Comorbidities on IPF: an underestimated issue

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Conflict of interests disclosures

Boehringer Ingelheim

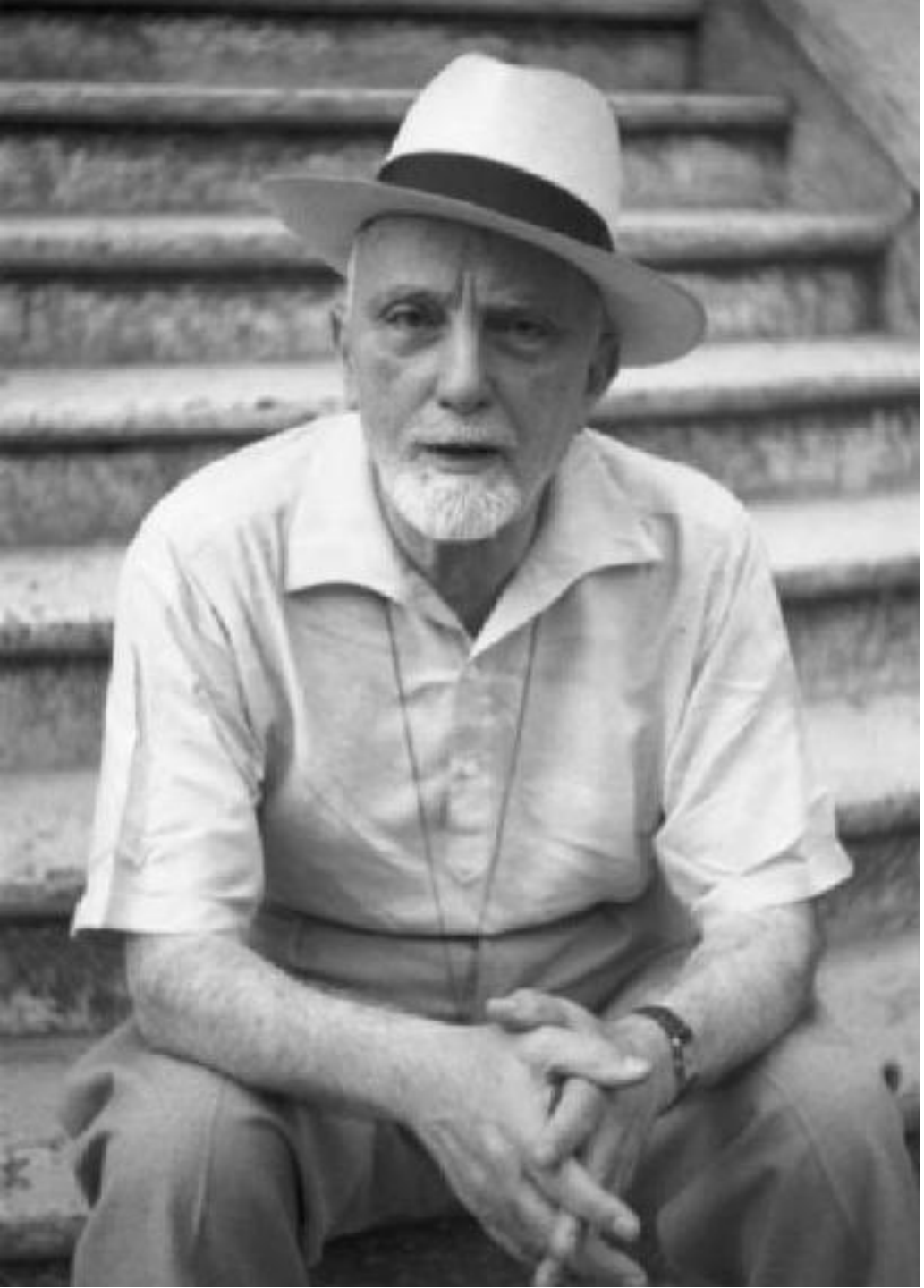
Roche

The clinical management of IPF is challenging.

For patients with a progressive disease with **unknown cure**, realistic goals include

- slowing the rate of disease progression
- **optimizing comorbidities and functional status**
- managing symptoms, and
- preventing what is preventable

KA Johannson, Thorax 2018; 73: 103-104



The prevalence of IPF increases with age

Estimates of the mean annual standardized IPF incidence rates (for 100000 person/years) in Lombardy during 2005 -2010 by age and NCD

Age classes	
<55	0.39 (0.33–0.46)
55–59	2.22 (1.75–2.70)
60–64	4.13 (3.45–4.80)
65–69	5.59 (4.78–6.39)
70–74	7.53 (6.52–8.53)
75–79	10.40 (9.08–11.72)
80–84	11.45 (9.81–13.10)
85+	8.29 (6.69–9.88)

