# Sarcoidosis-associated pulmonary fibrosis: joining the dots

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**A minority of patients with sarcoidosis develop pulmonary fibrosis, which is clinically diverse but may lead to progressive pulmonary fibrosis (PPF) and complications such as bronchiectasis and pulmonary hypertension.** https://bit.ly/3sh7Trv

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## Abstract

Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology. A minority of patients with sarcoidosis develop sarcoidosis-associated pulmonary fibrosis (SAPF), which may become progressive. Genetic profiles differ between patients with progressive and self-limiting disease. The mechanisms of fibrosis in SAPF are not fully understood, but SAPF is likely a distinct clinicopathological entity, rather than a continuum of acute inflammatory sarcoidosis. Risk factors for the development of SAPF have been identified; however, at present, it is not possible to make a robust prediction of risk for an individual patient. The bulk of fibrotic abnormalities in SAPF are located in the upper and middle zones of the lungs. A greater extent of SAPF on imaging is associated with a worse prognosis. Patients with SAPF are typically treated with corticosteroids, second-line agents such as methotrexate or azathioprine, or third-line agents such as tumour necrosis factor inhibitors. The antifibrotic drug nintedanib is an approved treatment for slowing the decline in lung function in patients with progressive fibrosing interstitial lung diseases, but more evidence is needed to assess its efficacy in SAPF. The management of patients with SAPF should include the identification and treatment of complications such as bronchiectasis and pulmonary hypertension. Further research is needed into the mechanisms underlying SAPF and biomarkers that predict its clinical course.

## Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology [1, 2]. Although estimates vary, data from the UK and the US suggest an incidence rate of five to 10 cases per 100 000 per year [3–5]. Some patients with sarcoidosis develop sarcoidosis-associated pulmonary fibrosis (SAPF) [6]. The factors that increase the risk of SAPF are not fully understood, but are believed to involve genetic susceptibility, environmental factors and epigenetic changes [7]. A proportion of patients with fibrosing interstitial lung diseases (ILDs) develop progressive fibrosing ILD, which has recently been termed progressive pulmonary fibrosis (PPF) [8]. SAPF is one of the types of pulmonary fibrosis that may develop into PPF [8–10]. More research is needed, but experts have estimated that approximately 15% of patients with SAPF develop PPF [8]. However, SAPF has several features that distinguish it from other forms of fibrosing ILD. In this review, we describe the characteristics of SAPF, with an emphasis on its genetics and immunopathology, and the evidence supporting therapeutic options.

## Natural history of SAPF

The majority of granulomatous inflammation in sarcoidosis resolves spontaneously or with therapy, but in about 20% of cases, the disease progresses to a fibrotic stage [11–13] (figure 1). Sarcoidosis is more common in black than white individuals [12, 13]. In addition, black patients are more likely to develop sarcoidosis-associated pulmonary hypertension (SAPH) and have a worse prognosis [14].

The lungs are the organ most commonly affected by sarcoidosis. Risk factors for the development of SAPF and its progression have been identified, but current understanding of risk factors does not enable robust

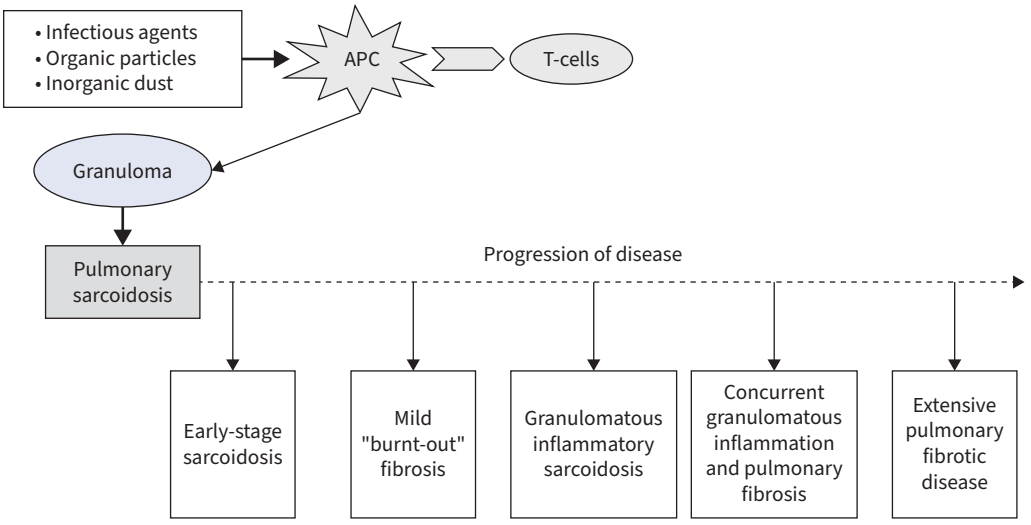


**FIGURE 1** Progression from early stage sarcoidosis to sarcoidosis-associated pulmonary fibrosis. Robust fibrosis exacerbates pulmonary dysfunction. Concurrent granulomatous inflammation worsens pulmonary function. Early-stage sarcoidosis is radiologically stage II sarcoidosis. APC: antigen-presenting cell.

