Respiratory Research

REVIEW

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Diagnosis of early idiopathic pulmonary fibrosis: current status and future perspective

Xinya Wang[1†], Xinrui Xia[1†], Yihan Hou[1], Huaizhe Zhang[3], Wenyang Han[3], Jianqi Sun[3*] and Feng Li[2*]

Abstract

The standard approach to diagnosing idiopathic pulmonary fibrosis (IPF) includes identifying the usual interstitial pneumonia (UIP) pattern via high resolution computed tomography (HRCT) or lung biopsy and excluding known causes of interstitial lung disease (ILD). However, limitations of manual interpretation of lung imaging, along with other reasons such as lack of relevant knowledge and non-specific symptoms have hindered the timely diagnosis of IPF. This review proposes the definition of early IPF, emphasizes the diagnostic urgency of early IPF, and highlights current diagnostic strategies and future prospects for early IPF. The integration of artificial intelligence (AI), specifically machine learning (ML) and deep learning (DL), is revolutionizing the diagnostic procedure of early IPF by standardizing and accelerating the interpretation of thoracic images. Innovative bronchoscopic techniques such as transbronchial lung cryobiopsy (TBLC), genomic classifier, and endobronchial optical coherence tomography (EB-OCT) provide less invasive diagnostic alternatives. In addition, chest auscultation, serum biomarkers, and susceptibility genes are pivotal for the indication of early diagnosis. Ongoing research is essential for refining diagnostic methods and treatment strategies for early IPF.

Keywords Early idiopathic pulmonary fibrosis, Diagnosis, Artificial intelligence, High resolution computed tomography

Background

Interstitial lung disease (ILD) is a heterogeneous group of lung parenchymal diseases that are clinically characterized by exertional dyspnea, dry cough, inspiratory crackles and clubbed fingers, and pathologically characterized by varying degrees of inflammation and fibrosis. Some ILD may be secondary to known triggers such as autoimmune diseases, hypersensitivity reactions to inhaled antigens or environmental stimuli, or granulomatous diseases, while other ILD has no identified cause [1]. Idiopathic pulmonary fibrosis (IPF) is the most aggressive form of ILD from an unknown cause, characterized by chronic progressive fibrosis leading to irreversible lung function decline, progressive respiratory failure, and high mortality rates. The adjusted incidence and prevalence of idiopathic pulmonary fibrosis (IPF) are 0.09–1.30 and 0.33–4.51 per 10,000 persons [2], respectively. Based on

†Xinya Wang and Xinrui Xia contributed equally to this work.

*Correspondence:
Jianqi Sun
milesun@sjtu.edu.cn
Feng Li
lifeng741@aliyun.com
[1]Department of Basic Medical Sciences, School of Medicine, Shanghai Jiao Tong University, No.227, South Chongqing Road, Huangpu, Shanghai 200025, P.R. China
[2]Department of Pulmonary and Critical Care Medicine, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, No.241, West Huaihai Road, Xuhui, Shanghai 200030, P.R. China
[3]School of Biomedical Engineering, School of Shanghai Jiao Tong University, No. 800, Dongchuan Road, Minghang, Shanghai 200240, P.R. China

historical data, untreated IPF patients have a median survival of 3 to 5 years after diagnosis [1, 3]. Timely antifibrotic treatment with drugs including pirfenidone and nintedanib has been shown to slow, rather than reverse, the decline in lung function and to prolong patients' survival [4–7]. However, the benefits of this early intervention rely on early diagnosis, making the diagnosis of early IPF very important.

Given the current research gaps and clinical gaps in the diagnosis of early IPF, this review proposes the definition of early IPF, summarizes the diagnostic methods for early IPF, with a special focus on radiology, i.e., application of artificial intelligence (AI) with machine learning (ML) and deep learning (DL) into the analysis of thoracic images including interstitial lung abnormalities (ILAs), use of bronchoscopic examination and adoption of chest auscultation, serological biomarkers and susceptibility genes, and discusses current challenges and future directions in the diagnosis of early IPF.

The current diagnostic criteria and procedure of IPF

International consensus guidelines recommend a multidisciplinary approach to diagnosing IPF, which involves ruling out known ILD causes and performing high-resolution computed tomography (HRCT) or lung biopsy with a usual interstitial pneumonia (UIP) pattern [1]. HRCT plays a crucial role in IPF diagnosis, with radiologists categorizing it into four types based on confidence levels in UIP: UIP pattern, probable UIP pattern, indeterminate UIP pattern, and alternative diagnosis [8]. Patients with a UIP pattern or probable UIP pattern on HRCT can be diagnosed as IPF following multidisciplinary discussion in the appropriate clinical context. Further diagnostic evaluation based on histopathology is necessary for patients with an indeterminate UIP pattern or an alternative diagnosis. Pathologically, UIP serves as the characteristic histopathological hallmark of IPF, characterized by fibrotic temporal and spatial heterogeneity, fibroblastic foci, collagen deposition, and excessive deposition of extracellular matrix (ECM) leading to distortion of normal lung architecture, which is usually accompanied by honeycombing cyst formation [9]. Transbronchial lung cryobiopsy (TBLC) may be preferred over surgical lung biopsy (SLB) in certain patient populations. For patients with inconclusive TBLC results, subsequent SLB may be reasonable [10]. Considering the morbidity and mortality associated with surgical biopsies [11], HRCT imaging is the primary choice for IPF diagnosis.