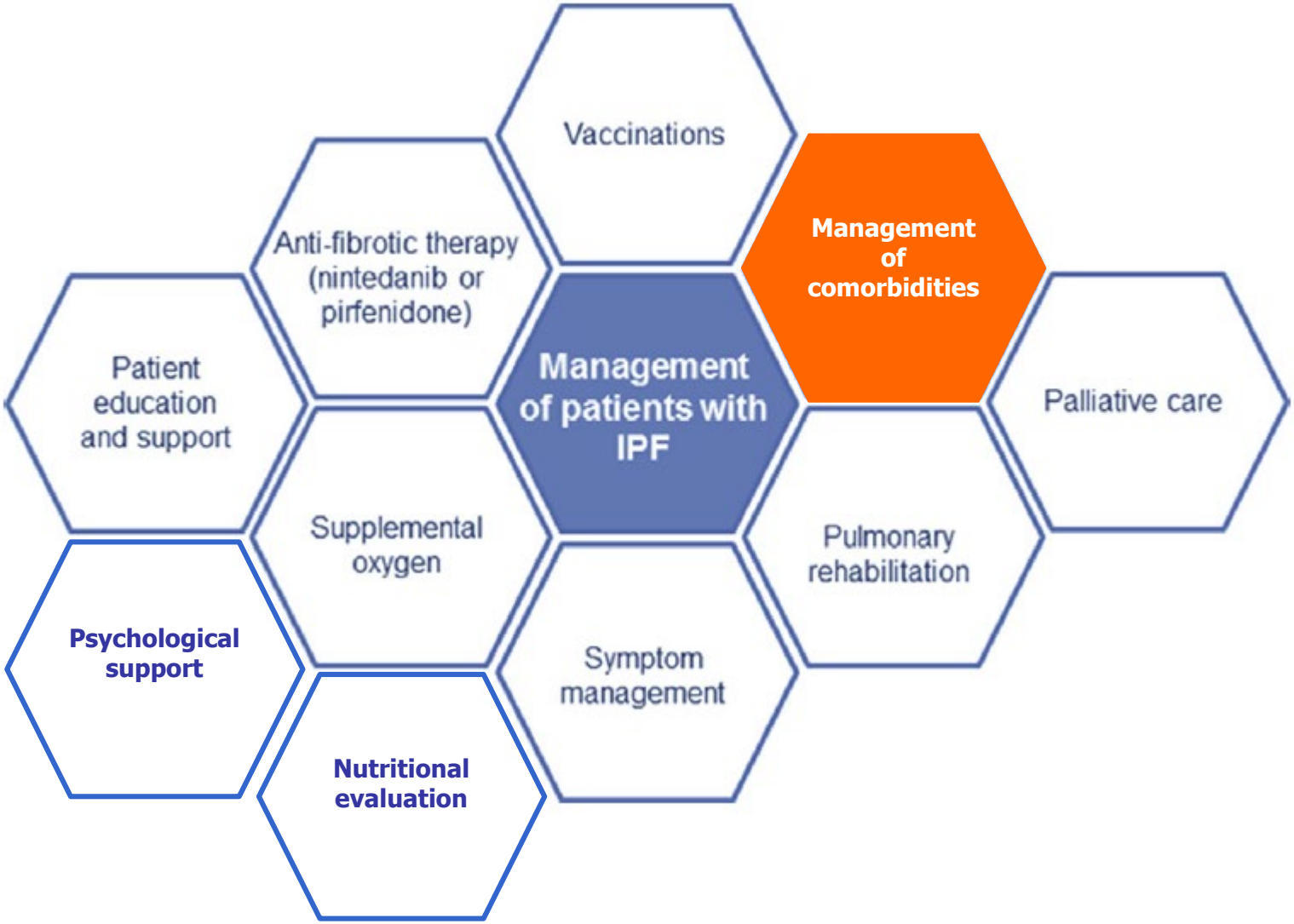
Harari S et al. PLoS ONE 2016; 11 (2): e0147072.

Elderly population with a smoking history

Shortening of telomeres is involved

Optimal clinical management of patients with IPF is multifaceted

Modified from Raghu G and Richeldi L. Respir Med 2017, 129: 24-30



- Prospective multicenter clinical trials provided many valuable informations about the natural history of IPF
- The inclusion/exclusion criteria of these studies are restrictive relating to disease severity
- Patients with unstable or deteriorating cardiac or pulmonary disease or **severe comorbidities** are excluded

- *Real-world evidence suggests that comorbid conditions are prevalent in patients with IPF in clinical practice*
- *In a recent study about 272 patients with IPF at a tertiary care centre is found that 12% had no comorbidities, 58% had 1-3 comorbidities and 30% had 4-7 comorbidities*

  Kreuter M et al. PLoS ONE 2016; 11 (3): e0151425
- ***Identification and treatment of comorbidities may help to improve patients' health-related quality of live and survival***

What's the prevalence of comorbidities in IPF?

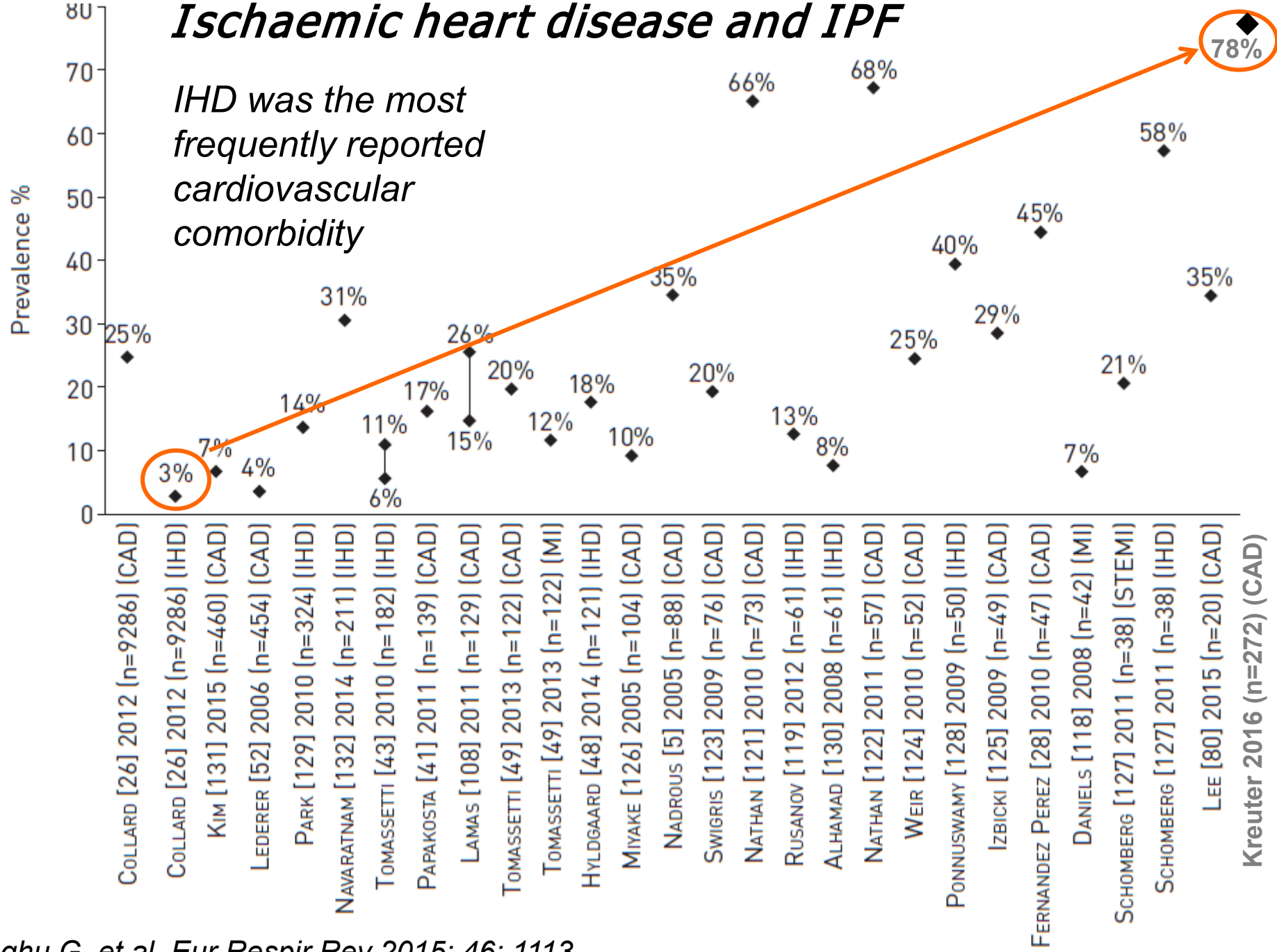
The reported prevalence of comorbidities is variable; this depends on the type of studies in which the data were analyzed and how comorbidities were studied and defined

