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RESEARCH ARTICLE

FIBROTIC INTERSTITIAL LUNG DISEASES- A CURRENT OUTLOOK

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Abstract

Interstitial lung diseases (ILDs) are a group of diffuse parenchymal lung disorders associated with considerable morbidity and mortality. These include a large number of conditions, with a wide range of underlying causes, clinical manifestations, imaging, and distinct pathological features with variable outcomes. Pulmonary fibrosis is a pathologic process that arises from multiple underlying causes. Monitoring disease progression has become a priority in guiding treatment decisions. This article aims to review pulmonary fibrosis in various interstitial lung disease entities along with underlying pathophysiological features, clinical features, diagnostic workup and current possible treatment modalities of these fibrotic lung diseases.

Introduction:-

Interstitial lung diseases (ILDs) are a group of diffuse parenchymal lung disorders associated with considerable morbidity and mortality. These include a large number of conditions, with a wide range of underlying causes, clinical manifestations, imaging and distinct pathological features with variable outcomes. Despite the intrinsic heterogeneity of this group of diseases, in the majority of these diseases, the pulmonary alveolar walls are infiltrated by various combinations of inflammatory cells, fibrosis and proliferation of certain cells that make up the normal alveolar wall. Since these pathologic abnormalities predominate in the lung interstitium, the disorders are termed interstitial lung diseases. ILDs are typically assigned to many disease categories for classification and management purposes, roughly based on a known underlying disease like pulmonary fibrosis associated with rheumatoid arthritis, and inciting agent (pneumoconiosis), or the absence of a known cause (Idiopathic pulmonary fibrosis).[1,2] Present write-up aims to review pulmonary fibrosis in various interstitial lung disease entities, pathophysiological features, clinical manifestations, and diagnostic workup and possible treatment of these fibrotic lung diseases.

Epidemiology:-

The overall prevalence of ILD is estimated to be up to 76 cases per 100,000 people in Europe and 74.3 cases per 100,000 in the United States. Sarcoidosis, connective tissue disease (CTD)–associated ILDs, and IPF are the most common fibrotic ILDs, with an estimated prevalence of 30.2, 12.1, and 8.2 cases per 100,000, respectively. Among all patients with fibrotic ILDs other than IPF, 13 to 40% have a progressive fibrosing phenotype representing up to 20 patients per 100,000 people in Europe and up to 28 patients per 100,000 in the United States.[3] Pulmonary fibrosis occurs throughout the world, with a geographic variation.[4] The prevalence of IPF, is estimated to be 8 to 60 cases per 100,000 which are higher in North America and Europe than in the rest of the world[5,6] Whereas the prevalence of sarcoidosis is higher in northern Europe and among Black persons and is lower in Japan[7]. In a study done in

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India, Out of 92 patients with Diffuse parenchymal lung disease, Idiopathic pulmonary fibrosis(IPF) was the commonest diagnosis(38.04%) followed by Connective tissue disease-associated interstitial lung disease(CTD-ILD)(31.5%), hypersensitivity pneumonitis (10.9%), sarcoidosis (5.4%) and silicosis (5.4%).[8] According to Indian prospective registry on ILD, out of 1,084 patients with ILD, hypersensitivity pneumonitis (HP) was the most common diagnosis (47.3%) followed by Connective tissue disease-associated interstitial lung disease(13.9%),idiopathic pulmonary fibrosis(13.7%), idiopathic nonspecific interstitial pneumonia (iNSIP)(8.5%),sarcoidosis(7.8%),pneumoconiosis(3%) and other ILD were 5.7% [9]. While In another study done in Chandigarh, Sarcoidosis was the most common ILD (42.2%), followed by IPF (21.2%). CTD-ILDs, HP, and non-IPF IIPs were diagnosed in 12.7%, 10.7%, and 9.2% of subjects, respectively.[10] In another study done in India there has been a steady increase in both the absolute number and the relative percentage of attendance (4.36% in 2009 to 6.9% in 2019) of new registration of Diffuse parenchymal lung disease (DPLD) patients over the years.[11]