Diagnostic delay in IPF

Delays in the diagnosis of IPF are usual in clinical practice. A recent prospective study in Denmark investigated all new IPF patients ($n = 204$) from two ILDs centers, finding a median time of 2.1 years from symptom onset to IPF diagnosis, with 25% of patients experiencing delays exceeding five years [12]. From a survey conducted in Germany, France, the United States, and Japan and the other study using data from the IPF-PRO Registry, the median time from symptom onset to diagnosis was reported to be 13 months and 13.6 months, respectively [13, 14]. In contrast, surveys based on large claims-based data sets tend to have worse outcomes than those based on IPF registries. Herberts et al. reported that 98% of patients had other initial respiratory diagnoses before the index diagnosis of IPF, and the average time to a diagnosis of IPF was 2.7 years [15]. In a survey of medicare beneficiaries, nearly one-third had their first CT scan more than 3 years before diagnosis, indicating a considerable diagnostic delay [16]. Reasons for delayed IPF diagnosis vary, including its early nonspecific symptoms such as dry cough and exertional dyspnea being misdiagnosed as more common conditions like asthma, chronic obstructive pulmonary disease (COPD), or heart disease [17]. According to the current guideline, some early-stage patients may fail to meet the diagnostic standard at their visit [8]. Examinations to prove or diagnostic treatment of other suspected diseases will prolong diagnostic time and delay antifibrotic therapy [12]. The complexity of the IPF diagnostic process, such as multidisciplinary discussion (MDD), may lead to a longer diagnosis time [18]. Given that IPF is relatively rare, healthcare professionals encountered by patients in the early stage of the disease may lack knowledge and awareness of IPF, resulting in delayed referral to specialized ILD centers [19]. A specialized ILD center can make a diagnosis and provide more specialized care and extra benefits such as disease education or support groups [20].

Counterintuitively, there are conflicting views across studies on whether there is a correlation between the delay in diagnosis and patient survival [13, 21–23]. However, when patients are stratified according to disease severity, the positive prognostic effect of a shorter delay in diagnosis is more pronounced in patients with mild disease [13, 21]. Longer delay in diagnosis is associated with poorer quality of life, and worse quality of life is associated with lung function deterioration, comorbidity development, disease progression such as emergency, hospitalization, and mortality [7, 21].

The definition and significance of early IPF

In this review, we tentatively propose a definition of early IPF. Early IPF refers to a disease stage of IPF where CT presentation of interstitial changes with a fibrosis score less than 10%, in which UIP /probable UIP on CT can be present or absent with UIP/probable UIP on histopathology by lung biopsy (see Fig. 1) [24–26]. Extra attention should be paid to ruling out known causes of UIP, such

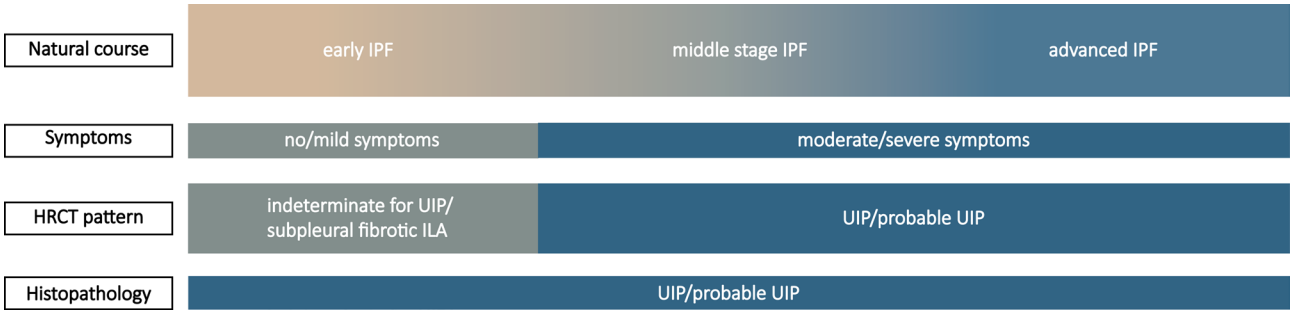

Fig. 1 The natural history of IPF and definition of early IPF. In this review, the natural history of IPF can be broadly divided into 3 stages: early, middle stage and advanced. Early IPF refers to a disease stage where the patient's symptoms(dry cough and exertional dyspnea) are usually mild or absent, HRCT pattern is mostly indeterminate UIP or subpleural fibrotic ILA. However, the biopsy result reveals histologic UIP or probable UIP. As the disease progresses to the middle stage IPF or the advanced IPF, symptoms become increasingly severe, and the HRCT pattern may evolve towards UIP or probable UIP.

as hypersensitivity pneumonia (HP) and autoimmune diseases. Considering the complexity of ILD, early IPF could be a provisional diagnosis and should be reviewed during the follow-up. If remission occurs on subsequent CT follow-up or the etiology of other ILD is found, the diagnosis of early IPF should be removed or replaced with an alternative diagnosis. The diagnosis of early IPF can be crucial for optimizing the treatment strategy and improving the prognosis for these patients. The diagnosis of early IPF may allow healthcare providers to engage with patients and their families in a more focused pattern and offer a better management of the disease [5].

Thoracic image analysis with AI for early IPF diagnosis

The image features of HRCT play a crucial role in the diagnosis of IPF. Drawbacks to the manual interpretation of these HRCT features include subjectivity of interpretation, low inter-observer agreement, and visual fatigue of radiologists or respiratory clinicians. An AI-based computer vision can overcome these challenges. Computer-aided diagnosis (CAD) systems can be developed based on AI technology to realize the classification of HRCT images. DL is a subset of AI and a form of artificial neural network (ANN) [27], while ML is a branch of AI that enables computer systems to learn from data and improve performance without explicit programming [28].

