Reviewer's report

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

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Reviewer: Andreas Kistler

Reviewer's report:

This interesting manuscript examines the significance of asymptomatic pyuria in ADPKD and finds an association of asymptomatic pyuria with GFR decline. This finding is important, since there is still a limited knowledge about risk factors for progression in ADPKD and in particular since asymptomatic pyuria might – if it is the sign of asymptomatic UTI – be a treatable factor. Unfortunately, however, I am based on the currently presented analyses, not sure whether the conclusions are justified, since several confounding factors were not properly dealt with.

Major points:

1) Groups A and B differ relevantly with respect to duration of follow up and logically, the group with a longer follow up ended up with a lower eGFR. The authors try to adjust for this by adjusting for follow up duration in multiple regression analysis. However, I am still concerned that there is a major confounding factor, which has not been corrected for: assuming that advanced disease stage or reduced GFR is a risk factor for pyuria, the chance to detect recurrent or persisten pyuria would then be increased in patients at late stages of disease. These are likely the patients with longer follow up, that end up with lower GFR and hence had a higher GFR decline calculated over total follow up time, although the decline of GFR might have happened mainly late during follow up. This bias can be eliminated by a different design of the analysis (which also makes much more sense since the authors aimed to test whether pyuria is a risk factor for progression): They should divide the patients into two groups A and B based on only the initial 6 or 12 months of follow up and then assess whether pyuria in this phase was associated with future GFR decline.

2) Another factor for confounding (detection bias) is the frequency of follow up visits of patients. How often were patients seen in the clinic? Were all patients seen in similar intervals or was the interval for visits based on clinical need? In the latter case, patients with more severe disease would have more clinical visits and therefore have a higher chance for the detection of pyuria.

3) Likewise, it should be defined whether patients were regularly questioned for intercurrent UTI symptoms on every visit. The rate of cystitis in this study was very low – much lower than for non-ADPKD women. Also, there was no gender difference in the risk of overt UTI in this study, which would be very unusual if all
cystitis episodes were reported. Hence, I suspect that many cystitis episodes went undiagnosed. This point needs to be clarified and discussed.

4) A major limitation of the study is that urine culture was performed in very few cases. Hence, it is unclear whether most asymptomatic pyuria episodes were asymptomatic infections (and thus potentially treatable) or whether these were cases of sterile pyuria, which has been suggested to be frequent in ADPKD (ref. 7 of the manuscript; in contrast, a study evaluating the frequency of asymptomatic bacteriuria in ADPKD did not find an increased incidence compared to healthy controls: Pietrzak-Nowacka M, Pol Merkur Lekarski. 2010 Sep;29(171):173-6). At least, the authors should report in how many of the urine cultures performed there were no microorganism identified.

5) Please report in the methods section how cyst infection was diagnosed / defined. Comparison of APN and cyst infection with regards to clinical and laboratory characteristics (page 10) makes only sense if these characteristics were not used to identify cyst infections. CT / MRI and ultrasound evaluation (see discussion section of manuscript) are not reliable for diagnosing cyst infection. I would consider to omit this paragraph on the comparison cyst infection vs. APN since it is not the main focus of the manuscript.

6) The CKD-EPI formula should be preferably used rather than the MDRD formula, since many patients had a preserved eGFR.

Minor:

7) Table 6: “urine nitrogen positive” should probably mean “urine nitrite positive”

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests