Reviewer’s report

Title: Disease progression in Idiopathic Pulmonary Fibrosis with mild physiological impairment: Analysis from the Australian IPF Registry

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Reviewer: Justin Oldham

Reviewer's report:

In this investigation, Drs. Jo, Corte and colleagues conduct a retrospective analysis of clinical variables collected as part of a prospective, multi-center Australian IPF observational study to determine whether disease progression varies by stage of disease, as measured by various proposed clinical metrics. Overall, this is a very nice study with impactful results that reaffirm what many of us already believe, which is that "mild" IPF does not exist, but merely represents early stage disease that will progress just like other stages. This study lends real-world data to support similar data generated by post-hoc analyses of clinical trial datasets.

My only major concern is the stratification points chosen in this analysis. A relative balance between "mild" and "moderate-to-severe" cohorts seemed to drive the chosen stratification points for FVC, DLCO and CPI rather than more intuitive stratification points driven by previous data/publications. Brett Ley's GAP paper shows that mortality in those with DLCO<50% is quite high relative to those >50%, which resulted in a 55% cut point for DLCO in the GAP score. Using this sort of data-driven stratification point irrespective of how many patients fall into each resulting group would make for a cleaner study in my mind. Alternatively, focusing the analysis on FVC-stratified groups with secondary analyses for GAP and CPI would alleviate the DLCO issue altogether. A primary focus on FVC would make sense b/c the inability to obtain anti-fibrotic therapy is often based on the FVC % predicted (at least in the US) rather than DLCO. This approach would make your choice of FVC as the stratification variable in Tables 1 and 4 more consistent with the overall approach.

Other minor concerns:

Introduction
No issues

Methods
- Please briefly explain why a random intercept and slope mixed model was chosen. Was this based on an information criterion (Aikake/Baysian?)

- What type of variance-covariance correlation structure was chosen for the mixed model (exchangeable, autoregressive, independent, etc)?
Please explain how time points were treated in your mixed model? It's unlikely that all patients underwent follow-up PFTs at the same time point, so it should be mentioned how alignment of data was performed (i.e., 1-year intervals, 6-month intervals, etc).

Why was progression-free survival only modeled over 12 months in your logistic regression analysis? Your KM's and mixed model plots show 5-year follow-up and your median survival is almost 3 years so it seems valuable data may be lost by limiting this analysis to 12-months. More importantly, it's unclear to me why logistic regression for binary death/progression was used in Table 4 rather than Cox regression, using time to death/progression.

Results
- Please consider using "mild" and "moderate-to-severe" for your groupings throughout the manuscript, as there likely exists at least two groups with progressively worse survival within the current "more severe" group (the data for GAP increasing mortality risk for GAP stage II to GAP stage III supports this).

- For Table 1, please mention how many patients in the "mild" and "moderate-severe" groups (using FVC cut-off) received anti-fibrotic therapy. If there was a substantial number, please include this as a variable in your survival and longitudinal FVC analyses, as this could arguably influence the results of both.

- Exclusion of patients unable to perform the DLCO maneuver is not appropriate in my mind because these patients often cannot perform the test due to advanced disease. This finding is informative (as supported by the GAP paper) so should not be treated the same as other missing data. Depending on how you decide to proceed with DLCO modeling, please conduct a sensitivity analysis (ok for the supplement) to determine whether exclusion of patients unable to perform DLCO influenced your results. Imputation of missing DLCO data to the lowest quartile mean or lowest observed value seems like reasonable ways to account for these data in the sensitivity analysis. This obviously doesn't need to be done if the study becomes more narrowly focused on FVC.

- Please check your results for Table 2a. A HR of 0.03 for FVC (% predicted) seems a rather low (i.e., for every 1-unit increase in FVC % predicted, you get a 33-fold reduction in mortality risk?) Next, the HR for DLCO(% predicted) is 0, which seems incorrect. Next, the HR for 6MWT is 1.0 with CI that crosses 1 but a p-value of 0.001, suggesting this was calculated incorrectly.

- In Table 2b, please reverse your baseline group in your Cox model as it currently appears as though your mild groups have higher mortality risk than your severe groups (i.e., I read that FVC >80% increases the risk of death by 3-fold compared to FVC <80%, GAP stage 1 increases the risk of death 7-fold compared to GAP stage 2-3, etc).

- For Table 3, please include the confidence intervals and p-value for each group's point estimate to show that the decline observed in each group was statistically different than 0 despite being no different than each other.
- For each of the tables, please include the number of missing data in the footer. Given the major limitation of missing data, it would be helpful to know how many patients were included in an analysis of any given variable. This is true especially for 6MWT data, which was highlighted as a significant predictor.

- Please include the number of patients included the unadjusted and adjusted Cox/logistic analyses since missing data will reduce the number of patients included in a final adjusted model.

Please include a multivariable adjusted analysis for Table 4 to help address whether other variables with clear confounding potential influence the point estimates for any given variable of interest.

- For figure 3, please clarify which set of criteria were used to determine "mild" and "moderate-to-severe?" Additionally, please include data points and a fitted LOWESS curve (ok to put into supplement if similar to current Figure 3). The current mean curves for the two groups don't take into account patient dropout over time so it would be helpful to see a rough estimate of how many patients informed the mean at any given timepoint.

Discussion
- In the limitations section please mention that this was a retrospective analysis of a prospective observational study, as these patients were not prospectively followed with this study in mind (similar to retrospective (post-hoc) analysis of prospectively followed clinical trial cohorts).

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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