Author’s response to reviews

Title: Epidemiology and risk factors in CKD patients with pulmonary hypertension: a retrospective study

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1. Several major limitations were not mentioned. The biggest limitation in terms of extrapolating this data to the population at large is confounding by indication. In this retrospective only patients who had received echos were included. Clearly then there must have been a reason why a physician felt the patient should have an echo and in many cases that may have been symptoms related to PH.

Answer: “All patients with CKD who received echocardiography were included from July 2013 to September 2015” was described in methods section, line 3, page 4 in our text. Here, we want to explain more in details. Echocardiography was routinely arranged for every hospitalized CKD patient no matter symptoms relating to PH were present or not. However, a few CKD patients failed for the following reasons. Firstly, our hospital is a higher-level referral hospital instead of a primary medicare one. Therefore, some patients may refuse to receive echocardiography when their medical insurances could not cover such examinations. Secondly, some patients showed low compliance and the lengths of hospital were too short to accomplish the routine evaluations including echocardiography. Thirdly, some patients had received an echo in a local hospital and refused to repeat such an examination in our hospital. These data were excluded because a unified quality control procedure could not be carried out. Finally, a very small amount of patients could only receive bedside echos by portable devices. Bias might exist due to the inconsistent ultrasonic machine.

2. A significant limitation not mentioned is that this is a single center study. I think this risk can actually be overblown in some cases but not here. As the authors note in several places in their discussions, there are different mechanisms whereby different diseases that lead to CKD can also lead to PH. Some diseases that causes CKD are more likely to also cause PH than others (despite
lack of statistical significance for that here). The generalizability of a single center study looking at this then depends on the generalizability of causes of CKD at this hospital to the causes worldwide. While there is significant national variation, the finding here of 68% GN, 14% DM and 8% HTN clearly are at odds with many countries.

Answer: The prevalence of chronic kidney disease in China was 10.8%. The most common causes for CKD were primary glomerulonephritis, hypertension and diabetes. Although hypertension and diabetes have increased rapidly in the past 15-20 years, primary glomerulonephritis was still the first cause of CKD. The etiology of CKD was reported 55.2% GN, 11.78% DM and 14.55% HTN in Second Xiangya Hospital of Central South University, 57.26% GN, 13.34% DM and 13.69% HTN in multicenter in China in nondialysis CKD. So the overall trends of our data are similar to other hospital in China. On the other hand, socioeconomic status, the accompanying changed lifestyle and the disparity in health care have varied substantially between rural and urban areas in China. Therefore, the prevalence of GN, hypertension and diabetes varied greatly among different geographical regions. The data mentioned above were form urban populations. Unfortunately, the data from rural population are unavailable for now. Most of the patients admitted in our hospital were from rural areas where the prevalence of hypertension was relatively lower compared to that in urban areas. (PMID: 22386035, 20543476, 27310973) So it is reasonable that the prevalence of HTN was lower in comparison to data mentioned above. It is supposed that our data were more representative of population in Chinese rural population.

3. When looking at laboratory risk factors for PH, I would really like to see PO4 and Ca as these (along with PTH) are intimately associated with vascular calcification and may well associate with pulmonary small vessel disease. If the authors have data on these it would be great to see them included in the model.

Answer: The data of Ca and P was supplemented and re-tested. The results can be found in revised tables.

4. Do the authors have any data about the prevalence of PH in non-CKD patients in their region? It would be nice to see if CKD Stage 1 actually has any increased risk vs the population at large.

Answer: Concerning the prevalence of PH in non-CKD patients, no solid data are available until now. We have reviewed patients admitted in other units from July 2013 to September 2015, and it was found that echos were not necessarily performed when symptoms relating cardiovascular diseases were absent. Therefore, we could not gather enough data to evaluate the prevalence of PH in non-CKD patients admitted in our hospital.

5. In the discussion it states that patients with cardiac diseases were excluded. However, in the Methods section on exclusions, it only mentions patients with congenital cardiac disease were excluded. Is this what the Discussion is referring to by "cardiac disease"? This should be clarified.
Answer: Apologize for the lack of the article rigor on the presentation. We have revised the paper. (methods, line 11, page 4; discussion, line 7, page 11)

6. Were there any patients with more than one echo during the study period? It would be interesting to see if any changes in their GFR tracked with any changes in their PH.

Answer: This was a retrospective study in a single center, most of the patients only had an echo once during hospitalization (average length of stay was about 7 days). In particular, all patients were required to repeat an echo when departing the hospital. However, most of them followed up in local hospitals because of the Chinese medical policy. Therefore, we could not gather subsequent data. However, only a small number of patients reexamined echos in our hospital and it showed that pulmonary artery pressure decreased more or less after discharge. However, we assumed that such decreases might not be necessarily related to renal function alterations, and too many confounding factors participated to the changes including dialysis, the drug prostacycllin or the other treatments. So we did not mention the follow-up of echos because it was difficult to directly connect changes of PH to the status of GFR.

7. The paper reports there were 318 patients with Stage 5 CKD but also that there were 331 on dialysis. How do these numbers match up?

Answer: Not only patients on stage 5 CKD but also some CKD 4 patients received dialysis. For example, the time of dialysis would be relatively earlier in patients with diabetic nephropathy. Some patients would be on early dialysis because of poor appetite or too many oral medications. And some other patients were advanced into dialysis due to less urine, sever edema or hyperkalemia.

8. Just as a comment, I am surprised at how high the PTH levels are in Stage 1 and 2 CKD patients, they do not look any different from those in Stage 4 and Stage 5, which is certainly not what is usually seen.

Answer: It is also a fact that confuses us. Both the original data and statistical processes were rechecked, and the same conclusion was drawn as it was seen in the previous manuscript. Although we could not give explanations, the data provided clues for us for a further investigation to find the underlying factors resulting in elevated PTH in early stages of CKD.