Article Type: Original Article

The prognostic role of Gender-Age-Physiology system in idiopathic pulmonary fibrosis patients treated with pirfenidone.

Sergio Harari[1], Antonella Caminati[1], Marco Confalonieri[2], Venerino Poletti[3,4], Carlo Vancheri[5], Alberto Pesci[6], Paola Rogliani[7], Fabrizio Luppi[8], Carlo Agostini[9], Paola Rottoli[10], Alessandro Sanduzzi Zamparelli[11], Alfredo Sebastiani[12], Rossana Della Porta[2], Francesco Salton[2], Barbara Messore[13], Sara Tomassetti[3], Roberta Rosso[5], Alice Biffi[6], Ermanno Puxeddu[7], Stefania Cerri[8], Francesco Cinetto[9], Rosa Metella Refini[10], Marialuisa Bocchino[11], Loreta Di Michele[12], Claudia Specchia[14,15], Carlo Albera[13] for the ILDINET (Interstitial Lung Diseases Italian Network).

[1]U.O. di Pneumologia e Terapia Semi-Intensiva Respiratoria – Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare. Ospedale San Giuseppe – MultiMedica, IRCCS, via San Vittore 12, 20123 Milano (MI), Italy. sharari@hotmail.it, lafitta@libero.it

[2]Department of Pulmonology, University Hospital of Cattinara, Azienda Ospedaliero-Universitaria Ospedali Riuniti di Trieste, Trieste, Italy marco.confalonieri@aots.sanita.fvg.it, rossana.dellaporta@gmail.com, francesco.salton@gmail.com

[3] U.O. di Pneumologia Dipartimento dell'Apparato Respiratorio e del Torace Ospedale G.P. Morgagni –L. Pierantoni, Forlì, Italy venerino.poletti@gmail.com, s.tomassetti@gmail.com

[4]Department of Respiratory Diseases & Allergy Aarhus University Hospital (DK)

[5]Regional Referral Centre for Rare Lung Disease, University of Catania, A.O.U. Policlinico-Vittorio Emanuele, Catania, Italy vancheri@unict.it, rosso.roberta@yahoo.it

[6]Respiratory Unit, Department of Health Science, University of Milano Bicocca, AO San Gerardo, Monza, Italy alberto.pesci@unimib.it, alicebiffi@alice.it

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/crj.12999

[7]Respiratory Unit Policlinico Tor Vergata, Department of "Systems Medicine" University of Rome "Tor Vergata" Roma. paola.rogliani@uniroma2.it, ermannopux@libero.it

[8]Center for Rare Lung Diseases, University Hospital Policlinico di Modena, Modena, Italy fabrizio.luppi@unimore.it, stefania.cerri@unimore.it

[9]Department of Medicine – DIMED, University of Padova Italy carlo.agostini@me.com, francesco.cine@gmail.com

[10]Respiratory Diseases and Lung Transplant Unit, Department of Internal and Specialist Medicine, AOUS, Siena, Italy paola.rottoli@unisi.it, rosa.refini@unisi.it

[11]UOC II Pneumotisiologia, Scuola di specializzazione in malattie respiratorie Università degli Studi di Napoli Federico II A.O.R.N. Monaldi-Cotugno-CTO Piazzale Ettore Ruggieri, Napoli , sanduzzi@unina.it, marialuisa.bocchino@unina.it

[12]UOS Interstiziopatie Polmonari Az Osp. S. Camillo-Forlanini, Roma, Italy alfredosebastiani23@gmail.com lorydm1965@libero.it

[13]University of Turin, Department of Clinical and Biological Sciences, Interstitial and Rare Lung Disease Unit AOU San Luigi Gonzaga, 10043 Orbassano, (Turin) Italy carlo.albera@yahoo.it, barbara.messore@gmail.com

[14] Department of Molecular and Translational Medicine, University of Brescia, 25121, Italy;
[15] IRCCS MultiMedica

Corresponding author:

Sergio Harari, MD

U.O. di Pneumologia e Terapia Semi-Intensiva Respiratoria – Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare. Ospedale San Giuseppe – MultiMedica IRCCS, via San Vittore 12, 20123 Milano (MI), Italy.