Pathophysiology:-

The development of fibrosis in fibrotic lung diseases is the result of the body's response to pathogens and in normal wound healing. [12] Various disease-specific triggers set off an exaggerated cascade of inflammatory and fibrotic responses leading to fibrotic tissue remodeling and extracellular matrix deposition leading to fibrosis formation[13.] Although the exact pathophysiological mechanism remains unclear, it is thought to be a combination of aberrant wound healing and inflammatory response, especially in the later phases.[13] Various genetic studies have identified both common and rare variants which are associated with enhanced susceptibility to pulmonary fibrosis, with remarkable similarities between familial IPF and other fibrotic ILD's.[14]Polymorphism in the promoter of MUC5B, which is involved in airway clearance and bacterial host defense, is associated with increased risks of IPF, Rheumatoid arthritis-ILD(RA-ILD) and Chronic hypersensitivity pneumonitis (CHP) but not systemic sclerosis with ILD(ssc-ild), sarcoidosis and antisynthetase syndrome[15] Similarly, telomere shortening and telomere related gene mutations (TERT, TERC, RTEL1, and PARN) are found in IPF, RA-ILD and CHP.[14,15] some rare genetic mutations are associated with progressive diseases. Different ILDs have overlapping initial pathways.[2] IPF results due to an insult to alveolar epithelial cell integrity which results through the interaction between epithelial cells and myofibroblasts.[16]Sarcoidosis results in response to an unknown trigger which progresses to fibrosis in only a small percentage of patients.[17] Fibrosis in SSc-ILD is the result of the combination of inflammation, endothelial dysfunction and vasculopathy.[13]

Interstitial Lung Diseases With Pulmonary Fibrosis:-

ILDs with pulmonary fibrosis can be divided into 5 broad clinical categories:

1. ILDs related to distinct primary diseases like sarcoidosis, Langerhans-cell granulomatosis, eosinophilic pneumonia, lymphangioleiomyomatosis, pulmonary alveolar proteinosis,
2. ILDs related to environmental exposures, including pneumoconiosis due to inhalation of inorganic substances and hypersensitivity pneumonitis mostly related to inhalation of organic particles like domestic or occupational exposure to mold or birds or other exposures
3. ILDs induced by drugs and irradiation
4. ILDs associated with connective tissue diseases including rheumatoid arthritis associated–Interstitial lung disease(RA-ILD), systemic sclerosis-ILD (SSc–ILD), idiopathic inflammatory myopathy, primary Sjögren's disease
5. Idiopathic interstitial pneumonias which include Idiopathic pulmonary fibrosis (IPF), idiopathic non-specific interstitial pneumonia(i-NSIP), and other less common entities like cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP).[28]

A division can be made between pulmonary fibrosis in the context of underlying systemic diseases, such as connective tissue diseases (CTD) and sarcoidosis, and conditions that are restricted to the lung such as chronic hypersensitivity pneumonitis (CHP), drug-induced pulmonary fibrosis, idiopathic nonspecific interstitial pneumonia, and IPF. [18,19] There is also overlap between groups (drug-induced pulmonary fibrosis in CTD and a genetic predisposition in various ILDs). Owing to the epidemiology and burden of fibrosis within each diagnostic category, clinicians most often see patients with CTD–ILD, IPF, CHP, sarcoidosis, or unclassifiable fibrotic ILD

Post-Covid Fibrosis:-

Currently, there is a precise interest in the potential development of fibrosis after coronavirus disease 2019 (Covid-19). Although infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a range of pulmonary symptoms. Male sex, older age, obesity, and coexisting conditions appear to be risk factors for the

development of Severe acute respiratory syndrome.[20] Pulmonary fibrosis is a known complication of acute respiratory distress syndrome (ARDS), and there are similarities in the fibroproliferative response and risk factors between lung fibrosis in the context of ARDS and lung fibrosis in the context of other diseases.[21] Nevertheless, analysis of long-term follow-up data after ARDS or infection with another strain of SARS-CoV in 2003[22] showed fibrotic changes that remained mostly stable over time and had little clinical relevance.[22] The long-term effect and the disease course of pulmonary fibrosis caused by Covid-19 are presently under investigation in many studies.

