Nationwide cloud-based integrated database of idiopathic interstitial pneumonias for multidisciplinary discussion

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Online Data Supplement

METHODS

Subject

The development of the nationwide cloud-based database for patients with idiopathic interstitial pneumonias (IIPs) was undertaken by the Diffuse Lung Diseases Research Group from the Ministry of Health, Labor and Welfare, Japan. The Japanese Respiratory Society certifies institutions and training programs. Each institution has multiple board-certified specialists, including those certified as trainers who have passed an accreditation examination. Physicians wanting to specialize in pulmonary medicine must train at a certified institution for at least 3 years. We first administered a survey of 707 certified institutions of the Japanese Respiratory Society to assess the number of patients diagnosed with IIPs in each institution from April 2009 to March 2014. One hundred and fifty-nine institutions replied to the survey. There were 13,598 patients with a diagnosis of IIPs, of whom 1,311 had biopsy-proven IIPs. Of the 159 responding institutions, 39 agreed to the study proposal and participated in the present study. The study subjects were patients diagnosed with IIPs who had undergone chest high-resolution computed tomography (HRCT) and surgical lung biopsy from April 2009 to March 2014 in these institutions. This retrospective study was approved by the Institutional Review Board of the Hamamatsu University School of Medicine (approval number E14-360) and the respective ethics committees of each participating institution. The Institutional Review Board waived patient approval or informed consent because the study involved a retrospective review of patient records.

Collection of clinical, radiologic, and pathological data

A case identification number was allocated to each patient for de-identification purposes. The patients' clinical and HRCT data within 3 months before surgical lung biopsy were retrospectively collected. The clinical data, including symptoms, environmental exposures,

smoking history, family history, comorbid illnesses, physical examination findings, blood test results, arterial blood gas analysis (or SpO_2), pulmonary function tests (FVC, FEV1, DLCO), 6-minute walk tests, and treatment were extracted from the medical records as text data files using commercially available software (Filemaker: FileMaker, Inc. Santa Clara, CA, USA). Data from bronchoscopy, including bronchoalveolar lavage, were collected if it had been performed. Results of arterial blood gas analysis, pulmonary function testing, and 6-minute walk tests 1 year after lung biopsy were obtained if the data were avilable. Treatment after lung biopsy was also recorded. The diagnosis at each institution was reported as the institutional diagnosis. These diagnoses were generally made by attending chest physicians at each institution based on their clinical assessment of the patient and review of radiology and pathology reports. In most cases in which an IIP was diagnosed, these physicians would not have discussed the case with a thoracic radiologist or pulmonary pathologist, as there are very few such specialists in Japan. Therefore, most pulmonologists would not have the opportunity for multidisciplinary discussion (MDD) in person. We did not survey in detail how institutional diagnoses were made, but we assume that MDD was not performed for the majority of the cases. HRCT images were obtained as digital imaging and communications in medicine (DICOM) files. Clinical data files and HRCT DICOM files were preserved on CD-ROM at each institution and collected at Hamamatsu University School of Medicine. Histology specimens from the lung biopsies were collected on glass slides (at least 2 slides for each specimen) and stained with hematoxylin-eosin or elastica van Gieson at Hamamatsu University School of Medicine (one slide with each stain for each specimen). They were then digitized by whole slide image instruments using formats of Philips Digital Pathology Solutions (Philips, Amsterdam, Netherlands). The vital status of the patients was ascertained on October 2017 for survival analysis.

Development of the cloud-based integrated database including clinical, radiologic, and pathological data

The method for developing the database is shown in Figure 1. The web viewer system and data servers were provided by Esite Healthcare Co., Ltd (Tokyo, Japan). The data center

included three servers, one each for clinical, radiologic, and pathological data. The clinical data files, HRCT DICOM files, and biopsy specimen slide images of were uploaded to each web server separately. The DICOM images were displayed using the XTREK Web View software (J-MAC SYSTEM, Inc. Sapporo, Japan) and the whole slide images with the Image Managing System (Philips, Amsterdam, Netherlands). In order to construct a virtually integrated database, the clinical, radiologic, and pathological data on the separate servers were interlinked by the respective case identification numbers. HTTP and Referer were set to access the clinical data server through the Internet. A log-in ID and password were configured to access the clinical data server. Links to access the DICOM and whole slide image files were placed on the web page of the clinical data for each case.

