 3.1 mm (Table 1). In two cases, the subsequent insertion of longer coils attained complete closure following the initial attempt with short coils. Four cases with postoperative BPF had immediate closure after the insertion of embolization coils (Supplementary Table S1). Most of the studies did not report the closure time after coil insertion. The embolization coils failed in three patients with BPF sizes over 3 mm and one with multiple organ failure after the insertion of eight Gianturco Stainless Steel Coils into several distal bronchi (Supplementary Table S1, details). During a median follow-up period of 12 months (range, 1–24 months), there was no fistula recurrence in patients who achieved complete closure with the insertion of embolization coils. During the follow-up, one coil was expectorated out of the mouth without causing hypoxia, and another was dislodged into the thoracic cavity without causing fistula recurrence. Three patients passed away after the insertion of embolization coils, but not due to the procedure.

Discussion

Postoperative BPF is a rare but severe consequence of pneumonectomy or lobectomy characterized by the formation of a pathological connection between the bronchial stump and pleural cavity, resulting in persistent air leakage, empyema, respiratory failure, and a high mortality rate (15). Surgical repair or additional resection should be recommended for BPF closure if patients are willing and able to endure the reoperation (16). However, surgical procedures for postoperative BPF closure were occasionally associated with a low success rate and a high overall mortality rate (17). Bronchoscopic intervention has evolved to diagnose and treat postoperative BPF with sealants, embolization coils, and ventricular septal defect occluders, depending on the size and location of the fistula (3–5). Embolization coils are initially used for permanent vessel occlusion without inducing ischemia in downstream vessels when deployed properly and precisely (18). They have been applied in limited cases for postoperative BPF closure since the 1990s (6). As far as we know, no previous systematic review has reported using embolization coils in treating postoperative BPF. This systematic review evaluated the most recent clinical studies on embolization coils in treating postoperative BPF. We observed that embolization coils with sealants achieved a complete closure in patients (16/20, 80%) with postoperative BPF ranging in size from 2 to 3.1 mm but failed in three patients with BPF sizes more than 3 mm and one with multiple organ failure. Embolization coils carry an overall success rate comparable to surgical procedures in treating postoperative BPF with a size less than 3 mm (19, 20).

The insertion of embolization coils in treating postoperative BPF is a safe procedure, according to the complications observed in the available literature. These complications included coil migration and expectoration without causing respiratory failure due to its modest size (7, 8). In this systematic review, no deaths were related to the insertion of embolization coils. The BPF size might be a major predictor of the prognosis and complications of bronchoscopic intervention with embolization coils in treating postoperative BPF (21, 22). Large postoperative BPF was associated with treatment failure with embolization coils and expectoration of fibrin glue (23). Unfortunately, many studies included did not report information on

TABLE 1 Characteristics of postoperative BPF receiving embolization coils in included cases.

	n/N	Percentage
Demographics		
Age (years), median (range)	52 (33–80)[a]	
Male sex	9/14[b]	64.3%
Female sex	5/14[b]	35.7%
Underlying diseases		
Lung cancer	12/20	60%
Tuberculosis	3/20	15%
Cystic pulmonary hydatidosis	2/20	10%
Others	3/20	15%
BPF location		
Right upper lobe	5/20	25%
Right lower lobe	3/20	15%
Left upper lobe	3/20	15%
Left lower lobe	3/20	15%
Right main bronchus	2/20	10%
Left main bronchus	2/20	10%
Bronchus intermedius	2/20	10%
BPF size (mm), median (range)	3.1 (2–6)[c]	
Numbers of coils used (per patient), median (range)	3 (1–10)[d]	
Coil brands		
Gianturco Stainless Steel Coils	3/20	15%
Boston Scientific Platinum Coils	3/20	15%
COOK Spring Embolization Coils	13/20	65%
TRUFILL Pushable Coils	1/20	5%
Coil insertion methods		
Endoscopic and fluoroscopic guidance	3/20	15%
Endoscopic guidance	14/20	70%
CT guidance (percutaneously)	2/30	10%
Fluoroscopic guidance	1/20	5%
Sealants		
Fibrin glue	11/20	55%
NBCA + Lipiodol	4/20	20%
NBCA	3/20	15%
Fibrin glue, NBCA + Lipiodol	1/20	5%
Surgical cottons soaked in fibrin glue	1/20	5%
Follow-up months, median (range)	12 (1–24)[e]	
Outcomes		
Complete closure with coils initially	16/20	80%
Expectoration or dislodge of coils	2/20	10%
Recurrence of BPF	0/16	0%
Death not related to coil insertion	3/20	15%

[a]Ages of 5 patients were not reported.
[b]Genders of 6 patients were not reported.
[c]BPF sizes of 13 patients were not reported.
[d]Coil numbers of 10 patients were not reported.
[e]Follow-up time of 5 patients were not reported. BPF: bronchopleural fistula; NBCA: N-butly-2-cyanoacrylate; CT: computer tomography.

BPF size. The thin-section computer tomography could determine the size of postoperative BPF (the narrowest part of the fistula tract), which could help in evaluating treatment strategies and the diameter of the medical device used to close the fistula (24). The diameter of the initial embolization coil inserted should be 10–20% larger, or at least 2 mm oversized, than the fistula tract being occluded to increase the success rate and decrease the migration rate.

In the studies included in this systematic review, four different commercially available brands of pushable embolization coils were employed, with COOK Spring Medical Coils being the most prevalent. The pushable Nester® Embolization Coils (Cook Medical) are made of platinum with spaced synthetic fibers, which can be delivered safely and effectively to the target location through the standard angiographic catheter with a flexible guide wire (25). Once delivered, it will form a tight occluding mass that anchors into the target location and occludes the vessel or fistula tract. Since the 1990s, embolization coils have been applied to treat postoperative BPF (6). The embolization coils generate a core for the occlusion of liquid sealants, thereby reducing the risk of cured sealant migration and fistula recurrence (6, 8, 12). As reported in porcine arteries, the synthetic fibers may cause local inflammation and promote the development of granulation tissue, thoroughly blocking postoperative BPF and probably reducing the number of coils required (26). The detachable coil was also used to successfully treat pneumonia-induced BPF in a two-year-old child (27). In managing postoperative BPF, the pushable Nester® Embolization Coils are more cost-effective than the detachable coils because they are significantly less expensive (28).

The literature described four monitoring strategies for the insertion of embolization coils into a fistula: fluoroscopic inspection, endoscopic and fluoroscopic surveillance, computer tomography guidance percutaneously, and bronchoscopic observation (the most prevalent) (6–14). The precise occlusion of the fistula in the distal bronchial stump was made possible by the angiography catheter-guided or directed insertion of embolization coils under bronchoscopic observation and/or fluoroscopic inspection (6–10, 12–14). With the computer tomography-guided transthoracic needle, embolization coils could be inserted transversally into the fistula tract, and cyanoacrylate glue could be injected into and adjacent to the fistula (11). Although there is no risk of pneumothorax with the percutaneous insertion of embolization coils under computer tomography guidance in patients with postoperative BPF, there is still a risk of hemorrhage. We prefer not to insert the embolization coils percutaneously under computer tomography guidance for postoperative BPF in patients tolerating bronchoscopy.

Several limitations in this systematic review must be acknowledged. The interpretation of the present findings was predominantly constrained by the small sample size and the heterogeneity of the case reports, which makes it difficult to reach a definitive conclusion. Studies demonstrating positive outcomes are more likely to be published, which could lead to an overestimation of the efficacy of embolization coils in treating postoperative BPF. The evidence-based data on how to treat postoperative BPF is still limited, consisting mainly of case reports and case series. Well-designed prospective studies, randomized controlled trials, or cohort studies with larger sample sizes and standardized methodologies are needed to evaluate the efficacy of embolization coils in treating postoperative BPF, especially with long-term follow-up data.

Conclusion

In conclusion, with a high success rate and low complication rate, embolization coils might offer a minimally invasive, cost-effective, and relatively easy-to-perform alternative to surgical repair for small postoperative BPF (less than 3 mm in size). Not all patients with postoperative BPF are appropriate candidates for coil embolization. The decision to apply this technique should be made on a case-by-case basis, considering factors such as the size and location of the fistula and the patient's overall health status. Further studies are needed to evaluate their long-term efficacy and safety.

Data availability statement

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

Author contributions

XL: Data curation, Investigation, Writing – original draft. KZ: Data curation, Investigation, Writing – original draft. YB: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

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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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1364994/full#supplementary-material

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Granulomatosis with polyangiitis: clinical characteristics and updates in diagnosis

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Granulomatosis with polyangiitis (GPA) is a rare systemic disease characterized by granulomatous inflammation of the respiratory tract and necrotizing vasculitis of small and medium vessels often associated with the production of anti-neutrophil cytoplasmic antibodies (ANCA) directed mainly against leukocyte proteinase 3 (PR3). Usually, it involves upper airways, lungs, and kidneys, however any organ may be affected. The diagnosis is based on clinical, radiological, and serological findings. Biopsies, although strongly recommended, are not always feasible and often provides non-specific features. ANCA plays a crucial role in the diagnosis of GPA; nevertheless, ANCA detection is not a substitute for biopsy, which plays an important role in suspected cases, particularly when histological confirmation cannot be obtained. Significant advances have been made in classification criteria and phenotyping of the disease, particularly in determining the nuances between PR3-ANCA and myeloperoxidase (MPO)-ANCA vasculitis. This has led to better characterization of patients and the development of targeted treatment in the future. In addition, better identification of cytokine and immunological profiles may result in immuno-phenotyping becoming a new approach to identify patients with ANCA-associated vasculitis (AAV). Due to the chronic relapsing–remitting nature, strict follow-up of GPA is necessary to provide appropriate management. The search for the accurate marker of disease activity and to predict relapse is still ongoing and no predictor has been found to reliably guide therapeutic decision-making.

KEYWORDS

anti-neutrophil cytoplasmic antibodies, vasculitis, granulomatosis with polyangiitis, inflammation, diagnostic techniques, leukocyte proteinase 3, myeloperoxidase

1 Introduction

Granulomatosis with polyangiitis (GPA; formerly known as Wegener's granulomatosis) is a rare necrotizing vasculitis combining inflammation of the vascular wall and peri- and extravascular granulomatosis (1). According to current nomenclature classification it belongs to the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) group, alongside microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (2). Each of these conditions is associated with a circulating ANCA targeted mainly against leukocyte proteinase 3 (PR3), and myeloperoxidase (MPO). Patients with GPA tend to be PR3-ANCA positive, while those with MPA and EGPA are predominantly MPO-ANCA positive (3).

AAV is a group of rare diseases with an estimated prevalence of 200–400 cases per million people. Although there was an increase in incidence over time, this is likely due to increased

awareness of the diagnosis and yield in ANCA testing methodologies (4). In the recent study from Sweden the incidence of AAV was stable over the course of 23 years (15.4/million), while the prevalence markedly increased due to improved management and survival (5). Among all three types of AAV, GPA is the most common with an average annual incidence/million adults from 7.7 to 15.4 in European countries (5, 6). The peak age at diagnosis varies, depending on the study population, such as 45–55 years (in an Italian cohort) (7) and 65–74 years (in the UK) (8). However, a shift in the peak age at onset toward the higher age range between the groups has been observed, during the last two-three decades (5). AAV may also occur in pediatric populations but epidemiological data are scarce and poorly characterized. Childhood primary vasculitis is diagnosed in 3% of all children referred to pediatric rheumatology departments, while the incidence of GPA ranges from 0.88 to 1.8 per million individuals (9).

GPA typically involves the upper respiratory tract, lungs, and kidneys (acronym ELK); however, any organ can be involved. The spectrum and severity of the disease are heterogeneous, ranging from indolent disease involving only one site to fulminant, multiorgan vasculitis leading to death (10). The variety and non-specificity of symptoms often contribute to diagnostic delays. In a report of 912 patients with GPA, the time from initial symptoms to diagnosis varied greatly, from one month to over three years, with 36% of all symptoms reported more than one year prior to diagnosis (11).

To date, diagnostic criteria are established neither for GPA nor for special diagnostic tests. Therefore, diagnosis is mostly based on clinical features, in combination with laboratory and imaging findings; it may be supported by the presence of ANCA and histological examination. Nonetheless, in recent decades, notable progress has been made in understanding the disease and development of diagnostic techniques, particularly imaging modalities, thus contributing to early diagnosis and early implementation of appropriate treatment to avoid essential organ damage. In the present study, we review the clinical features of GPA (focusing on pulmonary symptoms) and updates in diagnosis, considering disease assessment and monitoring.

Abbreviations: AAV, Anti-neutrophil cytoplasmic antibody-associated vasculitis; AIDS, Acquired immune deficiency syndrome; ANA, Anti-nuclear antibodies; ANCA, Anti-neutrophil cytoplasmic antibody; Anti-GBM, Anti-glomerular basement membrane antibodies; APS, Antiphospholipid syndrome; BAFF, B-cell activating factor; BALF, Bronchoalveolar lavage fluid; BALT, Bronchus-associated lymphoid tissue; BNP, Brain natriuretic peptide; CD, Crohn's disease; CHCC, Chapel Hill Consensus Conference on the Nomenclature of Systemic Vacsulitides; CNS, Central nervous system; COP, Cryptogenic organizing pneumonia; Cr, Creatinine; CT, Computed tomography; CTD, Connective tissue disease; DAH, Diffuse alveolar hemorrhage; DM, Diabetes mellitus; ECHO, Echocardiography; EGPA, Eosinophilic granulomatosis with polyangiitis; EMA, European Medicines Agency; ENT, Ear, nose, throat; FDG-PET/CT, F-18 fluorodeoxyglucose - positron emission tomography; FOB, Fiberoptic flexible bronchoscopy; GPA, Granulomatosis with polyangiitis; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HP, Hypersensitive pneumonia; IFN, Interferon; IL, Interleukin; IPF, Idiopathic pulmonary fibrosis; LVEF, Left ventricular ejection fraction; MCTD, Mixed connective tissue disease; MPA, Microscopic polyangiitis; MPO, Myeloperoxidase; MR, Magnetic resonance; NETs/osis, Neutrophil extracellular traps/formation; NSIP, Non-specific interstitial pneumonia; OP, Organizing pneumonia; PBC, Primary biliary cholangitis; PFTs, Pulmonary function tests; PR3, Proteinase 3; PSC, Primary sclerosing cholangitis; PTX3, Pentraxin 3; RA, Rheumatoid arthritis; ROS, Reactive oxygen species; SGS, Subglottic stenosis; SLE, Systemic lupus erythematosus; TB, Tuberculosis; AIH, autoimmune hepatitis; TEE, Transesophageal echocardiography; TGFβ, Transforming growth factor β; TNFα, Tumor necrosis factor α; UC, Ulcerative colitis; UIP, Usual interstitial pneumonia; USG, Ultrasonography.

2 Pathogenesis

The pathogenesis of GPA is complex and multifactorial, with ANCA, neutrophils, B and T lymphocytes, monocytes, endothelial cells, and the alternative complement pathway playing important roles (12, 13). The pathogenic hallmark is the loss of immunological T and B cell tolerance to neutrophilic proteins, namely PR3 or MPO (12). This process occurs alongside risk factors such as genetic background, age, environmental factors, and inflammation and/or infection (Figure 1) (14, 15). Interestingly, there are reports that GPA may arise from a similar genetic predisposition as rheumatoid arthritis (RA) (16). Therefore, a rare case of two family members with GPA highlights the potential genetic underpinnings of this disease (17).

3 Clinical features

The classic form of GPA involves upper airway (ear, nose, throat; ENT), lung, and kidney involvement; however, any organ can be affected. Constitutional symptoms, such as myalgias, loss of appetite, weight loss, fatigue, fever, night sweats, and migratory arthropathy, appear in 50% of patients and may precede weeks to months prior to the onset of clinically apparent organ-involvement (18). However, in about one third of patients, GPA begins with granulomatous inflammation of the upper respiratory tract, without general symptoms, and the presence of ANCA is detected only in a part of such patients. This phase may last for variable times and the disease at this stage is hard to recognize (19). More often, GPA is a rapidly progressive disease from the onset, with systemic presentation; however, the findings that should raise suspicion for this vasculitis include involvement of multiple organs.

3.1 Pulmonary involvement

The incidence of pulmonary involvement in GPA varies between 62 and 90%, depending on the study (20–22). The clinical symptoms are heterogeneous, ranging from asymptomatic cases through non-specific signs as cough, dyspnea, or hemoptysis, to acute respiratory failure requiring ventilatory support. In GPA, three main presentations of lung involvement can be distinguished: necrotizing granulomatous inflammation (NGI), tracheobronchial inflammation, and pulmonary capillaritis manifesting as DAH. The next rare presentation is interstitial lung disease (ILD) which occurs more frequently in MPA (23).

3.1.1 NGI

The NGI is the hallmark feature defining GPA, and the main feature distinguishing GPA from MPA (2). This inflammation in the lungs manifests as nodules (single or multiple) or mass lesions being the most common lung manifestation of GPA (40–70%) (24). In 20–50% of patients, cavities are observed (25), which develop when the central

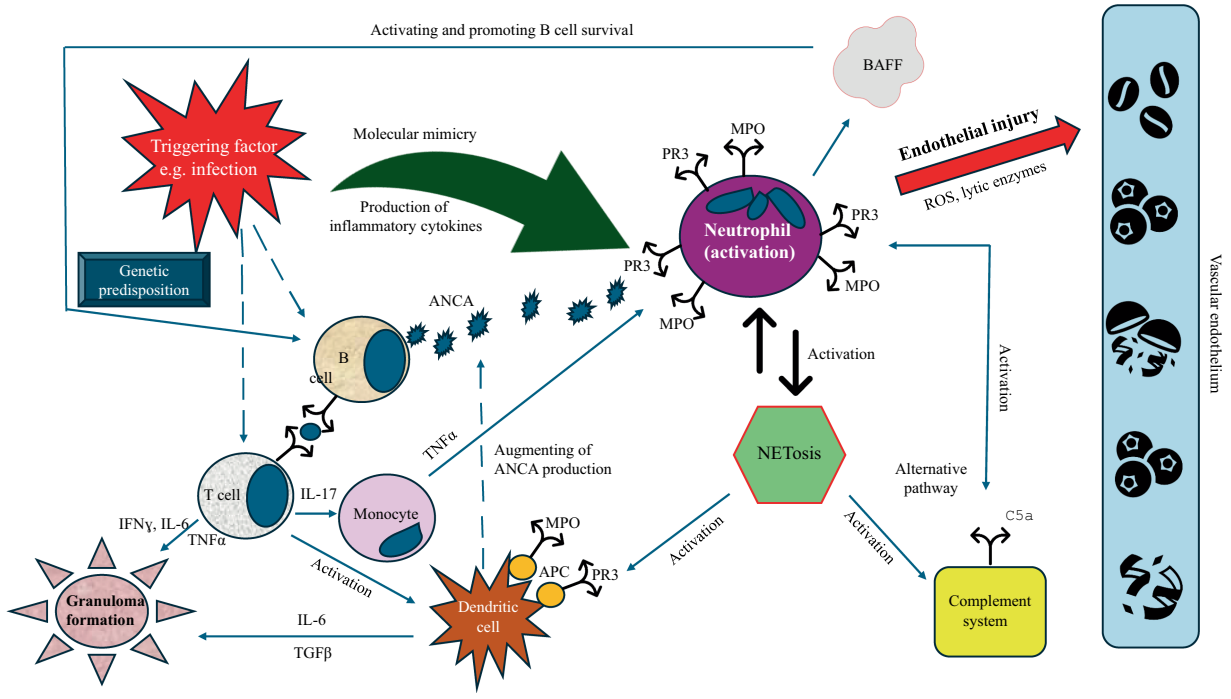

FIGURE 1
Pathogenesis of GPA. Some trigger (e.g., infection) to genetically predisposed subject stimulates neutrophils and B and T cells. As a result of neutrophil activation, PR3 and MPO are expressed and translocate into the cytoplasmic membrane and the production of BAFF increases, which promotes B cells survival and stimulates them to produce ANCA. These antibodies bind to PR3 and/or MPO and activate neutrophils, which subsequently accumulate at the wall of the vessel and release reactive oxygen species and proteases leading to endothelium injury and necrosis. The activation of neutrophils results in the NETs formation, which, in turn, augment the production of ANCA by stimulating (together with T cells) of the dendritic cells. NETs activate also the complement system that additionally stimulates neutrophils through the release of neutrophil-activating chemokines (e.g., C5a). In addition, the abnormal T and dendritic cells cytokine response provides help to B cells for the production ANCA and granulomas formation (Abbreviations: PR3, proteinase 3; MPO, myeloperoxidase; BAFF, B-cell activating factor; ROS, reactive oxygen species; ANCA, antineutrophil cytoplasmic antibody; NETs, neutrophil extracellular traps; TNFα, tumor necrosis factor α; IL, interleukin; TGFβ, transforming growth factor β; IFNɣ, interferon ɣ).

necrosis of the granulomatous lesion feeds into a draining airway, and this may cause coughing and hemoptysis, and always require differentiation from infection and neoplasms (26). Other manifestations include bilateral parenchymal infiltrates and consolidations presenting in around half of the patients (27). Lung lesions related to the NGI may wax or wan spontaneously, with some nodules disappearing and others appearing over time (23). Although these patients usually respond well for corticosteroids (CS) and immunosuppressive (IS) therapy, they often have fibrotic strands as residual scars, and should not be confused with ILD, which is mostly associated with MPO-AAV (26).

