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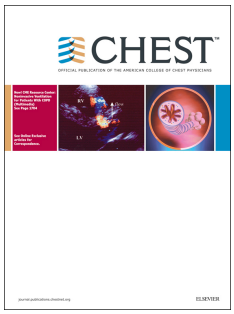

Diagnostic ability of a dynamic multidisciplinary discussion in Interstitial Lung Diseases: a retrospective observational study of 938 cases

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Diagnostic ability of a dynamic multidisciplinary discussion in Interstitial Lung Diseases: a retrospective observational study of 938 cases.

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Diagnostic ability of a MDD in ILD

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Competing Interests

Dr Meert, Dr Yserbyt, Prof Dr Verschakelen, Prof Dr Verbeken, Prof Dr De Langhe, Dr Lenaerts, Prof Dr Nemery, Prof Dr Van Raemdonck and Prof Dr Verleden have nothing to disclose.

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Abstract

Background: The advice of a dynamic multidisciplinary discussion (MDD) is believed to be important in the diagnosis of interstitial lung diseases (ILD). However, to what extent MDD diagnoses differ from the preliminary diagnoses before formal work-up and MDD (preMDD diagnoses), is still insufficiently studied.

Methods: We compared preMDD and MDD diagnoses in patients discussed at the Leuven University Hospitals MDD between January 2005 and December 2015.

Results: Of 938 consecutive patients discussed in MDD, 755 (80.5%) received a specific diagnosis. From the 183 patients with unclassifiable ILD, 150 patients (16.0%) received suggestions concerning further investigations to establish a definite diagnosis. In 191 patients (41.9% of patients with a preMDD diagnosis), the MDD changed the diagnosis. In 384 cases (79.5% of patients without preMDD diagnosis), MDD provided a diagnosis where the referring physician did not. MDD diagnosis showed a trend towards better prognostic discrimination between IPF and other ILDs compared to preMDD diagnosis (Harrell's c-index 0.666 vs 0.631, p-value 0.08), which was particularly clear in patients with a discordant MDD and preMDD diagnosis (HR 2.68 vs 0.84, p-values 0.012 vs 0.768).

Conclusions: The MDD provided a definite diagnosis in 80.5% of presented cases, suggesting further investigations in almost all others. Given the high rate of patients without preMDD diagnosis, the rate of change in preMDD diagnoses (41.9% of patients with a preMDD diagnosis) probably is an underestimation. Together with the better prognostic discrimination between ILDs by the MDD, this indicates the added value of MDD in ILD.

Abbreviations list

MDD = dynamic multidisciplinary discussion; ILD = interstitial lung diseases; preMDD = preliminary diagnosis before formal work-up and MDD; HRCT= high-resolution computed tomography; CTD-ILD = connective tissue disease related ILD; BAL = broncho-alveolar lavage; IPF = Idiopathic Pulmonary Fibrosis; NSIP = Non-specific Interstitial Pneumonia; HP = Hypersensitivity Pneumonitis; COP = Cryptogenic Organizing Pneumonia, RB-ILD = Respiratory Bronchiolitis Interstitial Lung Disease; DIP = Desquamative Interstitial Pneumonia; IIP = Idiopathic Interstitial Pneumonia; HR = hazard ratio

Main text

Introduction

Classification and diagnosis in patients with ILD is often difficult, due to the broad differential diagnosis[1,2], the absence of robust diagnostic criteria for some ILDs[3,4], and a limited ability to differentiate specific ILD entities based on clinical data[3,5–7], radiology[8–10], or histopathology alone[11,12], reflected by high interobserver variability[13–15]. Accurate diagnosis is critically important because of prognostic and therapeutic implications[16–21]. Therefore international guidelines emphasized the importance of a dynamic multidisciplinary diagnostic process[22], in which expert ILD clinicians, radiologists, and pathologists integrate all available clinical data, laboratory results, high-resolution computed tomography (HRCT) findings, and lung biopsy (when performed).

Evidence in favor of this approach has been emerging in recent years. Flaherty et al. demonstrated a better outcome prediction when histopathology and HRCT findings were reconciled[23]. Following the landmark paper of Walsh et al. providing evidence of low interobserver variability between MDD performed in different centers for IPF and connective tissue disease-related ILD (CTD-ILD) (kappa 0.7), the central role of MDD in ILD diagnosis seems indisputable[24]. Recently, multiple papers observed an important discordance between referring diagnosis and MDD diagnosis[25–27].

However, it is unclear in what proportion of cases a confident diagnosis can be made after formal work-up and MDD in a real-life setting; and to what extent MDD alters the diagnosis when compared to the preliminary diagnosis made at the time of referral. Furthermore, MDD diagnosis validation based on prognosis is lacking in most MDD literature.

In this retrospective study, we analyzed data of all patients presented at the University Hospitals Leuven MDD between January 2005 and December 2015. Our study has three main aims: 1) to ascertain the number of cases where a final diagnosis was obtained after work-up and MDD expert discussion (“diagnostic ability”), 2) to assess the proportion of cases where preMDD diagnosis was changed after formal work-up and discussion (“comparison with preMDD diagnosis”) and 3) to validate MDD diagnosis by determining the survival separation between IPF and other diagnoses in preMDD and MDD (“validation by outcome”).

Materials and Methods

PATIENT SELECTION

Data were collected from all patients referred to our tertiary academic center for multidisciplinary expert discussion between January 2005 and December 2015. Criteria for inclusion in this study were availability of the MDD report and of referring documents, HRCT images and histopathology (if biopsy had been performed). If a case was discussed more than once, the final diagnosis after the last multidisciplinary discussion was considered.

MULTIDISCIPLINARY DISCUSSION

Referring physicians were requested to provide all relevant data available to the MDD. In those cases where the essential diagnostics had not yet been performed or were inadequate at referral,

additional tests were made at the tertiary center before the MDD when necessary. During MDD meeting, exhaustive history as well as clinical examination data, laboratory results, pulmonary function tests, HRCT images, broncho-alveolar lavage (BAL) counts and surgical lung biopsies were discussed among ILD experts in pulmonology, radiology, and histopathology, assisted by other specialists when needed (e.g. rheumatology, occupational medicine, …). At the end of the discussion, participants attempted to make a consensus diagnosis, guided by international ILD peer-reviewed literature and guidelines. A concise description of the MDD protocol can be found in the supplementary (e-Appendix A1).

DATA ANALYSIS

Data for this study were based on the final MDD report of the included patients. Diagnosis after the MDD was coded into one of ten categories, as presented in Table 1. Similarly, the preliminary diagnosis was also coded into one of the ten categories. Actual diagnoses in the categories CTD-ILD, 'other interstitial lung diseases' and non-ILD diagnosis were considered as well as the advice provided when no final diagnosis was possible at the MDD. STROBE guidelines were followed.

