PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	RAPID-ADPKD (Retrospective epidemiologic study of Asian-Pacific patients with rapId Disease progression of Autosomal Dominant Polycystic Kidney Disease): Study Protocol for a Multinational, Retrospective Cohort Study
AUTHORS	Ryu, Hyunjin; Park, Hayne; Oh, Yun Kyu; Sangadi, Irene; Wong, Annette; Mei, Changlin; Ecder, Tevfik; WANG, Angela; Kao, Tze-Wah; Huang, Jenq-Wen; Rangan, Gopala; Ahn, Curie

VERSION 1 - REVIEW

REVIEWER	Makoto Fukuda Saga University Hospital Internal medicine division of Nephrology Japan
REVIEW RETURNED	12-Oct-2019

GENERAL COMMENTS	This is an important study to clarify the actual situation of ADPKD in Asia and Oceania. The problem is that the evaluation of renal function has not been standardized as described in Limitation. Evaluation with eGFR using creatinine and creatinine may not reflect the exact renal function of patients with sarcopenia that have a large hepatic renal cyst and poor food intake. However, this study is a retrospective observational study, and there is a limit to data collection. Ideally, eGFR using cystatin and cystatin and renal function evaluation using inulin clearance would be desirable.

REVIEWER	JPH Drenth radboudumc, Netherlands
REVIEW RETURNED	16-Oct-2019

GENERAL COMMENTS	Key questions 1. Is there an unmet need The authors have inserted a reasoning why the south Asian ADPKD population should be characterized. I am not fully convinced here “differences in other genetic backgrounds, race, climates, culture, and lifestyle of Asian population can also affect the disease progression”. I fail to see a good biological plausible explanation why disease behavior should be different here. Also, the authors plan to include patients from Turkey and Australia.

	While I am not an ethnologists I am not sure whether patients from Turkey and Australia fall under the broad umbrella of being labelled as “Asian”. You really need to have a good reason to start this study, and after reading the introduction I am not swayed by their reasoning. The assumption that polycystic liver disease is more sever in the Asian ADPKD population should be supported by some evidence. 2. Which answer will be addressed The authors ask hypothesize that there is a need for epidemiologic data regarding the clinical manifestations and disease progression of rapid progressing ADPKD patients coming from 6 hospitals from Australia, China, Hong Kong, South Korea, Taipei, and Turkey in the Asia-pacific region. The question is whether there are phenotypes specific to the Asian ADPKD population that drive rapid progression. That is reasonable, but a careful drafted hypothesis is lacking. The last line of the introduction inserts “incidence of cardiovascular complications”. Where does that come from? There is nothing in the introduction that leads up to any interest of cardiovascular complications. 3. Is the methodology sound Key is the selection of patients. The definition of rapid progression is based on the ERA-EDTA guideline. Follow-up comes with measurements of relevant clinical endpoints. The authors plan to include 1000 patients. For me it is unclear why 1000, it is a magic number, but the question is whether there is any advanced power planning underlying this number. The limitations of the study as acknowledged graciously is its retrospective nature, and the fact that comparisons can only be done in an indirect manner. This methodology will see missing relevant datapoints, and / or measurement of data points at different (and not aligned) time points. Definition of key inclusion criteria are clear and I appreciate the fact that the study has clear definitions with respect to the renal phenotype. I fail to understand how “severe heart failure, severe liver disease” is being defined. Use specific criteria. I appreciate the use of the PRO-PKD score, but that score is driven by presence of genetic mutations (6/9 points allowed). I am happy that the authors also use the Mayo ADPKD score that calculates the progression according to renal volume. The calculation of serum creatinine will be focus of intense scrutiny from within the nephrology community. The methods used in different hospitals will differ, normal values will have been adapted over time, methods change, etc. In other words standardization is absent. This is important as it is one of the outcomes and inclusion criteria of the study. I do not think that the authors are able to overcome the methodological issues. They are just there. Please consider to have as primary outcome was change in kidney function, assessed by the patient’s slope via serial eGFR measurements over time (calculated using the creatinine values measured). If the answer is given, do we care? I think that here, the authors may give some additional input. One of the possible outcomes is that there is a higher CVD impact on Asian ADPKD and that could be of relevance.

