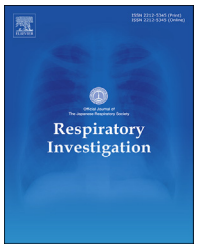
Available online at www.sciencedirect.com

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv



Review

The potential role of artificial intelligence in the clinical practice of interstitial lung disease

Tomohiro Handa [a,b]

[a] *Department of Advanced Medicine for Respiratory Failure and Graduate School of Medicine, Kyoto University, Kyoto, Japan*

[b] *Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan*

ARTICLE INFO

Article history:
Received 4 April 2023
Received in revised form
26 July 2023
Accepted 9 August 2023

Keywords:
Artificial intelligence
Deep learning
Molecular classifier
Neural network

ABSTRACT

Artificial intelligence (AI) is being widely applied in the field of medicine, in areas such as drug discovery, diagnostic support, and assistance with medical practice. Among these, medical imaging is an area where AI is expected to make a significant contribution. In Japan, as of November 2022, 23 AI medical devices have received regulatory approval; all these devices are related to image analysis. In interstitial lung diseases, technologies have been developed that use AI to analyze high-resolution computed tomography and pathological images, and gene expression patterns in tissue taken from transbronchial lung biopsies to assist in the diagnosis of idiopathic pulmonary fibrosis. Some of these technologies are already being used in clinical practice in the United States. AI is expected to reduce the burden on physicians, improve reproducibility, and advance personalized medicine. Obtaining sufficient data for diseases with a small number of patients is difficult. Additionally, certain issues must be addressed in order for AI to be applied in healthcare. These issues include taking responsibility for the AI results output, updating software after the launch of technology, and adapting to new imaging technologies. Establishing research infrastructures such as large-scale databases and common platforms is important for the development of AI technology: their use requires an understanding of the characteristics and limitations of the systems.

Clinical trial registration: Not applicable.

Contents

Abbreviations: AI, Artificial intelligence; AIQCT, Artificial intelligence-based quantitative CT image analysis software; CT, Computed tomography; HRCT, High resolution CT; IPF, Idiopathic pulmonary fibrosis; ILD, Interstitial lung disease; UIP, Usual interstitial pneumonia.

E-mail address: hanta@kuhp.kyoto-u.ac.jp (T. Handa).

https://doi.org/10.1016/j.resinv.2023.08.006

1. Introduction

With the development of computer technology, widespread use of the internet, and advent of deep learning, artificial intelligence (AI) is currently experiencing its third boom. Various applications have been attempted in the field of medicine, with medical imaging being the field where AI has made the greatest progress in practical application. This paper outlines the current status, future possibilities, and issues in the application of AI in the clinical practice of interstitial lung disease (ILD).

2. AI and deep learning

AI does not have a fixed definition; however, according to John McCarthy, who coined the term, AI is the science and engineering of making intelligent machines, especially intelligent computer programs. In general, it refers to a technology that allows computers to have intelligence similar to that of humans (Fig. 1). Machine learning is a class of AI in which computer systems adapt to sample data to perform a given task [1]. Machine learning can be broadly divided into supervised learning, unsupervised learning, and reinforcement learning. Random forests, support vector machines, and neural networks are among the supervised learning methods that have been utilized to analyze medical images. Support vector machines differentiate two classes by mathematically transforming the input data into a high-dimensional space and then generating a hyperplane that optimally separates the classes [2]. Before the advent of deep learning, support vector machines were widely used as they were the most powerful method for classification; they continue to be used in novel medical image analysis techniques [3]. However, conventional algorithms have complex processes and a greater reliance on manual input, which may limit their performance [4]. Neural networks are a method of information processing that mimics the neuronal mechanisms in the brain. A neural network consists of hierarchical layers of nonlinear processing units and, between the layers, weights indicate the strength of the connections between neurons. By repeatedly providing inputs and correct answers, these weights are adjusted. A multilayered neural network with multiple intermediate layers is called deep learning, which is the mainstream in state-of-the-art AI technology.

3. Medical applications of AI

AI is widely used in the field of medicine and holds great promise for future advances in ILD practice (Table 1). Its application areas include drug discovery (e.g., discovery of new targets, drug repositioning, and prediction of side effects) [5], risk assessment based on omics data [6], cohort identification from electronic health records [7], epidemiological data analysis, diagnostic support, treatment decision-making [8], medical assistance including home medical care [9], and many others. However, medical image analysis is the area where AI is the most utilized. Dwivedi et al. [10] divided the application of AI in medical imaging into three phases—(1) image classification and quantification, (2) diagnosis, and (3) prognostic estimation—stating that setting more clinically important objectives will increase the clinical impact of the technology. Image classification and quantification techniques are expected to achieve higher reproducibility than visual evaluation and quantify lesions that are difficult to assess visually (e.g., pulmonary vessel volume [11]). Diagnostic technologies are expected to reduce time, help meet the increasing demand for image reading, improve phenotyping, and clarify the relationship between genomic and imaging information. Prognostic estimation technologies are expected to predict treatment response, derive imaging biomarkers, and establish precision medicine [10]. Each of these technologies can serve as the basis for the next phase of technology. For instance, quantification techniques can be applied for diagnostic technologies [12], and quantification indices are often associated with prognosis [11,13]. Furthermore, AI technology is being used to enhance the resolution of computed tomography (CT) images and to automatically

