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Diagnosis of idiopathic pulmonary fibrosis by virtual means using "IPFdatabase"- a new software

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ABSTRACT

Background: The diagnostic algorithm for idiopathic pulmonary fibrosis (IPF) guidelines has some shortcomings. The aim of the present study was to develop a novel software, "*IPFdatabase*", that could readily apply the diagnostic criteria per IPF guidelines and make a 'virtual' diagnosis of IPF.
Methods: Software was developed as a step-by-step compilation of necessary information according to guidelines to enable a diagnosis of IPF. Software accuracy was validated primarily by comparing software diagnoses to those previously made at a Center for Interstitial Lung Diseases.
Results: Clinical validation on 98 patients (68 male, age 61.0 ± 8.5 years), revealed high software accuracy for IPF diagnosis when compared to historical diagnoses (sensitivity 95.5%, specificity 96.2%; positive predictive value 95.5%, negative predictive value 96.2%). A general radiologist and a general pathologist reviewed relevant data with and without the new software: interobserver agreement increased when they used the *IPFdatabase* (kappa 0.18 to 0.64 for radiology, 0.13 to 0.59 for pathology).
Conclusion: IPFdatabase is a useful diagnostic tool for typical cases of IPF, and potentially restricts the need for MDDs to atypical and complex cases. We propose this web-designed software for instant accurate diagnosis of IPF by virtual means and for educational purposes; the software is readily accessed with mobile apps, allows incorporation of updated version of guidelines, can be utilized for gathering data useful for future studies and give physicians rapid feedback in daily practice.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) as a specific form of chronic, progressive fibrosing interstitial pneumonia (IP) of unknown cause with poor prognosis, occurring primarily in older adults and limited to the lungs [1]. It is characterized by radiological and histological evidence of usual interstitial pneumonia (UIP); in the appropriate clinical setting, the diagnosis can be made based on UIP on high resolution computed tomography (HRCT) without surgical lung biopsy (SLB) [1]. In order to make an accurate diagnosis of IPF, clinical practice guidelines strongly recommend multidisciplinary discussion (MDDs) among experts, including pulmonologists, radiologists and pathologists [1]. A recent report confirmed that diagnosis of IPF is more frequently made with higher confidence through MDDs than by clinicians or radiologists alone [2].

Many software platforms has been proposed to facilitate clinical decision making demonstrateing successful in boosting physicians' diagnostic confidence, reducing costs and improving patient outcomes

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[3].

The challenge of making an accurate diagnosis of IPF is evident from the high rate of screen failure in clinical trials when 2011 IPF guidelines were applied [4–8]. While diagnostic accuracy of IPF by community physicians and centers is low, there are practical issues associated with having patients seen at regional expert centers where MDD is used to increase diagnostic accuracy and confidence. Hurdles to obtaining an accurate yet timely diagnosis by expert evaluation and MDD include time to obtain an appointment, time and travel costs and difficulty of travel for sick patients requiring supplemental oxygen [9].

Since IPF is fatal and antifibrotic agents (nintedanib and pirfenidone) are now available for patients diagnosed with IPF [10], patients suspected to have IPF should be diagnosed promptly in order to derive potential treatment benefits, including lung transplantation; [11]. In the present study, we developed a novel web-designed software based on the current established criteria for diagnosis of IPF [1] and propose it as a tool for rapid accurate diagnosis of IPF by virtual means.

2. Methods

2.1. Software design

We designed a software, named "*IPFdatabase*", specifically to ascertain IPF diagnosis according to IPF clinical practice guidelines [1]. We used Oracle MySQL, the most popular open source relational database management system (RDBMS). The visual web interface was drawn with HTML (HyperText Markup Language) and CSS (Cascading Style Sheets). Some functions were written with PHP (Hypertext Preprocessor) and JavaScript. *IPFdatabase* can be accessed by portable devices (Fig. 1).

All patients must give their consent before their data are entered into the software.

2.2. IPFdatabase design

IPFdatabase consists of two major sections: 1. medical and family history (one page) and 2. IPF features (four pages). The software requires step-by-step compilation of both sections with the patient's data. Once all pages are complete, the software automatically produces a diagnosis of IPF, if all guideline criteria are met. The software also serves to generate a data repository for future studies. The software gives the possibility to save entered data at every encounter and to reopen each form/page afterwards or to correct data if necessary.

2.2.1. Medical and family history

This includes information on patient history and attributes including smoking status and occupational or environmental exposures as well as family history. Please see Part A of the supplement for full details.