3.1.2 Tracheobronchial inflammation

The frequency of tracheobronchial involvement varies from 13.6–55% in patients with GPA (28, 29), and is more frequent in women and younger patients (26, 29). Tracheobronchial inflammation may occur anywhere in the tracheobronchial tree, with subglottic region is most involved in this region (26, 29). Furthermore, tracheobronchial involvement may occur at any stage of the disease, even in patients being in remission. On rare occasions, it may be the only feature of GPA, making a proper diagnosis difficult, especially in cases of ANCA negativity (28, 29). The pattern of lesions is heterogeneous, however, four main types are distinguished: mucosal abnormalities, masses and polyps, subglottic stenosis (SGS), and tracheobronchial inflammation and stenoses (TBISs). Other rarer complications include tracheo- or bronchomalacia as well as bronchiectasis (29), with the latter occurring more frequently in patients with AAV and MPO positivity (30). Generally, inflammatory processes affecting lower airways in GPA are similar to those affecting nasal mucosa; however, they are non-specific and should be differentiated from other causes (29).

Regarding mucosal abnormalities, they may occur anywhere in the tracheobronchial tree, be patchy in distribution, and occur as isolated lesions. The most common forms are mucosal edema, erythema, thickening, and granularity and/or ulceration of mucosal surface (29). Purulent secretions and excessive mucous production are also common, especially in active disease. Masses and polyps are usually a reflection of active disease. They are also referred to as inflammatory pseudotumor, and because they mimic malignancy, biopsy and histological examination is necessary (31). These lesions may ulcerate, cause cough, and hemoptysis.

SGS is the most common manifestation of tracheobronchial involvement in GPA occurring in 10–20% of patients and may occur in any stage of the disease (19). In one of the cohorts (28) SGS developed in 13.6% of patients with GPA and its frequency increased in parallel with patient survival time; furthermore, SGS was not reflective of disease activity in the organs in 44% of cases (28). Patients with SGS are more likely to be female, younger at time of diagnosis, and have saddle-nose deformities, however, are less likely to have renal involvement (32). Symptoms can be non-specific, and increase gradually, allowing the patient to adjust his breathing pattern until the

critical stenotic airway area is reached (19). Patients may present with progressive dyspnea and stridor, dry cough, wheeze, and hoarseness (33). The stridor and wheeze may be confused with the wheeze of asthma, often leading to misdiagnosis, especially when there is no other organ involvement. Of note, as the airway caliber narrows, mucous plugging becomes a great concern, as it can cause acute stridulous exacerbations and airway obstruction (19). Patients with significant stenosis (approximately 80%) can present life-threatening respiratory symptoms requiring even tracheostomy (19). The diagnosis of SGS in patients with known GPA is straightforward and must be presumed, even when histology is not definitive (10). The diagnostic challenges are cases of isolated SGS, without the presence of ANCA, where the diagnosis should be based on histological examination, after exclusion of other causes (33).

TBISs are less frequent than SGS, and often associated with GPA activity elsewhere (32). The inflammation may be localized or complex involving multiple tracheal or bronchial segmental stenoses with luminal distortion; however, isolated bronchial stenosis has been described (34). The stenoses can be mild to severe, and typically can vary in their severity from one bronchus to another in the same lobe (29). Most of the severely narrowed bronchi become irreversibly occluded from fibrotic scarring (29). Rarely, complete closure of the bronchus may occur, which may even require pneumonectomy (35). Generally, symptoms of TBISs are similar to those in the patients with SGS. When inflammation is accompanied by mucosal ulceration, hemoptysis may occur (29).

GPA affecting the airways occasionally leads to tracheo- or bronchomalacia (31). This situation may occur in cases of cartilage involvement or by stenosis. Tracheo- and/or bronchomalacia predispose the trachea or bronchi to dynamic collapse during expiration or inspiration. Patients may present with nonspecific symptoms like dyspnea, cough, or hemoptysis. In addition, they may develop recurrent infections and bronchiectasis, due to poor clearance of secretions (36).

Bronchiectasis is more prevalent in AAV with MPO-ANCA positivity (30), and associated with distinct phenotypes (female, older age, common nerve involvement and renal disease) (30). In GPA, bronchiectasis in imaging studies is found in about 20% of patients, but significant clinical features of this condition are described occasionally (29).

3.1.3 DAH

According to various studies, the frequency of DAH in GPA cases ranges from 8.8 to 36% of patients (20, 37); however, it is frequent in MPA (25–60%) (38), and rare in EGPA (0–4%) (39, 40). This condition implies pulmonary capillaritis, leading to fibrinoid necrosis of the capillary walls with the loss of the integrity of the alveolar-capillary membrane, and resulting erythrocyte extravasation into the alveolar space with impairment of the gas exchange (23). The combination of DAH and kidney failure defines the pulmonary–renal syndrome, which presents in up to 97% of cases of MPO-AAV (41). DAH is a potentially life-threatening manifestation but milder forms also occur, and the course may be subclinical and recurrent. Symptoms are non-specific and include dyspnea of various degrees, hypoxemia, anemia, and hemoptysis, with the latter occurring only in about 50% of patients (10, 23, 26). Thus, DAH should be suspected in patients with GPA who have alveolar filling defects on chest imaging, independently of the clinical symptoms. Results of the systematic review showed that patients with GPA and presenting with DAH were 49.55 ± 17.54 years on average and were predominantly male (59%). Low hemoglobin levels were a constant clinical feature, and almost all patients had anemia at presentation, with only 61.5% reporting hemoptysis on presentation. Renal involvement and the need for mechanical ventilation were present in two-thirds of the cases (42). Factors independently associated with the development of respiratory failure include the high degree of hypoxemia, a high percentage of neutrophils in the bronchoalveolar lavage fluid (BALF) cell count, and high C-reactive protein (CRP) levels (43). Whereas the need for dialysis, low oxygen saturation $< 90\%$ at admission, need of mechanical ventilation (44), and age > 65 years (42) were the factors found as associated with unfavorable prognosis and higher mortality.

3.1.4 ILD

The ILD is more likely to affect MPA than GPA. In MPA, ILD has been reported in 2.7–45% of patients, while in GPA this manifestation is present in about 23% of cases (45, 46). Furthermore, prevalence of ANCA in individuals initially presenting with isolated ILD ranges between 4 and 36% for MPO-ANCA, and only 2–4% for PR3-ANCA (45). It is suggested that MPO-ANCA may play a direct role in the pathogenesis of ILD, while PR3-ANCA seems not to be associated with ILD (47). Nonetheless, the presence of PR3-ANCA in patients with idiopathic interstitial pneumonia may be associated with a poor prognosis, similar to those with idiopathic pulmonary fibrosis (IPF) (47). ILD may occur in any time; that is before, simultaneously or after diagnosis of AAV (45, 46). Symptoms are non-specific and include progressive dyspnea and nonproductive cough, and physical examination typically reveals crackles, while digital clubbing are rather rare (23, 45). In most cases ILD progresses to pulmonary fibrosis, especially in MPA, while in GPA, ILD tends to be less aggressive and better respond to treatment (48). In the recent study of 684 AAV cohort (470 with MPO-ANCA and 214 with PR3-ANCA positivity), 13% of patients had ILD which preceded the diagnosis of AAV by a mean of 2.2 years. AAV-ILD patients were older, more often MPO-ANCA + (93% vs. 65%), and had a lower baseline disease activity than those without ILD. Indeed, among patients with MPO-ANCA + AAV, 18% had AAV-ILD, while among patients with PR3-ANCA+ AAV, only 3% develop AAV-ILD (49). The majority of patients had fibrotic ILD, with usual interstitial pneumonia (UIP) was the most common ILD type (42%), followed by fibrotic organizing pneumonia (OP) (21%), non-fibrotic OP (15%), and fibrotic non-specific interstitial pneumonia NSIP (11%) (49). In another study of AAV-ILD patients (56 with MPA and 39 with GPA), NSIP was the most common detected ILD (61%), followed by UIP (48%), and OP (10.5%), with NSIP was mainly observed in patients with c-ANCA positivity, while UIP was mainly found in patients with p-ANCA (50). In this study, ILD preceded vasculitis diagnosis in 22.1% of cases and mainly in p-ANCA positive patients (85.7%), while among those with c-ANCA, only one patient developed ILD before vasculitis (in 44.2% of cases the diagnoses were concomitant, and in 33.7% ILD followed the diagnosis of AAV). These results suggest the need for a regular assessment also for ILD in patients with AAV, particularly in those with GPA; on the other hand, patients with ILD and p-ANCA positivity (often initially classified as IPF) should be regularly assessed for the development of vasculitis (50).

Regarding the prognosis, many studies demonstrated that patients with MPA and ILD, but not with GPA, have worse prognosis compared

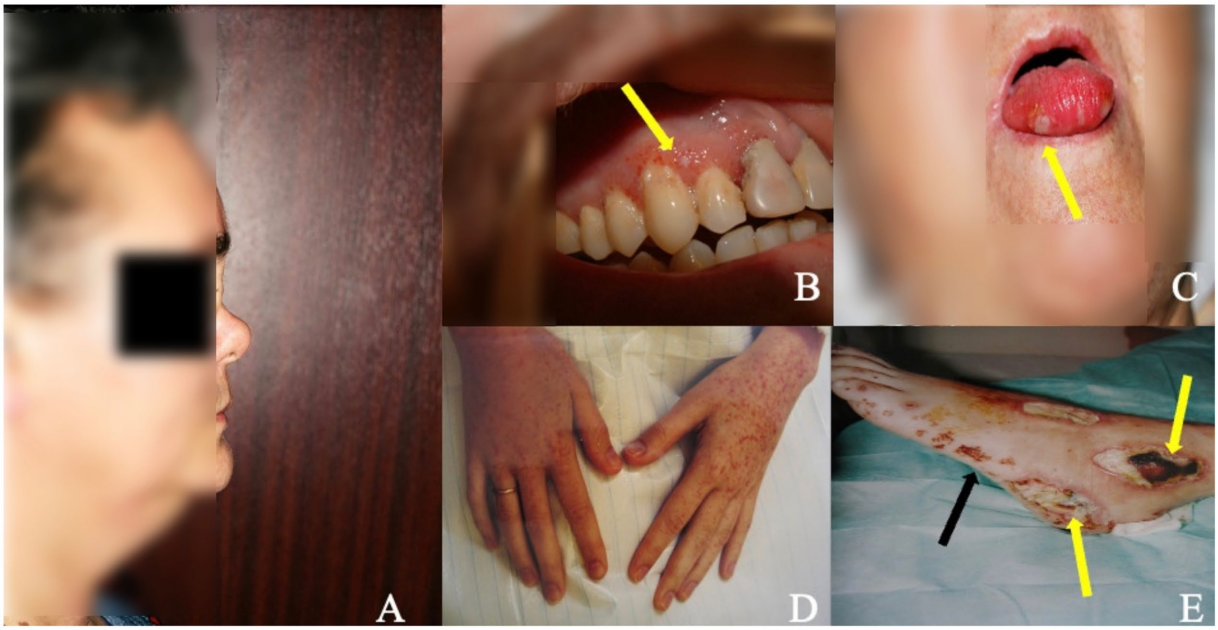

FIGURE 2
ENT involvement and skin/mucosal lesions in patients with GPA. **(A)** Saddle nose deformity (lateral view) in patient with long-term GPA and ENT involvement as a result of septal cartilage destruction with subsequent nasal collapse caused by granulomatous inflammation. **(B,C)** Mucosal lesions in the oral cavity in two patients with GPA manifesting in one as gingival hyperplasia with petechiae and small foci of necrosis **(B)** (arrow) and in the other as small necrotic lesions on the tongue **(C)** (arrow). **(D,E)** Purpuric lesions on the skin of hands **(D)** and of the left foot **(E)** (black arrow) accompanied by ulcerations and necrosis **(E)** (yellow arrows) in patient with generalised GPA.

to those with alone AAV, without ILD (51, 52). In one of the recent study, fibrotic AAV-ILD was associated with a 58% higher risk of death compared with AAV patients without ILD (49). In another study, patients with UIP patterns had an approximately 5-fold risk of death compared to those with NSIP (53). Factors identified as associated with mortality include chronic respiratory insufficiency, induction therapy with CS alone, and initial weight loss (54). In another study, an age > 65 years at AAV diagnosis, DAH at the time of AAV diagnosis, and an UIP pattern (compared to NSIP) were associated with shorter survival in AAV patients and ILD that those with alone AAV, without this manifestation (51).

3.2 Extrapulmonary involvement

ENT signs are present in 80–100% of cases (18, 20). The most prominent manifestations include nasal crust formation (75%), followed by excessive nose-blowing (70%), nasal obstruction (65%), epistaxis (59%), septal perforation, and saddle-nose deformity (Figure 2A) (27), the latter presenting in 25% of patients as a result of septal cartilage destruction with subsequent nasal collapse, caused by granulomatous inflammation (27). Ear involvement is almost always secondary to nasal involvement and leads to hearing loss, which may be the first GPA symptom. Involvement of the oral cavity is present in 6–13% of patients (55) (Figures 2B,C), with strawberry" gingival hyperplasia is the most common (61.5%) and most characteristics sign of GPA (55). Renal involvement occurs in 70–85% of patients during the course of the disease, while renal insufficiency occurs in 11–17% of patients at presentation (10) and 24.3% of patients experience worsening of glomerular filtration rate (GFR) over time (20). The clinical presentation is heterogeneous, from the indolent course progressing over months to years, to the rapidly progressive glomerulonephritis (GN) (20, 56). The frequency of cardiac involvement ranges from 1 to 61%, dependent on the study and diagnostic technique used (20, 22, 57–59); however, clinically overt cardiac involvement is reported in 3.3% of patients, with pericarditis and myopericarditis are the most common cardiac manifestation (58). Nevertheless, significant proportions of patients are asymptomatic or have few clinical symptoms, which may be easily overlooked (59, 60). Peripheral nervous system (PNS) involvement has been reported in 11–44% of GPA cases (61). The classic presentation is pain of acute onset, weakness, and sensory loss in the distribution of a named nerve (mononeuritis), followed by involvement of additional nerves in a stepwise fashion over weeks to months (multifocal neuropathy or mononeuritis multiplex) (62). Central nervous system (CNS) involvement is rarely seen in GPA (3–11.7%) (20, 22) and the most common form is hypertrophic pachymeningitis (HP) (10) typically manifesting as headaches and cranial neuropathies (10, 63). The autonomic nervous system (ANS) may also be involved (64). Clinical presentations of skin involvement encompass a wide range of symptoms (Figures 2D,E), however, pyoderma gangrenosum and palpebral xanthoma were identified as specific to GPA (65). Ophtalmological signs occur in 50–60% of patients (66), with orbital lesions (manifesting as pseudotumor or granulomatous inflammation) develop in 5–30% (67) and are considered the second most prevalent ophthalmic manifestation after conjunctivitis/episcleritis (67). Finally, gastrointestinal involvement has been reported in 1–26.5% of cases (20–22, 68, 69), with the most frequently symptoms include abdominal pain and bloody diarrhea (20, 21, 70).

4 Diagnosis, classification, and phenotypes

4.1 Diagnostic and classification criteria

To date, there are no validated diagnostic criteria for GPA, and there is no single test confirming the diagnosis. The Chapel Hill Consensus Conference (CHCC) provided a nomenclature classification and not a diagnostic classification (2, 71). However, in 2007 the British Society for Rheumatology (BSR) together with the British Health Professionals in Rheumatology (BHPR), proposed criteria which must be fulfilled to diagnose of AAV (72). In fact, current diagnosis of GPA is mostly based on clinical features, imaging findings, and supported, whenever possible, by the presence of ANCA and histological examination (73). Although many of the signs and symptoms discussed above can be seen in other diseases, multiorgan involvement is a key diagnostic clue, and the index of suspicion should be high if at least two of these symptoms are present (18).

Unlike the diagnostic criteria, the classification criteria have been developed for the purposes of clinical trials, to ensure that homogeneous populations are selected for inclusion. They are not appropriate for use in establishing a diagnosis of vasculitis, but to differentiate cases of GPA from other types of vasculitis; therefore, they should only be applied when a diagnosis of small or medium vessel vasculitis has been made, and other vasculitis mimics conditions have been excluded (74–76). The review of definition, diagnostic and classification criteria of GPA is presented in Table 1.

4.2 Diagnostic tools and differential diagnoses

As in GPA each organ may be affected, therefore, it is essential to conduct a detailed interview of medical history and perform diagnostic tests assessing the organ lesions (Table 2). As mentioned above, there is no single test to confirm GPA, therefore, the diagnosis is based on the combination of serological tests, imaging studies, and biopsies with histological examinations; however, all results should be interpreted in the correlation with clinical picture. Additional tests include endoscopies, particularly a flexible fiberoptic bronchoscopy (FOB), and pulmonary function tests (PFTs), which both are important informative procedures in patients with respiratory manifestations, with FOB allows to take biopsy and exclude other causes, for example infection or malignancy. All these techniques are not only of diagnostic importance but can also be used to monitor organ damage.

Of note, the exclusion of other causes is an important component of GPA diagnosis; however, when the diagnosis remains uncertain, observation over time, repeat investigation, and a therapeutic trial may improve the probability of the GPA diagnosis or identify an alternative disease (77).

4.2.1 Laboratory testing

4.2.1.1 Routine laboratory tests

In patients with suspected GPA, the following routine laboratory tests should be performed: complete blood count with differential and blood smear, renal function (creatinine with eGFR and urea), electrolytes, liver enzyme, coagulation tests (with D-dimer), erythrocyte sedimentation rate (ESR) and CRP, and complete urinalysis with urinary sediment and 24-h proteinuria collection (73). As cardiac involvement may be often asymptomatic, the determination of basic cardiac markers such as troponin T and brain natriuretic peptide (BNP) should be considered. Results of routine tests are usually non-specific, however, in GPA, as in other inflammatory diseases, patients usually have leukocytosis with increased neutrophilia, normocytic normochromic anemia (as an expression of inflammation), thrombocytosis and increased CRP or ESR. The latter can be normal even in active GPA, if limited to a single organ disease (10).

Other laboratory studies, which should be performed include immunoglobulins concentrations, complement (C3, C4), serum protein electrophoresis, QuantiFERON test, viral serologies, such human immunodeficiency virus (HIV), and hepatotropic viruses (hepatitis B virus; HBV and hepatitis C virus; HCV), and ANCA serology with target antigens (78).

4.2.1.2 ANCA testing

ANCA is an important diagnostic marker in patients with AAV (1, 79) and should be performed in every patient with clinical features suggesting AAV (80). There are reports indicating that these antibodies may be present years before AAV symptoms to support the important role of ANCA in AAV pathogenesis (81). Alternatively, ANCA is not a specific marker for AAV because it can be detected in other conditions (82). In addition, the absence of ANCA does not exclude AAV, when it is supported by clinical symptoms and histological examination, after excluding other causes (80). The recent meta-analysis demonstrated that PR3-ANCA has greater sensitivity than MPO-ANCA for GPA (74% vs. 11%), while MPO-ANCA has greater sensitivity for MPA (73% vs. 7%), with consistently high specificities of both types of ANCA (mean 97%; range 93–99%) (83). According to current international consensus on ANCA testing, the use of antigen-specific assays for PR3- and MPO-ANCA is recommended as the first line of testing over indirect immunofluorescence (IIF) method in patients suspected AAV (80). Some studies demonstrated, that a higher ANCA titer and multiple affected organ systems may help to discriminate between AAV and other systemic diseases in anti-PR3 and anti-MPO positive patients. Using four different immunoassays for the ANCA test, ≥4 times the upper limit was a reasonable cut-off point to discriminate between AAV and alternative diagnoses (84). However, ANCA is not a substitute for the biopsy and has an important role in suspected cases when histological confirmation cannot be obtained (33).

Although ANCA is a valuable diagnostic tool of GPA, in about 8.5% of patients ANCA serology results are negative (20). In the absence of ANCA, the diagnosis may be difficult to assess, and new reliable biomarkers for diagnosis of AAV, particularly in seronegative cases, are being sought. Anti-pentraxins (anti-PTX3) antibodies may become a promising candidate as a novel diagnostic biomarker of AAV, including patients with negative serology for MPO- and PR3-ANCA. High levels of PTX3 have been found in active AAV, large vessel vasculitis, and connective tissue diseases (CTDs), as in systemic lupus erythematosus (SLE) (85). Next, in the study focusing on AAV only, plasma and urinary PTX3 correlated with disease activity, particularly in patients with renal involvement (86). Finally, anti-PTX3 antibodies have been detected in almost 40% of AAV patients,

TABLE 1 GPA – definition, diagnosis, and classification.

