To Reviewer 2

Thank you very much for giving me good advice. Hereafter, the comments by the reviewers are shown in bold text. In the revised manuscript, red text indicates portion revised according to the comments.

Reviewer: 2

Comments to the Author

I congratulate you on completing your study and writing up your results. I have several comments and questions.

Comment 1. I believe the authors missed some opportunities to include several important citations. These are enumerated below.

1) Introduction, page 5, row 101, I think the authors should cite and comment on [Margaritopoulos et al. BMC Pulmonary Medicine (2018) 18:177 https://doi.org/10.1186/s12890-018-0736-z] which showed that the effect of Pirfenidone on survival is remarkable taking into account that patients with comorbidities and severe disease have been included in the cohort.

2) Introduction, page 6, row 111, I think the authors should cite the previous reported work and these others [Brunnemer E et al. Real-World Experience with Nintedanib in Patients with Idiopathic Pulmonary Fibrosis. Respiration DOI: 10.1159/000485933; Toellner et al. Clin Trans Med (2017) 6:41 DOI 10.1186/s40169-017-0172-3; Effectiveness and tolerability of pirfenidone (PFD) in patients with idiopathic pulmonary fibrosis (IPF) from a large Italian practice cohort. Vancheri C, Sebastiani A et al European Respiratory Journal Sep 2018, 52 (suppl 62) OA5358; DOI:10.1183/13993003.congress2018.OA5358]

3) Discussion, page 15, I think the authors should cite and comment on [Ekström M, Bornefalk Hermansson; Cardiovascular and antacid treatment and mortality in oxygen dependent pulmonary fibrosis: A population-based longitudinal study. Respirology (2016) 21, 705–711 doi:10.1111/resp.12781]

4) Discussion, page 17, row 325, I think the authors should cite and comment on these real world studies [Harari, S. et al. Efficacy of pirfenidone for idiopathic pulmonary fibrosis: an Italian real life study. Respir. Med. 109, 904–913 (2015); Biondini et al. Scientific Reports (2018) 8:5961 DOI:10.1038/s41598-018-24303-4]

5) Discussion, page 17, row 328, I think the authors should add this citation [María Molina-Molina, Myriam Aburto, Orlando Acosta, Julio Ancochea, José Antonio Rodríguez-Portal, Jaume Sauleda, Carlos Lines & Antoni Xaubet (2018) Importance of early diagnosis and treatment in idiopathic pulmonary fibrosis, Expert Review of Respiratory Medicine, 12:7, 537-539, DOI: 10.1080/17476348.2018.1472580]

“RESPONSE,”

We appreciate this suggestion. We have included all the references that were pointed out and added the comments, as follows:

“The effect of pirfenidone on survival was remarkable if ones takes into account that patients with
**Comment 2.** In the Methods section, more information on the ECOG is needed. What are the categories? What does a higher score connote?

**RESPONSE,**

Thank you for your suggestion. We have incorporated them to revised manuscript, as follows:

“The ECOG PS is a scale used to assess how a patient’s disease is progressing, and how the disease affects the daily living abilities of the patient. It is comprised of five statements (0 = “normal activity,” 1 = “some symptoms, but no bed rest during daytime,” 2 = “bed rest for less than 50% of daytime,” 3 = “bed rest for more than 50% of daytime,” 4 = “unable to get out of bed”), and poor PS was defined as ECOG PS 2 or more.”

**Comment 3.** Is the ECOG determined at the time of a clinic visit for each patient, or was it determined retrospectively? If it was determined retrospectively, this determination is subject to substantial bias and must be recognized as an additional limitation of this retrospective study.

**RESPONSE,**

Thank you for your pointed out. ECOG PS was determined at the time of a clinic visit for each patient. We have incorporated them to revised manuscript, as follows:

“Eastern Cooperative Oncology Group (ECOG) performance status (PS) and the modified Medical Research Council (mMRC) grades were assessed by the study physicians at the time of the visit.”

**Comment 4.** Was FVC collected only at entry and week 52? What is the median and range of days for FVC at week 52? Were additional values collected over the 52 weeks? Might the authors display results or trends over time?