Conducting web-based MDD using the cloud-based integrated database

The database allowed user access to all three types of data for the enrolled cases through the Internet regardless of a user's physical location. We devised an MDD model using the cloud-based database. A clinician, radiologist, and pathologist, all experts in interstitial lung diease, each used the database to examine the case records by themselves, after which they discussed the case via video-conferencing (Arcstar Web Conferencing: NTT Communications Co., Ltd, Tokyo, Japan), leading to a multidisciplinary diagnosis (Figure 1). The diagnosis made by MDD was categorized according to the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) IPF statements [1] and ATS/ERS IIPs classification [2]. The categories included idiopathic pulmonary fibrosis, idiopathic nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, desquamative interstitial pneumonia/respiratory bronchiolitis-associated interstitial lung disease, acute interstitial pneumonia, lymphoid interstitial pneumonia, idiopathic pleuroparenchymal fibroelastosis, unclassifiable IIPs, and other diseases (not IIPs). To facilitate recording of the diagnosis, a data input interface was built into the cloud-based database system. The specialists performing web-based MDD for

the study included pulmonologists (K. K, C. S., H. K., and N. E.), radiologists (R. E., H. S., T. I., S. M., and H. S.), and pathologists (M. H., T. T., Y. T., S. K., and M. K.). All have a minimum of 10 years of experience in the diagnosis of interstitial lung diseases including IIPs, and they are each currently working in university hospitals or interstitial lung disease centers. To perform web-based MDDs for the more than 500 cases enrolled in the cloud-based database, we had four MDD teams, each of which consisted of a pulmonologist, a radiologist, and a pathologist. When the MDD was conducted, the three participants were blinded to the institutional diagnosis. Rheumatologists or occupational medicine specialists did not participate in the MDDs. We initially examined inter-team agreement on the first-choice diagnosis for the first 15 cases in the database using Cohen's kappa coefficient (κ). Agreement for any diagnosis was moderate ($\kappa = 0.55$), while that for a diagnosis of IPF was good ($\kappa = 0.69$). Each team conducted an MDD for about 130 cases.

Survival analysis

Survival analyses of the enrolled patients were performed for both the institutional and MDD diagnoses, The cumulative survival rates were calculated using the Kaplan-Meier method. The observation period was calculated from the date of the first visit to each institution for an IIP to the last date of contact or time to death. The log-rank test was employed to compare survival between each IIP diagnostic entity. To control for the family-wise error rate, p values in multiple comparisons were adjusted using Holm's method. Cox proportional hazard models were employed to identify variables associated with survival. To compare prognostic discrimination between institutional and MDD diagnoses, we determined Harrell C-indexes for both [3, 4]. Statistical analyses were performed using commercially available software (JMP version 9.0: SAS Institute, Inc., Cary, NC, USA and R version 3.4.3: The R Foundation for Statistical Computing, Vienna, Austria). A p value <0.05 was considered statistically significant.

References

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Table E1. Survival analysis of IIP entities based on MDD diagnosis by multivariate Cox proportional hazard regression analysis

Unclassifiable IIPs and iNSIP

	HR	95% CI	p value
Age (years)	1.03	0.997–1.070	0.07
%FVC (%)	0.982	0.964–0.900	0.04
Unclassifiable IIPs vs. iNSIP	3.73	1.33–15.5	0.01

IPF and Unclassifiable IIPs

	HR	95% CI	p value
Age (years)	1.05	1.03–1.08	< 0.0001
%FVC (%)	0.976	0.966–0.987	< 0.0001
IPF vs. unclassifiable IIPs	2.11	1.43–3.17	0.0001

iPPFE and IPF

	HR	95% CI	p value
Age (years)	1.08	1.04–1.11	< 0.0001
%FVC (%)	0.974	0.962–0.986	< 0.0001
iPPFE vs. IPF	2.24	1.09–4.22	0.03

IIP: idiopathic interstitial pneumonia; FVC: forced vital capacity; iNSIP: idiopathic non-specific interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; iPPFE: idiopathic pleuroparenchymal fibroelastosis.

Figure legends

Figure E1. Web page showing the cloud-based integrated database

Users could click on (A) the 'list of enrolled cases,' (B) 'display' to see the data for each case, or (C) 'DICOM' and 'pathological data' to view the high-resolution computed tomography images and whole slide images, respectively.

