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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

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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

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Running title: Design and Methods of RAPID-ADPKD study

Abstract

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) patients reach end-stage renal disease (ESRD) in their fifth decade on average. For effective treatment and early intervention, identifying subgroups with rapid progression is important in ADPKD. However, there are no epidemiologic data regarding the clinical manifestations and disease progression of ADPKD patients from the Asia-pacific region.

Methods and analysis: RAPID-ADPKD (Retrospective epidemiologic study of Asian-Pacific patients with rapId Disease progression of Autosomal Dominant Polycystic Kidney Disease) is a multinational retrospective observational cohort study of ADPKD patients in the Asia-pacific area. This study was designed to identify the clinical characteristics of ADPKD patients with rapid progression. Six hospitals from six regions (Australia, China, Hong Kong, South Korea, Taipei, and Turkey) are participating in this study. Adult ADPKD diagnosed by the Unified ultrasound criteria and with estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73m^2 at baseline will be included. The cohort will include patients with more than two records of eGFR and at least 24 months follow up data. Demographic information, clinical characteristics, comorbidities, medications, eGFR, radiologic findings that can calculate height-adjusted total kidney volume (htTKV), ADPKD-related complications and the PRO-PKD score will be collected using an electrical case report form. Rapid progression will be defined based on the ERA-EDTA guideline. All other patients without any of the criteria are classified as slow progression. The clinical characteristics will be compared between patients with rapid progression and slow progression. Also, the incidence of complications, effects of race and water intake on the renal progression will be analyzed. The planned sample size of the cohort is 1,000 patients, and data from 600 patients have been collected by May 30th, 2019.

Ethics and dissemination: This study was approved by the Institutional Review Boards at Seoul National University Hospital, Istanbul Bilim University Hospital, National Taiwan University Hospital, Westmead Hospital, and Shanghai ChangZheng Hospital and on a process with Queen Mary Hospital. The result will be presented in the conferences and published as a journal to represent the clinical characteristics, risk factors for disease progression, and patterns of complications in Asian populations with ADPKD.

Strengths and limitations of this study

The strength of this study is that this is the first collaboration study in the Asia-Pacific region, which will include more than 1,000 patients to identify the clinical characteristics of ADPKD patients with rapid progression.

Our strengths include that thorough clinical information during ≥ 2 years of follow-up of the enrolled patients will be collected, including clinical manifestations, laboratory results, renal radiologic findings, PRO-PKD scores and genotype information, which would give the information of the clinical characteristics of ADPKD patients in Asian-Pacific, such as the incidence of renal and extra-renal complications, diagnostic and assessment pattern, and the effects of race and water intake on the progression.

The limitation of the study is that due to the nature of retrospective observational study, we could not unify the serum creatinine and renal volumes measurement methods, but instead will collect the values that have been measured in each center and used in the real clinical practice.

We anticipate more collaborating studies among Asia-Pacific countries will be derived from our study, which can benefit the Asia-Pacific ADPKD population.

Introductions

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease in all races.[1] About 50% of ADPKD patients progress to end-stage renal disease (ESRD) in their fifth decades, and ADPKD is currently the fourth main cause of ESRD.[2] In addition to renal progression, various renal and extra-renal symptoms and complications occur in ADPKD patients during their life. ADPKD is a heterogeneous set of diseases caused by a mutation in either two genes, *PKD1* and *PKD2*. Patients with *PKD2* mutation show a milder clinical course compared to those with *PKD1* mutation.[3] However even in the same family, with the same germ-line mutation in *PKD1/PKD2* gene, manifestation and severity of disease differ from person to person.[2] These difference in disease manifestation and progression might be due to the influence of various environmental factors in addition to genetic factors.[4] Therefore, finding patients who will develop the severe disease is important in the clinical management of ADPKD. Moreover, since the approval of vasopressin V2 receptor antagonists by the US-FDA as the first medication to slow ADPKD progression, identifying the 'rapid progressor' has been a crucial step to decide who will benefit from the treatment.[5]

However, there have been only a few studies to characterize the disease nature and to analyze the progression of ADPKD in the Asian-Pacific population (**Table 1**). From the previous studies, a few unique characteristics of the Asian ADPKD population were noticed. About 50%-80% of genetic mutations in *PKD1* or *PKD 2* gene of Asian population were novel compared to previous genetic mutation database based on Western population.[6-8] In addition, differences in other genetic backgrounds, race, climates, culture, and lifestyle of Asian population can also affect the disease progression differently. Limited data suggest the possibility of faster renal progression in Asian chronic kidney disease (CKD) patients

compared to the Western population.[9-11] However previous studies of Asian ADPKD population were conducted in a single country which under-represented the whole Asian ADPKD population.[12-27] Moreover, to date, the studies to identify the rapid progression population of ADPKD patients were mostly conducted in the Western population.[5, 28-30] Therefore, a larger number, multicenter study to find the clinical characteristics of Asian ADPKD population and to define the risk factors for the rapid progression of the disease are needed for Asian ADPKD patients.

Therefore, the aim of this multinational, multicenter, retrospective cohort study was to determine the clinical characteristics of rapidly progressing ADPKD patients in the Asia-Pacific region using the current recommendation for identification of rapid progression.[5] The data of clinical characteristics, complications, and disease courses that represent ADPKD patients in the Asia-Pacific region will also be collected. In addition, an exploratory goal of this project is to determine whether there are racial differences in disease progression and the incidence of cardiovascular complications in Asian ADPKD population, and thus contribute to a baseline knowledge to inform future studies in this group of patients.

Methods and Analysis

Study design

The RAPID-ADPKD (**R**etrospective epidemiologic study of **A**sian-**P**acific patients with rap**I**d **D**isease progression of **A**utosomal **D**ominant **P**olycystic **K**idney **D**isease) is a multinational retrospective observational cohort study. This study was designed to determine the prevalence of rapid progressor category of ADPKD patients in the Asia-pacific region based on the change

of renal function, kidney size, and progression to ESRD.

Organization

This study will enroll ADPKD patients who have visited one of six hospitals from six nations in the Asia-pacific area: (ⅰ) Australia: Westmead Hospital, Westmead; (ⅱ) China: Changzheng Hospital of Shanghai; (ⅲ) Hong Kong: Queen Mary Hospital of Hong Kong; (ⅳ) South Korea: Seoul National University Hospital of South Korea; (ⅴ) Taiwan: National Taiwan University hospital of Taipei; and (ⅵ)Turkey: Istanbul Bilim University of Turkey.