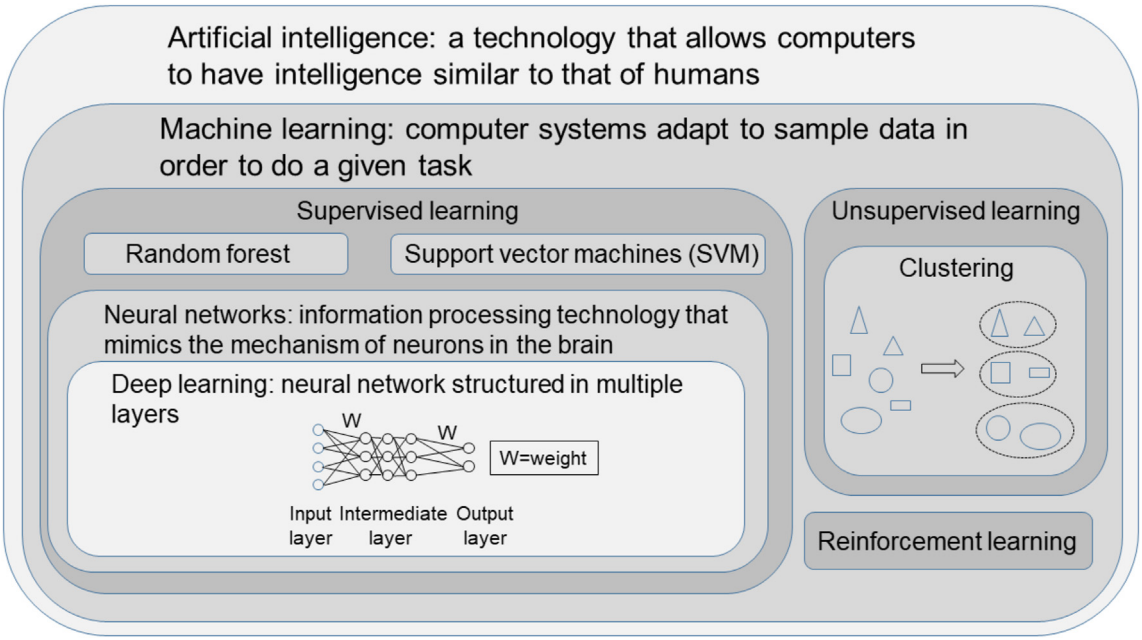


Fig. 1 – Concepts of artificial intelligence, machine learning, and deep learning.

generate image reports. The data covered include a wide range of image types, including chest radiographs, CT, endoscopic images, ultrasound images, and skin findings. As of November 2022, 23 AI devices have been approved as medical devices in Japan, all of which are related to diagnostic imaging support.

IDx-DR is the world's first autonomous AI diagnostic system certified by the United States Food and Drug Administration to detect diabetic retinopathy; the system used AI to analyze data from fundus cameras. More than 120,000 images that were linked to a specialist's diagnosis for learning were used

Table 1 – Potential role of artificial intelligence in the research and clinical practice of interstitial lung disease.

1	New drug discovery/drug repositioning/prediction of adverse events
2	Analysis of chest CT images [15] and pathological [16] imaging of the mouse model of pulmonary fibrosis
3	Application for clinical trials of new drugs (Physiological and/or radiological features that capture subtle changes in disease extent over shorter follow-up periods may provide new endpoints [17–19].)
4	Preventive medicine (e.g., risk assessment through genomic and/or radiomics analysis [20,21])
5	Cohort identification [7] and/or epidemiological studies (automated analysis of rich data in administrative databases or electronic health records)
6	Diagnostic support
	Chest radiography [22,23], MRI [24], histopathology (UIP diagnosis [25], detection of histological features [26]), CT (detection of abnormalities including ILA, pattern segmentation [3,27–39], diagnosis [40–46]), automated reporting systems, etc.
	Reduction of radiation dose of chest CT [52]
	Gene expression analysis (lung tissues [53], bronchoalveolar lavage, blood, etc.)
	Automated medical interview
	Detection of abnormal breath sounds (e.g., fine crackles)
	Visual examination, including skin findings
	Automated interpretation of pulmonary function test
7	Patient care
	Prognostic estimation based on chest CT [11,13,20,21,47–51] or metadata [54]
	Assessment of disease progression based on CT parameters [56–61]
	Prediction of comorbidity (e.g., lung cancer [55])
	Treatment decision-making, personalized medicine
	Detecting abnormalities in hospitalized patients
	Treatment (operation, radiation, chemotherapy) risk assessment for concurrent lung cancer
	Use of medical robots in the clinic (injection and blood collection robots, AI on smart speakers)
	Biometric analysis based on home monitoring devices

Abbreviations: AI, artificial intelligence; CT, computed tomography; ILA, interstitial lung abnormality; MRI, magnetic resonance imaging; UIP, usual interstitial pneumonia.

to develop this technology [14]. Generally, deep learning requires large amounts of high-quality data.

4. Development of medical technology using AI in ILDs

In recent years, the application of AI has been widely attempted in the field of ILD, and many reports have been published on the use of AI in the diagnostic support of CT imaging [40–46], the quantification of parenchymal lesions [3,27–39], and prognostic prediction using quantitative CT parameters [11,13,20,21,47–51,54]. Quantitative CT parameters are useful for objectively assessing disease progression [56–61] and have been used as endpoints in clinical trials [17–19]. AI has also been applied to analyze chest radiographs [22,23,62–64] and magnetic resonance images [24]. Among these, some representative technologies will be presented.

4.1. *Application of AI in the diagnostic support of chest CT*

Idiopathic interstitial pneumonias are interstitial pneumonias with no identifiable cause or background and are classified into nine categories based on the histopathological findings of the lungs [65]. Among idiopathic interstitial pneumonias, idiopathic pulmonary fibrosis (IPF) is the most common subtype with a poor prognosis. The diagnosis of IPF is critically important because treatment with corticosteroids is ineffective or harmful and antifibrotic agents are used to treat it [66]. IPF is diagnosed by confirming a usual interstitial pneumonia (UIP) pattern on chest high-resolution CT (HRCT) or histopathology [67]. Recently, AI-based technologies have been applied to diagnose UIP patterns on chest CT. Walsh et al. [40,68] developed a deep learning-based technology (SOFIA) to diagnose UIP using chest CT. Using a CT pattern diagnosed by a large number of radiologists as a reference, the agreement rate between the AI and 91 radiologists was compared. The agreement rate of AI was 73.3% and that of the radiologists was 70.7%, indicating that, with CT chest imaging, AI was as accurate in diagnosing a UIP as a specialist. The study used data from approximately 1000 cases as training data, but to overcome the limitation of the number of cases, a maximum of 500 sets of any four-slice combination were created for each case, providing a total of more than 400,000 datasets. The study also showed that diagnostic accuracy actually improved as the number of training images increased [40].

Walsh et al. [68] further examined the prognostic utility of SOFIA in predicting outcomes in an Australian cohort of patients with fibrotic interstitial pneumonia. Two radiologists rated the UIP probability of HRCT in 5% increments and SOFIA was used to quantify the UIP probability as a continuous variable. The higher UIP probability quantified using SOFIA was associated with poorer prognosis and the UIP probability generated by SOFIA was a significant prognostic factor when adjusted for the extent of ILD shown on CT; however, the UIP probability assessed by radiologists was not. The authors noted that humans tend not to evaluate more detailed findings once an image has been classified into a certain pattern, and AI technology may compensate for this.

Since the diagnosis of idiopathic interstitial pneumonias is based on information from the peripheral histopathology of the lung, attempts are being made to evaluate the corresponding area on CT images (virtual wedge resection). Shaish et al. [41] used HRCT images from 221 ILD cases, including pathological UIP patterns, as training images and extracted approximately 500 virtual wedges ($4 \times 4 \times 2$ cm in size) per case to differentiate pathological UIP cases from others. When evaluated in a test cohort using a cutoff of 16.5% or more of wedges being classified as UIP, the sensitivity was 74% and the specificity was 58% [41]. That the severity of disease may affect the diagnosis when assessed by the percentage of the classified wedges is of concern; however, focusing on information from the peripheral lung may be useful.

Furukawa et al. [42] recruited 1068 patients with ILD and attempted to diagnose IPF by combining data obtained through chest CT images and clinical information. Deep learning, using four fifths of the data for training and one fifth for validation, showed good diagnostic performance. The diagnostic accuracy was approximately 65% without taking into account the location of the abnormality, approximately 80% with region-specific image information, and over 80% when clinical data were added [42]. The addition of clinical information to the imaging information was shown to improve the accuracy of diagnosis.

Content-based image retrieval is a technology that selects images similar to a given image from a large number of images, and it has been used to support the diagnosis of ILD. AI is used to identify similar images by dividing the image into 64 compartments, calculating the percentage of each of the six imaging patterns of the lung parenchyma, and then evaluating the similarity of the images based on the percentage and distribution information of each pattern. For one image, the system presents three similar images from 288 candidate images. Diagnosis with reference to the presented images improves diagnostic accuracy compared to that without reference [44].

4.2. *Application of AI in chest radiography*

AI has been applied to detect ILD on chest radiographs [22,23,62–64]. Nishikiori et al. [22] developed a deep learning algorithm to detect chronic fibrotic ILD on plain chest radiographs. A second cohort of 1280 radiographs linked to CT was used to confirm the performance of the algorithm, which showed a high accuracy of AUC 0.910 in differentiating fibrotic ILDs from other pulmonary lesions.

4.3. *Use of AI in pathological diagnosis*

Using AI diagnostic techniques for histopathology images is difficult and reports are limited: histopathology images are affected by staining conditions and, even in the same case, information varies by biopsy site and the size of tissues. Uegami et al. [25] developed an AI model to diagnose UIP patterns from histopathological images. In this model, histopathological images of ILDs were segmented, and focal pathological findings were clustered by the model. Pathologists then annotated the clustered pathological images into any pathological pattern, for example, lymphoid follicles. The

whole image was mapped based on the clustered images, and the information was used for machine learning to determine whether the image showed UIP or not. They confirmed that the model provided high diagnostic accuracy of UIP (validation set, AUC 0.90; test set, AUC 0.86), as well as the pathological findings associated with prognosis. In this technology, the addition of human evaluation improved diagnostic accuracy and ensured explainability.