Figure E2. Clinical data on the portal site

(A) Diagnosis in each hospital, (B) patient background, (C) findings on surgical biopsy, symptoms and signs, autoimmune features, autoantibodies, bronchoscopy, and diagnosis after surgical lung biopsy.

Figure E3. Clinical data on the portal site (laboratory findings)

Figure E4. Clinical data on the portal site (treatment)

Figure E5. Proportion of IIP disease entities of MDD diagnoses in institutional diagnoses

Figure E6. Proportion of IIP disease entities of institutional diagnoses in MDD diagnoses

Figure E7. Major causes of unclassifiable IIPs for the 168 patients with MDD diagnosis of unclassifiable IIPs

(1) inadequate clinical, radiologic, or pathologic data

(2) major discordance between clinical, radiologic, and pathologic findings that may occur in the following situations:

(2a) previous therapy resulting in substantial alteration of radiologic or histologic findings.

(2b) new entity, or unusual variant of recognized entity, not adequately characterized by the current American Thoracic Society/European Respiratory Society classification.

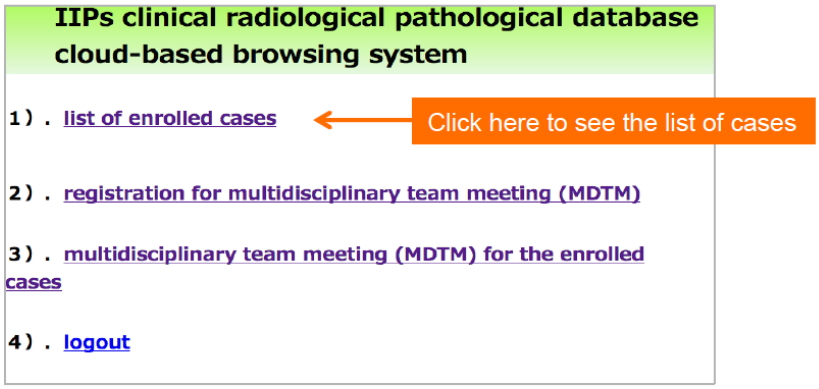
(2c) multiple high-resolution computed tomography and/or pathologic patterns that may be encountered in patients with idiopathic interstitial pneumonia.

(3) others reasons

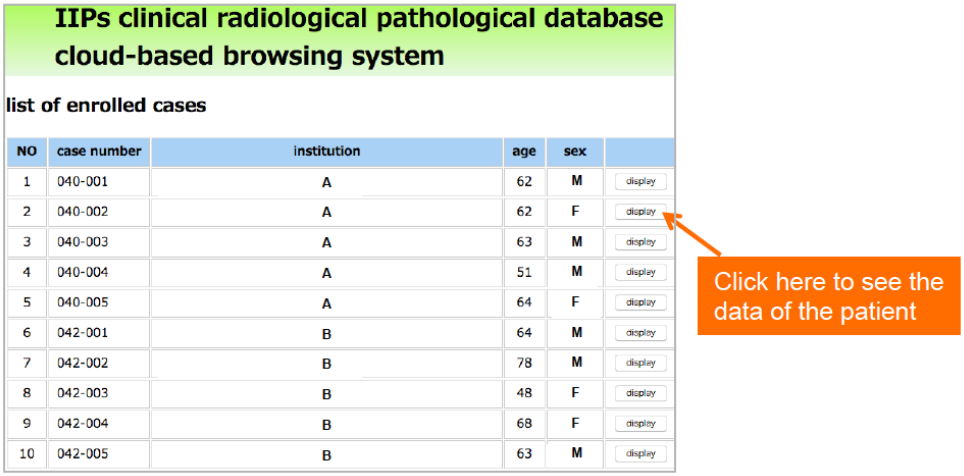
Figure E8. Survival curves for patients in the cohort subdivided by pulmonologist diagnoses, radiologist diagnoses and pathorogist diagnoses

Figure E1

A.



B.



C.