REVIEWER	LAIA SANS ATXER HOSPITAL DEL MAR
REVIEW RETURNED	23-Oct-2019

GENERAL COMMENTS	The paper reports on the protocol for a future retrospective study to assess the progression of asian ADPKD patients. No results shown as the study is ongoing. Anyway, serious concerns might be noticed for the protocol such as: - 2 years of follow up of the patients is not enough under my point of view to assess the progression (esepcially if normal renal function patients are included) - authors do not explain why patients with eGFR lower than 45 are not included, - different methods for creatinine to estimate eGFR are used - different radiologic techniques are used to assess TKV - what is the % of patients for whom a genetic test is expected to be available? fast progression in terms of PROPKD score must count on that and I'm not sure if it wil be available for the greatest part of the patients... - Mayo Clinic progression method is not used...? will it be used either using MRI, TC or ultrasound? shouldn't be like this - how will they assess rapid progression in terms of eGFR lowering greater than 2.5 ml/min/year during 5 years if follow up is less than that? - how is water intake assessed in a retrospective study? - they exclude patients with comorbidites that might affect renal function such a heart and hepatic disease, but others, such as diabetes, vascular disease and so on will be included. Comment on that. - authors comment on the limitation of the study : methods to measure creatinine. I think much more limitations must be noticed.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

This is an important study to clarify the actual situation of ADPKD in Asia and Oceania. The problem is that the evaluation of renal function has not been standardized as described in Limitation. Evaluation with eGFR using creatinine and creatinine may not reflect the exact renal function of patients with sarcopenia that have a large hepatic renal cyst and poor food intake. However, this study is a retrospective observational study, and there is a limit to data collection. Ideally, eGFR using cystatin and cystatin and renal function evaluation using inulin clearance would be desirable.

▶ We agree with your recommendation but unfortunately, as this retrospective study, it was not possible to standardize creatinine measurements or perform addition evaluation methods (such as cystatin and inulin clearance) in the study protocol. We have included this limitation comment in the limitation section, page 18.

We also have experience that in 90% of cases, the renal event of 50% eGFR declining occurred at the same time using both eGFRCr and eGFRCys in a prospective study (Kim H. et al., Nephrology, 2019 Apr; 24(4): 422-429. doi: 10.1111/nep.13407). Furthermore, in 75% of discordance patients, renal events calculated using eGFRCr proceeded the event calculated using eGFRCys in 75% of the

patients. From this previous result, we speculated that using eGFRCr in the longitudinal follow-up of Asian ADPKD in this study would not underestimate the renal function change in our study.

Reviewer 2

1. The authors have inserted a reasoning why the south Asian ADPKD population should be characterized. I am not fully convinced here “differences in other genetic backgrounds, race, climates, culture, and lifestyle of Asian population can also affect the disease progression”. I fail to see a good biological plausible explanation why disease behavior should be different here. Also, the authors plan to include patients from Turkey and Australia. While I am not an ethnologist I am not sure whether patients from Turkey and Australia fall under the broad umbrella of being labelled as “Asian”. You really need to have a good reason to start this study, and after reading the introduction I am not swayed by their reasoning.

► There is little published data regarding the influence of ethnicity on the progression of the disease. Freedman et al. and Murphy et al., showed the possibility of the racial influence on the ADPKD progression even in the same nation using the US data. (Freedman BI et al., Am J Kidney Dis 2000;35(1):35-9 and Murphy et al., BMC Nephrol 2019;20(1):55). To our knowledge, no study has compared the pattern of disease progression in Asian patients compared to other ethnic groups. The current study was established to evaluate the characteristics in the Asia-Pacific ADPKD region (which includes various races to analyze the effect of racial difference to comparing data in Asian countries to the Turkey and Australia data). However, there is a significant lack of evidence in this area, and we think this approach is important in the recent era of precision medicine and provides some basic knowledge to seek the high-risk patients and modifiable risk factors. The RAPID-ADPKD study will begin to address this major gap in knowledge.