Diagnostic Approach Clinical Evaluation:-

Main presenting symptoms include cough, progressive exertional dyspnea, and exercise limitation, other than disease specific symptoms. The diagnosis is often delayed by several months. A thorough history including environmental exposure, medication use, and extra-pulmonary signs should be assessed.[23] On chest auscultation, fine crepts (end- inspiratory) also called Velcro crepitations are indicative of fibrosis,[24]squeaks may be heard in patients with hypersensitivity pneumonitis. In connective tissue disorders, pulmonary fibrosis may develop either after the underlying condition is diagnosed or before the extra-pulmonary manifestations are observed.[25]Hands, joints and skin should be thoroughly examined.[25] Serologic testing is recommended including antinuclear antibodies and anti-citrullinated peptide antibodies.[2] If there is a clinical suspicion of an autoimmune condition, consultation with a rheumatologist and more extensive serologic testing are recommended.

High Resolution Computed Tomography (Hrct) Of Thorax Technique:-

The diagnostic approach is highly reliant on images of the lungs generated from volumetric scanning of the chest. This mode has essentially replaced sequential CT scanning, as it improves the detection of all abnormalities even if subtle or focal. It also ensures precise analysis of lesion characteristics and distribution based on both cross-sectional images and multiplanar reformations. Good quality non-contrast high resolution computed tomography of chest (HRCT) done with specifications shows reticulation, architectural distortion, and lung volume loss often establishes the diagnosis of pulmonary fibrosis and may identify patterns suggestive of specific causes.[6,14] The thinnest collimation, shortest rotation time, and highest pitch ensure the creation of motion-free images. The kilovoltage and milliamperage selection should follow current recommendations for reduced-dose CT[27-30]. If films are taken; they should be 12 on 1 format (3*4). The first acquisition is obtained in supine position at sustained end-inspiration (supine inspiratory), the second is obtained in supine position over the entire thorax at sustained end-expiration (supine expiratory), after a prolonged expiration [27,31] and the third acquisition is aimed at clearing position-induced changes in the dependent lung of the first acquisition [32] (prone). Technical requirements of HRCT thorax are tabulated in table 1.

Table 1:- Recommended HRCT Thorax Scanning Protocol.

1. Non-contrast examination **2. Volumetric acquisition with the selection of:** • Sub-millimetric collimation • Shortest rotation time • Highest pitch • Tube potential and tube current appropriate to patient size ◦Typically 120 kVp and ≤240 mAs ◦ Lower tube potentials (e.g., 100 kVp) with adjustment of tube current encouraged for thin patients • Use of techniques available to avoid unnecessary radiation exposure **3. Reconstruction of thin-section CT images (≤1.5mm):** • Contiguous or overlapping • Using a high-spatial-frequency algorithm • Iterative reconstruction algorithm if validated on the CT unit (if not, filtered back projection) **4. Number of acquisitions:**

- Supine: inspiratory (volumetric) obtained at full inspiration
- Supine: expiratory obtained at full expiration
- Prone: only inspiratory scans

5. Recommended radiation dose for the inspiratory volumetric acquisition:

- 1–3 mSv (i.e., "reduced" dose)
- Strong recommendation to avoid "ultralow-dose CT" (<1 mSv)

Hrct Thorax Pattern In Uip:-

4 diagnostic categories incorporate the HRCT features which include UIP pattern, probable UIP pattern, indeterminate for UIP pattern, and alternative diagnosis

Uip Pattern:-

UIP is the hallmark radiologic pattern of IPF. Honeycombing is a distinguishing feature of UIP and must be present for a definite HRCT diagnosis of UIP to be made and can be seen with or without peripheral traction bronchiectasis or bronchiolectasis. The typical distribution of UIP is sub-pleural with basal predominance, although some upper lobe involvement is common [33,34]. Mediastinal lymphadenopathy may be present in patients with UIP [35]. Ground glass opacification (GGO) may be present, but it is not a dominant feature and is usually accompanied by a superimposed reticular pattern.

