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Serum and urine prognostic biomarkers for autosomal dominant polycystic kidney disease: a systematic review and meta-analysis

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Title Page:

Title: Serum and Urine Prognostic Biomarkers for Autosomal Dominant Polycystic Kidney Disease: A Systematic Review and Meta-analysis

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Abstract:

Background: Autosomal dominant polycystic kidney disease (ADPKD), the leading monogenic cause of kidney failure, exhibits heterogeneous clinical

progression. This systematic review and meta-analysis synthesize and evaluate current evidence on blood and urine prognostic biomarkers in ADPKD, addressing gaps in understanding their role in predicting progression and guiding clinical trial selection and management.

Methods: We searched PubMed, Embase, and Cochrane up to April 2025 and screened articles in duplicate. We included longitudinal studies evaluating the blood and urine prognostic biomarkers in patients with ADPKD with at least 10 participants and 1 year of follow-up. We used the Quality in Prognosis Studies tool to assess risk of bias, random effects meta-analyses to pool effect estimates, and the GRADE approach to assess the certainty of evidence.

Results: We included 58 studies, with 33 urinary biomarkers and 29 serum/blood biomarkers identified. The most frequently studied biomarkers were urine osmolality, copeptin, proteinuria, Monocyte Chemoattractant Protein-1, and uric acid, whereas the most studied outcomes were estimated Glomerular Filtration Rate and Total Kidney Volume. The urinary biomarkers that showed the largest association with ADPKD were Monocyte Chemoattractant Protein-1, Kidney Injury Molecule-1, albumin, and Beta 2 microglobulin. Serum biomarkers associated with outcomes were primarily copeptin and Fibroblast Growth Factor-23, with β-Hydroxybutyrate and bicarbonate exhibiting lesser association.

Conclusion: In conclusion, this systematic review highlights the potential prognostic value of blood and urine biomarkers in ADPKD. It also verified the need for further validation of biomarker use in ADPKD.

Keywords: ADPKD, biomarker, prognosis, serum, urine

Background:

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, causing 4.4% of kidney failure with replacement therapy in the United States. The progression to kidney failure varies between patients, with the average age of onset of end-stage renal disease (ESRD) at 54 years vs. 74 years in patients with PKD1 and PKD2 mutations, respectively(1). Kidney failure begins in the 4th to 5th decade of life, with an average decline of estimated glomerular filtration rate (eGFR) of 4 to 6 ml/min per 1.73 m^2/year which is comparable to diabetic kidney disease (varying between 3 to 5 ml/min per 1.73 m^2/year) and faster than in patients with eGFR decline due to hypertension (average of 1.7 to 2.4 ml/min per 1.73 m^2/year)(2-5). Additionally, decline in kidney function is non-linear and displays intra-familial variability, necessitating the use of non-GFR biomarkers for prognosis.

Prognostic biomarkers are crucial for predicting ADPKD progression, particularly in identifying patients at risk of rapid progression who may benefit from targeted interventions through surrogate endpoints in clinical trials. Till now, some radiological and genetic biomarkers have been identified. Some well-known imaging biomarkers are height-adjusted total kidney volume (htTKV) (6, 7) and Mayo Imaging Classification (MIC), which

is age-adjusted htTKV (8). Genotype (*PKD1/2* genotype(9, 10), *PKD1* Truncating vs *PKD1* Non-truncating)(11), especially in combination with imaging biomarkers, also adds to the prognostic predictive capacity(12). In addition, some scores were developed to give an overall picture of the disease, such as the PROPKD score, which utilizes mutation classification, sex, and early disease complications to predict the likelihood of progression (11, 13) .

ADPKD is uniquely characterized by tubular involvement resulting in defects in urine concentration. Fluid-based biomarkers studies have primarily targeted these two pathophysiologic mechanisms and are broadly categorized into biomarkers involved in the vasopressin-urine concentration axis (serum copeptin, serum apelin, urine osmolality, urine/plasma urea ratio), urine glomerular biomarker (albuminuria), tubular inflammatory biomarkers (urine monocyte chemoattractant protein-1, suPAR), tubular injury biomarkers (urine b2-microglobulin, urine kidney injury molecule 1, Interleukin (IL-18), NGAL, metabolic biomarkers (urine alanine/citrate ratio) and miscellaneous biomarkers (serum fibroblast growth factor 23, urine exosomal polycystins and urine miRNA). These biomarkers have been studied individually or in combination with validated biomarkers. Serum and urine biomarkers may be preferred over imaging/genetic biomarkers based on the lower cost, convenience of use, and rapid turnaround. Therefore, in this study, we aim to summarize and analyze published evidence on the use of serum and urine biomarkers for ADPKD prognosis.

Methods:

This review was reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines. The protocol was registered in Open Science Framework (OSF) (ID: https://doi.org/10.17605/OSF.IO/G6FKS).

Search Strategy: The search was conducted from inception to April 22,2025 using the following databases: Embase, PubMed, and Cochrane libraries. The detailed search strategy is in **Supplementary Material S1**.

Eligibility Criteria:

Population: We included patients with ADPKD defined by the authors of the published studies followed up for a minimum of 1 year. We included patients regardless of their risk of progression. We excluded patients who were receiving renal replacement therapy (RRT) or those receiving tolvaptan, and who had diagnosed ESRD.

Intervention: Serum or urine biomarker assessment at baseline.

Outcomes: Glomerular Filtration Rate (GFR) change, whether reported as measured GFR (mGFR), or estimated GFR (eGFR), Total Kidney Volume (TKV) change, including height-adjusted TKV (htTKV), incidence of renal replacement therapy (RRT), development of end-stage renal disease (ESRD), and ADPKD progression (defined differently across studies). Outcomes should have been tested longitudinally to be included.

Study designs: Prospective and retrospective cohorts, RCTs, with a sample size of at least 10 participants. We also included abstracts if informative. We excluded in vitro studies, reviews, and protocols.

Language: We included only English studies.

Study Selection: Two independent reviewers screened the title and abstract, and full text using Covidence. We resolved discrepancies by either consensus or a third reviewer. We contacted authors to inquire if studies have been published if an abstract had missing information, and the full text has not been found.

Data extraction and risk of bias assessment: We extracted included studies using Microsoft Excel. Extracted data included study characteristics, patient characteristics, biomarker and outcome types, assay methods, follow-up time, and statistical findings. Two reviewers (JK and VR) made sure there was no duplication of populations across studies. The risk of bias was assessed for each study using the QUIPS tool by three reviewers separately: one from the methodology team (JK, VR), one from the review team (NG, AC, DR), and one expert in the field (AY, KH, RP)(14).When pooling studies, the risk of bias was assessed for each outcome as high if one or more of the studies included had a high risk of bias and low if all studies included had a low risk of bias.

Data analysis: Using the “metan” program in STATA (v18/SE), we pooled the effect measures for each pair of biomarkers and outcomes separately, prioritizing standardized regression coefficients (β) and their 95%

confidence intervals (CI), using random effects meta-analyses with restricted maximum likelihood (REML) estimators. When standardized regression coefficients (β) were not amenable to meta-analysis, we prioritized unstandardized regression coefficients (B) followed by correlation coefficients. We pooled standardized and unstandardized regression coefficients separately. Time-to-event data were pooled as hazard ratios (HR) and 95%CIs, and dichotomous data were pooled as odds ratios (OR) and 95% CIs. We did not aim to pool heterogeneous effect measures to avoid inappropriate transformation and preserve the interpretability of the original estimates. In addition, we did not pool log-transformed and non-transformed effect estimates. As such, outcomes that were not pooled were summarized narratively in GradePro by stating each outcome in a separate row. When studies reported more than one regression estimate for a biomarker, we used the estimate corresponding to the analysis with the greatest number of covariates.

Certainty Assessment: We applied the GRADE approach using GradePro software to assess the certainty of the evidence for the prognostic value of the assessed biomarkers on different outcomes. The GRADE approach involves assessing the risk of bias, inconsistency, indirectness, imprecision, and publication bias. To assess imprecision, we used the line of no effect to determine whether the results were precise (i.e., crossing the line of no effect), taking into consideration the sample size as well.

Results:

We identified 4177 records. After screening, 58 studies were included in this review. The screening process is illustrated in the PRISMA flow diagram in **Figure 1**. Their primary characteristics are summarized in **Table 1(15-70)**. Data was presented in different ways, such as standardized beta, unstandardized beta, correlation coefficients, as well as hazard and odds ratios. The covariates adjusted for are also included in **Table 1** and are comparable between most studies with age and sex/gender being the most two variables adjusted for.