2. The assumption that polycystic liver disease is more severe in the Asian ADPKD population should be supported by some evidence.

► In Korean ADPKD patient cohorts, we found that ~16% of patients have moderate to severe polycystic liver disease based on height adjusted liver volume and ~30% of ambulatory ADPKD patients have nutritional risk associated with height-adjusted total kidney and liver volume (Kim H et al., PLoS One, 2015;10(12):e0144526 and Ryu et al., BMC Nephrol). Since the Asian population has lower height and body mass compared to the Western country population, we suggested in the manuscript that there might be a higher incidence of complications due to polycystic liver disease and organomegaly in Asian ADPKD patients even with the same volume of liver. By establishing the characteristics of the Asian-Pacific ADPKD cohort, and comparing the baseline characteristics among the countries and ethnicities, we hope that we could characterize some of the unique and urgent problems in the Asian ADPKD population.

3. Which answer will be addressed: The authors ask hypothesize that there is a need for epidemiologic data regarding the clinical manifestations and disease progression of rapid progressing ADPKD patients coming from 6 hospitals from Australia, China, Hong Kong, South Korea, Taipei, and Turkey in the Asia-pacific region. The question is whether there are phenotypes specific to the Asian ADPKD population that drive rapid progression. That is reasonable, but a careful drafted hypothesis is lacking.

► Characterizing ‘rapid progressors’ among ADPKD patients for active treatment is important in the era of precision medicine. Therefore, there have been efforts to establish the clinical models based on

the epidemiologic data to predict the rapid progressors among ADPKD patients including Mayo imaging classifications and PRO-PKD score. However, these studies are conducted in Western populations and Asian patients are usually not included in the studies. In addition, the model has not been validated systematically in the Asian ADPKD population. Using the retrospective cohort data from the RAPID-ADPKD study, we believe we may validate the previously known prediction model for rapid progressor in the Asian population and depict out some clinical characteristics of rapid progressors in Asians. By comparing the data with Australia and Turkey we expect to analyze if there is a racial difference in the Asian population compared to the Turkish and Australian population in the same cohort.

3. The last line of the introduction inserts “incidence of cardiovascular complications”. Where does that come from? There is nothing in the introduction that leads up to any interest of cardiovascular complications.

► We are planning to analyze the incidence of cardiovascular complications in the Asia-Pacific ADPKD population. However, we agree with you that this is not the main purpose of the study, and therefore we have erased the sentence from the Introduction and only discuss it in the section on clinical significance on page 16.

4. Is the methodology sound: Key is the selection of patients. The definition of rapid progression is based on the ERA-EDTA guideline. Follow-up comes with measurements of relevant clinical endpoints. The authors plan to include 1000 patients. For me it is unclear why 1000, it is a magic number, but the question is whether there is any advanced power planning underlying this number.

► Since this is a epidemiologic study, we plan to enroll as many subjects as possible to establish the representative Asian-Pacific ADPKD cohort. Before designing the study we first surveyed the number of ADPKD patients following each participating center who are eligible for the study. After the survey, eligible patient number was found to be ~1,000 patients.

5. The limitations of the study as acknowledged graciously is its retrospective nature, and the fact that comparisons can only be done in an indirect manner. This methodology will see missing relevant datapoints, and / or measurement of data points at different (and not aligned) time points.

► We fully agree with your comments about the limitations that exist due to the nature of the multicenter retrospective study. As described in the manuscript, we tried to minimize these errors by gathering the data from a large number of patients and collecting the clinical information with specific evaluating methods in dense intervals. Also we tried to collect the data from patients who have followed the center during the last 24 months as mentioned in page 10. However we fully agree with your comments and describe these limitations in the limitation section in page 18.