Probable Uip Pattern:-

Sub-pleural, basal-predominant reticular abnormalities with peripheral traction bronchiectasis or bronchiolectasis in the absence of honeycombing should be considered as probable UIP. As with a UIP pattern, GGO may be present in probable UIP, but it is not a dominant feature.

Indeterminate For Uip Pattern :-

It should be considered when HRCT demonstrates features of fibrosis but does not meet UIP or probable UIP criteria and does not suggest an alternative diagnosis. This category includes a subset of patients with very limited sub-pleural GGOs or reticulation without evident CT features of fibrosis, for whom there is a suspicion that early UIP or probable UIP is present. In such cases, it should be confirmed with prone inspiratory views that the sub-pleural opacities do not represent dependent atelectasis.

Alternative Diagnosis Pattern :-

In some cases of fibrotic lung disease, there is clinical suspicion of IPF, but the HRCT pattern suggests an alternative diagnosis like bronchocentric fibrosis in the upper lobes or profuse mosaic attenuation that suggest Hypersensitive pneumonitis, posterior fibrotic retraction of the hila in sarcoidosis or extensive Ground glass opacities with subpleural sparing in fibrotic non-specific interstitial pneumonia (NSIP)

Patients with an acute exacerbation of IPF have bilateral GGO with or without consolidation on a background of lung fibrosis. In the absence of a previous HRCT study, bilateral GGO and/or consolidation on a background of a UIP pattern is highly suggestive of an acute exacerbation and can be used to confirm an underlying IPF diagnosis in the appropriate clinical context. These features are tabulated in table 2.

Table Number 2:- Hrct Thorax Patterns.

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
• Sub-pleural and basal predominant and distribution are often heterogeneous • Honeycombing with or without	• Sub-pleural and basal predominant and distribution is often heterogeneous • Reticular pattern with peripheral	• Sub-pleural and basal predominant • Subtle reticulation and may have mild GGO or distortion (early	Findings suggestive of another diagnosis include: • **CT features of:** ◦ Cysts ◦ Marked mosaic attenuation ◦ Predominant GGO ◦ Profuse micronodules ◦ Centrilobular nodules

peripheral traction bronchiectasis or bronchiolectasis	traction bronchiectasis or bronchiolectasis • May have mild GGO	UIP pattern) • CT features and/or distribution of lung fibrosis that does not suggest any specific etiology (truly indeterminate for UIP)	◦ Nodules ◦ Consolidation • **Predominant distribution:** ◦ Peribronchovascular ◦ Perilymphatic ◦ Upper or mid-lung • **Other findings:** ◦ Pleural plaques (consider asbestosis) ◦ Dilated esophagus (consider CTD) ◦ Distal clavicular erosions (consider Rheumatoid arthritis) ◦ Extensive lymph node enlargement (consider other etiologies) ◦ Pleural effusions, pleural thickening (consider CTD/drugs)

HRCT thorax establishes the diagnosis of pulmonary fibrosis by revealing reticulations, architectural distortion and lung volume loss and may identify patterns suggestive of a specific cause. The UIP pattern consists of honeycombing and reticulation in the absence of features suggesting an alternative diagnosis with basal and sub-pleural predominance which is often heterogenous and is the hallmark of pulmonary fibrosis, observed frequently in IPF, RA- ILD, and in advanced disease irrespective of the underlying condition.[18,36] In contrast, the most common HRCT pattern in SSc-ILD is that of Nonspecific interstitial pattern (NSIP) which consists of mixed reticulation and Ground glass opacities to a varying extent, often with traction bronchiectasis, central axial distribution and sparing of the sub-pleural area. Expiratory image may be useful in chronic hypersensitivity pneumonitis.