prediction of risk for an individual patient. Dyspnoea at presentation, initiating anti-sarcoidosis therapy at the initial visit and receiving therapy beyond 2 years have been associated with an increased risk of progression to fibrotic disease [15, 16]. Pulmonary fibrosis is associated with significant morbidity and mortality [17–21]. A recent study involving 45 patients with pulmonary sarcoidosis found a moderate/severe burden of dyspnoea and cough in 56% and 36% of patients, respectively [21]. In a French retrospective study, 10- and 15-year survival in patients with stage IV sarcoidosis was 84% and 78%, which was significantly lower than a general population matched for age and sex [17]. Respiratory complications were the cause of death in 75% of the patients with sarcoidosis. The extent of radiographic fibrosis is associated with poor prognosis [17, 18]. In a study of 251 patients, a score >40 on the composite physiologic index, which is based on the results of pulmonary function tests (PFTs), as well as high-resolution computed tomography (HRCT) variables (extent of fibrosis >20% and ratio of main pulmonary artery to ascending aortic diameter >1), identified SAPF patients at a greater risk of mortality [22].

## Genetics of SAPF

Conceptually, SAPF is not merely an end spectrum of inflammatory sarcoidosis, but a distinct aetiopathogenic process. An intense immune response is responsible for the clinical expression of SAPF in genetically susceptible individuals. Sarcoidosis is influenced by a diverse range of genetic susceptibilities. Genetic profiles indicate a differential between patients with progressive SAPF and those with self-limiting disease, with many genes involved in aspects of immune activation and host defence upregulated in the former group, similar to that seen in patients with hypersensitivity pneumonitis (HP) [23].

Genome-wide association studies and other genetic studies have identified single-nucleotide polymorphisms (SNPs) associated with an increased risk of SAPF. SNPs that encode gremlin for tissue repair after injury (GREM1), caspase recruitment domain-containing protein 15 (CARD15), also known as nucleotide-binding oligomerisation domain containing protein 2 (NOD2), and cytokine transforming growth factor (TGF) β3 enhance susceptibility to SAPF [24–26]. A study conducted in white patients found that a promoter polymorphism in prostaglandin-endoperoxide synthetase 2 (PTGS2) was associated with an increased risk of SAPF [27]. Annexin A11 (ANXA11) is a calcium-dependent membrane-binding protein that has been associated with the risk of developing sarcoidosis [28]. Patients who carry ANXA11 inborn errors may show altered activation of $CD8^+$ and $CD19^+$ [29]. In a small study of black patients with sarcoidosis, ANXA11 SNPs (rs1049550 and rs12779955) were linked to an increased susceptibility to pulmonary fibrosis [30]. Those who carried genotype T of rs1049550 had a 4.5 times higher risk of developing pulmonary fibrosis [30].

The anti-inflammatory cytokine TGF-β has garnered particular interest, as TGF-β SNPs differ in patients with acute remitting and chronic progressive sarcoidosis [31]. Polymorphisms in the TGF-β2 or TGF-β3

genes have been associated with fibrotic sarcoidosis [24, 31], but have not been validated in large multicentre cohorts. The human leukocyte antigen class II gene on antigen-presenting cells has been implicated in the progression of SAPF [32]. An association has been noted between the butyrophilin-like-2 gene variant and an increased risk of SAPF [33], but this association remains uncertain.

SAPF is presumed to be the consequence of chronic granulomatous inflammation. However, only a small number of patients with sarcoidosis develop SAPF, suggesting that mechanisms other than those underlying sarcoidosis are involved in its development. Genetic studies have enhanced our understanding of the fibrotic transformation. The challenge now is to identify how susceptible alleles interact with environmental factors and steer cellular mechanisms to develop a high-risk phenotype.

## Pathobiology of SAPF

SAPF is characterised by granulomatous inflammation due to dysregulated immune response. "Burnt-out" sarcoidosis reflects the end-stage fibrotic sequelae of granulomatous inflammation. Explanted lungs from patients with end-stage fibrotic sarcoidosis show characteristic lymphocytic infiltrates [34]. The prevalent notion is that pulmonary fibrosis develops as the inflammatory process continues [35]. This concurrent dual process contributes to end-organ damage and worsening symptoms. A T-helper (Th) 1-mediated immune response results in activation of fibroblasts and the secretion of fibrogenic cytokines. Circulating levels of interleukin (IL)-5 and IL-7 have been shown to be higher, and levels of granulocyte-macrophage colony stimulating factors lower, in patients with fibrotic *versus* nonfibrotic sarcoidosis [36].

The mechanisms underlying the evolution of fibrosis in sarcoidosis are poorly understood, but are thought to involve a complex interplay of cells and immune mediators (figure 2). It is believed that fibrosis in sarcoidosis originates from the granulomas, although fibrosis can occur in the context of resolving granulomas. Evidence from human tissues indicates that fibroblasts become attracted to the periphery of granulomas and may form a fibrous capsule around a granuloma [37, 38]. Persistent granulomatous inflammation can give rise to vast fibrotic remodelling and this process is probably influenced by pro-fibrotic risk factors such as age, smoking and exposure to environmental factors. Fibrosis itself may perpetuate fibrotic remodelling by increasing tissue stiffness and extracellular matrix composition [39]. However, it remains unclear why some patients with persistent inflammation develop progressive fibrosis while others do not.