4.4. *AI diagnostic technology based on tissue gene expression patterns*

A diagnostic technology for IPF that uses lung tissue from a transbronchial lung biopsy, which is less invasive than a surgical lung biopsy, has been developed and put into use in clinical practical in the United States. In the development of this technology, transcriptome analysis was performed on lung tissue from patients with ILD and deep learning was performed on the discrimination of pathological UIP patterns. The results showed that the expression pattern of 190 genes could differentiate UIP from other pathological patterns, with a sensitivity of 88% and a specificity of 70% for the diagnosis of UIP when validated in transbronchial lung biopsy tissue from 49 cases of ILD, including 23 cases of UIP [53]. This technology is commercially available in the United States under the name Genomic Classifier and is used as diagnostic support for IPF. The IPF guidelines, revised in 2022, describe Genomic Classifier but opinions are divided and it has no recommendation due to its high specificity but insufficient sensitivity, lack of established response to deal with false-negatives, and lack of widespread use [67].

4.5. *Quantitative CT technology for ILD*

Some ILDs, other than IPF, also show progressive fibrosis over time and are called progressive fibrosing ILD, progressive phenotype, or progressive pulmonary fibrosis [67]. The efficacy of antifibrotic agents has been confirmed in several clinical trials for such diseases. The inclusion criteria for these trials included fibrosis greater than 10% on chest HRCT and an increase in the extent of fibrosis on HRCT over time [69], increasing the importance of quantitative assessment of fibrosis on chest CT. Visual evaluation of HRCT has poor inter-reader consistency and little sensitivity to changes in disease severity over time. To overcome this limitation, in recent years several technologies have been developed to quantify the parenchymal lesions of chest HRCT using texture analysis, support vector machines, or deep learning [3,27–39,57,70]. These systems are now being applied in the clinical trials of novel drugs [17,18].

Kyoto University has developed AI-based quantitative CT image analysis software (AIQCT) in collaboration with Fujifilm Corporation [28]. This technology consists of four discriminators: lung field extraction, airway extraction, pulmonary vessel extraction, and parenchymal pattern classification. Training for parenchymal pattern classification is performed in two dimensions, but the central voxel is discriminated by the analysis in three directions to improve accuracy. The software automatically classifies the lung fields into ten parenchymal patterns and outputs their volume percentages (Fig. 2). When the prognostic indices were investigated in 120 IPF cases, the results of multivariable analysis adjusted for GAP stage—a prognostic index of IPF—showed that lower normal lung volumes and higher bronchial volumes were significant poor prognostic factors [28]. Traction bronchiectasis is a prognostic factor in IPF [11,71] and other ILDs, and bronchial volume measured with AIQCT is thought to reflect it. AIQCT can also measure airway volumes below the main carina of the trachea, and the ability to evaluate volumes in the central airways and bronchi in lung fields is a unique feature of this software. AIQCT is expected to be applied to ILD and other lung diseases in the future; however, as scanner manufacturers, models, acquisition protocols, and reconstruction algorithms may affect the results, it must be performed under appropriate conditions. More detailed imaging evaluation is needed in the clinical practice of ILD. Ichikado et al. [72] reported on chest CT indices that reflect the prognosis of acute interstitial pneumonia, in which GGO and consolidation with traction bronchiectasis were evaluated in the scoring. Aoki et al. [30] developed a deep learning-based chest CT quantification technology that assesses consolidation with traction bronchiectasis and reported its usefulness in predicting the prognosis of ILD. A more detailed classification of GGO and consolidations according to whether they are associated with traction bronchiectasis may be important in evaluating pulmonary fibrosis.

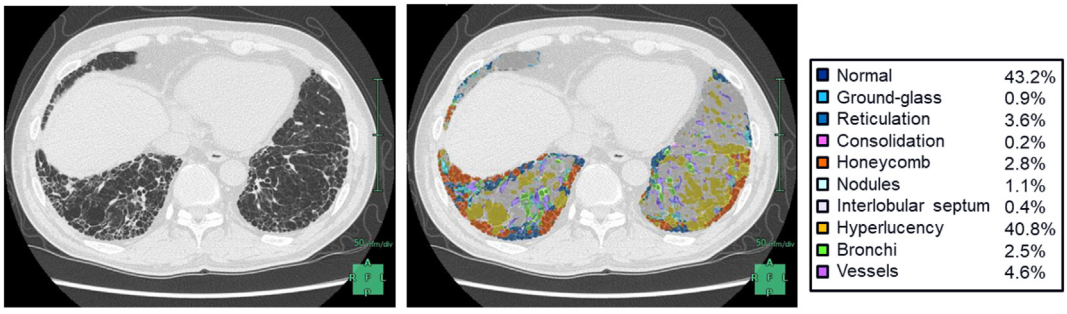


Fig. 2 – Quantification of lung lesions by artificial intelligence-based quantitative computed tomography image analysis software. (A) A high-resolution computed tomography scan and (B) the corresponding overlaid image.

5. Potential and challenges of AI-based medical systems and devices

AI is expected to contribute to a wide range of areas in the research and clinical practice of ILD (Table 1). AI-assisted diagnosis and online medical consultation are anticipated to be countermeasures to the shortage and regional disparities of ILD specialists. The development of AI technology for medicine is predicted to improve home medical care and provide personalized medicine that applies imaging and genomic information.

However, the number of patients with ILD is generally small, making it difficult to obtain sufficient data for constructing AI systems. In this regard, establishing large-scale digital information cooperations, building a public database of ILD images with standardized CT protocols coupled with clinical data, and developing algorithms to compensate for the shortage of data is important. Another issue is that a set of CT or pathology images with universally accurate and objective ILD diagnoses that can be used for AI training does not exist, as the diagnostic process contains a subjective element. Therefore, AI programs are likely to be influenced by the specific physician who provided the diagnoses included in the training data. Additionally, imaging findings may vary according to the disease of origin. For example, the AI evaluation of honeycombing may differ when images of the honeycombing present in IPF are used in the training data rather than images of the honeycombing present in other types of ILDs. Thus, when using AI software, understanding which type of training data was used to develop the technology is important. Imaging technology should be validated against different imaging conditions and patient populations.

