Original Article

A survival analysis of idiopathic pulmonary fibrosis in the context of antifibrotic therapy in Saudi Arabia

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Submission: 14-07-2022
Revised: 14-10-2022
Accepted: 19-10-2022
Published: 25-04-2023

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/atm.atm_264_22

Abstract:

BACKGROUND: The prognosis of idiopathic pulmonary fibrosis (IPF) can be predicted by the gender, age, and physiology (GAP) index. However, antifibrotic therapy (i.e., nintedanib and pirfenidone) may improve survival.

AIMS: This study aimed to compare the outcomes of antifibrotic-treated IPF with the survival predicted by the GAP index.

METHODS: A retrospective cohort study was conducted from March 2014 to January 2020. The electronic health-care records of all IPF patients treated with nintedanib or pirfenidone were reviewed. Besides standard demographic and mortality data, the variables required to calculate the GAP index were also extracted.

RESULTS: Eighty-one patients (male 55, 68%; age 71.4 ± 10.2 years) with IPF received antifibrotic therapy (nintedanib 44.4%; pirfenidone 55.6%; mean follow-up 35 ± 16.5 months). Cumulative mortality (whole cohort 3 years 12%; 4 years 26%; 5 years 33%) was significantly less than predicted by the GAP index.

CONCLUSIONS: The survival of antifibrotic-treated IPF is better than predicted by the GAP index. Novel systems for prognostication are required. The survival benefit from pirfenidone and nintedanib seem similar overall.

Keywords:

Antifibrotic therapy, idiopathic pulmonary fibrosis, mortality, nintedanib, pirfenidone, survival analysis

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic disease of the lungs.[1,2] It is characterized by nonproductive cough and exertional breathlessness.[2-4] The median survival of patients with IPF has been reported to range from 2.5 to 3.5 years.[2,5]

The clinical course of IPF varies considerably. Progression may occur gradually over years or acute exacerbation may cause rapid deterioration of lung function that could result in death within months.[6-8] Treatment guidelines have stated that death from respiratory failure is inevitable within 5 years of diagnosis.[2] Various patient characteristics have been associated with increased risk of mortality.[8,9] These predictors have been combined into scoring systems to stage IPF and facilitate prognostication. The gender (G), age (A), and physiology (P) index[9] is one of the most widely used staging systems for IPF. The data used to derive the gender, age, and physiology (GAP) model was obtained from three large cohorts of patients in the United States of America (USA) and Italy.[9] Stages of IPF (I, II and III) can be defined by the GAP index. This simple screening tool for

How to cite this article: Khan MA, Ghamdi BA, Alhamadi M, Rajendram R, Alyami S, Ghamdi MA, *et al*. A survival analysis of idiopathic pulmonary fibrosis in the context of antifibrotic therapy in Saudi Arabia. Ann Thorac Med 2023;18:79-85.

risk stratification and prognostication can guide clinical decisions in individual patients.[10] However, these data were derived from studies conducted prior to the advent of antifibrotic therapies.

Randomized controlled trials have reported that pirfenidone and nintedanib can slow the rate of fall in their forced vital capacity in patients with IPF.[11-13] Thus, antifibrotic therapies have been approved for the treatment of IPF.[14]

In 2011 pirfenidone became the first therapy to be licensed for the treatment of IPF in Europe.[15] Then, in 2014 pirfenidone and nintedanib were both approved by the food and drug administration of the USA.[1]

Very few studies have compared the efficacy of pirfenidone and nintedanib. A meta-analysis published in 2016 failed to find any significant differences in safety or disease progression.[16] Two other retrospective observational studies have also suggested that the efficacy and tolerability of the two antifibrotic drugs are similar.[17,18]

Pragmatic analyses have suggested that pirfenidone and nintedanib can slow the progression of IPF and may improve survival.[19-21] Thus, it is important to re-validate the GAP index in a cohort of patients established on antifibrotic therapy.

The primary objective of this pragmatic study was to compare the mortality of IPF treated with antifibrotic therapy at a tertiary center in Saudi Arabia with the mortality predicted by the GAP index. The secondary objective was to compare the mortality in the nintedanib-treated subgroup with that in pirfenidone-treated subgroup.

Methods

A single-center retrospective cohort study was performed. All patients who were treated for IPF with an antifibrotic agent between March 2014 and December 2020 were identified. Pirfenidone has been available for prescription at our institution since March 2014. Nintedanib was added to the hospital formulary in December 2015.