Some representative diagnostic models for IPF using HRCT images and their key attributes including sample size, parameters adopted, key methods, and major results are listed in Table 1 based on publication year [23–34]. The CAD systems can be divided into DL diagnosis systems (can be combined with ML) and radiomics diagnosis systems (can be combined with ML/DL). At present, the DL diagnosis system has been relatively mature. Walsh et al. took expert consensus as the reference standard and used DL to classify CT-UIP patterns in ILDs patients, and its accuracy was 0.73 in the external test set [29]. The INTACT diagnosis system developed by Christine et al. combines DL semantic segmentation and a random forest classifier to classify CT patterns of ILDs, and the accuracy was 0.81 [30]. Maddali et al. used pretrained DL models by CT to distinguish IPF from ILDs. The c-statistic of this model was 0.87 [32]. Radiomics has also been incorporated into the IPF diagnostic model in recent years. Refaee et al. developed a CT-based diagnosis tool for IPF through hand-crafted radiomics(HCR) and DL(3D Densenet-121), which combines patients' gender, age, BMI, and lung function data, and realized model integration by obtaining the mean prediction of two models, achieving an AUC of 0.917 [28]. Recently, Fontanellaz et al. used a 3D CNN-MLP Mixer to segment lungs and airways, a UNet and 2D CNN-MLP Mixer for semantic segmentation, and a random forest classifier for diagnosis. In the case of classifying the combined patterns of UIP according to the need for biopsy or not, both accuracy and F-score were 0.77 [34]. The prediction model for histopathological UIP has also been developed in recent years. Shaish et al. developed the first prediction model for histopathological UIP, which divided HRCT into wedges to simulate SLB and used the DL model to predict histopathological UIP, with sensitivity of 0.74 and specificity of 0.58 [25]. The DL model developed by Bratt et al. used CT scans of ILDs patients with three pathological types: UIP, nonspecific intersitial pneumonia (NSIP), and chronic HP to predict histopathological diagnosis, achieving an AUC of 0.87 [27].

The procedure of the CAD model

There are four processes for training an ML computer-aided diagnostic model. The first is data preparation, i.e. data collection, preprocessing, and dataset splitting. After preprocessing, the dataset needs to be split. Currently, the commonly used splitting method is a training set (60% for modeling), a validation set (20% to prevent overfitting), and a test set (20% to validate the model). The second step is model selection, i.e. selecting a model

Table 1 Diagnostic models for IPF using HRCT images

Research	Sample size	Other parameters				Key methods	Results
		Basic information	Medical history	Blood test	Pulmonary function test		
Walsh et al.,2018 [29]	1157 CT scans					CNN(Inception-ResNet-v2) classifier	AUC:0.85, accuracy:0.73, sensitivity:0.79, specificity:0.90
Christine et al.,2019 [30]	105 cases	√	√	√	√	anatomy segmentation, CNN tissue characterization, random forest classifier	accuracy:0.81, sensitivity:0.79, specificity:0.67, F-score:0.80
Shaish et al., 2021 [86]	301 CT scans					virtual wedge resection, CNN classifier, logistic regression	accuracy: 0.68, sensitivity: 0.74, specificity: 0.58
Yu et al., 2021 [42]	1020 CT scans					CNN classifier (baseline, MobileNet, VGG16, ResNet-50, DenseNet-121) with domain knowledge enhanced loss function	baseline: sensitivity:0.86, specificity:0.94, accuracy:0.91 four other models: overall accuracy greater than 0.95
Bratt et al., 2022 [87]	1236 cases					CNN (EfficientNet-B3) classifier	AUC:0.87
Refaee et al., 2022 [88]	474 CT scans					handcrafted radiomics feature extraction, random forest classifier, CNN (Densenet-121) classifier, model ensemble	AUC:0.92, accuracy:0.85, sensitivity:0.89, specificity:0.82
Furukawa et al., 2022 [84]	1068 cases	√	√	√	√	DL (FCN-Alexnet) tissue characterization, SVM classifier	accuracy:0.84, sensitivity:0.81, specificity:0.86
Mei et al., 2023 [89]	449 cases	√	√	√	√	DCNN classifier, ViT classifier, MLP classifier, XGBoost classifier, SVM classifier, model ensemble	AUC:0.83, sensitivity:0.82, specificity:0.68
Yu et al., 2023 [43]	878 CT scans					multi-scale, domain knowledge guided attention, random forest classifier	AUC: 0.99
Maddali et al., 2023 [90]	more than 2590 cases					pre-trained CNN(3D ResNet) classifier, model ensemble	c-statistic: 0.87, PPA:0.81, NPA:0.75
Chung et al., 2024 [91]	3155 CT scans					Wide Residual Networks based CNN feature extraction, SVM classifier	sensitivity:0.81, specificity:0.77
Fontanellaz et al., 2024 [92]	338 cases					3D CNN-MLP-Mixer anatomic segmentation, 2D-UNet,3D-UNet, and 2D CNN-MLP Mixer tissue characterization, Radiomics	balanced accuracy:0.77 F-score:0.77

Abbreviations: CNN = Convolutional Neural Network, AUC = Area Under Curve, SVM = Support Vector Machine, DCNN = Deep Convolutional Neural Network, ViT = Vision Transformer, MLP = Multilayer Perception, XGBoost = eXtreme Gradient Boosting, PPA = Positive Percent Agreement, NPA = Negative Percent Agreement

and cross-validation. The third step is to train the model to obtain optimal parameters and tune hyperparameters. Lastly, model evaluation involves assessing the model in the previously mentioned test set, with evaluation metrics typically including accuracy, precision, recall, F1 score, etc. The confusion matrix presents the correspondence between predicted results and true labels of a classification model on the test set in matrix form. Then the performance and efficacy of ML models can be more intuitively reflected (see Fig. 2a).