Study population

After retrospectively reviewing the patients' data from each hospital, we will enroll patients ≥18 years old (≥19 years old for Taiwan patients due to different age criteria for the adults) adult ADPKD patients with estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73m^2 at the index date of the study. The index date is the first available date of reviewed medical records between January 2010 and the enrollment period. The enrolled patients are diagnosed ADPKD patients based on Unified ultrasound criteria for the patients with ADPKD family history[31]: at least two (unilateral or bilateral) renal cysts in age of 18-29, at least two cysts in each kidney in age of 30-59 year old and more than 4 bilateral renal cysts in age ≥60 year old. For the patients without a family history of ADPKD, the clinical diagnosis of ADPKD based on typical radiologic findings and/or clinical evaluation will be also accepted. The patients should have at least two clinical visits with eGFR measurements between January 1^{st,} 2010 and the time at enrollment. In addition, at the time of enrollment, patients should have followed the center during the last 24 months. Patients should also have at least two-year clinical records of follow-ups from the index date**. (Figure 1).** Patients with severe heart failure, severe liver disease,

chronic inflammatory disease and/or other comorbidities that can affect renal function will be excluded. Active cancer patients who underwent chemotherapy during the observation period will be excluded from the study. Any medical or surgical conditions that can affect renal function or kidney volume will be excluded as well. The expected sample size of this multinational retrospective observational cohort is more than 1,000 patients.

Data collection

Demographic information at index dates such as gender, date of birth, race, height, and body weight will be collected. Comorbid conditions including diabetes mellitus, dyslipidemia, hypertension, valvular heart disease, pericardial effusion or left ventricular hypertrophy based on echocardiography, chronic pulmonary disease, coronary artery disease, cerebrovascular disease, and cancer will be investigated. In addition, blood pressure, smoking history and CKD stage based on CKD-EPI eGFR at index date calculated using the formula of $eGFR = 141 \times \min(Scr \times 0.0113/k, \ 1)^{\alpha} \times \max(Scr \times 0.0113/k, \ 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black], where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, $^{\alpha}$ is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1,[32] family history of ESRD, medications (anti-hypertensive agents including calcium channel blocker, angiotensin converting enzyme, angiotensin receptor blocker and beta blocker, uric acid lowering agent, anti-diabetic agents including metformin, DPP4 inhibitor and SGLT2 inhibitor, lipid lowering agents including statins and others) and laboratory results (serum albumin, total bilirubin, cholesterol, high density lipid, low density lipid, triglyceride, ALT, AST, sodium, potassium, chloride, blood urea nitrogen, glucose and uric acid) will be gathered. At the index date and during the follow up visits, serum creatinine, urine protein/creatinine ratio, height-adjusted total kidney volume

(htTKV) from radiologic findings of MRI, CT or ultrasound sonography, renal and extra-renal ADPKD-related complications (cyst infection, events or image diagnosed hemorrhagic cysts, proteinuria, kidney stone, gross hematuria, microscopic hematuria, chronic pain, upper urinary tract infection, hypertension, hyperuricemia, hernia, liver cysts, intracranial aneurysms, subarachnoid hemorrhage, abdominal aorta aneurysms, and infertility) and procedure (nephrectomy, sclerotherapy, embolization, renal replacement therapy, hepatectomy, liver transplantation, embolization, fenestration and intervention for intracranial aneurysm) will be investigated.

From the reviewed data, the PRO-PKD score and event information including ESRD, major cardiovascular events (myocardial infarction, hospitalization for unstable angina, transient ischemic attack and stroke, heart failure requiring hospitalization and peripheral artery revascularization procedure), and death will be collected using an electronic case report form. PRO-PKD score will be calculated based on the followings: score 1 for male, score 2 for hypertension before 35 years of age, score 2 for having first urologic event such as macroscopic hematuria, flank pain or cyst infection before 35 years of age, score 2 for non-truncating *PKD1* mutation and score 4 for truncating *PKD1* mutation based on genetic testing results.[28] **(Figure 1)**

Serum creatinine measurement and eGFR calculation

To define the patients with rapid progression, standardizing creatinine measurement is important. However, this is a multi-national retrospective study, and serum creatinine measuring methods are inevitably different from centers and dates. To reduce the error in the interpretation of eGFR caused by various creatinine measurement methods, in addition to collecting serum creatinine value itself, we will also collect the creatinine measurement

methods such as Jaffe methods (calibrated with isotopic dilution mass spectrometry), enzymatic methods, alkaline picrate kinetic, alkaline picrate rate-blanked with compensation and alkaline picrate rate–blanked without compensation for the supporting information during the analysis. In the eGFR calculation, 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.[33] All eGFR will be calculated based on the CKD-EPI equation.[32]

Total kidney volume calculation

In order to collect the maximal amount of the htTKV data, we will gather information about the renal images from MRI, CT, or ultrasound undertaken during the follow-ups. The imaging dates and methods will be collected. If the htTKV was already measured using the images, the value and the measurement methods of total kidney volume (TKV) (ellipsoid, stereological measurement or other) will be collected. If there is no measurement done previously, the htTKV will be calculated using the ellipsoid methods.[34] For the analysis, htTKV calculated by ellipsoid methods would be used mainly to define the rapid progression. However, if other htTKV calculating methods such as stereological or planimetry are used in the same patient, the progression will be determined using the values also. 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.

Follow-up

Follow-up duration will be defined from the index date until the enrolled date. Date of events such as ESRD, major cardiovascular events, and death during the follow-up will be collected and used for the analysis. (**Figure 1**)

Outcome variables

The cohort will include patients with more than two records of eGFR and, ≥24 months of follow up. The primary outcome of the study is to find out the clinical characteristics of the rapid progressor among the Asia-Pacific ADPKD population. Rapid progression will be defined as when any of following criteria are met, based on ERA-EDTA recommendations[5]: (i) an annual eGFR decline ≥5 mL/min/1.73m^2 within 1 year and/or ≥2.5mL/min/1.73m^2 per year over a period of 5 years; (ii) an increase in htTKV ≥ 5% per year measured from ≥3 radiologic images; (iii) Mayo classification 1C, 1D, or 1E or kidney length from ultrasonography of >16.5 cm; (iv) *PKD1* truncated mutation with early symptoms (PRO-PKD score > 6). The remainder of the patients will be classified as slow progressors. The clinical characteristics will be compared between patients with rapid progression and slow progression. The secondary outcome of the study is to determine the difference in 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 will be included in secondary outcome measures.