Macrophages and cells derived from macrophages such as epithelioid cells and giant cells are considered to drive fibrosis in the context of sarcoidosis. Factors produced by these cells attract fibroblasts, increase their proliferation and increase collagen production. These factors include pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β, which activate profibrotic signalling cascades in fibroblasts [40, 41]. While in

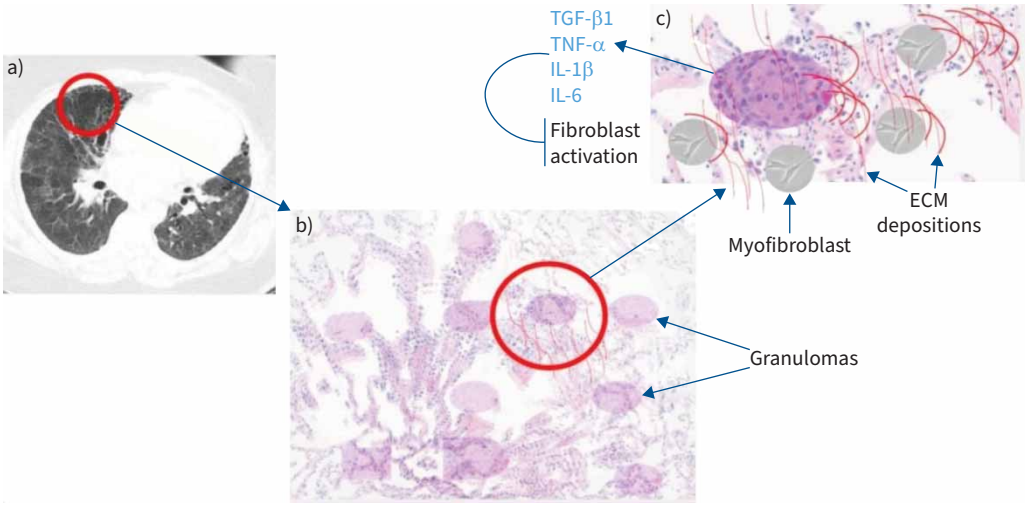


**FIGURE 2** Pathobiology of fibrosis in sarcoidosis. a) Representative chest computed tomography image from a patient with sarcoidosis. b) Granulomas in the lung tissue. c) Granuloma with myofibroblasts and the effects of cytokines on the production of extracellular matrix (ECM) in the lung. IL: interleukin; TGF: transforming growth factor; TNF-α: tumour necrosis factor-α.

early disease, TGF-β1 produced by T-cells appears to favour resolution of granuloma [42], later in the disease course, TGF-β production by giant cells may favour fibrosis [40, 43]. Elevated alveolar macrophage TNF-α in the culture supernatants of alveolar macrophages and bronchoalveolar lavage (BAL) cells can distinguish patients with progressive *versus* stable sarcoidosis [42]. In a study of patients with pulmonary sarcoidosis, levels of TGF-β in culture supernatants of BAL cells were increased in patients with active sarcoidosis who underwent spontaneous remission within 6 months, but were within the normal range in patients with persistent active disease [44]. In another study, TGF-β levels in BAL fluid (BALF) and alveolar macrophage supernatant were not significantly different between patients with pulmonary sarcoidosis and healthy subjects, but TGF-β levels were increased in BALF from patients with pulmonary sarcoidosis who had impaired pulmonary function compared with those who had normal lung function [45]. Upregulation of interferon pathways and chemokine ligand 9, as well as downregulation of T receptor signalling pathways, also play vital roles in the development of SAPF [46]. CC chemokine ligand 18 is upregulated in patients with fibrotic sarcoidosis, as well as other types of fibrotic ILDs, including idiopathic pulmonary fibrosis (IPF) [47]. Elevated levels of hypoxia-inducible factor-1α, platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) have also been reported in fibrotic sarcoidosis [48, 49], indicating that some profibrotic pathways are common between sarcoidosis and IPF.

$CD4^+$ effector T-cell–Th17 cells participate in granuloma formation and progression to fibrosis [50]. Th17 axis cells are substantially increased in peripheral blood and BAL in active sarcoidosis. The Th17 inflammatory axis is also implicated in secretions of pro-inflammatory cytokines including interferon-γ [51]. Uninhibited mammalian target of rapamycin complex 1 signalling in macrophages results in excessive granuloma formation and may direct towards progressive fibrotic sarcoidosis [52].

## HRCT features of SAPF

The main features of SAPF on HRCT are bronchial distortion, diffuse linear opacities and large cystic honeycombing along with traction bronchiectasis [53]. The bulk of fibrotic processes in sarcoidosis are located in the upper and middle zones, mimicking HP. However, lobular areas of hypoattenuation and centrilobular nodules are common in HP, unlike the bronchovascular distribution of nodules in sarcoidosis [54]. Mosaic attenuation and air trapping have been uncommonly described in SAPF.