SURVIVAL ANALYSIS

Based on the knowledge that IPF carries a worse prognosis than other types of ILD[17], we validated MDD diagnosis using differences in natural history. As the validity of this approach (to use prognosis to validate diagnosis) depends on differences in survival between IPF and the other ILD entities, end-stage fibrosis patients (n=22) were excluded for the survival analysis. Core analyses were:

1) Diagnoses were categorized broadly as IPF or non-IPF before and after MDD. Survival of the four groups was analyzed using cox proportional hazard's models.
2) We determined whether the prognostic separation between the two classes (IPF vs non-IPF) was more pronounced with MDD diagnoses than with preMDD diagnoses. We determined hazard ratios and related p-values as well as Harrell's c-index for both MDD and preMDD. We used a non-parametric approach to compare c-indices[28].

Multivariate analyses were performed correcting for baseline disease severity (DLCO% and FVC%). A concise protocol of data and survival analysis can be found in the Supplementary (e-Appendix A2). Statistical analysis was performed using R (version 3.3.1). The study was conducted according to the principles of the Declaration of Helsinki.

Results

DIAGNOSTIC ABILITY OF THE MDD

Between January 2005 and December 2015, 938 patients were discussed in a multidisciplinary discussion. Mean age was 60.8 year (range 14-90), 65.2% of patients were men. Evolution of the patient numbers that were discussed yearly is shown in Supplementary e-Figure 1.

The number of diagnoses within each diagnostic category is presented in Table 1: 690 patients (73.6%) received a diagnosis within the ILD spectrum, with IPF as the most prevalent entity (326 diagnoses, 34.8%); 65 patients (6.9%) were diagnosed with another (non-ILD) illness (e.g. emphysema). In 183 cases (19.5%), the MDD did not come to a definite diagnosis (unclassifiable ILD);

however, in 150 of those patients (16.0% of the total cohort), suggestions for further investigations were given. The MDD was unable to provide advice concerning diagnosis or further work-up in only 33 patients (3.5%).

COMPARISON WITH preMDD DIAGNOSES

In 455 patients (48.5%), the referring physician had provided a preMDD diagnosis. In the other 483 patients (51.5%), no preliminary diagnosis was given, or multiple differential diagnostic options were provided. An overview of concordance between preMDD and MDD diagnosis is shown Figure 1 and Supplementary e-Table 4.

MDD resulted in a change in the preMDD diagnosis in 191 patients (41.9% of patients with a preMDD diagnosis): in 118 patients (25.9% of patients with a preMDD diagnosis), another entity was diagnosed, an additional 73 patients (16.0%) were regarded as unclassifiable as further investigations were needed before a definite diagnosis could be established. Additionally, MDD established a definite diagnosis in 384 patients where the referring physician did not provide a preMDD diagnosis (79.5% of patients without a preMDD diagnosis).

Preliminary diagnosis and MDD diagnosis differed substantially, especially in non-IPF IIPs and HP. Thus, referring physicians drew the same conclusion as MDD only in 13.9% and 20.8% of MDD diagnoses respectively. Comparison between preliminary diagnosis and MDD diagnosis is shown in Figure 1.

An analysis of patients re-reviewed on MDD was made, 81 patients were presented at least twice. In 73 patients (89.0%), a definite diagnosis was obtained after the second MDD, further advice was given in seven cases (8.5%), and in two cases (2.5%) no diagnosis or advice was provided. Substantial differences were seen depending on the type of referring physician, as more concordance was seen with non-university based respiratory physicians compared to general practitioner physicians (Supplementary e-Table 5).

VALIDATION BY OUTCOME

Patients with both a preMDD and MDD diagnosis of non-IPF showed a significantly better prognosis compared to patients with both a preMDD and MDD diagnosis of IPF (HR 0.24, p-value <0.001). Patients with a non-IPF preMDD diagnosis with a subsequent IPF diagnosis at MDD (non-IPF->IPF patient group) showed a significantly worse survival compared to patients with both a preMDD and MDD diagnosis of non-IPF (HR 4.31, p <0.001). Patients with a preMDD diagnosis of IPF which were diagnosed with another ILD entity at the MDD showed a trend towards better prognosis compared to patients diagnosed with IPF by both MDD and referring physician (HR 0.37, p = 0.094), as shown in Figure 2.

MDD consistently showed a trend towards superiority in separating IPF and non-IPF prognostically, both with regard to hazard ratios (4.13 vs 3.13), related p-values (2.78×10^{-10} vs 2.48×10^{-7}) and Harrell's c-indices (0.666 vs 0.631, p-value = 0.084)(Supplementary e-Figure 2). This trend is particularly clear in patients with a discordant MDD and preMDD (HR 2.68 vs 0.84, p-values 0.012 vs 0.768).

As patients without a preMDD could represent a more difficult subgroup to diagnose, we performed an additional analysis of patients where the referring physician was not able to suggest a preMDD diagnosis. Patients diagnosed with IPF by the MDD showed a worse survival compared to the other

patients (HR 2.24, p-value <0.0001), as illustrated in Figure 3. Multivariate analyses, correcting for baseline disease severity (i.e. DLCO% and FVC%) are depicted in Table 2. A more concise description of the survival analysis is available in Supplementary e-Appendix 3.

Discussion

This study shows that MDD was able to provide a confident diagnosis in 80.5% of patients, providing suggestions concerning further work-up in almost all others. Discrepancy between preMDD diagnosis before work-up and discussion was remarkable. In 41.9% of patients with a preMDD diagnosis, the MDD diagnosis differed from the preMDD diagnosis: in 25.9% another ILD entity was diagnosed, 16.0% were classified as (temporary) unclassifiable ILD as further investigations were deemed necessary before a definite ILD entity could be established. However, given the observation that in 51.5% of cases no preMDD diagnosis was provided (and in almost 80% of those patients MDD established a definite diagnosis), this 41.9% rate probably underestimates the positive influence of MDD. Hence, our observations are concordant with other case series[26,27,29]. Especially, in nonIPF IIP's and HP, concordance was very low. Importantly, 62.2% of IPF patients would not have been diagnosed with IPF, resulting in an erroneous treatment option. No reference standard exists against which to validate diagnoses made by MDD, as MDD includes all available data including histologic information. We validated the MDD diagnoses by quantifying the prognostic value of such diagnosis, in the knowledge that IPF has a worse prognosis: though not statistically significant, a trend toward better prognostic discrimination in MDD diagnosis was seen.