- Some comorbidities are consequence of the IPF itself (i.e. pulmonary hypertension)
- Others can be explained by common risk factors (i.e. smoke for lung cancer and COPD)
- Some comorbidities, especially gastroesophageal reflux disease, are discussed as a potential cause of IPF
- Their presence may also be associated with a higher risk of acute exacerbations and mortality

Some examples…

Ischaemic heart disease and IPF

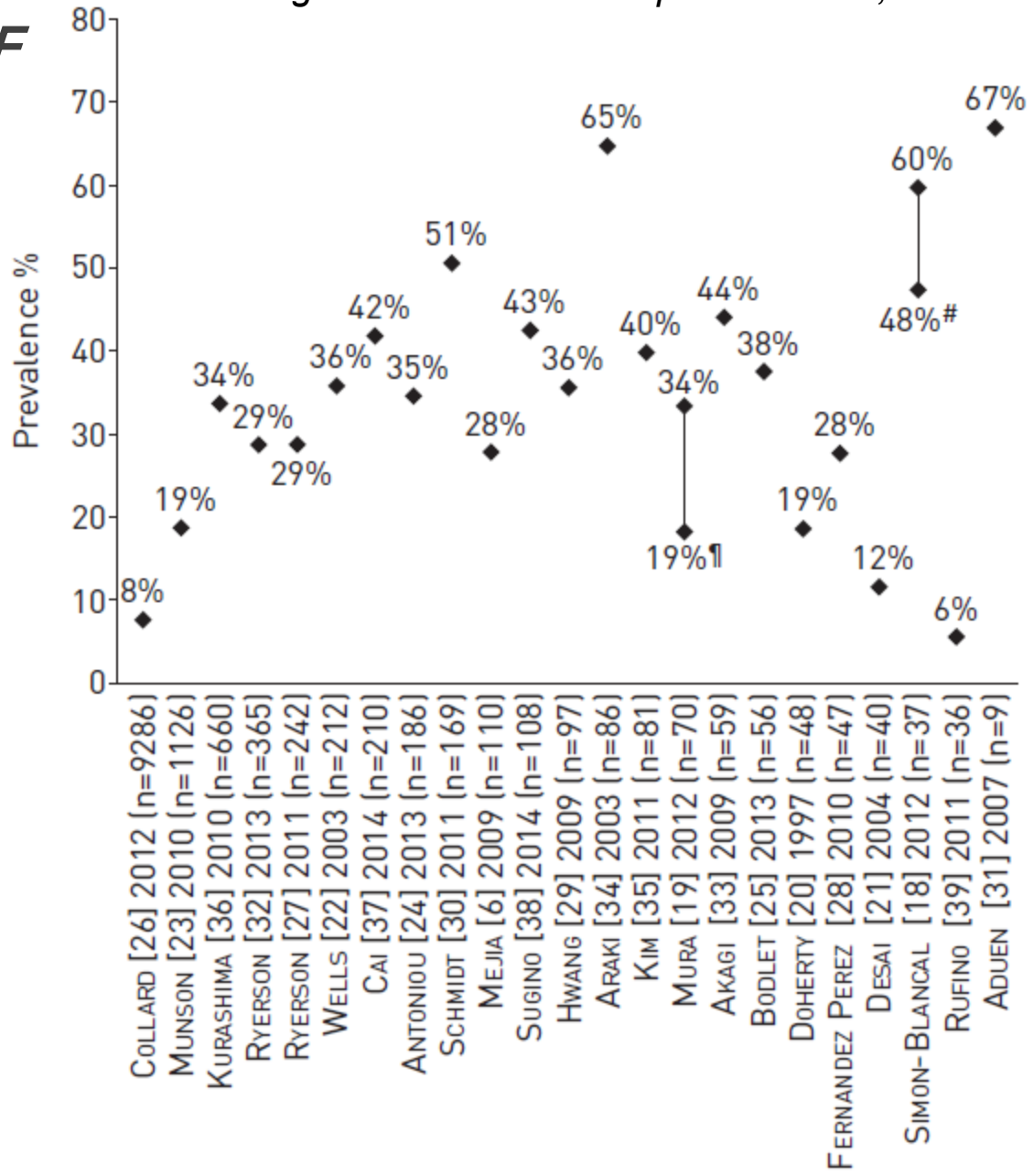
IHD was the most frequently reported cardiovascular comorbidity