All included patients were diagnosed with IPF according to international guidelines (ATS/ERS/JRS/ALAT 2011) after discussion in interstitial lung disease (ILD) multi-disciplinary team meetings involving pulmonologists, radiologists, and pathologists with subspecialty training in ILD. Prior to initiation, the risks and benefits of anti-fibrotic therapy were discussed with the patients and their families. Antifibrotic agents were prescribed as per their manufacturer's recommendations (nintedanib 150 mg twice daily or pirfenidone titrated up to 801 mg three times a day as tolerated). Lung function tests, full blood count, urea and electrolytes, bilirubin, albumin, and liver enzymes were performed prior to initiating antifibrotic therapy and periodically thereafter. Each patient had 3 monthly follow-ups in the outpatient clinics. Each visit addressed compliance with antifibrotic therapy and evaluated dosing and side effects as well as screening for any change in symptoms, intervening infections, and hospital admissions.

In addition to standard demographic data (i.e., age and sex), information was also collected about smoking, imaging, pathology, lung function tests, walk tests, antifibrotic therapy (i.e., choice of agent, the time from diagnosis to initiation, and duration of therapy), and mortality.

The relevant data were used to calculate the GAP index and stage as described by Ley *et al*.[9,10] and Kolb and Collard. The Institutional Review Board of our institution approved this study.

Study outcomes

Mortality data were stratified by antifibrotic therapy (i.e., nintedanib or pirfenidone) and disease stage according to the GAP index (stage 1: 0–3; stage 2: 4–5; stage 3: 6–8). The mortality associated with each stratum was compared with the predicted mortality based on the GAP stage.

Data analysis

Continuous data are presented as means ± standard deviation. These data were compared using Student's *t*-tests, analysis of variance (ANOVA), and Tukey's honest significant difference (HSD) test as appropriate. Categorical variables presented as frequency (n) and percentage were compared using the Fisher's exact test or the Chi-squared test. Confidence intervals (CIs) were also determined. Standardized mortality ratios (SMRs) were also calculated using the predicted mortality based on the GAP stage. Risk ratios were calculated to compare the mortality associated with nintedanib and pirfenidone. When no deaths occurred in either of the subgroups being compared, the SMR was considered to be 1. A priori subgroup analyses were performed on antifibrotic therapy, GAP stages, and duration after diagnosis. All statistical analyses besides the Kaplan–Meier survival analyses were performed using Excel version 2016 (Microsoft, Redmond, United States of America). Statistical significance was accepted when $P < 0.05$.

Results

The study included 81 patients; male 55 (68%); mean age 71.4 ± 10.2 years, 36 (44.4%) were treated with nintedanib and the rest 45 (55.6%) were treated with pirfenidone. The patients' characteristics are presented in Table 1. One patient was initially treated with pirfenidone but was subsequently changed to nintedanib. This patient was analyzed with the nintedanib subgroup. Two patients were initially treated with nintedanib but were subsequently changed to pirfenidone. These patients were analyzed with the pirfenidone subgroup.

The mean duration of follow-up was nearly 3 years (35 ± 16.5 months). The follow-up of the pirfenidone-treated subgroup (42 ± 17 months) was longer than that of the patients who received nintedanib (27 ± 11 months). Table 1 describes the follow-up period.

The disease stage as defined by the GAP index is presented in [Table 2]. Nearly half of the study population 39 (48.1%); nintedanib 15 (41.7%); pirfenidone 24 (53.3%) were classified as stage 3. Approximate a quarter 19 (23.5%), nintedanib 11 (30.6%) and pirfenidone 8 (17.8%), were stage 1 and the rest 23 (28.4%), nintedanib 15 (27.8%) and pirfenidone 13 (28.9%), were stage 2.

One-way ANOVA revealed that there was a statistically significant difference in mean age between at least two disease stage groups in the whole cohort $P = 0.01$) as well as the nintedanib $P = 0.026$) and pirfenidone subgroups $P = 0.01$). Tukey's HSD Test for multiple comparisons found that the mean age of the stage 3 subgroups was significantly different from the mean age of the stage 1 and stage 2 subgroups for the whole cohort (1 vs. 3, $P = 0.001$; 2 vs. 3, $P = 0.001$; 1 vs. 2, $P = 0.37$) and the pirfenidone subgroup (1 vs. 3, $P = 0.001$; 2 vs. 3, $P = 0.001$; 1 vs. 2, $P = 0.59$). Tukey's HSD Test for multiple comparisons found that the mean age of the stage 3 subgroup was significantly different from the mean age of the stage 1 subgroup for the nintedanib subgroup (1 vs. 3 $P = 0.048$; 2 vs. 3, $P = 0.066$; 1 vs. 2, $P = 0.90$).