Some aspects of this cohortal survey deserve special attention. First, in our cohort 19.5% of cases were scored as unclassifiable, compared to the 10% unclassifiable disease rate in the paper by Ryerson et al. In our opinion, a major part of patients scored as unclassifiable in our cohort should rather be regarded as 'not yet classifiable'. We believe that in a substantial part of these patients a specific ILD entity could have been diagnosed if these patients had been presented at the MDD a second time after performing the suggested additional investigations. The observation that MDD succeeded in providing a definite diagnosis in 89% of cases who were presented a second time at the MDD supports this statement.

Secondly, to validate MDD diagnoses, the natural history of the disease is used to discriminate IPF from the other ILDs, as in other recent studies in MDD research[24,30]. We assessed whether the diagnostic reclassification of the MDD lead to a more distinct prognostic separation between IPF and other ILDs, using Harrell's c-index as a quantitative tool. However not statistically significant, a trend towards a better separation was seen (0.666 vs 0.631, p-value 0.08), which is similar to other recent MDD papers using this approach[24]. This MDD superiority is particularly manifest in the patient group with the highest discriminatory information: i.e. patients with a discordant MDD and preMDD diagnosis (HR 2.68 vs 0.84, p-values 0.012 vs 0.768 for MDD and preMDD respectively). Moreover, as patients diagnosed with IPF are nowadays treated with antifibrotics in the vast majority of cases (where IPF->non-IPF patients were not) – thus experiencing a better outcome than purely based on natural history, the actual difference in prognostic separation probably is even greater.

Furthermore, to what extent MDD referral proved to be an added value, is difficult to answer. However, assuming that MDD would be the 'gold standard', we believe that in 69.5% of patients a referral to MDD added value. In the remaining patients, the preliminary diagnosis was confirmed or no diagnosis was obtained nor advice given by the MDD. However, it can be argued that diagnostic confirmation by an expert group increases diagnostic confidence. Similarly, confirmation that ILD is

currently unclassifiable provides an important reassurance to referring physicians who are unable to make a pre-MDD diagnosis. It is clear that the quality of a MDD discussion depends not only on the expertise and the experience of the participating members, but is also dependent on the quality of the clinical work-up. Hence, the evidence for MDD superiority suggested in this study clearly underpins the importance of a complete and highly qualitative clinical work-up.

Finally, as this study demonstrated important discrepancies between referring and MDD diagnoses, one could argue that all ILD patients should be discussed at an MDD. On the other hand, Walsh et al.[24] showed that ILD experts performed similarly to MDDs in IPF and CTD diagnoses. While these findings could seem contradictory on first hand, we believe our data could be of additional value: Walsh et al. compared clinicians with MDDs in very experienced centers. Our study however, strengthens the evidence that MDD in experienced centers outperforms in diagnostic accuracy over a situation where a very experienced multidisciplinary team is not available.

Being a single center study performed in a tertiary referral center, our study is subject to referral bias. The increase in IPF diagnoses over time is noteworthy (Supplementary e-Figure 1). Although an increase in IPF incidence has been reported in other expert centers[16], this seems logic in our center which is the largest ILD expert center in Belgium where IPF diagnosis results in reimbursement for antifibrotics. This explains the steep increase in 2012, the year in which reimbursement of Pirfenidone started in Belgium. However, both high IPF and complex case referrals are a daily reality in tertiary centers and in this way these factors contribute to the 'real world'-character of our data. The observation that even in this context high diagnostic yield can be achieved, supports the ability of the MDD. Another weakness is the retrospective nature of our study. One could argue that the learning curve of the MDD has not been attributed. However, we would like to emphasize that the MDD at the Leuven University Hospitals already existed several years before 2005. Furthermore, each professional group of the MDD (i.e. pulmonologists, radiologists, pathologists) had already >10 year experience with interstitial lung diseases.

However, we believe our study has some major strengths. To our knowledge, this is the first study combining three essential strengths of current MDD research: a large patient cohort (almost 1000) in a real life setting, comparison of preMDD and MDD diagnosis and validation of MDD diagnosis using prognostic discrimination between IPF and other ILDs.

Conclusions

MDD diagnosed a specific ILD entity 80.5% of patients and provided advice concerning additional investigations in almost all unclassifiable patients. MDD changed preMDD diagnosis in 41.9% of patients with a preMDD diagnosis, probably being an underestimation given the high rate of patients without a preMDD diagnosis (51.5% of total cohort). Finally, MDD probably resulted in a better prognostic separation of IPF vs other ILDs compared to preMDD diagnosis. Hence, we believe MDD should be a common practice in the diagnosis of every patient with suspected ILD.

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Guarantor statement
Laurens De Sadeleer, MD, will take full responsibility for the content of the manuscript, including the data and analysis.

Author Contributions
Dr Laurens De Sadeleer has made substantial contributions concerning the literature search, study design, data collection, data analysis, data interpretation, writing, tables & figures.
Dr Caressa Meert has made substantial contributions concerning data collection and data analysis.
Dr Jonas Yserbyt, Dr Hans Slabbynck, Prof Dr Johny Verschakelen, Prof Dr Eric Verbeken, Prof Dr Birgit Weynand, Prof Dr Ellen De Langhe, Dr Jan Lenaerts, Prof Dr Benoit Nemery, Prof Dr Dirk van Raemdonck, Prof Dr Geert Verleden and Prof Dr Athol Wells have made substantial contributions to the interpretation of the data and critically revised the manuscript for important intellectual content.
Prof Dr Wim Wuyts has made substantial contributions concerning study design, data interpretation, writing and critically revising for important intellectual content.

All authors have provided final approval of the version to be published and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Graphs/tables

MDD Diagnoses			
TYPE	**DIAGNOSIS**	**N**	**%**
ILD Diagnosis	IPF	326	34.8
	Idiopathic NSIP	33	3.5
	Hypersensitivity pneumonitis	77	8.2
	Sarcoidosis	82	8.7
	CTD-ILD	60	6.4
	COP	17	1.8
	Drug/exposure-related ILD	42	4.5
	RB-ILD/DIP	22	2.3
	Other ILD-diagnosis	31	3.3
Other diagnosis	Non-ILD diagnosis	65	6.9
Unclassifiable, advice given*		150	16.0
Unclassifiable, no advice given*		33	3.5
TOTAL		**938**	**100**

Table 1. Overview of the 938 MDD diagnoses obtained at the University Hospitals Leuven from 2005 until 2015. More detailed information on the specific diagnosis within CTD-ILD, "other ILD-diagnosis" and "non-ILD diagnosis" groups can be found in Supplementary e-Table 1 and 2. An overview of the type of advice can be found in Supplementary e-Table 3. *Definition of abbreviations:* MDD = Multidisciplinary Dynamic Discussion, ILD = Interstitial Lung Diseases, IPF = Idiopathic Pulmonary Fibrosis, NSIP = Non-specific Interstitial Pneumonia, CTD-ILD = Connective Tissue Disease-related Interstitial Lung Disease, COP = Cryptogenic Organizing Pneumonia, RB-ILD/DIP = Respiratory Bronchiolitis Interstitial Lung Disease/Desquamative Interstitial Pneumonia; * Patients with unclassifiable ILD were divided as whether suggestions for further investigations were made.