Email: sharari@hotmail.it

Tel. +39 02 85994580

FAX: +39 02 85994400

Short running title: GAP-system in IPF treated with pirfenidone

Authorship statement: All authors have approved the final version of manuscript for submission and participated to the conception and design of the study, acquisition and interpretation of data and critical revision of manuscript. Sergio Harari and Antonella Caminati wrote the paper and Claudia Specchia is responsible for data statistical analysis.

Disclosure Statement: Dr. Harari reports personal fees from Roche, grants and personal fees from Intermune, grants and personal fees from Boehringer Ingelheim, outside the submitted work . Dr. Caminati reports personal fees from Roche, personal fees from Bohringer, outside the submitted work. Dr. Vancheri reports grants and personal fees from Roche, grants and personal fees from Boehringer Ingelheim, outside the submitted work. Dr. Rogliani participated as a lecturer, speaker, and advisor in scientific meetings and courses under the sponsorship of Boehringer Ingelheim, Intermune and Roche and consultant for Zambon. She also acted as a sub-investigator for clinical trials sponsored by Boehringer Ingelheim and Intermune. Dr. Luppi reports personal fees from Boehringer-Ingelheim, grants and personal fees from Roche, during the conduct of the study. Dr. Agostini reports personal fees from Boehringer Ingelheim, personal fees from Roche, outside the submitted work. Dr. Rottoli reports personal fees and other from Roche , personal fees from Boehringer ingelheim, grants and personal fees from Novartis , personal fees from TEVA, other from Menarini , outside the submitted work. Dr. Tomassetti reports personal fees from Roche, personal fees from Boehringer, outside the submitted work. Dr. Puxeddu participated as a lecturer, speaker, and advisor in scientific meetings and courses under the sponsorship of Boehringer Ingelheim. He also acted as a sub-investigator for clinical trials sponsored by Boehringer Ingelheim. Dr. Cerri reports personal fees from Roche, personal fees from Boehringer-Ingelheim, outside the submitted work. Dr. Cinetto reports personal fees from Boehringer Ingelheim, outside the

submitted work. Dr. Albera reports grants and personal fees from Roche, during the conduct of the study; personal fees from Roche, personal fees from Boheringer Ingelheim, outside the submitted work. Dr. Confalonieri, Dr. Poletti, Dr. Pesci, Dr. Sanduzzi Zamparelli, Dr. Sebastiani, Dr. Della Porta, Dr. Salton, Dr. Messore, Dr. Rosso, Dr. Biffi, Dr. Refini, Dr. Bocchino, Dr. Di Michele, Dr. Specchia, have no conflicts of interest to disclose

Abstract

Introduction: GAP system have proven to be an easy tool for predicting disease stages and survival in IPF patients.

Objective: To validate mortality risk as determined by the GAP system in a real-life multicenter IPF population treated with pirfenidone.

Methods: The study included patients who received pirfenidone for at least 6 months. The GAP calculator and the GAP index were determined. The primary outcome was all-cause mortality. The prognostic accuracy of the GAP system was evaluated with respect to calibration and discrimination.

Results and Conclusion: 68 IPF patients were enrolled in the study. The median follow-up was 2.4 years (range 0.1-7.4 years). A total of 22 deaths as first event (32%) and of 10 lung transplantation (15%) were recorded. The cumulative incidence of mortality at 1, 2, and 3 years was 10.4%, 22.4%, and 38.4%, respectively. The differences between the predicted and observed mortality were not significant for the GAP index while the observed mortality become comparable to that predicted by the GAP calculator only in the third year of follow up. The C-index for the GAP index was 0.74 (95% CI 0.57-0.93) while the C-statistic value for the GAP calculator was 0.77 (95% CI 0.59-0.95).

This is the first study that investigate the reliability of the GAP system as a predictive tool in the era of antifibrotic therapies in a national real life IPF population. In our cohort the GAP system showed a good discrimination index. Additional studies would be evaluable to determine the impact of treatment on model performance.

Keywords: mortality, survival, idiopathic pulmonary fibrosis, anti-fibrotic therapies, prognosis, staging.

Main text

Introduction

In recent years, there has been a growing interest in scores that allow to determine the severity of patients with idiopathic pulmonary fibrosis (IPF), to assess the prognosis, to evaluate possible treatment options including timing to transplant and to standardize cohorts of patients in controlled clinical studies (1-6). Among a number of different methods, the GAP index and the GAP calculator for the GAP Risk Assessment System (GAP system) have proven to be the most easy and applicable tool in the current clinical practice (1); however, there are still only few studies that have assessed their applicability and usefulness in daily practice. Furthermore, ethnicity has been reported as a factor that can influence the reliability of these two scoring systems, as demonstrated by the Korean and Japanese experiences (7, 8). Indeed, up until now most of the data have been derived from American studies (1). Finally, to our knowledge, there are still very few clinical trials that have evaluated the applicability of the GAP system in the era of antifibrotic therapies (9, 10).

We herewith report an Italian national multicentre experience aimed to validate the predictive value of the risk of death determined by these two indicators in a retrospective analysis of a cohort of patients with IPF who received pirfenidone, the first antifibrotic drug marketed for the treatment of this disease.

Materials and methods

Patient population and study design.

The study sample herewith considered is in part derived from a previous retrospective observational study carried out on continuous patients diagnosed with mild, moderate and severe IPF and treated with pirfenidone in the period between April 2011 and January 2013 (11); the study involved 12 interstitial lung disease centers across Italy that joined the European Named Patient Access Program (NPP). The Company that was involved in the development and marketing of pirfenidone in Europe has supported this program: InterMune Inc. has in fact allowed qualified physicians to make the newly approved pirfenidone available to their IPF patients, provided that pre-specified medical criteria and conditions were met, before it was commercially available within a given European country. The drug was made available to patients free of charge. Patients who had received steroids, azathioprine, or N-acetylcysteine (NAC) before pirfenidone therapy initiation were not excluded from the analysis; azathioprine and NAC were stopped before treatment with pirfenidone, low dose steroids (<15 mg/day) were continued in some patients. Data of patients who had been enrolled in the CAPACITY trials and subsequently entered the NPP program were also included (11).

All patients who received at least 6 months of treatment with the new antifibrotic drug and who had pulmonary function data available at six months after pirfenidone initiation where included in the study and followed up. The diagnosis of IPF was performed with criteria of the statement of ATS/ERS/JRS/ALT in 2011 (12).

The primary outcome was all-cause mortality ascertained. Lung transplantation was treated as a competing risk.

The GAP Risk Assessment System (1), which combines commonly measured clinical (age and gender) and physiologic variables, forced vital capacity (FVC) and capacity of the lung for carbon monoxide (DLCO), was used as predictor variable. The individual risk calculator (the GAP calculator) and the staging system (the GAP index), were evaluated after six months of pirfenidone therapy. The formula of the GAP calculator is described in the Appendix (online material).

Purpose of this study was the validation of the GAP system evaluated after six months of pirfenidone therapy in predicting the subsequent risk of death in an Italian population of patients affected by IPF.

This study was approved by the San Giuseppe Hospital Ethical Committee (protocol number 27/13) and patient's confidentiality was maintained.

Statistical analysis

Patients were followed up after six months of pirfenidone treatment. Vital status was ascertained by each participating center until July 2015.

Mortality risk was estimated in terms of cumulative incidence failure (CIF) taking into account lung transplantation as a competing cause of event. The Gray's test was used to assess cumulative incidence differences between groups.

Using the GAP Risk Assessment System (1) the predicted 1-, 2- and 3-yr risk of death after six months of pirfenidone treatment has been calculated for each patient in the cohort. The GAP system consists in a point scoring stage model (GAP index) and a continuous calculator (GAP calculator) derived from variables available at study entry (clinical visit at six months after pirfenidone treatment).

The prognostic accuracy of the GAP system was evaluated with respect to discrimination and calibration.

Discrimination was measured by the Harrell's concordance statistics (c-index), which is the probability that given two randomly selected patients, the survival time predicted by the GAP system is greater for the subject who survived longer. A value of 1 denotes perfect concordance, while a value of 0.5 is no better than chance.

Calibration was evaluated by a visual inspection of the plot comparing the 1-yr, 2-yr and 3-yr average mortality predicted by the GAP model with cumulative incidence of mortality observed in groups defined by the GAP stage (i.e. stage I, stage II and stage III). The Hosmer-Lemeshow test was used to formally compare predicted and observed risks.

All statistical analyses were performed with SAS software, version 9.3 (SAS Institute Inc., Cary, North Carolina) and R-software (R Foundation for Statistical Computing, Vienna, Austria). A p-value<0.05 was considered statistically significant. All reported p-values are two sided.

Results

Sixty eight IPF patients treated for at least 6 months with pirfenidone were studied. The characteristics of the sample are shown in Table 1.