Data collection, monitoring, and management

Whole data collection and monitoring will be managed by Contract Research Organization (CRO). The person who enters data at each center will be educated by the clinical research associate (CRA) before enrollment of the first patients from each center for the unity of the data and to minimize the data input errors. Depending on the inclusion and exclusion criteria, patients' eligibility for the study and final inclusion will be decided by the clinician at each center. All the retrospective data will be collected using an electronic case report form (eCRF). During the data collection, the CRA will visit the center during the input time period and keep communicating with the person at centers to discover the data input errors earlier and handle the possible upcoming issues. When the data are entered, internal monitoring will be conducted

at each center. After the data are entered from all centers, external monitoring will be performed by the CRO. The missing data of the continuous variable will be categorized as the 'missing' category. Currently, the data from 600 patients have been collected by May 30th, 2019.

Statistical methods

After all the data are entered and monitored, the statistical analysis will be conducted with both the total population and national levels. If a certain variable is not able to be collected at a specific center, the analysis of the variable will be done after excluding the missing values. The analysis will be done under the guideline of the International Committee on Harmonisation E9: Statistical principles for clinical trials.[35]

For the primary analysis, all the clinical variables will be analyzed according to two categories: the rapid progressor and the slow progressor. Additional analysis will be conducted according to CKD stages and age groups (≤30 years old, 31 to 40 years old, 41 to 50 years old and ≥51 years old), countries, and races. For the statistical analysis of the categorical variables, Chi-square test will be used. With the continuous variables, Student's t-test and Analysis of Variance will be conducted. For the comparison of changes of eGFR and htTKV, the generalized linear mixed model will be used to adjust the baseline difference between the individuals. The event data will be analyzed using Cox-proportional hazard model. The value of $P<0.05$ will be interpreted as statistically significant. For multiple comparisons, the Holm-Bonferroni method will be used.

Clinical significance of the study

This RAPID-ADPKD study has been designed to represent the clinical data profile of the ADPKD population in the Asia-Pacific region. In this study, ADPKD patients from six different countries in Asia-Pacific region, Australia, China, Hong Kong, South Korea, Taiwan,

and Turkey, will be included and will have heterogeneity ADPKD population consisted of different races such as Han Chinese, Korean, Turks, Kurds, Taiwanese aborigines, Caucasians, etc. By using the data from ADPKD patients in six Asia-Pacific countries, we aim to identify the risk factors for the rapid disease progression of Asian-Pacific ADPKD patients. To address the renal progression of the study population, htTKV and eGFR of enrolled patients' will be retrospectively reviewed and collected.

We also expect to analyze the current status of Asian-Pacific ADPKD patients, such as the pattern of extra-renal complication, diagnosis, treatment, and medical resource utilization in Asian-Pacific ADPKD patients. Patients with ADPKD are known to have a higher risk of hypertension and cardiovascular events compared to the general population.[36-38] However, in the CKD population, there have been studies that reported that hypertension is better controlled and the incidence of cardiovascular events is lower in Asian population compared to the Western CKD population.[39-41] Whether the incidence of hypertension and cardiovascular event are relatively low in Asian ADPKD patients compared to the Western population as in other CKD patients are unknown. In addition, the Asian population has relatively smaller body mass compared to the western population, and there might be a higher incidence of complications due to severe polycystic liver disease and organomegaly in Asian ADPKD patients. Using the retrospective data from RAPID-ADPKD study, we are planning to analyze the incidence of extra-renal complications and seek the meaning in the Asian ADPKD population. Also the medical resource utilization is influenced by the medical system and the government reimbursement system. Therefore, the diagnostic pattern and assessment method of disease progression during the follow-up would be different in Asian-Pacific ADPKD countries compared to Western countries. For example, MRI is a gold standard tool for total kidney volume measurement, but it is not reimbursed by the medical system in most Asian-Pacific

countries and ultrasonography, or computed tomography is preferred in the clinical setting of Asia Pacific regions. Results from the current study would give us much information about current assessment protocol in Asian ADPKD population, which would be valuable data in planning for future clinical studies in Asian ADPKD patients.

In this study, the ethnical data will also be collected for the analysis of racial differences in Asian ADPKD population. Only a couple of studies evaluated ADPKD progression in racial differences. Freedman et al., reported that African American ADPKD patients showed faster renal progression compared to Caucasian ADPKD patients in the United States.[42, 43] In the respect of Asian population, Muto et al. reported from the Japanese subset study of TEMPO 4:3, the response to Tolvaptan on the annual rate of TKV growth was different in Japanese population compared to that of total population.[20] Further studies regarding the racial difference on the disease would give us an in-depth understanding of disease pathophysiology and the identification of the rapid progressor. Therefore, the effect of race on the clinical manifestation and renal progression that could be analyzed from RAPID-ADPKD study would be another valuable finding.

It is known that the serum level of antidiuretic hormone vasopressin is elevated at the status of dehydration and this is related to cyst growths in ADPKD.[44] Based on this, sufficient water intake, as well as vasopressin V2 receptor antagonist, has been applied to slow renal progression in ADPKD patients.[4, 45] Even though the beneficial effect of increased water intake has been supported by animal studies, there are not enough human studies to support the recommendation. Therefore, currently, a randomized controlled trial, PREVENT-ADPKD to determine the effect of increased water intake in ADPKD is underway.[45] In this RAPID-ADPKD study, by collecting and analyzing the data of specific gravity of spot urine as a marker

of water intake in a relatively large number of patients, we expect to provide baseline data for the effect of the water intake on ADPKD patients.

Limitations

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. Nevertheless, we believe that our analysis using eGFR and htTKV would become valuable findings since we will collect data from actual clinical practice and a large number of patients across different nations. Even though there are some limitations due to the nature of multinational retrospective observational study, we expect our results will give us valuable knowledge about clinical characteristics and rapid progressor of Asian ADPKD patients and basic information of current practice in Asian ADPKD clinics.