Raghu G. et al. Eur Respir Rev 2015; 46: 1113

Emphysema and IPF

- Males
- Smokers
- Severe PH
- Worse survival than IPF



Lung cancer and IPF

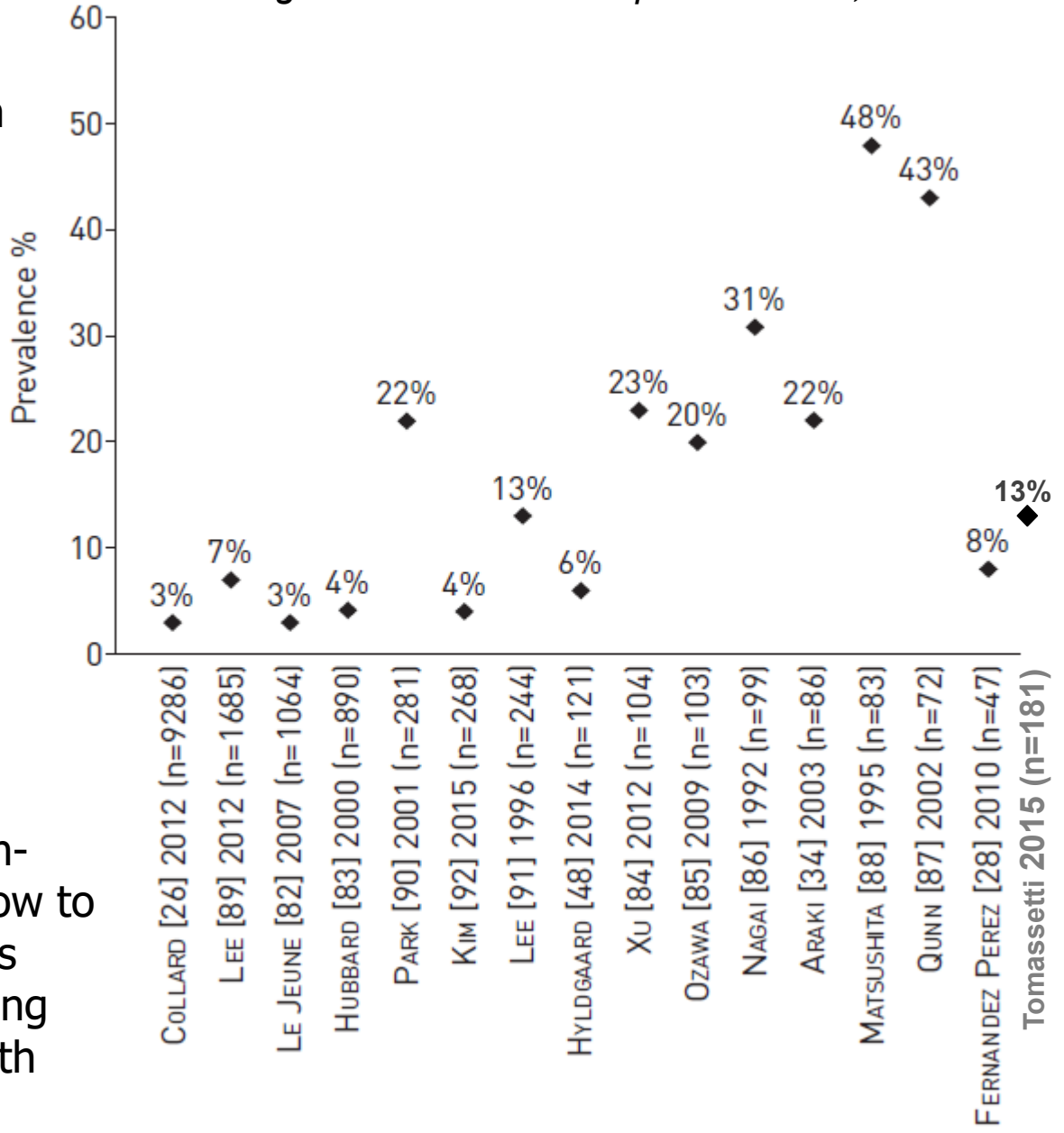
The mortality in IPF patients with lung cancer is confounded by:

- different follow-up times across studies,
- different severity of cancer and IPF,
- differences in cancer treatments, and other patient characteristics

The papers that report mortality and survival among IPF patients with lung cancer are limited by small sample size

In the clinical setting, the decision-making regarding whether and how to treat lung cancer in IPF patients is extremely difficult because any lung cancer treatment is associated with significant toxicity

Raghu G. et al. Eur Respir Rev 2015; 46: 1113



What's the role of comorbidities on survival and hospitalizations in IPF?