6. Definition of key inclusion criteria are clear and I appreciate the fact that the study has clear definitions with respect to the renal phenotype. I fail to understand how “severe heart failure, severe liver disease” is being defined. Use specific criteria.

► We have added the definition of severe heart failure and severe liver disease in the modified manuscript page 10 as below.

“Patients with severe heart failure (with symptoms of New York heart association (NYHA) class 3 and 4), severe liver disease (Child-pugh class B or C), chronic inflammatory disease, diabetic

nephropathy, vascular disease and/or other comorbidities that can affect renal function will be excluded based on each clinician's judgment."

6. I appreciate the use of the PRO-PKD score, but that score is driven by presence of genetic mutations (6/9 points allowed).

► In Seoul National University Hospital, about 80% of the patients undergo genetic analysis (Kim H & Park HC et al., Sci Rep. 2019 Nov 18;9:16952.), and we hope to gather more genetic data from patients following other participating centers. We are planning to conduct subgroup analysis in patients with genetic mutation data regarding the PRO-PKD score.

7. I am happy that the authors also use the Mayo ADPKD score that calculates the progression according to renal volume. The calculation of serum creatinine will be focus of intense scrutiny from within the nephrology community. The methods used in different hospitals will differ, normal values will have been adapted over time, methods change, etc. In other words standardization is absent. This is important as it is one of the outcomes and inclusion criteria of the study. I do not think that the authors are able to overcome the methodological issues. They are just there.

► Since this is a multinational multicenter retrospective cohort study, we could not unify the creatinine measuring methods and we fully agree that this is a limitation of the study. Nevertheless, we believe that our analysis using eGFR will provide valuable insights since real-world data from actual clinical practice and a large number of patients across different nations, will be collected. We expect that a patient attending a single center will usually have creatinine measured by the same laboratory. Furthermore, preliminary analysis performed using data to date, showed that ~75% of patients had creatinine data using the Jaffe method calibrated with isotopic dilution mass spectrometry, which is the current standardized method. In addition, if the creatinine measurement is not calibrated with isotopic dilution mass spectrometry, eGFR will be calculated using the 5% reduced value of the recorded serum creatinine for the correction according to previous report [Levey AS et al., Clin Chem. 2007;53(4):766-72, Skali H et al., Am Heart J. 2011;162(3):548-54]. We hope this effort would minimize the errors that may exist in the multicenter retrospective study.

8. Please consider to have as primary outcome as change in kidney function, assessed by the patient's slope via serial eGFR measurements over time (calculated using the creatinine values measured). If the answer is given, do we care? I think that here, the authors may give some additional input. One of the possible outcomes is that there is a higher CVD impact on Asian ADPKD and that could be of relevance.

► We agree and have changed the primary outcome to the eGFR slope using serial eGFR measurement over time between rapid and slow progressors in this Asian-Pacific ADPKD cohort. As secondary outcome, other clinical characteristics (including TKV changes, complication rate, age of complication presentation and treatment aspects) will be compared between patients with rapid progression and slow progression. We have made changes in the outcomes variables section in page 14 as below.

"The primary outcome of the study is the rate of kidney function decline among the Asia-Pacific ADPKD population. Changes in eGFR slope during the follow up will be calculated using generalized linear mixed model and compare between patients with rapid progression and slow progressor in Asia-Pacific ADPKD population.

…

The secondary outcome of the study is to determine the difference in other clinical characteristics including TKV changes, complication rate, age of complication presentation and treatment aspects between patients with rapid and slow progression. In addition, the subgroup analysis according to age groups, ethnicities will be conducted in secondary outcome measures."

Reviewer 3

1. 2 years of follow up of the patients is not enough under my point of view to assess the progression (especially if normal renal function patients are included).