Ethics and dissemination

The basic protocol of the study was approved by most of participating center's Institutional Review Boards (IRB) (Seoul National University Hospital, Seoul No 1801-114-917; Istanbul Bilim University Hospital, Turkey No 19.12.2017/65-11; National Taiwan University Hospital, Taiwan, No 201801072RSA; Westmead Hospital, Australia No LNR/17/WMEAD/444; Shanghai ChangZheng Hospital, China, No 2018SL025) and on process with Queen Mary Hospital of Hong Kong. This study is a retrospective observational cohort study, and there are

no interventions to the study subjects. Therefore, this study presents no more than minimal risk of harm to the study subjects, and all IRB approved the consent waiver. All the collected data for the study will be handled according to non-disclosure agreement and privacy legislation. The data will be stored for at least five years after the completion of the enrollment but can be deleted according to each nations' privacy regulations. The result will be presented in the conferences and published as a journal to represent the clinical characteristics, risk factors for disease progression and patterns of complications in Asian populations with ADPKD.

Patient and Public Involvement

In this study, patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research.

List of abbreviations

ADPKD Autosomal dominant polycystic kidney disease

CKD Chronic kidney disease

CRA Clinical research associate

CRO Contract research organization

eCRF Electronic case report form

eGFR Estimated glomerular filtration rate

ESRD End-stage renal disease

htTKV Height adjusted total kidney volume

IRB Institutional Review Boards

RAPID-ADPKD Retrospective epidemiologic study of Asian-Pacific patients with rapId Disease progression of Autosomal Dominant Polycystic Kidney Disease

TKV Total kidney volume

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Authors' contribution

HR participated in design of the work, data acquisition, data analysis and drafting the work, HCP and YKO participated in the design of the work, interpretation of data and revising the manuscript. IS, AW, CM, TE, AW, TWK and JWH have been worked in the design of the work, acquisition and monitoring the data for the improvement of the accuracy. GR participated in the design of the work, acquisition, interpretation of the data, revising the manuscript and final approval of the manuscript to be published. CA designed the study, gathered study collaborators and finalizing the manuscript. All authors read and approved the manuscript.

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Competing interests

The study was supported by Korea Otsuka International Asia Arab Co., Ltd. and GR received grant support from Danone Nutricia research for clinical research into ADPKD

License Statement

Figure Legends

Figure 1. The planned structure and the data collections in RAPID-ADPKD study

Table Legends

Table 1. The summary of studies regarding clinical characteristic or renal progression in Asian ADPKD patients

28

Country	Subject of the journal	Number of analyzed patients	Study type	Published year	Reference
Australia	Genotype-Phenotype correlation	285	Cross-sectional study	1992	12
China	Clinical manifestation	205	Cross-sectional study	1995	13
China	Clinical characteristics and disease progression	541	Prospective cohort study	2014	14
China	Genotype-Phenotype correlation	148	Cross-sectional study	2016	15
China	Clinical feature of inpatient ADPKD patients	168	Retrospective study	2018	16
Iraq	Clinical manifestation	30	Cross-sectional study	2011	17
Japan	Renal progression	255	Retrospective study	2012	18
Japan	Genotype and renal progression	112	Retrospective study	2014	19
Japan	Renal progression and effect of Tolvaptan in Japanese patient subset from TEMPO3:4 trial	177	Subgroup study of clinical trial	2015	20
Japan	Clinical characteristics according to mayo classification	296	Retrospective study	2019	21
Pakistan	Clinical presentation	56	Cross-sectional	2008	22

			study		
South Korea	Clinical characteristics	461	Cross-sectional study	2015	23
South Korea	Clinical characteristics	364	Prospective cohort study	2018	24
Taipei	Incidence of cardiovascular complications in ADPKD patients compared to general population	2062	National database study	2017	25
Turkey	Clinical characteristics	1139	Cross-sectional study	2011	26
Turkey	Clinical characteristics and predictor of renal progression	323	Retrospective study	2013	27

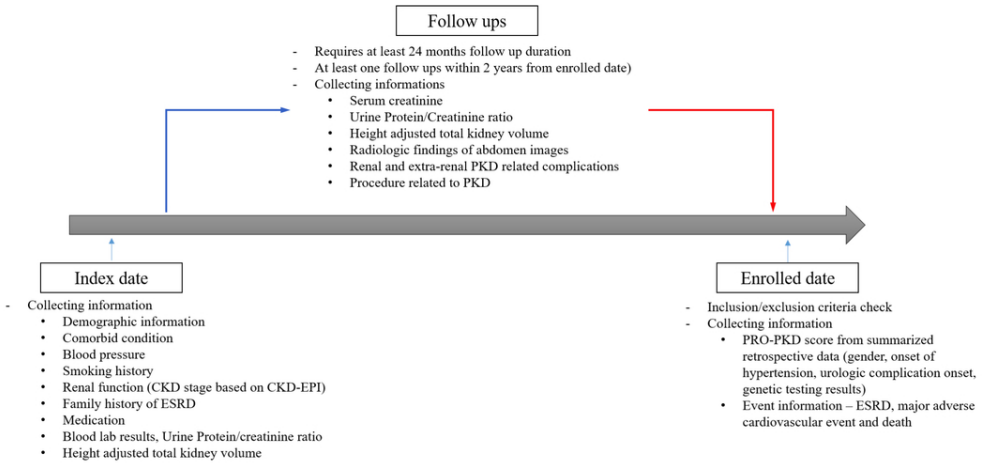

Figure 1. The planned structure and the data collections in RAPID-ADPKD study

90x41mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Check list
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	√ Page 1, 5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	√ Page 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	√ Page 8-9
Objectives	3	State specific objectives, including any prespecified hypotheses	√ Page 9
Methods			
Study design	4	Present key elements of study design early in the paper	√ Page 9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	√ Page 10, Figure 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	√ Page 10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	√ Page 11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	√ Page 11-13
Bias	9	Describe any efforts to address potential sources of bias	√ Page 11-13
Study size	10	Explain how the study size was arrived at	√ Page 14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	√ Page 15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	√ Page 15
		(*b*) Describe any methods used to examine subgroups and interactions	√ Page 15
		(*c*) Explain how missing data were addressed	√ Page 15
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	√ Page 15
		(*e*) Describe any sensitivity analyses	√ **Page 14**
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**NA**

		(b) Give reasons for non-participation at each stage	**NA**
		(c) Consider use of a flow diagram	**NA**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**NA**
		(b) Indicate number of participants with missing data for each variable of interest	**NA**
Outcome data	15*	Report numbers of outcome events or summary measures	**NA**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**NA**
		(*b*) Report category boundaries when continuous variables were categorized	**NA**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**NA**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	√ Page 15-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	√ Page 15-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	√ Page 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	√ Page 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	√ Page 26

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

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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

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Running title: Design and Methods of RAPID-ADPKD study

Abstract

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) patients reach end-stage renal disease (ESRD) in their fifth decade on average. For effective treatment and early intervention, identifying subgroups with rapid progression is important in ADPKD. However, there are no epidemiologic data regarding the clinical manifestations and disease progression of ADPKD patients from the Asia-pacific region.