Definition	Diagnosis	Classification		
CHCC 2012	BSR and BHPR 2007	EMA 2007	ACR 1990	ACR 2022
Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels; necrotizing GI is common Ocular vasculitis and pulmonary capillaritis with haemorrhage are frequent Granulomatous and non-granulomatous extravascular inflammation are common Limited expression also occur, especially confined to the upper or lower respiratory tract, or the eye	1. Symptoms and signs characteristic of systemic vasculitis 2. At least one of the following: a.histological evidence of vasculitis and/or granuloma formation b. positive serology for ANCA (either cANCA/PR3 or pANCA/MPO) c. specific indirect evidence of vasculitis 3. No other diagnosis to account for symptoms or signs All criteria must be fulfilled	1. Fulfilled 1990 ACR for WG or 2. Histology compatible with CHCC for WG or 3. Histology compatible with CHCC for MPA but WG surrogate markers* are present or 4. There is lack histology, but WG surrogate markers* and ANCA positivity are present * Fixed pulmonary infiltrates, nodules or cavitations present for >month, bronchial stenosis, bloody nasal discharge and crusting for >1 month or nasal ulceration, chronic sinusitis, otitis media or mastoiditis for>3 months, retro-orbital mass or inflammation,SGS Only one surrogate marker is necessary to support of diagnosis of GPA Surrogate markers for renal vasculitis: haematuria (red cell casts or > 10% dysmorphic erythrocytes) or haematuria (2+) and proteinuria (2+)	1. Nasal or oral inflammation (oral ulcers, purulent or bloody nasal discharge) 2. Abnormal chest X-Ray (nodules, fixed infiltrates, cavities) 3. Urinary sediment (microhaematuria >5 RBC) or red cell casts in urine 4. Granulomatous inflammation on biopsy granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area At least 2 of 4 criteria are needed for classification of GPA	1.ENT symptoms: bloody discharge, ulcers, crusting, congestion, blockage, septal defect/perforation (+3 points) 2.Cartilaginous involvement: inflammation of ear or nose cartilage, hoarse voice, stridor, endobronchial involvement, saddle nose (+2 points) 3.Conductive or sensorineural hearing loss (+1 point) 4.Positive test for ANCA (cANCA or anti-PR3) (+5 points) 5.Pulmonary nodules, mass, cavitation (+2 points) 6.Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy (+2 points) 7.Sinusitis or mastoiditis (+1point) 8.Pauci-immune GN in biopsy (+1 point) 9.Positive test for pANCA or anti-MPO (−1 point) 10.Blood eosinophilia $\geq 1\times10^9$/liter (− 4 points) A score ≥ 5 is needed for classification of GPA

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TABLE 2 GPA - organ manifestations, differential diagnoses, and diagnostic techniques.

Organ involved/main features	Clinical symptoms	Differential diagnoses	Diagnostic techniques
Lungs/pleura			
Nodules and masses (with or without cavitation)	Cough (often with the sputum), hemoptysis, dyspnea, chest pain, fever	Acute or chronic bacterial infections (e.g., TB or other *Mycobacteria*), fungal infection, as aspergillosis or cryptococcosis (others such as histoplasmosis, coccidiomycosis, blastomycosis should be considered in endemic areas), Nocardia, aspiration pneumonia, malignancy, NSG, RA, COP, lymphomatoid granulomatosis, BALT lymphoma, pulmonary infarct	X-ray, CT, FOB with cytological and microbiological examinations, PFTs, lung biopsy
Pulmonary infiltrates/opacities/alveolitis DAH	Dyspnea until respiratory failure, hemoptysis (in part of cases), anemia	Primary (anti-GBM disease, MPA, cryoglobulinaemic vasculitis), and secondary vasculitides (APS, SLE, RA, MCTD, drug-induced), other non-immune mediated causes (infectious, CHF, coagulation disorders, acute respiratory failure syndrome, inhalation of toxic substances, hemosiderosis)	X-ray, CT, FOB and BALF (determination of hemosiderin-laden macrophages), basic laboratory tests (including Cr, blood count), immunological examinations (e.g., ANA, anti-GBM and anti-phospholipids antibodies), cultures, ECHO, BNP, detailed medical interview
ILD	Progressing dyspnea, dry cough, limited exercise tolerance	CTD, drug-induced, smoking-related, chronic HP, IgG4-related disease, idiopathic	Detailed medical interview, occupation, environmental exposure, drugs taking, immunological examinations (e.g., ANA, serum precipitins, anti-IgG-4 antibodies), PFT, FOB, BALF, lung biopsy
Pleuritis	Chest pain, dyspnoea	Infection, pleural effusion secondary to heart or renal failure	USG, thoracocentesis with fluid examination and cultures, pleural biopsy
Trachea and bronchi			
SGS Mucosal abnormalities, masses and polyps, TBISs, trachea- or bronchomalacia, bronchiectasis	Dyspnea, stridor, hoarseness, cough, hemoptysis, recurrent infections	Polychondritis, inflammatory bowel disease, sarcoidosis, infection (especially fungal), asthma, allergy, neoplasm, amyloidosis, postintubation stenosis	CT, FOB, PFT, cultures, biopsy

(Continued)

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TABLE 2 (Continued)

Organ involved/main features	Clinical symptoms	Differential diagnoses	Diagnostic techniques
ENT			
Chronic rhinosinusitis, often purulent and with bone destruction, nasal septum perforation	Nasal obstruction, sinus pain, nose deformity (collapse of the nasal bridge)	Chronic infection (especially TB and fungal), sarcoidosis, cocaine abuse, lymphoma	Complete ENT assessment (with nasal endoscopy), sinus CT, or MR (of the ear), laryngoscopy, nasal swabs cultures, audiogram, biopsy
Otitis media unilateral or bilateral, with the obstruction of the eustachian tube, which may be complicated by facial nerve palsy and mastoiditis	Gradual or fluctuating hearing loss conductive (more common), sensorineural or mixed, otorrhea, earache		
Kidney			
GN (usually pauci-immune necrotizing, often crescentic)	Microscopic and dysmorphic hematuria, sub-nephrotic proteinuria, with or without rapid serum Cr increase, hypertension, with or without azotemia	Urinary tract infection, urolithiasis, CKD, CTD (e.g., SLE), hypertensive or diabetic nephropathy, bladder or renal malignancy, drug-induced kidney failure, anti-GBM disease	Urinalysis, 24-h proteinuria collection, blood urea, Cr, eGFR, anti-GBM, urine culture, USG, kidney biopsy
Interstitial nephritis	Sediment alterations with or without Cr increase (acute or subacute)		
Heart/pericardium			
Pericarditis (the most common)	Chest pain, dyspnea	Infection, CTD, pericarditis secondary to malignancy (e.g., lung or breast cancer) or radiation	ECG, ECHO, serum troponin and BNP, 24-h ECG, cardiac MR (optionally FDG-PET/CT), rare cardiac biopsy
Cardiomyopathy/myocarditis, valvular disease, conduction disorder	Chest pain, palpitations, syncope, dyspnoea	Cardiomyopathy related to atherosclerosis or hypertension, infective myocarditis	
Artery disease (vasculitis)		Coronary artery disease (of atherosclerotic aetiology),	Coronary artery angiography
Rare: coronary artery aneurysms, coronary artery dissection, tumor of the heart, endocarditis	Chest pain, dyspnoea, palpitations, fever	Atherosclerosis, neoplasm, sepsis	CT or MR angiography, TEE, blood cultures, rare conventional angiography

(Continued)

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TABLE 2 (Continued)

Organ involved/main features	Clinical symptoms	Differential diagnoses	Diagnostic techniques
Digestive tract			
Any organ may be affected			
Intestine, stomach	Abdominal pain and bloody diarrhea, nausea, vomiting, hematochezia or melena, dysphagia, perforation, may be subclinical course with positive occult blood in the feces	Infection, inflammatory bowel disease (e.g., CD, UC), peptic ulcer disease, malignancy, diverticulitis, neoplasm	Fecal occult blood tests (3x), liver enzymes (cholestatic and hepatocellular pattern), lipase, amylase, abdominal USG, CT/MR, endoscopy, biopsy
Liver	Elevated liver enzymes, organ enlargement, rare vasculitis on the portal spaces and centrolobular territories	Viral hepatitis, autoimmune liver diseases (AIH, PSC, PBC), drug - induced liver damage, CTD, steatohepatitis, post-alcoholic liver injury and cirrhosis, neoplasm	
Spleen	Segmental infarction, rather asymptomatic		Screening for HBV and HCV infection is recommended at the beginning of GPA diagnosis in all patients
Pancreas	Recurrent pancreatitis, pseudotumoral masses	Pancreatitis of the other cause (alcohol, drugs, cholelithiasis), malignancy	
Gallbladder	Cholecystitis, infarction	Cholelithiasis, infection, dietary mistake, other causes of acute abdominal pain (gastritis, appendicitis, biliary colic, peptic ulcer disease), neoplasm	
Nervous system			
Peripheral			
Distal symmetrical sensory neuropathy, mononeuritis multiplex, peroneal, tibial, ulnar, and median nerves are commonly involved	Pain, burning sensation, numbness, limb weakness, foot or wrist drop and other sensory and/or motor deficits	Paraneoplastic, AIDS, DM, chronic liver disease, infection (Guillain-Barre syndrome), vit B6 or B12 deficiency, drugs, other type of vasculitis	Clinical evaluation, EMG, nerve biopsy, laboratory and serological tests
Cranial neuropathies (II-VIII)	Often secondary to the external compression from ENT and/or orbit mass	Tumor, stroke	MR

(Continued)

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TABLE 2 (Continued)

Organ involved/main features	Clinical symptoms	Differential diagnoses	Diagnostic techniques
Central			
Brain parenchyma (symptoms related to vasculitis)	Ischemic or hemorrhagic events	Vascular atherosclerotic disease, acute disseminated encephalomyelitis	
Posterior reversible encephalopathy syndrome (PRES) (rare)	Headache, seizures, altered mental status and visual loss	Primary and secondary degenerative diseases, age-related dementia, brain tumor, infection (AIDS)	
Isolated parenchymal mass lesions (very rare)	Variable symptoms due to CNS compression, seizures are the most common	Primary (i.e., glioma) or secondary (metastases) brain tumors, infection (e.g., in the course of AIDS)	MR/MR angiography, cerebrospinal fluid examination and cultures, biopsy (rare)
Cognitive impairment	Mostly subclinical or mild, affecting mainly abstract reasoning, attention and non-verbal memory	Degenerative diseases (e.g., Alzheimer disease), age-related – dementia, infection	
Meninges			
Hypertrophic pachymeningitis of the brain	Headache, dizziness, seizures, cranial neuropathy, e.g., paresis of the ocular motor nerves		
Spinal pachymeningitis	Paraplegia, truncal sensory abnormality, neck and back pain	Infection, neoplasms (e.g., lymphomas), sarcoidosis	
Skin/mucosa			
Skin			
Purpura, ulcers, nodules, pyoderma, gangrenosum - like lesions, other (e.g., livedo reticularis)	Pain, necrosis	Infection, allergic vasculitis, cutaneous vasculitis in CTD, Henoch – Schonlein purpura, HCV - induced vasculitis, cryoglobulinemic vasculitis, vasculitis associated with vasculopathic disorders (e.g., factor V Leiden mutation), immunodeficiency (e.g., AIDS), classic pyoderma gangrenosum, lymphoproliferative disorders, ulcerative colitis, pseudovasculitis	Clinical and serological evaluation, biopsy
Mucous membranes			
Strawberry gingivitis, oral or nasal ulcers, genital ulceration	Pain, bleeding, nasal crusting, purulent or blooding nasal discharge		

(Continued)

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TABLE 2 (Continued)

Organ involved/main features	Clinical symptoms	Differential diagnoses	Diagnostic techniques
Ocular			
Orbit			
Orbital or retro-orbital mass, usually unilateral, often coexists with sinus disease with bone destruction	Pain, proptosis, diplopia, eyelid swelling, periorbital cellulitis, ocular movement impairment, visual loss	Infection, lymphoma, sarcoidosis, cellulitis, cavernous hemangioma, venolymphatic malformation	MR, optic tomography, fluoroangiography, slit lamp examination, USG (in some cases), biopsy (rare)
Eye			
Conjunctivitis, scleritis, episcleritis, keratitis, retinal involvement	Red eye, tearing, corneal ulceration, blurred vision	Infection, CTD, sarcoidosis, IgG4-related disease, inflammatory bowel disease	
General/ Musculoskeletal			
	Fever, weakness, weight loss, malaise, myalgia, arthralgia, arthritis usually not-deformative	Infection (including TB), malignancy, CTD, polymyalgia rheumatica, hormonal disorders (e.g., hyperthyroidism)	Clinical evaluation, laboratory and immunological tests, hormone examinations, articular USG, cancer screening
Other rare involvements			
Urogenital			
Prostatitis, renal pseudotumor, orchitis, epididymitis, ureteral stenosis, penis ulceration	Pain, swelling, fever, difficulty urinating	Infection, neoplasm, benign prostatic hyperplasia	CT or MR, cystoscopy, biopsy
Endocrine			
Salivary glands	Swelling, pain, necrosis, dry mouth	Infection, Sjogren syndrome	Clinical evaluation, USG, MR, biopsy
Lacrimal glands	Pain, tearing, reddening	Infection, allergy	Clinical evaluation
Pituitary	Cranial diabetes insipidus, hypogonadism, secondary hypothyroidism, hyperprolactinemia, growth hormone deficiency, polyuria, polydipsia, decreased libido, muscular atrophy, asthenia, amenorrhea, compressive symptoms (headache, vomiting, visual field loss)	Adenoma, lymphoma, metastasis, radiation, LCH, post-traumatic damage, stroke, sarcoidosis	MR, hormone examinations
Thyroid	Hypothyroidism	Hashimoto disease, cancer, subacute thyroiditis, drug-induced	USG, hormone and serology examinations, scintigraphy, biopsy
Adrenal glands	Adrenal insufficiency	CS treatment, infection (TB), autoimmune adrenal inflammation, stroke of the hypothalamic–pituitary region, neoplasm	USG, MR, hormone examinations, biopsy (rare)

(Continued)

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TABLE 2 (Continued)

Organ involved/main features	Clinical symptoms	Differential diagnoses	Diagnostic techniques
Breast			
Breast	More common in women, pain, ulceration	Breast cancer	Biopsy is decisive
Vertebral			
Paravertebral masses, usually not associated with bone erosion or compression of vessels	Often asymptomatic, sometimes back pain	Cancer, lymphoma	MR
Large and medium-sized vessels			
Thoracic and abdominal aorta (periaortitis the most common), carotid and subclavian artery, pulmonary arteries, renal arteries	Stenosis, occlusion, aneurysms, periaortic mass, thoracic or abdominal pain, fainting, stealing syndrome, low cardiac output syndrome, decrease of blood pressure, may be asymptomatic	Isolated large vessel vasculitis, atherosclerosis, thrombosis, congenital	CT/MR angiography, optionally FDG-PET/CT, conventional angiography (rare)

GPA, granulomatosis with polyangiitis; CT, computed tomography; FOB, fiberoptic flexible bronchoscopy; PFTs, pulmonary function tests; RA, rheumatoid arthritis; COP; cryptogenic organizing pneumonia; BALT, bronchus-associated lymphoid tissue; DAH, diffuse alveolar hemorrhage; anti-GBM, anti-glomerular basement membrane antibodies; MPA, microscopic polyangiitis; BALF, bronchoalveolar lavage fluid; APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus; CTD, connective tissue disease; MCTD, mixed connective tissue disease; HP, hypersensitive pneumonia; ANA, anti-nuclear antibodies; Cr, creatinine; ECG, electrocardiography; ECHO, echocardiography; BNP, brain natriuretic peptide; USG, ultrasonography; ENT, ear, nose, throat; MR, magnetic resonance; FDG-PET/CT, F-18 fluorodeoxyglucose - positron emission tomography; TEE, transesophageal echocardiography; HBV, hepatitis B virus; HCV, hepatitis C virus; AIDS, acquired immune deficiency syndrome; DM, diabetes mellitus, CNS, central nervous system, TB, tuberculosis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cholangitis; CD, Crohn's disease; UC, ulcerative colitis.

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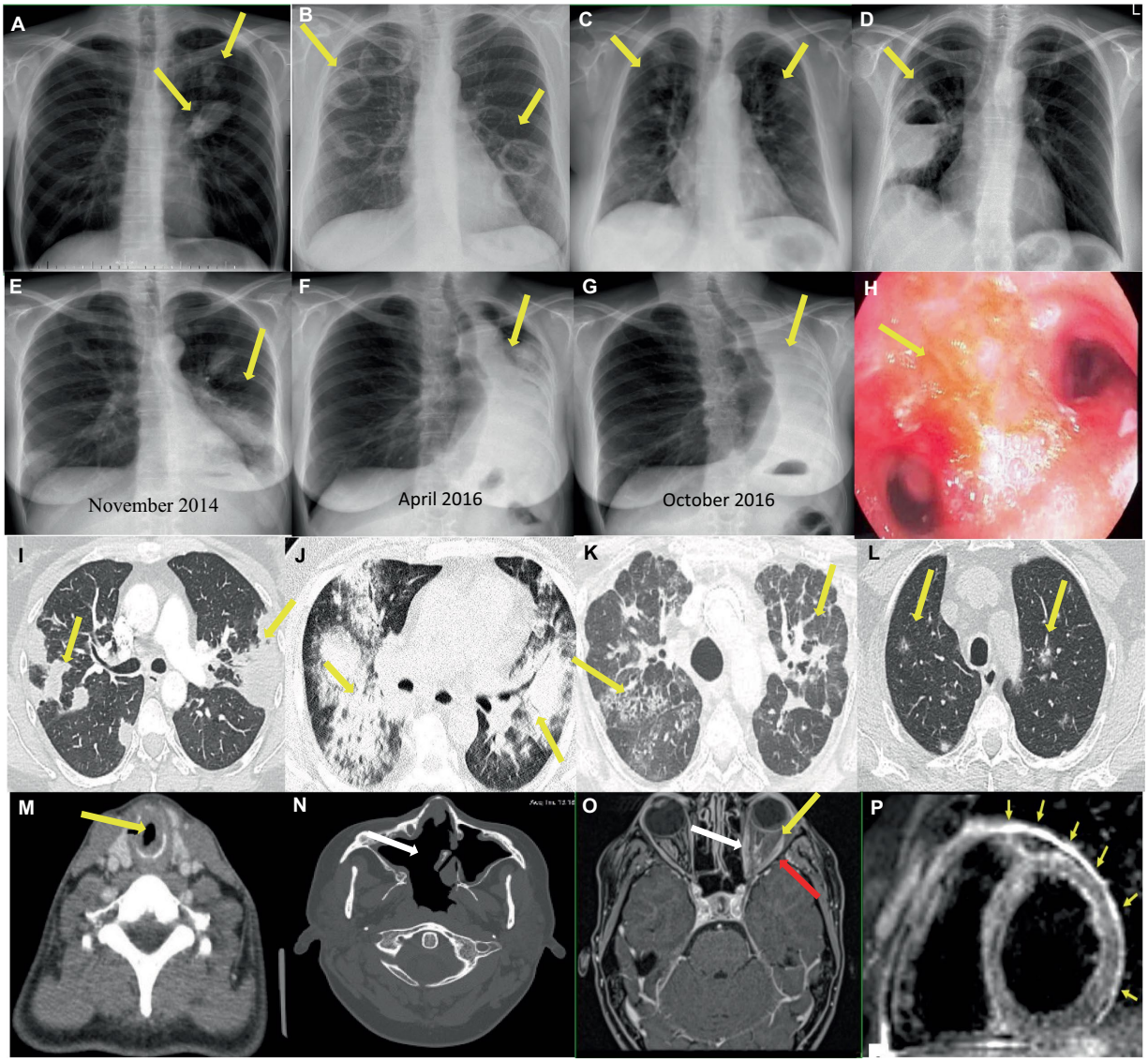

FIGURE 3
Imaging findings in patients with GPA. **(A–G)** Chest x-rays showing **(A)** Two nodular lesions (arrows) in the hilum and in the upper field of the left lung suspected initially for lung cancer. **(B)** Bilateral tumors with cavities (arrows) and **(C)** spread small lung nodules. **(D)** A thick-walled cavity with a fluid level in the right lung (arrow) suspected initially for lung abscess, and then for mycetoma. **(E–G)** Increasing obstruction of the left main bronchus **(E,F)**, up to its complete closure and the formation of atelectasis of the left lung (arrows) **(G)** in the patient with tracheobronchial involvement. **(H)** Endoscopic image of endobronchial lesions (arrow). **(I–L)** Chest CT scans showing **(I)** Bilateral parenchymal infiltrations and consolidations (arrows) corresponding to OP pattern (axial image, lung window). **(J)** Bilateral ground-glass opacities in patient with diagnosed DAH (axial image, lung window). **(K)** Features of ILD (NSIP pattern) (arrows), which appeared after many years of suffering from vasculitis (axial image, lung window). **(L)** Bilateral small and randomly distributed nodules with "ground-glass" component (arrows) corresponding to GPA in histological examination (axial image, lung window). **(M–N)** Head and neck CT scans showing **(M)** SGS in the course of GPA - tracheal narrowing and thickening of the tracheal wall (arrow) (axial image). **(N)** A large single sinus cavity (arrow) as a result of the destructive granulomatous process of the nasal septum (axial image). **(O–P)** Contrast-enhanced MR showing **(O)** orbital mass in the left orbit (yellow arrow) with extraocular muscle enlargement (red arrow) and optic nerve sheath enhancement (white arrow) (T1-weighted, axial image). **(P)** Myocardial edema and thickened pericardium with hyperintense signal (arrows) corresponding to cardiac and pericardial involvement in the patient with GPA (black blood T2-weighted STIR images in short axis plane).

with half of the patients with undetectable MPO- and PR3-ANCA, were positive for anti-PTX3 (87).