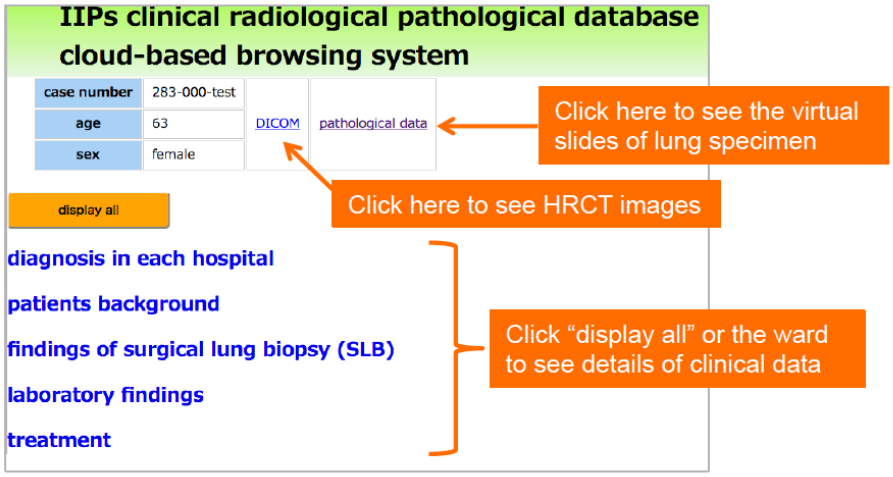


Figure E2

A.

diagnosis in each hospital

final diagnosis	NSIP
final diagnosis (other)	
date of outcome	2014/07/03
outcome	alive
outcome (other)	changing hospital
cause of death	
cause of death (other)	

B.

patients background

reason for hospital visit	find at the operation for thyroid cancer
symptom; cough	-
symptom; sputum	+
dyspnea during effort (mMRC)	NA
form of onset	chronic
smoking history	never
smoking history; duration	
smoking history; number of cigarettes / day	
family history of interstitial lung diseases	-
if yes, describe detail	
inhalation history of dust	-
if yes, describe detail	
other	

C.

findings of surgical lung biopsy (SLB)

date	2012/07/10
site of biopsy	Rt S3, Rt S8
pathological diagnosis	NSIP

clinical symptons of autoimmune features

mechanics hands	-
distal digital tip ulceration	-
inflammatory arthritis or polyarticular morning joint stiffness	-
palmar telangiectasia	-
Raynaud's phenomenon	-
unexplained digital edema	-
unexplained fixed rash on the digital extensor surfaces (Gottron's sign)	-
dry eyes or dry mouth	- -
other	

autoantibody

date	2012/06/25
rheumatoid factor	-
antinuclear antibody (ANA)	+
ANA; fold	40
ANA; pattern	speckled
anti-double stranded DNA	-
anti-Smith	-
anti-SS-A	-
anti-SS-B	-
anti-Scl-70	-
anti-RNP	-
anti-centromere	-
anti-Jo-1	-
anti-aminoacyl-tRNA Synthetase (ARS)	-
anti-cyclic citrullinated peptide (CCP)	-
anti-PM-Scl	NA

bronchoscopy

performed or not performed	performed
date	2012/07/02
bronchoalveolar lavage: recovery rate	60
total cell count	0.19
AM (%)	91.4
Lym (%)	6
Neut (%)	2.2
Eos (%)	0.4
CD4/CD8	0.66

diagnosis after surgical lung biopsy (MDD)

findings	NSIP

Figure E3

laboratory findings

arterial blood gas analysis

		findings of surgical lung biopsy (SLB)
arterial blood gas analysis	performed or not performed	
	date	07 2 2012 12:00AM
	condition	room air
	O2 inhalation	
	PaCO2 (Torr)	45
	PaO2 (Torr)	64
SpO2	performed or not performed	
	date	
	SpO2%	97
	condition	
	O2 inhalation	

serum markers

	findings of surgical lung biopsy (SLB)
performed or not performed	
date	2012/07/02
KL-6 (U/ml)	3200
SP-D (ng/ml)	205
LDH (IU/l)	189

pulmonary function tests

	findings of surgical lung biopsy (SLB)
performed or not performed	performed
date	2012/07/02
FVC (L)	2.7
%FVC (%)	102.5
FEV1L	2.23
%FEV1%	112

lung diffusing capacity test

	findings of surgical lung biopsy (SLB)
performed or not performed	performed
date	2012/07/02
DLco (ml/min/mmHg)	18.35
%DLco (%)	111

6 minute walk test

	findings of surgical lung biopsy (SLB)
performed or not performed	performed
date	2012/07/02
walk distance (m)	532
minimun SpO2 (%)	93