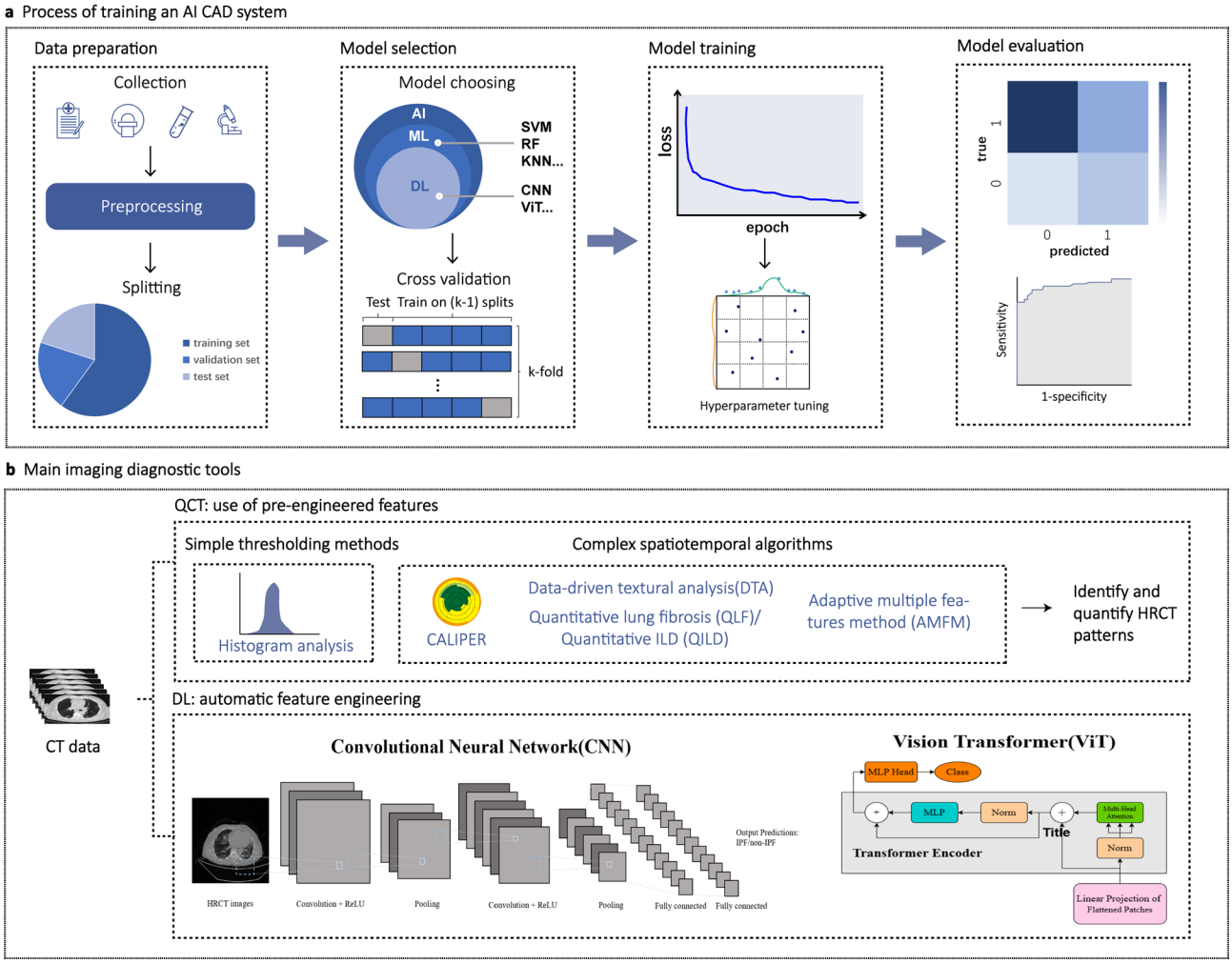

Fig. 2 The procedure of training a medical image-based CAD model and main imaging diagnostic tools in IPF CAD models. **a**) Training a machine learning diagnostic model mainly includes the following processes. The first is data preparation, including data collection, preprocessing, and dataset splitting. Data preprocessing includes normalization, data cleaning, feature selection, denoising, etc. After preprocessing, the dataset needs to be split. Currently, the commonly used splitting method is a training set (60% for modeling), a validation set (20% to prevent overfitting), and a test set (20% to validate the model). Choose the appropriate machine learning (ML) model based on the problem type and data characteristics, then cross-validation must be conducted to select the best-performing model. After selecting a model, it's necessary to train the model to obtain optimal parameters and tune hyperparameters, which is also called Tuning. Lastly, model evaluation involves assessing the model using the test set, with evaluation metrics typically including accuracy, precision, recall, F1 score, etc. **b**) Machine learning image processing methods for IPF can be divided into two categories: (1) quantitative CT, which includes simple thresholding methods, e.g., histogram analysis, and complex spatiotemporal algorithms, e.g., data-driven textural analysis (DTA), quantitative lung fibrosis(QLF), quantitative ILD(QILD) and adaptive multiple features method (AMFM); (2) deep learning (DL), which includes convolutional neural network (CNN) and vision transformer(ViT)

Major imaging diagnostic tools in CAD models of IPF

Quantitative CT

The focus of quantitative CT methods is on the grayscale and geometric structures of the images, which is well-suited for CAD systems to excel [31]. Hartley et al. compared the histograms of HRCT scans from 24 IPF patients and 60 individuals with extensive occupational asbestos exposure. The histogram distribution of IPF patients was significantly shifted to the right (higher density) and flatter compared to asbestos-exposed participants [32]. Computer-aided lung informatics for pathology evaluation and rating (CALIPER) utilizes computer vision techniques based on local volume histograms and morphological analysis to characterize and quantify different HRCT patterns. Pulmonary vascular-related structures derived from CALIPER can be utilized to predict histological UIP patterns in IPF patients whose HRCT indicates non-IPF [33]. Uppaluri et al. compared adaptive multiple features method (AMFM) with mean lung density (MLD) and histogram-based analysis, demonstrating that the AMFM method outperformed the other two methods in characterizing four groups of subjects: normal lung, emphysema, IPF, and nodules [34]. Quantitative lung fibrosis (QLF) is a set of measurements that

include quantitative scores of honeycombing, ground-glass, and composite ILD [35]. A study on scleroderma-associated pulmonary fibrosis indicated that QLF scores are sensitive in detecting mild PF, and are appropriately conservative in estimating the extent of pulmonary fibrosis [36]. Most conventional quantitative CT methods rely on feature engineering, which means manual selection or construction of features relevant to the accurate output of the model. Feature engineering is time-consuming and highly specific, requires high-level domain expertise, and might overlook clinically significant image features yet undetectable by the human eye [37].