The presence of honeycombing correlates with the severity of pulmonary restriction [55], but unlike other fibrotic ILDs, has not been shown to have prognostic value. Linear fibrosis can present with airway obstruction due to bronchial distortion [56]. The linear streaks and interlobular septal thickening are often associated with peri-lymphangitic nodules or ground-glass opacities (GGOs) and represent potentially reversible active inflammatory sarcoidosis [53]. However, GGOs may also represent early fibrosis. Figure 3 illustrates the typical fibrotic pattern of sarcoidosis seen on HRCT and the histopathology of SAPF.

### *SAPF* versus *other fibrotic lung diseases*

The fibrosis observed in end-stage sarcoidosis predominantly affects the upper and mid lung regions, similar to HP. It is distinct from the usual interstitial pneumonia (UIP) pattern present in IPF, which shows a peripheral lower lobe propensity of fibrotic processes. It is not known if fibrosis in sarcoidosis can occur at sites distant from the location of perilymphangitic granuloma. A small subset of patients with end-stage fibrotic sarcoidosis shows a UIP-like pattern [34]. It is unclear whether patients with SAPF are more prone to develop IPF or if this is a subset of pathologically distinct end-stage sarcoidosis. A retrospective study of 25 patients with clinical and histological characteristics of sarcoidosis and definite or possible UIP on HRCT showed that the clinical behaviour of these patients was similar to that of IPF [57]. However, histology of explanted lungs from patients with SAPF demonstrated a pattern distinct from IPF: honeycombing and fibroblastic foci were located predominantly in the central and perihilar regions and cases with active inflammation had granulomatous disease [37]. Another study reported a subset of patients with end-stage sarcoidosis with a UIP pattern who had rapid clinical progression and epithelioid granuloma on lymph node biopsy [58]. A phenotype of “combined sarcoidosis and IPF” at high risk of rapid progression has been described [59], but its existence remains open to debate.

The potential role of the PTGS2 promoter polymorphism has been explored in fibrotic sarcoidosis, akin to IPF. This polymorphism inhibits upregulation of prostaglandin E2 (PGE2). PGE2 inhibits fibroblast proliferation and differentiation into myofibroblasts. Low levels of PGE2 are seen in IPF [60]. Similarly, reduced PTGS2 expression has been reported in patients with persistent sarcoidosis [27, 58]. However, gene expression profiling has shown upregulation of genes involved in host defence and immune response in SAPF, resembling HP rather than IPF [23].

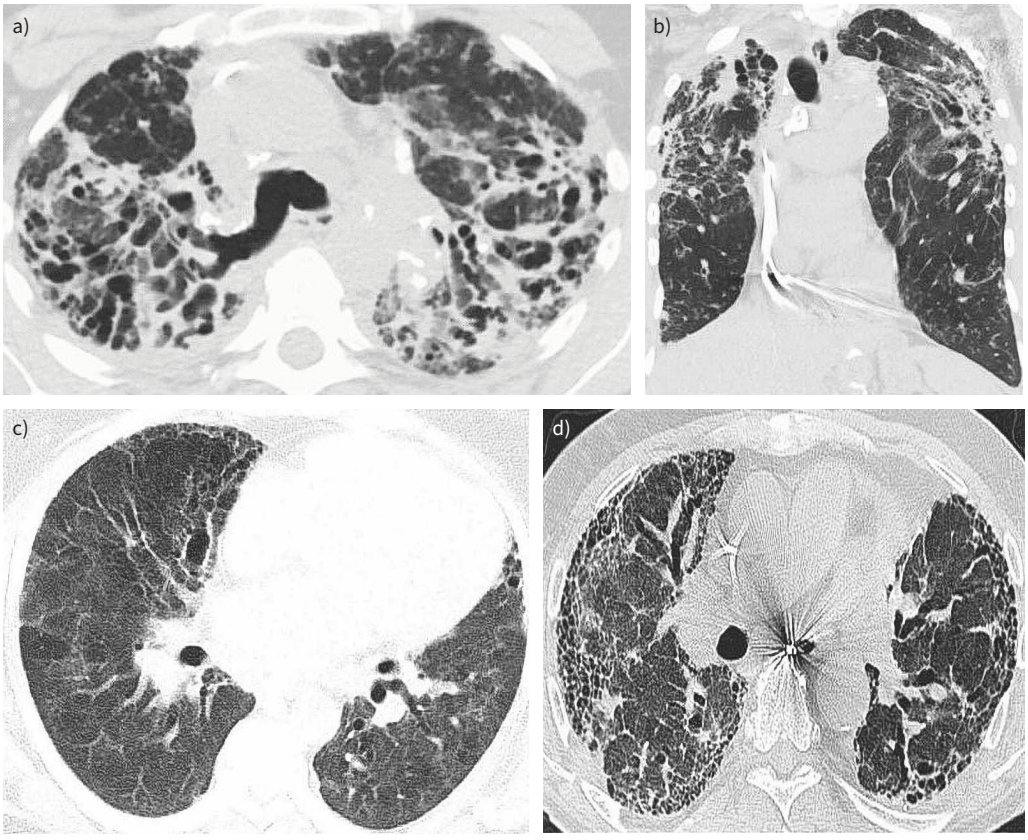


**FIGURE 3** a) Sagittal plane of computed tomography (CT) demonstrating distribution of fibrosis in sarcoidosis. b) Typical coronal CT of sarcoidosis-associated pulmonary fibrosis (SAPF). c) Nonspecific interstitial pneumonia pattern of SAPF. d) Upper lobe usual interstitial pneumonia pattern of SAPF with mediastinal lymphadenopathy.