4.2.2 Imaging techniques

Further evaluation should be made of the affected organs, using imaging as an integral part of the diagnostic evaluation in patients with GPA to detect organ involvement and to identify potential biopsy sites (73). Furthermore, chest imaging should be performed in any patient in whom GPA is suspected, since up to one-third of patients may be asymptomatic yet have pulmonary radiographic findings (88). Imaging abnormalities in GPA are non-specific, and overlapping patterns are common, moreover, lesions may evolve with the stage of the disease (active or chronic persistent lesions) and treatment (89). Knowledge of the clinical background of the patient, experience, and

TABLE 3 Features of main CT-patterns of GPA-related ILD.

NSIP pattern	UIP pattern	OP pattern
1. Bilateral ground-glass areas predominantly located in the middle and lower lung with or without a. Reticular opacities (which can be superimposed on a ground-glass pattern) b. Traction bronchiectases 2. Honeycombing rare 3. Subpleural areas usually not involved	1. Basal and subpleural predominance 2. Reticular pattern, with associated traction bronchiectasis 3. Honeycombing appearance 4. Absence of features* listed as inconsistent with UIP pattern *Upper or mid-lung predominance, peribronchiovascular predominance, extensive ground-glass abnormality, profuse micronodules, discrete cysts, diffuse mosaic attenuation/air-trapping, parenchymal consolidations	1. Peripheral or peribronchial patchy consolidations, often with air bronchograms and mild cylindrical bronchial dilatation 2. Ground-glass opacities with tendency to migration, change of location and size 3. Rarely mass or nodule that may cavitate or reproduce the typical appearance of an "atoll sign" (the presence of a ring consolidation surrounding normal lung or ground-glass opacification), considered as relatively specific for OP

CT, computed tomography; GPA, granulomatosis with polyangiitis; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia; OP, organizing pneumonia.

close cooperation between clinician and radiologist are necessary for the appropriate assessment of imaging lesions and further management.

4.2.2.1 Conventional X-ray

Chest X-ray is the preliminary screening examination for pulmonary involvement in GPA and should be performed in every patient suspected of GPA regardless of whether there are respiratory symptoms or not. However, chest X-ray has limited sensitivity, and some lesions may not be visible as well as a precise determination of the nature of lesions or their precise location may not be possible. Abdominal X-ray may be used as screening in cases of acute abdominal pain in patients suspected of gastrointestinal involvement. With this method pneumoperitoneum can be identified, and using oral contrast medium, increased wall thickness could be visualized (70). In turn, sinus X-ray has low diagnostic value, however, acute sinusitis with the fluid level may be visible.

4.2.2.2 CT imaging

4.2.2.2.1 Conventional CT and CT angiography

CT is more sensitive than conventional radiographs and is the technique of choice for the characterization of manifestations in GPA, especially in patients with respiratory symptoms, as it presents high diagnostic performance in paranasal cavities and ear pathology (showing both features of inflammation as well as bone destruction and intracranial extension of nasal lesions), and in the assessment of the thorax, especially the lung, tracheobronchial tree, mediastinum, and vascular structures (90). In addition, in some cases, chest CT may help to distinguish GPA manifestations from infection and other comorbidities (73). This technique allows for a precise assessment of the morphology and distribution of lung lesions and is helpful in selecting the biopsy site. The most common manifestation related to GPA include nodules and masses with or without cavitation, and usually at random distribution; followed by ground-glass opacities (diffuse or local, related to alveolitis or DAH), parenchymal consolidations, and tracheal or bronchial abnormalities as thickening wall and stenosis; rarer findings include pleural changes and ILD (24, 25, 49, 50, 53); the latter corresponding primarily to NSIP, UIP or OP patterns (49, 91) (Table 3). In up to 15% of patients, enlarged mediastinal lymph nodes may be found which are usually seen in association with lung abnormalities (92). In some cases, the mosaic attenuation or the "tree – in – bud" pattern is present which may indicate pulmonary arterioles involvement secondary to GPA (27). As conventional CT is the preferred method for large airway disease detection, the competitive technique is the dynamic expiratory chest CT which has been revealed as a potential screening test to evaluate for SGS and tracheobronchomalacia, where it has been demonstrated to better evaluate degree of collapse than other imaging (32). Whereas, CT angiography is useful in the involvement of large vessels, rarely seen in GPA, as aneurysms and aortitis manifesting as diffuse thickening of the arterial wall with edema and delayed enhancement (93).

In patients suspected of gastrointestinal involvement, abdominal CT might be a useful diagnostic tool and should be considered; however, the signs are non-specific and have to be correlated with clinical symptoms and patient medical history (70). In GPA, CT findings of bowel involvement include bowel dilatation and wall thickening, abnormal bowel wall enhancement, mesenteric vessels in a comb-like configuration, ascites, lymphadenopathy (27) or mesenteric fat haziness stemming from inflammation of the mesenteric vessels (94). Abdominal CT can also visualize splenic infarction because of diffuse arteritis resulting in occlusion of distal parenchymal splenic arteries. In renal involvement, this technique is usually negative, except when it presents as a nodule or renal mass (90).

4.2.2.2.2 F-18 fluorodeoxyglucose (FDG) - positron emission tomography (Pet)/CT

There are reports about a high sensitivity of FDG-PET/CT in AAV, especially in active GPA. In one of the cohorts of mixed AAV, FDG-PET/CT at baseline was positive in 100% of GPA patients, and sinonasal, lung, cardio-vascular and kidney involvements were all accurately identified by FDG-PET/CT (95). In another study of GPA, lesions of respiratory tract and lung were more clearly detected by FDG-PET/CT than by conventional CT scan alone, with high sinus mucosal, cartilaginous and bone uptake in early stages, even with normal CT (96). The FDG-PET/CT has also shown high positivity in cardiac involvement with great concordant with cardiac magnetic resonance (MR) lesions (95). Furthermore, the correlation between FDG uptake intensity and GPA activity has been also reported demonstrating that this method might be useful for the control treatment and follow-up in AAV patients (95). However, although FDG-PET/CT has many advantages, it has several imperfections. Despite this, it accurately identifies organ localizations in GPA, it does not bring additional benefit to the usual organ screening. In addition,

its sensitivity of skin, eye, and nervous system involvement is significantly low (95). Finally, findings are non-specific, and the FDG uptake intensity does not distinguish GPA from other entities, such malignancy, infection, or other granulomatous processes (96). For now, FDG-PET/CT should not be carried out routinely for the assessment of the spread of GPA, nor for its monitoring. On the contrary, it cannot be ruled out that in certain specific situations, this method will find a place in the future to distinguish active lesions from fibrous sequelae (e.g., orbital mass during GPA) (97).

4.2.2.2.3 MR imaging and MR angiography

MR imaging is most useful in cardiac, encephalic, and ocular manifestations in GPA patients (90). Cardiac MR is a recommended imaging tool for diagnosis of suspected myocarditis and is most accurate in diagnosing cardiac lesions in vasculitis (98). In patients with clinically silent cardiac involvement, this technique is of great value in early diagnosis and follow-up (99, 100). This method provides essential information about the morphology and function of cardiac structures and has also a unique potential for myocardial tissue characterization, identifying inflammation and fibrosis, myocardial and vessel acuity and evaluating biventricular function (99). However, specific abnormalities associated with GPA remain undefined, and correlation with patient's clinical background, laboratory and other findings is necessary. The late gadolinium enhancement (LGE) lesions are the most common cardiac MR findings in GPA patients as are detected in one-third of cases (60, 101). This pattern corresponds to myocardial fibrosis (99) and may be associated with cardiac damage (100, 101) and higher mortality (39, 59).

MR imaging combined with MR angiography is the first-choice method of central nervous assessment in GPA patients, including meningeal involvement, brain parenchyma lesions and cranial nerves involvement (27, 90), while MR angiography may visualize the vessels' lumens, and stenoses, occlusions or aneurysms (102). Regarding to meningeal involvement, two MR patterns have been identified: diffusely abnormal meninges (unrelated to sinus or orbital disease), and focal dural thickening and enhancement adjacent to sinus or orbital disease (27). Whereas, typical findings of vasculitis in brain parenchyma include luminal stenosis alternating with dilatation (the "beading sign"), while secondary signs comprise structural damage of brain tissue as a result of the ongoing inflammation (multiple small, microvascular infarctions in different vascular territories and of different ages, visible as white matter lesions with patchy high T2 signal intensity) (102). Functional MR may be relevant as an additional diagnostic tool, as it can provide information on both – structure and potential damage of the brain as well as the function of the selected brain centers (64).

Orbital involvement is the next GPA manifestation where MR imaging has a high diagnostic value, demonstrating orbital lesions, involvement of adjacent structures, and the extent of tissue damage. This examination is complemented with CT, as CT offers the ability to depict sinus structure disorders and osseous invasion, while MR is helpful for identifying granulomas and delineating orbital mucosal changes (103).

The MR/MR angiography remains the preferred imaging modality in large vessels assessment, although, CT combined with CT angiography is an alternative technique to MR, and according to some authors, the preference of one method over another will depend on its availability, and factors such as contraindications to the iodine contrast, presence of artifacts or considerations regarding radiation (90). However, MR angiography of large vessel can provide functional data such as flow volume and velocity, which is a major advantage compared to CT angiography (104).

4.2.2.2.4 Ultrasonography (USG)

In GPA, USG is reserved primarily for the assessment of extrapulmonary (e.g., kidney, liver) and thoracic involvement. Cardiac ultrasonography (echocardiography; ECHO) is recommended as the first-choice modality to screen cardiac involvement in AAV patients (73) as evaluating atrial and ventricular masses, valves lesions, left ventricular wall motor abnormalities and abnormalities of pericardium (105). Regarding the lung lesions, the efficacy of USG is well documented in many pulmonary conditions, such as pneumonia, pneumothorax, or pulmonary edema (106) while its efficacy in AAV-related lung lesions is not well established. However, in the recent study examining the utility of USG in AAV patients, it has been shown a high consistency of this method with CT findings (107). In turn, ultrasound examination of the pleural space is a highly sensitive and specific diagnostic tool in cases of pleural involvement and pleural effusion, allowing for the designation of a biopsy site, if needed and monitoring fluid dynamics (106).

4.2.3 Endoscopy

FOB is indicated for GPA patients who have respiratory symptoms, abnormalities on pulmonary function testing, or abnormal findings on chest imaging (26). Samples obtained during FOB for microbiology and histology examinations are important parts of the differential diagnosis of lung nodules and masses. FOB is the gold standard for the diagnosis of airway involvement. It allows for direct visualization of the tracheobronchial tree, detecting mucosal lesions, SGS, bronchial stenoses and mass-like granulomatosis (108). It may detect also not advanced inflammatory lesions that have only subtle pulmonary consequences, but may explain some clinical symptoms, such as cough or localized wheezing (23). In addition, bronchoscopy allows to obtain a biopsy and precise mapping of inflammatory lesions before therapeutic interventions (23, 26, 108) as well as it is useful tool to treat and monitor tracheobronchial lesions.

FOB with BALF examination is the gold standard procedure to diagnose DAH (23, 26, 108) and might confirm the diagnosis despite the absence of clinical or biological arguments even in 16% of patients (108), with an increasingly hemorrhagic BALF after sequential sampling is specific for DAH and is the best diagnostic test (46). In addition, BALF examination is a valuable to rule out other etiologies for pulmonary infiltrates (infections in particular) (23, 26, 108). Classically, BALF confirms DAH with one of the following features: bloodier BALF return, Golde score > 20 (>100 for severe) or hemosiderin-laden macrophages >20%. However, DAH may have a subclinical course, with 5% defined as the upper limit of hemosiderin-laden macrophages (108). Although FOB is necessary for the unequivocal diagnosis of DAH, it could temporarily worsen the patient's respiratory status. Therefore, it is essential to make sure before performing this procedure, that there are facilities to upgrade the level of care of patients, including the possibility of intubation and mechanical ventilation (26, 108).

The role of endoscopy of the diagnosis of gastrointestinal involvement in GPA patients is being debated because findings are not specific and it is common with normal macroscopic findings even

in cases with severe involvement (70); however, it can be of differential diagnostic importance and should be considered in patients with gastrointestinal manifestations. The most frequent findings include erosions and ulcers with obstructed blood flow involving mainly gastroduodenal and colonic tract, however, esophagus may be also affected (109, 110). Other endoscopic features are nonulcerative uncharacteristic inflammations manifesting as red and swollen mucosa in affected parts of the digestive tract (70).

In patients with ENT manifestations, nasal endoscopy should also be considered. It usually reveals crusting, friable erythematous mucosa, and granulation. In turn, laryngoscopy is an alternative technique for SGS confirmation and grading in GPA patients (111).

Selected imaging findings in patients with GPA shows Figure 3.

4.2.4 Biopsy and histology examination

Biopsy remains a gold standard of diagnosis GPA and is strongly recommended (73, 76). However, the biopsy may not be feasibly obtained in every patient and starting of treatment should not be delayed by waiting for histological examination (73, 78). The role of the biopsy may be particularly important in cases when ANCA is negative, and in limited form of the disease. Major histological features characterized GPA include necrosis, granulomatous inflammation, and vasculitis (112); however, it is rare for biopsy specimens to present with all three of them (113) and biopsies may show atypical or incomplete histological features, therefore correlation with clinical, serological, and radiological findings, and experience and close collaboration of pathologist and clinician are necessary to make the correct diagnosis (114). Of note, the diagnostic yield of the histological examinations may vary significantly depending on the biopsied site (78), and in many cases biopsies of affected organs must be repeated several times to confirm diagnosis (115, 116). Furthermore, the lack of typical histological features does not exclude GPA.

Regarding the respiratory tract, the sensitivity of biopsies is not satisfactory. Although the upper respiratory tract is easily accessible, biopsy of this localization shows non-specific inflammation even in 61% of patients (117), while only in 24% biopsy is diagnosed as typical of GPA, and diagnosis could be confirmed in 42% as typical of GPA from the results of multiple biopsy specimens (116). In turn, in patients with pulmonary lesions, in cases of transbronchial lung biopsies the diagnostic yield is about 12% (118). Whereas, in cases of visible endobronchial lesions, bronchoscopically obtained samples may support the diagnosis in about 50% of patients when other supportive features are present, while only in 25% are diagnostic by themselves (26). Surgical lung biopsy provides a greatest diagnostic value (117), but it is no longer used routinely due to the risk of serious complications; however, in patients with isolated pulmonary lesions that cannot be clearly attributed to GPA, thoracoscopic or open lung biopsies should be considered (73).

In contrast, to the respiratory tract, the diagnostic yield of a kidney biopsy in AAV patients can be as high as 91.5% (119). According to current guidelines, kidney biopsy should be performed where possible, however, in the context of positive MPO- or PR3-ANCA serology and a clinical picture compatible with AAV, an immediate biopsy may not be necessary and should not delay the initiation of treatment (73, 119). Biopsy specimens in GPA usually show a pauci-immune GN, with segmental necrotizing pattern (often crescentic) and extra-capillary proliferation are the most common findings (85.1 and 91.5% respectively) (120). The histopathological subtypes of kidney involvement do not guide treatment decisions (73), however, kidney biopsy provides prognostic information (121, 122), while repeated kidney biopsy may be useful to differentiate recurrent or refractory disease activity from damage or other alternative diagnoses (123).

Although the nerve biopsy remains the gold diagnostic standard, diagnosis of peripheral neuropathy is mainly based on clinical evaluation and can be confirmed by electrodiagnostic studies (124). In a large cohort of 955 AAV patients (DCVAS study), only 12% had nerve biopsies, of which 53% had definitive vasculitis (125). The most common nerves chosen for this procedure include the sural, superficial peroneal, and superficial radial nerves (126). The histological findings are characterized by the axonal degeneration of the nerve fibers and inflammation of the epineurial vessels accompanied by the destruction of vascular structures (126). Diagnostic yield of muscle biopsy is 51%, with factors predicting of diagnostic accuracy include ANCA type (MPO), sex (female) and higher neutrophil count (127).

Skin biopsy, while underutilized (performed in 22–44% of patients), is frequently found to be an effective test suitable for diagnosis of AAV (diagnostic in 68–94% of patients) (128). In the large study of 1,553 patients with mixed AAV, pathological analysis showed vasculitis and/or granulomatous infiltrates in 87.5% of GPA patients with skin manifestations, with vasculitis was more frequently observed in purpura and nodules, while granulomas were differently located and organized within vessels or the interstitium according to the type of lesions (129). Although these lesions are specific for GPA, they do not occur exclusively in GPA and can also be seen in other vasculitic disorders (65).

Cardiac biopsy is rarely performed to confirm cardiac involvement in GPA, as this manifestation is usually recognized based on the clinical background and non-invasive imaging modalities (ECG, ECHO, and cardiac MR) (73). In cases with known GPA, multiorgan manifestation and ANCA presence, the diagnosis is quite straightforward, and biopsy can usually be avoided. However, when symptoms are not attributable to GPA or cardiac disease is the only manifestation of vasculitis, cardiac biopsy may be necessary to confirm diagnosis (130). However, typical histological GPA features are rarely found (in less than in 2% of patients) (113). The low diagnostic accuracy is likely due to the rates of sampling errors. Additionally, the patchy cardiac lesions might complicate diagnosis (131).

Finally, the histopathological confirmation of gastrointestinal vasculitis is also difficult to obtain. Tissue samples collected during endoscopy usually reveal nonspecific inflammation or ulcers (69), while vasculitis can be detected histologically only in 8% of patients (109). Some authors speculate that this may be a result of biopsy taken too superficially during the endoscopy procedures, as the small and medium vessels, typically involved in GPA, are located deeper in the submucosa (69). Indeed, the results may be better for surgical removed specimens where signs of necrosis related to vasculitis may be found even in 90% of cases (109).

4.2.5 Pulmonary function tests (PFTs)

PFTs are an integral part of the examination of the GPA patients, especially when respiratory symptoms or radiographic abnormalities of the lung or airway are present. The most common findings include airflow obstruction (40% of cases) (132) often in association with reduced diffusion lung capacity for carbon monoxide (DLCO), especially when accompanied by ILD (26). However, an alteration in the DLCO may be the first sign of DAH (26). In SGS, typically, the flow-volume curve shows a flattening in both respiratory and expiratory phase, consistent with an extrathoracic airway obstruction (28). It has been demonstrated

the correlation between PFTs results and chest imaging findings in AAV patients. Patients with pulmonary fibrosis suffer more often from impaired DLCO whereas patients who show signs of lung consolidation, had a high risk for a restrictive pattern (133). Interestingly, it has been shown that abnormalities in PFTs in GPA patients are not always related to pulmonary involvement. In the study of 147 mixed AAV, for GPA, forced vital capacity expiratory (FVCex), residual volume (RV) and DLCO were statistically lowered compared to expected values of 100% predicted, and there was no significant difference between patients with or without pulmonary manifestations. In contrast, in patients with MPA, relevant impairments of FVCex, total lung capacity (TLC) and DLCO were observed compared to the standard population, and these changes were significantly stronger in MPA-patients with pulmonary involvement (133).

4.3 Differential diagnoses

As GPA has a multisystemic nature, the differential diagnosis is broad, and many conditions could mimic GPA, and should be ruled out before a final diagnosis can be established (Table 2). Differentiation is particularly difficult when the disease is confined to one organ. For example, isolated lung disease must be primarily differentiated with infection and malignancy, with the tests should include tuberculosis and fungal infections. Similarly, in the isolated sinus disease, infectious cause as the first should be excluded (88). On the contrary, infection can coexist with GPA and does not exclude active vasculitis. The appearance of the air-fluid levels in the lung cavities may indicate that they become infected, what should lead to a careful microbiological evaluation with subsequent targeted antibiotic therapy (26). Cavities may be also colonized by fungi - mostly *aspergillus fumigatus*, what may pose a particular difficult diagnostic challenge, because the radiographic features of fungal infections are often similar to those of GPA, and tests for fungal infections are often negative in patients without criteria for invasive aspergillosis (23). Next, pulmonary consolidations, reflecting the NGI, may be radiographically indistinguishable from pneumonia and organizing pneumonia (OP), with the latter representing the diagnostic challenge (26). Namely, the radiological pattern is very similar and practically indistinguishable from GPA limited to the lung and manifested by non-cavitated nodules or pulmonary consolidations. In addition, OP responds very well to CS treatment, similarly as GPA; and finally, OP pattern can occur in GPA (26).

Due to the different management, outcome, and prognosis, differentiating GPA from other AAV is also important. Despite GPA, MPA and EGPA belong to the same group of vasculitis, they have some unique features (Table 4) (88). However, polyangiitis overlap syndromes may occur, when the disease does not fit precisely into a single category of vasculitis classification and/or overlaps with more than one category (76). Particularly, differentiating between GPA and MPA can be demanding because of significant overlap in the signs and symptoms and in the ANCA serologies. In addition, patients initially presenting with only symptoms consistent with MPA, could later develop manifestations more compatible with GPA. A key distinguishing feature of these entities is the presence of granulomatous inflammation in GPA and its lacking in MPA (2).