DL

DL can automatically learn task-relevant features, and attenuate and eventually filter out irrelevant features [38]. By harnessing the power of DL algorithms such as convolutional neural network (CNN) and vision transformer (ViT), it becomes feasible to detect novel imaging feautures that may not be readily identifiable. This is particularly true when early CT images of IPF patients exhibit atypical patterns besides UIP or probable UIP [8].

CNN represents a specialized class of ANN that draw its architectural inspiration from neurons within biological visual systems [39]. Two important applications for CNN in IPF diagnostic imaging are segmentation and classification. Semantic segmentation plays an important role in image understanding by assigning a categorical label to every pixel in an image [40]. For example, nnU-Net is a novel self-configuring tool for biomedical image segmentation that is readily available for immediate use without expert knowledge or computing resources beyond standard network training [41]. The classification capabilities of CNN extensively utilized in the diagnostic algorithms for IPF. In the context of diagnostic imaging, classification can be achieved by assigning medical images to different categories, i.e. with/without disease. For example, Yu et al. developed efficient diagnostic models for IPF using chest CT scans and domain knowledge. The models input HRCT and outputs the disease label (IPF/non-IPF) [42, 43].

ViT applies the transformer architecture directly to sequences of image patches for image recognition tasks. ViT achieves excellent results in image classification when pre-trained on large datasets [44]. Wu et al. proposed a ViT model that classified HRCT emphysema into three subtypes, with an average accuracy of 0.96, surpassing conventional methods such as ResNet50 [45]. Mei et al. created a DCNN and a ViT to learn the HRCT image patterns of 5 different ILDs and integrated them with classifiers using clinical information to develop a joint model. For UIP classification, the joint model reached an AUC of 0.83 [30] (see Fig. 2b).

Identification and classification of ILAs for early IPF diagnosis

ILAs refer to radiological abnormalities in the lung interstitium on CT scans in individuals who were previously undiagnosed or suspected of having ILDs. The Fleischner Society has published a position paper that proposed a standardized definition of ILA [46]. ILAs can be further classified according to the presence and distribution, i.e. non-subpleural ILAs, subpleural nonfibrotic ILAs, and subpleural fibrotic ILAs, as depicted in Fig. 3. A study revealed that during a 2-year follow-up period, 49% of non-fibrotic ILA showed improvement, 1% of non-fibrotic ILA progressed, and 37% of fibrotic ILAs progressed. Certain imaging characteristics can increase the likelihood of progression, such as reticular opacities in the subpleural region, predominantly lower lung distribution [47].

The clinical manifestations of ILAs mainly include dyspnea, cough, fatigue, chest pain, decreased appetite, weight loss, and anxiety, which share similarities with ILDs or IPF. The risk factors of ILAs progression include age, smoking history, gender, environmental exposure, and genetics, which also share similarities with ILDs or IPF. ILAs may represent early manifestations of ILDs or IPF, and classifying the types of ILAs can help understand the natural course of ILDs or IPF, enabling early management and timely intervention. Recently, among 41 patients with ILAs detected on baseline CT, 10 cases

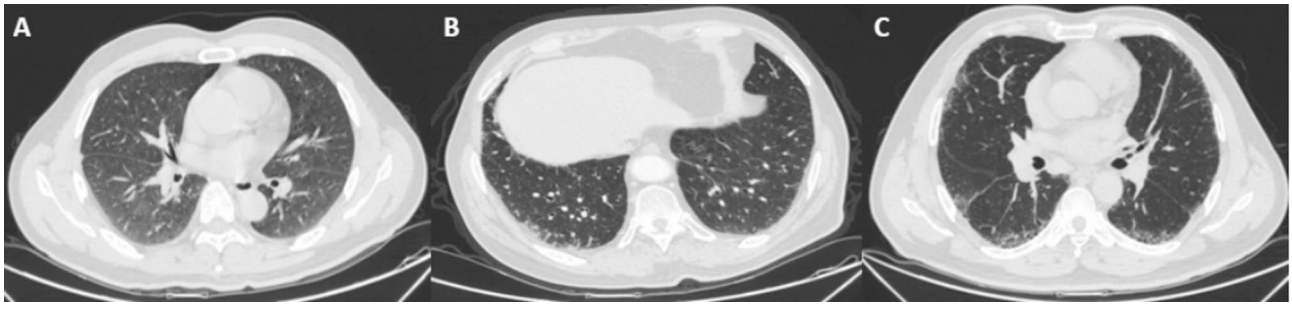

Fig. 3 Major types of ILA. ILAs are divided into three subcategories, non-subpleural ILAs (**A**), subpleural nonfibrotic ILAs (**B**), and subpleural fibrotic ILAs (**C**)

(24.4%) were diagnosed as ILDs on baseline CT, with an average time to diagnosis of 4.47 years [48]. This suggests that ILAs may serve as a basis for early ILDs or IPF diagnosis.