Figure E4

treatment

treatment before surgical lung biopsy (data not performed)

performed or not performed	not performed
date	
treatment	
corticosteroid + immunosuppressant	
corticosteroid + immunosuppressant; other	
anti-fibrotic agents	

treatment after surgical lung biopsy (data perfomed)

performed or not performed	perfomed
date	2012/08/10
treatment	corticosteroid
corticosteroid + immunosuppressant	
corticosteroid + immunosuppressant; other	
anti-fibrotic agents	

2nd line trreatment (data not performed)

performed or not performed	not performed
date	
treatment	
corticosteroid + immunosuppressant	
corticosteroid + immunosuppressant; other	
anti-fibrotic agents	

Figure E5

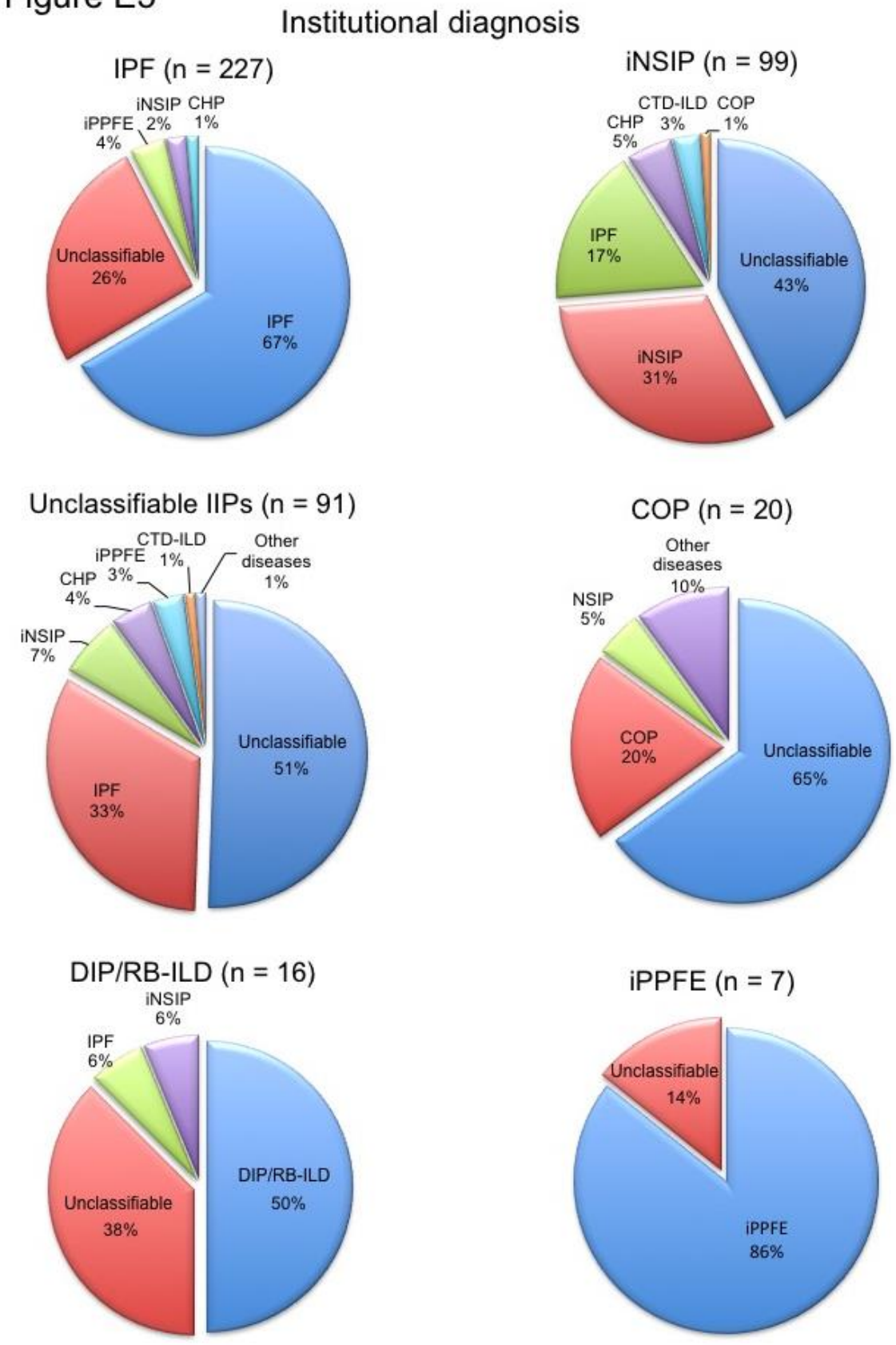

Institutional diagnosis
IPF (n = 227)
iNSIP 2%
CHP 1%
iPPFE 4%
Unclassifiable 26%
IPF 67%
iNSIP (n = 99)
CTD-ILD 3%
COP 1%
CHP 5%
IPF 17%
Unclassifiable 43%
iNSIP 31%
Unclassifiable IIPs (n = 91)
CTD-ILD 1%
Other diseases 1%
iPPFE 3%
CHP 4%
iNSIP 7%
Unclassifiable 51%
IPF 33%
COP (n = 20)
Other diseases 10%
NSIP 5%
COP 20%
Unclassifiable 65%
DIP/RB-ILD (n = 16)
iNSIP 6%
IPF 6%
Unclassifiable 38%
DIP/RB-ILD 50%
iPPFE (n = 7)
Unclassifiable 14%
iPPFE 86%