We identified a comprehensive list of 33 urinary biomarkers and 30 serum/blood biomarkers shown in **Table 2.** Almost all biomarkers were studied in association with either eGFR or TKV, and the results were reported in various ways. **Figures 2 and 3** present the pooled results of studies reporting standardized and unstandardized betas, respectively, concerning eGFR and TKV. Due to the large number of biomarkers identified, we talk about all association with eGFR and TKV and then present some of the associations that were of the most interest to the PKDOC committee in details per biomarker, whereas all the data is provided in detail in **Tables 3 and 4** and the evidence profiles for all biomarkers in **Supplementary Materials S2 and S3.**

I. Urinary Biomarkers:

We identified 33 unique urinary biomarkers studied with urine osmolality (9 studies), proteinuria (9 studies), albuminuria (8 studies), NGAL (7 studies) and MCP-1 (6 studies) being the most studied.

Based on high certainty evidence, the increase of MCP-1, albumin and β2M showed a decrease in annual change in eGFR based on standardized or unstandardized betas. Similarly, based on moderate certainty evidence, NGAL, KIM-1, FABP, showed a decrease in annual change in eGFR. In contrast, based on high certainty evidence, the increase in urine-to-plasma-urea ratio showed an increase in eGFR and based on moderate certainty evidence, urine osmolality and urinary EGF showed an increase in eGFR. suPAR was also measured in 1 study for association with eGFR decline, where the highest tertile of suPAR showed a greater decrease in eGFR than the lowest tertile(37). Moreover, based on low or very low certainty evidence, an increase in betaine, citrate, HIF-1, urine volume, IL-18, microRNAs, PGE2, protein, VEGF, YKL-40 and the presence of pyuria, showed a decrease in eGFR. In contrast, the increase in clusterin, EGF, maximal urine concentrating capacity, MIF, NAG, U alpha-GST, urine pH and calcium, sodium and potassium excretion, was associated with an increase in eGFR.

All associations with TKV, except for urine osmolality, were based on low and very low certainty evidence. The increase in albumin, urine-to-plasma urea ratio, EGF, FABP, IL-18, MIF, NGAL, urine osmolality, and YKL-40 was associated with an annual decrease in TKV. On the other hand, the increase in protein, MCP-1, β2M, KIM-1, clusterin, NAG, potassium, and sodium excretion, and the presence of pyuria were associated with an increase in TKV.

MCP-1: Two studies reported an association between MCP-1 and rapid disease progression, although each study defined 'rapid progression' differently: the first by eGFR loss of ≥3 ml/min per 1.73 m2 per year, which showed an OR 1.78 (95%CI 1.4 to 2.27)(69), while the other by annual change in eGFR≥–3.5 mL/ min/1.73 m2, which showed OR 1.63 (1.09 to 2.44)(41). Therefore, both showed the same result, which is that eGFR loss was associated with increased odds of having a rapidly progressive disease. In addition, a composite outcome of kidney failure or 30% eGFR decline was reported, which showed an increase in the presence of MCP-1 with HR=1.69(95%CI 1.01 to 2.83)(69).

NGAL: Even though eGFR was reported in different ways (standardized, unstandardized and mGFR), all showed a decrease in eGFR with the increase in NGAL. The incidence of RRT showed a HR 1.02 (95%CI 0.97-1.03) while ADPKD progression showed a HR 0.9(95%CI 0.89 to 1.01)(20).

β2M: Some outcomes defined rapid progression, in 2 different ways, the first by eGFR loss of ≥3 ml/min per 1.73 m2 per year which showed an OR 1.25 (95%CI 0.98 to 1.6)(69), while the other by annual change in eGFR≥–3.5 mL/ min/1.73 m2, which showed OR 1.49 (0.9 to 2.23)(41). In addition, 1 study also reported on the incidence of RRT and ADPKD progression as a composite endpoint of significant decline in mGFR, increase in TKV exceeding 5% per year, or ESRD in the presence of β2M, which showed a HRs of 1.01 (95% CI 0.98 to 1.02) and 1.01 (95% CI 0.99 to 1.02),

respectively(20). Another composite outcome was kidney failure or 30% eGFR decline in which the HR was 1.21 (95%CI 1.03 to 1.42)(69).

II. Serum Biomarkers:

We identified 29 serum/blood biomarkers presented in **Table 2,** with the most studied being copeptin (9 studies), uric acid (9 studies), and FGF23(6 studies).

Based on high certainty evidence, the increase in BHB showed an increase in eGFR. In contrast, the increase in bicarbonate, copeptin and FGF23, showed a decrease in eGFR. Similarly, the increase in plasma osmolality showed a decrease in eGFR based on moderate certainty evidence. Based on low and very low certainty evidence, the increase in anadamide, apelin, HDL, hemoglobin, Klotho, microRNAs, palmitoylethanolamide, C3M and somatostatin showed an increase in eGFR. In contrast, the increase in calcium, glucagon, IL-16, and uric acid showed a decrease in eGFR.

On the other hand, based on high certainty evidence, an increase in copeptin showed an increase in TKV, while the increase in bicarbonate was associated with a decrease in TKV based on moderate certainty evidence. All other associations with TKV were based on low or very low certainty evidence, where the increase in anandamide, apelin, hemoglobin, LDL, plasma osmolality, somatostatin, and uric acid was associated with a decrease in TKV. In contrast, the increase in BHB, FGF23, FBS, and HDL was associated with an increase in TKV.

Copeptin: Incidence of RRT was reported in 2 different studies, both showing an increase in the incidence, having HR 1.03 (95%CI 1.01 to 1.04) (19)and HR=5.73 with a p value 0.1(17), respectively. Other outcomes reported were rapid progression, defined as eGFR loss ≥3 ml/min per 1.73 m2 per year, in which there was an increase in rapid progression in the presence of copeptin [(OR 2.49 (95%CI 1.09 to 5.7)](69). In addition, some studies reported composite outcomes such as kidney failure or 30% eGFR decline [HR 1.9 (95%CI 0.87 to 4.13)](69), and ADPKD progression as a composite endpoint of significant decline in eGFR, increase in TKV exceeding 5% per year, or ESRD [HR 1.03 (95%CI 1.01 to 1.04)](20). The latter was also reported in the same study as a prognostic test accuracy, considering the best cut-off as 9.56 pmol/L with a sensitivity of 66.6 (48.2–82.0), specificity of 84.2 (60.4–96.6)(20).

FGF23: Some outcomes reported are rapidly progressive disease, defined as eGFR loss of ≥3 ml/min per 1.73 m2 per year, which showed OR 1.3(95%CI 0.96 to 1.75)(69). In addition, 1 study reported on the 50% reduction in eGFR in high vs low levels of FGF23, where the HR between the two was 2.91 (95%CI 1.64 to 5.19)(26). ESRD was studied in various ways, either as a separate outcome or as part of a composite outcome. Firstly, the ESRD occurrence was higher in patients with higher FGF23 vs those with lower levels of FGF23 HR 2.04 (95%CI 0.9 to 4.65)(26). When reported as part of a composite outcome, both definitions [1) ESRD, death, or 50% reduction in eGFR and 2) ESRD or death] showed the same result,

which is that patients with higher baseline FGF23 had an increased risk of the ESRD, death or even 50% reduction in eGFR (p-value<0.05)(26, 51). Another composite outcome was kidney failure or 30% eGFR decline, where the presence of FGF23 was associated with an increase in this outcome [HR 1.35 (95%CI 1.12 to 1.63)](69).

Serum Bicarbonate: Some outcomes reported for this biomarker were annual change in % total liver volume (TLV) in patients with polycystic liver disease, too, in which the presence of increased serum bicarbonate was associated with a decrease in TLV [Standardized Beta -0.2 (-0.8 to 0.3)](49). Moreover, a composite outcome of >30% decrease in baseline eGFR or kidney failure was assessed in the 1 study in 2 different ways, one as a comparison between patients with high baseline serum bicarbonate compared to normal value, and the other in a continuous manner of baseline serum bicarbonate. Both studies showed an increase of >30% decrease in baseline eGFR or kidney failure with the increase of baseline bicarbonate having HRs of 2.95 (95%CI 1.21 to 7.19) and 1.21 (95%CI 1.06 to 1.37), respectively(49).

Uric acid: Outcomes reported for uric acid were overall survival, renal survival defined as kidney disease progression or start of RRT, and incidence of ESRD. The overall survival showed a HR 1.57 (95%CI 0.97 to 2.55)(40), while the incidence of kidney disease progression or the start of RRT was increased with increased baseline uric acid(39, 48, 50, 66). In

addition to that, the incidence of ESRD was also increased with an increased baseline uric acid level (p value>0.05)(23).

Discussion:

Our systematic review provides a comprehensive insight into the biomarkers that have potential prognostic value, especially as the field evolves. Our focus was to assess each biomarker separately and its effect on the prognosis of ADPKD, rather than comparing the efficacy of biomarkers with each other.