Pulmonary Function Test:-

Pulmonary-function testing measures the level of disease impairment and is used for monitoring the course of disease and response to therapy. In patients with pulmonary fibrosis, it typically shows a restrictive lung-function pattern (decreased forced vital capacity [FVC], normal or increased ratio of forced expiratory volume in 1 second to FVC, decreased total lung capacity, and low residual volume), together with a decreased diffusing capacity of the lung for carbon monoxide. Normal lung function does not rule out the presence of pulmonary fibrosis.

Other Investigations:

If the combination of clinical findings and imaging is not diagnostic, more invasive procedures may be required. Bronchoalveolar lavage contributes to the diagnosis of hypersensitivity pneumonitis and sarcoidosis. Bronchial mucosa and lymph-node biopsies are performed when sarcoidosis is suspected. All collected information is synthesized by multidisciplinary ILD boards experienced in ILD, which may either establish a diagnosis or discuss the indication for further diagnostic procedures such as thoracoscopic lung biopsy or transbronchial cryobiopsy. The course of the disease in a given patient is to be considered in guiding diagnosis and management and it may reduce the need for invasive diagnostic procedures. Diagnosis can be made with sufficient confidence in the majority of cases[37]. A subgroup of ILD cases remains unclassifiable even after thorough assessment.[38]

Progressive Pulmonary Fibrosis:-

The natural course of untreated IPF is characterized by progression to respiratory failure in virtually every patient with a secure diagnosis.[18]In contrast, more than half of all patients with a diagnosis of pulmonary fibrosis other than IPF have stable, chronic disease or improvement with immunomodulatory therapy.[39] Despite appropriate treatment, a proportion of patients will have progressive pulmonary fibrosis associated with worsening respiratory symptoms, a decline in lung function, decreased quality of life, and risk of early death independent of the classification of the ILD.[39,40] Outcomes may be similar to those of IPF, especially in patients with a UIP pattern, such as those with RA–ILD and some patients with CHP. The risk of progressive disease and the prognosis depend on the underlying entity. However, the longitudinal disease course varies and needs to be identified individually, since it has implications for management decisions and occasionally may lead to a reconsideration of the diagnosis. [4,21]No serum biomarker has been validated for monitoring disease progression or assessing the respective components of inflammation and

fibrosis. Scores especially those based on sex, age, FVC and diffusing capacity of the lung for carbon monoxide have been developed to assess the prognosis.[41]

There is no standard definition of disease progression in patients with pulmonary fibrosis. Patients are required to meet at least one of the following criteria for disease progression within 24 months, a relative decline in the FVC of 10% or more of the predicted value, a composite of a relative decline in the FVC of 5 to 10% of the predicted value and worsening symptoms or an increase in disease extent on chest CT, or worsening symptoms and an increase in disease extent on chest CT. In clinical practice, no threshold or rate of decline has been formally accepted, however, assessment of the progression of fibrosis is usually based on serial lung-function tests performed at 3-to-6- month intervals. Since small variations in FVC may be confounded by measurement errors, multimodal assessment of disease progression also includes worsening of symptoms and exercise capacity, increased fibrosis on chest CT, decreased diffusing capacity of the lung for carbon monoxide, need for oxygen supplementation, and clinical events predicting early death like acute exacerbation of fibrosis and hospitalization.

