Author's response to reviews

Title: Chronic Asymptomatic Pyuria Precedes Overt Urinary Tract Infection and Deterioration of Renal Function in Autosomal Dominant Polycystic Kidney Disease

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Author's response to reviews: see over
Dear Dr. Henderson,

Re: manuscript MS:1403982156752251 - Chronic Asymptomatic Pyuria Precedes Overt Urinary Tract Infection and Deterioration of Renal Function in Autosomal Dominant Polycystic Kidney Disease

Thank you very much for reviewing our manuscript. We do greatly appreciate the editor and reviewers for going through our manuscript again and for providing insightful and constructive comments. We have addressed several comments and added additional points in the cover letter and the manuscript.

Thank you again for your kind consideration.

Yours sincerely,

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Reviewer 1:

Major points:

1. The authors now provide an additional analysis defining the pyuria and non-pyuria groups based on the first year of follow up, as I had suggested. These groups did not differ with respect to GFR decline during further follow up. In their response to my comment, the authors suggest that one year may not be enough to show the impact of recurrent pyuria on renal function. However, these patients were followed for much more than a year after the first year of follow up on which the group definitions were based. I rather think that this new additional analysis suggests, as I had suspected, that pyuria is likely not the cause of future GFR decline. I still believe that the greater GFR decline in Group B is just due to the fact that group B comprised patients that were followed until they had more advanced disease and that these patients were more likely to experience asymptomatic pyuria due to more advanced disease and pyuria was more likely to be detected due to more frequent controls.

Therefore, I think the authors should take more emphasis away from the point that pyuria may contribute to GFR decline in ADPKD. Also, they should state the rationale for performing the new analysis based on the first year of follow up and discuss the probable possibility that more frequent diagnosis of pyuria was a consequence rather than a cause of progressive disease. Another additional analysis of interest, which could clarify this point, would be to check whether asymptomatic pyuria became more common over time (with disease progression) within individual patients.

Although the hypothesis of pyuria leading to GFR decline in ADPKD patients is interesting and might be true, I do not think that the design of the current study does really support this hypothesis (due to the reasons outlined above).

Thank you for your thoughtful comments. We agree that our study design is insufficient to confirm the causal relationship between chronic asymptomatic pyuria and future GFR decline. In the new analysis based on the number of pyuria in the first year, groups did not differ with respect to GFR decline. However, what we wanted to
show from this conclusion was that 1 year is not enough to define recurrent or persistent pyuria. Although our retrospective study design is not enough to prove the causal relationship between chronic pyuria and renal progression, we still believe our results suggest some clues due to the reasons outlined below.

First, as we have presented in our original study, group B demonstrated a faster annual eGFR decline than group A (-2.7 ± 4.56 vs. -1.17 ± 5.8 ml/min/1.73m² per year, \( P = 0.01 \), Figure A). The result remained true when we re-analyzed the data after excluding the patients with previous overt UTI episodes (-2.6 ± 4.4 vs. -0.9 ± 5.7 ml/min/1.73m² per year, \( P = 0.009 \), Figure B). Although group B showed longer follow-up duration, as you have mentioned, the final eGFR in both groups were in their CKD stage 1-2. As you may know, eGFR slope starts to decline faster in the later phase in ADPKD. Therefore, we think our study suggests the possible link between chronic pyuria and renal function decline. Second, moreover, overt UTI group showed even faster decline of eGFR compared to Group B\(^\text{UTI} \) (-3.6 ± 5.6 vs. -2.6 ± 4.4 ml/min/1.73m² per year, Figure B) in the comparable follow-up duration (83.1 ± 43.3 vs. 86.2 ± 37.5 months). As we have mentioned in the discussion (Page 13, Lines 17-19), chronic pyuria may be a form of undetected subclinical bacterial infection that causes renal function deterioration when it happens repeatedly. In our opinion, to prove the effect of recurrent or persistent pyuria on renal function deterioration, the definition of chronic pyuria (recurrent and persistent pyuria, group B) should not be confined to 1 year (just like the new prospective data analysis we have added to the manuscript) but for the longer period of time. Third and the last, we performed subgroup analysis according to the initial CKD stages. In CKD I-II group, chronic pyuria group (group B) showed much greater annual decline of eGFR compared to group A (-3.36 ± 3.47 vs. -1 ± 5.97 ml/min/1.73m² per year, \( P = 0.002 \), Figure C). The follow up duration between the groups were significantly different (Group A vs. Group B, 54.12 ± 41.0 vs. 95.08 ± 34.3 months). However, this result indirectly suggests that chronic asymptomatic pyuria may contribute to renal function decline.

