Author’s response to reviews

Title: Change in Forced Vital Capacity and Associated Subsequent Outcomes in Patients with Newly Diagnosed Idiopathic Pulmonary Fibrosis

Authors:

William Reichmann (bill.reichmann@gmail.com)

Yanni Yu (Yanni.Yu@boehringer-ingelheim.com)

Dendy Macaulay
(Dendy.Macaulay@analysisgroup.com; Todor.Totev@analysisgroup.com; Emi.Terasawa@analysisgroup.com)

Eric Wu (Eric.Wu@analysisgroup.com)

Steven Nathan (Steven.Nathan@inova.org)

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Author’s response to reviews:

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Sanjay Haresh Chotirmall, MD, PhD
Section Editor, Infectious, Rare, and Idiopathic Pulmonary Diseases

BMC Pulmonary Medicine
BioMed Central
236 Gray’s Inn Road
London WC1X 8HB
United Kingdom

Re: Manuscript PULM-D-15-00025
Dear Dr. Chotirmall:

Thank you for the review and consideration of our manuscript, “Change in Forced Vital Capacity and Associated Subsequent Outcomes in Patients with Newly Diagnosed Pulmonary Fibrosis” for publication in BMC Pulmonary Medicine.

The reviewers’ comments enabled us to improve the manuscript, and point-by-point responses to the reviewers’ comments are included below. The revised manuscript addressing these comments has been submitted.

Thank you in advance for your consideration.

Sincerely,

Dendy Macaulay, PhD
Analysis Group, Inc.
10 Rockefeller Plaza, Floor 15
New York, NY 10020
United States
Email: dendy.macaulay@analysisgroup.com
Phone: 212.492.8172
Fax: 212.492.8188

Suggestion, Question, or Comment from Reviewer #1:

Some conclusions could reflect a bias in this industry sponsored and authored study. For example, the conclusion that the study "highlights the importance of preservation of lung function in IPF patients" suggests that a decline in FVC is causal with regards to the reported outcomes. It is unclear if the intervention to alter a decline in FVC would actually decrease the risk of an acute exacerbation (and the associated risk of mortality).

Authors’ Response:

Thank you for your comments. We’ve modified the sentence in the Conclusions section to soften its language and clarify that causality is unclear. (The edits are shown in the next column.)
Change in the Manuscript:

Conclusions Section: Page 11

We have added the following edits—

“The incremental burden of FVC% decline on patients and the healthcare system may underscores the importance of preservation of lung function in IPF patients. Future studies examining treatments that help slow lung function deterioration are warranted along with additional studies identifying predictors of patients at greatest risk of FVC% decline in the months following diagnosis and evaluating variation in effect of lung-function change across subgroups of patients.”

Suggestion, Question, or Comment from Reviewer #1:

This study shows that 51% of the population did not have a decline in FVC and, therefore, may not benefit from "management that ameliorates" a decline in FVC.

Authors’ Response:

We’d like to clarify that 51% of the patients did not show no decline in FVC%. Instead, these patients, categorized as Stable, exhibited <5% FVC% decline in the ~6 months following diagnosis. Assessing whether these patients may benefit from management/treatment designed to preserve FVC is an interesting question, however, it is currently beyond the scope of our project. We have noted in the Conclusions section that future studies examining this may be warranted. Additionally, patients who don’t have a decline in lung function over any given time period are certainly at risk of future such declines. Such is the natural history of IPF where declines are unpredictable and prior lung function behavior does not predict the future course. Therefore, the reviewer’s point that stable patients might not benefit does not account for the long-term natural history of the disease.

Change in the Manuscript:

Conclusions Section: Pages 11

We have added the following sentence—

“Future studies examining treatments that help slow lung function deterioration are warranted along with additional studies identifying predictors of patients at greatest risk of FVC% decline
in the months following diagnosis and evaluating variation in effect of lung function change across subgroups of patients.”

Suggestion, Question, or Comment from Reviewer #1:

Unfortunately, this study is limited in that it does not advance our ability to predict those patients who will have a decline in FVC and might benefit most by intervention.

Authors’ Response:

Thank you for the note on this. We agree that identifying predictors for FVC decline would be valuable; however, it is currently beyond the scope of our project. We do, however, examine and compare baseline characteristics associated with the 3 FVC% decline groups. We find that patients in the Significant decline group were more likely to have the following characteristics at baseline compared to patients in the Stable group: dyspnea, gradual unintended weight loss, lower FEV1, and lower DLCO. We’ve added descriptions of these results to the Patient Characteristics section. We’ve also noted in the Conclusions section that future studies examining predictors of patients at increased risk of FVC% decline may be warranted.