Management Of Pulmonary Fibrosis And Future Outlook:-

Nonpharmacological treatment:

For most patients, a diagnosis of pulmonary fibrosis is a life-threatening verdict. The uncertainty about prognosis in combination with an increasing symptom burden has a major effect on the quality of life of patients and their family members. Treatment can be aimed at ameliorating the disease or slowing down disease progression while improving or maintaining the quality of life,[42] educating patients, sharing decisions, preventing exposures and events that may lead to disease progression, avoidance of the offending antigen in patients with chronic hypersensitivity pneumonitis and cessation of tobacco smoking. Pneumococcal and influenza vaccinations are recommended. Supplemental oxygen is indicated in patients with resting hypoxemia (partial pressure of arterial oxygen [Pao2] of< 55mmhg, oxygen saturation as measured by pulse oxymetry of <89%, or Pao2 of <60mmHg and or cor pulmonale or polycythemia)[43]. Pulmonary rehabilitation and use of ambulatory oxygen in patients with isolated exertional hypoxemia[43]improve the quality of life, reduce breathlessness and increase walking ability.[42] Identification and accurate treatment of coexisting conditions are essential. Lung transplantation is an option in selected patients, although extrapulmonary disease or severe coexisting conditions may disqualify some patients, especially those with CTDs from consideration as candidates for transplantation.[45] Many patients may need palliative care.[46]

Pharmacological Treatment:-

Decisions about pharmacologic treatment are guided by the underlying diagnosis and by the disease course. For patients with IPF, treatment with antifibrotic drugs like pirfenidone or nintedanib is recommended.[47]In most cases of fibrosing ILD other than IPF, immunomodulation with the use of glucocorticoids, immunosuppressive therapy or both is indicated and is generally used as first-line therapy if there is a suspicion of inflammation-driven disease .[3,40,48]Except for SSc– ILD and sarcoidosis, however, the evidence in support of this approach is very weak.[48]In patients with a UIP pattern, there is a theoretical concern that immunosuppression may not be beneficial or might even be harmful, as was previously shown in IPF.[45]Nintedanib has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for patients with SSc–ILD and for patients with chronic fibrosing ILDs with a progressive phenotype. It is not associated with an improvement in function but reduces the decline in FVC by about half.[50]Pirfenidone reduces disease progression in patients with progressive unclassifiable fibrotic ILD.[48]In considering pharmacologic treatment, the benefit of long-term preservation of lung function should be balanced against the risk of side effects. Many questions remain about the appropriate timing and sequence of these treatments.

Monitoring disease progression has become a priority in guiding treatment decisions. Different biomarkers and novel techniques such as molecular classifiers [51] will provide more insights into assessing and monitoring fibrosis-driven as compared with inflammation-driven disease activity resulting in more individualized targeted treatments. A "one size fits all" approach does not apply to the broad spectrum of fibrosing diseases. Current research efforts may lead to earlier diagnosis and interventions to prevent, halt, and potentially reverse the development of lung fibrosis.

References:-

1. Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ. What's in a name? That which we call IPF, by any other name would act the same. Eur Respir J 2018;51