4.4 Phenotypes

In the last decade, several studies have indicated that ANCA specificity better characterized AAV patients, than clinical diagnoses of GPA or MPA, regarding to clinical features, treatment response, and prognosis (134, 135). Moreover, the rationale for an ANCA serology-based subclassification was further supported by evidence of genetic susceptibility (14), and immunological profile (136). Generally, patients with PR3-ANCA positivity more often have a presentation consistent with GPA, whereas those with MPO-ANCA tend to have features of MPA [however, about 10% of GPA patients are MPO-ANCA positive, and in MPA, PR3-ANCA can be also detected (137)]. Consistently, in AAV with PR3-ANCA positivity granulomatous pattern dominates, while in AAV with MPO-ANCA, vasculitic pattern is predominantly present (138). Given the significant overlap in clinical presentations and the separate genetic associations, reclassification of AAV is being considered according to the ANCA type (PR3 versus MPO) rather than traditional clinical phenotype (GPA versus MPA).

The combination of ANCA type with clinical phenotype identifies additional subtypes with unique features. Several studies have shown that MPO-ANCA positive GPA patients have more frequently limited disease, and a high prevalence of SGS, as well as fewer constitutional symptoms and milder renal lesion at diagnosis compared with those tested as PR3-ANCA positive. In addition, they are predominantly female and younger, and have significantly lower relapse rates (134, 137). However, in the recent study, within the GPA group (N = 151, 29% MPO+) patients with MPO-ANCA were older, and characterized

TABLE 4 Differentiating GPA from other AAV.

GPA	MPA	EGPA
Typically ENT, lung and kidney involvement (ELK) ENT-necrotizing, destructive lesions Lung – nodules, masses, cavities, infiltrates, DAH Kidney – higher eGFR at presentation, more active lesions (necrosis and crescents) Heart – rare involved, often asymptomatic ANCA-more often, but not exclusively associated with PR3 Histology – granulomatous inflammation, vasculitis	Typically lung and kidney involvement ENT – considered to be rare Lungs – pulmonary fibrosis, DAH Kidney – more chronic lesions (sclerosis and tubulointerstitial fibrosis) Heart –uncommon ANCA-more often, but not exclusively associated with MPO Histology - only vasculitis, lacking of granulomatous inflammation	Associated with eosinophilia, asthma is a predominant respiratory symptom ENT – allergic symptoms, non-destructive Lungs – infiltrates and nodules, DAH rarely seen but also may occur Kidney – occurs less likely and a lesser degree Heart – often involved and associated with damage and higher mortality ANCA – mainly MPO, but detected only in about 40% of patients Histology – granulomatous inflammation usually accompanied by eosinophils, eosinophilic vasculitis

GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear, nose, throat; DAH, diffuse alveolar hemorrhage; ANCA, antineutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase 3, eGFR: estimated glomerular filtration rate.

by less prevalent ENT and neurological manifestations, increased end-stage renal disease (ESRD) and mortality (139).

In part of patients with AAV, co-presentation of ANCA and anti-GBM antibody occurs, what is associated with distinguish phenotype. This dualism affects predominantly patients with MPO-AAV (10–40%), while among those with PR3-AAV about 5–14% have circulating anti-GBM (3). Double-positive patients share characteristics of AAV, such as older age and longer symptom duration before diagnosis, and features of anti-GBM disease, such as severe renal disease and high frequency of lung hemorrhage at presentation (140).

Finally, recently three subclasses of AAV have been proposed, based on ANCA specificity during it clinical course, and described as non-severe AAV (mainly PR3-AAV limited disease), severe PR3-AAV (with multiorgan potentially life-threatening manifestation), and severe MPO-AVV (with dominant symptoms of vasculitis and chronic organ damage) (138). More recently, the new fourth subphenotype has been identified based on serological (including ANCA type) and clinical features, characterized by multiorgan involvement, high risk relapse, relatively young age, and marked mortality (141).

Interestingly, there are preliminary studies reported the association between clinical characteristics and specific peripheral immunological profile in patients with AAV allowing classify these patients into originally useful subgroups associated with specific organ involvement (CNS and kidneys) and defined therapeutic prognosis. These promising results suggest that immuno-phenotyping may become a new way to better identify and classify patients with AAV in the future (142).

5 Disease assessment and prediction of relapse

5.1 Severity of the disease

After diagnosis, GPA should be classified according to its extent and severity. There have been several methods to grade disease severity in patients with GPA (Table 5) (68, 73, 143–145); however, the most recent EULAR recommendations maintained the AAV categorization proposed in 2016 that distinguishes patients with and without organ-threatening or life-threatening disease, instead into those with "severe" and "non-severe" AAV, with the classification of the organ symptom as life-threatening or not, depends on the clinical assessment of individual patients (73). In 1996, the FVSG created the Five Factor Score (FFS), a prognostic score for patients with PAN, EGPA and MPA associated with severe organ involvement (146), while revised in 2009 (published in 2011) included all types of small vessel vasculitis, with the addition of GPA particularly. This scoring system distinguishes AAV with good (FFS = 0) or bad (FFS ≥ 1) prognosis with the sole criterion of measuring mortality (68).

5.2 Disease activity and monitoring

5.2.1 Laboratory markers

Due to the chronic nature, the tight follow-up of GPA is necessary to provide an appropriate management, however, for date, no reliable marker for disease activity or to predict relapse has been found (147–150). Basic inflammatory markers, as ESR and CRP are non-specific with limited clinical use (151); however, some studies demonstrated that when a combined rise in CRP, neutrophil count, and PR3-ANCA was observed in the 6-month period before a relapse event, 59% of patient relapses could be predicted (152). The new intensively developing technology is metabolomics analysis exploring metabolic changes in AAV patients well separating these entities from other diseases (153). Furthermore, in recent study, in patients with PR3-AAV, homozygosity for PRTN3-Val^{119}Ile polymorphism appears associated with higher frequency of severe relapse. However, further studies are necessary to better understand the association of this observation with the risk of severe relapse (154).

Regarding the ANCA, the value of its testing in GPA monitoring remains controversial and still is being debated (135, 155–159). Some studies indicated that patients achieving ANCA negativity during remission are 40% less likely to relapse (160), while those with persistent ANCA have higher risk of relapse, with a higher rate among positive PR3 patients with renal involvement or DAH treated with rituximab (57). However, in other studies, decreases in PR3-ANCA levels were not associated with shorter time to remission, and increases were not associated with relapse (158, 161). This discordance between ANCA serology and GPA activity limits support for its use as a reliable biomarker. However, despite these discrepancies, results of recent clinical studies demonstrated that in patients PR3-ANCA positive treated with rituximab, relapses without at least one event between B-cells repopulation or rise of ANCA titers were unusual, what could indicate that combining use of these two biomarkers may be value to predict relapse, especially in this specific cohort (159). Nevertheless, it is not currently recommended to perform ANCA testing for GPA monitoring and the sole increase in ANCA concentrations or reappearance of ANCA is not an indication for treatment implementation, if it is not accompanied by clinical symptoms (73, 76).

Although we still do not have sufficient knowledge how to predict relapse of GPA, some clinical and serological features associated with higher risk of relapse have been reported (156, 159, 162) (Figure 4). More recently, the FVSG has been proposed and validated a relapse scoring system for AAV patients based on the PR3-ANCA positivity, older age (≥ 75 years), and higher eGFR (≥ 30 mL/min/1.73 m^2). Each of these items was assigned one point (range 0–3), with the 5-year relapse risk at 8% for zero points, 30% for one point, 48% for two points, and 76% for three points in the validated cohort (63). This score may be used in clinical practice, however its significant to tailored duration of maintenance therapy requires further prospective studies.

5.2.2 Clinical assessment

While the search for a marker of disease activity is still ongoing, the structural clinical patient evaluation is recommended (73), with the Birmingham Vasculitis Activity Score (BVAS) is an approved, easily available, and effective tool to evaluate disease activity in clinical practice (163). BVAS has negative prognostic value (164) and it has been identified as predictive factor for relapse (162) and a risk factor for venous thromboembolism in patients with AAV (165). Interestingly, patients with AAV who were ever smoked have increased BVAS and more frequent renal replacement therapy and IS treatment, resulting in a poorer survival prognosis (166). The next clinical score system designed and validated for use in patients with GPA is the Disease Extent Index (DEI), but it involves only symptoms attributable to active vasculitis (not persistent symptoms) (167). This system correlates well with the BVAS, however, it quantifies different domains of the disease, and some authors recommend its use in conjunction with the BVAS in assessments of patients with GPA (167). Finally, the Vasculitis Damage Index (VDI) is a sensitive and credible clinical tool for quantifying

TABLE 5 Assessment of extension and severity of AAV (including GPA).

WGET Research Group 2002	EUVAS 2009	FVSG (FFS) 2009	ACR 2021		EULAR 2022	
			Severe disease	Non-severe disease	Disease with organ/life-threatening manifestations	Disease without organ/life-threatening manifestations
1.Limited -disease which do not pose an immediate threat to either a critical organ or to the patient's life, specifically: - There are not RBC casts in the urine - The serum Cr must be ≤1.4 mg/dL and the rise in serum Cr cannot be greater than 25% above the patient's baseline - Lug involvement must be circumscribed (the room air $Pa0^2 > 70$ mmHg or air 0^2 saturation by pulse oximetry >90%) - No disease may exist within any other critical organ (e.g., GI, eyes, CNS) 2. Severe – disease which is not classifiable as limited	1. Localized – limited to the upper and/or lower respiratory tract 2. Early systemic-any, without organ-threatening disease 3. Generalised-renal or other organ-threatening disease, Cr < 500 µmol/L (5.6 mg/dL) 4. Severe – renal or other vital organ failure, Cr > 500 µmol/L (5.6 mg/dL) 5. Refractory – progressive disease unresponsive to treatment	1.Age > 65 years 2.Cardiac insufficiency 3.Renal insufficiency (stabilized peak Cr ≥ 150 µmol/L) 4.GI 5.Absence of ENT FFS = 0 non-severe disease FFS ≥ 1 severe disease Mortality rates: FFS = 0 9% FFS = 1 21% FFS ≥ 2 40%	Vasculitis with life- or organ-threatening manifestations, e.g., DAH, glomerulonephritis, CNS involvement, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, limb/digit ischemia	Vasculitis without life- or organ-threatening manifestations, e.g., rhinosinusitis, mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis	DAH Glomerulonephritis Meningeal involvement CNS involvement Retro-orbital disease Cardiac involvement Mesenteric involvement Mononeuritis multiplex	Nasal and paranasal disease (without bony erosion, cartilage collapse or olfactory dysfunction or deafness) Skin involvement (without ulceration) Myositis (skeletal muscle only) Non-cavitating lung nodules Episcleritis
					There are only examples (many other symptoms of AAV exist); assessment of severity may differ in the individual patients	

FFS, five-factor score; GPA, granulomatosis with polyangiitis; GI, gastrointestinal involvement; Cr, creatinine; RBC, red blood cells; CNS, central nervous system; ENT, ear, nose, throat; DAH, diffuse alveolar haemorrhage; ACR, American College of Rheumatology; FVSG, French vasculitis study group; EULAR, European league against rheumatism; EUVAS, European vasculitis study group; WGET, Wegener's granulomatosis etanercept trial.

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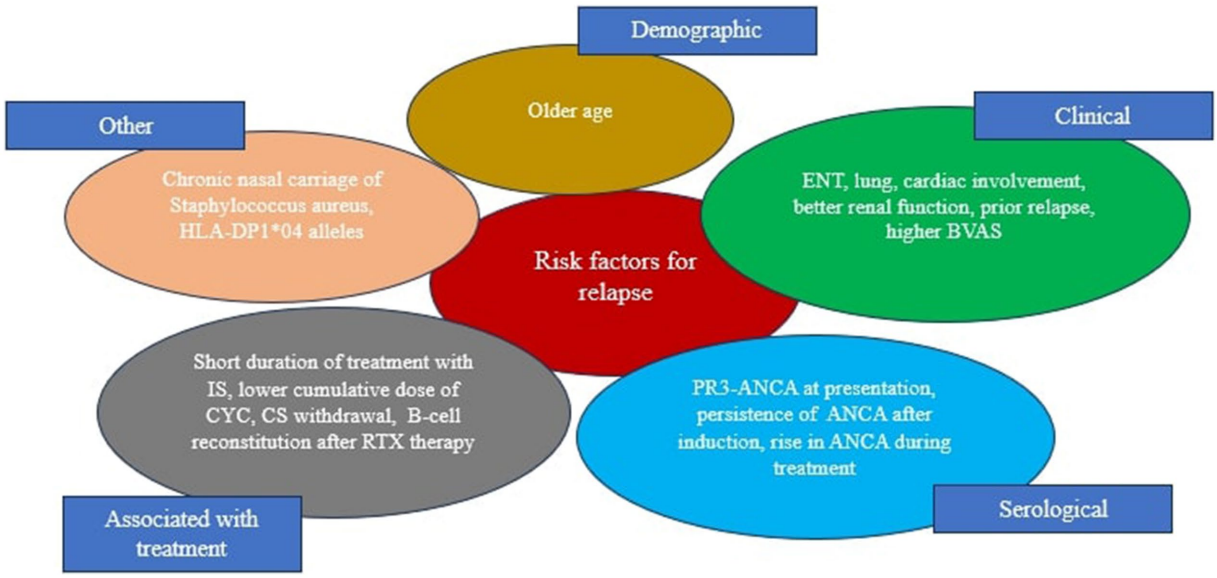

FIGURE 4
Factors increasing the risk of relapse of AAV.

damage in patients with AAV (168), however, it should be well differentiated from active vasculitis. VDI has been identified as one of the factors associated with higher mortality in AAV patients (169). In addition, although VDI and BVAS are separate systems scores, the link between them has been demonstrated. In the recent study analyzing the prevalence and impact on damage accrual of different levels of disease activity in AAV patients, the prolonged low disease activity state (defined as $0 < \text{BVAS} \leq 3$ and taking low dose of $\text{CS} \leq 7.5$ mg/day and lasting ≥ 2 consecutive years) correlated with increased VDI (170).

As AAV has progressed from a life-threatening disease to a chronic, relapsing condition, the importance of assessing the disease from the patients' perspective has become increasingly important. The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group drew attention to this issue and proposed a composite assessment tool for AAV based on the BVAS, VDI, mortality and including patient reported outcomes (PROs) (171). More recently, an international survey has been conducted (Delphi exercise) aimed to reach consensus about which measures are considered by patients and physicians to be most important when assessing activity of AAV (172). The consensus between patients and physicians on many items has been found, however, achievement of specific BVAS scores were highly rated only by physicians, while items highly rated only by patients included laboratory measures (changes on urinalysis and acute phase reactants), pain and fatigue. These data indicates that patients' participation in the assessment of disease activity may increase significantly in the future.

6 Conclusion

Major developments in the diagnosis of GPA have been made over the past decades. New imaging techniques allow recognition of specific organ involvement, and the new classification criteria contributes to better qualify the patients for the epidemiological and therapeutic studies. However, the needs such as the lack of uniformity and validated diagnostic criteria remain unmet, and the question is, whether and how the current classification criteria could help to develop the diagnostic criteria to be translated into clinical practice (173). Furthermore, a reliable biomarker to predict relapse is still lacking, which poses a risk of suboptimal disease control or unnecessary patient exposure to potentially toxic therapy (151). A big step forward is distinguishing new AAV phenotypes based on the ANCA specificity and significant advances in identifying the nuances between PR3-ANCA and MPO-ANCA vasculitis. In turn, the increasing knowledge about the distinct immunological profiles may provide an understanding disease pathophysiology and prognosis, with the result that immuno-phenotyping may become a new way to better identify patients with AAV in the future (142).

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

MP-P: Writing – original draft. JF: Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

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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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Regional diversity in drug-induced lung diseases among the USA, European Union, and Japan

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Background: Drug-induced lung disease (DILD) is a considerable and potentially fatal adverse event with poorly understood risk factors. Large-scale, data-driven analyses investigating regional discrepancies in DILD incidence are lacking. The aim of this study was to investigate the potential association among DILD prevalence, regional differences and other factors based on large-scale data base.

Methods: This retrospective observational study analyzed spontaneous adverse event reports from the FDA Adverse Event Reporting System (FAERS) database between January 2010 and December 2020. Regional disparities in DILD incidence were assessed among reports from the United States of America (USA), the European Union (EU), and Japan (JP). Using multivariate logistic regression accounting for age, sex, and reporting years, we calculated the reporting odds ratios (RORs) with 95% confidence intervals. Subgroup analyses were performed for different types of anticancer agents, including tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors (ICIs), antibody–drug conjugates (ADCs), and cytotoxic agents.

Results: Regional differences in RORs were observed for anticancer drugs in reports from JP and the EU compared with those from the USA (JP, ROR 4.432; EU, ROR 1.291) and for non-anticancer drugs (JP, ROR 3.481; EU, ROR 1.086). Significantly higher RORs were observed for all anticancer drug regimens reported in JP than in the USA (TKIs, ROR 3.274; ICIs, ROR 2.170; ADCs, ROR 2.335; cytotoxic agents, ROR 3.989). The EU reports exhibited higher RORs for TKIs and cytotoxic agents than the USA reports, with no significant differences in ICIs or ADCs (TKIs, ROR 1.679; ICIs, ROR 1.041; ADCs, ROR 1.046; cytotoxic agents, ROR 1.418).

Conclusion: The prevalence of DILD in JP, the EU, and the USA differed. These findings have important implications in evaluating the safety profiles of drugs and patient safety in drug development and clinical practice. This study is the first to identify regional differences in DILDs using a large global database.

KEYWORDS

drug-induced lung disease, FDA adverse event reporting system, ethnic diversity, interstitial lung disease, real-world data

1 Introduction

Drug-induced lung disease (DILD) is an adverse event (AE) with a fatality rate of up to 40% (1–3). Anticancer drugs are the most common cause of DILDs, and their prevalence has increased with the use of recently developed anticancer drugs (3). Specifically, the occurrence rate of DILDs in patients administered with tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) is 5–20%, which is higher than the approximately 2% rate in patients administered with classical cytotoxic agents (2, 4). The mortality rate of DILDs associated with anticancer drugs, particularly TKIs and ICIs, is extremely high, with mortality rates of 35–40% and 15–20%, respectively (2, 5). Although DILDs have a considerable clinical impact, their associated predictive factors have not been elucidated.

Regional differences in DILD incidence have been noted in several clinical trials, with relatively high incidences reported in Asia (4). The incidence of DILDs after treatment with molecularly targeted drugs [e.g., epidermal growth factor receptor (EGFR) TKIs] in Asia is 10 times higher than that in non-Asian regions. The mortality rate of DILDs associated with molecularly targeted drugs is higher than that of DILDs associated with drugs with other mechanisms of action (1). For antibody–drug conjugates (ADCs) and ICIs, the incidence of DILDs is relatively high in Asian (Japanese) patients. In clinical studies of ICIs in Asia (Japan), regional differences in DILD prevalence have been observed, with a reported rate of 15–20% (4, 6–8).

Large-scale database analyses investigating the regional differences in DILDs have not yet been reported. The Food and Drug Administration Adverse Event Reporting System (FAERS) is the largest database of spontaneous reports on drug-related AEs worldwide. However, no previous reports have employed these types of large-scale databases to examine ethnic differences in DILD development. This study aimed to investigate the potential associations among DILD prevalence, regional differences, and other factors by using FAERS data.

2 Materials and methods

2.1 Study design and data source

This retrospective observational study was conducted using data from the FAERS database. FAERS data were downloaded through the USA Food and Drug Administration (FDA) website,[1] and DILD reports issued between January 2010 and December 2020 were identified. As of January 2023, more than 14 million reports have been collected and analyzed by downloading raw data. AEs suspected to be associated with DILD in the FAERS were reviewed separately. The following information was collected: patient characteristics (date of AE, date of report to the FDA, age at AE, sex, weight, reporter, reporting country, and country of occurrence), drug information (suspected drug identification, drug name, route of administration, dose, administration date, treatment start date, and treatment end date), patient outcomes (death and hospitalization), and source of information (foreign, clinical trial, and consumer). The FAERS is a publicly accessible, anonymous database. The requirement for informed consent and approval from the institutional review board was waived.

2.2 Data collection and definition

We investigated AEs reported between January 2011 and December 2020 in patients aged 20–100 years at the time of AE occurrence. In the FAERS, the Medical Dictionary of Regulatory Activities organ system classification and preferred term level were used to describe suspected AEs.

The investigators (respiratory physicians) reviewed all reported AEs and defined DILD items that could be clinically determined as DILDs. A comprehensive inventory of DILD items was compiled (Supplementary Table S1).

All reported drugs were reviewed by the investigators and classified as either anticancer or non-anticancer. Anticancer drugs were further classified into TKIs, ICIs, ADCs, antibodies, cytotoxins, hormones, and others according to their mechanisms of action (Supplementary Table S2). The causal relationship between a combined regimen (drugs with different modes of action) remains unclear, and only monotherapeutic anticancer drugs or drugs with the same known mechanisms of action were included in the analyses.

Regional differences in DILD incidence were examined using data from the USA, the European Union (EU), and Japan (JP) reports. The names of the reporting countries were collected from the FAERS data, and the EU included member countries as of August 2022.[2] Members of the EU were identified and listed by country codes, and the program automatically identified matching records.

2.3 Statistical analysis

Patient characteristics in each region were collected as follows. The median and the interquartile range were calculated for continuous patient characteristics. For categorical patient characteristics, frequencies were tabulated.