► Thank you very much for commenting on this. We fully understand your concerns and authors also have considered this issue while designing the study. The main purpose of this study was to establish a large number of representative Asian-Pacific ADPKD cohort that would combine the multinational and multicenter data retrospectively. We planned this study to provide cross-sectional knowledge about clinical manifestations and current practice status in Asian-Pacific ADPKD patients and compare the characteristics according to current ERA-EDTA guidelines. We want to validate current guidelines and find out the clinical manifestation based on the guideline in the Asian-Pacific population. This approach can also be seen in a recently published study from Spain (Furlano M et al., Am J Nephrol. 2018;48(4):308-317).

2. Authors do not explain why patients with eGFR lower than 45 are not included,

►To analyze the sufficient follow-up duration in each patient in the retrospective cohort, we planned to enroll ADPKD patients with relatively preserved renal function. In addition we are also considering the next level study from the extension of this cohort. We have explained this in the study population section of manuscript in page 10 as below. We appreciate very much for your helpful comments

"To analyze the sufficient follow-up duration in each patient in both retrospective and possible next step study, we planned to enroll ADPKD patients with relatively preserved renal function."

3. Different methods for creatinine to estimate eGFR are used

► We authors fully agree with your comment that non-unified creatinine measurement methods are a major limitation of the study. Since this is a multinational, multicenter retrospective cohort study unifying the eGFR and TKV evaluation methods was impossible. However, we expect that a patient following a single center would have creatinine values measure by the same method from the same laboratory. Additionally, when we analyzed so far collected data, 75% of patients had creatinine data measured using Jaffe methods calibrated with isotopic dilution mass spectrometry which is the current standardized method. In addition, if the creatinine measurement was not calibrated with isotopic dilution mass spectrometry, eGFR will be calculated using the 5% reduced value of the recorded serum creatinine for the correction, which was validated in previous studies (Levey AS et al., Clin Chem. 2007;53(4):766-72, Skali H et al., Am Heart J. 2011;162(3):548-54). Since we will collect data from actual clinical practice and a large number of patients across different nations, we hope these efforts would minimize the errors and provide meaningful results.

4. Different radiologic techniques are used to assess TKV

► We also agree that this is another major limitation in the study. However, since each country has different medical reimbursement policies and we want to validate the current guideline and provide knowledge based on the current clinical practice situation in Asian-Pacific countries. Longitudinal TKV change in a single patient will be analyzed only if the patients have TKV data calculated from the same imaging and volumetry methods for the consistency and we have mentioned more clearly on page 13.

“However, if other htTKV calculating methods such as stereological or planimetry are used in the same patient using the same imaging methods, the progression will be determined using the values also.”

5. What is the % of patients for whom a genetic test is expected to be available? Fast progression in terms of PROPKD score must count on that and I'm not sure if it will be available for the greatest part of the patients...

► In the Seoul National University Hospital, about 80% of the patients following the PKD clinic underwent genetic analysis (Kim H & Park HC et al., Sci Rep. 2019 Nov 18;9:16952.). We are also expecting genetic mutation data from other participating centers including China. We are planning to conduct subgroup analysis in patients with genetic mutation data regarding the PRO-PKD score.

6. Mayo Clinic progression method is not used...? will it be used either using MRI, CT or ultrasound? shouldn't be like this

► Thank you for commenting on the imaging classification methods. The preferred imaging methods for ADPKD patients differ according to each nation’s medical reimbursement systems in the Asian-Pacific area. We are planning to evaluate the patients using the current medical practice in the Asian-Pacific area. Also recently published studies and reviews support that TKV from CT images is as accurate as MRI in TKV volumetry (Magistroni R et al., Am J Nephrol. 2018;48(1):67-78, and Sharma K et al., PLoS ONE. 2017;12(5):e0178488) Although the TKV from ultrasound has lower accuracy, it is suggested that ellipsoid formula by ultrasound could be a viable alternative where access to MRI or CT for TKV are limited (Magistroni R et al., Am J Nephrol. 2018;48(1):67-78). To speculate the errors by collecting volume data from various imaging modality, we will analyze and represented volume data according to imaging methods as both separately and all-together in both cross-section and longitudinal analysis as mentioned in page 13.