**RESPONSE,**

No. The number of pulmonary function tests varies depending on the patient. Fifty-one patients were evaluated at entry and week 52. Twenty-three patients were evaluated at entry, week 24 and week 52. Due to the large number of missing values, we cannot display results or trends. The median time from 52 weeks was 1 day, and the range was ± 28 days. We have incorporated them to revised manuscript, as follows:
Anti-fibrotic agent efficacy was evaluated in 51 patients who underwent spirometry 52 weeks after starting anti-fibrotic therapy. The median time from 52 weeks was 1 day, and the range was ± 28 days.”

Comment 5. Overall, I struggle with the overall messages of this manuscript. PS seems like nothing more than a surrogate for lung function; indeed, the results suggest as much. The authors conclude that PS should be used as a guide for starting anti-fibrotic therapy; however, this makes little sense. Are the authors suggesting that anti-fibrotic therapy should be withheld until PS declines to a certain level? Surely not, as many experts believe anti-fibrotic therapy should be initiated as early as possible. Or are the authors suggesting that anti-fibrotic therapy not be given to patients with poor PS, because they are destined to discontinue it anyway? They don’t send a clear message to the reader of how to use the PS, and this reviewer is not convinced that it has any use at all for the purposes of making treatment decisions in patients with IPF.

“RESPONSE,”

We are sorry for unclear message to the reader of how to use the PS. We would not like to convey that we should withhold until PS worsen. We also would not like to convey that we should not give anti-fibrotic agents if the patient goes poor PS.

Compared to the spirometry, PS which was the tool evaluated noninvasively and does not require any special examination can be measured quickly and repeatedly regardless of any medical facilities. Because PS and %FVC had a good correlation (ρ = 0.65, P < 0.01), PS could be used as a simple, robust surrogate marker of pulmonary function. We recognize that this is a very valuable finding. On the other hand, according to the correlation chart, there are not a few cases of divergence. For examples, the patient of %FVC 77% was PS 3 and the patient of %FVC 37% was PS 1. Moreover, we found that PS had better ability to predict discontinuation than %FVC, and that the poor the PS, the higher the discontinuation rate. Considering the figure of anti-fibrotic agents’ persistence rate by the PS, although it is strongly suggested that the patient with good PS can continue anti-fibrotic agents, it is not always suggested that the patient with poor PS cannot continue. In other words, patients with poor PS require various plans and considerations not to discontinue. For example, it may consider starting with a low dose of antifibrotic agents, or it may be necessary to be more careful with countermeasures for adverse events. Therefore, we suggest that PS should be used as a guide for starting anti-fibrotic agents of IPF patients in everyday practice and that in the case of patients with poor PS, various plans and considerations not to discontinue is required.

In our revised manuscript, we added the comparison of AUC for factors that showed significant differences in univariate analysis (Table 4) and added the correlation chart between PS and %FVC (Figure 4). Moreover, we have revised the manuscript, as follows:

“In the ROC analysis associated with the discontinuation of anti-fibrotic agents, PS was the highest AUC value (cut-off value, 2; AUC, 0.83; specificity, 63%; sensitivity, 87%).” on lines 65-67.

“We revealed two important clinical issues. PS was the accurate predictive factor for the discontinuation of anti-fibrotic agents in patients with IPF.” on lines 306-307.

“Firstly, PS was the accurate predictive factor for the discontinuation of anti-fibrotic agents in the patients with IPF.” on lines 311-312.

“Because PS and %FVC had a good correlation, PS could be used as a simple, robust surrogate marker of pulmonary function. On the other hand, according to the correlation chart, there are not a few cases of divergence. When PS and %FVC have deviated, it may be necessary to confirm the quality for
spirometry or search for causes such as comorbidities. Anyway, compared to the spirometry, PS which was the tool evaluated noninvasively and does not require any special examination can be measured quickly and repeatedly regardless of any medical facilities.” on lines 321-328.