Figure E6

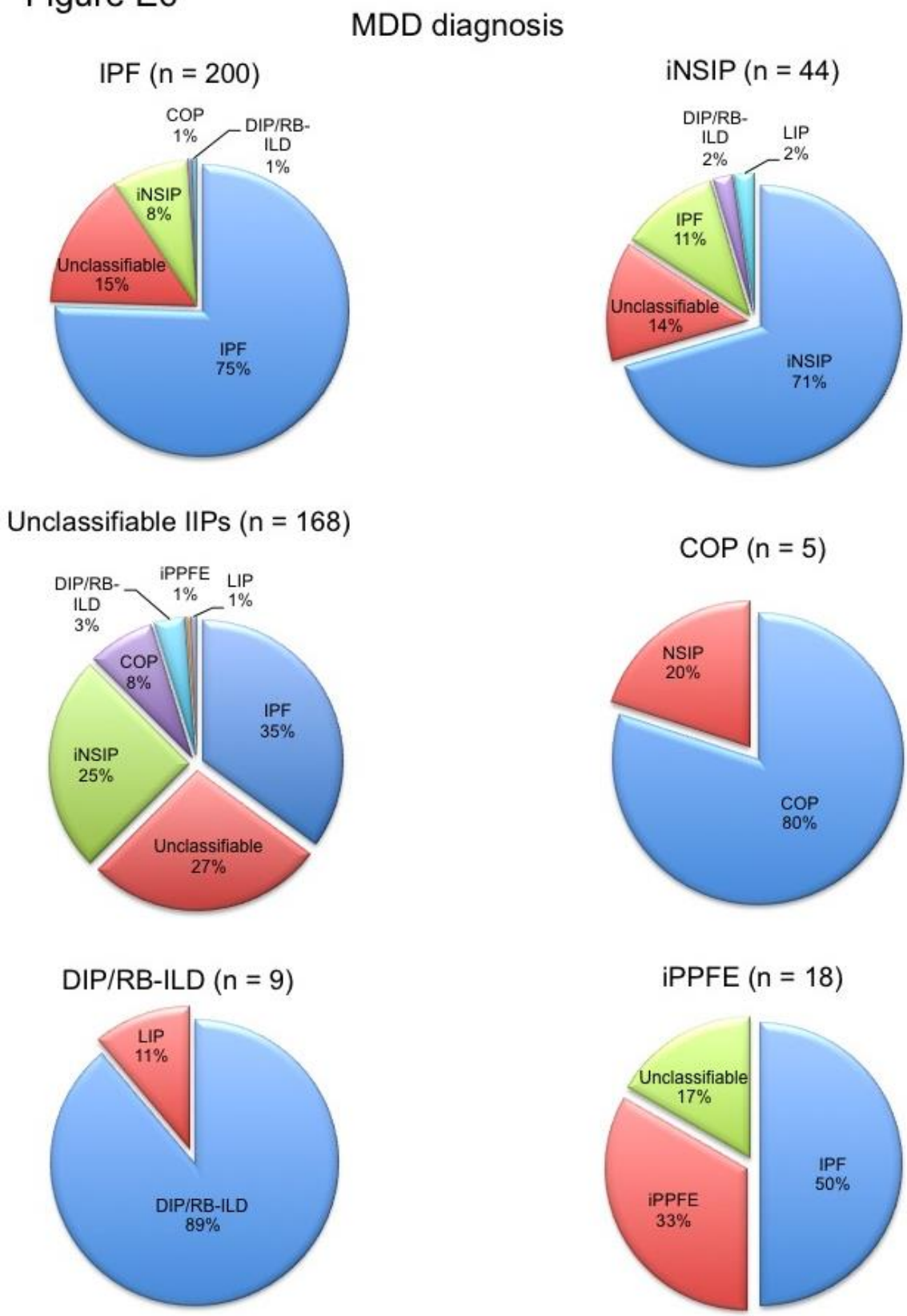

MDD diagnosis
IPF (n = 200)
COP 1%
DIP/RB-ILD 1%
iNSIP 8%
Unclassifiable 15%
IPF 75%
iNSIP (n = 44)
DIP/RB-ILD 2%
LIP 2%
IPF 11%
Unclassifiable 14%
iNSIP 71%
Unclassifiable IIPs (n = 168)
DIP/RB-ILD 3%
iPPFE 1%
LIP 1%
COP 8%
iNSIP 25%
IPF 35%
Unclassifiable 27%
COP (n = 5)
NSIP 20%
COP 80%
DIP/RB-ILD (n = 9)
LIP 11%
DIP/RB-ILD 89%
iPPFE (n = 18)
Unclassifiable 17%
iPPFE 33%
IPF 50%