Bronchoscopic examination for early IPF diagnosis

TBLC

SLB is used to apply to patients with suspected IPF or patients with indeterminate IPF in a multidisciplinary discussion [10]. However, SLB has substantial morbidity and mortality rates [52–54]. TBLC is performed by using a cryoprobe inserted into a bronchoscope placed at the target site to obtain peripheral lung tissue [55]. Recent evidence suggests that TBLC is less invasive and less costly, with fewer respiratory infections and less procedural mortality [10, 56]. TBLC is recommended as an acceptable alternative to SLB. However, it is a conditional recommendation with very low-quality evidence and the practice of TBLC is restricted to medical centers with experience in performing TBLC and interpreting pathological data [8]. When the TBLC result is inconclusive or suggestive of an alternative diagnosis, SLB can be performed to provide additional information [57]. Overall, TBLC is becoming a first-line minimally invasive method for tissue biopsy of ILDs or IPF.

Genomic classifier

The Envisia Genomic Classifier is an RNA sequencing-based molecular diagnostic tool that analyzes the expression of 190 genes in transbronchial lung biopsy (TBLB) samples. Utilizing ML algorithms, it differentiates between UIP and non-UIP patterns, providing critical evidence for precise diagnosis [49]. A validation study involving 96 patients demonstrated the classifier's sensitivity of 60.3% and specificity of 92.1% for histologically-confirmed UIP patterns [50]. Another study revealed that incorporating the genomic classifier with TBLC significantly increased diagnostic confidence from 43 to 93% ($P = 0.023$) [51]. These findings suggest the Envisia Genomic Classifier holds substantial promise as a future auxiliary diagnostic tool that could reduce reliance on lung biopsies for IPF diagnosis.

Endobronchial optical coherence tomography (EB-OCT)

The EB-OCT technique generates high-resolution images of tissue structures with a resolution of 10–15 μm and a depth of 2–3 mm using scattered near-infrared light under the guidance of bronchoscopy [58]. Wijmans et al. identified OCT patterns of fibrotic ILDs in a patient cohort of 11 ILDs patients, which included thickening and loss of alveolar network structure (fibrosis), round-shaped air-filled spaces (cysts), and tube-like structures in peripheral lung areas (bronchiectasis) [59]. EB-OCT can help physicians identify UIP/IPF patients by detecting the microstructural features of UIP [60]. A prospective diagnostic study involving 27 patients showed that EB-OCT had both sensitivity and specificity of 100% for the histopathological UIP and clinical diagnosis of IPF. Furthermore, EB-OCT exhibited high concordance with histopathology in diagnosing fibrotic patterns [61]. Polarization-sensitive(PS)-EB-OCT is a functional extension of EB-OCT that allows the simultaneous detection of endogenous birefringence in ordered tissues [62]. A recent study demonstrated that PS-EB-OCT can accurately visualize and classify fibrotic patterns in both UIP and non-UIP fibrotic ILD. Furthermore, it can quantitatively differentiate the birefringence of fibrosis types [63]. An abstract presented at the 2021 ERS International Congress suggested that PS-EB-OCT may enable the quantification of fibrosis without the need for tissue sampling, providing information on the progression of fibrosis during continuous surgeries [64]. EB-OCT, as a safe, non-invasive, and bronchoscope-compatible microscopic diagnostic method for ILDs, holds significant importance for early ILDs or IPF diagnosis. While some small-scale studies have shown its potential in diagnosing and evaluating fibrotic ILDs, large-scale clinical studies are still lacking. Future research efforts should focus on further validating the diagnostic accuracy and clinical application prospects of EB-OCT to promote its widespread use in ILDs or IPF diagnosis.

Other diagnostic tools for early IPF diagnosis

Chest auscultation

Compared to HRCT scanning, chest auscultation is simple and convenient, offering a great value in screening for ILDs or IPF in the early stages. The wet crackle sound is a discontinuous, brief explosive non-musical sound mainly heard during inhalation [65]. Fine wet crackles are softer, shorter in duration, and higher-pitched compared to coarse wet crackles, and are associated with the sudden opening of airways in restrictive lung diseases [66]. The particular fine wet crackles heard in ILDs or IPF are commonly referred to as "Velcro crackles (VC)" and are typically heard in the lower posterior regions during late inspiration [67]. Compared to the later appearance of the UIP pattern, VC can be heard earlier in the fibrotic process [68].

A prospective study of 132 suspected ILDs patients showed that all IPF patients had VC on auscultation. Furthermore, auscultatory VC was associated with radiological UIP pattern [69]. A study utilizing ML to quantitatively analyze fine wet crackles for diagnosing ILDs showed that fine wet crackles had a higher sensitivity in distinguishing ILDs compared to chest X-rays [70]. Fine wet crackles are more common than symptoms or signs in IPF patients, and the identification of fine wet crackles is not influenced by obesity, symptoms, lung function,

emphysema, COPD, or clinical experience. The presence of fine wet crackles in chest auscultation is a sensitive, reliable, and useful screening tool, aiding in early ILDs or IPF diagnosis [71].