There are other issues related to AI technology in general. First, AI can only perform tasks that it has been trained to do. AI technologies are unable to solve problems when they encounter unknown situations that are not part of their training experience. Technologies that use online information may output incorrect results which reflect errors in the information. The black box problem is another issue: checking the basis of the results output by the AI is difficult, which may make it challenging to evaluate the cause of a mistake and solve it. Algorithm interpretability is a key factor in applying AI technology to healthcare [1]. At present, it is generally recognized that the physician should make the final judgment and take responsibility for the results; however, this seems to be an issue that should be considered in the future as technology advances. How to learn and improve the software after it is launched on the market is also an issue, as are whether software updates are done by the developer or by the user and who is responsible for its evaluation and liability. In the field of image analysis, the response to advances in hardware is also a concern. Technologies will need to be adapted to ultrahigh resolution CT, photon counting CT, and other technologies that are expected to become popular in the future. In addition, with respect to the use of data, adherence to data-privacy regulations to ensure patient privacy is necessary.

6. Conclusion

Medical imaging is a representative area in which AI is being applied. In the clinical practice of ILDs, attempts are being made to introduce AI technology to diagnostic imaging of chest radiography, CT, and pathology. Several AI-based quantitative CT technologies for ILD have been developed and are expected to be clinically applied to a wide variety of respiratory diseases. While the use of AI has the potential to address clinical issues that have been difficult to solve in the past, various challenges remain in its interpretation and application. In the use of AI, understanding the characteristics and limitations of AI technologies is necessary.

Funding

This work was supported by a research grant from FUJIFILM Corporation.

Role of the funding source

The funder was not involved in the collection, analysis, or interpretation of the data or in the preparation of the paper.

Ethics approval

Not applicable.

Informed consent

Not applicable.

Data availability

Not applicable.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used DEEPL TRANSLATE in some parts of the manuscript, in order to TRANSLATE Japanese sentences into English. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Conflict of interest

Tomohiro Handa received a research grant from FUJIFILM Corporation and belongs to an endowed department sponsored by Teijin Pharma Ltd.

Acknowledgements

We would like to thank the following doctors for their cooperation in the development of AIQCT: Dr. Kiminobu Tanizawa,

Dr. Tsuyoshi Oguma, Dr. Naoya Tanabe, Dr. Takafumi Niwamoto, Dr. Hiroshi Shima, Dr. Ryobu Mori, and Dr. Toyohiro Hirai (Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University); Dr. Tomomi W Nobashi, Dr. Ryo Sakamoto, and Dr. Yuji Nakamoto (Department of Diagnostic Imaging and Nuclear Medicine, Graduate School of Medicine, Kyoto University); Dr. Takeshi Kubo (Department of Radiology, Tenri Hospital), Dr. Atsuko Kurosaki (Department of Diagnostic Radiology, Fukujuji Hospital), Dr. Kazuma Kishi (Department of Respiratory Medicine, Graduate School of Medicine, Toho University), Dr. Ryuji Uozumi (Tokyo Institute of Technology), Dr. Kizuku Watanabe (Department of Respiratory Medicine, Japanese Red Cross Wakayama Medical Centre), and Dr. Shingo Iwano (Department of Radiology, Nagoya University Graduate School of Medicine).