Pulmonary function profile and stratification of the population based on GAP severity index, as well as GAP calculator, of studied sample at six months after pirfenidone treatment is reported in Table 2.

The median duration of follow-up time, which started from the sixth month of treatment, was 2.4 years (range 0.1-7.4 years). A total of 22 deaths as first event (32%) and of 10 lung transplantation (15%) occurred during follow up. The cumulative incidence of mortality at 1, 2, and 3 years was respectively 10.4% (95% CI: 4.6%-19.2%), 22.4% (13.2%-33.0%), and 38.4% (95% CI 24.9%-51.7%) (Fig. 1).

Mortality risk was significantly different according to GAP index stage (Gray's test $p<0.0001$). The cumulative incidence of mortality at 3 years was 14.8% (95% CI 1.7%-40.8%) for stage I, 36.9% (95% CI 20.0%-53.9%) for stage II and 80% (95% CI 32.6%-95.7%) for stage III (Fig. 2).

The cumulative incidence of mortality observed among the study sample and that predicted by the GAP Risk Assessment System were reported in Table 3 separately by year of follow up and stratified by GAP stage.

The risk of death predicted by the GAP system was compared with the observed mortality using calibration plots (Fig. 3 and 4).

The observed cumulative incidence of mortality for stage I and for stage II was lower while, for stage III was higher than mortality predicted by both the GAP index and the GAP calculator at each year of follow up. However, while the GAP index was quite precise in predicting mortality and the

differences between the predicted and observed risks were not significant (Hosmer-Lemeshow p=0.088, p=0.218 and p=0.778 at 1, 2, and 3 years, respectively), the observed mortality becomes comparable to that predicted by GAP calculator only in the third year of follow up (Hosmer-Lemeshow p=0.014, p=0.019 and p=0.061 at 1, 2, and 3 years, respectively).

The C index for the GAP index was 0.74 (95% CI 0.57-0.93) while the C statistic value for the GAP calculator was 0.77 (95% CI 0.59-0.95).

The median difference of the GAP index before and after the administration of pirfenidone was equal to zero.

Discussion

This is the first study investigating the use of the GAP system, a validated tool to assess mortality risk, in the era of antifibrotic therapies in a national multicenter case series of real life patients with IPF. The use of a simple staging system is very important to properly plan the therapeutic actions and some important decisions, such as the timing for lung transplantation and in helping clinicians to more accurately counsel patients with IPF (1-6). Being able to assess the clinical course and response to therapy of individual IPF patients is still both an open issue and a major objective to be achieved. The difficulty stems from the fact that the course of the disease is extremely variable for each individual patient. Reliable prognostic indicators have therefore not yet been identified (9). Guidelines consider the variations of FVC as an indicator of response to therapy and as a prognostic indicator, but this topic is still subject to much debate (12-19). Some authors have found significant mortality also in patients with stable FVC (5) and it has recently been reported that a 10% decline in FVC during pirfenidone therapy does not necessarily represent a treatment failure. Indeed, patients who continue getting pirfenidone despite progression of the disease may not experience further decline of FVC (19). The GAP index and disease staging system has been proposed as a quick and

simple prognostic tool for estimating mortality risk in patients with IPF, while the GAP calculator is a tool to estimate individuals' risk (1). In this real-life study conducted in patients treated with pirfenidone, the GAP system proved to be a reliable tool to predict mortality at 3 years. It seemed less sensitive at 1 and 2 years. The observed cumulative incidence of mortality for stage I and II patients was lower than the mortality predicted by both the GAP index and the GAP calculator for all follow-up time points. On the contrary, it was higher for stage III patients. The GAP index was quite accurate in predicting mortality, and the differences between the predicted and observed mortality were not significant (Hosmer-Lemeshow $p = 0.088$, $p = 0.218$ and $p = 0.778$ at 1, 2, and 3 years, respectively). However, the observed mortality became comparable to that predicted by the GAP calculator only in the third year of follow-up (Hosmer-Lemeshow $p = 0.014$, $p = 0.019$ and $p = 0.061$ at 1, 2, and 3 years, respectively).The discrimination ability of the GAP index and the GAP calculator in our study was slightly higher than those obtained both in the original article (1) and in the validation study among Korean patients (7) (c-index 0.74 vs 0.70 and 0.66 respectively for the GAP index; c-index 0.77 vs 0.69 and 0.68 respectively for the GAP calculator).