The survival and mortality in the cohort over the entire follow-up period are shown in Table 2. It is stratified

Table 1: Demographic and baseline clinical data

	Antifibrotic therapy			Whole cohort (*n*=81), *n* (%)
	Nintedanib (*n*=36), *n* (%)	Pirfenidone (*n*=45), *n* (%)	*P*	
Demographics				
Age (years), mean±SD	68.8±11.5	73.4±8.8	0.04	71.4±10.2
Gender				
Male	24 (67)	31 (68)	0.83	55 (67.9)
Female	12 (33)	14 (32)		26 (32.1)
Smoking history				
Current	2 (6)	3 (7)	0.71	5 (6.2)
Ex-smoker	14 (39)	13 (29)		27 (33.3)
Nonsmoker	20 (56)	29 (64)		49 (60.5)
Investigations				
UIP pattern on CT				
Definite	18 (50)	27 (60)	0.34	45 (55.6)
Probable	12 (33)	15 (33)		27 (33.3)
Inconsistent	6 (17)	3 (7)		9 (11.1)
Surgical lung biopsy				
No	22 (61)	38 (84)	0.02	60 (74.1)
Yes	14 (39)	7 (16)		21 (25.9)
Lung function tests (percentage predicted), mean±SD				
FEV1	67.7±17.6	69±16.8	0.76	68.3±16.3
FVC	58.8±16.5	62.9±16.8	0.54	61.5±14.4
TLCO	52.8±10.8	54.5±13.7	0.66	53.7±12.2
6 min walk test				
Distance (m), mean±SD*	275.6±105.4	257.2±85.6	0.72	266.9±96.1
O_2 desaturation (<90%)				
No	6 (17)	5 (11)	0.5263	11 (13.6)
Yes	30 (83)	20 (44)	0.0005	50 (61.7)
Unable to walk/could not attempt	6 (16.7)	20 (44)	0.0091	20 (24.7)
Follow-up				
Duration (months), mean±SD	27±11	42±17	0.000015	35±16.5

*Mean significant. SD=Standard deviation, FEV1=Forced expiratory volume over 1 second, FVC=Forced vital capacity, UIP=Usual interstitial pneumonia, CT=Computerized tomography, TLCO=Transfer capacity of lung for carbon monoxide uptake

by antifibrotic therapy, and the disease stage as defined by the GAP index. The distribution of the patients who died by age and gender is shown in Table 3. Kaplan–Meier survival analyses for the whole cohort and each antifibrotic therapy and subdivided by the GAP stage are shown in Figures 1 and 2. The data presented in Table 4 are derived from the Kaplan–Meier survival analyses [Figures 1 and 2].

The cumulative mortality of the whole cohort was only 12% at 3 years but increased to 26.3% at 4 years and 33% at 5 years, the mortality in the pirfenidone-treated subgroup 5 years after diagnosis was 31% and the mortality in the nintedanib-treated subgroup 4 years after diagnosis was 32% [Table 4]. As shown in Table 4, 5 years after diagnosis mortality was greater in stage 3 IPF (63%) than in stage 2 (25%) or stage 1 (6%) and mortality was greater in stage 3 IPF (56%) than in stage 2 (25%) or stage 1 (0%).

The predicted mortality of the present cohort based on the GAP stage is shown in Table 5. The observed cumulative annual mortality in each GAP stage subgroup of the whole cohort was significantly lower than that predicted by the GAP index (i.e. 95% CIs of SMR <1, except for the GAP stage 1 patients at years 2 (SMR 0.51, CI – 0.46–1.49) and 3 (SMR 0.34, CI – 0.31–1) after diagnosis. Similarly, the 95% CI of the SMR of each GAP stage subgroup of the nintedanib-treated patients was below 1 besides those GAP stage 1 patients at 2 (0.83, CI – 0.8–2.47) and 3 years (0.56, CI – 0.54–1.65) after diagnosis. The SMR of each GAP stage subgroup of the pirfenidone-treated patients was significantly below 1.