Methods and analysis: RAPID-ADPKD (Retrospective epidemiologic study of Asian-Pacific patients with rapId Disease progression of ADPKD) is a multinational retrospective observational cohort study of ADPKD patients in the Asia-pacific area (Australia, China, Hong Kong, South Korea, Taipei, and Turkey). This study was designed to identify the clinical characteristics of ADPKD patients with rapid progression. Adult ADPKD diagnosed by the Unified ultrasound criteria and with estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73m^2 at baseline will be included. The cohort will include patients with ≥2 records of eGFR and at least 24 months follow up data. Demographic information, clinical characteristics, comorbidities, medications, eGFR, radiologic findings that can calculate height-adjusted total kidney volume, ADPKD-related complications and the PRO-PKD score will be collected. Rapid progression will be defined based on the ERA-EDTA guideline. All other patients without any of the criteria are classified as slow progression. The clinical characteristics will be compared between patients with rapid progression and slow progression. Also, the incidence of complications, effects of race and water intake on the renal progression will be analyzed. The planned sample size of the cohort is 1,000 patients, and data from 600 patients have been collected by May 30th, 2019.

Ethics and dissemination: This study was approved or on process by the Institutional Review

Boards at each participating centers. The result will be presented in the conferences and published as a journal to represent the clinical characteristics, risk factors for disease progression, and patterns of complications in Asian populations with ADPKD.

Article summary

Strengths and limitations of this study

The strength of this study is that this is the first collaboration study in the Asia-Pacific region, which will include more than 1,000 patients to identify the clinical characteristics of ADPKD patients with rapid progression.

Detailed clinical information of at least two years of follow-up will be collected including clinical manifestations, laboratory results, renal radiologic findings, and PRO-PKD scores which expect to provide knowledge about the incidence of renal and extra-renal complications, diagnostic pattern, and the effects of ethnicities and water intake on the progression.

Due to the nature of the retrospective observational study, measurement of renal function and kidney volumes measurement methods could not be unified, and follow-up durations and intervals would differ among patients.

We anticipate more collaborating studies among Asia-Pacific countries will be derived from our study, which can benefit the Asia-Pacific ADPKD population.

Introductions

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease in all races.[1] About 50% of ADPKD patients progress to end-stage renal disease (ESRD) in their fifth decades, and ADPKD is currently the fourth main cause of ESRD.[2] In addition to renal progression, various renal and extra-renal symptoms and complications occur in ADPKD patients during their life. ADPKD is a heterogeneous set of diseases caused by a mutation in either two genes, *PKD1* and *PKD2*. Patients with *PKD2* mutation show a milder clinical course compared to those with *PKD1* mutation.[3] However even in the same family, with the same germ-line mutation in *PKD1/PKD2* gene, manifestation and severity of disease differ from person to person.[2] These difference in disease manifestation and progression might be due to the influence of various environmental factors in addition to genetic factors.[4] Therefore, finding patients who will develop severe disease is important in the clinical management of ADPKD. Moreover, since the approval of vasopressin V2 receptor antagonists by the US-FDA as the first medication to slow ADPKD progression, identifying the 'rapid progressor' has been a crucial step to decide who will benefit from the treatment.[5]

However, there have been only a few studies to characterize the disease nature and to analyze the progression of ADPKD in the Asian-Pacific population (**Table 1**). From the previous studies, a few unique characteristics of the Asian ADPKD population were noticed. About 50%-80% of genetic mutations in *PKD1* or *PKD 2* gene of Asian population were novel compared to previous genetic mutation database based on Western population.[6-8] In addition, differences in other genetic backgrounds, races, climates, cultures, and lifestyles of Asian population can also affect the disease progression differently. Limited data suggest the possibility of faster renal progression in Asian chronic kidney disease (CKD) patients

compared to the Western population.[9-11] However previous studies of Asian ADPKD population were conducted in a single country which under-represented the whole Asian ADPKD population.[12-27] Moreover, to date, the studies to identify the rapid progression population of ADPKD patients were mostly conducted in the Western population.[5, 28-30] Therefore, a larger number, multicenter study to find the clinical characteristics of Asian ADPKD population and to define the risk factors for the rapid progression of the disease are needed for Asian ADPKD patients.

Therefore, the aim of this multinational, multicenter, retrospective cohort study was to determine the clinical characteristics of rapidly progressing ADPKD patients in the Asia-Pacific region using the current recommendation for identification of rapid progression.[5] The data of clinical characteristics, complications, and disease courses that represent ADPKD patients in the Asia-Pacific region will also be collected. In addition, an exploratory goal of this project is to determine whether there are racial differences in disease progression, and thus contribute to a baseline knowledge to inform future studies in this group of patients.

Methods and Analysis

Study design

The RAPID-ADPKD (**R**etrospective epidemiologic study of **A**sian-**P**acific patients with rap**I**d **D**isease progression of **A**utosomal **D**ominant **P**olycystic **K**idney **D**isease) is a multinational retrospective observational cohort study. This study was designed to determine the prevalence of the rapid progressor category of ADPKD patients in the Asia-pacific region based on the change of renal function, kidney size, and progression to ESRD.

Organization

This study will enroll ADPKD patients who have visited one of six hospitals from six nations in the Asia-pacific area: (ⅰ) Australia: Westmead Hospital, Westmead; (ⅱ) China: Changzheng Hospital of Shanghai; (ⅲ) Hong Kong: Queen Mary Hospital of Hong Kong; (ⅳ) South Korea: Seoul National University Hospital of South Korea; (ⅴ) Taiwan: National Taiwan University hospital of Taipei; and (ⅵ)Turkey: Istanbul Bilim University of Turkey.