Studies have shown that the use of pirfenidone reduces pulmonary function loss at all stages of the disease (patients with FVC > 80% were compared to patients with FVC ≤ 80% and patients in GAP I stage were compared to patients in GAP II and III stages) (9, 20); on the other hand, FVC is considered a surrogate endpoint of mortality (14-18). In our study, the observed mortality was lower than the expected mortality in the GAP I and II stages the first two years and higher in the GAP III stage. This could be attributed to the different prevalence and influence of comorbidities in the various patient groups. Comorbidities may represent an additional factor to be taken into account for the GAP system to have a clinical relevance as a prognostic tool. Comorbidities may add their effect to age, gender and pulmonary function thereby modifying the overall mortality. This could explain why the GAP system might not be fully applicable when considering patients coming from real-life studies, with different comorbidities compared to clinical trial patients, who

may have been selected based on exclusion criteria (21, 22). However, this remains a hypothesis as the presence of comorbidities has not yet been analyzed for our study.

A pooled analysis of the data from phase III pirfenidone studies (CAPACITY and ASCEND) showed that pirfenidone significantly reduced all-cause mortality and IPF treatment-related mortality at 1 year (23). The reduction in mortality observed in GAP I and II stage patients could therefore be attributed to a greater effect of therapy in the first 2 years of treatment. The difference observed in GAP III stage patients may be unreliable because of the small number of individuals in this group of seriously ill patients.

Our study has all the known limits and all the bias of a retrospective research, but it also possesses the strengths of real-life studies. The other major limitation of our study is the small number of patients. However, our work describes a population certainly representative of the disease in a major European nation. All Italian centers that were considered in the study had participated in the NPP program and represent the most important reference centers for diagnosis and treatment of interstitial diseases. The follow-up period was long enough and suitable (2.4 years) and the average survival recorded was of 3.7 years from the time of diagnosis, in line with the IPF experience and comparable to the Korean series (7). However, differences emerge from the comparison of this latest study and our own data. While the Koreans have in fact found differences in the calculation of the 2-year mortality and particularly at the 3-year mark, we instead had the opposite experience: being the figure predicted at 3 years the closest to real.

Significant differences do however exist between the two studies: in 17.9% of Korean patients the diffusion value was missing, while we instead only considered patients for whom a complete set of data was available. Furthermore, we only assessed patients taking pirfenidone while the Korean trial did not specify what therapy patients were following. Most probably, being this a cohort studied

between 2005 and 2009 nobody was taking pirfenidone. Also in our experience the GAP system proves to be a good staging system able to discriminate well among the three different risk classes.

The GAP system is a simple-to-use disease staging system. It has found more applications than the previously proposed prediction models, which so far have had little impact in the daily clinical practice. This might be due to their complexity, time-consuming character or because they were never validated (2-4, 24, 25). The difference between the predicted and observed variables in our study population suggests that there may have been important factors (e.g. nature of IPF treatment or comorbidities) that were not captured by the GAP model. Additional studies would be valuable to determine the impact of treatment on model performance. This study was the first to evaluate the GAP system in the era of antifibrotic therapies and analyze its reliability in a multicenter Italian real-life population of patients treated with pirfenidone for almost six-months. Our results raise some concerns about the use of GAP system in the clinical practice that deserve further study.The GAP model showed a similar discrimination index in our study population compared to Ley *et al.* (1). However, the GAP calculator did not accurately predict the 1- and 2-year mortality in individual patients with IPF treated with pirfenidone. In our cohort, the GAP system was more accurate in predicting mortality than the GAP calculator. The re-assessment of the GAP system in the era of new therapies for IPF is an important topic: we hope we gave our small contribution to have begun to address this new frontier that will anyway require further validation studies.