The Kaplan–Meier curves are shown in Figures 1 and 2; the mortality in the pirfenidone subgroup gradually increased from 27 months after diagnosis. The survival of the nintedanib subgroup fell gradually from 7 to 20 months then fell sharply at 42 months. However, survival with nintedanib and pirfenidone did not differ significantly in the Kaplan–Meier analyses. The mortality associated with pirfenidone was significantly lower than that associated with nintedanib in some GAP stage subgroups.

Discussion

Physicians often view IPF with a degree of therapeutic nihilism. This is not surprising as the most recent guidelines state that death from respiratory failure is inevitable within 5 years of diagnosis.[2] However, the

Table 2: Mortality data with the duration of follow-up

Treatment	Whole cohort				Nintedanib				Pirfenidone			
	Alive, *n* (%)	Died, *n* (%)	Total, *n* (%)	Mean follow-up (months), *n* (%)	Alive, *n* (%)	Died, *n* (%)	Total, *n* (%)	Mean follow-up (months), *n* (%)	Alive, *n* (%)	Died, *n* (%)	Total, *n* (%)	Mean follow-up (months), *n* (%)
GAP score (stage)												
0-3 (1)	18 (94.7)	1 (5.3)	19	37.7	10 (90.9)	1 (9.1)	11	29	8 (100)	0	8	50
4-5 (2)	21 (91.3)	2 (8.7)	23	37.6	10 (100)	0	10	22	11 (84.6)	2 (15.4)	13	49.9
6-8 (3)	26 (66.7)	13 (33.3)	39	32.1	12 (80)	3 (20)	15	28	14 (58.3)	10 (41.7)	24	34.5
All	65 (80.2)	16 (19.8)	81	35	32 (88.9)	4 (11.1)	36	27	33 (73.3)	12 (26.7)	45	41.7

GAP=Gender, age, and physiology

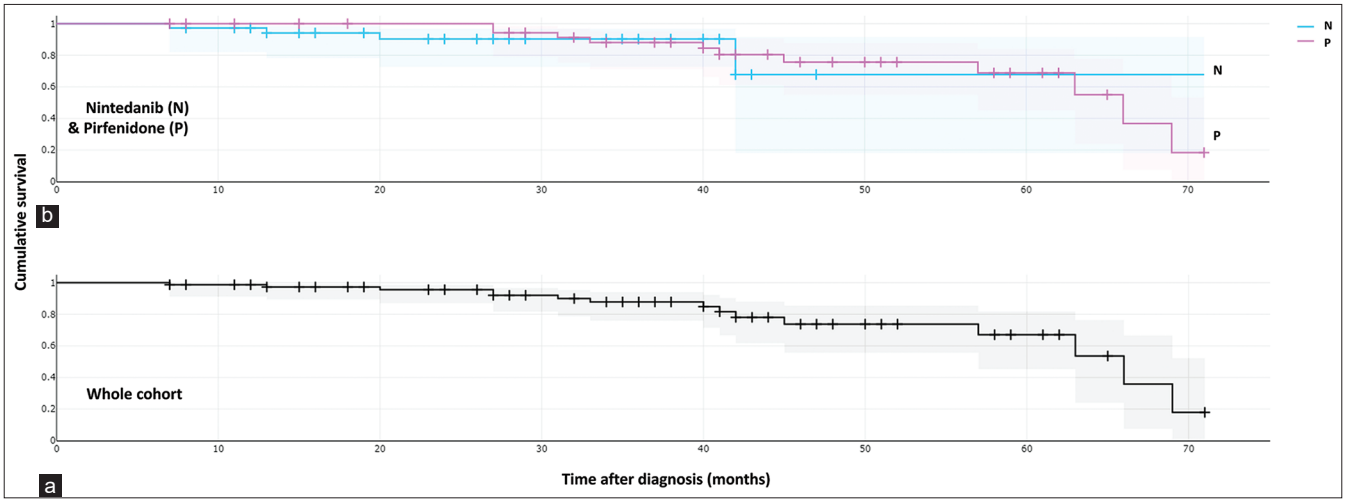

Figure 1: Kaplan–Meier survival curves showing the whole cohort (a) with idiopathic pulmonary fibrosis and the subgroups of patients treated with antifibrotic therapy (nintedanib and pirfenidone; (b). There is no statistically significant difference between pirfenidone and nintedanib. Figure adapted from Statistics Kingdom (2017)