2.2.2. IPF diagnosis

This section consists of four pages where users fill in yes/no questions regarding symptoms, radiological findings and histopathology. We also included precise domains for the evaluation of specific comorbidities to refine IPF diagnosis and exclude similar entities with potentially different outcomes [13–15].

In this section radiological and pathological interpretations must be provided reporting the presence/absence of specific features concordant or against the UIP pattern, in accordance with 2011 guidelines.

Radiologic data: This gathers data on HRCT. The data entered include presence/absence of: subpleural basal predominance; reticular abnormality; honeycombing with or without traction bronchiectasis; upper or mid-lung predominance; peribroncovascolar predominance, ground glass; profuse micronodules; discrete cysts; mosaic attenuation; consolidations (Supplement Fig. 3 SM).

Histopathology data: The entered data include presence/absence of: marked fibrosis/architectural distortion, with or without honeycombing; patchy fibrosis; absence of patchy fibrosis or fibroblast foci; presence of fibroblast foci; honeycomb changes only; hyaline membranes; organizing pneumonia; granulomas; marked interstitial inflammation; predominant airway centered changes; nonclassificable fibrosis ((Supplement Fig. 3 SM).

After all required data is entered into this page, a Java application makes a determination regarding HRCT features: definite UIP, possible UIP, inconsistent with UIP. The application then makes a determination regarding histopathology features from SLB: UIP, probable UIP, possible UIP, inconsistent with UIP. Other details of this section are included in Part B of the supplement.

Once all data is entered, the software assembles and evaluates the data and then labels the patient to have the diagnosis of IPF or not IPF. If some entered data was discordant with diagnostic criteria presented in the IPF guidelines, an alert pops up and prompts further review of specific aspects of the case. If one of the following eight alerts appears, the user can review the data, add missing data, or accept the outcome, opting for a definitive diagnosis of IPF. In all cases a specific disclaimer state that this is not a definite method for the diagnosis of IPF, false positives and negatives are possible.

The following are examples of warnings and software alerts in cases of discordance with 2011 guideline diagnostic criteria:

1. HRCT pattern is not UIP; consider referral to ILD Center or obtaining tissue for histopathology
2. Combination of HRCT and histopathology findings is not conclusive for IPF.
3. Combination of HRCT and SLB histopathology pattern is conclusive for IPF, however there is occupational/environmental exposure; please verify.
4. Combination of HRCT and SLB histopathology pattern is conclusive for IPF, however PFTs show obstructive pattern; please verify.
5. Combination of HRCT and SLB histopathology pattern is conclusive

Fig. 1. Home page of the *IPFdatabase,* user can add a new record, search for a specific patient or explore records.

for IPF, however serology is indicative of CTD; please verify.
6. Combination of HRCT and SLB histopathology pattern is conclusive for IPF, however BAL features are indicative of another diagnosis; please verify.
7. Combination of HRCT and SLB histopathology pattern is conclusive for IPF, however TBBx features suggest another diagnosis; please verify.
8. Combination of HRCT and SLB histopathology pattern is conclusive for IPF, however presence of emphysema is indicative of CPFE; please verify.

2.3. Patient application

To validate the clinical utility of *IPFdatabase*, we gathered clinical data retrospectively from medical records and applied our software to a population of 98 patients with bilateral pulmonary fibrotic disorders of unknown cause, suspected to be IPF. All patients were seen at the Regional Referral Center for Sarcoidosis and Other Interstitial Lung Diseases, Respiratory Diseases and Lung Transplantation Unit, University Hospital (AOUS), University of Siena, Italy for at least 12 months. The University of Siena Institutional Review Board approved this project. Clinical, serological, respiratory function and HRCT data was entered for all subjects; SLB was available in 38/98 cases.

The accuracy of the *IPFdatabase* to ascertain the diagnosis of IPF ("virtual" diagnoses) was compared to diagnoses made by MDD: a pulmonologist (DB), a radiologist (MAM) and a pathologist (DS) from Siena University Hospital, experts and familiar with clinical manifestations of ILD, ran the software with the patients' data (Rad1: MAM, Path1: DS). Results were compared with historical diagnosis made at Siena University Hospital. To validate Siena's radiological and pathological interpretation, an experienced chest radiologist (SP) and pulmonary pathologist (RS) from the Center for ILD (CILD) at the University of Washington, Seattle WA, USA, who regularly take part in MDDs with a recognized and experienced ILD expert (GR) at CILD, participated in the study. They independently (without access to clinical data), interpreted all radiological and histopathologic data of the population, using established IPF criteria on which the new software was based (Rad 2: SP, Path 2: RS). The other purpose of this was to ensure that the software understood the data entered by the 2 different expert providers (2 radiologists and 2 pathologists) and generated the same output/results.