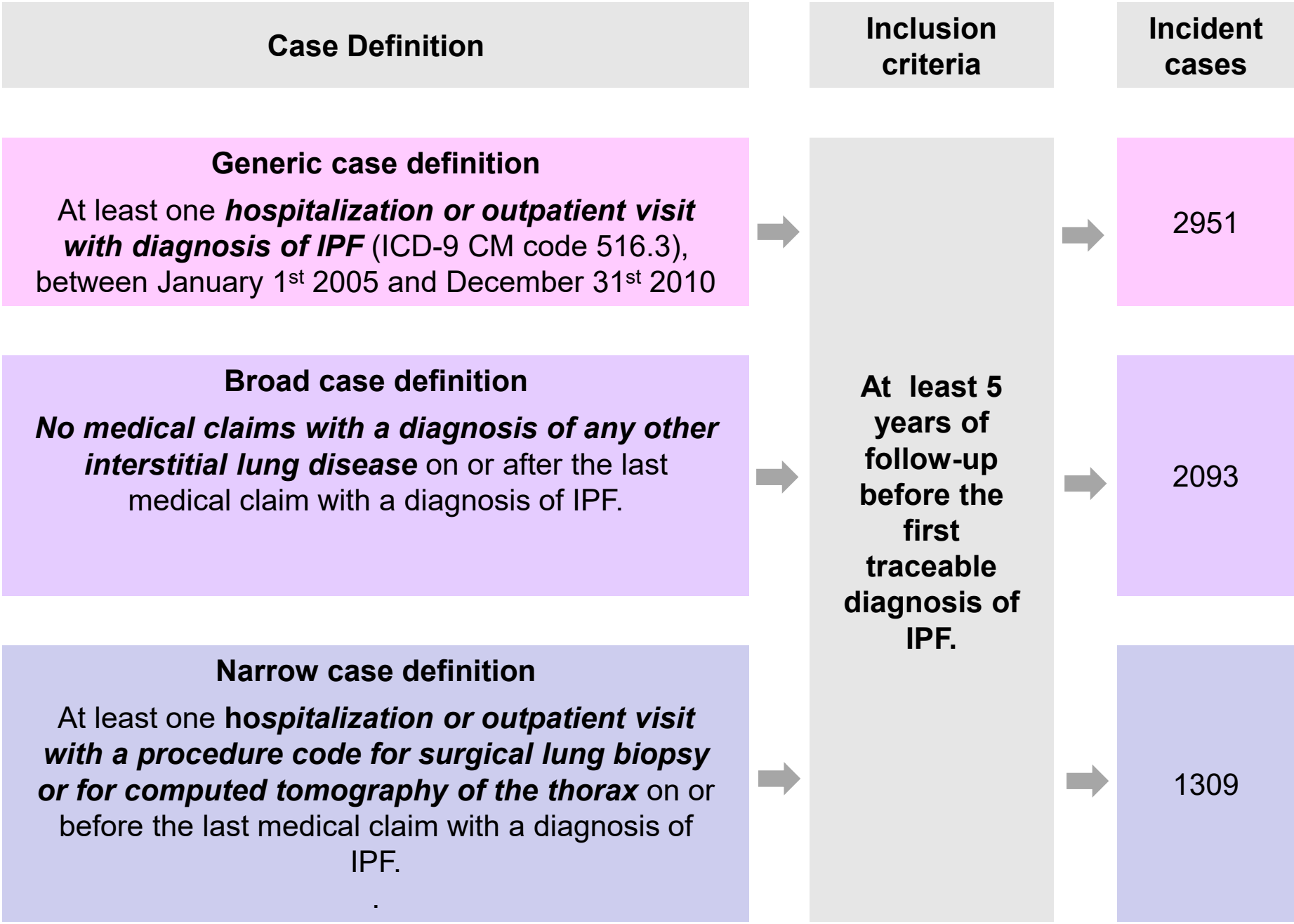
Objective

To describe the course of IPF in an unselected sample of cases from Northern Italy

To evaluate how demographic characteristics (age, sex) and ***patient complexity (comorbidities)*** *could affect mortality and hospitalization frequency after the diagnosis*

Methods

- This is a retrospective observational study using administrative databases of Lombardy region
- Incident IPF cases from 2005 to 2010 are identified based on hospitalizations and outpatient visits
- Healthcare accesses and vital status are traced up to December 31st 2010
- Demographic and clinical characteristics at onset are evaluated
- The effect of sex, age and Charlson Comorbidity Index (CCI) on survival and time to first hospitalization are assessed through Cox proportional hazard models


Case Definition
Inclusion criteria
Incident cases
Generic case definition
At least one hospitalization or outpatient visit with diagnosis of IPF (ICD-9 CM code 516.3), between January 1st 2005 and December 31st 2010
Broad case definition
No medical claims with a diagnosis of any other interstitial lung disease on or after the last medical claim with a diagnosis of IPF.
Narrow case definition
At least one hospitalization or outpatient visit with a procedure code for surgical lung biopsy or for computed tomography of the thorax on or before the last medical claim with a diagnosis of IPF.
.
At least 5 years of follow-up before the first traceable diagnosis of IPF.
2951
2093
1309

Characteristics of the study population

	Female	Male	Total
N (%)	841 (40.18)	1,252 (59.82)	2,093
Age at onset			
mean ± sd	70.69 ± 13.55	69.71 ± 12.60	69.98 ± 12.99
Chronic comorbidity			
Myocardial Infarction*	39 (4.64)	185 (14.78)	224 (10.70)
Congestive Heart Failure*	153 (18.19)	269 (21.49)	422 (20.16)
Peripheral Vascular Disease*	29 (3.45)	134 (10.70)	163 (7.79)
Dementia	16 (1.90)	18 (1.44)	34 (1.62)
Chronic Pulmonary Disease*	283 (33.65)	520 (41.53)	803 (38.37)
Peptic Ulcer Disease*	7 (0.83)	30 (2.40)	37 (1.77)
Renal Disease*	48 (5.71)	120 (9.58)	168 (8.03)
AIDS/HIV*	0 (0.00)	3 (0.24)	3 (0.14)
Diabetes*	111 (13.20)	214 (17.09)	325 (15.53)
Cerebrovascular Diseases*	97 (11.53)	190 (15.18)	287 (13.71)
Liver Diseases	60 (7.13)	116 (9.27)	176 (8.41)
Tumour*	95 (11.30)	175 (13.98)	270 (12.90)
Charlson Comorbidity Index			
0*	303 (36.03)	319 (25.48)	622 (29.72)
1-2	353 (41.97)	548 (43.77)	901 (43.05)