## Clinical profile and complications of SAPF

The development of SAPF leads to pulmonary dysfunction. Cough and dyspnoea are common. Wheezing occurs more frequently in fibrotic sarcoidosis due to bronchial distortion from airway-centric fibrosis. Bronchiectasis may develop due to endobronchial sarcoidosis or to traction bronchiectasis in the upper lobes. The clinical course of bronchiectasis may be complicated by airway obstruction, recurrent exacerbations and bacterial infections, and it may lead to recurrent haemoptysis [16]. Other complications of SAPF include airway stenosis, mycetoma/aspergilloma (chronic cavitary pulmonary aspergillosis), haemoptysis, SAPH and pulmonary embolism. Mycetoma are conglomerations of *Aspergillus* hyphae intertwined with fibrin, mucus and cellular debris that grow inside fibrotic sarcoidosis in about 2% of cases and can lead to severe haemoptysis [61].

Profound hypoxaemia may be seen in SAPF, but SAPH should also be considered. The incidence of SAPH in patients with sarcoidosis varies between 5 and 20% and is higher in stage IV disease [62]. The origins of SAPH are multifactorial, including fibrotic destruction of the interstitium, vasculopathy, external pulmonary artery compression from nodules/lymphadenopathy and cardiomyopathy [63]. SAPH is the most robust predictor of mortality in patients with sarcoidosis, associated with an eight-fold increase in risk of mortality and a median survival of 5.7 years [17, 64]. Persistent severe dyspnoea, resting hypoxia, 6 min walk distance <300 m or forced vital capacity (FVC)/diffusing capacity of the lung for carbon monoxide ($D_{LCO}$) >1.5 raises the possibility of SAPH [61]. Given its poor prognosis, screening algorithms have been proposed to aid early detection [63, 65].

An acute pulmonary exacerbation of sarcoidosis (APES) has been defined as progressively worsening symptoms over a month along with ⩾10% decline in FVC and/or forced expiratory volume in 1 s [66]. Clinically it is worth distinguishing an APES from complications of SAPF such as infection or pulmonary embolism. The incidence of APES is unknown, but in a cohort of 129 patients with SAPF, 73% reported

two or more APES in the previous year [62]. Retrospective studies have shown that patients who have SAPF, are African American, have prolonged use of high-dose corticosteroid or use anti-TNF-α therapy are at higher risk of APES [66, 67]. Data from sarcoidosis centres in the USA have shown that patients with fibrotic sarcoidosis and bronchiectasis experience a median of three APES a year, more than patients without bronchiectasis [67].

## PFTs

The most common PFT abnormality seen in SAPF is pulmonary restriction with a reduction in $D_{LCO}$ [7]. Obstructive airway disease may reflect bronchial distortion rather than airway disease and the potential benefit of a bronchodilator is debatable. In contrast to IPF, PFTs usually remain relatively stable for a prolonged period in patients with SAPF. Indeed, PFTs improve in 39% of cases, indicating amelioration of inflammation [17]. There is no consensus on what constitutes progressive SAPF, but a clinical practice guideline issued by international societies in 2022 identified an absolute decline in FVC % predicted ⩾5% within 1 year, an absolute decline in $D_{LCO}$ % predicted ⩾10% within 1 year, radiological evidence of progression and worsening of symptoms as criteria for PPF in patients with ILDs other than IPF [8].

## Biomarkers of progression to fibrotic sarcoidosis

### *Serum biomarkers*

Biomarkers that predict progression to fibrotic sarcoidosis or prognosis in patients with SAPF remain elusive. As previously mentioned, certain SNPs have been identified as associated with progression to end-stage disease [24–26]. Serum angiotensin converting enzyme (SACE), soluble IL-2 receptor (sIL-2R) and chitotriosidase are fairly reliable predictors of sarcoidosis disease activity. IL-5 and possibly IL-7 levels are elevated in patients with a fibrotic phenotype [36].

### *BALF*

Analysis of BALF reflects disease activity in sarcoidosis, but does not reliably predict progression to advanced stage disease. High lymphocyte count and $CD4^+/CD8^+$ ratio in BALF indicate the intensity of alveolitis, but are not indicators of poor prognosis, nor do they correlate with lung function deterioration [68, 69]. Radiological staging is associated with differential BALF lymphocyte profiles. Contrary to advanced stage disease, BALF from early-stage sarcoidosis shows elevated $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$ subsets and an increased $CD4^+/CD8^+$ ratio [70], while BALF neutrophilia is seen in stage IV disease [71]. Some experts believe these findings are relevant for predicting fibrotic transformation, while others disagree [72, 73].