Table 3: Observed mortality with antifibrotic treatment

Treatment group	Whole cohort				Nintedanib				Pirfenidone			
GAP index	0-3	4-5	6-8	0-8	0-3	4-5	6-8	0-8	0-3	4-5	6-8	0-8
Stage	1	2	3	All	1	2	3	All	1	2	3	All
n	19	23	39	81	11	10	15	36	8	13	24	45
Mortality												
Female, *n* (%)	9 (47.4)	7 (30.4)	10 (25.6)	26 (32.1)	5 (45.5)	5 (50)	2 (13.3)	12 (33.3)	4 (50)	2 (15.4)	8 (33.3)	14 (31.1)
Male, *n* (%)	10 (52.6)	16 (69.6)	29 (74.4)	55 (67.9)	6 (54.5)	5 (50)	13 (86.7)	24 (66.7)	4 (50)	11 (84.6)	16 (66.7)	31 (68.9)
Age (mean±SD)	64.6 (7.9)	67.3 (11.1)	77.1 (7.4)	71.4 (10.3)	64.4 (8.7)	64.7 (14.5)	74.7 (8.6)	68.8 (11.5)	65 (7.3)	69.2 (7.7)	78.5 (6.4)	73.4 (8.8)

SD=Standard deviation, GAP=Gender, age, and physiology

5-year mortality in the present cohort was only 33%. This is substantially better than that predicted by the GAP index stage. A study by Kim *et al*. in non-Western evaluated the clinical course of IPF and validated the GAP model in Korean patients with IPF reached same conclusion.[22] Another study included 832 with interstitial lung fibrosis using composite physiologic index and GAP as a predictor of outcome concluded both indexes have limited capability to accurately predict survival outcomes.[23]

A recent study reported incorporating semi-quantitative fibrotic score from thin-section Computed tomography and GAP score provided a better prediction for survival in IPF.[24] However, these findings need to be confirmed in prospective studies.

Ley *et al*.[9] developed the GAP index from cohorts that did not receive antifibrotic therapy. Consistent with previous studies our observations suggest that antifibrotic therapy improves survival in patients with IPF.[19-21]

In the present study, the overall mortality with nintedanib was similar to that with pirfenidone. There are no randomized data directly comparing these antifibrotic agents and previous observational studies have not found any significant differences in disease progression.[16-18] However, in some GAP stage subgroups of our cohort the survival with pirfenidone may have been better than that with nintedanib. However, this is a small sample and large randomized controlled head-to-head trials are required to clarify this.

In our study, the mortality in the GAP stage 3 subgroup was greater than the mortality in the stage 1 and 2 subgroups. This suggests that the mortality increases with the severity of disease. However, age is one of the variables included in the GAP index.[9] The patients in the GAP stage 3 subgroup were significantly older than those in the GAP stage 1 and 2 subgroups. The cumulative mortality in the present cohort also increased with time. This suggests that the efficacy of antifibrotic therapy may decrease with severity of the disease or aging.

The lack of data on the cause of death and single-center experience are important limitations of the present study. The cause of death of some patients in the present cohort may not have been due to IPF. Indeed, the follow-up period of the present study also included the Coronavirus disease 2019 (COVID-19) pandemic. Thus, some of the mortality reported in the present study may have been related to COVID-19. Other limitations include the retrospective and observational nature of this single-center study.