Serological biomarkers

Biomarkers are typically defined as characteristics that measure normal biological processes, pathogenic processes, or responses to exposure or intervention [72].Various blood biomarkers have been studied in IPF, which are related to different pathogenic pathways. Some biomarkers have shown promise for further research in early IPF diagnosis. For example, S100 calcium-binding protein A4 (S100A4), which belongs to the S100 superfamily of intracellular binding proteins, plays an important regulatory role in the fibrotic process [73]. Compared to healthy control groups, IPF patients have significantly elevated levels of circulating fragments of cytokeratin-18 (cCK-18) in the serum [74]. A meta-analysis demonstrated that serum levels of surfactant proteins(SP)-A are significantly higher in IPF patients compared to non-IPF ILDs, pulmonary infections, and healthy control groups. However, there is no significant difference in serum levels of SP-D between IPF and non-IPF ILDs patients [75]. Additionally, Krebs von den Lungen-6 (KL-6) is elevated in the serum of several ILDs including IPF, but it is not specific enough to distinguish IPF from other ILDs [76]. Serum levels of matrix metalloproteinase-7 (MMP-7) and osteopontin (OPN) are elevated in IPF patients. Furthermore, the combined use of multiple biomarkers can effectively differentiate IPF from other ILDs [77, 78]. A study analyzing plasma concentrations of 49 proteins in 79 IPF patients and 53 control subjects identified a five-protein signature (MMP7, MMP1, MMP8, IGFBP1, and TNFRSF1A) that distinguished IPF patients from controls with 98.6% sensitivity and 98.1% specificity [79]. Another investigation demonstrated that elevated C-proSP-B levels could effectively differentiate IPF patients from those with other pulmonary diseases ($p < 0.0001$) [80]. Overall, the application of serological tests in early IPF diagnosis is not widely utilized, and their role requires further research [17, 66].

Susceptibility genes

Several genes are associated with IPF susceptibility. A three-stage genome-wide association study (GWAS) revealed that different variants of TOLLIP could either decrease or increase the risk of pulmonary fibrosis development [81]. Additionally, multiple other polymorphisms in genes such as TGFβ-1, IL1RN, IL8, and HLA DRB1∗1501 have also been implicated in IPF susceptibility, though their exact roles remain unclear and require larger-scale studies [82]. The strongest genetic association with pulmonary fibrosis development and pathogenesis is the polymorphism in the MUC5B promoter region [82]. The common polymorphism in the MUC5B promoter is related to both familial interstitial pneumonia and IPF. The single nucleotide polymorphism (SNP) rs35705950 in the MUC5B promoter region correlates with elevated MUC5B expression levels, potentially because of its role in mucosal host defense. IPF subjects demonstrated higher pulmonary MUC5B expression compared to controls, with MUC5B protein expression also detected in fibrotic lesions of IPF [83]. This makes genomic screening potentially beneficial for identifying at-risk individuals for IPF.

Challenges and opportunities for early IPF diagnosis

There remain some challenges in the development and clinical application of CAD systems for IPF. First, model development requires abundant high-quality, unbiased training data. Supervised models, such as CNN, also require a lot of effort to annotate images. However, the incidence rate of ILDs is relatively low, so it is hard for healthcare workers to obtain adequate data. To address this issue, we need to strengthen data sharing while protecting patient privacy, merging confidential databases across institutions to create open-access databases. Alternative solutions to data scarcity include data augmentation which works by creating more training data by flipping, rotating, or scaling the images, and supervised pre-training which means that the parameters that solve one type of problem are taken directly as the initial parameters of the training to solve another problem. Unsupervised models have developed rapidly in recent years, which are suitable for scenarios with limited labeled data and relevant large unlabeled data, thereby making heavy annotation work unnecessary. Second, DL models can be developed on image biomarkers not previously visualized by the human eye, making them behave like black boxes. The complex architecture and numerous parameters of neural networks also make interpretation difficult. Before applying a model to the clinical setting, we need to understand why the model makes particular mistakes. Saliency maps can enhance explainability by helping people identify which part of the image is important to the algorithm. Image segmentation can also enhance explainability [84]. In many studies, the performance of an algorithm is assessed by classification accuracy or area under curve (AUC), which does not reflect the clinical utility of the algorithm. Clinicians and patients are more concerned about whether they will benefit from the algorithm, rather than the algorithm's technical performance. The research should be performed in collaboration with clinicians for a more comprehensive evaluation of the performance of the algorithm [85]. Moreover, how to apply the algorithm in