Figure 1. Comparison of preMDD and MDD diagnosis, stratified by ILD entity. The Y-axis shows the ten diagnostic categories of the MDD (plus overview of all patients (i.e. "TOTAL")). For each category, it is shown to which extent the referring physician provided the same diagnosis, a different diagnosis or no diagnosis. *Definition of abbreviations:* MDD = Multidisciplinary Dynamic Discussion, IPF = Idiopathic Pulmonary Fibrosis, NSIP = Non-specific Interstitial Pneumonia, CTD-ILD = Connective Tissue Disease-related Interstitial Lung Disease, COP = Cryptogenic Organizing Pneumonia, RB-ILD/DIP = Respiratory Bronchiolitis Interstitial Lung Disease/Desquamative Interstitial Pneumonia, ILD = Interstitial Lung Diseases.

Figure 2. Kaplan Meier curve of the patient cohort subdivided by both preMDD and MDD diagnosis. Analysis was confined to patients with a preMDD diagnosis. Patients diagnosed with IPF at the MDD show similar outcome irrespective of preMDD diagnosis. Patient diagnosed with another diagnosis at the MDD show a better outcome, irrespective of preMDD outcome. For explanation concerning the distribution in different subgroups, we refer to the main text. *Definitions of abbreviations:* preMDDx = preliminary diagnosis before formal work-up and multidisciplinary discussion.

Figure 3. Kaplan Meier curve confined to patients without a preMDD diagnosis according to MDD diagnosis. *Definition of abbreviations:* MDD = Multidisciplinary discussion, preMDD = preliminary diagnosis before formal work-up and discussion, IPF = patients diagnosed with Idiopathic Pulmonary Fibrosis, non-IPF = patients diagnosed with all other ILDs.

Multivariate analyses of survival data

	Univariate			Multivariate		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
nonIPF->nonIPF vs IPF->IPF	0.24	(0.15-0.38)	<0.001	0.37	(0.21-0.67)	<0.001
nonIPF->IPF vs nonIPF->nonIPF	4.31	(2.05-9.08)	<0.001	3.11	(1.32-7.34)	0.01
IPF->nonIPF vs IPF->IPF	0.37	(0.11-1.18)	0.094	0.36	(0.05-2.69)	0.32
MDD: IPF vs nonIPF	4.13	(2.66-6.42)	<0.001	2.78	(1.58-4.90)	<0.001
preMDD: IPF vs nonIPF	3.13	(2.03-4.82)	<0.001	1.93	(1.15-3.24)	0.013
Disc pts*: MDD: IPF vs nonIPF	2.68	(1.24-5.78)	0.012	2.65	(1.03-6.82)	0.044
Disc pts*: preMDD: IPF vs nonIPF	0.84	(0.25-2.74)	0.768	0.60	(0.08-4.51)	0.619
MDD w/o preMDD: IPF vs nonIPF	2.24	(1.55-3.25)	<0.001	1.51	(0.95-2.41)	0.08

Table 2. Multivariate analyses of survival data. Cox regression hazard's models were used, correcting for DLCO% and FVC% baseline. Analyses were depicted chronologically as displayed in the results section. Disc pts*: analysis confined to patients with a discordant preMDD-MDD diagnosis. *Definition of abbreviations:* MDD = Multidisciplinary discussion, preMDD = preliminary diagnosis before formal work-up and discussion, IPF = patients diagnosed with Idiopathic Pulmonary Fibrosis, non-IPF = patients diagnosed with all other ILDs.

MDD Diagnoses

TYPE	DIAGNOSIS	N	%
ILD Diagnosis	IPF	326	34.8
	Idiopathic NSIP	33	3.5
	Hypersensitivity pneumonitis	77	8.2
	Sarcoidosis	82	8.7
	CTD-ILD	60	6.4
	COP	17	1.8
	Drug/exposure-related ILD	42	4.5
	RB-ILD/DIP	22	2.3
	Other ILD-diagnosis	31	3.3
Other diagnosis	Non-ILD diagnosis	65	6.9
Unclassifiable, advice given*		150	16.0
Unclassifiable, no advice given*		33	3.5
TOTAL		**938**	**100**

Multivariate analyses of survival data

	Univariate			Multivariate		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
nonIPF->nonIPF vs IPF->IPF	0.24	(0.15-0.38)	<0.001	0.37	(0.21-0.67)	<0.001
nonIPF->IPF vs nonIPF->nonIPF	4.31	(2.05-9.08)	<0.001	3.11	(1.32-7.34)	0.01
IPF->nonIPF vs IPF->IPF	0.37	(0.11-1.18)	0.094	0.36	(0.05-2.69)	0.32
MDD: IPF vs nonIPF	4.13	(2.66-6.42)	<0.001	2.78	(1.58-4.90)	<0.001
preMDD: IPF vs nonIPF	3.13	(2.03-4.82)	<0.001	1.93	(1.15-3.24)	0.013
Disc pts*: MDD: IPF vs nonIPF	2.68	(1.24-5.78)	0.012	2.65	(1.03-6.82)	0.044
Disc pts*: preMDD: IPF vs nonIPF	0.84	(0.25-2.74)	0.768	0.60	(0.08-4.51)	0.619
MDD w/o preMDD: IPF vs nonIPF	2.24	(1.55-3.25)	<0.001	1.51	(0.95-2.41)	0.08