We have added this information in the main manuscript (Result part, Page 11, Lines 11-13) and the Supplementary Figure 2.

As you have suggested, it is true that reviewing the number of pyuria episodes over time in the individual patients may help us to elucidate the causal relationship between asymptomatic pyuria and GFR decline. However, as we have addressed in the previous cover letter, we have seen patients more frequently as GFR declines. Therefore, even if we perform additional analysis, this relationship is not likely to be seen clearly. We believe that this point
also should be clarified in the prospective study setting.

In summary, we think another prospective study with regular visiting interval (eg. every 6 months) is necessary to prove that recurrent or persistent pyuria overtime will affect GFR decline in the future. However, our retrospective study can suggest that recurrent or persistent pyuria may affect GFR decline in the future. In part, we admit that there is still a possibility that asymptomatic pyuria is merely a marker of renal progression but not a risk factor for future GFR decline, and we clarified this point in our discussion (Page 14, Lines 11-14).

Minor points:

1. The authors gave the frequency of patient visits in their response letter, but I think this information should also be included in the methods section.

   As you have recommended, we added the information on the frequency of patient visits in the method section (page 6, Methods, lines 5-9).

Discretionary points:

1. Page 9, 2nd para: I would add the percentage of negative cultures (can be calculated from the numbers given, but makes it easier for the reader if this number is given directly).

   We have made changes according to your recommendation (Page 9, Lines 14-16) as follows: Urine culture was performed in only 4.6% of the patients with asymptomatic pyuria. In most of asymptomatic pyuria cases (95.4%), urine culture was not performed. Among those who underwent urine culture study, 6.5% showed negative results. The most common microorganisms were *Escherichia coli* (34.5%),…

2. Page 9, bottom: “In addition, when we used the new prospective groups” leave away “new” since the reader of the article will not know that this analysis has been added for the revision of the article and the groups are therefore “new”. Same for page 11, top.

   Thank you for the comment. We have made change according to your recommendation (Page 10, Line 5; Page 11, Line 11).
Figure A

Initial eGFR

<table>
<thead>
<tr>
<th>Group A (N=162)</th>
<th>Group B (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>92.5±27.1</td>
<td>88.7±32.5</td>
</tr>
</tbody>
</table>

$P=0.35$

Final eGFR

<table>
<thead>
<tr>
<th>Group A (N=162)</th>
<th>Group B (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>85.5±31.7</td>
<td>63.3±37.0</td>
</tr>
</tbody>
</table>

$P<0.001$

$\Delta$eGFR/yr

<table>
<thead>
<tr>
<th>Group A (N=162)</th>
<th>Group B (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.17±5.60</td>
<td>-2.70±4.56</td>
</tr>
</tbody>
</table>

$P=0.01$

ESRD

<table>
<thead>
<tr>
<th>Group A (N=162)</th>
<th>Group B (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3</td>
<td>16.0</td>
</tr>
</tbody>
</table>

$P=0.001$
Figure B

![Bar chart showing comparisons between three groups: Group A\(^{UTI}\) (N=151), Group B\(^{UTI}\) (N=72), and Overt UTI (N=33). The chart displays the difference in mL/min/1.73m\(^2\) along the y-axis and indicates P-values for each comparison: P=0.03, P=0.09, and P=0.67 respectively.](image)
Figure C

\( \triangle \text{eGFR/yr (CKD I-II)} \)

\[ P = 0.002 \]

Group A
(N=139)

\[-1.0 \pm 5.97\]

Group B
(N=75)

\[-3.36 \pm 3.47\]
Reviewer 2:

Thank you for reviewing our revised manuscript and I appreciate your help in publishing this paper. Your comments really helped us to improve the quality and completeness of our manuscript. Thank you again.