Interpretation of the results: Despite the results being reported in various ways, the results of specific biomarkers stayed consistent. For example, all results consistently showed that the increase of copeptin was associated with a decrease in annual eGFR. Similarly, MCP-1 and β2M showed association with the progression of ADPKD, especially rapidly progressive disease, as results were consistent despite the variability in how the outcome was defined. This contrasts with some other biomarkers, such as NGAL, as the results were reported in different ways (standardized vs unstandardized Beta).

As an overall summary, the biomarkers with the strongest and most consistent prognostic signal for ADPKD were copeptin, MCP-1, β2M, KIM-1, FGF23, and albuminuria, based on the change in eGFR in the increase of these biomarkers (Figure 2). Most conclusions were primarily driven by eGFR-based evidence asthe biomarkers had a higher certainty when associated with eGFR change compared to when associated with TKV, as

seen in **Figure 2** compared to **Figure 3**. This could be due to the decreased number of readings of TKV, and the fact that some included studies had a shorter follow-up duration than others. Other biomarkers that showed potential prognostic impact were NGAL, FABP, bicarbonate, urine-plasma urea ratio, and BHB. In addition, while some studies adjusted for other biomarkers when assessing the biomarker of interest, none of these biomarkers were closely related to the point where it might affect the overall result. These biomarkers have been previously linked to proposed mechanisms of progression. For example, while copeptin is a surrogate marker for vasopressin which plays a central role in promoting cyst growth, MCP-1 reflects intrarenal inflammation and NGAL, KIM-1 and FABP have been linked to tubulointerstitial injury(17, 71, 72). Therefore, given the results of this manuscript and their link to renal damage through the above mechanisms, we believe these biomarkers could be of value to support previously established predictors such as GFR and TKV, however, they might have more impact on enriching clinical trials rather than establishing clinical care after further validation.

Strengths: While one systematic review reported comprehensively on predictors of disease progression in ADPKD, this study did not include a meta-analysis and was published in 2015(73). Other reviews focused on the role of each biomarker in ADPKD, especially with specific treatments(74), or on the reported outcomes in ADPKD without studying biomarkers(75). Therefore, to our knowledge, this is the first systematic review with meta-

analysis done to evaluate potential prognostic serum and urine biomarkers in ADPKD. Our study included all biomarkers found, even the ones that might be considered less important. In addition, the exclusion of patients having a treatment that is considered to change results gives more credible results. Also, we have captured abstracts; therefore, we are certain that our study is comprehensive. In addition, even though we included only patients who were not taking medications that might affect the results, we did not limit our population to patients who would be considered eligible for studies assessing interventions. Moreover, we have looked at all the different measures of the outcomes and highlighted consistencies and inconsistencies between those different measures in specific biomarkers. Luckily, there were no obvious differences in calibration between assays measuring the same biomarker, nor were there differences in the modalities used to measure TKV as an outcome, as most studies used Magnetic Resonance Imaging (MRI).

Limitations: There were a few challenges with determining the real prognostic ability of each biomarker. A limitation was the difficulty in interpreting the results due to the variability in how the results were reported between studies, which affected the pooling of the results in this study. For example, the same outcome would be reported as standardized beta, unstandardized beta, odds ratio, or hazard ratios. In addition, even studies that reported the outcome in the same way might have used different measures (log transformation versus not); however, we tried our

best efforts to conclude even without the ability to pool most of the time. Moreover, because we were not able to assess the minimal clinically important difference, given how the data was reported, we reported on any statistical difference that was shown.

Future Research: While some studies reported biomarkers other than the ones mentioned, they did not include the association between baseline biomarker and the follow-up of outcome, instead, they either reported on the correlation between biomarker and outcome in a cross-sectional manner or they reported on the biomarker as a time-dependent variable instead of using a single baseline value as the predictor. For example, despite the Hallows 2023 study including biomarkers that were not mentioned in other studies (succinate, pyruvate, lactate, PKM2, PDK1, and LDH), we could not include it as they treated the biomarkers as time-dependent variables. A follow-up on this study, previously published, will include the analysis mentioned above with the biomarkers mentioned previously (76). Moreover, until now, none of the serum or urine biomarkers is a strong predictor in clinical practice. This could be either because the biomarkers are truly not strong predictors, or that most studies have a high risk of bias, for which studies with larger sample size and lower risk of bias are needed. In addition, while there was high or moderate certainty data available for associations with eGFR, the results for TKV were based on low and very low certainty evidence, which reflects a need for better evidence to assess the association of biomarkers with TKV. One more thing to consider is the

availability and cost of these potential biomarkers when translating these findings into clinical practice. While some potential biomarkers studied here are widely available and relatively inexpensive (e.g., electrolytes), others are either not widely available (e.g., copeptin, FGF23) or their cost-effectiveness has not been evaluated (e.g., miRNA).

Therefore, although an increasing body of evidence shows that multiple candidate biomarkers may improve risk stratification in ADPKD, several gaps are yet to be tackled regarding generalizability across diverse populations and reproducibility, including feasibility and cost effectiveness. Targeting these gaps through future research will be essential to transform results into actionable tools.

Declarations:

List of abbreviations:

ACEI: Angiotensin converting enzyme inhibitor

ADPKD: Autosomal Dominant Polycystic Kidney Disease

AGT: Angiotensinogen

β: Standardized beta regression

B: Unstandardized beta regression

β2M: Beta 2 Microglobulin

BHB: Beta-hydroxybutyrate

BMI: Body-mass Index

BP: Blood pressure

BSA: Body Surface Area

CI: Confidence Interval

CKD: Chronic kidney disease

Cr: Creatinine

CRP: C-Reactive Protein

DBP: Diastolic Blood Pressure

EGF: Epidermal Growth Factor

eGFR: estimated GFR

ESRD: End stage renal disease

ET-1: Endothelin-1

FABP: Fatty acid binding protein

FBS: Fasting blood sugar

FGF23: Fibroblast Growth Factor 23

GFR: Glomerular Filtration Rate

HDL: High-Density Lipoprotein Cholesterol

HIF-1: Hypoxia-Inducible Factor-1

HR: Hazard ratio

htTKV: height adjusted TKV

IL-18: Interleukin-18

IL-1β: Interleukin-1 Beta

IL-6: Interleukin-6

K excretion: Potassium excretion

KIM-1: Kidney Injury Molecule-1

LDL: Low-Density Lipoprotein Cholesterol

MCP-1: Monocyte Chemoattractant Protein-1

mGFR: measured GFR

MIC: Mayo Imaging Classification

MIF: Macrophage Migration Inhibitory Factor

miR: MicroRNAs

NAG: N-Acetyl-β-D-Glucosaminidase

NGAL: Neutrophil Gelatinase-Associated Lipocalin

OR: Odds ratio

PGE2: Prostaglandin E2

PTH: Parathyroid Hormone

RCT: Randomized controlled trials

RRT: Renal replacement therapy

SBP: Systolic Blood Pressure

Serum C3M: C3 Matrix Protein Fragment

suPAR: Soluble Urokinase Plasminogen Activator Receptor

TKV: Total kidney volume

U alpha-GST: Urinary Alpha-Glutathione S-Transferase

Uosm: Urine Osmolality

Urinary PRO-C3 and PRO-C6: Indicators of collagen formation

VEGF: Vascular Endothelial Growth Factor

YKL-40: Chitinase-3-Like Protein 1

Clinical trial number: Not applicable.

Ethics approval and consent for publication: Not applicable.

Data Availability: The data underlying this article are available in the article and in its online supplementary material.

Competing Interests:

R.A.M.: Led this systematic review under a contractual agreement between the University of Kansas Medical Center and PKDOC and has received research grants and consulting fees for other organizations not related to this work.

J.K.: Coordinated the systematic review team completed under a contractual agreement between the University of Kansas Medical Center and PKDOC.

S.F.: Served on the Scientific Advisory Board of Renasant Bio and received consulting fees.

M.A., Q.H., H.K, A.C.: Review team members of this work completed under a contractual agreement between the University of Kansas Medical Center and PKDOC

K.H.: Received research funding and consulting fees for other PKD-related studies from pharmaceutical companies.

A.S.L.Y.: Received research funding and consulting fees for other PKD-related work. Serves on the PKD Foundation Scientific Advisory Board and is a Deputy Editor of the *Journal of the American Society of Nephrology*.

R.P.: Received research funding and consulting fees for other PKD-related studies. Serves on the American Society of Nephrology Board Review

Course faculty is a co-director of the PKD Outcomes Consortium and is a member of the PKD Foundation Registry Advisory Board.