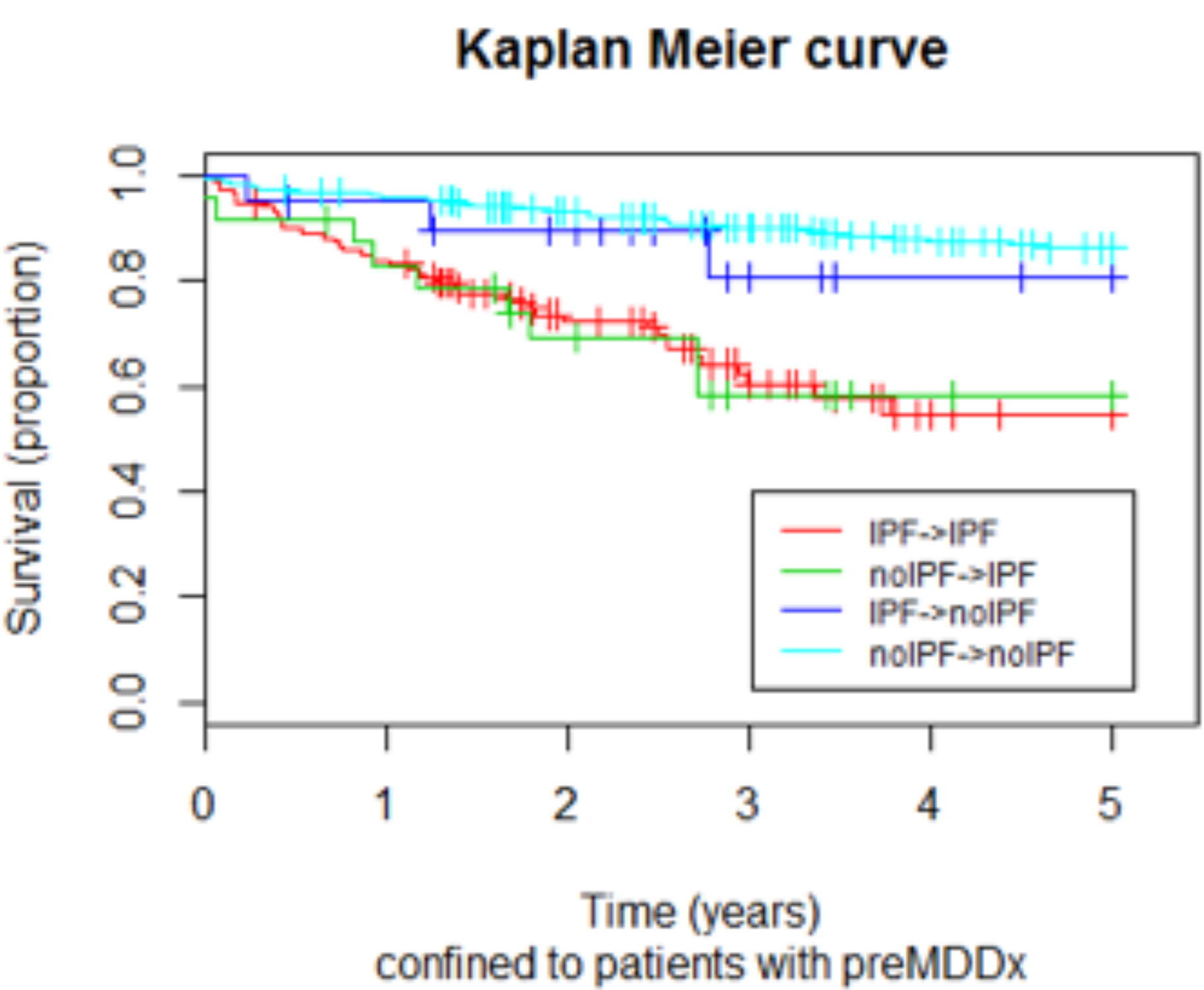
Diagnostic Agreement

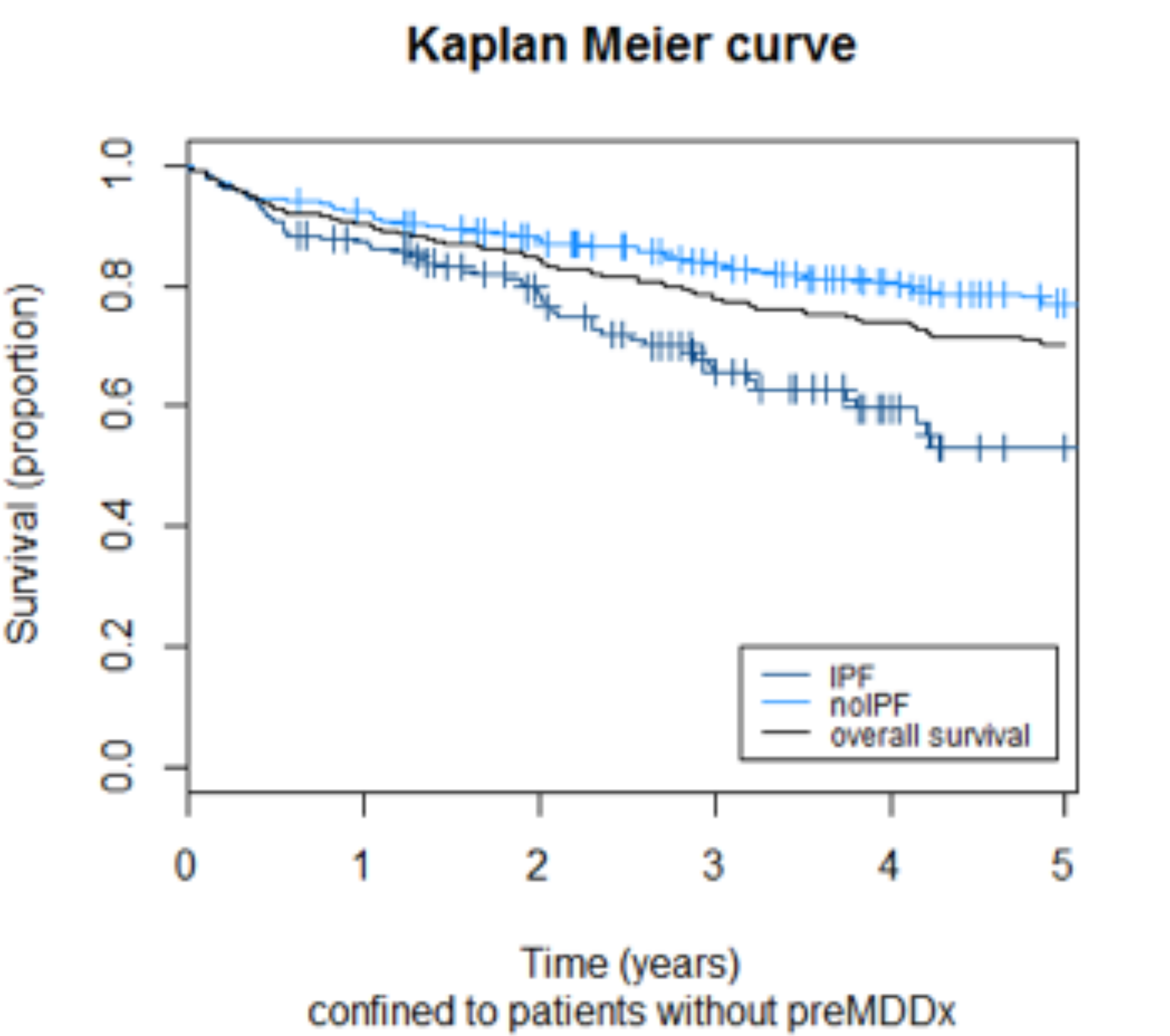
MDD Diagnosis

Non-ILD diagnosis
Other ILD-diagnosis
RB-ILD/DIP
Drug/exposure-related ILD
COP
CTD-ILD
Sarcoidosis
Hypersensitivity pneumonitis
Idiopathic NSIP
IPF
TOTAL