2. Wolters PJ, Blackwell TS, Eickelberg O, et al. Time for a change: is idiopathic pulmonary fibrosis still idiopathic and only fibrotic? Lancet Respir Med 2018;6:154-60
3. Wijsenbeek M, Kreuter M, Olson A, et al. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. Curr Med Res Opin 2019;35:2015-24
4. Olson AL, Gifford AH, Inase N, Fernández Pérez ER, Suda T. The epidemiology of idiopathic pulmonary fibrosis and interstitial lung diseases at risk of a progressive-fibrosing phenotype. Eur Respir Rev 2018;27:180077.
5. Duchemann B, Annesi-Maesano I, Jacobe de Naurois C, et al. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. Eur Respir J 2017;50:1602419
6. Raghu G, Chen S-Y, Hou Q, Yeh W-S, Collard HR. Incidence and prevalence of idiopathic pulmonary fibrosis in US adults 18-64 years old. Eur Respir J 2016;48:179-86
7. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Müller-Quernheim J. Sarcoidosis. Lancet 2014;383:1155-67.
8. Kundu, et al.: Spectrum of diffuse parenchymal lung diseases. Lung India 2014;30:354-60.
9. Singh S, Bridget F. Collins, Bharat B. Sharma,et al. Interstitial Lung Disease in India, American Journal of Respiratory and Critical Care Medicine 2017;195:801-13
10. Dhooria S, Agarwal R, Singh I, Sehgal,et al. Spectrum of interstitial lung diseases at a tertiary center in a developing country: A study of 803 subjects, . PLoS ONE, 2018;13:0191938
11. Bhattacharyya P, Jana MK, Saha D, Paul M, Mukherjee A, Saha R. The increasing trend and the seasonal variation in attendance of diffuse parenchymal lung disease patients presenting to a pulmonary clinic in Eastern India. Lung India. 2021 Nov-Dec;38:529-532.
12. Thannickal VJ, Zhou Y, Gaggar A, Duncan SR. Fibrosis: ultimate and proximate causes. J Clin Invest 2014;124:4673-7
13. Distler JHW, Györfi A-H, Ramanujam M, Whitfield ML, Königshoff M, Lafyatis R. Shared and distinct mechanisms of fibrosis. Nat Rev Rheumatol 2019;15:705-30
14. Adegunsoye A, Vij R, Noth I. Integrating genomics into management of fibrotic interstitial lung disease. Chest 2019; 155:1026-40
15. Ley B, Torgerson DG, Oldham JM, et al. Rare protein-altering telomere-related gene variants in patients with chronic hypersensitivity pneumonitis. Am J Respir Crit Care Med 2019;200:1154-63
16. Rockey DC, Bell PD, Hill JA. Fibrosis — a common pathway to organ injury and failure. N Engl J Med 2015;372:1138-49.
17. Grunewald J, Grutters JC, Arkema EV, Saketkoo LA, Moller DR, Müller-Quernheim J. Sarcoidosis. Nat Rev Dis Primers 2019;5:45.
18. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med 2018;378:1811-23
19. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/ European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013;188:733-48.
20. Figliozzi S, Masci PG, Ahmadi N, et al. Predictors of adverse prognosis in Covid-19: a systematic review and meta-analysis. Eur J Clin Invest 2020;50:e13362
21. Burnham EL, Janssen WJ, Riches DW, Moss M, Downey GP. The fibroproliferative response in acute respiratory distress syndrome: mechanisms and clinical significance. Eur Respir J 2014;43:276-85
22. Chang YC, Yu CJ, Chang SC, et al. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. Radiology 2005;236:1067-75
23. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018;1985:44-68
24. Sgalla G, Walsh SLF, Sverzellati N, et al. "Velcro-type" crackles predict specific radiologic features of fibrotic interstitial lung disease. BMC Pulm Med 2018;18:103.
25. Mathai SC, Danoff SK. Management of interstitial lung disease associated with connective tissue disease. BMJ 2016;352:6819.
26. Kubo T, Lin PJP, Stiller W, Takahashi M, Kauczor HU, Ohno Y, et al. Radiation dose reduction in chest CT: a review. AJR Am J Roentgenol 2008;190:335–43.
27. Braun FM, Johnson TRC, Sommer WH, Thierfelder KM, Meinel FG. Chest CT using spectral filtration: radiation dose, image quality, and spectrum of clinical utility. Eur Radiol 2015;25:1598–606.
28. Pontana F, Billard AS, Duhamel A, Schmidt B, Faivre JB, Hachulla E, et al. Effect of iterative reconstruction on the detection of systemic sclerosis-related interstitial lung diseases: clinical experience in 55 patients. Radiology 2016;279:297–305.