Change in the Manuscript:

Results Section—Patient Characteristics: Page 7

We have added the following detail—

“The significant decline group had lower DLCO and FEV1 values than the stable group (47.7% vs. 53.4% for DLCO, p=0.033; 1.7 vs. 2.0 liters for FEV1, p=0.021) (Table 2). The significant decline group also had higher rates of dyspnea and gradual, unintended weight loss than the stable group (93.0% vs. 83.6% for dyspnea, p=0.030; 16.9% vs. 6.8% for unintended weight loss, p=0.035).”

Conclusions Section: Page 11

We have added the following sentence—

“Future studies examining treatments that help slow lung function deterioration are warranted along with additional studies identifying predictors of patients at greatest risk of FVC% decline in the months following diagnosis and evaluating variation in effect of lung function change across subgroups of patients.”
Suggestion, Question, or Comment from Reviewer #1:

Discussion regarding the heterogeneity of IPF and the need for studies to determine which patients should be targeted for treatment is warranted...

Authors’ Response:

Thank you for the comment. We agree that studies identifying which patients should be targeted for treatment would be a valuable contribution to the IPF literature. We have added text to the Conclusions section, noting that this is an area deserving future research. It is noteworthy that our current manuscript is not about treatment and there is no platform from within our study results to interject too much commentary about treatment. We feel that if we provide any further commentary on treatment it will deviate from the focus of our study.

Change in the Manuscript:

Conclusion Section: Page 11

As previously mentioned, we have added the following sentence—

“Future studies examining treatments that help slow lung function deterioration are warranted along with additional studies identifying predictors of patients at greatest risk of FVC% decline in the months following diagnosis and evaluating variation in effect of lung function change across subgroups of patients.”

Suggestion, Question, or Comment from Reviewer #1:

… discussion regarding the relationship between FVC and risk of acute exacerbation [is warranted].

Authors’ Response:

Thank you for highlighting this. We have added discussion of the relationship between FVC and acute exacerbations to the Discussion section, noting findings from Kondoh et al. (2010).

Change in the Manuscript:

Discussion Section: Page 9

We have added the following text—

“Results for AEx were also in line with prior studies. For instance, Kondoh et al. found a higher risk of subsequent AEx for patients with a significant FVC decline (i.e., ≥10%) at 6 months
compared to those without a significant decline, reporting a HR of 2.6 (p=0.049) [27]. The HR for our significant decline group relative to the stable group was similar at 2.86.”

Suggestion, Question, or Comment from Reviewer #1:

Notably, the average age of the patients included in this study (61 years) is below that which would be expected for a population of IPF patients. This raises the possibility of recall bias of the reporting physicians, and suggests that the patient population included may not accurately reflect the broader population of IPF patients.

Authors’ Response:

While the average age of patients (61 years) at IPF diagnosis may be lower than what has been reported in some studies, there is variation across studies in terms of age of IPF onset (e.g., 68.7 for Behr et al. (2015), 72 for Yu et al. (2014)), which can be influenced by study setting and requirements. We don’t believe that patient age in our study is subject to recall bias of reporting physicians, because the data were extracted from patient medical charts, which capture this information. Instead, differences may simply reflect the composition of the physician panel, which included both academic and community medical centers from across the U.S. It may also reflect the study requirement that patients have at least 2 FVC readings, which may tend to eliminate very severe patients and more stable ones, as noted in the limitations discussion.

Suggestion, Question, or Comment from Reviewer #1:

There is no discussion or comment regarding the fact that patients in the "significant" progression group were more likely to be treated with Azathioprine and prednisone…

Authors’ Response:

Currently, the manuscript does not include information on whether patients in the “significant” group were more likely to be treated with both AZA + Pred. Use of AZA + Pred in the concurrent period is, however, controlled for in the Cox regressions for mortality, hospitalization, and AEx in the subsequent period. (This variable is only significant in the mortality regression (HR=2.48, 95% CI=(1.19–5.19)).)

Suggestion, Question, or Comment from Reviewer #1:

…(there is no specific information included regarding treatment with the triple therapy of AZA/Pred/NAC). Given the association of AZA/Pred/NAC with increased mortality in IPF, this should be acknowledged in the text as a potential contributing factor to the worse outcomes observed in the "significant" group.
Authors’ Response:

Thank you for your comments on this. We have added discussion of the triple drug combination of AZA + Pred + NAC to the manuscript, noting findings from the PANTHER-IPF trial. We have also added the rationale behind our use of double drug combination of AZA + Pred as a variable to the Statistical Analysis discussion of the Methods section.