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Risk of bias assessment: J.K., D.G.R., V.R., R.D.P., N.G., K.H., A.S.L.Y., A.C.

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Writing – Review & Editing: All authors contributed to drafting and revising the manuscript.

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Figure 1: PRISMA flow chart

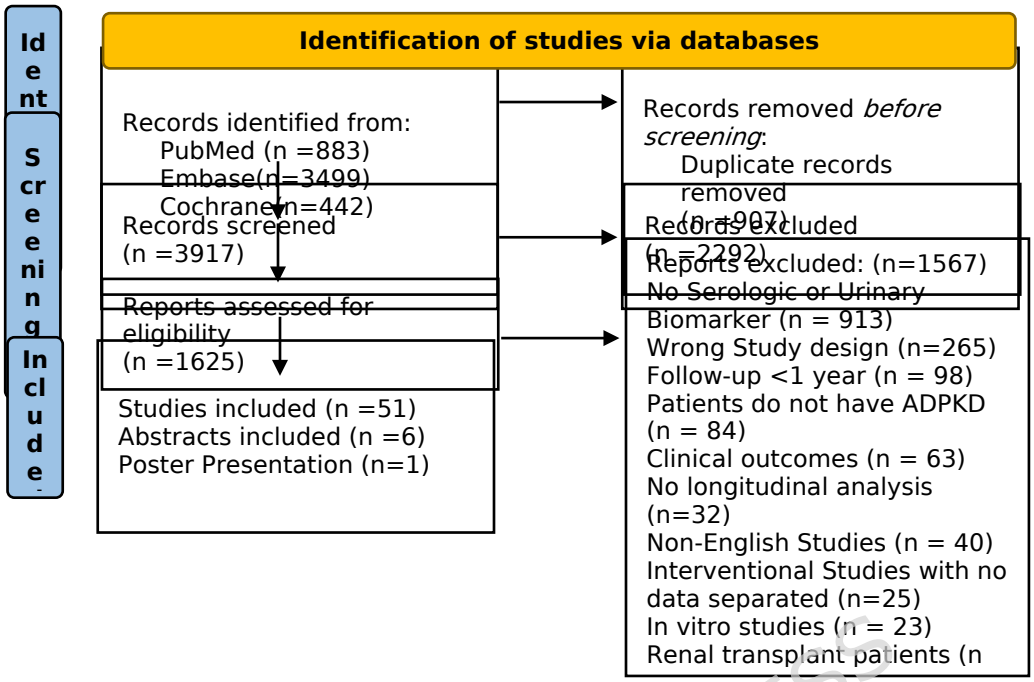


Figure 2.a: Pooled Standardized Beta of Annual Change in eGFR per biomarker

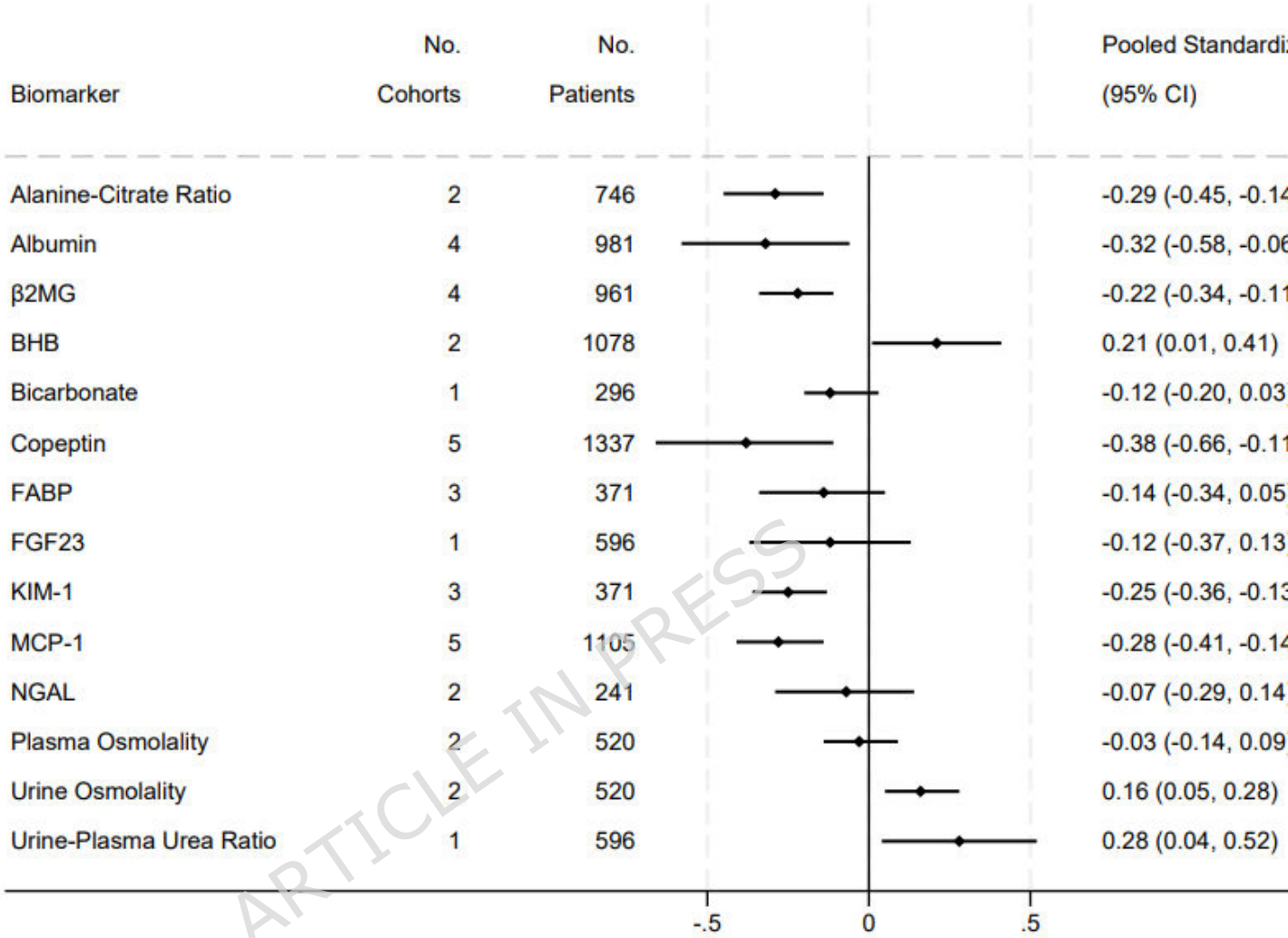
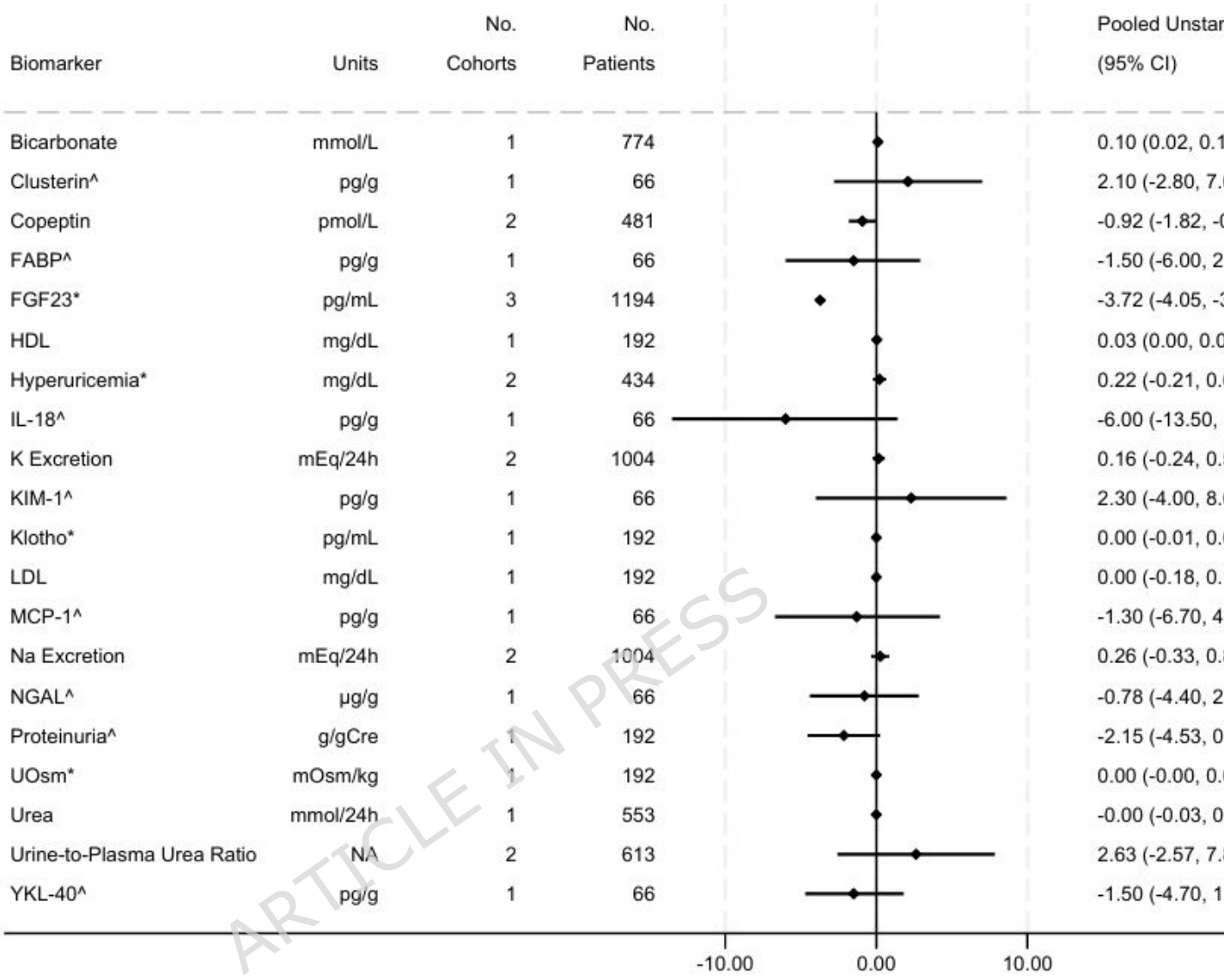