“Considering the figure of anti-fibrotic agents’ persistence rate by the PS, although it is strongly suggested that the patient with good PS can continue anti-fibrotic agents, it is not always suggested that the patient with poor PS cannot continue. In our study, patients in the good PS group showed a high continuation rate and the lower annual decline in FVC than those in the poor PS group. Our data support the importance of early anti-fibrotic treatment intervention in patients with IPF. Importantly, the data that -6.8% decline in FVC at 12 months of poor PS group is also satisfactory efficacy. For this reason, it is important not to give up anti-fibrotic treatment intervention even if in patients with poor PS. Patients with poor PS require various plans and considerations not to discontinue. With regard to dose of anti-fibrotic agents, the annual rate of decline in FVC in patients with a low dose anti-fibrotic agents was similar in patients with high dose anti-fibrotic agents. It may consider starting with a low dose of antifibrotic agents, or it may be necessary to be more careful with countermeasures for adverse events.” on lines 376-389

“Our findings underscore the fact that PS is the accurate predictive factor for the discontinuation of antifibrotic agents in patients with IPF.” on lines 409-410.

“In conclusion, we suggest that PS should be used as a guide for starting anti-fibrotic agents of IPF patients in everyday practice and that in the case of patients with poor PS, various plans and considerations not to discontinue is required.” on lines 414-416.

Comment 6. It seems like there must be fairly strong correlation among many variables and that the inclusion of certain combinations of variables in a multivariable model is not justified. For example, how strong is the correlation between FVC and PS? Since FVC is included in the GAP, why would one include both FVC and GAP in the same model? This likely has large influence on the estimates for these (and potentially other) variables in the model.

“RESPONSE,”

Thank you for your suggestion. There was certainly a strong correlation between PS and %FVC. ($\rho = 0.65$, $P < 0.01$) As you pointed out, FVC is included in the GAP. Moreover, our sample size was too small to obtain the statistical power by the multivariate analysis. In consideration of them, we deleted the results of the multivariate Cox proportional hazard analysis. We added the comment as follows:

“A multivariate Cox proportional hazard analysis was not performed, because our sample size was too small to obtain the statistical power by the multivariate analysis.” on lines 177-179.

“The current study has some limitations. First, it was a retrospective study with a small number of patients. Because the multivariate analysis could not be performed due to sample size, we could not exclude the possibility that confounding factors affected the result.” on lines 390-393.

Comment 7. I don’t understand the inclusion of variable comparisons between subjects with good performance and those with poor performance. This merely affirms PS as a surrogate for lung function or vice-versa.

“RESPONSE,”

We apologize that we included the variable comparisons between subjects with good PS and poor PS. Certainly, the intention to compare between good PS group and poor PS group was unclear.
There was a good correlation between PS and %FVC. ($\rho = 0.65$, $P < 0.01$) However, according to the correlation chart, there are not a few cases of divergence. For examples, the patient of %FVC 77% was PS 3 and the patient of %FVC 37% was PS 1. The purpose of this comparison was to examine whether there is a difference in characteristics such as age, comorbidity other than pulmonary function. We have incorporated the manuscript, as follows:

“The proportion of patients with preceding home oxygen therapy, and prednisone in the poor PS group was higher than in the good PS group. There was no significant difference in the age and the prevalence of patients with comorbidities except for pulmonary hypertension showed no significant differences between the two groups.” on lines 238-241.

Comment 8. Where the adverse events determined and scored retrospectively or at the time of the visit? I think it’s hard to grade adverse effects retrospectively and it should be addressed as a limitation to the study.

“RESPONSE,”

The timing of the adverse events determined and scored was at the time of the visit. We have incorporated them to revised manuscript, as follows:

“We evaluated the adverse events and the severity of them at the time of the visit. The severity of adverse events was assessed by grading according to the Common Terminology Criteria for Adverse Events (CTCAE).” on lines 150-152.

Comment 9. Does any of the patients undergo pulmonary rehabilitation program?

“RESPONSE,”

No. Pulmonary rehabilitation program did not undergo in any patients. We have incorporated them to revised manuscript, as follows:

“There were no patients undergoing pulmonary rehabilitation program.” on lines 206-207.

We believe that incorporating your advice into revised version has made the manuscript better. We are appreciated you once again.