The combination therapy of prednisone and azathioprine was included per the findings of the PANTHER-IPF clinical trial, which found the triple drug combination of prednisone, azathioprine, and n-acetylcysteine to significantly increase mortality risk relative to placebo. We have chosen to only include the two drugs, prednisone and azathioprine, in our multivariable analyses for the following reasons. First, results from the PANTHER-IPF trial suggest that the effect of the triple drug combination may have been predominantly driven by the combination of prednisone and azathioprine. Second, use of the two drugs allowed for fewer dummy variables in the model with more meaningful patient counts. (Inclusion of all three drugs would have required 8 dummy variables for comparison of the triple drug combination versus use of none of the drugs with only 5% of patients in the triple drug category.)

Change in the Manuscript:

Statistical Analysis—Methods Section: Page 6

We have added the following text, explaining the rationale behind use of the double drug combination, AZA + Pred—

“For each model, the main independent variable of interest was the FVC% change group while the control variables consisted of physician’s main practice setting, patient characteristics and symptoms at IPF diagnosis, smoking status, GAP index, suspected AEx in the concurrent period, and use of prednisone and azathioprine in the concurrent period. The combination therapy of prednisone and azathioprine was included per the findings of the PANTHER-IPF clinical trial, which found that triple drug combination with prednisone, azathioprine, and n-acetylcysteine to significantly increase mortality risk relative to placebo [21].”

Discussions Section: Page 10

We have added the following text—

“Combination therapy of prednisone and azathioprine was associated with significantly higher mortality risk relative to use of neither drug with a HR of 2.48 (p=0.016). This result is consistent with the PANTHER-IPF trial [21].”
Suggestion, Question, or Comment from Reviewer #1:

The introduction should be revised to include the recently updated ATS guidelines on IPF, which do include recommendations regarding recently approved therapies for IPF.

Authors’ Response:

Thank you for this suggestion. We have included discussion of the 2015 updated ATS guidelines for IPF in the Introduction.

Change in the Manuscript:

Background Section: Page 3

We have added the following text—

“Until recently, treatment options for IPF patients in the U.S. had been recommended by the 2011 American Thoracic Society (ATS) guidelines are limited to oxygen therapy, pulmonary rehabilitation, and, in some cases, lung transplantation [5,6]. In October 2014, the Food and Drug Administration approved two new pharmacologic agents for IPF expanding treatment options [7,8]. Both drugs have been recommended for use in the 2015 update to the 2011 ATS/ERS/JRS/ALAT IPF clinical practice guidelines [9].”

Suggestion, Question, or Comment from Reviewer #2:

My critique rests mainly with the discussion. There are several pieces of interesting observations that are not discussed. For example, Table 7 has some very interesting and clinically relevant differences that should be discussed, even if the discussion is speculative. For example, the difference in hospitalization in the subsequent period between the white and non-white patients.

The authors should mention the importance of comorbidities on IPF mortality such as heart disease or unintended weight loss. There should be citation of other work in this area. I think this represents a missed opportunity to discuss and review how these data fit into the context of other prognostic studies in IPF.

Authors’ Response:

Thank you for your suggestion. We have added a section to the Discussion portion of the manuscript that discusses the significant control variables in the multivariable Cox regressions
and puts their results into context with references to prior studies: Lettieri et al. (2006), Whelan et al. (2005), Nadrous et al. (2005), and Judge et al. (2012).

Change in the Manuscript:

Discussions Section: Page 10

We have added the following text—

“In addition to evaluating the relationship between FVC% change and outcomes, our multivariable models provide information on patient characteristics associated with mortality, hospitalization, and AEx, adding to the literature on risk factors for these outcomes. AEx in the concurrent period was a consistent and strong risk factor across all these outcomes and was the strongest predictor of a subsequent AEx. Combination therapy with prednisone and azathioprine was associated with a significantly higher mortality risk relative to use of neither drug with an HR of 2.48 (p=0.016), which is consistent with the findings of the PANTHER-IPF trial [21].

Select comorbidities were also significant predictors of worse outcomes as determined through our multivariable Cox regression models. In particular, pulmonary hypertension was a strong risk factor of all three adverse outcomes. While our result for mortality is concordant with the findings of numerous other studies, there is only a single prior report attesting to a relationship between pulmonary hypertension and AEx [29-32]. Furthermore, our finding of non-Caucasian patients being associated with worse outcomes adds to the literature on the disparities in health outcomes among IPF patients.”