### *Imaging biomarkers*

#### *Fluorodeoxyglucose-positron emission tomography*

Fluorodeoxyglucose-positron emission tomography (FDG-PET) computed tomography (CT) scanning is a technique for detecting metabolic activity. FDG-PET has shown promise as a marker for distinguishing pulmonary fibrogenesis from burnt-out or end-stage fibrosis. Correlations have been observed between FDG-PET findings and biomarkers of sarcoidosis activity such as SACE, sIL-2R and BALF CD4/CD8 ratio, as well as pulmonary function. In a retrospective series among 26 patients who had pulmonary fibrosis on HRCT, 85% had positive pulmonary FDG-PET findings [74]. However, another study found that among 24 patients with positive PET findings, only three had pulmonary fibrosis on HRCT [75]. Pulmonary inflammation leads to enhanced $^{18}$F-FDG uptake, resulting in a higher standardised uptake value (SUV). In the retrospective series of 26 patients with pulmonary fibrosis on HRCT, an SUV >2.5 was demonstrated in 23 patients, suggesting simultaneous inflammation and fibrosis [74]. In a small trial of infliximab in patients with sarcoidosis, a decrease in SUV correlated with improvement in vital capacity, suggesting that enhanced $^{18}$F-FDG uptake indicates more active disease [76]. However, the SUV threshold of 2.5 remains contentious. Fibrosis is not metabolically inert. Low-grade metabolic activity occurs during fibrogenesis due to glucose uptake in inflammatory cells and erythrocytes and neovascularisation around fibrosis [77]. In a study conducted in 35 patients with pulmonary sarcoidosis, correlations between conventional markers of disease activity and volumetric FDG-PET/CT parameters (*i.e.* the percentage of lung volume with increased metabolic activity or the average metabolic activity in the lung) were better than those observed with qualitative FDG-PET/CT parameters or $SUV_{max}$ [78]. Larger studies are needed to confirm the utility of these novel measures in patients with pulmonary sarcoidosis.

#### *Other imaging modalities*

Radiomics is an emerging field, which involves the extraction of sub-visual quantitative image features from radiological images [79]. Studies suggest that radiomic HRCT can differentiate disease state abnormalities and stages of disease severity in sarcoidosis and that radiomic measurements correlate with FVC [80].

Hyperpolarised xenon or helium magnetic resonance imaging has emerged as a functional pulmonary imaging modality that can identify inflammatory lesions (which have a high water content) as areas of high signal intensity and fibrotic lesions as areas of low signal intensity [81].

## Management of SAPF

In the absence of an adequate evidence base, therapeutic discussions about sarcoidosis are riddled with questions around whom, when and how to treat. Decisions about when to start therapy and which therapies should be used should be based on shared decision-making with the patient, taking into account symptoms and the risk of progression. Early institution of therapy has not been shown to alter the natural course of the disease or to prevent progression to advanced stage disease. The early detection of radiological changes and the use of corticosteroids may improve symptoms initially, but there is no evidence that this improvement is sustained beyond 2 years [82]. Impaired organ function in pulmonary fibrosis would be a compelling indication to treat, but a carefully delineated goal is needed before deciding to initiate therapy. This is challenging in the absence of a reliable marker to assess treatment response.

### *Immunosuppression in SAPF*

A subset of patients with SAPF have ongoing inflammation, but identification of these patients is difficult. Inflammatory biomarkers SACE, sIL2 and C-reactive protein may be elevated. The presence of nodules and peribronchial/interstitial GGOs may suggest active sarcoidosis, but the utility of HRCT is limited. The typical approach to treatment of SAPF comprises corticosteroids and second-line agents such as methotrexate or azathioprine [83]. There is some evidence to support a benefit of infliximab on lung function in patients with pulmonary sarcoidosis, although more research is needed. In a placebo-controlled trial of infliximab in 19 patients, the improvement in vital capacity at week 6 was numerically greater in the infliximab group [84]. However, this trial was terminated early due to low enrolment. In another trial in 138 patients, patients treated with infliximab had a mean increase in FVC % predicted of 2.5% over 24 weeks, compared with no change in the placebo group [85].

### *Antifibrotic treatment of SAPF*

Although the aetiopathogenesis of SAPF, IPF and other ILDs differ in crucial ways, the clinical and pathophysiological characteristics of PPF have many overlapping traits [86, 87]. Explanted lungs show augmentation of PDGF, fibroblast growth factor (FGF), VEGF and macrophage colony-stimulating factor pathways to a similar degree across progressive fibrosing ILDs, including progressive SAPF [88]. Nintedanib inhibits tyrosine kinase receptors in the VEGF, PDGF and FGF pathways, and nonreceptor tyrosine kinases such as the Src family [87]. The Src family may be particularly relevant in sarcoidosis given its role in T-cell activation and proliferation [89]. Preclinical studies have shown that nintedanib has antifibrotic effects, including inhibition of fibroblast proliferation and migration and reduced deposition of extracellular matrix, as well as anti-inflammatory effects [87]. The randomised placebo-controlled INPULSIS [90], SENSCIS [91] and INBUILD [92] trials established the benefit of nintedanib in slowing the progression of fibrosing ILDs. The INBUILD trial enrolled 663 patients with PPF (other than IPF) who had progressed despite management in clinical practice. The adjusted rate of decline in FVC over 52 weeks was reduced by 107.0 mL·year$^{-1}$ (95% CI 65.4–148.5) in patients treated with nintedanib *versus* placebo [92]. The absolute rate of decline in FVC over 52 weeks was higher in patients with a UIP-like fibrotic pattern on HRCT than in patients with other fibrotic patterns, but the relative effect of nintedanib was consistent between these subgroups [92]. While the INBUILD trial was not powered to study the effect of nintedanib in subgroups based on diagnosis, no heterogeneity was detected in its treatment effect among patients with HP, autoimmune disease-related ILDs, idiopathic nonspecific interstitial pneumonia, unclassifiable ILD and other ILDs [93]. Its results support the hypothesis that once PPF has developed, it will progress despite standard of care and led to nintedanib being licensed by the US Food and Drug Administration, European Medicines Agency and other regulators for the treatment of progressive fibrosing ILD of any aetiology. A clinical practice guideline issued by international societies in 2022 provided a conditional recommendation for the use of nintedanib in patients with PPF who have failed standard management, but highlighted that it remains unclear how to identify the patients best suited for antifibrotic therapy [8]. Many questions remain about the clinical behaviour of PPF and indications for antifibrotic therapy (table 1). Further, it should be noted that the INBUILD trial included only 12 patients with SAPF [9] and no clinical trials of nintedanib specifically in patients with SAPF have been conducted.