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

MDD confirmed preMDD
MDD disproved MDD
no preMDD available


Kaplan Meier curve
Survival (proportion)
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
IPF->IPF
noIPF->IPF
IPF->noIPF
noIPF->noIPF
Time (years)
confined to patients with preMDDx


Kaplan Meier curve
Survival (proportion)
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
IPF
noIPF
overall survival
Time (years)
confined to patients without preMDDx

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Diagnostic ability of a MDD in ILD: Supplement

e-Appendix 1: concise description of MDD protocol

The Leuven MDD met biweekly and discussed all patients that were referred for MDD specifically as well as patients referred to the outpatient clinic where the clinician deemed a MDD would be an added value. In Belgium, every patient eligible for antifibrotics on medical grounds is discussed at the MDD, as it is obliged before reimbursement of antifibrotics. Referring physicians were requested to provide, on a standard template, a summary of history, including familial history, exposures, comorbidities, and medication use, as well as physical examination, laboratory results, including serology, and pulmonary function tests. HRCT images, broncho-alveolar lavage (BAL) cell counts, and surgical lung biopsies were reviewed by ILD experts from our center, whenever possible. In those cases where the essential diagnostics had not yet been performed or were inadequate at referral, additional tests were made at the tertiary center when necessary. During multidisciplinary discussion, cases were discussed among ILD experts in pulmonology, radiology, and pathology, assisted by specialists in rheumatology, thoracic surgery, lung transplantation, and occupational medicine when necessary. At the end of the discussion, participants strived for consensus, guided by international ILD peer-reviewed literature and guidelines. A final MDD report was made by the clinician in charge of the ILD clinic and consisted of a summary of referring data, review of HRCT and biopsy by the MDD radiologist and pathologist respectively, additional work-up at our center, and the conclusion of the MDD.

e-Appendix 2: Concise description of the data and survival analysis

DATA ANALYSIS

Data for this study was based on the final MDD report of the included patients. Diagnosis after the MDD was coded into one of ten categories: idiopathic pulmonary fibrosis (IPF), idiopathic non-specific interstitial pneumonia (NSIP), hypersensitivity pneumonitis (HP), sarcoidosis, connective tissue disease-related interstitial lung diseases (CTD-ILD), cryptogenic organizing pneumonia (COP), drug-, environmental and occupational exposure-related ILD, smoking-associated ILD (respiratory bronchiolitis interstitial lung disease (RB-ILD) or desquamative interstitial pneumonia (DIP)), other interstitial lung diseases, non-ILD diagnosis, unclassifiable ILD. Similarly, preliminary diagnosis was also coded into one of the ten categories. Actual diagnoses in the categories CTD-ILD, 'other interstitial lung diseases' and non-ILD diagnosis were assessed as well as the type of advice suggested when no final diagnosis was possible at the MDD. A table comparing the preliminary diagnosis (before MDD and additional work-up) with the MDD diagnosis was composed. Finally, the above mentioned analysis was performed separately for the subgroup of patients that were presented more than once at the MDD. STROBE guidelines were used for data analysis.

SURVIVAL ANALYSIS

We used differences in natural history between IPF and the other ILDs to validate MDD diagnosis. Patients were scored whether the ILD diagnosis was IPF on the one hand or another ILD entity (or no diagnosis) on the other hand, for both MDD and preMDD diagnoses. As the

validity of this approach (to use prognosis to validate diagnosis) depends on differences in survival between IPF and the other ILD entities, end-stage fibrosis patients were excluded as their prognosis is similar to IPF but their diagnosis is differently. Afterwards, a double statistical approach was used.

First, we divided the cases according to MDD and preMDD diagnosis (IPF or non-IPF diagnosis), resulting in 4 groups: patients with both a preMDD and MDD diagnosis of IPF (IPF->IPF group), patients with both a preMDD and MDD diagnosis of another ILD (non-IPF->non-IPF group), patients with a preMDD diagnosis which was not retained by the MDD (IPF->non-IPF group) and patients with a preMDD diagnosis of non-IPF, where MDD diagnosed IPF (non-IPF->IPF) group. Survival of the four groups were analyzed using a cox proportional hazard's model with post-hoc analysis for IPF->IPF vs non-IPF->non-IPF, IPF->IPF vs IPF->non-IPF, non-IPF->non-IPF vs IPF->non-IPF using false discovery rate for multiple comparison correction.

Secondly, we determined whether the prognostic separation between the two classes (IPF vs non-IPF) was more pronounced with MDD diagnoses compared to preMDD diagnoses. We determined hazard ratio's and related p-values as well as Harrell's c-index for both MDD and preMDD (i.e. a non-parametric approach to compare c-indices [28]).

e-Appendix 3: Concise description of the results of the survival analysis

To evaluate the validity of MDD diagnoses, we analyzed survival data of the cohort using a binary model (IPF vs non-IPF). As IPF prognosis is worse compared to other ILDs, proven in historical cohorts17, we determined whether the prognostic separation between IPF and non-IPF patients was larger with MDD diagnoses compared to preMDD. Twenty-two patients were excluded for survival analysis, having end-stage fibrosis. Analysis was performed separately for patients with and without a preMDD diagnosis.

In the first approach, patients were divided in four groups, depending on both MDD and preMDD diagnosis . Data are presented in Figure 3: patients with both a preMDD and MDD diagnosis of non-IPF showed a significantly better prognosis compared to patients with both a preMDD and MDD diagnosis of IPF (HR 0.24, p-value <0.001). Patients with a non-IPF preMDD diagnosis with a subsequent IPF diagnosis at MDD (non-IPF->IPF patient group) showed a significantly worse survival compared to patients with both a preMDD and MDD diagnosis of non-IPF (HR 4.31, p <0.001). Patients with a preMDD diagnosis of IPF which were diagnosed with another ILD entity at the MDD showed a trend towards better prognosis compared to patients diagnosed with IPF by both MDD and referring physician (HR 0.37, p = 0.094), as shown in Figure 2.