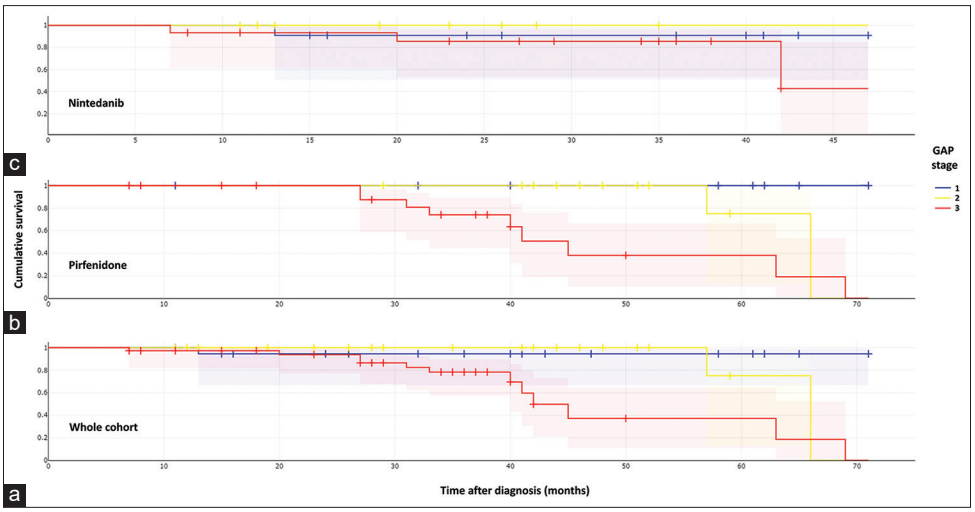

Figure 2: Kaplan–Meier survival curve showing the whole cohort (a) of patients with idiopathic pulmonary fibrosis and the subgroups of patients treated with either pirfenidone (b) or nintedanib (c) stratified into disease stages by the GAP index points (stage 1: 0–3 points; stage 2: 4–5 points; stage 3: 6–8 points) Confidence intervals are shown. Figure adapted from Statistics Kingdom (2017). GAP: Gender, age, and physiology

Table 4: Cumulative annual mortality on antifibrotic therapy

Treatment group	Whole cohort				Nintedanib				Pirfenidone			
GAP index	0-3	4-5	6-8	0-8	0-3	4-5	6-8	0-8	0-3	4-5	6-8	0-8
Stage	1	2	3	All	1	2	3	All	1	2	3	All
Time after diagnosis (years)	Mortality (%)											
1	0.0	0.0	2.8	1.3	0.0	0.0	6.7	2.8	0.0	0.0	0.0	0.0
2	5.6	0.0	6.3	4.4	9.1	0.0	14.4	9.7	0.0	0.0	0.0	0.0
3	5.6	0.0	21.7	12.2	9.1	0.0	14.4	9.7	0.0	0.0	21.7	10.6
4	5.6	0.0	62.7	26.3	9.1	NA	57.2	32.3	0.0	0.0	56.3	24.5
5	5.6	25.0	62.7	33.0	NA	NA	NA	NA	0.0	25.0	56.3	31.3

GAP=Gender, age, and physiology, NA=Not available

Table 5: Predicted annual mortality based on disease stage as defined by the gender, age, and physiology index

Treatment group	Whole cohort				Nintedanib				Pirfenidone			
GAP index	0-3	4-5	6-8	0-8	0-3	4-5	6-8	0-8	0-3	4-5	6-8	0-8
Stage	1	2	3	All	1	2	3	All	1	2	3	All
Time after diagnosis (years)	Mortality, *n* (%)											
1	1.1 (5.6)	3.7 (16.2)	15.3 (39.2)	20.1	0.6 (5.6)	1.6 (16.2)	5.9 (39.2)	8.1	0.4 (5.6)	2.1 (16.2)	9.4 (39.2)	12
2	2.1 (10.9)	6.9 (29.9)	24.2 (62.1)	33.2	1.2 (10.9)	3 (29.9)	9.3 (62.1)	13.5	0.9 (10.9)	3.9 (29.9)	14.9 (62.1)	19.7
3	3.1 (16.3)	9.7 (42.1)	30 (76.8)	42.7	1.8 (16.3)	4.2 (42.1)	11.5 (76.8)	17.5	1.3 (16.3)	5.5 (42.1)	18.4 (76.8)	25.2

GAP=Gender, age, and physiology

The accurate staging of IPF is important. It can guide treatment decisions and patient counseling. Besides this important role of staging systems in clinical practice, trial design also requires precise measurements of disease severity to allow risk prediction.[10] Our observations similar to other studies[22,23] suggest that the GAP index should not be used for prognostication in clinical practice or research. Thus, there is an urgent need for a novel staging system that uses composite of radiological, physiological, and biomarkers to accurately reflect the survival of patients with IPF in the era of antifibrotic therapy.

Although still in its infancy, the development of biological biomarkers of several diseases is advancing rapidly.[25,26] The most dynamic system of gauging disease severity in IPF is likely to integrate biomarkers with longitudinal physiological data and changes identified on imaging.[10,24]

Conclusions

There were no significant differences in the overall survival of patients treated with nintedanib or pirfenidone. However, subgroup analyses suggested that in select cases the mortality with pirfenidone may have been lower than with nintedanib. A large, randomized head-to-head comparison is required to clarify this. The survival of patients with IPF treated with antifibrotic

therapy is significantly better than that predicted by the GAP index. Novel staging systems for IPF are urgently required. As understanding of the pathophysiology of IPF improves, biomarkers may become increasingly important in the assessment of disease severity.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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