Figure E7

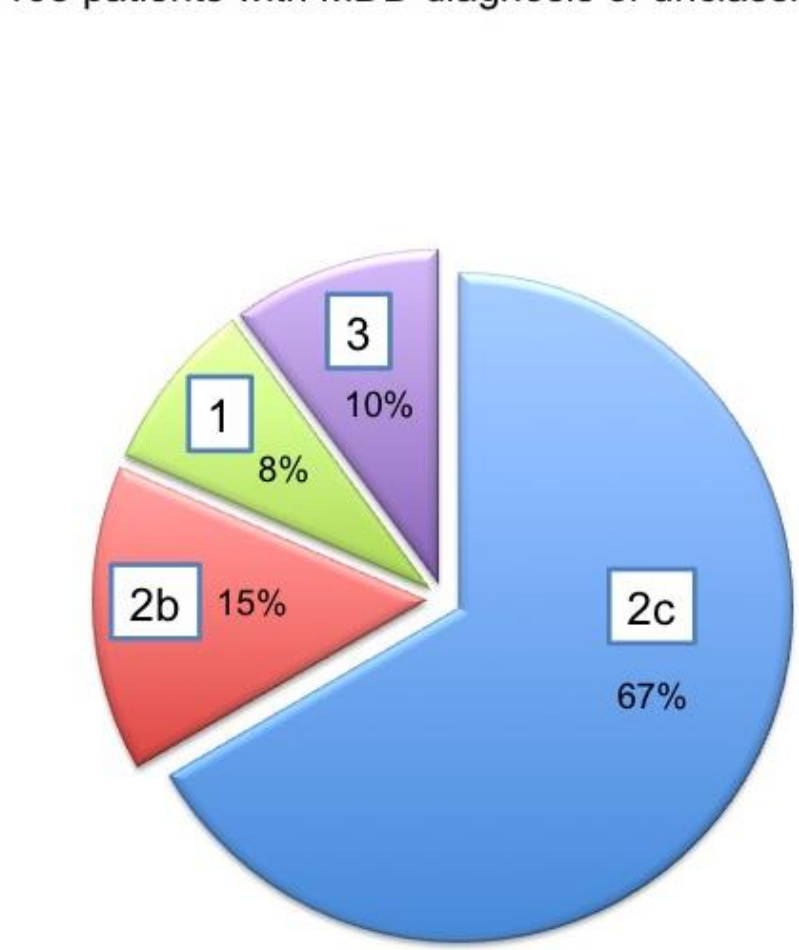
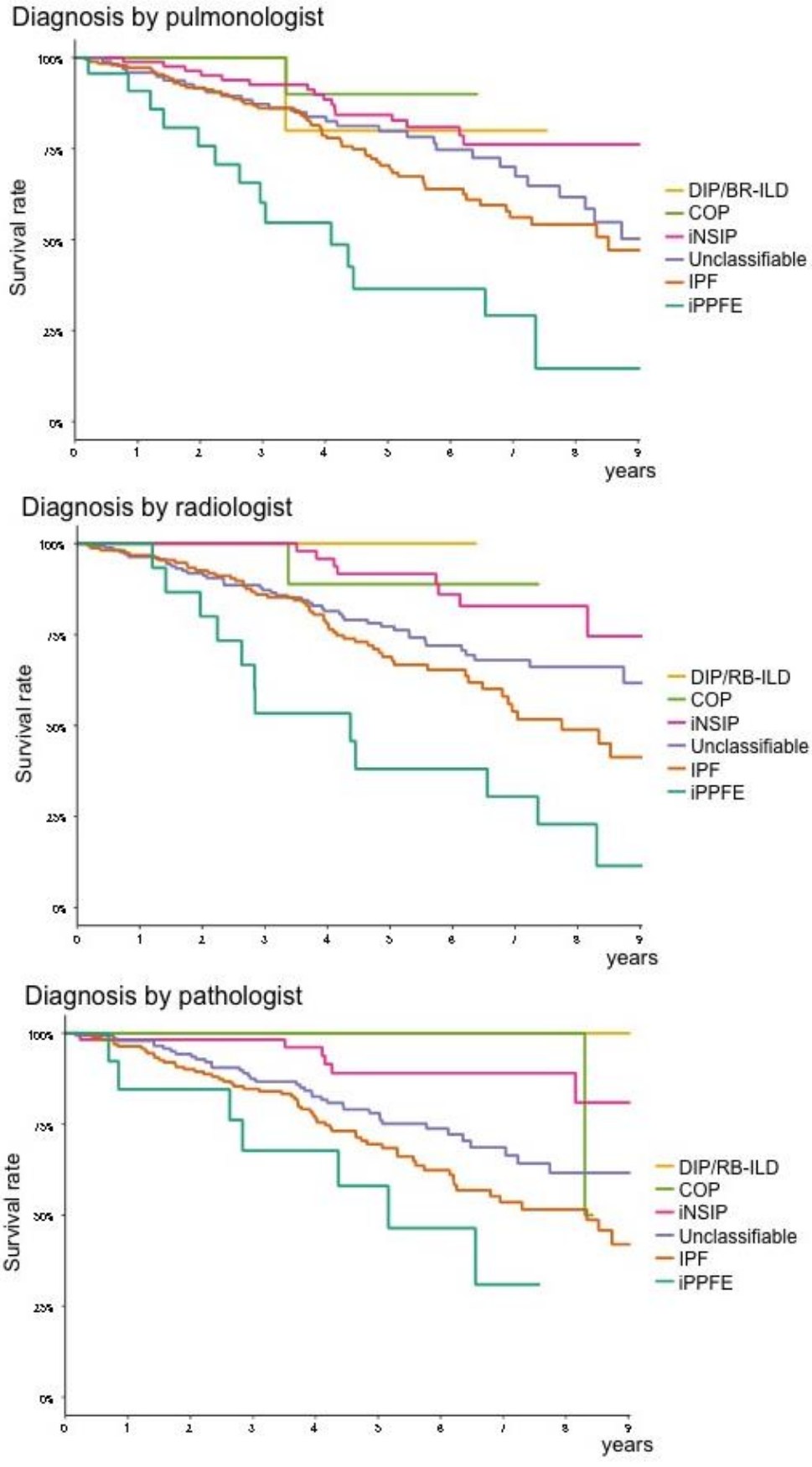

168 patients with MDD diagnosis of unclassifiable IIPs
3
10%
1
8%
2b
15%
2c
67%

Figure E8


Diagnosis by pulmonologist
Survival rate
100%
75%
50%
25%
0%
0
1
2
3
4
5
6
7
8
9
years
DIP/BR-ILD
COP
iNSIP
Unclassifiable
IPF
iPPFE
Diagnosis by radiologist
Survival rate
years
DIP/RB-ILD
COP
iNSIP
Unclassifiable
IPF
iPPFE
Diagnosis by pathologist
Survival rate
years
DIP/RB-ILD
COP
iNSIP
Unclassifiable
IPF
iPPFE