Using the second approach, cox proportional hazard's models for MDD and preMDD were calculated separately using the binary model explained before (IPF vs non-IPF). Hazard ratios (4.13 vs 3.13), related p-values (2.78 $x10^{-10}$ vs 2.48$x10^{-7}$) and Harrell's c-indices (0.666 vs 0.631, p-value = 0.084) for MDD and preMDD consistently showed a trend towards superiority of MDD in separating IPF and non-IPF prognostically, (Supplementary e-Figure 2). This trend is particularly clear in patients with a discordant MDD and preMDD (HR 2.68 vs 0.84, p-values 0.0.012 vs 0.768).

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Non-ILD diagnoses			
Infections	**14**	**Other chronic lung disease**	**33**
Fungal infection	4	Bronchiectasis	3
Viral Infection	1	Emphysema	12
Mycobacterium	3	Bronchiolitis	6
Agent not specified	6	PHT/PE/PVOD	5
		Idiopathic hemosiderosis	2
Inflammation	**6**	Fibrothorax	1
Yellow Nail Syndrome	1	ABPA	2
Amyloidosis	3	Lymphocytic pleuritis	2
IBD-related granulomatous inflammation	2		
Neoplasm	**5**	**Other**	**7**
Broncho-alveolar carcinoma	2	Neuromuscular disease	3
Spinocellular carcinoma	1	Obesity induced dyspnea	1
Mesothelioma	1	Thoracic endometriosis	1
Lymphoma	1	No other disease specified	2
TOTAL			65

e-Table 1. Overview of non-ILD diagnoses, divided in five subgroups: Infections, Inflammation, Neoplasm, Other chronic lung diseases, Other. *Definition of abbreviations:* IBD = Inflammatory Bowel Disease, PHT = Pulmonary Hypertension, PE = Pulmonary Embolism, PVOD = Pulmonary Veno-occlusive Disease, ABPA = Allergic Bronchopulmonary Aspergillosis.

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Other interstitial lung diseases	
Lymphocytic Interstitial Pneumonia	5
Pulmonary Alveolar Proteinosis	3
Langerhans Cell Histiocytosis	12
Lymphangioleiomyomatosis	4
Chronic eosinophilic pneumonia	2
Secondary BOOP	3
Pleuroparenchymal Fibro-elastosis	1
CVD-related ILD	1
TOTAL	**31**

CTD-ILD	
Systemic Sclerosis	12
RA-related ILD	12
Sjögren's disease	9
PM/DM/antisynthetase syndrome	7
Granulomatosis with Poly-angiitis	6
Systemic Lupus Erythematosus	3
EGPA	1
Behcet's disease	1
Primary Billiary Cirrhosis	1
Not specified	8
TOTAL	**60**

e-Table 2. Overview of the diagnoses in the 'other interstitial lung diseases' and CTD-ILD diagnostic subgroups. *Definition of abbreviations:* CTD-ILD: Connective Tissue Disease-related Interstitial Lung Disease, ILD = Interstitial Lung Disease, BOOP = Bronchiolitis obliterans organizing pneumonia, CVID-related ILD = Common Variable Immunodeficiency-related Interstitial Lung Disease, RA = Rheumatoid Arthritis, PM/DM = Polymyositis/Dermatomyositis, EGPA = Eosinophilic Granulomatosis with Poly-angiitis.

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Advice			
"Non-invasive" investigation		**Therapeutic advice**	
Imaging	20	Corticosteroid	28
Investigate exposure	8	Other immunosuppression	7
Pulmonary Function	11	Other medication	3
Echocardiography	2	Stop provoking medication	6
Rheumatological advice	9	Exposure termination	4
Follow-up	2	Stop corticosteroid treatment	1
Other (non)invasive	30	Smoking cessation	3
		Lung transplantation work-up	3
"Invasive" investigation		Other	2
Lung biopsy	25		
Other biopsy	12		
BAL	15		
Full work-up	8		

e-Table 3. Overview of the advices the MDD provided to the referring physician when a definite diagnosis was not possible at the time of MDD. Sometimes more than one advice per case was given. *Definition of abbreviations:* BAL = Broncho-alveolar Lavage.

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Contingency table													
		POST-MDD											
		IPF	Idiopathic NSIP	Hypersensitivity pneumonitis	Sarcoidosis	CTD-ILD	COP	Drug/exposure-related ILD	RB-ILD/DIP	Other ILD-diagnosis	Non-ILD diagnosis	Suggestions for further work-up*	No diagnosis, no advice*	**TOTAL PRE-MDD**
PRE-MDD	IPF	123	4	7	1	3	0	0	3	1	1	19	3	**165**
	idiopathic NSIP	4	4	2	0	0	0	0	0	0	1	4	1	**16**
	Hypersensitivity pneumonitis	5	1	16	1	0	1	1	0	1	1	7	0	**34**
	Sarcoidosis	2	1	3	51	2	0	1	0	0	9	10	1	**80**
	CTD-ILD	1	1	1	0	16	2	2	1	0	5	13	2	**44**
	COP	0	1	0	0	1	3	1	0	1	1	2	2	**12**
	Drug/exposure-related ILD	2	1	4	0	3	0	11	0	0	5	5	1	**32**
	RB-ILD/DIP	2	0	0	0	0	0	0	3	0	0	2	0	**7**
	Other ILD-diagnosis	2	0	1	0	2	0	0	0	12	1	4	0	**22**
	Non-ILD diagnosis	3	0	6	3	1	0	4	0	4	14	7	1	**43**
	No preMDD	182	20	37	26	32	11	22	15	12	27	77	22	**483**
	TOTAL POST-MDD	**326**	**33**	**77**	**82**	**60**	**17**	**42**	**22**	**31**	**65**	**150**	**33**	**938**

e-Table 4. Contingency table comparing the preMDD diagnosis of the referring physician with the MDD diagnosis, provided by the MDD after formal work-up. The columns show MDD diagnoses and the rows preMDD diagnoses. One can compare preMDD with MDD diagnoses, e.g. five patients receiving a hypersensitivity pneumonitis diagnosis from the referring physician were diagnosed with IPF at the MDD. *Definition of abbreviations:* MDD = Multidisciplinary Dynamic Discussion, IPF = Idiopathic Pulmonary Fibrosis, NSIP = Non-specific Interstitial Pneumonia, CTD-ILD = Connective Tissue Disease-related Interstitial Lung Disease, COP = Cryptogenic Organizing Pneumonia, RB-ILD/DIP = Respiratory Bronchiolitis Interstitial Lung Disease/Desquamative Interstitial Pneumonia, ILD = Interstitial Lung Diseases; * Unclassifiable ILD, however in some, suggestions concerning further diagnostic work-up were given; in the remaining cases, neither diagnosis nor advice could be given.

	same diagnosis	different diagnosis	no referring diagnosis	p-value
General practitioner	7	8	46	0.0005
Non-university respiratory physician	219	163	378	
University respiratory physician*	10	15	21	0.187
University, other specialty	16	17	28	0.506

e-Table 5. Concordance between MDD and referring physician according to the type of referring physician. Most patients were referred to the MDD by non-university based respiratory physicians. P-values were based on comparison with non-university based respiratory physicians as this group is the largest referral group. As expected, non-university based respiratory physician have higher concordance rates compared to primary physicians. Differences between non-university based and university based (non-ILD specialized) respiratory physician were not significant, as well as differences between non-university based respiratory physician and university based non-respiratory specialists. * Respiratory physician based at the University Hospitals Leuven without specific ILD expertise.