To further validate the clinical utility and diagnostic accuracy of *IPFdatabase*, a general radiologist (GB) and a general pathologist (AG), reviewed the same data with and without the new software. All assessments were performed independently and blindly. Preliminary findings were presented at the 2014 ERS Congress in Munich [12].

2.4. Statistical analysis

The data was expressed as mean ± standard deviation. Analysis of categorical variables was performed by contingency tables by chi-square test and Fisher's exact test. Specificity, sensitivity, positive and negative predictive values and likelihood ratio were also defined by contingency tables. Comparative analysis and interobserver agreement were based on Cohen's kappa coefficient: kappa < 0 indicated no agreement, while 0–0.20 indicated poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81–1 very good agreement.

3. Results

Study population was composed by 98 patients (61.1 ± 8.5 years, 69.3% male); description of clinical, physiologic and serologic data is reported in Table 1.

IPFdatabase diagnosed 43 patients with IPF (43.8%) (42 patients showed UIP pattern at HRCT, 14 of these patients had pathology as well: 13 with UIP patten and 1 with probable UIP; 1 patient showed possible UIP at HRCT and UIP at pathology). Other diagnoses given including hypersensitivity pneumonitis and connective tissue disease associated ILD are shown in Table 2. The algorithm of the diagnostic work-up including radiological and histological features, serology, BAL findings and MDD (if performed) of the population with final diagnosis by *IPFdatabase* is shown in Fig. 2. A final diagnosis was not reached for 7/98 patients in *IPFdatabase* largely because there was not an SLB and other data was not clearly conclusive (two patients were classified as possible UIP on the basis of HRCT and five as non-classifiable pulmonary fibrosis).

While entering data into *IPFdatabase* in the designated format, Siena's chest radiologist (Rad1) and pathologist (Path1) modified their historical interpretation in three and two cases, respectively. In particular, the specific *IPFdatabase* HRCT form prompted modification of interpretation regarding the presence of honeycombing in one case (previously possible UIP) and air-trapping in another two (previously both UIP). For the first patient final diagnosis remained IPF as pathology was UIP; the other two were previously classified as having IPF on the basis of the CT scan, no confident diagnosis was obtained with *IPFdatabase* (SLB histopathology was not available so these patients were deemed to have nonclassifiable pulmonary fibrosis). Regarding pathology-based interpretation, Path1 modified her interpretation in two cases: in both she reported significant inflammation otherwise interpreted as UIP. In both case final diagnosis did not change, one patient had rheumatoid arthritis based on serological and extrapulmonary symptoms (HRCT showed a possible UIP pattern). The other case was previously diagnosed with Possible IPF (inconsistent with UIP pattern at HRCT and UIP at histology): the different histological interpretation through *IPFdatabase* modified final diagnosis to suspected chronic HP, however no specific antigen exposure was reported.

Analysis of diagnostic power of *IPFdatabase* for the diagnosis of IPF, comparing final "virtual" diagnoses to historical diagnoses, revealed high accuracy (sensitivity 95.5% (84.8–99.4); specificity 96.2% (87.0–99.5); positive predictive value (PPV) 95.5% (84.8–99.4); negative predictive value (NPV) 96.2% (87.0–99.5); likelihood ratio 25.32) (Table 3). The number of patients who could not be diagnosed (HRCT not conclusive for UIP, no SLB available and no other data conclusive) lightly increased with *IPFdatabase* compared to previous diagnoses (from 5.1 to 7.2%), although difference was not statistically significant ($p = 0.76$).

There was internal consistency in the software and the interobservor agreement between the experts from the two centers was good (kappa 0.68 for both radiological and pathological interpretations). Interobserver agreement between the general and expert radiologists and the general and expert pathologists was initially low and increased with use of *IPFdatabase*: regarding the general radiologist, agreement with Rad1 and Rad2 was low without use of the software (kappa 0.18 and 0.14, respectively); using the IPFdatabase HRCT form, agreement improved significantly to 0.64 with Rad1 and 0.43 with Rad2. A similar effect was observed for the general pathologist, agreement was initially low (0.13 with Path1 and 0.08 with Path2) and increased after reviewing the data with the *IPFdatabase* histology form (0.59 with Path1 and 0.29 with Path2).