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

References

1) Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Buccioli M, Elicker BM, Jones KD, King TE Jr, Collard HR.
A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 2012;156:684-91.
2) King TE Jr, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med 2001;164:1171-81.
3) Wells AU, Desai SR, Rubens MB, Goh NS, Cramer D, Nicholson AG, Colby TV, du Bois RM, Hansell DM. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. Am J Respir Crit Care Med 2003;167:962-9.
4) du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Raghu G, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, King TE Jr. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;184:459-66.
5) King TE Jr, Safrin S, Starko KM, Brown KK, Noble PW, Raghu G, Schwartz DA. Analyses of efficacy end points in a controlled trial of interferon-gamma 1b for idiopathic pulmonary fibrosis. Chest 2005;127:171-7.
6) Kolb M, Collard HR. Staging of idiopathic pulmonary fibrosis: past, present and future. Eur Respir Rev 2014;23:220-4.
7) Kim ES, Choi SM, Lee J, Park YS, Lee CH, Yim JJ, Yoo CG, Kim YW, Han SK, Lee SM. Validation of the GAP score in Korean patients with idiopathic pulmonary fibrosis. Chest 2015;147:430-7.

8) Kondoh S, Chiba H, Nishikiori H, Umeda Y, Kuronuma K, Otsuka M, Yamada G, Ohnishi H, Mori M, Kondoh Y, Taniguchi H, Homma S, Takahashi H. Validation of the Japanese disease severity classification and the GAP model in Japanese patients with idiopathic pulmonary fibrosis. Respir Investing 2016;54:327-33.

9) Albera C, Costabel U, Fagan EA, Glassberg MK, Gorina E, Lancaster L, Lederer DJ, Nathan SD, Spirig D, Swigris JJ. Efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with more preserved lung function. Eur Respir J 2016;48:843-51.

10) Hosein K, Le J, Mura M. Assessing the therapeutic response to pirfenidone in idiopathic pulmonary fibrosis: can we do better than with forced vital capacity alone? Lung DOI 10.1007/s00408-016-9963-3.

11) Harari S, Caminati A, Albera C, Vancheri C, Poletti V, Pesci A, Luppi F, Saltini C, Agostini C, Bargagli E, Sebastiani A, Sanduzzi A, Giunta V, Della Porta R, Bandelli GP, Puglisi S, Tomassetti S, Biffi A, Cerri S, Mari A, Cinetto F, Tirelli F, Farinelli G, Bocchino M, Specchia C, Confalonieri M. Efficacy of pirfenidone for idiopathic pulmonary fibrosis: an Italian real life study. Respir Med 2015;109:904-13.

12) Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE Jr, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schünemann HJ; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183;788-824.

13) du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, King TE Jr, Lancaster L, Noble PW, Sahn SA, Thomeer M, Valeyre D, Wells AU. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med 2011;184:1382–9.

14) Richeldi L, Ryerson CJ, Lee JS, Wolters PJ, Koth LL, Ley B, Elicker BM, Jones KD, King TE Jr, Ryu JH, Collard HR. Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis. Thorax 2012;67:407–11.

15) Raghu G, Collard HR, Anstrom KJ, Flaherty KR, Fleming TR, King TE Jr, Martinez FJ, Brown KK. Idiopathic pulmonary fibrosis: clinically meaningful primary endpoints in phase 3 clinical trials. Am J Respir Crit Care Med 2012;185:1044-8.

16) Wells AU, Behr J, Costabel U, Cottin V, Poletti V, Richeldi L; European IPF Consensus Group. Hot of the breath: mortality as a primary end-point in IPF treatment trials: the best is the enemy of the good. Thorax 2012; 67:938-40.

17) Wells AU. Forced vital capacity as a primary end point in idiopathic pulmonary fibrosis treatment trials: making a silk purse from a sow's ear. Thorax 2013;68:309–10.

18) Nathan SD, Meyer KC. IPF clinical trial design and endpoints. Curr Opin Pulm Med 2014;20:463–71.

19) Nathan SD, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, Fishman RS, Glaspole I, Glassberg MK, Glasscock KF, King TE Jr, Lancaster L, Lederer DJ, Lin Z, Pereira CA, Swigris JJ, Valeyre D, Noble PW, Wells AU. Effect of continued treatment with pirfenidone following clinically meaningful declines in force vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis. Thorax 2016;71:429–35.

20) Noble PW, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, Fishman RS, Glaspole I, Glassberg MK, Lancaster L, Lederer DJ, Leff JA, Nathan SD, Pereira CA,

Swigris JJ, Valeyre D, King TE Jr. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from the three multinational phase 3 trials. Eur Respir J 2016;47:243–53.

21) Ley B, Bradford WZ, Weycker D, Vittinghoff E, du Bois RM, Collard HR. Unified baseline and longitudinal mortality prediction in idiopathic pulmonary fibrosis. Eur Respir J 2015;45:1374-81.