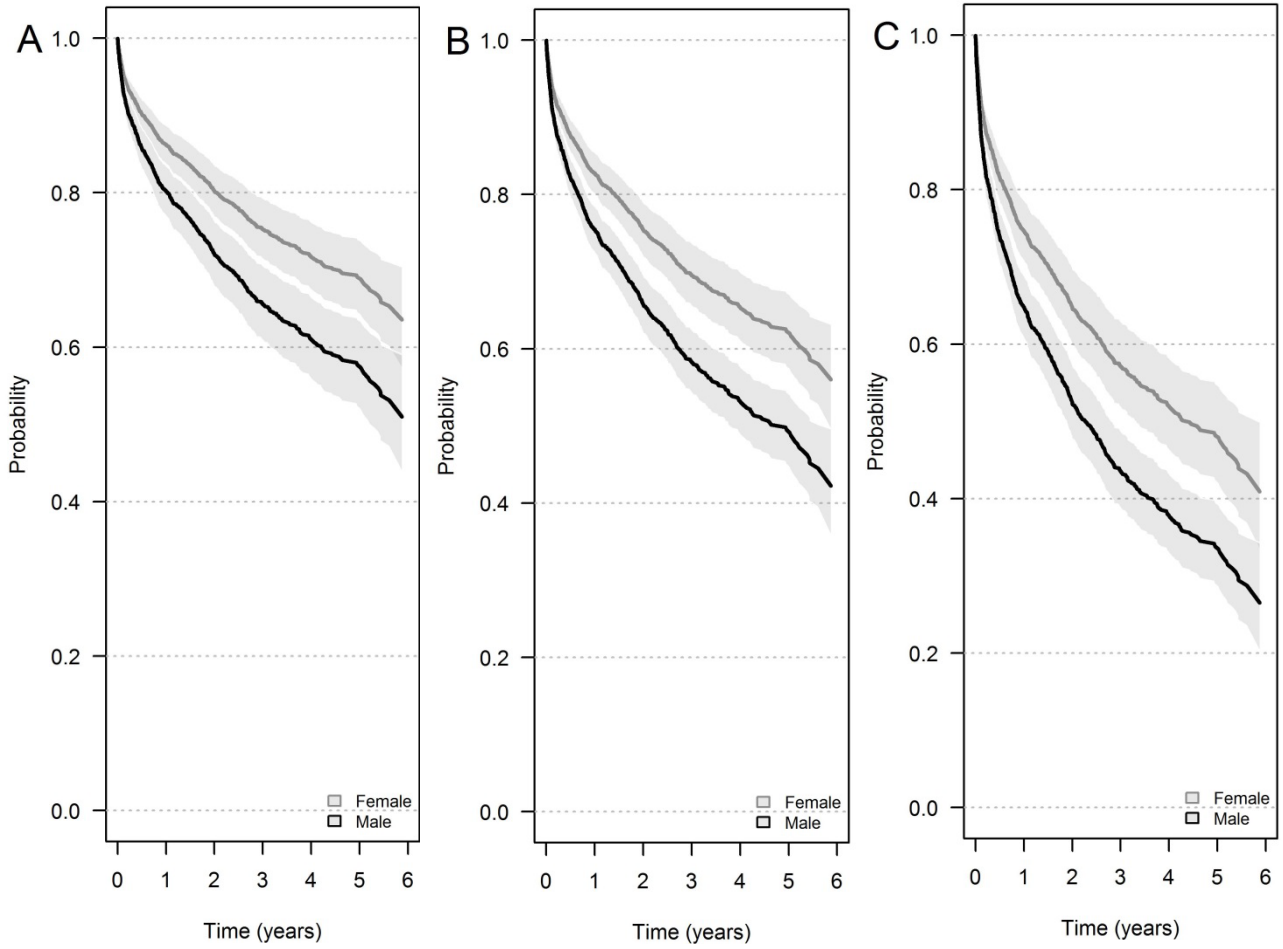
**p-value<0.05, Female vs. Male*

Outcomes of interest during the follow-up

	Female	Male	Total
N	841	1,252	2,093
Deaths, n (%)*	271 (32.22)	553 (44.17)	824 (39.37)
Drop-out, n (%)	6 (0.71)	12 (0.96)	18 (0.86)
Patients hospitalized, n (%)			
For any cause*	510 (60.64)	828 (66.13)	1,338 (63.93)
For causes related to IPF	221 (26.28)	375 (29.95)	596 (28.48)
Patients hospitalized in acute wards, n (%)			
For any cause*	449 (53.39)	759 (60.62)	1,208 (57.72)
For causes related to IPF*	161 (19.14)	311 (24.84)	472 (22.55)
Survival time (years), mean ± s.e.*	4.07 ± 0.09	3.39 ± 0.08	3.66 ± 0.06
Time to a 1st admission in hospital (years), mean ± s.e.			
For any cause*	1.94 ± 0.09	1.53 ± 0.07	1.71 ± 0.06
For causes related to IPF*	4.12 ± 0.10	3.84 ± 0.09	3.96 ± 0.07
Time to a 1st admission in acute hospital ward (years), mean ± s.e.			
For any cause*	2.46 ± 0.10	1.92 ± 0.07	2.14 ± 0.06
For causes related to IPF*	4.65 ± 0.09	4.19 ± 0.09	4.38 ± 0.06

** p value <0.05 female vs male*

Survival probability during follow-up

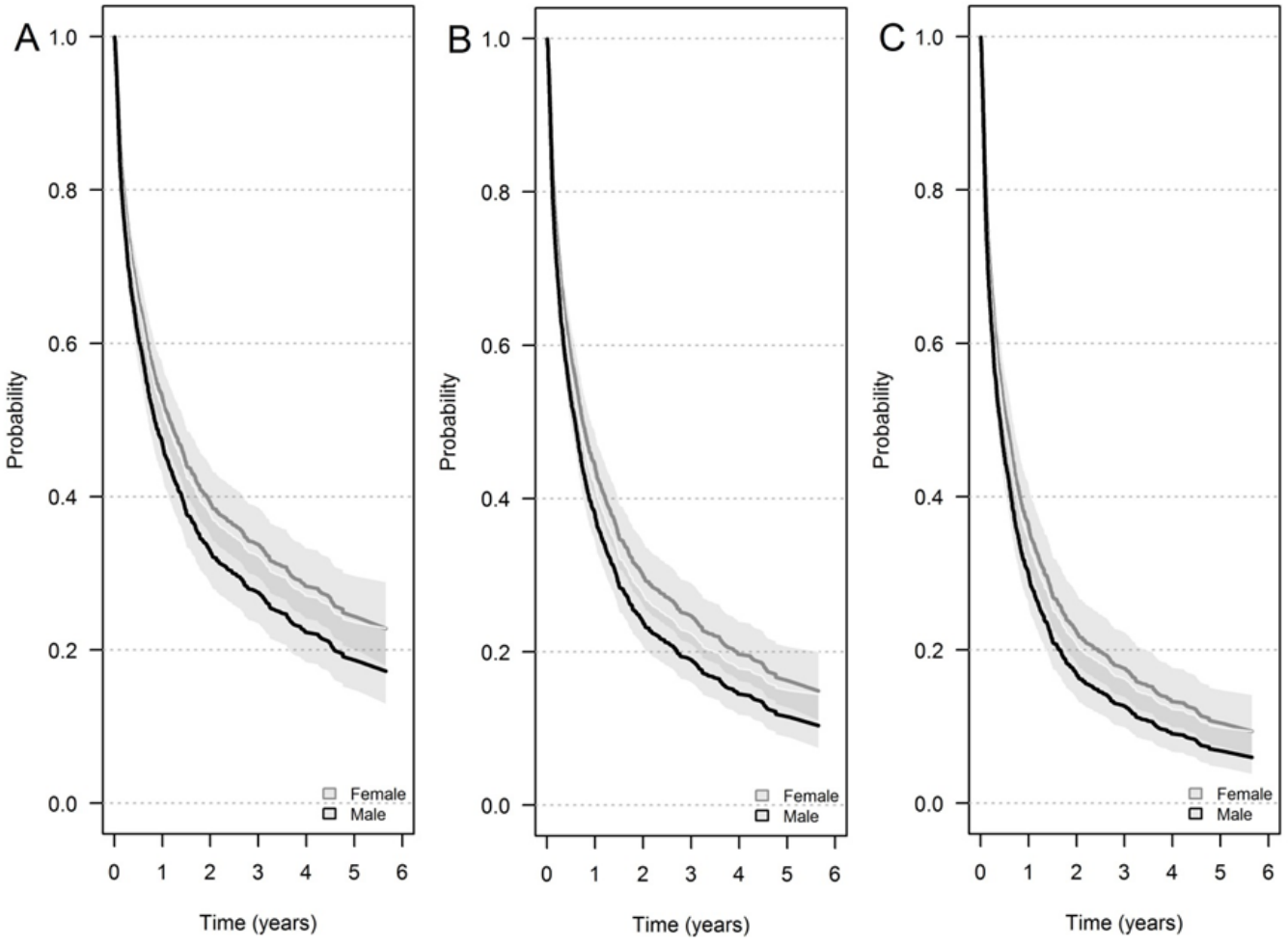


Panel A: *survival functions estimated by sex, for 70-year old patient (mean age at IPF onset) and no chronic comorbidities (CCI equal to 0).*