4. Discussion

The *IPFdatabase* was developed utilizing the current established IPF guidelines [1] to facilitate diagnosis of IPF by virtual means with the aim of increasing timely diagnoses of IPF and reducing the need for all patients suspected to have IPF to be seen for expert evaluation at tertiary centers for MDD. While software cannot replace MDD, it can increase application of IPF guidelines in the community and allow referral of the most complex cases to regional centers for MDD. Many software platforms have been proposed to facilitate clinical decision making, demonstrating successful reducing costs and improving patient outcomes [3].

Table 1
Clinical, physiological and serological data of the population (n = 98) to validate *IPFdatabase* at the University of Siena.

Age at diagnosis (years)	61.1 ± 8.5	**6MWT (n = 98)**	
Gender (male)	69.3%	• O2-tp (n, L/min)	37.7%,4.4 ± 2.9
Race (Caucasian)	97.8%	• Final SpO2	88.9 ± 4.3
BMI	27.1 ± 3.6	• Final Borg scale	4.3 ± 2.8
Smoke history	(50%)	• Walked distance (m)	263.4 ± 148.3
Pack/year	28.2 ± 20.8	**BAL (n = 38)**	
Sign & Symptoms at onset		• Macrophages %	64.3 ± 16.8
• Cough	68.3%	• Lymphocytes %	10.9 ± 8.0
• Dyspnoea	75.8%	• Neutrophils %	17.5 ± 18.6
• Digital clubbing	14.3%	• Eosinophils %	6.7 ± 6.0
• Crackles at auscultation	90.8%	• RCD4/CD8	1.2 ± 1.2
PFT (n = 98)		**Serology (n = 98)**	
• FVC (% pred.)	65.7 ± 21.3	• ANA	10.2%
• FEV1 (% pred.)	68.7 ± 23.5	• Anti-CCP	2%
• FEV1/VC	85.3 ± 19.2	• RF	2%
• RV (% pred.)	80.5 ± 24.9	• Anti DNA	0%
• TLC (% pred.)	67.8 ± 16.4	• SS-A	1%
• DLCO (% pred.) (n = 73)	43.0 ± 14.6	• SS-B	1%
• KCO (% pred.) (n = 73)	71.8 ± 19.9	• SCL-70	1%
ABG (n = 98)		• PM1	1%
• pH	7.42 ± 0.03	• Antisynthetase	1%
• pO2 (mmHg)	69.8 ± 12,8	**Pulmonary Hypertension assessment (n = 98)**	
• pCO2 (mmHg)	39.7 ± 5.3	• Echo sPAP mmHg	36.4 ± 12.4
• HCO3- (mmol/L)	22.9 ± 8.7	• % > 37 mmHg	42 pts, 42.8%
		• RHC mean PAP mmHg (n = 32)	23.6 ± 7.1
		• % > 25 mmHg	40.6%

Abbreviation: PFT pulmonary function tests; FVC Forced vital capacity; FEV1 Forced expiratory volume in the 1st second; RV residual volume; TLC total lung capacity; DLCO diffusing capacity of the lungs for carbon monoxide; KCO diffusing capacity of the lungs for carbon monoxide/alveolar volume; ABG arterial blood gas; 6MWT 6-minue walking test; BAL bronchoalveolar lavage; ANA antinuclear antibodies; ANTI-CCP Anti-cyclic citrullinated peptide; SCL 70 anti-topoisomerase I; RHC right heart catheterization.

Table 2
Diagnosis from *IPFdatabase* for 98 patients.

Diagnosis	Patients n (%)
Idiopathic pulmonary fibrosis (IPF)	43 (43.8)
Connective tissue disease associated ILD[a]	11 (11.2)
Familial pulmonary fibrosis	10 (10.2)
Hypersensitivity Pneumonitis	8 (8.2)
Nonspecific interstitial pneumonia	5 (5.1)
Possible IPF	4 (4.1)
Combined pulmonary fibrosis and emphysema	3 (3.1)
Nonclassifiable pulmonary fibrosis	3 (3.1)
Asbestosis	1
Chronic eosinophilic pneumonia	1
Bronchiolitis obliterans	1
Desquamative interstitial pneumonia	1
No final diagnosis	7 (7.1)

[a] Nine with rheumatoid arthritis (AR), one with mixed connective tissue disease (MCTD), one with undifferentiated connective tissue disease (UCTD).