Study population

After retrospectively reviewing the patients' data from each hospital, we will enroll patients ≥18 years old (≥19 years old for Taiwan patients due to different age criteria for the adults) adult ADPKD patients with estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73m^2 at the index date of the study. 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. The index date is the first available date of reviewed medical records between January 2010 and the enrollment period. The enrolled patients are diagnosed ADPKD patients based on Unified ultrasound criteria for the patients with ADPKD family history[31]: at least two (unilateral or bilateral) renal cysts in age of 18-29, at least two cysts in each kidney in age of 30-59 year old and more than 4 bilateral renal cysts in age ≥60 year old. For the patients without a family history of ADPKD, the clinical diagnosis of ADPKD based on typical radiologic findings and/or clinical evaluation will be also accepted. The patients should have at least two clinical visits with eGFR measurements between January 1^{st,} 2010 and the time at enrollment. In addition, at the time of enrollment, patients should have followed the center during the last 24 months. Patients should also have at least two-year clinical records of follow-ups from the index date**. (Figure 1).** 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. Active cancer patients who underwent chemotherapy during the observation period will be excluded from the study. Any medical or surgical conditions that can affect renal function or kidney volume will be excluded as well. The expected sample size of this multinational retrospective observational cohort is more than 1,000 patients.

Data collection

Demographic information at index dates such as gender, date of birth, race, height, and body weight will be collected. Comorbid conditions including diabetes mellitus, dyslipidemia, hypertension, valvular heart disease, pericardial effusion or left ventricular hypertrophy based on echocardiography, chronic pulmonary disease, coronary artery disease, cerebrovascular disease, and cancer will be investigated. In addition, blood pressure, smoking history and CKD stage based on CKD-EPI eGFR at index date calculated using the formula of $eGFR = 141 \times \min(Scr \times 0.0113/k, \ 1)^{\alpha} \times \max(Scr \times 0.0113/k, \ 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black], where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1,[32] family history of ESRD, medications (anti-hypertensive agents including calcium channel blocker, angiotensin converting enzyme, angiotensin receptor blocker and beta blocker, uric acid lowering agent, anti-diabetic agents including metformin, DPP4 inhibitor and SGLT2 inhibitor, lipid lowering agents including statins and others) and laboratory results (serum albumin, total bilirubin, cholesterol, high density lipid, low density lipid, triglyceride, ALT, AST, sodium, potassium, chloride, blood

urea nitrogen, glucose and uric acid) will be gathered. At the index date and during the follow up visits, serum creatinine, urine protein/creatinine ratio, height-adjusted total kidney volume (htTKV) from radiologic findings of MRI, CT or ultrasound sonography, renal and extra-renal ADPKD-related complications (cyst infection, events or image diagnosed hemorrhagic cysts, proteinuria, kidney stone, gross hematuria, microscopic hematuria, chronic pain, upper urinary tract infection, hypertension, hyperuricemia, hernia, liver cysts, intracranial aneurysms, subarachnoid hemorrhage, abdominal aorta aneurysms, and infertility) and procedure (nephrectomy, sclerotherapy, embolization, renal replacement therapy, hepatectomy, liver transplantation, embolization, fenestration and intervention for intracranial aneurysm) will be investigated.

From the reviewed data, the PRO-PKD score and event information including ESRD, major cardiovascular events (myocardial infarction, hospitalization for unstable angina, transient ischemic attack and stroke, heart failure requiring hospitalization and peripheral artery revascularization procedure), and death will be collected using an electronic case report form. PRO-PKD score will be calculated based on the followings: score 1 for male, score 2 for hypertension before 35 years of age, score 2 for having first urologic event such as macroscopic hematuria, flank pain or cyst infection before 35 years of age, score 2 for non-truncating *PKD1* mutation and score 4 for truncating *PKD1* mutation based on genetic testing results.[28] **(Figure 1)**

Serum creatinine measurement and eGFR calculation

To define the patients with rapid progression, standardizing creatinine measurement is important. However, this is a multi-national retrospective study, and serum creatinine measuring methods are inevitably different from centers and dates. To reduce the error in the

interpretation of eGFR caused by various creatinine measurement methods, in addition to collecting serum creatinine value itself, we will also collect the creatinine measurement methods such as Jaffe methods (calibrated with isotopic dilution mass spectrometry), enzymatic methods, alkaline picrate kinetic, alkaline picrate rate-blanked with compensation and alkaline picrate rate–blanked without compensation for the supporting information during the analysis. In the eGFR calculation, 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.[33] All eGFR will be calculated based on the CKD-EPI equation.[32]

Total kidney volume calculation

In order to collect the maximal amount of the htTKV data, we will gather information about the renal images from MRI, CT, or ultrasound undertaken during the follow-ups. The imaging dates and methods will be collected. If the htTKV was already measured using the images, the value and the measurement methods of total kidney volume (TKV) (ellipsoid, stereological measurement or other) will be collected. If there is no measurement done previously, the htTKV will be calculated using the ellipsoid methods.[34] For the analysis, htTKV calculated by ellipsoid methods would be used mainly to define the rapid progression. 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 also be determined using the values. 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.

Follow-up

Follow-up duration will be defined from the index date until the enrolled date. Date of events such as ESRD, major cardiovascular events, and death during the follow-up will be collected

and used for the analysis. (**Figure 1**)

Outcome variables

The cohort will include patients with more than two records of eGFR and, ≥24 months of follow up. 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. Rapid progression will be defined as when any of following criteria are met, based on ERA-EDTA recommendations[5]: (i) an annual eGFR decline ≥5 mL/min/1.73m^2 within 1 year and/or ≥2.5mL/min/1.73m^2 per year over a period of 5 years; (ii) an increase in htTKV ≥ 5% per year measured from ≥3 radiologic images; (iii) Mayo classification 1C, 1D, or 1E or kidney length from ultrasonography of >16.5 cm; (iv) *PKD1* truncated mutation with early symptoms (PRO-PKD score > 6). The remainder of the patients will be classified as slow progressors. 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.