Figure 2.b: Pooled Unstandardized Beta of Annual Change in eGFR per biomarker



^: Biomarker was normalized for creatinine. *: Biomarker was assessed in a non-linear method (Quartile differences)

Figure 3.a: Pooled Standardized Beta of Annual Change in TKV per biomarker

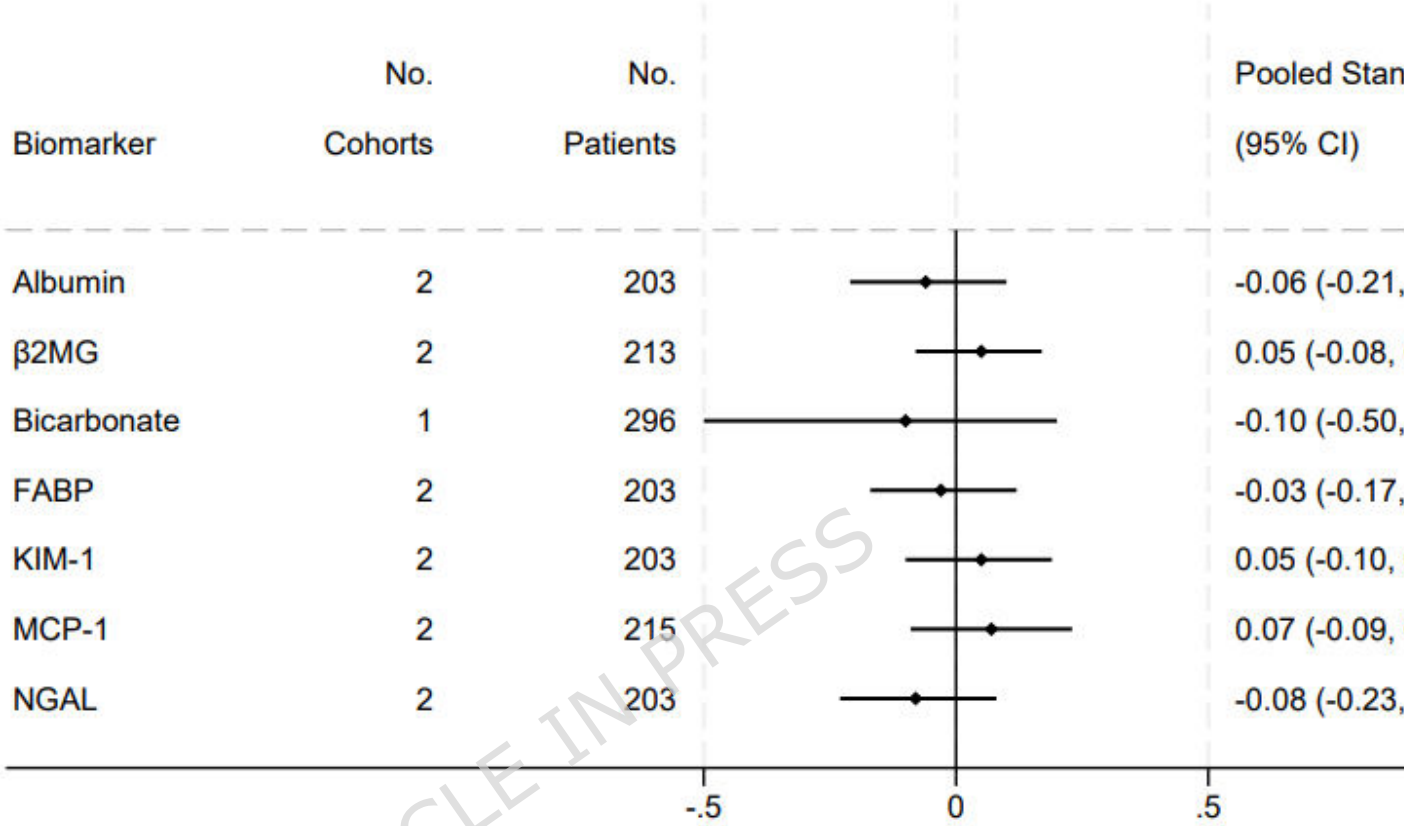
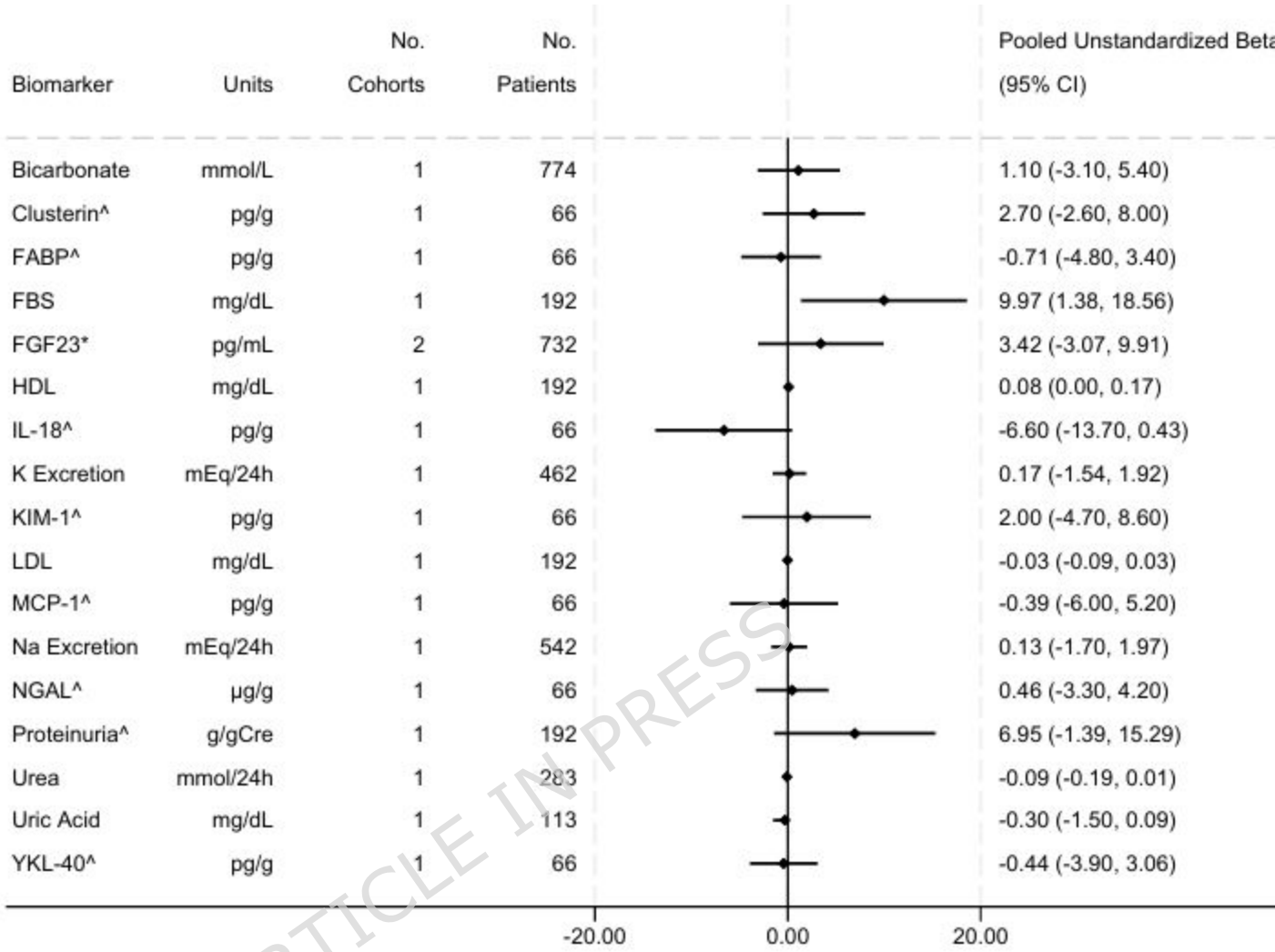