REFERENCES

[1] Barnes H, Humphries SM, George PM, Assayag D, Glaspole I, Mackintosh JA, et al. Machine learning in radiology: the new frontier in interstitial lung diseases. Lancet Digit Health 2023;5:e41–50.
[2] Yu W, Liu T, Valdez R, Gwinn M, Khoury MJ. Application of support vector machine modeling for prediction of common diseases: the case of diabetes and pre-diabetes. BMC Med Inf Decis Making 2010;10:16.
[3] Ohno Y, Aoyagi K, Takenaka D, Yoshikawa T, Ikezaki A, Fujisawa Y, et al. Machine learning for lung CT texture analysis: improvement of inter-observer agreement for radiological finding classification in patients with pulmonary diseases. Eur J Radiol 2021;134:109410.
[4] Zhang G, Luo L, Zhang L, Liu Z. Research progress of respiratory disease and idiopathic pulmonary fibrosis based on artificial intelligence. Diagnostics 2023;13:357.
[5] Sarkar C, Das B, Rawat VS, Wahlang JB, Nongpiur A, Tiewsoh I, et al. Artificial intelligence and machine learning technology driven modern drug discovery and development. Int J Mol Sci 2023;24:2026.
[6] Michelhaugh SA, Januzzi Jr JL. Using artificial intelligence to better predict and develop biomarkers. Clin Lab Med 2023;43:99–114.
[7] Farrand E, Gologorskaya O, Mills H, Radhakrishnan L, Collard HR, Butte AJ. Machine learning algorithm to improve cohort identification in interstitial lung disease. Am J Respir Crit Care Med 2023. https://doi.org/10.1164/rccm.202211-2092LE.
[8] Barough SS, Safavi-Naini SAA, Siavoshi F, Tamimi A, Ilkhani S, Akbari S, et al. Generalizable machine learning approach for COVID-19 mortality risk prediction using on-admission clinical and laboratory features. Sci Rep 2023;13:2399.
[9] Chae SH, Kim Y, Lee KS, Park HS. Development and clinical evaluation of a web-based upper limb home rehabilitation system using a smartwatch and machine learning model for chronic stroke survivors: prospective comparative study. JMIR Mhealth Uhealth 2020;8:e17216.
[10] Dwivedi K, Sharkey M, Condliffe R, Uthoff JM, Alabed S, Metherall P, et al. Pulmonary hypertension in association with lung disease: quantitative CT and artificial intelligence to the rescue? State-of-the-art review. Diagnostics 2021;11:679.
[11] Jacob J, Bartholmai BJ, Rajagopalan S, Van Moorsel CHM, Van Es HW, Van Beek FT, et al. Predicting outcomes in idiopathic pulmonary fibrosis using automated computed tomographic analysis. Am J Respir Crit Care Med 2018;198:767–76.
[12] Kataoka Y, Baba T, Ikenoue T, Matsuoka Y, Matsumoto J, Kumasawa J, et al. Development and external validation of a deep learning-based computed tomography classification system for COVID-19. Ann Clin Epidemiol 2022;4:110–9.
[13] Salisbury ML, Lynch DA, Van Beek EJ, Kazerooni EA, Guo J, Xia M, et al. Idiopathic pulmonary fibrosis: the association between the adaptive multiple features method and fibrosis outcomes. Am J Respir Crit Care Med 2017;195:921–9.
[14] Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. JAMA 2016;316:2402–10.
[15] Vincenzi E, Fantazzini A, Basso C, Barla A, Odone F, Leo L, et al. A fully automated deep learning pipeline for micro-CT-imaging-based densitometry of lung fibrosis murine models. Respir Res 2022;23:308.
[16] Heinemann F, Birk G, Schoenberger T, Stierstorfer B. Deep neural network based histological scoring of lung fibrosis and inflammation in the mouse model system. PLoS One 2018;13:e0202708.
[17] Van den Blink B, Dillingh MR, Ginns LC, Morrison LD, Moerland M, Wijsenbeek M, et al. Recombinant human pentraxin-2 therapy in patients with idiopathic pulmonary fibrosis: safety, pharmacokinetics and exploratory efficacy. Eur Respir J 2016;47:889–97.
[18] Kim GHJ, Goldin JG, Hayes W, Oh A, Soule B, Du S. The value of imaging and clinical outcomes in a phase II clinical trial of a lysophosphatidic acid receptor antagonist in idiopathic pulmonary fibrosis. Ther Adv Respir Dis 2021. https://doi.org/10.1177/17534666211004238.
[19] Lancaster L, Goldin J, Trampisch M, Kim GH, Ilowite J, Homik L, et al. Effects of nintedanib on quantitative lung fibrosis score in idiopathic pulmonary fibrosis. Open Respir Med J 2020;14:22–31.
[20] Budzikowski JD, Foy JJ, Rashid AA, Chung JH, Noth I, Armato 3rd SG. Radiomics-based assessment of idiopathic pulmonary fibrosis is associated with genetic mutations and patient survival. J Med Imaging 2021;8:031903.
[21] Xu W, Wu W, Zheng Y, Chen Z, Tao X, Zhang D, et al. A computed tomography radiomics-based prediction model on interstitial lung disease in anti-MDA5-positive dermatomyositis. Front Med 2021;8:768052.
[22] Nishikiori H, Kuronuma K, Hirota K, Yama N, Suzuki T, Onodera M, et al. Deep learning algorithm to detect fibrosing interstitial lung disease on chest radiographs. Eur Respir J 2022;61:2102269.
[23] Kim H, Jin KN, Yoo SJ, Lee CH, Lee SM, Hong H, et al. Deep learning for estimating lung capacity on chest radiographs predicts survival in idiopathic pulmonary fibrosis. Radiology 2023;306:e220292.
[24] Wang Z, Robertson SH, Wang J, He M, Virgincar RS, Schrank GM, et al. Quantitative analysis of hyperpolarized (129) Xe gas transfer MRI. Med Phys 2017;44:2415–28.
[25] Uegami W, Bychkov A, Ozasa M, Uehara K, Kataoka K, Johkoh T, et al. MIXTURE of human expertise and deep learning-developing an explainable model for predicting pathological diagnosis and survival in patients with interstitial lung disease. Mod Pathol 2022;35:1083–91.
[26] Mäkelä K, Mäyränpää MI, Sihvo HK, Bergman P, Sutinen E, Ollila H, et al. Artificial intelligence identifies inflammation and confirms fibroblast foci as prognostic tissue biomarkers in idiopathic pulmonary fibrosis. Hum Pathol 2021;107:58–68.
[27] Maldonado F, Moua T, Rajagopalan S, Karwoski RA, Raghunath S, Decker PA, et al. Automated quantification of