We tested our new web-designed software demonstrating the ability to make an instant and accurate diagnosis of IPF ensuring the presence of typical features of IPF according to guidelines. Accuracy of the software was assessed by interobserver agreement evaluation between diagnoses generated by the software and prior diagnoses by MDD at a tertiary ILD Center (University of Siena), which radiological and pathological interpretations were furthermore validated by an independent Center for ILD (University of Washington), showing an internal consistency in the software when data was entered by two different experts (kappa 0.68 for both radiological and pathological interpretations). Clinical validation of our tool demonstrated high confidence in the diagnosis of IPF: sensitivity, specificity, PPV and NPV were higher than 95% when compared to historical diagnoses (in only 4/98 cases did final diagnosis by software differ) (Table 3).

Established guidelines provide criteria for IPF diagnosis with well-defined radiological and histopathological criteria for UIP and exclusion of other causes of ILD [1]. The guidelines strongly recommend MDD among experts considering both histopathology and HRCT features of UIP when making the diagnosis of IPF [1]. When conducted by an expert panel, MDD has led to frequent modification of ILD diagnosis and subsequent management and increased diagnostic confidence, particularly in patients previously diagnosed with IPF in whom diagnoses were retracted in favour of another ILD [16]. However, MDD among experts has several intrinsic limitations: it is time consuming and requires multidisciplinary experts in ILD and rare respiratory diseases to convene together. Also, not all patients suspected to have IPF can be physically and practically seen at referral centers and have clinical data discussed in MDD at these centers in a timely manner. The diagnosis of IPF utilizing *IPFdatabase* was accurate when the software was run by expert clinicians in ILD, actually reducing the need for the classical face-to-face MDDs.

The *IPFdatabase* did not reach a final diagnosis in 7/98 patients. This may be due to the intrinsic limitations of the guidelines, principally regarding lack of specific recommendations for patients with highly suspected IPF but with possible UIP (2 patients in this study) or inconsistent (5 patients in this study) HRCT patterns who cannot or refuse to undergo SLB for medical or other reasons. Such patients have therefore been identified by the software as those most likely to benefit from face to face MDD at an expert referral center.

The diagnostic power of *IPFdatabase* was also evaluated through a general radiologist and a general pathologist. The need for MDD as recommended in the 2011 guidelines for diagnosis of IPF in the community is a major challenge as not all patients suspected with IPF can be seen at centers with expertise in ILD [2,5]. A general radiologist and pathologist blindly reviewed all data with and without the *IPFdatabase* and their results were compared with interpretations by experts. Agreement with the two ILD experts from Siena and Washington Universities increased when they used the *IPFdatabase* (kappa increased from 0.18 to 0.64 with Rad1 and from 0.16 to 0.43 with Rad2 for radiological evaluation and from 0.13 to 0.59 with Path1 and from 0.08 to 0.29 with Path2 for pathology). We attributed this to the specific design of *IPFdatabase* forms for radiological and pathological evaluation as they mandate the specifications of the presence/absence of all UIP features and thus help direct focus on each feature proposed for

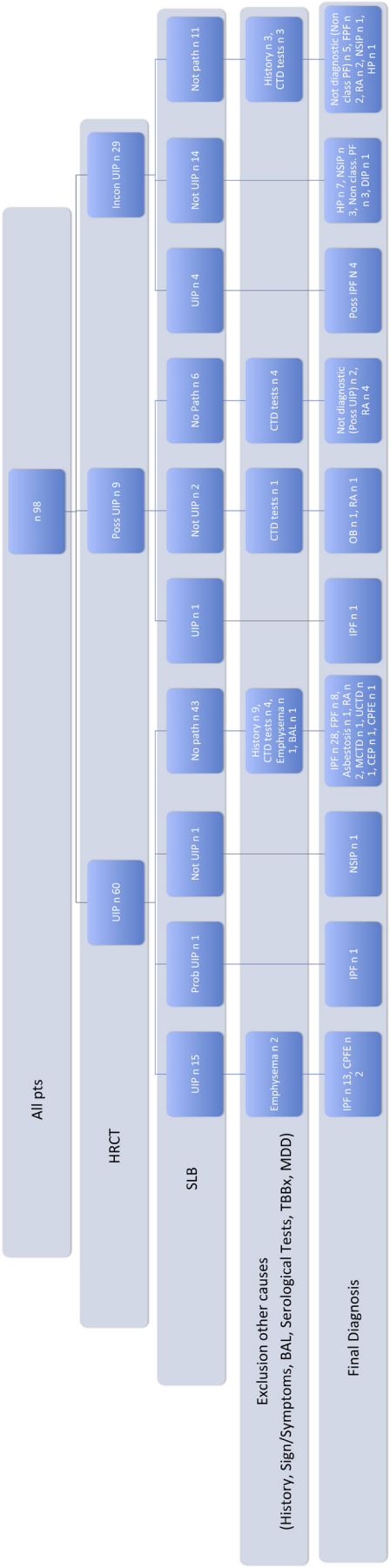

Fig. 2. The diagnostic algorithm of our population obtained by *IPFdatabase*, including radiological and histological features, serological and BAL findings and previous MDDs results to differentiate IPF from other interstitial lung diseases. Data collected during *IPFdatabase* validation at the University of Siena.

