Author's response to reviews

Title: Clinical features and survival of a large cohort of ADPKD patients receiving renal replacement therapy

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Author's response to reviews: see over
Dear Prof Anders,

We would respectfully like to submit the revision of manuscript entitled “Clinical features and survival of a large cohort of ADPKD patients receiving renal replacement therapy” for consideration to be published in BMC Nephrology.

We highly appreciate the reviewers comments and hope that you will find this article now suitable for publication in BMC Nephrol.

Please find below the response to reviewers:

**REFEREE 1: Vincenzo Bellizzi**

We appreciate the valuable comments of Referee 1 about the paper.

**Specific points:**

1. The Authors in the introduction discuss on characteristics, and mainly genetic characteristics, of ADPKD, but clear information on ADPKD epidemiology lack. This point, which is the aim of the study, has to be well introduced. We agree with the reviewer that epidemiology is an essential issue in this paper. Epidemiology data is already present in the introduction regarding: prevalence of ADPKD and age at ESRD. We have added the data on hypertension in ADPKD.

2. The Authors look for changes of ADPKD at start RRT over time, but this aim is too generic and it has to be better defined and argued (i.e. changes of patients characteristics and why they are expected – why it is expected changes of age/gender for a genetic disease; changes of modifiable CV risk factors – namely hypertension, and why; changes of RRT modalities – namely vascular access, type of RRT; changes in survival and why; etc.). The age at onset of ESRD is the main issue in ADPKD patients. All results recorded in the Registry forms have been addressed in the discussion. Unfortunately those not recorded in the files are beyond the possibilities of this paper.

3. ANOVA cannot be used to compare gender differences. Thank you so much for this observation. It was a mistake. The sentence on ANOVA has been deleted as this test has not been used in the present study.

4. The paragraph “Limitation” is useless since it refers to implicit characteristics of a registry study. If the editor agrees we appreciate keeping the paragraph as it insists that only information available in the registry forms has been used for the study. Also we have added there a comment of reviewer 2. However if the editor feels it is useless, it can be deleted.

5. Hypertension has to be defined. Agree. Provided in the Methods section now.

6. Authors aim at evaluating ADPKD changes over time, but they report only data on age and gender at RRT start over the three periods of time. To explore this aim all the data for different periods have to be analysed. All available data for the 3 periods of time has been analyzed and discussed.

7. Sometimes along the paper incidence and prevalence data have been mixed; they have to be separate and the latter have to be reported for different periods in order to obtain information of some clinical relevance. We highly appreciate this reviewer’s comment. Based on the reviewer’s smart observation we have added a sentence in the Methods section clarifying this aspect (study design section). Also a new footnote in table 1 has been provided to make clear this point.

8. A major drawback in the comparison of either comorbid disease profile or outcome among ADPKD and controls is the different age at start. Conclusions of the paper on both the reduced comorbidities and the lower death rate in ADPKD is not supported by data. The lower prevalence of CV risk factors in ADPKD at RRT start is entirely explained by age. As well, the longer survival of ADPKD during the first three years of RRT is not reliable, being associated with different age at start of RRT. Indeed, at the time of death both the age and the comorbidities were the same among groups. Overall, in contrast with Author’s conclusions, groups seem not to differ for this characteristics. More adequate statistical analyses have to be applied to overcome this bias (i.e.
We fully agree with the reviewer and appreciate his comments. However, regarding comorbidities, the discussion already includes a sentence attributing the lesser number of comorbidities to the younger age in ADPKD: *This higher rate of co-morbidities in non-ADPKD patients could be explained by the higher prevalence of diabetes and by initiation of RRT at an older age.*

On the other hand we only have data on cause of death, not on comorbidities at death, as this is unfortunately not a required field in the form. Also, in the discussion there is already a sentence attributing to earlier age at onset of ESRD the longer survival on RRT: *Longer survival of ADPKD patients has been associated with: starting RRT at a younger age.*

We hope this answer will satisfy the reviewer’s concern.

9. Authors discuss on a possible improvement of CV risk factors in ADPKD over time and the related effect on outcome. It would be interesting to explore changes of hypertension – likely the unique modifiable CV risk factor in this setting of patients – at start of RRT over time and the impact on patient outcome. We have no data on hypertension control but only “diagnosis of hypertension”. We agree with the reviewer that it would be great to have the degree of blood pressure control but it is not recorded in the registry forms.

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**REFEREE 2: Arlene Chapman**

We thank Referee 2 for her accurate comments about the study.

**Specific points:**

1) The authors should explain the limitations of the data only starting at the time of onset of ESRD. Also, whether the patient population is transient or not should also be addressed. Both issues have been addressed in the Limitations section and in the Study Design section.

2) The lower than expected preemptive transplant rate in a hereditary disorder should also be explained (are living related donors less common because of the familial nature of ADPKD? We appreciate this observation. A new comment has been added on that in the Discussion section, in the paragraph on transplantation.

3) The extremely low rate of hypertension compared to other cohorts deserves comment. Is the diet perhaps different in this region? This has been a very valuable comment. The reason for the low prevalence of hypertension was that from 1992 to 2000 there were several forms without comorbidities filled in. From 2000 it was compulsory and therefore we changed Table 2 using these data, which significantly raises the percentage of patients with hypertension. This has also been addressed in the Methods section.

4) African American race has not yet been associated with a poorer renal outcome, only in those with sickle cell disease as well. This should be modified. Thanks. It has been deleted.

5) The authors are encouraged to provide Kaplan Meier plots for patient survival and graft survival at three years. We highly appreciate this suggestion. They have been provided for renal survival, transplanted patient survival and graft survival (Figures 1 and 4a,b).

6) Can the authors provide insight into the time of first interaction with a medical specialist when they are diagnosed with ADPKD? Is this close to the time of RRT or years before. Perhaps this accounts for the lack of improvement in age of onset of ESRD. Unfortunately this data is not in the registry form and is not available. Therefore we cannot make any comment on this aspect even though it is extremely interesting.

**REFEREE 3: Giuseppe Conte**

We thank reviewer 3 for his kind comments on the paper.

**Specific points:**

1) The title can be modified in “ADPKD patients receiving renal replacement therapy: a 25-year survey from Catalan Registry”. We think this is also a good title. But perhaps this one including
reviewers suggestion sounds better: Renal Replacement Therapy in ADPKD Patients: A 25-Year Survey Based on the Catalan Registry.

2) The Authors report in the methods the intention to analyze “the time elapsed since start of dialysis to transplant surgery, and the age at the time of transplantation” in the two cohorts (ADPKD vs non-ADPKD) but they do not show any data. We really thank the reviewer for this observation. It has been addressed and included in Table 1.

3) In the Table 3, the Authors indicate “social” as cause of death. They might explain in the text what means it. Now explained as footnote in Table 2.

4) The reference 16 is incomplete, lacking the volume and the pages of the article. Thanks so much. Addressed.

Yours sincerely,

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