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A Systematic Review of Reported Outcomes in ADPKD Studies

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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is a progressive genetic kidney disease. Studies of ADPKD presented results using different outcome measures. We aimed to summarize outcomes reported in ADPKD studies, including composite outcomes.

Methods: We conducted a systematic review of published studies that included patients with ADPKD and measured kidney-related outcomes. We searched published databases and included all studies regardless of design with at least 100 participants for observational studies. We excluded studies that were limited to dialysis, transplant, or pregnancy outcomes in patients with ADPKD.

Results: This review includes data from 175 published articles (49 randomized controlled trials, 2 interventional clinical trials, 30 *post hoc* analyses, and 94 observational studies). We identified 214 different outcomes, and we categorized them into the 24 main outcome domains. In addition, the review identified 13 articles that reported 9 different composite outcomes.

Conclusion: The finding highlights the inconsistency in the outcomes reported by researchers and how they are measured in ADPKD studies. The variability in the outcomes reported supports the need to standardize outcomes in ADPKD studies.

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ADPKD is the leading inheritable cause of end-stage kidney disease (ESKD) among adults.[1,2] The risk of developing ADPKD has been estimated to be between 1 in 400 and 1 in 1000.[1] There are differences in the standards of care, diagnosis, and even modalities of renal replacement therapy.[3] With approval of the first treatment of ADPKD in the United States and other treatment options in the pipeline, patients and clinicians are excited about the potential to change the trajectory of ADPKD outcomes.[4]

The physical and psychologic burdens to patients with ADPKD are significant, yet they are incompletely characterized and difficult to quantify.[5] In addition, there is considerable variability in priorities for polycystic kidney disease (PKD) outcomes between clinical researchers and patients with kidney disease;[6] and there is an unclear appreciation of the significance of patient-centered outcomes in PKD research. Most ADPKD studies report outcomes concerning kidney function, change in total kidney volume (TKV), change in creatinine clearance, and the development of ESKD.[7] Nevertheless, there has been little reporting or discussion of patient-centered outcomes in the PKD literature.[8] Though efforts are underway to expand the role of patient-reported outcomes, validated patient-reported outcome measures for ADPKD are limited and mostly lacking.[9,10] In this review, we aimed to summarize reported outcomes and their measurements and to highlight composite outcomes and their components in ADPKD studies.

METHODS

Data Sources and Searches

We conducted this systematic review in accordance with a prespecified protocol. We reported the results according to Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (Supplementary Table S4).[11]

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We conducted a comprehensive database search from inception (January 1, 1958) to May 24, 2021, of PubMed/Medline, Cochrane, and Web of Science. The detailed search strategy is available in the supplemental material. We reviewed the reference lists of relevant articles and reviews as well as trials registered on the clinicaltrials.gov website.

Study Selection and Data Collection Process

This review included all studies regardless of design. For observational studies and *post hoc* analysis, we only included studies with more than 100 patients. We included studies that assessed at least one patient-centered outcome in adult and pediatric patients with ADPKD. We excluded prevalence studies, risk assessment studies, genotype phenotype correlation, conference proceedings, abstracts, protocols of unpublished studies and duplicate reports. In addition, we excluded studies that only reported dialysis, transplant or pregnancy outcomes in patients with ADPKD and studies in which patients with ADPKD were represented as a subgroup. We excluded studies of kidney volume reduction procedures including nephrectomy and arterial embolization. Two investigators independently screened the search results for articles based on title or title and abstract. At least 2 investigators then independently assessed the eligibility of each article by using a pilot-tested, standardized form with written instructions. Any disagreement was resolved by discussion until consensus was reached.

Data Extraction

We extracted data using a pilot-tested and standardized form. Two investigators independently abstracted all relevant data from each included study. Any discrepancy was resolved by discussion until consesus was reached. We collected the following information from each study: study characteristics (author name, year of publication, design, country, language, patient characteristics, number of patients included, and their age groups), intervention and comparison characteristics, and the outcomes measured in the study, including both composite and individual outcomes as well as the measures used to assess these outcomes.

Data Synthesis and Analysis

We aimed to summarize all patient-centered outcomes reported in ADPKD studies and how they were measured. As quantitative synthesis for this type of review would not be informative, the results were summarized qualitatively.

RESULTS

Study Selection

We identified 916 records. After reviewing 320 full text articles, we included 175 eligible studies with outcomes reported in patients with ADPKD. Details about study selection is presented in Figure 1. Summary of ADPKD patient-centered outcomes per category as well as components of composite outcomes is shown in Figure 2.

Study Characteristics

The studies included in this review are summarized in Table 1. The included studies were conducted across 32 countries, including a few that were multicenter international trials. We included 49 randomized controlled trials, 2 interventional clinical trials, 94 observational studies, and 30 *post hoc* analyses. A total of 6 studies were conducted in pediatric populations, 2 studies in adult and pediatric population, and the rest were among adults. Patient-centered outcomes in ADPKD are summarized in Supplementary Table S1. The details about characteristics of included studies are presented in Supplementary Table S2. Reported kidney outcomes by categories are illustrated in Supplementary Table S3.

Reported Kidney Outcomes

Blood Pressure (BP)

Number of BP Measurements. Multiple BP readings were measured in studies either to calculate the average[12–24] or to select one of the readings that fulfilled certain criteria.[25] Most of these studies calculated the average of 3 BP readings.[12–16,18,19,22,23,26,27] Nevertheless, some studies measured the mean of 2 or 5 BP readings.[20,21,24,28] Two studies calculated the average of selected BP values chosen according to specific criteria such as the mean of the last 3 BP readings or the average of the second and third BP measurements.[15,24]

Resting Time. The resting time before BP measurements ranged between 5 minutes to 20 minutes in different studies.[14,17,22–27,29–34]

Setting and Modality of BP Measurement. The settings of BP assessment in different ADPKD studies included home BP;[32,35–38] hospital or office BP;[12,16–19,21,22,25–28,30,35,37–49] the combination of both;[35,37,38] and ambulatory BP monitoring, which was used in 5 studies.[50–54] Reported ambulatory BP monitoring outcomes include nondipping, daytime, nighttime, 24-hour, and isolated nocturnal hypertension.[53]

Time of Measurement in Relation to Medications. Most studies did not specify the time of BP measurement in relation to timing of medications. One study specified that BP was taken 24 hours after the last medication dose or 12 hours after the last medication dose for twice

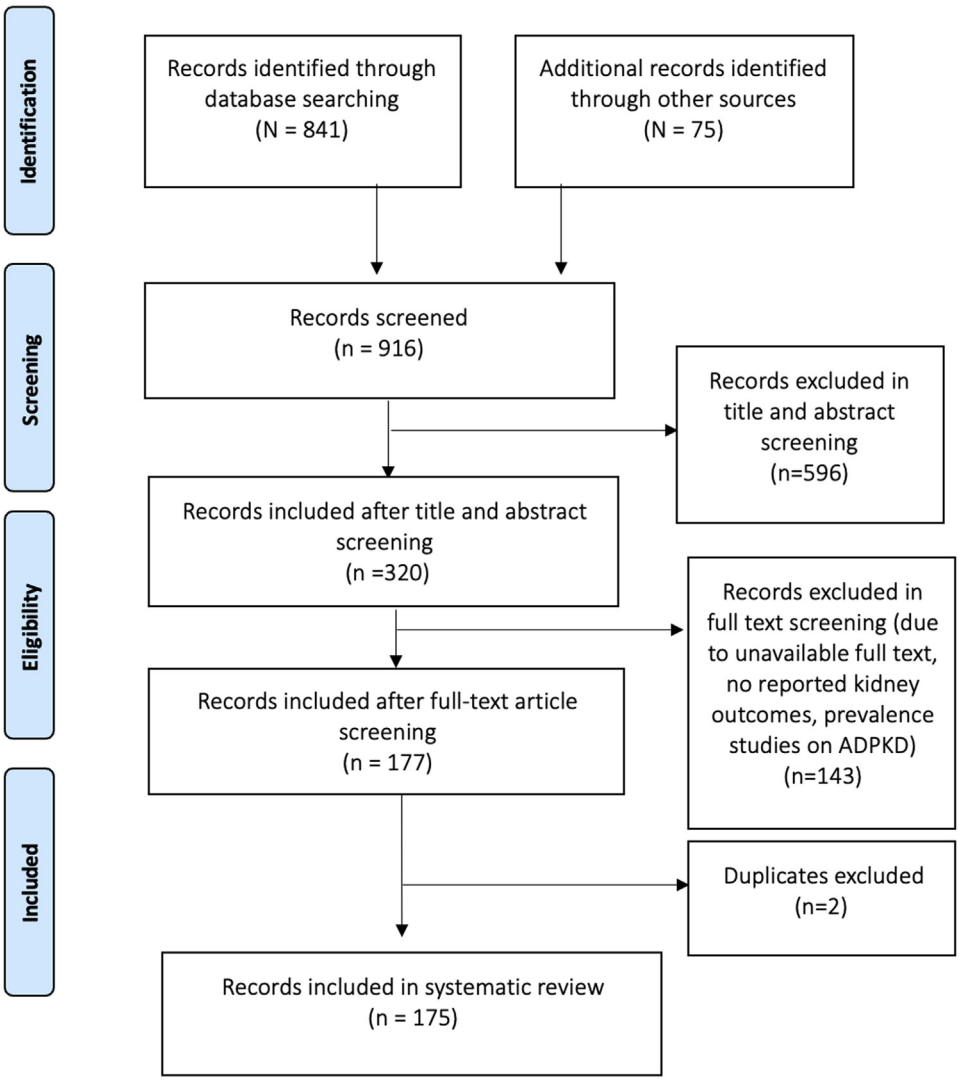

Figure 1. Preferred reporting items for systematic reviews and meta-analyses summary of studies selection ADPKD, autosomal dominant polycystic kidney disease.

daily dosing.[32] Others stated that BP was measured in the morning before medication intake.[26,30,33,34]

BP Parameters. BP outcome was reported as either systolic, diastolic, mean arterial pressure, or any combination of them.[12–19,21–36,39,40,42,44,47,49–51,53–70] Others examined central BP[20,71] and pulse pressure.[26,72]

Hypertension. Whereas some studies examined the presence of hypertension in patients with ADPKD,[34,48,67,73,74] others focused on the onset or worsening of hypertension,[66,75–81] age at hypertension diagnosis,[68,69,82] early onset hypertension,[83] and duration of hypertension.[30]

Hormonal Evaluation

Several neurohormonal biomarkers were checked in ADPKD studies. These biomarkers include plasma renin and aldosterone, urinary aldosterone excretion,[15,18–21,37,38,40,65] and plasma angiotensin II levels.[20]

Kidney Function

Kidney function was assessed using measured or estimated glomerular filtration rate (GFR), serum creatinine, specific kidney function reduction cutoff, GFR trajectory, and development of ESKD.

Measured GFR. Modalities for GFR measurement include inulin infusion,[12,28,84–86] iohexol plasma clearance,[13,14,22,57,87] chromium 51-ethylenediamine tetraacetic acid (51Cr-EDTA clearance),[20,24] iothalamate,[15,26,33,34,41,44,47,65,72,88–104] and creatinine clearance based on 24-hour urine creatinine.[17,19,25,28,30,32,35,42,45,56,59,101,105–111]

Estimated GFR. GFR estimation was performed using chronic kidney disease epidemiologic calculator,[24,29,37,38,40,52,63,64,66,75–77,80,82,86,92,94,98,103,105,112–137] Modification of Diet in Renal Disease calculator,[15,31,33,34,39,42,46,47,51,58,60,67,79,86,91,94,101,105,138–143] Cockcroft—Gault[25,50,70,73,86,101,137,144] and Schwartz formula.[45,48,

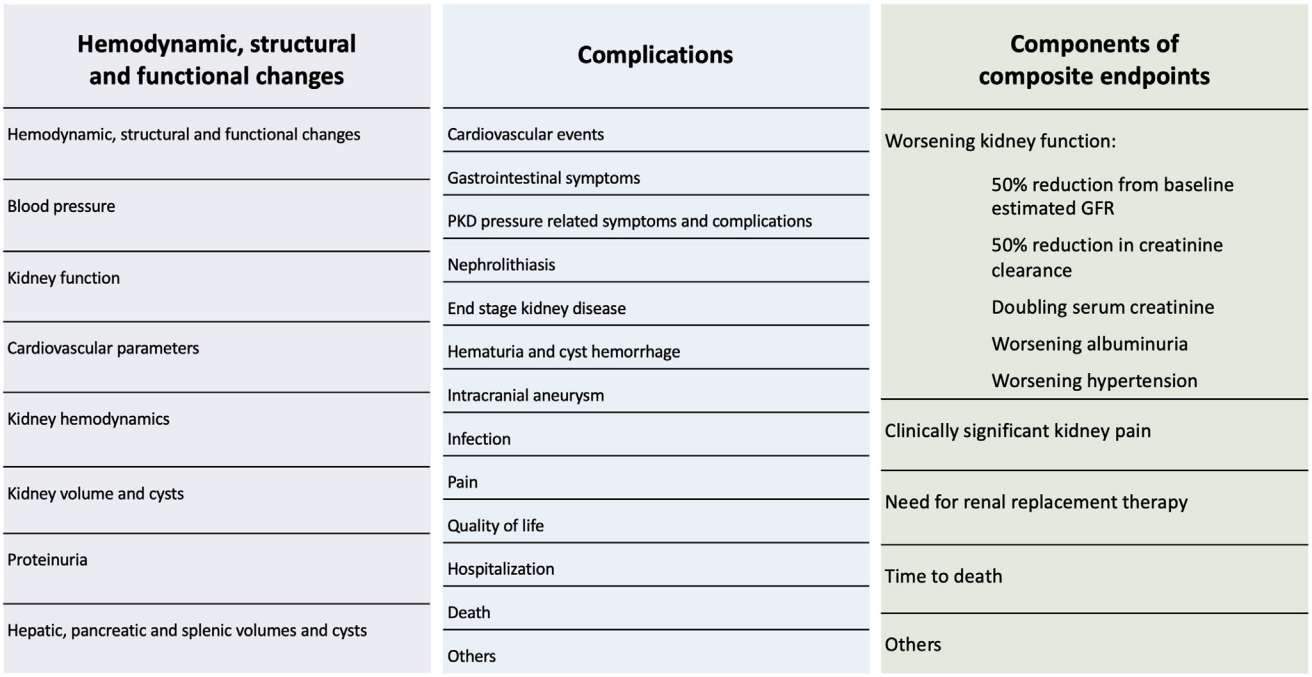

Figure 2. Summary of patient-centered outcomes per category and components of composite outcomes in PKD
GFR, glomerular filteration rate; PKD, polycystic kidney disease.

[49,64,79] One study calculated the mean of 3 baseline serum creatinine values to estimate GFR.[114] Four studies used cystatin C to estimate GFR.[15,86,105,126]

Serum Creatinine. Both serum creatinine [13,14,16,17,24,25,27,28,30,32,33,35,45,50,56,59,61,65,67,80,82,100,106-108,111,125,131,135,137,145–147] and reciprocal of serum creatinine[28,66,74–78,80,101,128,137,148] were used as kidney function outcomes.

Kidney Function Reduction Cutoff. Different cutoffs were applied in measuring kidney function change, including 57%, 50%, 40%, 33%, 30%, 20%, and 10% change in GFR,[38,50,52,91,94,113,116,118,120,126,140,149] GFR decline to less than 90 ml/min per 1.73 m^2,[79] 25 % change in the reciprocal of the serum creatinine level,[66,75–77,80] and doubling serum creatinine.[22,50,107] In addition, the development of chronic kidney disease stage I, II and V were considered as outcomes in some studies.[91,94,95,149]

GFR Trajectory. One study examined the GFR trajectory in patients with PKD and classified it as progressive linear, progressive nonlinear, and nonprogressive.[115]

Development of ESKD. The development of ESKD was reported in multiple studies.[22,31,38,45,50,70,79–83,94,113,116,118,126,128,131,133,140,141,150–154]

Kidney survival definition varied from the time to dialysis, transplantation or death,[74,155,156] time to ESKD or renal replacement therapy,[69,141,146,148] or time of serum creatinine value up to 10 mg/dl.[148]

Proteinuria

Albuminuria and proteinuria were evaluated in most studies by measuring either spot urine albumin-to-creatinine ratio,[12,17,29,50,56,65,66,75–78,112,129,131,135,144,145,157] spot urine protein-to-creatinine ratio,[31,64,65,80,125,134] urinary albumin excretion measured by 24-hour urine albumin,[13,14,25,27,28,32–34,36–38,40,47,49,59,62,87,93,99–102,104,106,107] or 24-hour urine protein.[13,22,25,28,36,42,45,46,48,49,51,52,67,69,70,87,100,107] Nevertheless, 4 studies assessed albuminuria and proteinuria by calculating the mean of 2 different 24-hour urine collections.[28,39,60,69]

Kidney Hemodynamics

Examined kidney hemodynamic parameters include kidney plasma flow which was measured either by para-aminohippuric acid infusion[12,18,19,28,65,84,100] or ^{131}I-hippuran clearance,[15,47,93,98,104] filtration fraction,[15,28,33,47,98] kidney blood flow by magnetic resonance imaging (MRI),[26,33,37,65,100] calculated kidney blood flow,[47,65,98–100,104] kidney vascular resistance,[18,19,26,28,33,37,47,98] resistive index,[26] kidney function reserve capacity,[98] peak systolic velocity, and end diastolic velocity.[26]

In regard to glomerular hyperfiltration, 2 studies defined glomerular hyperfiltration as creatinine clearance or estimated GFR of equal or more than 140 ml/min per 1.73 m^2,[79,108] another study used the definitions of increased filtration fraction and loss of kidney function reserve capacity.[98]

Kidney Volumes

Modality of Kidney Volume Measurement. Modalities to evaluate kidney volumes included MRI[26,29,

Table 1. Summary of included studies

Study characteristic	Number (%) of studies
Study design	
RCT	49 (28%)
Clinical trial	2 (1.1%)
Observational	94 (53.7 %)
Post hoc analysis	30 (17.1%)
Yr of publication	
1981–1990	6 (3.4%)
1991–2000	15 (8.5%)
2001–2010	41 (23.4%)
2011–2021	113 (64.5%)
Country	
Albania	2 (1.1%)
Australia	2 (1.1%)
Belgium	1 (0.5%)
Brazil	2 (1.1%)
Canada	2 (1.1%)
China	2 (1.1%)
Denmark	3 (1.7%)
Egypt	1 (0.5%)
Finland	1 (0.5%)
France	3 (1.7%)
Germany	2 (1.1%)
Italy	9 (5.1%)
Japan	12 (6.8%)
Multicenter international	24 (13.7%)
Netherlands	13 (7.4%)
Saudi Arabia	1 (0.5%)
Spain	3 (1.7%)
South Korea	4 (2.2%)
Switzerland	6 (3.4%)
Taiwan	1 (0.5%)
Turkey	5 (2.8%)
United Kingdom	3 (1.7%)
United States	74 (42.2%)
Participants	
Adults	167 (95.4%)
Pediatrics	6 (3.4%)
Adults and pediatrics	2 (1.1%)
Number of participants	
< 100	41 (23.4 %)
100–199	51 (29.1%)
200–299	25 (14.2%)
300–399	12 (6.8%)
400–499	10 (5.7%)
500–999	16 (9.1%)
≥1000	20 (11.4%)

RCT, randomized controlled trials.

[31,33,34,36,37,40,41,46,47,52,57,58,63–66,72,75,76,78–80,88–91,93–97,99,101–104,112,113,116–119,121–130,134–139,141,144,145,149,158–164], computed tomography scans[13,14,22,87,92,105,106,131,132,159,163,165] kidney ultrasound,[28,30,32,39,43,45,48,49,69,74,82,83,95,108,110,111,143,157,158,160] or a combination of 2 modalities.[95,158,160]

Types of Kidney Volume. Kidney volume assessment was performed by studying TKV,[13,14,22,26,29,31,33,34,36,37,40,41,46,47,57,58,63–66,72,75,76,78,80,82,83,87–90,92,93,99,101,102,104–106,112,113,116,117,119,121,124,125,127–131,137,139,142–145,157,158,162–164] height-adjusted TKV,[22,36,52,57,63,79,91,94–97,103,118,121–123,126,129,132,134–137,161,162,166] TKV normalized to the body surface area,[32,83,108,138,142,144] age-adjusted TKV,[144] kidney volume adjusted for sex and height,[32] mean kidney volume,[39,43,48,69,74,109–111] height-adjusted mean kidney volume,[48] age-adjusted mean kidney volume,[30,45,48,49] mean kidney volume adjusted to body surface area,[28] single kidney volume,[26,64,65,90,102,144] total cysts volume,[14,26,31,33,34,57,64,87,90,101,102,105,144,158,164] single kidney cysts volume,[64,144] percent cyst volume,[26,102] single cyst volume,[46,48,65,109,110,157] parenchymal volume,[14,31,87,105,109,110] intermediate volume,[87,105] residual volume,[14] and noncyst volume.[57,102,144]

Methods of Kidney Volume Measurement and Segmentation. Kidney volume measurements were analyzed using the ellipsoid formula,[28,30,32,39,43,45,48,49,69,82,83,95,106,108,109,121,131,132,143,157–159,163,165], mid-slice method,[52] stereology method,[26,31,33,34,36,37,41,79,88,90,91,95,96,101,102,106,134,141,145,158,164] manual planimetry,[22,47,57,58,64,72,87,92,97,105,112,122,125,126,130,144,162] or semiautomated methods.[46,134] Kidney segmentation was conducted by either Otsu's thresholding method[14,87,105] or by region-based threshold method.[26,31,33,34,36,64,90,101,102,144,145,158,164]

Other Imaging Parameters

Other reported kidney parameters were the number of kidney cysts,[32,45,48,49,73,109,110,157,160] cyst score,[53] kidney length,[53,73,95,109,121] nephromegaly,[73] and architectural severity index.[109,110]

Liver Volume

Liver volume was assessed as total liver volume,[63,88,89,105,161–163,166] height-adjusted total liver volume,[63,116,132,135,162] total hepatic cyst volume,[63,164] height-adjusted hepatic cyst volume,[63] hepatic parenchymal volume,[63] height-adjusted hepatic parenchymal volume,[63] maximal hepatic cyst size,[110] combined total liver and kidney volume,[159,162,163] and height-adjusted combined liver and kidney volume.[132,161,162,165] Four studies looked at the presence of hepatic cysts[70,73,74,110] and 2 studies examined hepatic cysts number.[73,110]

Splenic and Pancreatic Cysts

Few studies examined the presence of pancreatic cysts,[63,73] splenic cysts, splenic cyst volume, and height-adjusted splenic volume.[63]

Cardiac Evaluation

Nineteen studies assessed left ventricular mass indexed to body surface area,[16,23,27,28,30,32,35–37,40,45,50,54,55,62,74,142,167,168] whereas 2 studies evaluated left ventricular mass,[167,168] only one study evaluated percent predicted left ventricular mass based on height, weight, and biological sex.[167] Both left ventricular mass and left ventricular mass index were measured by either echocardiography,[16,23,27,28,30,32,35,45,50,54,55,62,74,168] or

by MRI.[36,37,40,167] Other evaluated cardiac parameters include epicardial adipose tissue thickness,[168,169] left ventricular twist and untwisting rate[23] left atrial volume, left ventricular ejection fraction,[23] mitral valve prolapse,[27,54,74,110] and other valvular abnormalities.[27] The full list of the evaluated cardiac outcomes is illustrated in Supplementary Table S3.

Vascular Parameters

Examined vascular parameters in ADPKD include carotid intima media thickness measurement,[71,169,170] pulse wave velocity,[20,71] flow mediated vasodilation,[51,71] peripheral augmentation index,[171] carotid artery compliance, carotid β-stiffness index,[71] carotid integrated backscatter signal, and fibromatosis percentage.[170]

Cardiovascular Events

Two studies examined acute myocardial infarction,[172,173] its clinical characteristics, management and/or mortality in patients with ADPKD.[173]

Pain

Studies evaluated kidney pain,[66,75–78,80,114,124,130,132,161,174] nonkidney pain,[37,66,76,80,114,132,161,166] PKD-specific pain,[37,66,75–78,80,101,114,124,130,132,134,157,161,166,174] and non-PKD pain.[66,76,80] Pain definition was variable among studies.[161,174]

Pain assessment was performed by either questionnaires and scales,[37,134,166] the need for intervention,[72,75–78,134,174] adjudication or physician judgment.[174] The used tools included Modified Wisconsin Brief Pain Survey[166] and HALT-PKD pain questionnaire.[37,38]

The severity of pain was assessed using one to 10 scale,[66,161] interference with daily life, medical leave, the need for documentation of clinical signs, the need for medical intervention, and the need for pharmacologic treatment, surgical or invasive radiological procedures.[66,75–78,134,174] One study reported pain outcome as area under the concentration-time curve.[66] Some studies did not specify the modality of pain assessment.[38,80,114,130]

Quality of Life (QoL)

Different questionnaires were used to assess QoL. Whereas many ADPKD studies applied Short Form 36 Questionnaire,[37,38,63,72,88,89,135,159,166] others followed either QoL EuroQoL questionnaire,[105] 12-item questionnaire to evaluate ADPKD specific symptoms[159] ADPKD-impact scale,[126,175] standardized Kidney Disease QoL Short Form questionnaire[176] or PKD-9 questionnaire.[134]

Gastrointestinal Symptoms

Symptom specific scores and questionnaires were used to assess the ADPKD-related gastrointestinal symptoms.[105,132,135,161] Satiety, abdominal fullness, nausea, and vomiting were also reported.[132,166]

Mass Pressure Related Symptoms and Complications

One study examined mass pressure related symptoms and mass pressure related complications such as leg edema, ascites, and hernia.[132]

Nephrolithiasis

One study compared the detection of nephrolithiasis between ultrasound kidney and computed tomography scan in patients with ADPKD.[157] The metabolic profile was also examined in these patients.[148,157]

Hematuria and Cyst Hemorrhage

Both cyst hemorrhage,[177] and hematuria[28,45,48,67,74,80,101,111,144,148,157,174] were reported in different ADPKD studies.

Intracranial Aneurysm (ICA)

One study looked at the influence of ICA on progression of kidney disease.[74] Another examined the role of magnetic resonance angiography screening in ICA diagnosis, prophylactic repair, ICA rupture events, and cost effectiveness in patients with ADPKD patients with and without familial risk for ICA.[178] In addition, the size and location of ICAs[178] and the risk of ICA treatment by endovascular coil embolization and clipping[179] were also studied.

Infections

Infection types that were examined in ADPKD studies included kidney cyst infection,[147,163,177,180] liver cyst infection,[132,147,163,177,180] urinary tract infection,[67,74,114,133,147,148,157] and infection as a side effect of medications.[22,25,31,46,57,66,75,92,112,114,126,139,162] Other reported parameters are cyst infection intractability,[163] used antibiotic regimen,[147,163] and blood, urine and/or cyst culture results.[147,163,177,180]

Hospitalization

Five studies reported on frequency and duration of hospitalizations.[37,38,114,163,179] The cause of hospitalization was cyst infection in one study,[163] however, it was not clear if the hospitalizations were PKD-related in the others.

Death

Fifteen studies reported death.[31,37,38,81,82,113,114,116,118,124,153,154,163,178,181] Death was secondary to PKD and non-PKD related causes. The PKD causes of death were cardiovascular, neurologic, and infectious.[31,38,124,163,181]

Predictive Models Development

A number of models and tools were developed and used to predict ADPKD outcomes including the PROPKD Score,[119,121,150] Mayo imaging classification,[78,

Table 2. Reported composite end points in ADPKD studies

Study	Composite end points
[116]	- Time to death - ESKD - 50% reduction from the baseline estimated GFR by CKD-EPI
[36]	Equal or more than 20% increase over the 3 yr interval in: - HtTKV (by abdominal MRI), - Left ventricular mass index (by cardiac MRI) - Urinary albumin exretion by (24-h urine collection)
[118]	- Time to death - ESKD - 50% reduction from the baseline estimated GFR by CKD-EPI
Devuyst *et al.*[77] *post hoc* TEMPO	- Worsening kidney function (a 25% reduction in the reciprocal of the serum creatinine level from the value at the end of the dose-adjustment period, reproduced after at least 2 wks) - Clinically significant kidney pain necessitating medical leave, pharmacologic treatment (narcotic or last-resort analgesic agents), or invasive intervention - Worsening hypertension (changes in blood-pressure category, as defined in the protocol, or worsening of hypertension requiring an increase in hypertensive treatment) - Worsening albuminuria (according to sex-specified categories as defined in the protocol)
Irazabal *et al.*[78] TEMPO 3:4	- Worsening kidney function (a 25% reduction in the reciprocal of the serum creatinine level from the value at the end of the dose-adjustment period, reproduced after at least 2 wks) - Clinically significant kidney pain necessitating medical leave, pharmacologic treatment (narcotic or last-resort analgesic agents), or invasive intervention - Worsening hypertension (changes in blood-pressure category, as defined in the protocol, or worsening of hypertension requiring an increase in hypertensive treatment) - Worsening albuminuria (according to sex-specified categories as defined in the protocol)
Muto *et al.*[76] TEMPO 3:4	Time to investigator reported multiple ADPKD clinical progression events - Onset or progression of hypertension, need for hypertensive treatment) - Severe kidney pain (requiring medical intervention) - Worsening albuminuria (by category) - Worsening kidney function (33% increase in serum creatinine) for tolvaptan (combining all doses) relative to placebo while on treatment
[107]	The primary outcome measure of this study was a composite endpoint of - Patient's serum creatinine levels increased two-fold over baseline or - Creatinine clearance decreased to half of the baseline
[22]	- Doubling of serum creatinine - ESKD
[80]	A 4-component composite disease progression endpoint was assessed, including - Onset/worsening of hypertension - Kidney pain - Proteinuria - Kidney function (defined as a 25% change from baseline in reciprocal serum creatinine levels)
Torres *et al.*[66] TEMPO	- Worsening kidney function (a 25% reduction in the reciprocal of the serum creatinine level from the value at the end of the dose-adjustment period, reproduced after at least 2 wks) - Clinically significant kidney pain necessitating medical leave, pharmacologic treatment (narcotic or last-resort analgesic agents), or invasive intervention - Worsening hypertension (changes in blood-pressure category, as defined in the protocol, or worsening of hypertension requiring an increase in hypertensive treatment); and - Worsening albuminuria (according to sex-specified categories as defined in the protocol)
Torres *et al.*[38] HALT-PKD B	- Time to death - ESKD; defined as the initiation of dialysis or preemptive transplantation - 50% reduction from the baseline estimated GFR by CKD-EPI
[75]	The composite secondary endpoint was the time to multiple investigator assessed ADPKD-related progression events. These events included - Worsening kidney function (a 25% reduction in the reciprocal of the serum creatinine level from the value at the end of the dose-adjustment period, reproduced after at least 2 wks) - Clinically significant kidney pain (requiring medical intervention) - Worsening hypertension (changes in BP category or worsening of hypertension requiring an increase in hypertensive treatment) - Worsening albuminuria (according to sex-specified categories)
[50]	- Doubling of serum creatinine - 50% reduction in GFR, or need for renal replacement therapy

ADPKD, autosomal dominant polycystic kidney disease; BP, blood pressure; CKD-EPI, chronic kidney disease epidemiology; ESKD, end-stage kidney disease; GFR, glomerular filteration rate; HtTKV, height-adjusted total kidney volume; MRI, magnetic resonance imaging.

[94,98,119,121,124,126,134,135,137,141,182,120] ADPKD outcomes model,[128] and European Renal Association-European Dialysis and Transplant Association Working Groups of Inherited Kidney Disorders and European Renal Best Practice algorithm.[121]

Clinical Patient Reporting Tool

Abraham *et al.*[182] developed clinical patient reporting tool to inform patients about their ADPKD indicators, disease current state, and disease trajectory.

Composite Endpoints

The reported composite endpoints in ADPKD studies and the different components of each of the composite are summarized in Table 2. We identified 13 articles that reported 9 different composite outcomes.

DISCUSSION

In this review, we summarize different reported outcomes and how they were measured in ADPKD studies. The most reported patient-centered outcomes in ADPKD studies are BP, kidney volume, and kidney function, with less focus on other important endpoints like pain and QoL.

TKV was assessed in multiple studies. This finding supported its utility as a surrogate for disease progression for approval by the US Food and Drug Administration in PKD drug trials. Whereas earlier studies relied on ultrasound to assess kidney volumes, more recent trials use MRI and computed tomography scans. MRI and computed tomography scans are more precise in measuring small yet clinically important changes in TKV.[183] In addition, both the time-consuming planimetry and stereology methods which are considered the reference standard and the fast, easy-to-implement ellipsoid method, which is less sensitive in detecting small changes in kidney volumes, were used to measure TKV in the studies.[184]

We observed the same inconsistency in assessments of kidney function. The different methods of kidney function measurement in ADPKD were compared in 5 studies.[101,185-188]

Patients with ADPKD face many challenges because of their disease and pain remains one of the most common symptoms they must deal with. Pain severity varies, which can be a frustrating problem that adversely affects QoL.[189] However, despite the significance of pain on patients' daily living, criteria to diagnose different types of PKD-related pain is absent. In addition, the available questionnaires and tools used for assessment of pain severity are not PKD-specific. Our findings of considerable variation among BP measurement are consistent with other reviews.[190] However, it remains unclear how the early and high prevalence of hypertension among patients with PKD can affect major adverse cardiac events outcomes.

Our review highlights the paucity of data about psychological and mental health-related outcomes among patients with ADPKD despite the high prevalence of depression and anxiety in this population.[191] Our review emphasizes the need for establishing validated patient-reported outcomes in ADPKD and developing tools better tailored to accurately assess PKD-related pain and the psychological impact of PKD similar to ADPKD-impact scale that was built to evaluate the effect of ADPKD on health-related QoL.

Development and validation of scores to identify patient groups that would benefit from regular screening for cerebral aneurysms and cardiac valvular disease is also urgently needed in clinical practice. Moreover, we think future studies should include major adverse cardiovascular events as a hard outcome in PKD studies.

To our knowledge, this review is the first review to highlight composite outcomes and their components in ADPKD studies We hope that this study will help shed light on the significance of the utilization of these patient-centered outcomes in future PKD research. This review could also affect the considerations for future clinical trials and inform investigators' decisions about outcomes when planning ADPKD studies. Guidance on optional endpoints that are feasible, and a clear regulatory pathway may stimulate further development in this area and ultimately support more treatments for ADPKD to successfully reach the market.

This review addresses an evidence gap by providing information about the outcomes reported in PKD studies and their measurement methods, which is usually missing. Our review extends beyond other PKD reviews[192] because it summarizes details about outcomes measurement. The Standardized Outcomes in Nephrology initiative aims at building core outcome sets that are of interest to all stakeholders.[9,193,194] Whereas the Standardized Outcomes in Nephrology initiative is key in highlighting the importance of minimizing outcome reporting bias,[9,193,194] this review is unique in its focus on the specifics regarding outcomes measures.

Our review is complementary to the Standardized Outcomes in Nephrology-PKD systematic review,[195] because both reviews provide a more complete picture of the status of outcome reporting in ADPKD. Our review has novelty by adding the following important elements: (*i*) we systematically reviewed both randomized controlled trials and nonrandomized studies, (*ii*) we focused on composite outcomes with detailed presentation of outcome components that are shared between trials, (*iii*) we reviewed studies that included both adults and children, (*iv*) our review is more updated with a date of last search ending on May 24, 2021, and (*v*) we focused on summarizing the granularity of outcome reporting, including different outcome measures rather than the outcome categories, which we believe is of added value to the reader and to researchers who will be informed by this review to design future studies, whereas Standardized Outcomes in Nephrology-PKD reported on the outcome measure of 3 most frequently reported domains in each outcome category. We outlined in detail the different measures of all patient-centered outcomes and we reported on composite outcomes.

Systematic reviews are an essential first step before discussing issues about outcomes and their measurements in any field.[10] Published reviews have highlighted concerns about inconsistency in outcomes reporting in chronic kidney disease and hemodialysis studies.[196–198]

This review has a few limitations. Studies that only reported dialysis, transplant, or pregnancy outcomes in patients with ADPKD were excluded. Though studies including such patient groups are important, these studies were beyond the scope of our review as including these important populations would require considerable focus on additional outcomes. This highlights the need for future reviews that address different outcomes in these patient groups. Our findings are limited to studies that included at least one patient-centered outcome. Therefore, we are not able to decisively comment on trends of reporting biomarkers in PKD studies. In addition, we did not assess the risk of bias in the included studies, which hinders our ability to associate study quality with the reported outcomes.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Summary of patient-centered outcomes per category.

Table S2. Characteristics of included studies with intervention, comparison, outcomes with outcome measures.

Table S3. Reported kidney outcomes by categories.

Table S4. Preferred reporting items for systematic reviews and meta-analyses (PRISMA)

Checklist

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