“In both cross-section and longitudinal analysis, the htTKV data will be analyzed and represented according to TKV measurement methods as both separately and all-together.”

7. How will they assess rapid progression in terms of eGFR lowering greater than 2.5 ml/min/year during 5 years if follow up is less than that?

► We appreciate your comments. We also think that patients with at least 2 years of retrospectively following data, cannot adopt the category of eGFR declining rate > 2.5mL/min/year during 5 years in the ERA-EDTA guideline. However, as we mentioned above, we are planned to validate the current ERA-EDTA guideline in our cohort to find out the characteristics of rapid progressor in the real clinical setting of Asian-Pacific area as in another study (Furlano M et al., Am J Nephrol. 2018;48(4):308-317). After establishing the cohort and when we possibly expand this study to a prospective study and collect longitudinal data of another 3 to 5 years, we hope that we can further analyze the data

according to the category of ‘eGFR declining rate >2.5mL/min/year during 5 years’ and ‘an increase in htTKV ≥ 5% per year measured from ≥3 radiologic images’.

8. How is water intake assessed in a retrospective study?

► In this study, we will collect the data of the specific gravity of spot urine during the visits, as mentioned in page 16. Urine specific gravity of ≤1.010 is correlated with a urine osmolality of ≤270 mmol/L, meaning adequate vasopressin suppression and fluid intake in the past few hours (Imran S et al., J Clin Lab Anal. 2010;24:426-30). This is also adopted methods for the secondary analysis parameter in DRINK study (El-Damanawi R et al., BMJ Open. 2018;8(5):e022859), and used as self-monitoring methods in DRINK and PREVENT-ADPKD study (Wong ATY et al., BMJ Open. 2018;8(1):e018794), which are randomized trials to find out the efficacy of water intake in ADPKD patients.

9. They exclude patients with comorbidites that might affect renal function such a heart and hepatic disease, but others, such as diabetes, vascular disease and so on will be included. Comment on that.

► In this study, we will exclude severe heart failure (with symptoms of New York heart association (NYHA) class 3 and 4) and severe liver disease (Child-pugh class B or C) as you mentioned and we clarified definition in page 9. Additionally, in the protocol we will exclude patients with any other comorbidities (including diabetes, vascular disease and chronic inflammatory disease) will be excluded on the each clinician’s judgment. This has been clarified in the statement on page 10-11 as below:

“Patients with severe heart failure (with symptoms of New York heart association (NYHA) class 3 and 4), severe liver disease (Child-pugh class B or C), chronic inflammatory disease, diabetic nephropathy, vascular disease and/or other comorbidities that can affect renal function will be excluded based on each clinician’s judgment.”

10. Authors comment on the limitation of the study: methods to measure creatinine. I think much more limitations must be noticed.

► Thank you for raising this point. We have added other expected limitations on page 18, as below:

“Since this is a retrospective observational cohort study from six different countries, we expect several limitations will exist. As we mentioned earlier, eGFR and htTKV, the two major indicators of disease progression in ADPKD, cannot be measured or interpreted by a unified method. Additionally, follow-up intervals or htTKV measurements will be different among different participating countries. In addition, there might be an insufficient number of patients who could provide genetic data, which is a known important prognostic marker of renal progression in ADPKD. Collecting data of a minimum of two years follow up would not be sufficient to use the rapid progressor categories that have been suggested in the ERA-EDTA guideline. Also relatively preserved renal function population would not show enough renal changes during the follow-ups of minimal two years of data. Also, we could not evaluate the renal function using cystatin C or inulin clearance which would be more appropriate methods especially for the sarcopenic patients with severe polycystic liver disease.”