Table 3
Analysis of diagnostic power of *IPFdatabase*, comparing final diagnosis to historical MDD.

sensitivity	95.5% (84.8–99.4)
specificity	96.2% (87.0–99.5)
positive predictive value (PPV)	95.5% (84.8–99.4)
negative predictive value (NPV)	96.2% (87.0–99.5)
likelihood ratio	25.32

radiological and pathological assessment of IPF. Nevertheless, kappa value remained fair-to-moderate, confirming that IPF diagnosis is still challenging; specific HRCT and histological features are not easily identifiable by general physicians that included radiologists and pathologists. It is not our software's task to make the interpretation of the images. In our program the radiologists and pathologists must answer if there are/are absent some specific modifications referring to what reported in the guidelines.

Our results must be interpreted with some caution. While our software facilitated correct diagnosis of IPF in the majority of "typical and straightforward cases", we emphasize the need for direct face-to-face MDD and physical evaluation of the patient and the clinical data by experts in specialized ILD centers for correct diagnosis in cases where there is uncertainty and/or discordance between HRCT and histopathology.

Main limitations of the study are the relatively small number of patients enrolled with a diagnosis of chronic hypersensitivity pneumonitis (CHP) that it is considered one of the main differential diagnosis at CT and pathology of IPF. Patients with different pulmonary fibrotic disorders that could be representative of a common population afferent to a tertiary centers for ILDs have been included in the study and the percentage of patients with CHP is in keeping with our epidemiology in middle Italy - our patients are from this region (personal observation, unpublished data). In a retrospective small pilot study undertaken following the analyses of data set of the present study, we have utilized the *IPFdatabase* in 15 different patients with confirmed/known diagnosis of CHP and the radiologists interpreted the patterns as inconsistent (unpublished data). We are hopeful that when new clinical practice guideline for the diagnosis of CHP will become available, similar tools with software database can be developed and tested in prospective larger patients cohorts in multicenters.

The relative high number with pathology available (38.8%) is because we included all patients who had pathology available to test the ability of our software in both radiological and pathological interpretations. This is not an epidemiological study and we selected patients with different diagnosis able to test our software.

Other limits are the design of the study that did not include validation in a larger population of community providers and that did not take clinical pre-test probability into account. However, pre-test probability is expected to vary by provider experience and confidence and therefore cannot be measured in a standardized way and is not included in the software algorithm.

While *IPFdatabase* has limitations and needs to be validated at the community level, it has potential merits. The validation process of our tool demonstrated the ability of *IPFdatabase* to make a confident diagnosis of IPF in expert hands; it was designed using smart informatics technology so that it can be updated to new recommendations and guidelines recently released by international respiratory societies [17]. The platform can also be accessed by portable devices at the bedside. It can also be recommended to regional and national IPF registries for correct diagnosis of IPF and for educational purposes. Our software may also assist physicians in screening candidates for participation in IPF clinical trials.

In conclusion, *IPFdatabase* is a potentially useful tool for IPF diagnosis facilitating application of the current established clinical practice guidelines by experts and providers when considering a diagnosis of

IPF. We propose it as a new "diagnostic" tool for instant accurate diagnosis of IPF by virtual means for patients suspected to have IPF with typical clinical features and demographics. Thus, the need for MDDs and the number of referrals to regional expert centers can be restricted to atypical and complex cases, saving substantial time, costs and physical burden for patients. It also provides a framework for collecting homogeneous data, data sharing and foster collaboration among investigators for future studies. The software can be accessed with mobile devices so physicians can receive rapid feedback in daily practice and it can be easily updated to new recommendations and guidelines recently released by international respiratory societies for the diagnosis of IPF. Future study of IPFdatabase performance when used by community providers is warranted.