The risk of DILDs in the EU and JP compared with that in the USA was assessed using the reporting odds ratio (ROR), defined as the ratio of the odds in reports from the JP or the EU to that in the USA, and the odds were defined as the ratio of the presence of DILD to the absence of DILDs in each region. An ROR close to one indicated no difference in the frequency of DILDs between the EU (or JP) and the USA reports. When the ROR was >1, the risk of DILDs in the EU (or JP) reports was higher than that in the USA reports.

A logistic regression model was used to calculate the DILDs and 95% confidence intervals (CIs) for the EU and JP reports relative to those for the USA reports. Multivariate analysis was performed using a logistic regression model to adjust for confounding variables, including sex (male/female), age (10-year range), and year of occurrence (2010–2014 or 2015–2020). To assess the risk of DILDs by drug type, we performed the same analysis for drug types (i.e., non-anticancer and anticancer drugs) with a reasonable prevalence in single agents or agents with the

1 https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html

2 https://www.eeas.europa.eu/_en?s=169

same mechanism of action (TKIs, ICIs, ADCs, and cytotoxic agents) in subgroup analyses. All analyses were performed using SAS version 9.4.

3 Results

3.1 Patient demographics

We identified patients with AEs and DILDs in reports from the USA [3,057,102 and 73,137 (2.39%), respectively], EU [934,576 and 29,533 (3.16%), respectively], and JP [228,064 and 22,463 (9.84%), respectively]. Sex-reporting bias was also observed. The reports indicated relatively older age in JP, fewer fatalities and more consumer reports in the USA, and more patients with onset within 90 days in JP. No other significant differences in characteristics were found among the reports from the three regions (Table 1). No significant difference was noted in the reporting proportion (DILD events per total AEs) based on the reported years (Figure 1).

TABLE 1 Country-wise characteristics of patients with DILDs in the FAERS (data available).

	USA	EU	JP
Total reports of AE	10,417,014	3,363,540	743,229
Total reports of DILD	73,137	29,533	22,463
Sex			
Male	29,674	15,513	14,244
Female	43,108	13,804	8,062
Unknown/missing	355	216	157
Age (years)			
Median (IQR)	65 (56–74)	67 (56–75)	71 (63–78)
Reporting year			
2010–2014	27,222	9,518	8,745
2015–2020	45,915	20,015	13,718
Outcome			
Fatal	4,439	3,663	3,491
Other/Missing	68,698	25,870	18,972
Type of reporter			
Physician	15,585	14,710	15,081
Consumer	30,520	4,409	3,018
Pharmacist	7,690	1,366	1,735
Other/Missing	15,585	14,710	15,081
Time to onset (days)			
<90	15,555	10,878	12,600
90–365	9,909	4,582	3,620
≥ 365	12,849	3,961	1,775
Drugs			
Non-anticancer drug	48,750	15,354	9,711
Anticancer drug	24,387	14,179	12,752
TKIs	4,489	2,047	2,160
ICIs	1,144	1,595	3,177
ADCs	88	78	64
Cytotoxics	3,359	3,778	2,269

AE, adverse event; DILDs, drug-induced lung diseases; FAERS, Food and Drug Administration Adverse Event Reporting System; US, United States; EU, Europe; JP, Japan; TKIs, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; ADCs, antibody–drug conjugates; cytotoxics, cytotoxic drugs; IQR, interquartile range.

3.2 Reported regions and DILDs

Univariate analysis results (Table 2) indicated that the incidence of DILDs was relatively low in females and increased with age. As shown in Figure 2 and Table 3, multivariate analysis revealed a higher reporting proportion and RORs of non-anticancer drugs in JP than in the USA. By contrast, no difference in DILD incidence rates associated with non-anticancer drugs was found between reports from the EU and USA. Significant differences in RORs were also observed across anticancer drugs in reports from JP and the EU compared with those from the USA (JP, ROR 4.432 [95% CI, 4.366–4.499]; EU, ROR 1.291 [95% CI, 1.274–1.308]). The fatality rates associated with DILDs in the USA, EU, and JP reports were 6.1, 12.4, and 15.5%, respectively, with a significantly higher proportion of DILDs in the EU and JP reports than in the USA reports.

3.3 Subgroup analysis

The results of multivariate analysis for each single-agent regimen of anticancer drugs showed that the RORs in reports from JP were significantly higher than those in reports from the USA (TKIs, ROR 3.274 [95% CI, 3.105–3.451]; ICIs, ROR 2.170 [95% CI, 2.025–2.325]; ADCs, ROR 2.335 [95% CI, 1.666–3.272]; and cytotoxic agents, ROR 3.989 [95% CI, 3.776–4.215]). Reports from the EU had higher RORs than those from the USA for TKIs and cytotoxic agents; no statistically significant differences were noted between the RORs of ICIs and ADCs (TKIs, ROR 1.679 [95% CI, 1.594–1.769]; ICIs, ROR 1.041 [95% CI, 0.965–1.123]; ADCs, ROR 1.046 [95% CI, 0.763–1.434]; and cytotoxic agents, ROR 1.418 [95% CI, 1.354–1.485]).

4 Discussion

This study is the first to identify regional differences in DILDs using a large, global database. This analysis revealed that the prevalence of DILDs was significantly higher in JP than in the USA for all anticancer and non-anticancer drugs. This study confirmed the previously reported higher prevalence of DILDs in clinical trials due to TKIs and ADCs as well as the previously unreported higher prevalence of DILDs due to ICIs in JP than in Western countries (4, 6–8). The EU had higher RORs than the US for TKIs and cytotoxic agents, and no significant differences in RORs were observed between ICIs and ADCs.

Previous clinical trials have shown that Asians, specifically Japanese, are susceptible to DILDs after treatment with certain drugs, and the incidence of DILDs caused by gefitinib, an EGFR-TKI, is relatively high in the Asian population (9). Similar trends have been reported for ADCs and TKIs, with Asians having a relatively high risk of developing DILDs (3). In the present study, a discernible discrepancy in the incidence rates of DILDs between reports from JP and the USA was observed. This disparity has been observed in the contexts of TKIs and ADCs. In terms of ICIs, a few

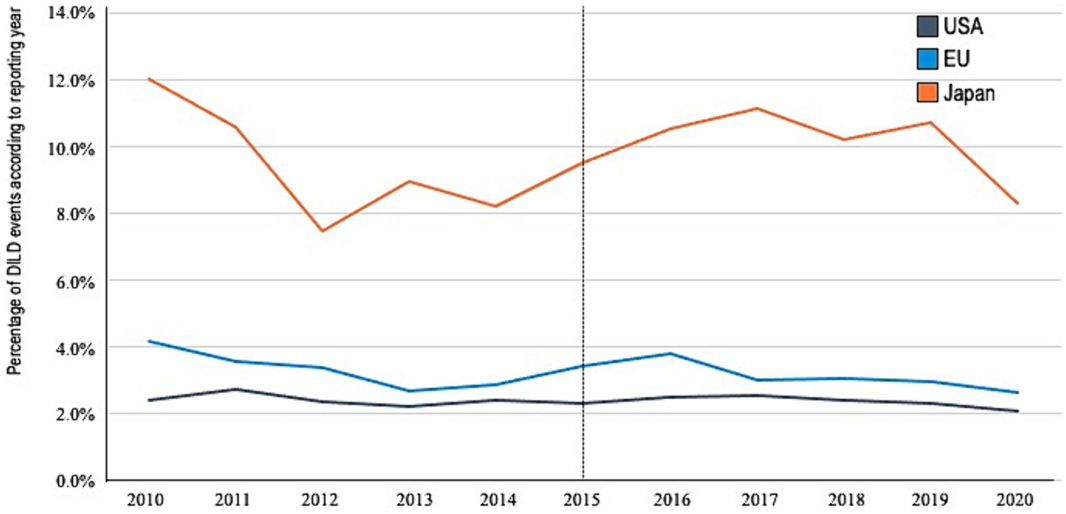

FIGURE 1
Reporting percentage by year. DILDs, drug-induced lung disease; US, United States; EU, European Union; JP, Japan.

TABLE 2 Univariate analysis of DILDs reported in the FAERS database.

	No. of DILD	Univariable analysis	
		Reporting odds ratio (95% CI)	*P*
Sex			
Male	61,522	1	
Female	67,039	0.616 (0.609–0.623)	<0.0001
Age group			
20–29	2,512	1	
30–39	4,741	1.309 (1.247–1.374)	<0.0001
40–49	9,973	1.907 (1.825–1.992)	<0.0001
50–59	21,591	2.590 (2.485–2.699)	0.0004
60–69	35,683	3.733 (3.585–3.887)	<0.0001
70–79	36,388	4.882 (4.688–5.084)	<0.0001
80–89	15,799	4.845 (4.645–5.054)	<0.0001
90–99	1,874	4.392 (4.136–4.664)	
Years			
2010–2014	46,747	1	
2015–2020	81,814	1.018 (1.007–1.030)	0.0019
Region			
USA	74,548	1	
EU	31,009	1.291 (1.274–1.308)	<0.0001
JP	23,004	4.432 (4.366–4.499)	<0.0001

DILDs, drug-induced lung diseases; FAERS, Food and Drug Administration Adverse Event Reporting System; USA, United States of America; EU, Europe; JP, Japan; CI, confidence interval.

previous studies have reported ethnic discrepancies in DILD prevalence that, as delineated in previous reports, ranges between 14.5 and 19.0% (7, 10, 11). This study elucidated a notable distinction in the incidence rates of DILDs across various drug types, including ICIs, when comparing reports from JP and the USA, using a large-scale database. A similar trend surfaced when comparing reports from JP, China, South Korea, and ASEAN countries with those from the EU and the USA (Supplementary Table S3). These findings implicate inherent factors, such as genomic variances and comorbid conditions, as potential drivers of discrepancies in DILD prevalence after treatment with anticancer drugs, including ICIs, between Asian and non-Asian populations.

This study investigated the differences in reporting propensity from JP, the EU, and the USA by comparing the reports from the three

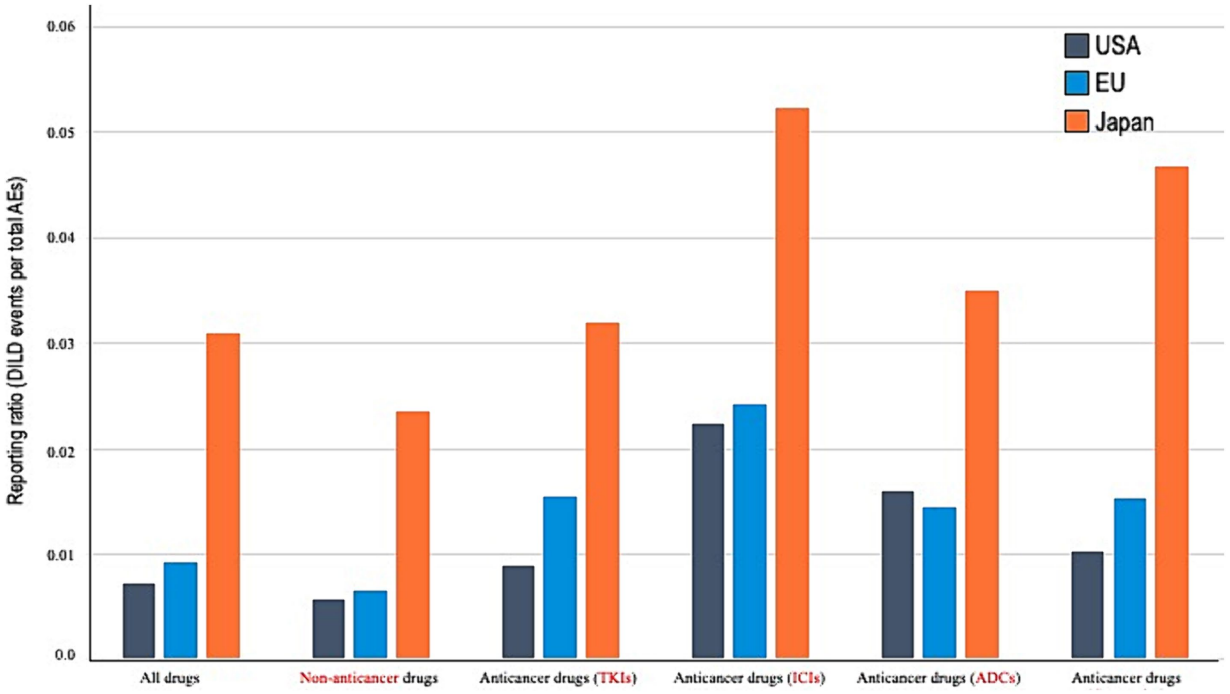

FIGURE 2
Reporting proportion according to the drug types. AE, adverse event; DILDs, drug-induced lung disease; US, United States; EU, European Union; JP, Japan; TKIs, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; ADCs, antibody–drug conjugates; cytotoxics, cytotoxic agents.

regions to ensure data robustness. The data among the three regions were possibly influenced by biases in reporting, healthcare access, language, and DILD severity. These biases were considered when interpreting the results of this study. We investigated reporter bias by examining the differences in reporting between the EU and the USA, considering reporting bias from regions other than the USA. The RORs of ICIs and ADCs showed only minor differences between the EU and USA, whereas clear differences were observed between the USA and JP. The high proportion of healthcare professionals as reporters in both the EU and Japan contribute to the higher number of severe cases being reported from these regions (Table 1). Regional differences in mortality from DILDs were notably higher in JP and the EU than in the USA. This result indicates that reporting relatively mild cases of DILDs does not result in a reporting bias that would increase the prevalence in JP and the EU. Moreover, significant DILDs that needed to be reported were recorded regardless of the region and country, including outside the USA. These findings eliminated reporting bias and strongly suggested ethnic differences in DILD incidence resulting from several agents.

The mechanisms by which anticancer drugs induce DILDs must be elucidated for the prevention and treatment of this AE. The results of the present study showed that the prevalence of DILD differed with each drug, indicating that the mechanism underlying DILD development differs for each drug. Two main mechanisms of DILD development have been proposed: direct drug-induced damage and immunological mechanisms. Several hypotheses on the mechanism of direct injury state that drugs induce the release of cytotoxic reactive oxygen species in the lungs, leading to the degeneration of alveolar cells and pulmonary macrophages owing to increased phospholipid accumulation in alveolar cells (1, 2, 12–15). In terms of immunological mechanisms, direct haptenic modification of tissue-resident proteins by immune cells and deposition of antigen–antibody complexes have been proposed (8, 12, 16). Few studies reported on the mechanism of DILD development using tissue samples from affected patients. Further research on each mode of action should be conducted using blood and tissue samples and various omics analyses to identify predictive biomarkers for DILD development, especially in Asians, where DILD is more common. Our team has initiated a study analyzing the immunological profile and genetic background of DILD tissue samples.

In conclusion, the prevalence of DILD was higher in JP than in the USA and EU across all anticancer drug regimens. These findings underscore the importance of considering differences in the prevalence of DILD in JP, the EU, and the USA when evaluating the safety profiles of drug development and patient safety in clinical practice.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or the patients'/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

TABLE 3 Regional differences of DILDs reported in the FAERS database.

	No. of DILDs	Multivariate analysis	
		Reporting odds ratio (95% CI)	*P*
All drugs			
USA	74,548	1	
EU	31,009	1.218 (1.202–1.234)	<0.0001
JP	23,004	3.608 (3.553–3.664)	<0.0001
Non-anticancer drug			
USA	49,707	1	
EU	16,103	1.086 (1.066–1.106)	<0.0001
JP	9,900	3.481 (3.404–3.560)	<0.0001
Anticancer drug (TKIs)			
USA	4,630	1	
EU	2,176	1.679 (1.594–1.769)	<0.0001
JP	2,232	3.274 (3.105–3.451)	<0.0001
Anticancer drug (ICIs)			
USA	1,221	1	
EU	1,685	1.041 (0.965–1.123)	0.2960
JP	3,308	2.170 (2.025–2.325)	<0.0001
Anticancer drug (ADCs)			
USA	93	1	
EU	78	1.046 (0.763–1.434)	0.7804
JP	65	2.335 (1.666–3.272)	<0.0001
Anticancer drug (Cytotoxics)			
USA	3,511	1	
EU	4,043	1.418 (1.354–1.485)	<0.0001
JP	2,329	3.989 (3.776–4.215)	<0.0001

DILDs, drug-induced lung diseases; FAERS, Food and Drug Administration Adverse Event Reporting System; US, United States; EU, Europe; JP, Japan; TKIs, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; ADCs, antibody–drug conjugates; cytotoxics, cytotoxic agents; CI, confidence interval.

Author contributions

JS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. RS: Data curation, Formal analysis, Methodology, Writing – review & editing. TK: Writing – review & editing. YK: Writing – review & editing. MO: Writing – review & editing. NY: Conceptualization, Writing – review & editing.

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Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2024.1390083/abstract#supplementary-material

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The role of digital health in respiratory diseases management: a narrative review of recent literature

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This review provides a detailed overview of how digital health can be utilized in the management of Interstitial Lung Disease (ILD), and Chronic Obstructive Pulmonary Disease (COPD). ILD encompasses a diverse range of lung disorders characterized by inflammation and scarring of lung tissue, leading to restrictive lung physiology and impaired gas exchange, with symptoms including progressive dyspnoea, cough, and hypoxia. COPD which ranks as the third leading cause of death globally, is characterized by chronic lung inflammation causing irreversible airflow obstruction, recurrent exacerbations. While recent advances in digital health have shown promise, predicting disease progression in patients with ILD and exacerbation in patients with COPD remains challenging. This review explores the role of digital health in managing ILD and COPD, particularly focusing on telehealth and digital health technologies. Telehealth, defined broadly as the use of electronic information and telecommunications technologies in healthcare, has become increasingly relevant, especially during the COVID-19 pandemic. This review examines the role of digital health technologies in the management of ILD and COPD, with particular focus on telemedicine, and digital health tools. Remote monitoring technologies, including home spirometry and wearable devices, have demonstrated feasibility in managing respiratory diseases. However, challenges such as evidence, data reliability, varying adherence, education, and the high costs of data collection and lack of qualified clinicians present barriers for many national health systems.

KEYWORDS

telehealth, digital health, mobile health (mHealth), interstitial lung diease, chronic obstructive pulmonary disease, respiratory disease, artificial intelligence, spirometry

Introduction

Telehealth is increasingly recognized as a transformative approach in chronic disease management, particularly for respiratory conditions, with the potential to enhance patient monitoring and inform clinical decision-making (1). By enabling digital health and data collection, digital health tools can potentially improve self-management and deliver timely clinical insights (1). The COVID-19 pandemic has not only driven the adoption of digital health solutions, but has also played a significant role in shaping the World Health Organisation's global strategy for digital health 2020–2025 (1). Providing access to remote health care services remotely can aid case prioritization and timely intervention, therefore reducing the increased load on health care system from direct patients visits thus reducing the costs of hospitalization, transportation, and exposure to hospital infectious disease (2–5). To fully realize the potential of digital health of physiological parameters and symptoms, an emphasis must be placed on producing high-quality data and evidence. However, digital health can only be the adopted after assessing the feasibility, utility/usage, and acceptability to patients with lung diseases.

This review provides an updated, in-depth overview of how digital health technologies are used to monitor and manage chronic respiratory conditions, particularly interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD). By synthesizing the most recent evidence, we demonstrate the benefits, challenges, and future directions for digital health in respiratory medicine.

Method

A comprehensive search of PubMed, Ovid-MEDLINE, and Google Scholar was conducted to identify relevant studies published prior to November 2023. References were reviewed for additional articles. MeSH terms were organized into categories related to diseases (e.g., "interstitial lung disease," "idiopathic pulmonary fibrosis," "COPD"), technologies (e.g., "telehealth," "remote patient monitoring," "wearables," "home spirometry," "mobile health," "mHealth," "Internet of Medical Things"), and outcomes (e.g., "exacerbations," "disease progression," "symptom monitoring," "adherence," "cost-effectiveness"). Eligible studies investigated digital health solutions in chronic respiratory disease care, provided data on outcomes including feasibility, usability, adherence, or clinical efficacy, and published in peer-reviewed journals in English. Initial search results were screened for relevance, followed by full text review of eligible studies. Data were extracted using a standardized template capturing study details, intervention type, and key outcomes.

The findings were synthesized into themes:

1 Global Burden of Disease: Epidemiology, economic costs, and care gaps in underserved areas.
2 Telehealth and RPM: Applications in exacerbation detection, patient engagement, and adaptations following COVID-19.
3 IoMT Infrastructure: Use of wearable sensors, AI-driven analytics, and data transmission challenges.
4 Clinical Applications: Feasibility and reliability of home spirometry, ePROM integration, and early detection of disease progression.
5 Patient Engagement: Adherence rates, psychological impacts, and barriers such as digital literacy.
6 Implementation Barriers: Usability challenges, cost-effectiveness, regulatory hurdles, and interoperability issues.
7 Future Directions: Standardization, AI/ML integration, and equity-focused policies to improve access and sustainability.

Given the narrative design of this review, formal quality appraisal tools like the RoB 2 or Newcastle-Ottawa Scale were not applied. The study also did not follow a pre-defined registered protocol or systematic review standards such as those outlined in the PRISMA guidelines.