29. de Margerie-Mellon C, de Bazelaire C, Montlahuc C, Lambert J, Martineau A, Coulon P, et al. Comparison among model-based type iterative reconstruction, hybrid iterative reconstruction and filtered back projection. Acad Radiol 2016;23:1246–54
30. Miller WT Jr, Chatzkel J, Hewitt MG. Expiratory air trapping on thoracic computed tomography: a diagnostic subclassification. Ann Am Thorac Soc 2014;11:874–81.
31. Tokura S, Okuma T, Akira M, Arai T, Inoue Y, Kitaichi M. Utility of expiratory thin-section CT for fibrotic interstitial pneumonia. Acta Radiol 2014;55:1050–55.
32. Kim M, Lee SM, Song JW, Do KH, Lee HJ, Lim S, et al. Added value of prone CT in the assessment of honeycombing and classification of usual interstitial pneumonia pattern. Eur J Radiol 2017;91:66–70
33. Hunninghake GW, Lynch DA, Galvin JR, Gross BH, Muller N, Schwartz DA, et al. Radiologic findings are strongly associated with a pathologic diagnosis of usual interstitial pneumonia. Chest 2003; 124:1215–23.
34. Gruden JF, Panse PM, Leslie KO, Tazelaar HD, Colby TV. UIP diagnosed at surgical lung biopsy, 2000-2009: HRCT patterns and proposed classification system. AJR Am J Roentgenol 2013;200:458-67
35. Souza CA, M ¨uller NL, Lee KS, Johkoh T, Mitsuhiro H, Chong S. Idiopathic interstitial pneumonias: prevalence of mediastinal lymph node enlargement in 206 patients. AJR Am J Roentgenol 2006;186: 995–9
36. Adegunsoye A, Oldham JM, Bellam SK, et al. Computed tomography honeycombing identifies a progressive fibrotic phenotype with increased mortality across diverse interstitial lung diseases. Ann Am Thorac Soc 2019;16:580-8.
37. Walsh SLF, Lederer DJ, Ryerson CJ, et al. Diagnostic likelihood thresholds that define a working diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2019;200:1146-53
38. Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity pneumonitis: perspectives in diagnosis and management. Am J Respir Crit Care Med 2017; 196:680-9
39. Cottin V, Wollin L, Fischer A, Quaresma M, Stowasser S, Harari S. Fibrosing interstitial lung diseases: knowns and unknowns. Eur Respir Rev 2019;28:180100.
40. George PM, Spagnolo P, Kreuter M, et al. progressive fibrosing interstitial lung disease; consensus recommendations, clinical uncertainties and research priorities. Lancet Respir Med2020;8:925-34.
41. Ryerson CJ, Vittinghoff E, Ley B, et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. Chest 2014;145:723-8.
42. Wijsenbeek MS, Holland AE, Swigris JJ, Renzoni EA. Comprehensive supportive care for patients with fibrosing interstitial lung disease. Am J Respir Crit Care Med 2019;200:152-9.
43. Lim RK, Humphreys C, Morisset J, Holland AE, Johannson KA, O2 Delphi Collaborators. Oxygen in patients with fibrotic interstitial lung disease: an international Delphi survey. Eur Respir J 2019;54:54
44. Visca D, Mori L, Tsipouri V, et al. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed method, crossover randomised controlled trial. Lancet Respir Med 2018;6:759-70
45. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014 — an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2015;34:1-15.
46. Kreuter M, Bendstrup E, Russell AM, et al. Palliative care in interstitial lung disease: living well. Lancet Respir Med 2017;5:968-80
47. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis — an update of the 2011 clinical practice guideline. Am J Respir Crit Care Med 2015;192:3-19
48. Maher TM, Wuyts W. Management of fibrosing interstitial lung diseases. Adv Ther 2019;36:1518-31
49. The Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012;366:1968-77
50. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019;381:1718-27
51. Raghu G, Flaherty KR, Lederer DJ, et al. Use of a molecular classifier to identify usual interstitial pneumonia in conventional transbronchial lung biopsy samples: a prospective validation study. Lancet Respir Med 2019;7:487-96.