Authors contribution

David Bennett performed literature search, study design, software design, data collection, data analysis, data interpretation, coordinated the study and wrote the manuscript; Maria Antonietta Mazzei performed radiological data collection, data analysis and participated to data interpretation; Bridget Collins participated to paper writing; Elena Bargagli participated to paper writing; Sudhakar Pipavath participated to radiological data analysis validating radiological interpretation; Donatella Spina performed pathological data collection, data analysis and participated to data interpretation; Maria Lucia Valentini participated to data collection; Cesare Rinaldi participated to software design and programmed the software; Gloria Bettini participated to radiological data analysis; Alessandro Ginori participated to pathological data analysis; Paola Rottoli performed study design, data analysis, data interpretation, paper writing; Ganesh Raghu performed study design, data analysis, data interpretation, paper writing. All author are guarantor of the paper, taking responsibility for the integrity of the work as a whole.

Conflicts of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Appendix A. Supplementary data

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References

[1] G. Raghu, H.R. Collard, J.J. Egan, F.J. Martinez, J. Behr, K.K. Brown, T.V. Colby, J.F. Cordier, K.R. Flaherty, J.A. Lasky, D.A. Lynch, J.H. Ryu, J.J. Swigris, A.U. Wells, J. Ancochea, D. Bouros, C. Carvalho, U. Costabel, M. Ebina, D.M. Hansell, T. Johkoh, D.S. Kim, T.E. King Jr., Y. Kondoh, J. Myers, N.L. Müller, A.G. Nicholson, L. Richeldi, M. Selman, R.F. Dudden, B.S. Griss, S.L. Protzko, H.J. Schünemann, ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, Am. J. Respir. Crit. Care Med. 183 (6) (2011) 788–824 Mar 15.

[2] S.L. Walsh, A.U. Wells, S.R. Desai, V. Poletti, S. Piciucchi, A. Dubini, H. Nunes, D. Valeyre, P.Y. Brillet, M. Kambouchner, A. Morais, J.M. Pereira, C.S. Moura, J.C. Grutters, D.A. van den Heuvel, H.W. van Es, M.F. van Oosterhout, C.A. Seldenrijk, E. Bendstrup, F. Rasmussen, L.B. Madsen, B. Gooptu, S. Pomplun, H. Taniguchi, J. Fukuoka, T. Johkoh, A.G. Nicholson, C. Sayer, L. Edmunds, J. Jacob, M.A. Kokosi, J.L. Myers, K.R. Flaherty, D.M. Hansell, Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study, Lancet Respir Med 4 (7) (2016) 557–565 Jul.

[3] A.I. Martinez-Franco, M. Sanchez-Mendiola, J.J. Mazon-Ramirez, I. Hernandez-Torres, C. Rivero-Lopez, T. Spicer, A. Martinez-Gonzalez, Diagnostic accuracy in Family Medicine residents using a clinical decision support system (DXplain): a randomized-controlled trial, Diagnosis (Berl) 5 (2) (2018) 71–76 Jun 27.

[4] G. Raghu, J. Behr, K.K. Brown, J.J. Egan, S.M. Kawut, K.R. Flaherty, F.J. Martinez, S.D. Nathan, A.U. Wells, H.R. Collard, U. Costabel, L. Richeldi, J. de Andrade, N. Khalil, L.D. Morrison, D.J. Lederer, L. Shao, X. Li, P.S. Pedersen, A.B. Montgomery, J.W. Chien, T.G. O'RiordanARTEMIS-IPF Investigators*, Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial, Ann. Intern. Med. 158 (9) (2013) 641–649 May 7.

[5] T.E. King Jr., W.Z. Bradford, S. Castro-Bernardini, E.A. Fagan, I. Glaspole, M.K. Glassberg, E. Gorina, P.M. Hopkins, D. Kardatzke, L. Lancaster, D.J. Lederer, S.D. Nathan, C.A. Pereira, S.A. Sahn, R. Sussman, J.J. Swigris, P.W. NobleASCEND Study Group, A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis, N. Engl. J. Med. 370 (22) (2014) 2083–2092 May 29.

[6] P.W. Noble, C. Albera, W.Z. Bradford, U. Costabel, M.K. Glassberg, D. Kardatzke, T.E. King Jr., L. Lancaster, S.A. Sahn, J. Szwarcberg, D. Valeyre, R.M. du BoisCAPACITY Study Group, Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials, Lancet 377 (9779) (2011) 1760–1769 May 21.