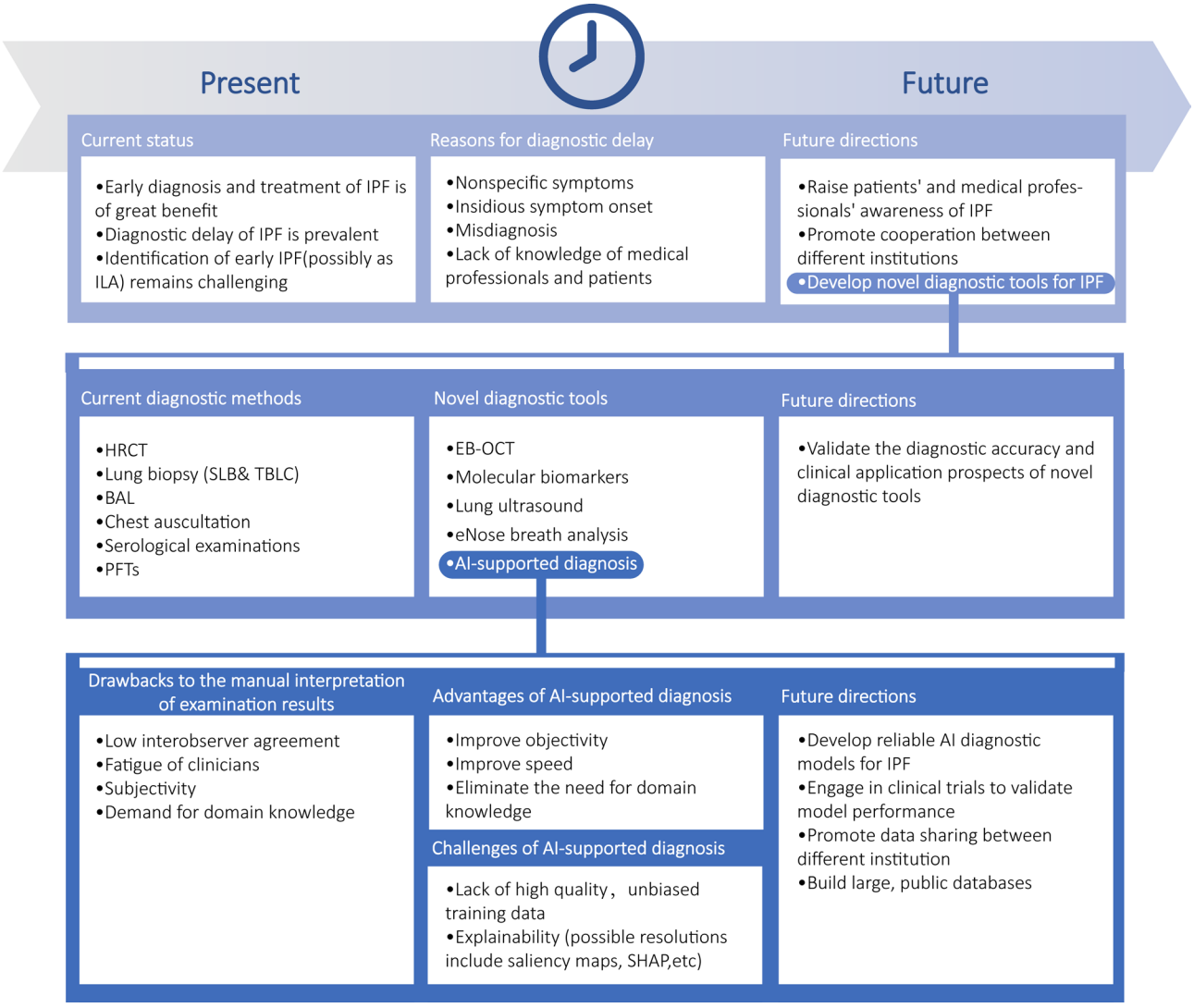

Fig. 4 Early IPF diagnosis: present and future. Early diagnosis and treatment are very beneficial for IPF patients, yet the diagnostic delay remains severe. Misdiagnosis, insidious onset, non-specific symptoms, and lack of knowledge are some of the main reasons leading to delayed diagnosis. It is urgent to raise awareness of IPF among medical professionals and patients, to promote cooperation between different medical institutions, and to develop new diagnostic tools for IPF. The image illustrates the current and future technologies for diagnosing IPF, focusing on AI diagnostic tools, BAL = Bronohoalveolarlavage, PFTs = Pulmonary Function Test, and SHAP = SHapley Additive exPlanations

clinical practice, whether it is used as a diagnostic criterion or an aid, needs further examination and validation.

Conclusion and future directions

This review analyzed the current status and discussed the future perspective for early IPF diagnosis. Delayed diagnosis is common in IPF patients and is associated with a worse life quality and a worse outcome. Indeterminate UIP or ILAs at radiology may be an early IPF, but needs histological evidence and long-term CT follow-up. DL models, with their unique advantages, can unearth new radiologic biomarkers related to early IPF. Bronchoscopic examination plays an increasing role in the histopathological diagnosis of IPF. Other methods include chest auscultation and serological examination, etc (Fig. 4). Developing a reliable early IPF diagnostic model is very important for early identification and intervention of IPF, which may prolong patient survival.

Abbreviations

AI	Artificial intelligence
AMFM	Adaptive multiple features method
ANN	Artificial neural network
AUC	Area Under Curve
BAL	Bronohoalveolarlavage
CAD	Computer-aided diagnosis
CALIPER	Computer-aided lung informatics for pathology evaluation and rating
cCK-18	Circulating fragments of cytokeratin-18
CNN	Convolutional Neural Network
COPD	Chronic obstructive pulmonary disease

DCNN	Deep Convolutional Neural Network
DL	Deep learning
EB-OCT	Endobronchial optical coherence tomography
ECM	Extracellular matrix
HP	Hypersensitivity pneumonia
HRCT	High resolution computed tomography
ILAs	Interstitial lung abnormalities
ILDs	Interstitial lung diseases
IPF	Idiopathic pulmonary fibrosis
KL-6	Krebs von den Lungen-6
ML	Machine learning
MLD	Mean lung density
MLP	Multilayer Perception
MMP-7	Matrix metalloproteinase-7
NPA	Negative Percent Agreement
NSIP	Nonspecific intersitial pneumonia
OPN	Osteopontin
PFTs	Pulmonary function tests
PPA	Positive Percent Agreement
PS-EB-OCT	Polarization-sensitive endobronchial optical coherence tomography
QLF	Quantitative lung fibrosis
S100A4	S100 calcium-binding protein A4
SHAP	SHapley Additive exPlanations
SLB	Surgical lung biopsy
SP	Surfactant proteins
SVM	Support Vector Machine
TBLC	Transbronchial lung cryobiopsy
UIP	Usual interstitial pneumonia
VC	Velcro crackles
ViT	Vision Transformer
XGBoost	eXtreme Gradient Boosting

Acknowledgements
Not applicable.

Author contributions
F.L. and X.W. conceived this review. X.W., X.X., Y.H., and H.Z wrote the manuscript. X.W. and X.X. created the literature table. F.L. and J.S. reviewed and edited the manuscript. All authors contributed to figure plotting, manuscript revision and have reviewed and approved the final manuscript.

Funding
This study was funded by the National Key Technologies R&D Program (No. 2021YFC2500700), Shanghai Municipal Health Commission (20244Z0019), Shanghai Chest Hospital (2024IIT-M002), and the Student Innovation Training Program of Shanghai Jiao Tong University School of Medicine (No.19250322).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 22 February 2025 / Accepted: 7 May 2025
Published online: 19 May 2025

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