radiological patterns predicts survival in idiopathic pulmonary fibrosis. Eur Respir J 2014;43:204–12.
[28] Handa T, Tanizawa K, Oguma T, Uozumi R, Watanabe K, Tanabe N, et al. Novel artificial intelligence-based technology for chest computed tomography analysis of idiopathic pulmonary fibrosis. Ann Am Thorac Soc 2022;19:399–406.
[29] Iwasawa T, Kanauchi T, Hoshi T, Ogura T, Baba T, Gotoh T, et al. Multicenter study of quantitative computed tomography analysis using a computer-aided three-dimensional system in patients with idiopathic pulmonary fibrosis. Jpn J Radiol 2016;34:16–27.
[30] Aoki R, Iwasawa T, Saka T, Yamashiro T, Utsunomiya D, Misumi T, et al. Effects of automatic deep-learning-based lung analysis on quantification of interstitial lung disease: correlation with pulmonary function test results and prognosis. Diagnostics 2022;12:3038.
[31] Choi B, Adan N, Doyle TJ, Estépar RSJ, Harmouche R, Humphries SM, et al. Quantitative interstitial abnormality progression and outcomes in the genetic epidemiology of COPD and pittsburgh lung screening study cohorts. Chest 2023;163:164–75.
[32] Kim HG, Tashkin DP, Clements PJ, Li G, Brown MS, Elashoff R, et al. A computer-aided diagnosis system for quantitative scoring of extent of lung fibrosis in scleroderma patients. Clin Exp Rheumatol 2010;28:S26–35.
[33] Chang Y, Lim J, Kim N, Seo JB, Lynch DA. A support vector machine classifier reduces interscanner variation in the HRCT classification of regional disease pattern in diffuse lung disease: comparison to a Bayesian classifier. Med Phys 2013;40:051912.
[34] Depeursinge A, Chin AS, Leung AN, Terrone D, Bristow M, Rosen G, et al. Automated classification of usual interstitial pneumonia using regional volumetric texture analysis in high-resolution computed tomography. Invest Radiol 2015;50:261–7.
[35] Gao M, Bagci U, Lu L, Wu A, Buty M, Shin HC, et al. Holistic classification of CT attenuation patterns for interstitial lung diseases via deep convolutional neural networks. Comput Methods Biomech Biomed Eng Imaging Vis 2018;6:1–6.
[36] Chong DY, Kim HJ, Lo P, Young S, McNitt-Gray MF, Abtin F, et al. Robustness-driven feature selection in classification of fibrotic interstitial lung disease patterns in computed tomography using 3D texture features. IEEE Trans Med Imag 2016;35:144–57.
[37] Kim GB, Jung KH, Lee Y, Kim HJ, Kim N, Jun S, et al. Comparison of shallow and deep learning methods on classifying the regional pattern of diffuse lung disease. J Digit Imag 2018;31:415–24.
[38] Huang S, Lee F, Miao R, Si Q, Lu C, Chen Q. A deep convolutional neural network architecture for interstitial lung disease pattern classification. Med Biol Eng Comput 2020;58:725–37.
[39] Chassagnon G, Vakalopoulou M, Régent A, Zacharaki EI, Aviram G, Martin C, et al. Deep learning-based approach for automated assessment of interstitial lung disease in systemic sclerosis on CT images. Radiol Artif Intell 2020;2:e190006.
[40] Walsh SLF, Calandriello L, Silva M, Sverzellati N. Deep learning for classifying fibrotic lung disease on high-resolution computed tomography: a case-cohort study. Lancet Respir Med 2018;6:837–45.
[41] Shaish H, Ahmed FS, Lederer D, D'Souza B, Armenta P, Salvatore M, et al. Deep learning of computed tomography virtual wedge resection for prediction of histologic usual interstitial pneumonitis. Ann Am Thorac Soc 2021;18:51–9.
[42] Furukawa T, Oyama S, Yokota H, Kondoh Y, Kataoka K, Johkoh T, et al. A comprehensible machine learning tool to differentially diagnose idiopathic pulmonary fibrosis from other chronic interstitial lung diseases. Respirology 2022;27:739–46.
[43] Agarwala S, Kale M, Kumar D, Swaroop R, Kumar A, Dhara AK, et al. Deep learning for screening of interstitial lung disease patterns in high-resolution CT images. Clin Radiol 2020;75:481.e1–8.
[44] Choe J, Hwang HJ, Seo JB, Lee SM, Yun J, Kim MJ, et al. Content-based image retrieval by using deep learning for interstitial lung disease diagnosis with chest CT. Radiology 2022;302:187–97.
[45] Yu W, Zhou H, Choi Y, Goldin JG, Teng P, Wong WK, et al. Multi-scale, domain knowledge-guided attention + random forest: a two-stage deep learning-based multi-scale guided attention models to diagnose idiopathic pulmonary fibrosis from computed tomography images. Med Phys 2023;50:894–905.
[46] Bratt A, Williams JM, Liu G, Panda A, Patel PP, Walkoff L, et al. Predicting usual interstitial pneumonia histopathology from chest CT imaging with deep learning. Chest 2022;162:815–23.
[47] Park HJ, Lee SM, Song JW, Lee SM, Oh SY, Kim N, et al. Texture-based automated quantitative assessment of regional patterns on initial CT in patients with idiopathic pulmonary fibrosis: relationship to decline in forced vital capacity. AJR Am J Roentgenol 2016;207:976–83.
[48] Kim GHJ, Weigt SS, Belperio JA, Brown MS, Shi Y, Lai JH, et al. Prediction of idiopathic pulmonary fibrosis progression using early quantitative changes on CT imaging for a short term of clinical 18-24-month follow-ups. Eur Radiol 2020;30:726–34.
[49] Jacob J, Bartholmai BJ, Rajagopalan S, Brun AL, Egashira R, Karwoski R, et al. Evaluation of computer-based computer tomography stratification against outcome models in connective tissue disease-related interstitial lung disease: a patient outcome study. BMC Med 2016;14:190.
[50] Jacob J, Bartholmai BJ, Rajagopalan S, Egashira R, Brun AL, Kokosi M, et al. Unclassifiable-interstitial lung disease: outcome prediction using CT and functional indices. Respir Med 2017;130:43–51.
[51] Moon JW, Bae JP, Lee HY, Kim N, Chung MP, Park HY, et al. Perfusion- and pattern-based quantitative CT indexes using contrast-enhanced dual-energy computed tomography in diffuse interstitial lung disease: relationships with physiologic impairment and prediction of prognosis. Eur Radiol 2016;26:1368–77.
[52] Zhao R, Sui X, Qin R, Du H, Song L, Tian D, et al. Can deep learning improve image quality of low-dose CT: a prospective study in interstitial lung disease. Eur Radiol 2022;32:8140–51.
[53] Raghu G, Flaherty KR, Lederer DJ, Lynch DA, Colby TV, Myers JL, 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.
[54] Yadav A, Saxena R, Kumar A, Walia TS, Zaguia A, Kamal SMM. FVC-NET: an automated diagnosis of pulmonary fibrosis progression prediction using honeycombing and deep learning. Comput Intell Neurosci 2022;2022:2832400.
[55] Liang CH, Liu YC, Wan YL, Yun CH, Wu WJ, López-González R, et al. Quantification of cancer-developing idiopathic pulmonary fibrosis using whole-lung texture analysis of HRCT images. Cancers 2021;13:5600.
[56] Jacob J, Bartholmai BJ, Rajagopalan S, Kokosi M, Egashira R, Brun AL, et al. Serial automated quantitative CT analysis in idiopathic pulmonary fibrosis: functional correlations and comparison with changes in visual CT scores. Eur Radiol 2018;28:1318–27.
[57] Humphries SM, Yagihashi K, Huckleberry J, Rho BH, Schroeder JD, Strand M, et al. Idiopathic pulmonary fibrosis:

data-driven textural analysis of extent of fibrosis at baseline and 15-month follow-up. Radiology 2017;285:270–8.
[58] Humphries SM, Swigris JJ, Brown KK, Strand M, Gong Q, Sundy JS, et al. Quantitative high-resolution computed tomography fibrosis score: performance characteristics in idiopathic pulmonary fibrosis. Eur Respir J 2018;52:1801384.
[59] Lee JS, Kim GJ, Ha YJ, Kang EH, Lee YJ, Goldin JG, et al. The extent and diverse trajectories of longitudinal changes in rheumatoid arthritis interstitial lung diseases using quantitative HRCT scores. J Clin Med 2021;10:3812.
[60] Aliboni L, Dias OM, Baldi BG, Sawamura MVY, Chate RC, Carvalho CRR, et al. A convolutional neural network approach to quantify lung disease progression in patients with fibrotic hypersensitivity pneumonitis (HP). Acad Radiol 2022;29:e149–56.
[61] Chassagnon G, Vakalopoulou M, Régent A, Sahasrabudhe M, Marini R, Hoang-Thi TN, et al. Elastic registration-driven deep learning for longitudinal assessment of systemic sclerosis interstitial lung disease at CT. Radiology 2021;298:189–98.
[62] Kim W, Lee SM, Kim JI, Ahn Y, Park S, Choe J, et al. Utility of a deep learning algorithm for detection of reticular opacity on chest radiography in patients with interstitial lung disease. AJR Am J Roentgenol 2022;218:642–50.
[63] Cho Y, Park B, Lee SM, Lee KH, Seo JB, Kim N. Optimal number of strong labels for curriculum learning with convolutional neural network to classify pulmonary abnormalities in chest radiographs. Comput Biol Med 2021;136:104750.
[64] Sung J, Park S, Lee SM, Bae W, Park B, Jung E, et al. Added value of deep learning-based detection system for multiple major findings on chest radiographs: a randomized crossover study. Radiology 2021;299:450–9.
[65] Travis WD, Costabel U, Hansell DM, King Jr TE, Lynch DA, Nicholson AG, 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.
[66] Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, 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:e3–19.
[67] Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2022;205:e18–47.
[68] Walsh SLF, Mackintosh JA, Calandriello L, Silva M, Sverzellati N, Larici AR, et al. Deep learning-based outcome prediction in progressive fibrotic lung disease using high-resolution computed tomography. Am J Respir Crit Care Med 2022;206:883–91.
[69] Wong AW, Ryerson CJ, Guler SA. Progression of fibrosing interstitial lung disease. Respir Res 2020;21:32.
[70] Park B, Park H, Lee SM, Seo JB, Kim N. Lung segmentation on HRCT and volumetric CT for diffuse interstitial lung disease using deep convolutional neural networks. J Digit Imag 2019;32:1019–26.
[71] Sumikawa H, Johkoh T, Colby TV, Ichikado K, Suga M, Taniguchi H, et al. Computed tomography findings in pathological usual interstitial pneumonia: relationship to survival. Am J Respir Crit Care Med 2008;177:433–9.
[72] Ichikado K, Suga M, Müller NL, Taniguchi H, Kondoh Y, Akira M, et al. Acute interstitial pneumonia: comparison of high-resolution computed tomography findings between survivors and nonsurvivors. Am J Respir Crit Care Med 2002;165:1551–6.