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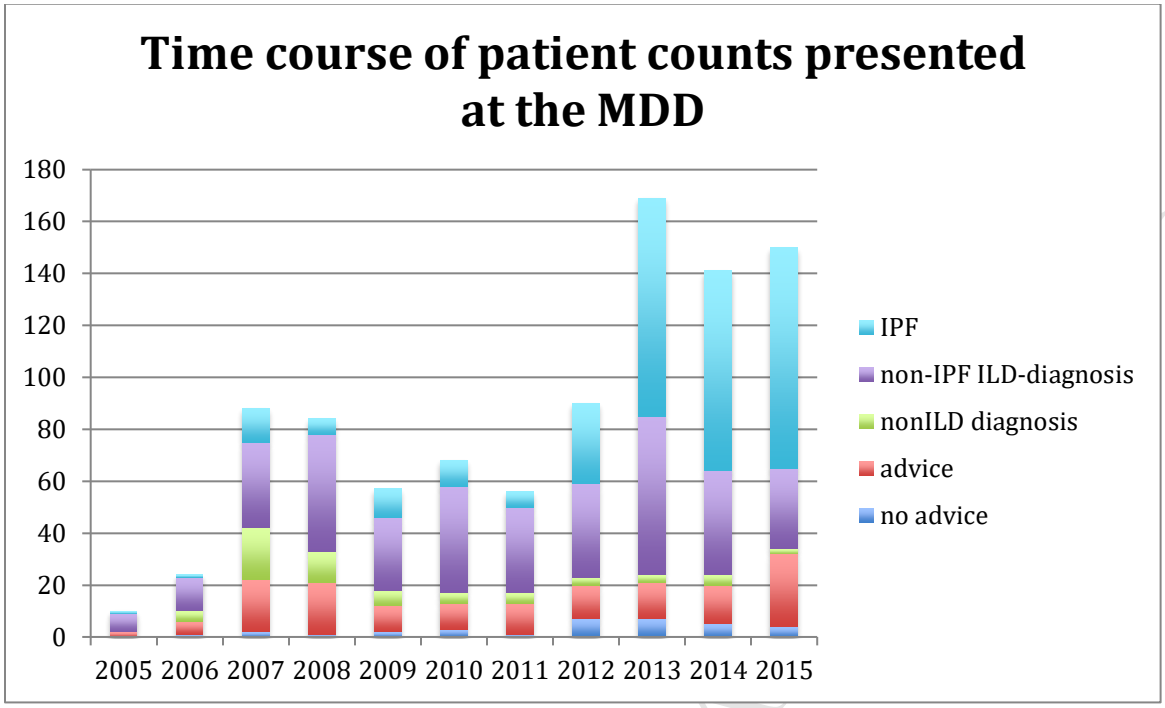

e-Figure 1. Time course of patient counts presented at the MDD during the study period. The rise in IPF diagnoses coincides with the introduction of antifibrotics. *Definition of abbreviations*: MDD = Multidisciplinary Dynamic Discussion, IPF = Idiopathic Pulmonary Fibrosis; non-IPF ILD-diagnosis: Interstitial Lung Disease diagnoses other than IPF; non-ILD diagnosis = Diagnoses other than ILD, as shown in Supplementary e-Table 1; Advice = unclassifiable, however, advice concerning diagnostic work-up and/or therapy was given; No advice = unclassifiable ILD where no advice concerning further work-up was.

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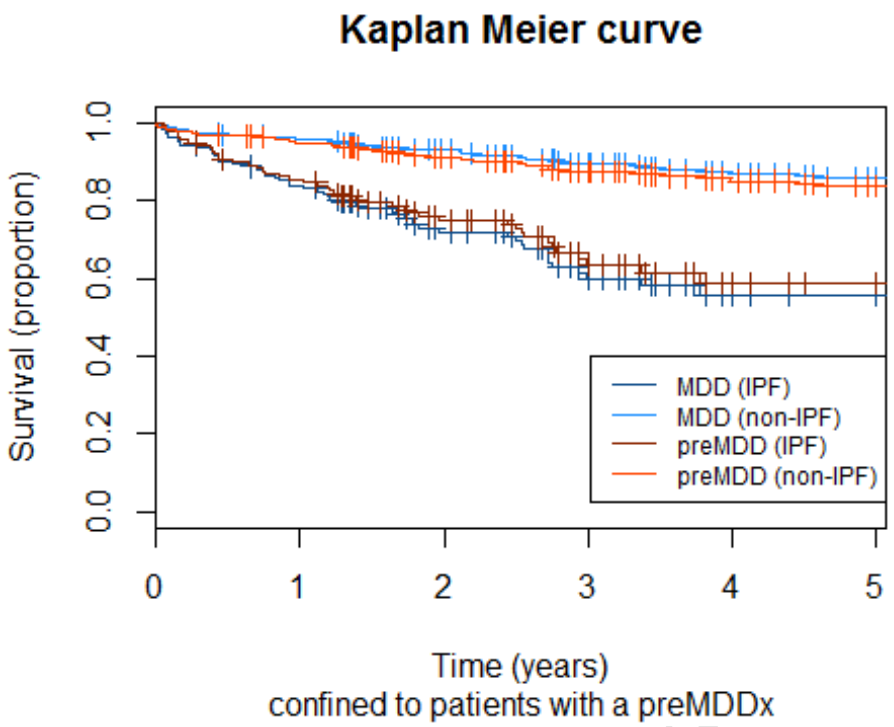

e-Figure 2. Kaplan Meier curve confined to patients with a preMDD diagnosis. Subdivision for MDD diagnosis, separating IPF (red line) and non-IPF (green line) patients. Superposition of the same graph by preMDD diagnosis (blue lines). *Definition of abbreviations:* MDD = Multidisciplinary discussion, preMDD = preliminary diagnosis before formal work-up and discussion, IPF = patients diagnosed with Idiopathic Pulmonary Fibrosis, non-IPF = patients diagnosed with all other ILDs.