Figure 3.b: Pooled Unstandardized Beta of Annual Change in TKV per biomarker



^: Biomarker was normalized for creatinine. *: Biomarker was assessed in a non-linear method (Quartile differences)

Table 1. C

Author (Year)	Country / Setting	Study Design	Population Characteristics	Biomarker(s) Studied*	Outcome(s) Assessed	Fol Du Mea /M (
Hebert 2003(13)	USA	Retrospective Cohort	Adults	Urine osmolality 24-hour urine volume	eGFR	2.3
Torres 2011(14)	USA	Prospective cohort	Adults and children	Urine osmolality Sodium excretion Uric acid	GFR TKV	6
Boertien 2012(15)	Netherlands	Prospective Cohort	Adults	Copeptin	eGFR RRT incidence	11 14.3
Parikh 2012(16)	USA	Prospective Cohort	Adults	NGAL IL-18	TKV	3
Boertien 2013(17)	USA Netherlands Germany	Prospective Cohort	Adults and children	Copeptin	mGFR TKV	8.5 y
Lacquaniti 2013(18)	Italy	Prospective Cohort	Adults	Apelin Albuminuria Uosm NGAL β2M Copeptin	mGFR TKV ADPKD progression RRT incidence	2

Ozkok 2013(19)	Turkey	Prospective cohort	Adults	Proteinuria	eGFR	10 m
Chen 2014(20)	China	Prospective Cohort	Adults and children	Proteinuria	eGFR TKV	14.3 y
Han 2014(21)	NR	Retrospective Cohort (Abstract only)	Adults	Uric acid	eGFR ESRD	≥6
Casteleijn 2015(22)	Netherlands	Prospective Cohort	Adults	Uosm Plasma Osmolality Copeptin	eGFR	2.8 y
Kocyigit 2016(23)	Turkey	Prospective Cohort	Adults	Copeptin	eGFR	3
Chonchol 2017(24)	USA	Prospective Cohort	Adults	FGF23	TKV ESRD eGFR	5.4
Devuyst	USA	Post hoc	Adults	Uosm	eGFR	3

2017(25)		analysis				
Gitomer 2017(26)	USA	Retrospective Cohort (Abstract only)	Adults	IL-6	eGFR	
Kocyigit 2017(27)	Turkey	Prospective Cohort	Adults	miR-3907	ADPKD Progression	1
Takayanagi 2017(28)	Japan	Prospective cohort (Abstract only)	Adults	NAG	TKV	1
Torres 2017(29)	N/A	Post hoc analysis	Adults and children	Sodium excretion Potassium excretion	TKV	8
Jovanovich 2018(30)	USA	Prospective Cohort (Abstract only)	Adults	FGF23	Live volume	5
Messchendorp 2018(31)	Netherlands	Prospective Cohort	Adults	β2M NGAL KIM-1 MCP-1	eGFR TKV	3.82 y
Messchendorp 2018(32)	Netherlands	Prospective Cohort	Adults	Somatostatin	eGFR	3.8 y

Yapa 2018(33)	N/A	Prospective cohort Poster Presentation	NR	Bicarbonate	GFR	2.5
Gansevoort 2019(34)	NR	Post hoc analysis	Adults	Urine Osmolality Plasma Osmolality Copeptin	TKV eGFR	3
Hayek 2019(35)	USA	Retrospectiv e Cohort	Adults	suPAR	Incidence of CKD	3
Kim 2019(36)	Korea	Prospective Cohort	Adults	Albuminuria AGT	All-cause mortality and renal function decline	4.6
Kocyigit 2019(37)	Turkey	Prospective Cohort	Adults	Uric acid serum ET-1 Calcium Phosphorus PTH CRP	Overall Survival Renal Survival	Patie follo the cardi r
Kocyigit 2019(38)	Turkey	Prospective Cohort	Adults	Metabolic syndrome IL-1β CRP	ADPKD Progression	1
Messchendor p 2019(39)	Netherlands	Prospective Cohort	Adults	KIM-1 MCP-1	eGFR TKV	2.43 y
Dekker 2020(40)	Netherlands	Prospective Cohort	Adults	Alanine/citrate ratio	eGFR	≥1

Griffin 2020(41)	N/A	RCT	Adults	KIM-1	eGFR	5
Kramers 2020(42)	Netherlands	Prospective Cohort	Adults	Sodium excretion Urea excretion	eGFR TKV	4
Magayr 2020(43)	Canada, UK	Prospective Cohort	Adults	miR-30e-5p miR-192-5p miR-194-5p	ADPKD Progression	5
Medrano 2020(44)	Spain	Prospective Cohort	Adults	β2M NGAL L-FABP HIF-1 KIM-1 MCP-1 VEGF	eGFR	□1
Park 2020(45)	Korea	Prospective cohort	Adults	Urine osmolality Proteinuria Albuminuria Serum albumin Urine pH AGT Uric acid	eGFR	49.9 m
Ushio 2020(46)	Japan	Retrospectiv e cohort	Adults	Uric acid Hemoglobin Triglycerides LDL cholesterol HDL cholesterol Proteinuria	eGFR	5.5

Blijdorp 2021(47)	Netherlands	RCT	Adults	Bicarbonate	eGFR Kidney function	2.5
Brosnahan 2021(48)	USA	RCT	Adults	Uric acid	eGFR	3.6 y
ElTers 2021(49)	USA	Prospective Cohort	Adults and children	Uosm MCP-1 FGF23 Klotho	GFR ESRD, death, or doubling of	13

					serum creatinine	
Fernandes 2021(50)	N/A	Prospective Cohort (Abstract only)	Adults	U alpha-GST/ U Cr	eGFR	3
Genovese 2021(51)	Netherlands	Retrospective Cohort (Abstract only)	Adults	PRO-C3 C3M PRO-C6 IL-6	eGFR	
Heida 2021(52)	Netherlands	Post hoc analysis	Adults	Urea	eGFR	6.3 y
Kramers 2021(53)	Netherlands	Prospective Cohort	Adults	Albuminuria	TKV	3.9 y
Phakdeekitcharoen 2021(54)	Thailand	Prospective Cohort	Adults	Proteinuria Albuminuria	mGFR	1.7 y
Uchiyama 2021(55)	Japan	Prospective cohort	Adults	Hemoglobin Proteinuria LDL cholesterol HDL cholesterol	eGFR TKV	□5
Dekker 2022(56)	Netherlands	Prospective Cohort	Adults	Alanine/citrate ratio Betaine Phenylacetyl	eGFR	□2

				glycine		
Jones 2022(73)	USA	Retrospective Cohort	Adults	Pyuria	eGFR	3 (1-
Klawitter 2022(57)	USA	Prospective Cohort	Adults	Anandamide Palmitoylethanolamide 2-arachidonoylglycerol	eGFR TKV	4
Arjune 2023(58)	Germany	Prospective Cohort	Adults	Copeptin	eGFR	2.3 y
Geurts 2023(59)	N/A	Prospective Cohort	Adults	PGE2	eGFR	4.4 (y
Harskamp 2023(60)	Netherlands	Retrospective Cohort	Adults	EGF excretion	eGFR TKV	2.4 y
Rocchetti 2023 (61)	Italy	Prospective cohort	Adults	MCP-1 EGF	eGFR	4
Dekker 2024(74)	Netherlands	Post hoc analysis	Adults	Calcium excretion	eGFR	
Knol 2024(62)	Netherlands	Prospective Cohort	Adults	BHB Copeptin	TKV eGFR	4
Lai 2024(63)	Italy	Prospective Cohort	Adults	h-miR17-5p h-miR 21-5p h-miR 199a-5p	eGFR	2
Nishimoto 2024(64)	Brazil	Retrospective Cohort	Adults	Uric acid	Renal outcomes	10 M