Data collection, monitoring, and management

Whole data collection and monitoring will be managed by Contract Research Organization (CRO). The person who enters data at each center will be educated by the clinical research associate (CRA) before enrollment of the first patients from each center for the unity of the data and to minimize the data input errors. Depending on the inclusion and exclusion criteria, patients' eligibility for the study and final inclusion will be decided by the clinician at each

center. All the retrospective data will be collected using an electronic case report form (eCRF). During the data collection, the CRA will visit the center during the input time period and keep communicating with the person at centers to discover the data input errors earlier and handle the possible upcoming issues. When the data are entered, internal monitoring will be conducted at each center. After the data are entered from all centers, external monitoring will be performed by the CRO. The missing data of the continuous variable will be categorized as the 'missing' category. Currently, the data from 600 patients have been collected by May 30th, 2019.

Statistical methods

After all the data are entered and monitored, the statistical analysis will be conducted with both the total population and national levels. If a certain variable is not able to be collected at a specific center, the analysis of the variable will be done after excluding the missing values. The analysis will be done under the guideline of the International Committee on Harmonisation E9: Statistical principles for clinical trials.[35]

For the primary analysis, all the clinical variables will be analyzed according to two categories: the rapid progressor and the slow progressor. Additional analysis will be conducted according to CKD stages and age groups (≤30 years old, 31 to 40 years old, 41 to 50 years old and ≥51 years old), countries, and races. For the statistical analysis of the categorical variables, Chi-square test will be used. With the continuous variables, Student's t-test and Analysis of Variance will be conducted. For the comparison of changes of eGFR and htTKV, the generalized linear mixed model will be used to adjust the baseline difference between the individuals. The event data will be analyzed using Cox-proportional hazard model. The value of $P<0.05$ will be interpreted as statistically significant. For multiple comparisons, the Holm-Bonferroni method will be used.

Clinical significance of the study

This RAPID-ADPKD study has been designed to represent the clinical data profile of the ADPKD population in the Asia-Pacific region. In this study, ADPKD patients from six different countries in Asia-Pacific region, Australia, China, Hong Kong, South Korea, Taiwan, and Turkey, will be included and will have heterogeneity ADPKD population consisted of different races such as Han Chinese, Korean, Turks, Kurds, Taiwanese aborigines, Caucasians, etc. By using the data from ADPKD patients in six Asia-Pacific countries, we aim to identify the risk factors for the rapid disease progression of Asian-Pacific ADPKD patients. To address the renal progression of the study population, htTKV and eGFR of enrolled patients' will be retrospectively reviewed and collected.

We also expect to analyze the current status of Asian-Pacific ADPKD patients, such as the pattern of extra-renal complication, diagnosis, treatment, and medical resource utilization in Asian-Pacific ADPKD patients. Patients with ADPKD are known to have a higher risk of hypertension and cardiovascular events compared to the general population.[36-38] However, in the CKD population, there have been studies that reported that hypertension is better controlled and the incidence of cardiovascular events is lower in Asian population compared to the Western CKD population.[39-41] Whether the incidence of hypertension and cardiovascular event are relatively low in Asian ADPKD patients compared to the Western population as in other CKD patients are unknown. In addition, the Asian population has relatively smaller body mass compared to the western population, and there might be a higher incidence of complications due to severe polycystic liver disease and organomegaly in Asian ADPKD patients. Using the retrospective data from RAPID-ADPKD study, we are planning to analyze the incidence of extra-renal complications and seek the meaning in the Asian ADPKD population. Also the

medical resource utilization is influenced by the medical system and the government reimbursement system. Therefore, the diagnostic pattern and assessment method of disease progression during the follow-up would be different in Asian-Pacific ADPKD countries compared to Western countries. For example, MRI is a gold standard tool for total kidney volume measurement, but it is not reimbursed by the medical system in most Asian-Pacific countries and ultrasonography, or computed tomography is preferred in the clinical setting of Asia Pacific regions. Results from the current study would give us much information about current assessment protocol in Asian ADPKD population, which would be valuable data in planning for future clinical studies in Asian ADPKD patients.

In this study, the ethnical data will also be collected for the analysis of racial differences in Asian ADPKD population. Only a couple of studies evaluated ADPKD progression in racial differences. Freedman et al., reported that African American ADPKD patients showed faster renal progression compared to Caucasian ADPKD patients in the United States.[42, 43] In the respect of Asian population, Muto et al. reported from the Japanese subset study of TEMPO 4:3, the response to Tolvaptan on the annual rate of TKV growth was different in Japanese population compared to that of total population.[20] Further studies regarding the racial difference on the disease would give us an in-depth understanding of disease pathophysiology and the identification of the rapid progressor. Therefore, the effect of race on the clinical manifestation and renal progression that could be analyzed from RAPID-ADPKD study would be another valuable finding.

It is known that the serum level of antidiuretic hormone vasopressin is elevated at the status of dehydration and this is related to cyst growths in ADPKD.[44] Based on this, sufficient water intake, as well as vasopressin V2 receptor antagonist, has been applied to slow renal

progression in ADPKD patients.[4, 45] Even though the beneficial effect of increased water intake has been supported by animal studies, there are not enough human studies to support the recommendation. Therefore, currently, a randomized controlled trial, PREVENT-ADPKD to determine the effect of increased water intake in ADPKD is underway.[45] In this RAPID-ADPKD study, by collecting and analyzing the data of specific gravity of spot urine as a marker of water intake in a relatively large number of patients, we expect to provide baseline data for the effect of the water intake on ADPKD patients.

Limitations

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. Nevertheless, we believe that our analysis using eGFR and htTKV would become valuable findings since we will collect data from actual clinical practice and a large number of patients across different nations. Even though there are some limitations due to the nature of multinational retrospective

observational study, we expect our results will give us valuable knowledge about clinical characteristics and the rapid progressor of Asian ADPKD patients and basic information of current practice in Asia-Pacific regions for the first time. Based on the findings from this study, we hope other well-organized multinational prospective studies are designed and conducted to find clinical characteristics and unique risk factors for the Asian ADPKD population.