Pirfenidone is an antifibrotic drug licensed for the treatment of IPF but no other forms of PPF. The mechanism of action of pirfenidone is unclear, but it has been shown to have antifibrotic and anti-inflammatory effects [94]. The double-blind, placebo-controlled PIRFS pilot study evaluated the efficacy of pirfenidone in 15 patients with progressive fibrotic sarcoidosis [95]. Although pirfenidone did

**TABLE 1** Unanswered questions about the use of antifibrotic therapy in sarcoidosis-associated pulmonary fibrosis (SAPF).

| | |
|---|---|
| 1) | **Appropriate patient population**<br>The criteria that should be used to identify patients with PPF remain a subject of debate. |
| 2) | **Treatment effect**<br>SAPF progresses more slowly than other forms of PPF, which makes it challenging to assess the effect of therapies. No dedicated trials of antifibrotic therapy in patients with SAPF have been completed. |
| 3) | **Quality of life**<br>An appropriate patient-reported outcome needs to be validated in patients with SAPF in order to assess the impact of therapies on patients' symptoms and quality of life. |
| 4) | **Positioning in management algorithm**<br>The potential roles of antifibrotic therapy as first-line therapy, upfront combination therapy with immunosuppression and second-line therapy after immunosuppression remain to be established. |
| 5) | **Escalation of therapy**<br>A subset of patients with SAPF will progress on antifibrotic therapy. There are no data to inform how therapy should be escalated in these patients. |
| 6) | **Assessment of treatment response**<br>There are no reliable biomarkers for prediction or confirmation of response to antifibrotic therapy. |

PPF: progressive pulmonary fibrosis.

not have a significant effect on time to clinical worsening, change in FVC or change in $D_{LCO}$ in the overall cohort, it may be beneficial in patients with severe disease ($D_{LCO}$ <40% predicted) [95].

The notion of "treatable traits" has been conceptualised to address heterogeneity in the management of complex airway diseases [96, 97]. This model of care assumes the principle of precision medicine by recognising different therapeutic targets through validated biomarkers, described as TIMS