Uysal 2024(65)	Turkey	Prospective cohort	Adults	Proteinuria NGAL NGR	ADPKD Progression eGFR	5
Wang 2024(66)	USA	post hoc analysis	Adults	NGAL KIM-1 MCP-1 IL-18 FABP Clusterin YKL-40	eGFR TKV	1
Bais 2025(67)	Netherlands	Retrospective and Prospective Cohort	Adults	Albuminuria MCP-1 Urea EGF β2M Copeptin PGE-2 Glucagon BHB FGF-23	eGFR TKV ADPKD Progression Kidney Failure	5
Nitta 2025(68)	Tokyo	Prospective Cohort	Adults	Phosphate Proteinuria	RRT eGFR	10

NR: Not reported; *: Biomarker abbreviations are explained in Table 2 ; BP: Blood pressure; GFR: Glomerular Filtration Rate; eGFR: estimated GFR; BSA: Body Surface Area; Cr: Creatinine; ACEI: Angiotensin converting enzyme inhibitor; TKV: Total kidney volume; mGFR: measured GFR, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure; BMI: Body-mass Index; CKD: Chronic kidney disease; MIC: Mayo Imaging Classification

Table 2. Biomarkers reported in the studies included with abbreviations

Urinary Biomarkers	Serum/Blood Biom
24-hour urine volume	Anandamide
Albumin	Apelin
Angiotensinogen (AGT)	Beta-hydroxybutyrate (BHB)
Beta 2 Microglobulin (β2M)	Bicarbonate
Betaine	Calcium
Calcium	Copeptin
Chitinase-3-Like Protein 1 (YKL-40)	C-Reactive Protein (CRP)
Citrate	Endothelin-1(ET-1)
Clusterin	Fasting blood sugar (FBS)
Epidermal Growth Factor (EGF)	Fibroblast Growth Factor 23 (FGF23)
Fatty acid binding protein (Including Liver FABP: L-FABP)	Glucagon
Hypoxia-Inducible Factor-1 (HIF-1)	Hemoglobin
Indicators of collagen formation (Urinary PRO-C3 and PRO-C6)	High-Density Lipoprotein Cholesterol
Interleukin-18 (IL-18)	Interleukin-1 Beta (IL-1β)
Kidney Injury Molecule-1(KIM-1)	Interleukin-6 (IL-6)
Macrophage Migration Inhibitory Factor (MIF)	Klotho
Maximal urine concentrating capacity	Low-Density Lipoprotein Cholesterol
MicroRNAs: miR-30a-5p, miR-30d-5p, miR-30e-5p,miR-192-5p,miR-194-5p	MicroRNAs (miR-3907, miR-3908, mi miR 21-5p, h-miR 199a-5p)
Monocyte Chemoattractant Protein-1 (MCP-1)	Palmitoylethanolamide
N-Acetyl-β-D-Glucosaminidase (NAG)	Phosphate
Neutrophil Gelatinase-Associated Lipocalin (NGAL)	Plasma Osmolality
Phenylacetylglycine	PTH: Parathyroid Hormone
Potassium excretion (K excretion)	Serum C3M: C3 Matrix Protein Fragr
Prostaglandin E2 (PGE2)	Soluble Urokinase Plasminogen Activ
Protein	Somatostatin
Pyuria	Triglycerides
Sodium	Uric acid
Urea	
Urinary Alpha-Glutathione S-Transferase (U alpha-GST)	
Urine Osmolality (Uosm)	
Urine pH	
Vascular Endothelial Growth Factor(VEGF)	

Table 3: Summarized Outcomes with Overall Certainty of Evidence per each Urinary Biomarker

arkers	N□ of Studies reported on the Biomarker	eGFR	TKV	Rapid Progression	ADPKD Progression	RRT incidence	Kidney Failure
tensinoge	1 (45)	Standardized Beta 0.023 (-1.264 to 0.095) [Low]	--	--	--	--	--
in	8(18, 31, 36, 39, 45, 53, 54, 67)	Standardized Beta -0.32 (-0.58 to -0.06) [High]	Standardized Beta -0.06 (-0.21 to 0.1) [Low]	OR 1.67 (1.33 to 2.1) [a] [High]	HR 1.02 (0.96 to 1.3) [Very Low]	--	HR 1.52 (1.32 to 1.74) [High]
Beta 2 globulin	5(18, 31, 39, 44, 67)	Standardized Beta -0.22 (-0.34 to -0.11) [High]	Standardized Beta 0.05 (-0.08 to 0.17) [Low]	OR 1.25 (0.98 to 1.6) [a] [Low] OR 1.49 (0.99 to 2.23) [b] [Very Low]	HR 1.01 (0.99 to 1.02) [Low]	HR 1.01 (0.98 to 1.02) [Low]	HR 1.21 (1.03 to 1.42) [Moder
e	1(56)	Pearson correlation -0.236 with p value 0.03 [Very Low]	--	--	--	--	--
m	2(37, 74)	Pearson correlation 0.236 with p value 0.03 [Very Low]	--	--	--	--	--
e	3(40, 56, 67)	Standardized Beta -0.29 (-0.45 to -0.14) [Low]	--	--	OR 0.77 (0.39 to 1.5) [Very Low]	--	--

rin	1(66)	Unstandardized Beta 2.1 (-2.8 to 7) [Very Low]	Unstandardized beta 2.7 (-2.6 to 8) [Very Low]	--	--	--	--
Epidermal n Factor	3(60, 61, 67)	Standardized beta 1.51 p value <0.001 [Low]	Standardized beta -0.03 with p value 0.76 [Low]	--	--	--	HR 0.86 (0.73 to 1.03) [Low]
Fatty inding n	4(31, 39, 44, 66)	Standardized Beta -0.14 (-0.34 to 0.05) [Moderate]	Standardized Beta -0.03 (-0.17 to 0.12) [Low]	--	--	--	--
Hypoxia-ble -1	1(44)	Standardized Beta= -0.410 p value is 0 [Low]	--	--	--	--	--
ur urine e	1(13)	Standardized Beta was -1.220 p value 0.076 [Very Low]	--	--	--	--	--
ukin-18	2(16, 66)	Unstandardized Beta -6 (-13.5 to 1.4) [Very Low]	Unstandardized Beta -6.6 (-13.7 to 0.43) [Very Low]	--	--	--	--
Kidney Molecule-	5(31, 39, 41, 44, 66)	Standardized Beta -0.25 (-0.36 to -0.13) [Moderate]	Standardized Beta 0.05 (-0.01 to 0.19) [Low]	--	--	--	--
al urine ntrating ty	1(52)	Standardized Beta 0.07, p value 0 .03 [Very Low]	--	--	--	--	--
: cyte pattracta tein-1	6(31, 39, 44, 61, 66, 67)	Standardized Beta -0.28 (-0.41 to -0.14) [High]	Standardized Beta 0.07 (-0.09 to 0.23) [Low]	OR 1.78 (1.4 to 2.27) [a] [High]	--	--	HR 1.69 (1.01 to 2.83) [Low]

RNAs: 0a-5p	1(43)	Standardized beta -0.215 p-value 0.16 [Very Low]	--	--	--	--	--
RNA: miR- p	1(43)	Standardized beta -0.236 p-value 0.12 [Very Low]	--	--	--	--	--
RNA: 192-	1(43)	Standardized beta -0.236 p-value 0.12 [Very Low]	--	--	--	--	--
phage ion ory	1(31)	Standardized Beta = 0.070 P value 0.48 [Very Low]	Standardized Beta -0.01 with P value= 0.960 [Very low]	--	--	--	--
N-Acetyl- saminidas	1(31)	Standardized beta 0.06 p-value 0.57 [Very Low]	Standardized beta 0.01 with a p value 0.95 [Very Low]	--	--	--	--
ophil nase- ated lin	7(16, 18, 31, 39, 44, 65, 66)	Standardized Beta -0.07 (-0.29 to 0.14) [Moderate]	Standardized Beta -0.08 (-0.23 to 0.08) [Low]	--	HR 0.9 (0.89 to 1.01) [Very Low]	HR 1.02 (0.97 to 1.03) [Very Low]	--
lacetyl e	1(56)	--	--	--	Standardized beta 0.48 with standard error 0.13 [Low]	--	--
sium	1(29)	Unstandardized Beta 0.16 (-0.24 to 0.55) [Low]	Unstandardized Beta 0.175 (-1.542 to 1.921) [Low]	--	--	--	--
glandin	1(59)	Mean -0.34 (-0.59 to -0.09)	--	--	--	--	--