Global burden of respiratory diseases

Respiratory diseases encompass a wide range of different conditions that affect all individuals across all ages, presenting different symptoms and prognoses (6). The global burden of respiratory disease continues to rise, with high incidence and mortality rates becoming a serious concern (7–9). In 2017, approximately 544.9 million people worldwide were affected by chronic respiratory diseases (7, 8, 10). Given the diverse progression patterns of these diseases, predicting their actual costs and long-term outcomes remains a challenge (6). In the UK, Asthma + Lung UK estimates that 12.7 million people live with respiratory disease, including 1.2 million diagnosed with chronic obstructive pulmonary disease (COPD) (11), a condition that ranks as the third leading cause of death globally (10), and 150,000 were diagnosed with Interstitial Lung Disease (ILD) (11, 12). A recent Asthma + Lung UK report, indicates that respiratory diseases cost the UK £11 billion annually, with 29% of that expenditure allocated to COPD (7, 13). New research demonstrated the importance of early identification of exacerbations in COPD (14, 15); thus, continuous monitoring of symptoms and physiological parameters have the potential to allow earlier intervention (15). There remains a gap in the care of patients with respiratory conditions (13, 16). Particularly those with chronic respiratory diseases and those recently discharged from hospital, where changes in patients' health are not well predicted. In the face of this growing global burden, emerging telehealth solutions offer possibilities for improved patient monitoring and resources allocation, as we discuss in the following section.

Recent studies demonstrated the significance of timely identification of worsening respiratory symptoms (14, 15, 17–19); therefore, longitudinal monitoring of physiological parameters and symptoms have the potential to allow earlier identification (20). There is an unmet need in the care of patients with respiratory diseases (13, 16). Chronic respiratory diseases are especially at risk, with limited knowledge about changes in their symptoms and physiological parameters (21–23). Emerging modalities for remote data collection, such as home based spirometry, pulse oximeters, wearables and smartphone apps may offer potential to enhance self-management and offer better, timely information for clinical assessment (18). Digital health could serve as link between hospital care and home care for these patients (24, 25). Nevertheless, uncertainties persist regarding the feasibility and acceptability of digital health in monitoring symptoms and physiology for patients with respiratory diseases.

Telehealth and remote patient monitoring

Definitions and scope

Telehealth is a broad term that was defined previously as "the use of electronic information and telecommunications technologies to support and promote long-distance clinical health care, patient and professional health-related education, public health, and health administration, where technologies include video conferencing, the internet, store-and-forward imaging, streaming media, and terrestrial and wireless communications" (26). In particular, the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services defines remote patient monitoring (RPM) as "the use of connected electronic tools to record personal health and medical data in one location for review by a provider in another location, usually at a different time" (26). In the United Kingdom, and according to the New England Journal of Medicine, telehealth is "the delivery and facilitation of health and health-related services including medical care, provider and patient education, health information services, and self-care via telecommunications and digital communication technologies (27). Live video conferencing, mobile health apps, 'store and forward' electronic transmission, and remote patient monitoring (RPM) are examples of technologies used in telehealth," (27). Remote patient monitoring was defined as "the reporting, collection, transmission, and evaluation of patient health data through electronic devices such as wearables, mobile devices, smartphone apps, and internet-enabled computers. RPM technologies remind patients to weigh themselves and transmit the measurements to their physicians (27). Wearables and other electronic monitoring devices are being used to collect and transfer vital sign data including blood pressures, cardiac stats, oxygen levels, and respiratory rates" (27). The healthcare industry is going through rapid transformation, and new developments such as the Internet of Things and artificial intelligence are expected to be a driving force in this transformation. While telehealth and PRM improve patient access to health care, integrating these approaches with Internet of Medical Things (IoMT) technologies can further transform the management of chronic conditions, as we explore next.

The role of the internet of medical things

The Internet of Things (IoT), first mentioned by Ashton (28), was defined as "a global infrastructure for the information society, enabling advanced services by interconnecting (physical and virtual) things based on existing and evolving interoperable information and communication technologies according to the Internet of Things Global Standards Initiative" (Figure 1) (29). Artificial intelligence (AI), on the other hand, is defined as "the capability of a machine to imitate intelligent human behavior" (30).

The internet of medical things

The number of IoT devices has grown exponentially since 1999 (31). There are now an estimated 10 billion connected IoT devices, and this number is expected to reach 25 billion by 2025 (31, 32). IoT technology is already being used in healthcare applications, such as remote patient monitoring, medication adherence tracking, and surgical robotics. As IoT technology continues to develop, we can expect to see even more innovative healthcare applications emerge. The global market for IoT technology is expected to reach $6.2 trillion by 2025, with 30% of that coming from healthcare (33). This means that the healthcare industry will be a major driver of IoT growth in the coming years. In addition, the Internet of Medical Things (IoMT), sometimes referred to as the Internet of Healthcare Things (IoHT), is improving healthcare (Figure 2). In particular, remote patient monitoring via wearables (34), smartphone applications, and Bluetooth devices has increased dramatically (35). These IoMT driven innovations are already influencing the management of chronic respiratory diseases, particularly COPD and ILD, which will be the focus of the following sections.

Applications in chronic respiratory diseases

Telehealth and remote monitoring are utilized globally for managing chronic respiratory diseases and in the United Kingdom, particularly through the National Health Service (NHS). The NHS has integrated a range of technology-enabled care services (TECS) to

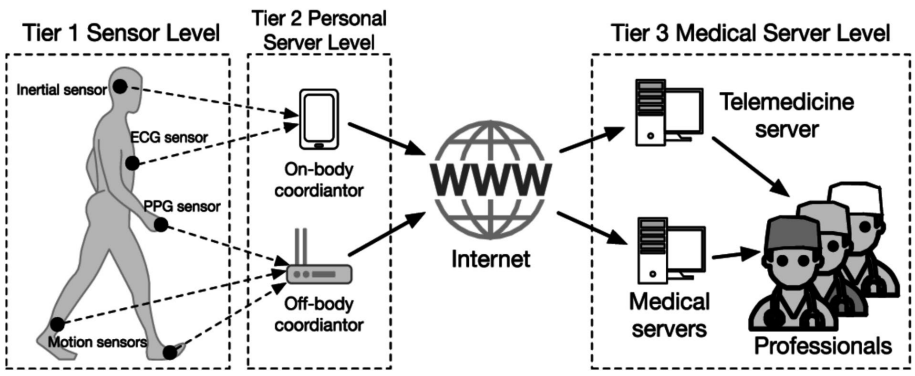

FIGURE 1
Architecture of IoMT-based healthcare system. The diagram illustrates a three-tier telemedicine system: Tier 1 with sensors—ECG (Electrocardiogram) for heart activity, PPG (Photoplethysmogram) for heart rate, and inertial and motion sensors.

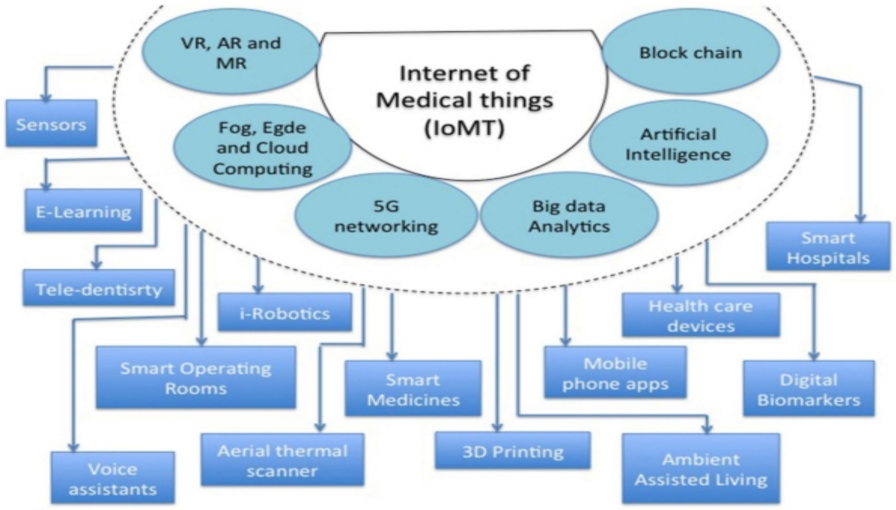

FIGURE 2
IoMT (Internet of Medical Things): A central system integrating health technologies for efficient patient care and data management. The centralized system connecting diverse health technologies to streamline patient treatment, data management, and medical services (91).

support patients with long-term conditions. These services include telehealth, telecare, telemedicine, telecoaching, and self-care apps. These technologies empower patients to manage their healthcare more independently and efficiently from home, improving access and reducing the need for in-person visits (1, 2). During the COVID-19 pandemic, the NHS significantly expanded its digital health capabilities. For example, over 487,000 people were supported at home with digital health and remote monitoring technologies through national funding between November 2020 and January 2023. These initiatives have been critical for managing chronic conditions such as Chronic Obstructive Pulmonary Disease (COPD) and heart failure, as well as for providing post-operative care and monitoring for mental health conditions (2). In North America, particularly in the United States and Canada, telehealth has become widely adopted for remote consultations, virtual care, and remote monitoring services. European countries like the United Kingdom, Norway, Sweden, Denmark, Germany, and Italy are at the forefront of telehealth adoption, utilizing it to reach patients in remote areas and enhance access to care. In Asia, countries such as China, Japan, and South Korea have embraced telehealth to address healthcare access challenges, especially in rural areas. Additionally, Australia leads telehealth utilization in the Australasian region. Despite infrastructural challenges, countries like South Africa and Kenya in Africa, as well as Brazil, Argentina, and Chile in South America, have implemented successful telehealth initiatives to improve healthcare access in underserved regions. In the Middle East, several countries have made significant progress in their utilization of telehealth services, integrating it extensively into their healthcare systems (36).

The advent of daily remote monitoring, particularly home based spirometry, offers a non-invasive solution to several challenges faced by ILD patients (19, 37, 38). These challenges include the infrequency of spirometry monitoring every 3 months at clinics, the high costs associated with hospital visits, and the inconvenience of commuting for tests (18). Additionally, in-clinic spirometry often faces delays due to high demand, with wait times exceeding 3months in some cases (39). There is also a risk of infection exposure during clinic visits, which has become particularly concerning during the COVID-19 pandemic (40). Digital health facilitates continuous monitoring of disease, and timely adjustments to treatment plans, which can significantly enhance patient management and outcomes (19). Furthermore, it can enhance the accuracy of treatment effect estimates by enabling more frequent measurements, improve patient engagement by encouraging active participation in their own care, and reduce the burden on healthcare systems by minimizing the need for frequent clinic visits (19, 41–43). In addition, remote patient monitoring, involving more than just FVC, may provide a more comprehensive and real-time assessment of physiological parameters and symptoms, addressing the limitations of conventional indicators. These devices offer a reliable way to identify patients at higher risk for developing AE-ILD, improve understanding of AE-PF clinical progression, and may facilitate the early detection of AE-IPF (19). With evidence supporting the ability of home handheld spirometry to improve clinical trail outcomes in IPF therapeutics, this approach can be highly valuable (18, 19), attention should be directed toward studies investigating the advantages of daily home handheld spirometry for patients with ILD. This naturally extends into the wider application of digital health. By utilizing questionnaire responses to monitor symptoms like fatigue, cough, anxiety, depression, and QoL, as well as monitoring key physiological parameters such as respiratory rate, oxygen saturation, heart rate, and FVC, a holistic understanding of the patient's condition can be obtained, promoting an effective disease management strategy.

In addition, mobile health (mHealth) refers to "health care applications and programs patients use on their smartphones, tablets, or laptops. These applications allow patients to track health measurements, set medication and appointment reminders, and share information with clinicians" (27). According to the World Health Organisation (WHO), mobile health, also known as mHealth, is defined as a term used for medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices (44). "mHealth applications include the use of mobile

devices in collecting community and clinical health data, delivery of health care information to practitioners, researchers, and patients, real-time monitoring of patient vital signs, and direct provision of care" (44). Telehealth was also defined as remote monitoring of patients in their homes to predict exacerbations early and build their self-care competencies, according to the NHS Commissioning Assembly (45). Finally, the health care industry is going through rapid transformation, and new developments such as the Internet of Things and artificial intelligence are expected to be a driving force in this transformation.

Applications in COPD management

The World Health Organisation reported that COPD is the third leading cause of death worldwide (10). In 2019, it was estimated to have caused 3.23 million deaths globally (10). COPD is characterized by inflammation of the lung, which causes irreversible airflow obstruction and, generally, an accelerated decline in lung function (6). Patients with COPD are prone to recurrent chest infections known as acute exacerbations (6, 46). Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is defined as an acute change of respiratory symptoms needing a change in treatment, and these events are generally associated with deterioration of lung function and QoL (46, 47). Previous studies suggest that longitudinal monitoring of physiological parameters and symptoms have the potential to provide earlier detection of exacerbation, but a history of frequent exacerbations and patient reporting remains the gold standard of exacerbation prediction and identification (48). Recent studies demonstrated the significance of timely identification of the exacerbation of COPD (6). Thus, patients with COPD could be continuously monitored outside clinical settings to mitigate the impact of exacerbation on health status (48).

Remote monitoring for exacerbation of COPD may be a valuable approach to facilitate appropriate health care. Remote monitoring of physiological parameters (respiratory rate, heart rate, and oxygen saturation) and self-reported outcomes both offer a unique combination that allows for earlier detection of AECOPD. This could aid in timely intervention, minimize exacerbation severity, and prevent hospitalization.

The findings from recent studies highlight the promising role of telehealth interventions in managing COPD (49). Telemonitoring, in particular, has demonstrated efficacy in reducing the frequency of emergency room visits, although its impact on hospitalization rates remains uncertain (50). High levels of patient satisfaction indicate that telemonitoring is well-accepted and can be effectively integrated into COPD care plans (51). Moreover, telemedicine interventions have been associated with reductions in respiratory exacerbations and improvements in physical activity levels and quality of life, suggesting their potential to supplement standard COPD care (52, 53). Despite these benefits, the variability in effectiveness across studies underscores the need for further high-quality research to establish standardized protocols and best practices (54). Wearable technology interventions also show promise, particularly in increasing physical activity, though their impact on quality-of-life measures and exacerbation prediction requires further investigation (49). Overall, these studies suggest that integrating telehealth into COPD management strategies can enhance clinical outcomes and patient experiences while potentially reducing the burden on healthcare systems. Building on these approaches in COPD, digital health interventions have also shown promise in detecting progression and managing patients with interstitial lung disease, discussed in the next section. A summary table of the included studies on digital health interventions in ILD is shown in Table 1.

Application in ILD management

Home handheld spirometry

Home handheld spirometry has gained increased attention, especially in recent times in light of the COVID-19 pandemic lockdown. Indeed, home handheld spirometry linked to smartphone apps have emerged as a contemporary solution to reducing the delays and risk of infection associated with hospitals (38). A newly developed devices for smart handheld spirometry facilitates the continuous measurement of FVC at home (18, 38, 55–57). This device would need to be connected via Bluetooth to a smartphone app, which means that patients are able to see their results in real-time through their smartphone. Moreover, clinicians can monitor the patient's spirometry using a web portal developed specifically for this task (43, 58–62). Numerous studies over the last decade investigated the use of a home handheld spirometry in patients with interstitial lung disease (ILD) (18, 38, 55–57). In general, this approach is feasible, reliable, acceptable, user-friendly and it results in high participant satisfaction (18, 63). However, several cautions and drawbacks associated with home handheld spirometry have been also reported (38). This section summarizes existing literature on home handheld spirometry.

In 2016, Russell et al. (58) conducted a single-center prospective study with the aim of assessing the feasibility and reliability of home handheld spirometry. Therein, patients with idiopathic pulmonary fibrosis (IPF) were requested to conduct daily FVC and forced expiratory volume (FEV1) measurements for up to 490 days. The 50 patients who took part in the study recorded for a median of 279 days (range 13–490 days) (58). Although no adherence percentage was reported, the results suggested that daily home handheld spirometry is feasible. Indeed, the study analyzed the FVC to determine the correlation between hospital and home measurements, and findings showed a strong correlation (58). The rate of FVC decline showed an association with mortality during the first 3 months, with high statistical significance (p-value < 0.0001) (58). However, the study found that FVC readings taken at home were typically lower compared with hospital readings. In addition, in some cases, home handheld discontinued because of cough, absence of flow volume or concerns about measurement quality. Finally, the need for patients to keep a diary of daily spirometry measurements raised concerns about data reliability (58).

In another study, Johannson et al. (64) conducted a single-center prospective study over 40 weeks investigating both the feasibility and reliability of a home handheld spirometer. In this study, 25 patients with IPF were requested to conduct weekly measurements of FVC using a personalized handheld spirometer. Although a decline in patient adherence was reported over time, adherence was generally good (90.5%), and a strong correlation between home based and hospital FVC measurements was observed ($r = 0.91$).

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TABLE 1 Summary of included studies on digital health interventions in ILD.

Author (year)	Country	Study design	Sample size	Disease group	Measures/ frequency	Study length	Key outcomes
Moor et al. (41)	Netherlands	RCT	*n* = 90	IPF	FVC (daily), K-BILD, PESaM, EQ-5D-5L, HADS, VAS	24 weeks	Improved psychological well-being, high correlation home vs. hospital spirometry
Maher et al. (70)	United States	RCT	*n* = 253	Unclassifiable ILD	FVC (daily), 6MWD, UCSD-SOBQ, SGRQ	24 weeks	Variability in home spirometry, FVC decline less in pirfenidone group
Russell et al. (58)	UK	PCS	*n* = 50	IPF	FEV1, FVC (daily)	279 days	Daily FVC predictive of disease progression and mortality
Johannson et al. (64)	United States	PCS	*n* = 25	IPF	FEV1, FVC (3x weekly), UCSD-SOBQ, Dyspnoea-VAS	24 weeks	High adherence to home spirometry, reliable FVC and dyspnoea tracking
Veit et al. (69)	Germany	PCS	*n* = 47	ILD	FVC (3x daily), 6MWD, DLCO, SGRQ, VAS	6 months	Adherence higher in first 3 months, strong correlation home vs. hospital spirometry
Edwards et al. (68)	Ireland/ United States	PCS	*n* = 36	PF	FVC (daily), mMRC (daily), IPF-PROM (weekly)	1 year	Positive impact on well-being, good correlation home vs. hospital spirometry
Moor et al. (65)	Netherlands	PCS	*n* = 10	Sarcoidosis	PEF, FEV1, FVC (daily), PROM, KSQ, EQ-5D-5L	4 weeks	High correlation between home and hospital FVC, 94.6% adherence
Moor et al. (43)	Netherlands	PCS	*n* = 10	IPF	Home spirometry (daily), K-BILD, HADS, EQ-5D-5L	4 weeks	Home spirometry correlated with hospital results, 98.8% adherence
Moor et al. (59)	Netherlands	PCS	*n* = 50	IPF	FVC (2x daily), K-BILD	6 weeks	Morning FVC higher than afternoon, step count correlated with FVC
Broos et al. (60)	Netherlands	PCS	*n* = 21	Sarcoidosis	FVC (daily), MRC, FAS, SGRQ, SF-36	3 months	Reliable home spirometry for sarcoidosis
Marcoux et al. (67)	Netherlands	PCS	*n* = 20	IPF	FVC (3 maneuvers daily), 6MWD	12 weeks	Strong correlation between office-based and handheld FVC
Noth et al. (92)	Netherlands	PCS	*n* = 346	IPF	FVC (weekly)	1 year	Strong home vs. clinic FVC correlation but weaker rate of decline
Moor et al. (59)	Netherlands	PCS	*n* = 10	Systemic sclerosis associated ILD	FVC (daily), K-BILD, HADS, EQ-5D-5L	3 months	High adherence (98.8%), 90% found home monitoring pleasant

However, 13% of patients found the spirometer challenging to use (64).

In a national multi-center prospective observational study conducted by Broos et al. (60), the effect of early steroid treatment on FVC was investigated. The study involved daily monitoring of 21 patients diagnosed with sarcoidosis over a study period of 3 months. Findings suggest that using a daily home handheld spirometry can potentially serve as a useful tool in monitoring steroid treatment effects in patients with sarcoidosis. However, the study lacked data on patient adherence to home handheld spirometry, which is a critical factor in assessing the success of this monitoring method. Furthermore, the study used specific software (Micro Diary; Carefusion), which was operated by the researchers for downloading readings, and the functionality of which may have had an influence on the data recording process (60).

Catharina et al. (65) carried out a single-center prospective study on 10 patients with IPF over 4 weeks to assess the feasibility of utilizing a wireless home handheld spirometry, using the MIR Spirobank smart spirometer. Results showed a high correlation between home and hospital spirometry measurements for both FVC and FEV1 ($r = 0.94$, $p < 0.001$ and $r = 0.97$, $p < 0.001$ respectively), and a mean patient adherence of 94.6%. This pilot study was followed by another single-center prospective study in 2019 involving 10 patients with sarcoidosis over a four-week study period (42). Again, high correlations were observed between home and hospital FVC and FEV1 measurements ($r = 0.97$, $p < 0.001$ and $r = 0.96$, $p < 0.001$), and a mean patient adherence of 94.6% (42).