22) Ryerson CJ, Vittinghoff E, Ley B, Lee JS, Mooney JJ, Jones K, Elicker BM, Wolters PJ, Koth LL, King TE Jr, Collard HR. Predicting survival across chronic interstitial lung disease. The ILD-GAP model. Chest 2014;145:723-8.

23) King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083–92.

24) Lee SH, Kim SY, Kim DS, Kim YW, Chung MP, Uh ST, Park CS, Jeong SH, Park YB, Lee HL, Shin JW, Lee EJ, Lee JH, Jegal Y, Lee HK, Kim YH, Song JW, Park SW, Park MS. Predicting survival of patients with idiopathic pulmonary fibrosis using GAP score: a nationwide cohort study. Respir Res 2016;17:131-9.

25) Salisbury ML, Xia M, Zhou Y, Murray S, Tayob N, Brown KK, Wells AU, Schmidt SL, Martinez FJ, Flaherty KR. Idiopathic pulmonary fibrosis: Gender-Age-Physiology Index Stage for predicting future lung function decline. Chest 2016;149:491-8.

Figure legend

Figure 1. Cumulative incidence of mortality from study entry (6 months after pirfenidone initiation).

Figure 2. Cumulative incidence of mortality by GAP index stage from study entry (6 months after pirfenidone initiation).

Figure 3. GAP index calibration plots. The x-axis shows the 1-yr (A), 2-yr (B), and 3-yr (C) cumulative incidence of mortality as predicted by the GAP model, and the y-axis shows the observed mortality. Every point represents a GAP stage. The solid line represents perfect agreement between predicted and observed mortality.

Figure 4. GAP calculator calibration plots. The x-axis shows the 1-yr (A), 2-yr (B), and 3-yr (C) cumulative incidence of mortality as predicted by the GAP model, and the y-axis shows the observed mortality. Every point represents a GAP stage. The solid line represents perfect agreement between predicted and observed mortality

Table 1. Patients' characteristics (N=68)

Characteristic	Levels	N (%)
Gender	Female	16 (24)
	Male	52 (76)
Age (years)*	≤60	7 (10)
	61-65	12 (18)
	>65	49 (72)
Smoking status	Ex-smoker	50 (74)
	Non smoker	15 (22)
	Smoker	3 (4)
Histological diagnosis	No	49 (72)
	Yes	19 (28)
Cortisone	No	27 (40)
	Yes	41 (60)
Azathioprine	No	50 (74)
	Yes	18 (26)
N-Acetylcysteine	No	38 (56)
	Yes	30 (44)
Time from diagnosis of IPF to start of pirfenidone therapy (years) **	< 1	22 (32)
	1-2	24 (35)
	>2	22 (32)

* Mean age: 69 years (SD: 7.9 years)
** Mean time from diagnosis of IPF to initiation of treatment with pirfenidone: 2 years (SD: 1.9 years)

Table 2. GAP index and GAP calculator of patients at study entry (six months after pirfenidone therapy) (N=68)

	Predictor	N (%)	Median, (Min-Max)
G - Gender	Female	16 (24)	
	Male	52 (76)	
A - Age class	≤60	7 (10)	
	61-65	12 (18)	
	>65	49 (72)	
Physiology	FVC %		
	>75	29 (43)	
	50-75	35 (51)	
	<50	4 (6)	
	DLCO %		
	>55	14 (21)	
	36-55	30 (44)	
	≤35	24 (35)	
GAP Risk Assessment System	GAP index		4 (2-7)
	Stage I (GAP index 0-3)	21 (31)	
	Stage II (GAP index 4-5)	37 (54)	
	Stage III (GAP index 6-8)	10 (15)	
	GAP calculator		
	1-yr mortality		16.3 (4.4-35.5)
	2-yr mortality		31.9 (9.2-61.2)
	3-yr mortality		45.4 (14.1-77.6)

Table 3. Comparison of predicted and observed cumulative incidence of mortality.

Year	GAP stage	Predicted by GAP index	Predicted by GAP Calculator	Observed
1	I	5.6	8.4	0.0
	II	16.2	17.2	5.5
	III	39.2	25.8	50.0
2	I	10.9	17.6	4.7
	II	29.9	34.2	19.4
	III	62.1	48.4	70.0
3	I	16.3	28.3	14.8
	II	42.1	51.2	36.9
	III	76.8	67.8	80.0