		[Low]					
n	9(19, 20, 44-46, 54, 55, 65, 68)	Unstandardized beta -4.57 with a p value <0.001 [Low]	Unstandardized beta 2.55 with a p value 0.05 [Very Low]	--	OR 1.85 (0.23 to 14.67) [Very Low]	--	--
	1(73)	Unstandardized Beta -3.810 (-4.11 to -3.51) [Low]	% change in TKV 59.02 (46.85 to 71.18) [Low]	--	--	--	--
m	4(14, 29, 42, 49)	Unstandardized Beta 0.26 (-0.33 to 0.85) [Low]	Unstandardized Beta 0.126 (-1.695 to 1.972) [Low]	--	--	--	--
a-GST: y alpha-hione S-erase	1(50)	Correlation Coefficient 0.04 p value 0.07 [Very Low]	--	--	--	--	--
	3(42, 52, 67)	Standardized Beta 0.28 (0.04 to 0.52) [High]	Unstandardized Beta -0.09 (-0.19 to 0.01) [Very Low]	OR 0.75 (0.55 to 1.02) [a] [Moderate]	--	HR 1.43 (1.11 to 1.85) [High]	HR 0.79 (0.69 to [High]
Urine ality	8(13, 18, 22, 25, 29, 34, 45, 49)	Standardized Beta 0.16 (0.05 to 0.28) [Moderate]	1 study with 465 patients showed standardized beta -0.02 with p value 0.72 [Moderate]	--	HR 0.95 (0.83 to 1.01) [Very Low]	--	--
y PRO-C3	1(51)	Linear mixed models p value= 0.001 [Very Low]	--	--	--	--	--
y PRO-C6	1(51)	Linear mixed models p value <0.001 [Very Low]	--	--	--	--	--

pH	1(45)	Unstandardized Beta 0.451 (0.065 to 0.837) [Low]	--	--	--	--	--
: Vascular helial n Factor	1(44)	Standardized Beta -0.19 P value 0.024 [Low]	--	--	--	--	--
0: ase-3- rotein 1	1(66)	Unstandardized beta coefficient -1.5 (-4.7 to 1.8) [Very Low]	Unstandardized Beta -0.440 (-3.9 to 3.06) [Very Low]	--	--	--	--

a: Defined as annual change in eGFR less than -3 ml/min per 1.73 m^2**; b:** Defined as annual change in eGFR less than –3.5 mL/ min/1.73 m^2**; --:** Not Reported**; HR:** Hazard Ratio; **OR:** Odds Ratio

Table 4: Summarized Outcomes with Overall Certainty of Evidence per each Serum Biomarker

kers	N□ of Studies reported on the Biomarker	eGFR	TKV	Rapid Progression	ADPKD Progression	RRT incidence	K F
mide	1(57)	Standardized beta 0.192 p value 0.006 [Low]	Standardized Beta -0.332 p value 0 [Low]	--	--	--	--
	1(18)	Standardized Beta 0.139 p value 0.001 [Low]	Standardized beta -0.339 with a p value of 0.02 [Low]	--	HR 0.95 (0.93 to 0.96) [Low]	HR 0.91 (0.8 to 0.93) [Low]	--
ta-butyrate	2(62, 67)	Standardized Beta 0.21 (0.01 to 0.41) [High]	Standardized Beta 1.001 (1 to 1.01) [Low]	OR 0.9 (0.74 to 1.11) [c] [Low]	--	--	H (1 [
nate	2(33, 47)	Standardized Beta -0.120 (-0.2 to -0.03) [High]	Standardized Beta -0.2 (-0.8 to 0.3) [Moderate]	--	--	--	--
rathyroid e	2(37, 38)	--	--	OR 1.06 (0.98 to 1.15) [Low][a]	--	--	--
	2(37, 74)	Pearson correlation -0.236 with p value 0.03 [Very Low]	--	--	--	--	--
n	9(15, 17, 18, 22, 23, 34, 58, 62, 67)	Standardized Beta -0.38 (-0.66 to -0.11) [High]	Standardized Beta 1.006 (1 to 1.01) [High]	OR 2.49 (1.09 to 5.7) [a] [Moderate]	HR 1.03 (1.01 to 1.04) [Low]	HR 1.03 (1.01 to 1.04) [Low]	H (4 [
ndothelin-1	1(37)	--	--	--	HR 1.05 (1 to 1.17) [Very Low]	--	--

Fibroblast Factor 23	4(24, 30, 49, 67)	Unstandardized Beta -3.72 (-4.05 to -3.39) [High]	Unstandardized Beta 3.42 (-3.07 to 9.91) [Very Low]	OR 1.3 (0.96 to 1.75) [a] [Moderate]	--	--	H (1 [
blood sugar	1(55)	--	Unstandardized Beta 9.970 (1.38 to 18.56) [Very Low]	--	--	--	--
n	1(67)	Standardized Beta -0.12 (-0.33 to 0.08) [Low]	--	--	--	--	--
olesterol: High- Lipoprotein erol	2(46, 55)	Unstandardized Beta 0.031 (0.0016 to 0.06) [Low]	Unstandardized Beta 0.082 (-0.0023 to 0.17) [Low]	--	HR 0.76 (0.29 to 1.88) [Very Low] [d]	--	--
obin	2(46, 55)	Unstandardized Beta 0.13 (-0.2 to 0.46) [Very Low]	Unstandardized Beta -0.17 (-1.2 to 0.87) [Very Low]	--	HR 0.69 (0.5 to 0.95) [d] [Very Low]	--	--
terleukin-1	1(38)	--	--	OR 1.05 (1.02 to 1.09) [c] [Low]	--	--	--
erleukin-6	1(26)	Standardized Beta -10.207 (-11.315 to -9.1) [Low]	--	--	--	--	--
	1(49)	Unstandardized Beta 0.002 (-0.007 to 0.011) [Low]	--	--	--	--	--
lesterol: Low- Lipoprotein erol	2(46, 55)	Unstandardized Beta 0 (-0.18 to 0.18) [Very Low]	Unstandardized Beta -0.028 (-0.087 to 0.031) [Very Low]	--	HR 1.29 (0.49 to 2.83) [d] [Very Low]	--	--

NAs: miR-3907	1(27)	--	--	OR 2.37[g] (1.66 to 3.4) [very low]	--	--	--
NA: h-miR17-5p	1(63)	Spearman correlation 0.34 p value <0.05 [Very Low]	--	--	--	--	--
NA: h-miR 21-	1(63)	Spearman correlation 0.41 p value <0.05 [Very Low]	--	--	--	--	--
NA: h-miR p	1(63)	Spearman correlation 0.37 p value <0.05 [Very Low]	--	--	--	--	--
Neutrophil ase-Associated n	1 (65)	--	--	OR 0.69 (0.57 to 0.84)[f] [Low]	--	--	--
rathyroid e	1(37)	--	--	--	HR 1.01 (1 to 1.02) [Very Low]	--	--
ylethanolamide	1(57)	Standardized Beta 0.189 p value 0.007 [Very Low]	--	--	--	--	--
ate	1(68)	--	--	--	HR 1.92 (1.43 to 2.56) [Low]	--	--
orus	1(37)	--	--	--	HR 2.03 (1.46 to 2.84)[d] [Very Low]	--	--

Osmolality	2(22, 34)	Standardized Beta -0.03 (-0.14 to 0.09) [Moderate]	Standardized beta- 0.078 p-value 0.15 [Low]	--	--	--	--
C3M: C3 Matrix Fragment	1(51)	OR=1.48 p-value 0.02 [Very Low]	--	--	--	--	--
statin	1(32)	Standardized Beta 0.03 p value=0.8 [Very Low]	Standardized Beta was -0.12 p-value 0.32 [Very Low]	--	--	--	--
Soluble se ogen Activator or	1(35)	--	--	--	HR 1.72 (0.83 to 3.68) e [Very Low]	--	--
rides	1(46)	--	--	--	HR 1.6 (0.85 to 2.9) [d] [Very Low]	--	--
d	9(14, 21, 37, 38, 45, 46, 48, 55, 64)	Standardized beta -0.212 p-value 0.443 [Low]	Unstandardized Beta -0.3 (-1.5 to 0.9) [Low]	--	--	--	--

a: Defined as annual eGFR change less than -3 ml/min per 1.73 m^2**; b:** Defined as annual change in eGFR less than –3.5 mL/ min/1.73 m^2; **c:** Defined as decrease of >10% of baseline eGFR over 12 months of follow-up; **d:** Defined as: ≥50% decline in eGFR from baseline (≥50% eGFR decline) or the initiation of RRT; **e:** Defined as ESRD incidence [suPAR,per100%increase(log2)]; **f:** Defined as eGFR decline more than5mL/min/1.73m2 per year or2.5mL/ min/1.73 m2 per year over 5years; **g:** decrease of>10% of baseline eGFR over 1 year ; **--:** Not Reported **; HR:** Hazard Ratio ; **OR:** Odds Ratio