Author’s response to reviews

Title: Prognostic Impact of the Ratio of the Main Pulmonary Artery to that of the Aorta on Chest Computed Tomography in Patients with Idiopathic Pulmonary Fibrosis

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Mar 23, 2019

Bruno Guedes Baldi
Editor
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Re: PULM-D-18-00592, entitled “Prognostic Impact of the Ratio of the Main Pulmonary Artery to that of the Aorta on Chest Computed Tomography in Patients with Idiopathic Pulmonary Fibrosis.”

Dear Editor
We appreciate the thoughtful comments of the reviewers and are submitting a revised manuscript that addresses the specific issues raised by the reviewers. A detailed description of our response and the changes are outlined below. We have clearly marked the changes in our manuscript (blue colors).

- Response to Reviewers -

Caio Julio Cesar dos Santos Fernandes, MD, PhD (Reviewer #1):

It is an interesting studies, but I think the pulmonary hypertension aspect of the main finding has been neglected. I also have some queries

1) Page 3, line 16. The statement is incorrect. Right Heart catheterization is not associated with several complications. In fact, Hoeper et. al have shown that the risk of complications due to RHC in an experienced center is 1.1% (J Am Coll Cardiol. 2006 Dec 19;48(12):2546-52). The text suggests otherwise. Please rephrase.

Response: Thank you for your comment. In our tertiary care university hospital, some patients were transferred with continuous and high oxygen and poor condition just before transplantation. Therefore, we occasionally could not conduct the right heart catheterization for those patients. And we could not conduct right heart catheterization in all patients due to economic issues. We absolutely agree with your advice, and have therefore revised that statement.

Changes in manuscript: We have edited the text to “The definition of PH is based on data obtained by right heart catheterization, which is an invasive and costly procedure.” (Page 3)

2) Discussion about the values of pulmonary pressure identified are virtually absent from the discussion. However, the main finding of the study should co-relate with a difference in pulmonary pressure, but apparently, it does not (at least from the values identified by echo). RVP measured by echo are quite similar from both groups (37 vs 43, table 2). Is this finding just because echo is not good enough to evaluate PH in interstitial lung disease, or the mPA/Ao ratio comprises and reflects other variables than merely the pulmonary pressure? What are the authors impressions? Was specific PH therapy implemented to any patient? If so, did the therapy impact in outcome? Did the patients that received (or required) specific PH therapy had a higher mPA/Ao ratio?

Response: Thank you for your comment. We absolutely agree with you. We also expected that there was significantly difference in RVP measured by echo between two groups. The RVP measured by echo were higher in the group with an mPA/Ao ratio > 1 in univariate analysis, but not in multivariate analysis. The only 54% patients (n = 163) were reported the RVP measured by echo. And, in patients with early stage of IPF who had no specific symptoms, it was possible that the echo was not performed due to economic issue. Furthermore, in previous study, the RVP measured by echo had limited accuracy for assessment of PH in patients with IPF [1-3].
Therefore, we think that the various non-invasive tests should be evaluated to predict PH in IPF patients, and the mPA/Ao ratio could be valuable methods as a non-invasive screening test to predict PH in IPF patients.

Two patients with severe pulmonary hypertension in our study were received the treatment of oral medication, phosphodiesterase-5 inhibitors, and they finally underwent lung transplantation. The mPA/Ao ratio of two patients was over 1.0. We also look forward to additional studies related with this point.

3) No information was provided about gas exchange. Was oxygenation levels different from both populations? This could co-relate with the eventual presence of PH. What about CO2 levels?

Response: Thank you for your comment. We agree with you that we need to provide the information of gas exchange, including O2 and CO2 levels. This is the part we were also interested. However, we didn’t routinely perform arterial blood gas test on baseline examination in IPF patients. Few patients underwent arterial blood gas test at the first diagnosis. We also look forward to additional prospective studies.

4) 58 patients of the study underwent lung transplantation. Probably, these patients underwent right heart catheterization prior to the transplant, since it is a pre-op requirement. It would be interesting to analyze the mean pulmonary pressure of this subgroup and its co-relation to mPA/Ao ratio

Response: Thank you for your comment. We absolutely agree with you.

Among 58 patients with lung transplantation, we performed right heart catheterization (RHC) prior to the transplant to only 36 patients. The remaining 22 patients could not underwent RHC due to their poor condition. Among them, 7 patients transferred to our hospital in acute respiratory failure status requiring ICU care and 15 patients with an oxygen demand over nasal 4L.

We have conducted additional subgroup analysis as your recommend including 8 patients who underwent RHC as pre-op evaluation but were not transplanted. In total 44 patients underwent RHC, 8 patients (18.2%) had an mPA/Ao ratio > 1.0, and 11 patients (22%) had an mPA/Ao ratio > 0.8. There were no statistically significant difference in mean pulmonary pressure between two group as ratio in both 1.0 and 0.8. However, the mean of mean pulmonary pressure was tend to be higher in the group with high mPA/Ao ratio (>1). Therefore, additional research about this point should be done in larger study sample size.

<table>
<thead>
<tr>
<th>Variables</th>
<th>p-value</th>
<th>mPA/Ao ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 1 (n=8)</td>
<td></td>
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</table>
≤ 1 (n=36)

<table>
<thead>
<tr>
<th>Variables</th>
<th>mPA/Ao ratio</th>
<th>p-value</th>
<th>Mean pulmonary artery pressure</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>0.8 (n=11)</td>
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<td>25.27 ± 8.01</td>
<td>0.813</td>
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<tr>
<td>&gt;0.8 (n=33)</td>
<td></td>
<td></td>
<td>26.12 ± 10.02</td>
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</tbody>
</table>

Reference


Roberta Ramos, (Reviewer #2):

The study included a large cohort of IPF with appropriate analysis. Conclusions are mostly well supported by the results.

Questions:
1) What was the agreement of mPAP/Ao measurements performed by 2 radiologists?

Response: Thank you for your question. Two reviewers who were blinded to the clinical data measured the mPA and Ao on the same CT image independently. Then we applied the average of the two measurements. The value of inter-observer correlation coefficient was 0.84 (95% confidence interval (CI), 0.80-0.87) for mPA, and 0.92 (95% CI, 0.90-0.94) for Ao. We added this point in the “Methods” on page 5.

2) Prognostic results are kept when only death events are taken into account?

Response: Thank you for your question. We evaluated the primary outcome of only death event except lung transplantation event using Kaplan-Meier curve analysis as your comment. The results showed that patients with an mPA/Ao ratio >1.0 had a worse outcome than those with an mPA/Ao ratio ≤1.0 (p = 0.05). Furthermore, the patients with an mPA/Ao ratio >0.8 also had a worse outcome than those with an mPA/Ao ratio ≤0.8 (P < 0.001).

Suggestions:

3) I suggest modification in conclusion because "association with poor exercise capacity" was not independent of pulmonary function tests.

Response: Thank you for your comment. We absolutely agree with you, and we have modified the sentence from our manuscript accordingly. We hope that this revised manuscript meets your expectations.

Changes in conclusion at abstract: We have edited the text to “A higher mPA/Ao ratio based on 1.0 and 0.8 is associated with unfavorable prognosis in patients with IPF.”

Changes in conclusion at main manuscript: We have modified the sentence to “An mPA/Ao ratio >1 was associated with poor outcome in patients with IPF.”

4) Kaplan-Meier: please include number of patients under risk.

Response: Thank you for your comment. As suggested by the reviewer, we modified the figure 2, the Kaplan-Meier analysis including number of patients under risk.