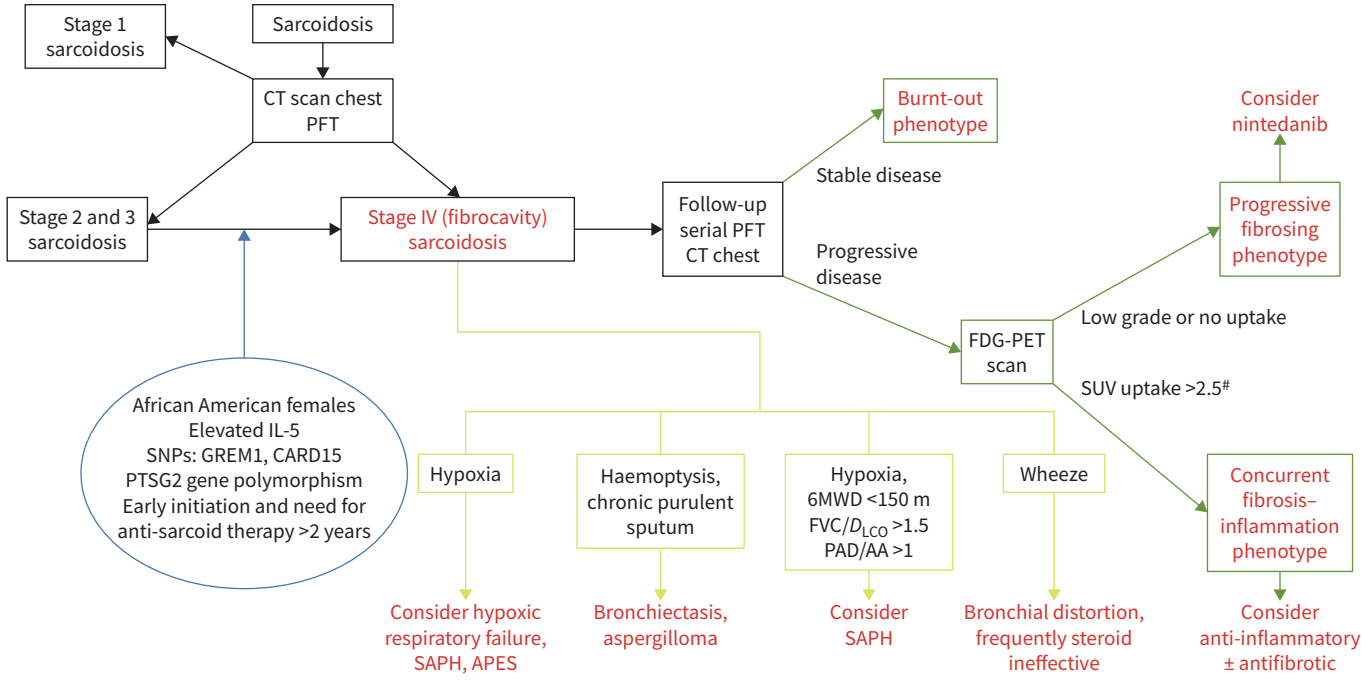


**FIGURE 4** A proposed approach for management of fibrotic sarcoidosis and its complications. The factors in the blue circle are likely prognostic indicators for progression to sarcoidosis-associated pulmonary fibrosis (SAPF). The green arrows indicate progression to various phenotypes of SAPF. The mustard yellow lines describe the complications of SAPF. 6MWD: 6-min walk distance; APES: acute pulmonary exacerbation of sarcoidosis; CARD15: caspase-recruitment domain-containing protein 15; CT: computed tomography; $D_{LCO}$: diffusing capacity of the lung for carbon monoxide; FDG-PET: fluorodeoxyglucose-positron emission tomography; FVC: forced vital capacity; GREM1: gremlin 1, DAN family BMP antagonist; IL-5: interleukin-5; PAD/AA: pulmonary artery diameter/ascending aorta diameter; PFT: pulmonary function test; PTSG2: prostaglandin-endoperoxide synthase 2; SAPH: sarcoidosis-associated pulmonary hypertension; SNP: single nucleotide polymorphism. #: this standardised uptake value (SUV) cut-off needs to be validated.

(trait-identification markers). Thus, patients are individually assessed for a specific set of problems and individualised treatment plans developed based on multidimensional assessment. We believe that a similar concept may be replicated in management approaches for SAPF. The proposed scheme implies an individualised approach to consideration of immunomodulator and/or antifibrotic therapy by detection of clinical characteristics, genetic traits and biomarkers for the risk of disease progression. Figure 4 depicts a flow diagram of proposed management approaches for SAPF, recognising current limitations and knowledge gaps and the need for testing in clinical practice.

### *Lung transplantation*

Lung transplantation is a therapeutic option for some patients with SAPF and/or SAPH who do not have severe extrapulmonary complications. The optimal timing for lung transplant referral is difficult to ascertain. The models predicting mortality in patients with IPF have not been validated in SAPF. However, patients with end-stage SAPF or SAPH respond poorly to medical therapy and should be referred early for lung transplant evaluation [98]. The lung allocation score prioritises patients with ILD who have concomitant pulmonary hypertension [99]. An analysis of the United Network for Organ Sharing database suggested that double lung transplants, young donors and white donors confer survival benefits in patients with SAPF [100].

### *Treatment of complications*

Treatment of SAPH poses considerable challenges, but limited evidence from patient registries suggests benefits of pulmonary arterial hypertension specific agents [101, 102]. The current clinical approach is off-label use of pulmonary vasodilators. Treatment recommendations for pulmonary mycetoma/aspergilloma (chronic cavitary pulmonary aspergillosis) include systemic antifungal therapy for progressive disease, bronchial artery embolisation for severe haemoptysis, and surgical resection in resistant haemoptysis. Immunosuppressive therapy needs to be de-escalated. A brief course of corticosteroids remains the first-line therapy for APES and has been shown to improve lung function and symptoms [103].

## Conclusions

Only a minority of patients with chronic sarcoidosis progress to SAPF, but SAPF and its complications are responsible for significant morbidity and mortality. There are no reliable tools to predict progression to SAPF. The mechanisms of fibrosis in SAPF are not fully understood, but SAPF might be a distinct clinicopathological entity, rather than a continuum of acute inflammatory sarcoidosis. SAPF exhibits wide clinical diversity, possibly related to genetics, epigenetics and host defence. The concept of PPF has aided therapeutic decision-making, but SAPF has many unique properties regarding aetiopathogenesis and clinicoradiological features. Our understanding of SAPF remains limited and needs further research.

**Questions for future research**

- Establish an international registry of patients with SAPF to study its natural history and investigate the roles of genetics and therapies.
- Study the mechanisms of fibrotic cascades in SAPF with relevance to therapy.
- Research how susceptible alleles, environmental agents and cellular pathways steer specific endotypes towards phenotypes of SAPF.
- Develop and validate molecular and imaging biomarkers for high risk of progression to SAPF and disease activities in SAPF.
- Conduct trials of established and novel antifibrotic agents in SAPF.
- Investigate appropriate clinical end-points, including quantitative imaging, to assess the efficacy of anti-inflammatory and antifibrotic therapies in SAPF.

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