Panel B*: survival functions estimated by sex, for 70-year old patient (mean age at IPF onset) and CCI equal to 1 or 2.*

Panel C: *survival functions estimated by sex, for 70-year old patient (mean age at IPF onset) and CCI more than 2.*

Probability of a first hospital admission for any cause during follow-up



Panel A: *functions estimated by sex, for 70-year old patient (mean age at IPF onset) and no chronic comorbidities (CCI equal to 0).*

Panel B*: functions estimated by sex, for 70-year old patient (mean age at IPF onset) and CCI equal to 1 or 2.*

Panel C: *functions estimated by sex, for 70-year old patient (mean age at IPF onset) and CCI more than 2.*

Effect of baseline characteristics on outcomes during follow-up

	Hazard ratio (95% confidence interval)				
	Death	**Hospitalization for any cause**	**Hospitalization for causes relates to IPF**	**Hospitalization in acute wards for any cause**	**Hospitalization in acute wards for causes relates to IPF**
Covariates in multivariate model					
Age, years	1.058 (1.050-1.066)	1.008 (1.0004-1.013)	n.s.	1.013 (1.008-1.018)	n.s.
Sex					
Male (reference Female)	1.486 (1.283-1.722)	1.189 (1.063-1.329)	1.246 (1.055-1.471)	1.274 (1.133-1.434)	1.431 (1.183-1.731)
Charlson Comorbidity Index					
1-2 vs (reference 0)	1.280 (1.060-1.545)	1.287 (1.128-1.468)	n.s.	1.268 (1.103-1.458)	n.s.
>2 (reference 0)	1.972 (1.624-2.394)	1.599 (1.376-1.859)		1.670 (1.426-1.956)	

Population-based studies of IPF have been limited by reliance on diagnostic code-based algorithms that lack clinical validation

The poor positive predictive value (PPV) of the IPF algorithm likely is due to a combination of misdiagnosis at the clinical level and miscoding at the administrative level

A modified IPF algorithm was derived and validated to optimise the PPV by Ley's study

Ley B et al. Ann Am Thorac Soc 2017; 14: 880

Table 4. Criteria for the modified idiopathic pulmonary fibrosis algorithm

Criteria	Notes
Inclusion criteria	
Age ⩾50 yr	At time of first claim for either ICD-9 code 516.3 or ICD-9-CM code 516.31
At least two IPF diagnostic claims	At least two claims for either ICD-9 code 516.3 or ICD-9-CM code 516.31 at least 1 mo apart
Chest CT procedure claim*	Any chest CT procedure code prior to the first diagnostic claim for IPF
Exclusion criteria	
Any diagnostic claim for an alternative ILD diagnosis†	Any claims for alternative ILD codes occurring on or after the first claim for IPF

Definition of abbreviations: CT = computed tomography; ICD-9 = *International Classification of Diseases, Ninth Revision*; ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis.

*Chest CT procedure codes: ICD-9-CM 87.41 and Current Procedural Terminology, 4th Edition, codes 71250, 71260, and 71270.

†Exclusionary ICD-9 codes for alternative ILD diagnoses: 135, 237.7, 272.7, 277.3, 277.8, 446.21, 446.4, 495, 500–505, 506.4, 508.1, 508.8, 516.0, 516.1, 516.32–516.37, 516.2, 516.8, 516.9, 517.0, 517.2, 517.8, 518.3, 555, 710.0, 710.0–710.4, 714.0, 714.81, 720, and 759.5.

Ley B et al. Ann Am Thorac Soc 2017; 14: 880

	Ley's definition	Added patients	Total (Ley's definition modified)	*p-value*
N	460	1,244	1,704	
Male, n (%)	286 (62.17)	737 (59.24)	1,023 (60.04)	*0.2731*
Age at onset				
mean ± sd	71.76 ± 9.19	72.96 ± 9.37	72.63 ± 9.34	
median (q1-q3)	73 (65-79)	74 (66-80)	74 (66-80)	*0.0222*
Chronic comorbities at IPF onset, n (%)				
Myocardial infarction	51 (11.09)	157 (12.62)	208 (12.21)	*0.3906*
Congestive heart failure	87 (18.91)	300 (24.12)	387 (22.71)	*0.0229*
Peripheral vascular disease	40 (8.70)	111 (8.92)	151 (8.86)	*0.8835*
Dementia	4 (0.87)	16 (1.29)	20 (1.17)	*0.4784*
Chronic pulmonary disease	190 (41.30)	547 (43.97)	737 (43.25)	*0.3239*
Peptic ulcer disease	6 (1.30)	22 (1.77)	28 (1.64)	*0.5035*
Renal disease	29 (6.30)	116 (9.32)	145 (8.51)	*0.0473*
AIDS/HIV	1 (0.22)	1 (0.08)	2 (0.12)	*0.4671*
Diabetes	88 (19.13)	220 (17.68)	308 (18.08)	*0.4912*
Cerebrovasular disease	58 (12.61)	197 (15.84)	255 (14.96)	*0.0973*
Liver disease	36 (7.83)	116 (9.32)	152 (8.92)	*0.3353*
Tumor	54 (11.74)	202 (16.24)	256 (15.02)	*0.0210*
Charlson comorbities index at onset				*0.0023*
No chronic comorbidities	136 (29.57)	306 (24.60)	442 (25.94)	*0.0378*
1-2	209 (45.53)	520 (41.80)	729 (42.78)	*0.1783*
≥3	115 (25.00)	418 (33.60)	533 (31.28)	*0.0007*