Moor et al. (59) conducted a further prospective observational study involving 50 patients with fibrotic ILD. In this study, FVC was measured twice daily over 6 weeks to evaluate its diurnal variation. Results indicated FVC is higher in the morning than in the afternoon, but several technical issues imply data that may be missing. In another randomized controlled study comparing home monitoring with standard care in 90 IPF patients (66), home monitoring appeared to be feasible and reliable, with home and hospital measurements being strongly correlated ($r = 0.97$ at baseline and 12 weeks, $r = 0.96$ at 24 weeks) with a mean adherence of 93%, this allowed for tailored medication adjustment and enhanced psychological well-being relative to standard care alone (mean difference 1.04 points; 95% CI, 0.09–2.00; $p = 0.032$) (66).

Another single-center prospective study by Moor et al. (56) involved the observation of 10 patients with systemic sclerosis-ILD over 3 months to determine the feasibility and optimal frequency of online home handheld spirometry. The authors found that readings from home handheld spirometry readings were highly correlated with readings from hospital spirometers ($r = 0.99$, $p < 0.001$). The mean adherence to home handheld spirometry herein was 98.8% (SD 1.5) (56).

Another single-center observational study conducted by Marcoux et al. (67) involved 20 patients with IPF over 12 weeks to assess the feasibility of daily home handheld spirometry. The results demonstrated a mean adherence of 84%, with a high correlation between home and hospital FVC values at baseline ($r = 0.97$), was shown, there was a lower correlation after 12 weeks ($r = 0.90$) (67).

A community-based participatory research program conducted by Edwards et al. (68) observed 36 patients with fibrotic ILD in two countries (24 participants from the US and 12 participants from Ireland). Herein, researchers used a mobile application called patientMpower to conduct home handheld spirometry testing for 1 year. In terms of adherence, 78% of participants recorded home handheld spirometry readings for 6 weeks, with 58% recorded home handheld spirometry for at least 180 days, and only 25% recorded home handheld spirometry for at least 360 days. The authors suggested that the independent use of the patientMpower application, without active involvement from health care providers, might have contributed to the decrease in adherence over time. Furthermore, in measuring their spirometry, 20 participants recorded oxygen saturation via Bluetooth pulse oximetry, averaging 58 times per person, and with 10 of these participants recorded oximetry for at least 180 days. The patient reported highly positive experiences with the patientMpower application, with the majority of respondents considering the application easy to use and helpful in managing their lung fibrosis. The participants also reported that the application positively affected their well-being and daily life (68).

A prospective observational study was conducted by Veit et al. (69) observing 47 patients with fibrotic ILD over 6 months to determining the prognostic potential of daily FVC measurements. Patient adherence to home handheld spirometry was 85.1%, reflecting high acceptance. Only three patients (8.5%) discontinued use within the first week; in these cases, use was discontinued because of dyspnoea. Another three (6%) were excluded because of technical issues and a poor-quality of measurements. Forty patients continued in the study for a mean duration of 161 days and performed home handheld spirometry measurements on 81.8% of those days, with 98.4% of the measurements being of good quality. Mean home FVC measurements showed a strong correlation with baseline hospital values over the first 7 days ($r = 0.96$, $p < 0.0001$) and at both the 3-month ($r = 0.95$, $p < 0.0001$) and 6-month visits ($r = 0.93$, $p < 0.0001$). Twelve patients (30%; 5 with IPF and 7 without IPF) experienced disease progression, with such outcomes as death, lung transplantation, acute exacerbation, and hospital-based FVC decline of more than 10%. Patients with progressive disease had significantly lower 6MWD values (301 ± 140 m vs. 433 ± 89 m; $p = 0.009$) and total scores on the King's Brief Interstitial Lung Disease ILD (K-BILD) instrument (46.3 ± 8.1 vs. 55.8 ± 12.7; $p = 0.004$), indicating physical and subjective wellbeing limitations.

In the first 28 days, 60% of patients demonstrated a FVC coefficient of variation (CoV) ≥ 5, and 15% showed an FVC CoV $\geq$10%. The median FVC CoV was 5.9%, with a range of 3.5 to 17.8%. The progressive group showed higher variation (8.6% median FVC CoV) than the stable group did (4.8% median FVC CoV, $p = 0.002$). Over 3 months, patients with disease progression demonstrated significantly higher FVC variability (8.4 ± 3.2%) compared to stable patients (5.5 ± 2.5%; $p = 0.002$). Finally, FVC variability over 28 days was found to be independently associated with disease progression (hazard ratio 1.203; 95% CI: 1.050–1.378; $p = 0.0076$), with the optimal cut-off for distinguishing low and high variability determined to be 7.9% (69).

Maher et al. (70) conducted an international multi-center, double-blind, randomized, placebo-controlled phase 2 trial involving 253 patients with unclassifiable ILD. The study sought to assess the mean predicted change in FVC from baseline over 24 weeks using daily home handheld spirometry. However, technical difficulties and issues with data reliability prevented statistical analysis. Problems included daily FVC readings that were physiologically impossible (<0.5 L or > 6 L), with predicted increases of 33 L at 24 weeks: thus, invalidating the application of the pre-planned statistical model.

Meanwhile, Noth et al. (62) carried out an international multi-center prospective study involving 346 patients with IPF over 52 weeks to evaluate the feasibility and validity of using home handheld spirometry to measure lung function decline. While patient adherence decreased over the course of the study, the overall mean and median adherence

rates remained high, at 86 and 96%, respectively. In addition, a strong correlation of home and hospital FVC was evident at all time points ($r = 0.72–0.84$). However, the variability in FVC change was higher with home handheld spirometry, and the correlation of home- and clinic-measured change in FVC was accordingly weak ($r = 0.26$) (62).

Khan et al. (71) carried out a multi-center observational cohort study over a period of 3 months, involving 82 patients with fibrotic ILD to evaluate the clinical use of home handheld spirometry as an alternative to hospital spirometry. Participants were asked to perform a single blinded, forced expiratory manoeuver on a daily basis. The full 3 months of home and hospital spirometry data were collected for only 43 participants; some patients' hospital spirometry data were not collected consistently because of the COVID-19 pandemic, leading to the exclusion of these participants from the analysis. The median adherence to daily home handheld spirometry readings for all participants was 81%, and this increased to 91% in those who completed the 3 months study period. A good correlation between home based and hospital based spirometry was observed both at baseline ($r = 0.89$) and at 3 months ($r = 0.82$). Consistent with the high home-hospital correlation, Bland–Altman plots showed that more than 90% of home handheld spirometry values were within the agreement limits of hospital values at both time points, although home values were lower than the hospital values (71).

A study in Serbia assessed the efficiency and practicability of home handheld spirometry tests in patients with ILDs. The study found home handheld spirometry tests to have a strong correlation with office spirometry tests both at baseline and at the end of the study. Despite this, the adherence rate was only 68%. The study found that home handheld spirometry tests did not affect patients' overall QoL or anxiety levels; indeed, patients expressed positive feedback and high satisfaction (72).

Finally, Miedema et al. (73) assessed the utility of home handheld spirometry in a multi-center prospective study wherein home handheld spirometry were used for patients with progressive asbestosis over 3 months. Using daily domiciliary spirometry readings taken over 24 weeks, the study aimed to assess the safety, efficacy and tolerability of pirfenidone in asbestosis patients with a progressive disease subtype. Prior to pirfenidone treatment, the data showed a significant decline in FVC during the 12-week observational period. Upon initiation of treatment, FVC levels remained stable throughout the 24-week treatment phase (73).

Electronic patient-reported outcome measures and mobile health

Patient-reported outcome measures (PROMs) are self-reported measures of patient (48) that can be used to assess patient QoL and symptoms. These measures can be collected in a variety of ways, including through paper-based surveys, telephone interviews, and online questionnaires. Online collection, in particular, has several advantages. First, it is more convenient and efficient for patients, as patients can complete online surveys at their own pace. Second, online collection is more accessible, especially for patients who are unable to travel to a clinic or hospital to complete a paper-based survey, such as those who live in rural areas or have limited mobility. Third, online collection can be integrated with electronic health records, making it easier for health care providers to track patient progress and to identify those potentially in need of additional care. The validity and reliability of online PROM collection have been well-established as equal to the validity and reliability of paper collection, and its reliability may even be greater, as online collection can reduce missing data (65, 74).

In this light, electronic platforms and mobile applications have been developed to monitor patients with heart failure, cancer, and other chronic conditions; however, platforms specific for ILD are limited (18, 55, 75, 76). The uses of E-health utilities for patients with ILD suggests that such applications may be beneficial for monitoring disease trajectory and symptom management, as well as for providing support such as reminding patients to take medication and report treatment responses to clinicians. In addition, such applications can provide those with ILD accessible information and educational tools.

Recently, several studies have demonstrated the feasibility of using E-health utilities for the online collection of patient-reported outcomes (65, 68). In a recent ILD guideline, E-health was defined as "an emerging field in the intersection of medical informatics, public health and business, referring to health services and information delivered or enhanced through the Internet and related technologies" (77). Catharina et al. (65) had patients use the home monitoring program IPF-online to submit four weekly reports of side effects and symptoms. This was followed by another study in which patients with sarcoidosis used the web application Sarconline to report VAS fatigue, dyspnoea, cough, and well-being each week. The overall patient experience was positive, with an overwhelming majority (90%) finding the Sarconline application to be user-friendly, and the daily spirometry, activity tracking, and PROM were reported to not be burdensome. Finally, the same group conducted a randomized control trial in which patients with IPF performed daily home handheld spirometry and used IPF-online for weekly reports of K-BILD, PESaM, EQ-5D-5L, HADS, VAS, GRC, and EQ-VAS. Patient satisfaction with and use of the home-monitoring program were notably high; the median adherence to daily home handheld spirometry was 97%, and the PROM completion rate was 93%. The patients were generally appreciative of the home monitoring program, with 95% stating that they would recommend it to others. A significant number reported that the program gave them insight into their disease course, made them feel reassured, and that the program facilitated easier communication with the hospital. In addition, the use of home-monitoring resulted in improvement of the mean total K-BILD score over the 24-week study period (2.70 ± 9.5 points, as compared to a negligible 0.03 ± 10.4 with standard care). However, the between-group difference of 2.67 points did not reach statistical significance (95% CI, −1.85 to 7.17; $i = 0.24$). The K-BILD psychological domain showed an increase of 5.12 (±15.8) points in the home monitoring group and a slight decline of 0.48 (±13.3) points in the standard care group; the between-group difference of 5.6 points (95% CI, −1.13 to 12.3; $p = 0.10$) indicated a positive yet statistically insignificant trend in psychological well-being for home-monitored patients. With regard to medication use and hospital visits, the home monitoring group showed more frequent adjustment of medication during the study, primarily due to side effects (41–43, 56, 59, 65, 66, 78).

Separately, Edward et al. (68) evaluated a newly developed mobile application called patientMpower, which was designed specifically to assess IPF symptoms and their impact on patient life via the IPF patient-reported outcome measure (IPF-PROM). In addition, patientMpower facilitates the use of home handheld spirometry. In this study, modified medical research council (mMRC) was collected once daily and IPF-PROM weekly. The results showed home use of patientMpower to be feasible and acceptable for patients with IPF (68).

Taken together, these findings indicate that developing a tool for the continual assessment of patient-reported outcomes is critical to accurately diagnosing and managing ILD (19, 79, 80). The validated tools used to collect patient-reported outcomes focus on emotional symptoms, response to therapy, well-being, and health-related QoL. The current gold standard endpoint measurement in clinical trials for idiopathic pulmonary fibrosis (IPF) is forced vital capacity (FVC), which is used for assessing disease progression and treatment efficacy (81). Nonetheless, physical activity, symptom burden, and HRQoL all convey important information; and given the association of subjective and objective measures, both data types may contribute to predicting significant events and disease trajectory. Recently, an international interdisciplinary expert reported the top patient-centered outcome in patients with ILD. The patient-centered outcomes focus on the issues of greatest concern to patients, includes; (1) health related QoL (general and disease-specific) (2) functional ability (daily living activities, ability to function at home and at work, ability to leave home for leisure or travel) (3) emotional and psychological well-being (anxiety, depression, freedom, grief, stress, emotional confidence) (4) symptoms (dyspnoea, cough, fatigue, medication side effects) (5) knowledge acquisition (therapeutic options and ongoing clinical trials, advantages and disadvantages of tests and interventions, prognosis and level of certainty for what the future holds, and the supportive care options) (6) hospitalizations and survival (hospital-free days) (7) assessing the need for oxygen (the prescribed dosage, the type and availability devices for oxygen delivery, along with cost and logistical concerns) (80, 82). Although home handheld spirometry and electronic PROMs have produced encouraging results, broader concerns around device usability, data quality, and long term adherence persist, as the next section examines.

Wearables and physical activity trackers

Wearables are defined as electronic devices that can be worn by individuals on the body to track physiological parameters such as respiratory rate, heart rate, physical activity, and sleep patterns (83). These devices include wristbands, trackers, smartwatches, and clothing with sensors. The collected data are transmitted wirelessly to a smartphone app or computer for continued tracking.

The WHO has defined physical activity as "any bodily movement produced by skeletal muscles that requires energy expenditure—including activities undertaken while working, playing, carrying out household chores, traveling, and engaging in recreational pursuits" (84). Exercise capacity refer to an individual's ability to endure physical activity, often involving different exercises to boost physical health.

As physical activity is known to be associated with symptoms, physical activity trackers are widely used in research involving patients with ILD (85). Root et al. (85) were among the first to report the use of a physical activity tracker in patients with idiopathic pulmonary fibrosis (85). Patients wore accelerometers and GPS trackers for seven consecutive days. Despite the short duration of the study, "Steps per day were correlated with symptoms and several quality-of-life domains." Bahmer et al. (86) found a significant decline in daily physical activity in patients with IPF, and this decline was strongly associated with factors such as increased fatigue, impaired lung function, and reduced exercise capacity (86).

Several studies have used the Fitbit Flex 2 device (Fitbit, Inc., San Francisco, CA, United States), in patients with ILD, specifically to record daily steps taken, distance walked, and active minutes (42, 67). Moor et al. reported patients with sarcoidosis using the Fitbit Flex 2 had a daily mean adherence of 91.3% (42). In a prospective cohort study of patients with IPF by Marcoux et al. (67), patients wore the Flex 2 during their waking hours, and the data uploaded to the Fitbit portal were made accessible to both study personnel and patients due to the study's exploratory nature. With a mean adherence of 91%, this study demonstrated that wearing a physical activity tracker is feasible over a period of 12 weeks (67). Despite these technological advances, implementing wearables and other digital solutions on a larger scale remains challenging, as we discuss in the following section on future directions.

Challenges and future directions

While this comprehensive review provides valuable insights into digital health for respiratory diseases, several challenges currently limit the utility of digital health for managing these conditions (18, 39, 49, 55, 87, 88). Usability remains a primary concern, especially for older adults and patients with limited digital literacy, who may benefit from more robust educational support and simpler device interfaces (55, 87, 89). In addition, the lack of clinical validation for consumer-grade wearable data reduces trust and poses challenges for clinicians interpreting this information outside of controlled settings (88). Moreover, the high costs of purchasing, maintaining, and integrating these technologies create sustainability issues for national health systems, especially in rural or lower-income areas with limited access to digital devices and internet infrastructure (39, 55, 87–89). To address the cost and resource demands, including the recruitment of skilled staff for data management, scalable solutions and advanced data integration, such as automatic data sharing and remote training are important (55, 90).

Data privacy and security concerns further impact patient engagement, also the potential psychological effects of continuous monitoring, and the burden of manual self-reporting which may reduce adherence over time (39, 87–89). Less intrusive, passive devices could potentially improve long-term comfort and engagement (55). Manual entry may demand more patient engagement and introduce variability, whereas automated collection can reduce user burden but requires thorough validation to ensure accuracy and data integrity. Finally, variability in healthcare infrastructure and funding across regions highlights the need for further research to assess digital health's cost-effectiveness and universal applicability across diverse healthcare settings (19) (Figure 3). Figure 3 illustrates the concept of a "Smart Health Revolution" by presenting key digital transformation technologies in healthcare, including remote monitoring, smart wearables, eHealth, mHealth, telehealth, virtual care, machine learning, and Artificial Intelligence. This figure highlights the benefits of these technologies, such as timely treatment and patient empowerment, while also addressing challenges related to cost, security, and scalability. In addition, many devices still lack standardized protocols for data integrity and calibration, emphasizing the need for robust clinical trials, including large-scale randomized studies to validate both cost-effectiveness and real-world utility. Clearer regulatory frameworks and reimbursement models must also be established to ensure data security, equitable access, and sustainable implementation. Collaboration among researchers, clinicians, policymakers, and technology developers will be critical to advance these efforts, thereby bridging the gap between innovation and meaningful clinical practice.

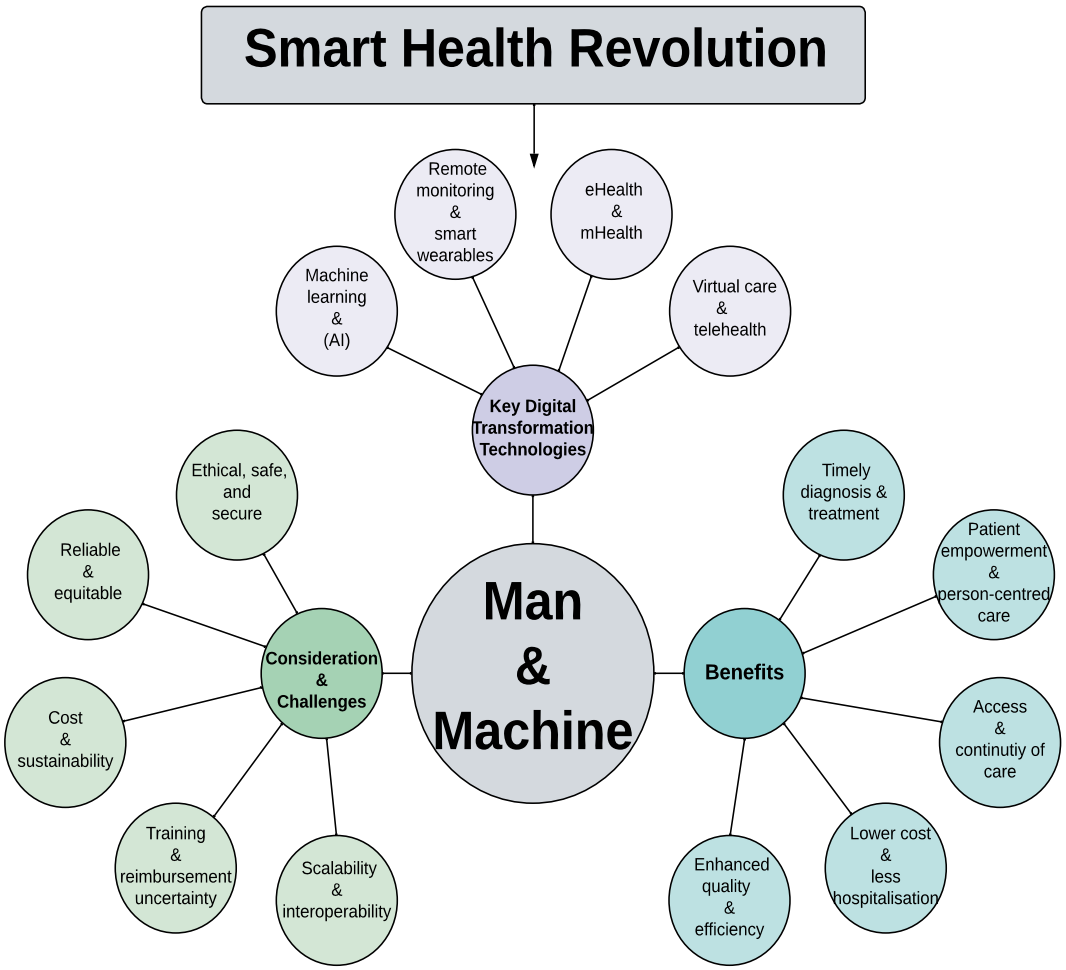

FIGURE 3
Smart health revolution. Overview of key digital transformation technologies in healthcare: benefits, considerations, and challenges.

Conclusion

In summary, digital health has proved to be a feasible, contemporary approach to healthcare, as it has bridged the gap between hospital and home for these patients. In particular, remote monitoring after hospital admission may empower patietns, improve access to care, and enable earlier detection of clinical deterioration. However, transitioning home monitoring from a research setting to standard practice will require robust evidence of its efficacy, cost effectiveness, and acceptability. Larger scale randomized controlled trails are needed to clarify the benefits of digital health interventions for ILD and other respiratory conditions, thereby informing the development of licnical guidelines and protocols. In addition, comparative effectiveness research could help to transition home monitoring from research setting to standard care, robust evidence of its efficacy, cost-effectiveness, and acceptability is essential. Large-scale randomized controlled trials (RCTs) are needed to provide conclusive data on its benefits for ILD patients, establishing clinical guidelines and protocols for routine integration. Comparative effectiveness research could further clarify the advantages of home monitoring over traditional methods, ultimately facilitating widespread adoption and improving patient outcomes.

Author contributions

JJ: Writing – review & editing. YR: Writing – review & editing. RA: Writing – review & editing. AF: Writing – review & editing. JH: Writing – review & editing. JP: Writing – review & editing. MA: Writing – original draft, Writing – review & editing. A-MR: Supervision, Writing – review & editing.

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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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