[7] G. Raghu, K.K. Brown, H.R. Collard, V. Cottin, K.F. Gibson, R.J. Kaner, D.J. Lederer, F.J. Martinez, P.W. Noble, J.W. Song, A.U. Wells, T.P. Whelan, W. Wuyts, E. Moreau, S.D. Patterson, V. Smith, S. Bayly, J.W. Chien, Q. Gong, J.J. Zhang, T.G. O'Riordan, Efficacy of simtuzumab versus placebo in patients with idiopathic pulmonary fibrosis: a randomised, double-blind, controlled, phase 2 trial, Lancet Respir Med 5 (1) (2017) 22–32 Jan.

[8] I. Noth, K.J. Anstrom, S.B. Calvert, J. de Andrade, K.R. Flaherty, C. Glazer, R.J. Kaner, M.A. Olman, Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet). A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis, Am. J. Respir. Crit. Care Med. 186 (1) (2012) 88–95 Jul 1.

[9] K. Raimundo, E. Chang, M.S. Broder, K. Alexander, J. Zazzali, J.J. Swigris, Clinical and economic burden of idiopathic pulmonary fibrosis: a retrospective cohort study, BMC Pulm. Med. 16 (2016) 2 Jan 5.

[10] G. Raghu, M. Selman, Nintedanib and pirfenidone. New antifibrotic treatments indicated for idiopathic pulmonary fibrosis offer hopes and raises questions, Am. J. Respir. Crit. Care Med. 191 (3) (2015) 252–254 Feb 1.

[11] G. Leuschner, F. Stocker, T. Veit, N. Kneidinger, H. Winter, R. Schramm, T. Weig, S. Matthes, F. Ceelen, P. Arnold, D. Munker, F. Klenner, R. Hatz, M. Frankenberger, J. Behr, C. Neurohr, Outcome of lung transplantation in idiopathic pulmonary fibrosis with previous anti-fibrotic therapy, J. Heart Lung Transplant. (2017) 31886–31887 Jul 5. pii: S1053-2498(17).

[12] D. Bennett, M.L. Valentini, D. Valecchi, E. Bargagli, M.A. Mazzei, G. Bettini, C. Rinaldi, S. Pipavath, G. Raghu, P. Rottoli, IPFdatabase – A New Tool for a Correct Application of Idiopathic Pulmonary Fibrosis Guidelines, ERS International Congress, Munich, 2014.

[13] L. Zhang, C. Zhang, F. Dong, Q. Song, F. Chi, L. Liu, Y. Wang, C. Che, Combined pulmonary fibrosis and emphysema: a retrospective analysis of clinical characteristics, treatment and prognosis, BMC Pulm. Med. 16 (1) (2016) 137 Nov 3.

[14] J.S. Smith, D. Gorbett, J. Mueller, R. Perez, C.J. Daniels, Pulmonary hypertension and idiopathic pulmonary fibrosis: a dastardly duo, Am. J. Med. Sci. 346 (3) (2013) 221–225 Sep.

[15] D. Bennett, M.A. Mazzei, N.C. Squitieri, E. Bargagli, R.M. Refini, A. Fossi, L. Volterrani, P. Rottoli, Familial pulmonary fibrosis: clinical and radiological characteristics and progression analysis in different high resolution-CT patterns, Respir. Med. 126 (2017) 75–83 May.

[16] H.E. Jo, I.N. Glaspole, K.C. Levin, S.R. McCormack, A.M. Mahar, W.A. Cooper, R. Cameron, S.J. Ellis, A.M. Cottee, S.E. Webster, L.K. Troy, P.J. Torzillo, P. Corte, K.M. Symons, N. Taylor, T.J. Corte, Clinical impact of the interstitial lung disease multidisciplinary service, Respirology 21 (8) (2016) 1438–1444 Nov.

[17] G. Raghu, M. Remy-Jardin, J.L. Myers, L. Richeldi, C.J. Ryerson, D.J. Lederer, J. Behr, V. Cottin, S.K. Danoff, F. Morell, K.R. Flaherty, A. Wells, F.J. Martinez, A. Azuma, T.J. Bice, D. Bouros, K.K. Brown, H.R. Collard, A. Duggal, L. Galvin, Y. Inoue, R.G. Jenkins, T. Johkoh, E.A. Kazerooni, M. Kitaichi, S.L. Knight, G. Mansour, A.G. Nicholson, S.N.J. Pipavath, I. Buendía-Roldán, M. Selman, W.D. Travis, S. Walsh, K.C. Wilson, American thoracic society, european respiratory society, Japanese respiratory society, and Latin American thoracic society. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline, Am. J. Respir. Crit. Care Med. 198 (5) (2018) e44–e68 Sep 1.