Ethics and dissemination

The basic protocol of the study was approved by most of participating center's Institutional Review Boards (IRB) (Seoul National University Hospital, Seoul No 1801-114-917; Istanbul Bilim University Hospital, Turkey No 19.12.2017/65-11; National Taiwan University Hospital, Taiwan, No 201801072RSA; Westmead Hospital, Australia No LNR/17/WMEAD/444; Shanghai ChangZheng Hospital, China, No 2018SL025) and on process with Queen Mary Hospital of Hong Kong. This study is a retrospective observational cohort study, and there are no interventions to the study subjects. Therefore, this study presents no more than minimal risk of harm to the study subjects, and all IRB approved the consent waiver. All the collected data for the study will be handled according to non-disclosure agreement and privacy legislation. The data will be stored for at least five years after the completion of the enrollment but can be deleted according to each nations' privacy regulations. The result will be presented in the conferences and published as a journal to represent the clinical characteristics, risk factors for disease progression and patterns of complications in Asian populations with ADPKD.

Patient and Public Involvement

In this study, patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research.

List of abbreviations

ADPKD Autosomal dominant polycystic kidney disease

CKD Chronic kidney disease

CRA Clinical research associate

CRO Contract research organization

eCRF Electronic case report form

eGFR Estimated glomerular filtration rate

ESRD End-stage renal disease

htTKV Height adjusted total kidney volume

IRB Institutional Review Boards

RAPID-ADPKD Retrospective epidemiologic study of Asian-Pacific patients with rapId Disease progression of Autosomal Dominant Polycystic Kidney Disease

TKV Total kidney volume

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None.

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Authors' contribution

HR participated in design of the work, data acquisition, data analysis and drafting the work, HCP and YKO participated in the design of the work, interpretation of data and revising the manuscript. IS, AW, CM, TE, AW, TWK and JWH have been worked in the design of the work, acquisition and monitoring the data for the improvement of the accuracy. GR participated in the design of the work, acquisition, interpretation of the data, revising the manuscript and final approval of the manuscript to be published. CA designed the study, gathered study collaborators and finalizing the manuscript. All authors read and approved the manuscript.

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Competing interests

The study was supported by Korea Otsuka International Asia Arab Co., Ltd. and GR received grant support from Danone Nutricia research for clinical research into ADPKD

License Statement

Figure Legends

Figure 1. The planned structure and the data collections in RAPID-ADPKD study

Table Legends

Table 1. The summary of studies regarding clinical characteristic or renal progression in Asian ADPKD patients

28

Country	Subject of the journal	Number of analyzed patients	Study type	Published year	Reference
Australia	Genotype-Phenotype correlation	285	Cross-sectional study	1992	12
China	Clinical manifestation	205	Cross-sectional study	1995	13
China	Clinical characteristics and disease progression	541	Prospective cohort study	2014	14
China	Genotype-Phenotype correlation	148	Cross-sectional study	2016	15
China	Clinical feature of inpatient ADPKD patients	168	Retrospective study	2018	16
Iraq	Clinical manifestation	30	Cross-sectional study	2011	17
Japan	Renal progression	255	Retrospective study	2012	18
Japan	Genotype and renal progression	112	Retrospective study	2014	19
Japan	Renal progression and effect of Tolvaptan in Japanese patient subset from TEMPO3:4 trial	177	Subgroup study of clinical trial	2015	20
Japan	Clinical characteristics according to mayo classification	296	Retrospective study	2019	21
Pakistan	Clinical presentation	56	Cross-sectional	2008	22

			study		
South Korea	Clinical characteristics	461	Cross-sectional study	2015	23
South Korea	Clinical characteristics	364	Prospective cohort study	2018	24
Taipei	Incidence of cardiovascular complications in ADPKD patients compared to general population	2062	National database study	2017	25
Turkey	Clinical characteristics	1139	Cross-sectional study	2011	26
Turkey	Clinical characteristics and predictor of renal progression	323	Retrospective study	2013	27

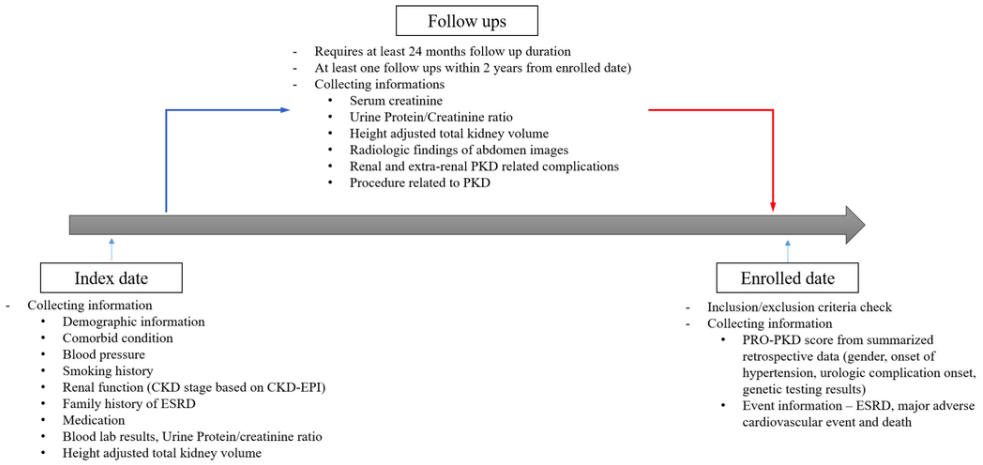

Figure 1. The planned structure and the data collections in RAPID-ADPKD study

90x41mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Check list
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	√ Page 1, 5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	√ Page 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	√ Page 8-9
Objectives	3	State specific objectives, including any prespecified hypotheses	√ Page 9
Methods			
Study design	4	Present key elements of study design early in the paper	√ Page 9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	√ Page 10, Figure 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	√ Page 10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	√ Page 11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	√ Page 11-13
Bias	9	Describe any efforts to address potential sources of bias	√ Page 11-13
Study size	10	Explain how the study size was arrived at	√ Page 14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	√ Page 15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	√ Page 15
		(*b*) Describe any methods used to examine subgroups and interactions	√ Page 15
		(*c*) Explain how missing data were addressed	√ Page 15
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	√ Page 15
		(*e*) Describe any sensitivity analyses	√ **Page 14**
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**NA**

		(b) Give reasons for non-participation at each stage	**NA**
		(c) Consider use of a flow diagram	**NA**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**NA**
		(b) Indicate number of participants with missing data for each variable of interest	**NA**
Outcome data	15*	Report numbers of outcome events or summary measures	**NA**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**NA**
		(*b*) Report category boundaries when continuous variables were categorized	**NA**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**NA**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	√ Page 15-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	√ Page 15-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	√ Page 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	√ Page 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	√ Page 26

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.