Outcome of interest during follow-up – COX models

Death

Ley's definition modified	
Parameter	**Hazard Ratio (95% CI)**
Male (ref. Female)	1.416 (1.216-1.649)
Age (year)	1.049 (1.040-1.058)
No comorbidities (ref. CCI >2)	0.548 (0.448-0.671)
CCI 1-2 (ref. CCI >2)	0.694 (0.591-0.814

Ley's definition	
Parameter	**Hazard Ratio (95% CI**
Male (ref. Female)	1.511 (1.159-1.971)
Age (year)	1.032 (1.018-1.047)
No comorbidities (ref. CCI >2)	0.732 (0.527-1.017)
CCI 1-2 (ref. CCI >2)	0.688 (0.511-0.925)

Hospital admission for any cause

Ley's definition modified	
Parameter	**Hazard Ratio (95% CI**
Male (ref. Female)	1.231 (1.092-1.387)
Age (year)	1.007 (1.001-1.014)
No comorbidities (ref. CCI >2)	0.621 (0.530-0.729)
CCI 1-2 (ref. CCI >2)	0.849 (0.742-0.972)

Ley's definition	
Parameter	**Hazard Ratio (95% CI**
Male (ref. Female)	1.169 (0.959-1.425)
Age (year)	0.996 (0.985-1.007)
No comorbidities (ref. CCI >2)	0.801 (0.616-1.043)
CCI 1-2 (ref. CCI >2)	0.930 (0.734-1.180)

Conclusions

Our data source provided one of the largest samples of unselected patients ever considered in recent years with a long period of follow up

Our study, based on real-life data, confirmed that the risk of death and hospitalization is high in IPF patients

Age, sex, and **comorbidities** play a role in the clinical course of the disease

Conclusions

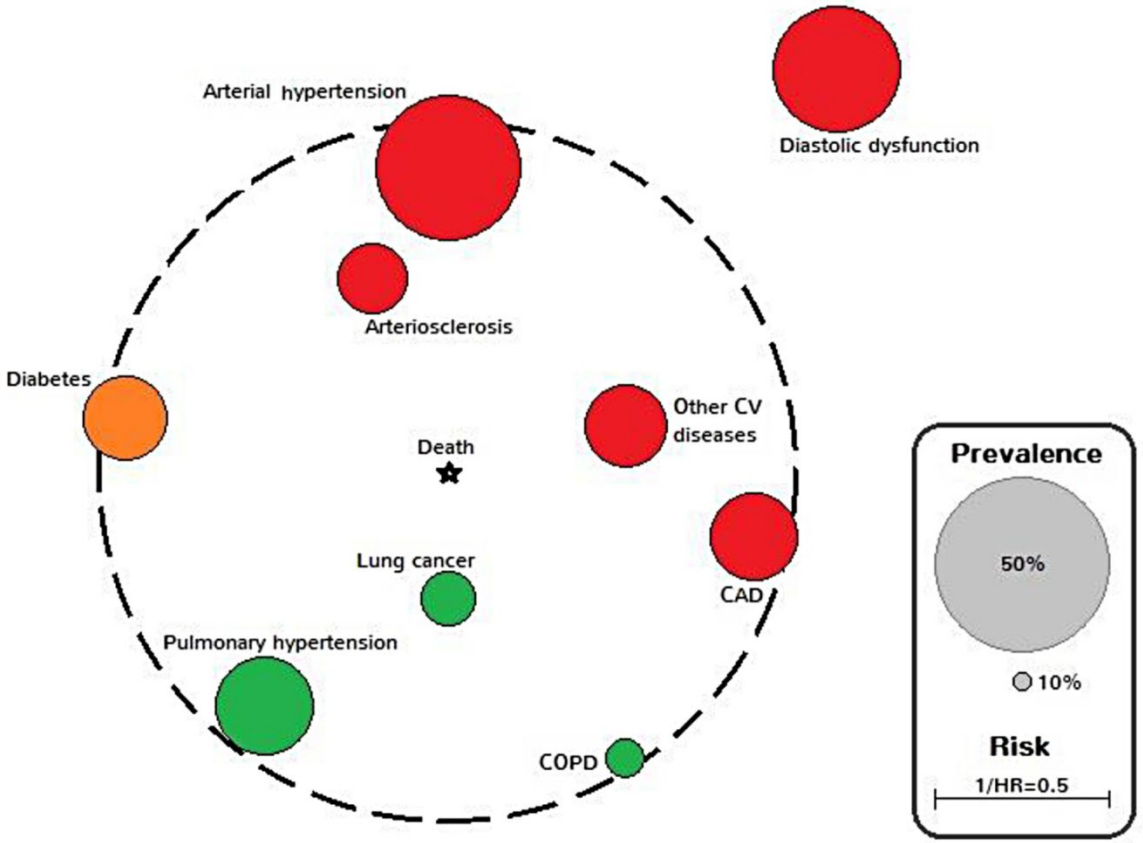
Our data provide evidence that disease prognosis is significantly worse in men both for a higher and earlier mortality and shorter time to first hospitalization

The number of comorbidities influences prognosis

From the methodological point of view, our data are confirmed and validated after application of Ley's criteria and definition and this support the confidence on our results

IPF comorbidome

Kreuter M et al. PLoS ONE 2016; 11 (3): e0151425



Red = CV
Green = pulmonary
Orange = others

Circle size relates to prevalence. Distance from the centre of the circle relates to the strength of the association with risk of death

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular.

The added value of comorbidities in predicting survival in idiopathic pulmonary fibrosis: a multicenter observational study

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Torrisi SE et al. Eur Respir J 2018; doi: 10.1183/13993003.01587-2018

The Gender-Age-Physiology (GAP) model was developed to predict the risk of death

We evaluated the ability of comorbidities to improve prediction of survival in IPF patients beyond the variables included in the GAP model.

We developed a prediction model named TORVAN using data from two independent cohorts.

The inclusion of comorbidities in TORVAN models significantly improved the discriminative performance in prediction of risk of death comparing to GAP.

Conclusions

- Comorbidities are common in IPF patients and many of these can have an impact on survival and prognosis
- The real prevalence of comorbidities varies in different studies and is difficult to define
- We have to adopt a global approach to IPF patients and consider all possible managing options, including the proactive identification and treatment of comorbidities
- We go toward the concept of personalized medicine also in IPF patients

Thank you