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Asymptomatic Pyuria as a Prognostic Biomarker in Autosomal Dominant Polycystic Kidney Disease

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Key Points:

*Asymptomatic pyuria is associated with kidney failure and faster kidney function decline irrespective of the ADPKD gene and cystic growth.

*The eGFR decline occurred after detection of asymptomatic pyuria without significant changes in rate of total kidney volume growth.

*This study supports the use of asymptomatic pyuria as an enriching prognostic biomarker to predict faster disease progression.

Abstract:

Background: Autosomal dominant polycystic kidney disease (ADPKD) has phenotypic variability only partially explained by established biomarkers that do not readily assess pathologically important factors of inflammation and kidney fibrosis. We evaluated asymptomatic pyuria, a surrogate marker of inflammation, as a biomarker for disease progression. Methods: We performed a retrospective cohort study of adult patients with ADPKD. Patients were divided into asymptomatic pyuria (AP) and no pyuria (NP) groups. We evaluated the effect of pyuria on kidney function and kidney volume. Longitudinal models evaluating kidney function and kidney volume rate of change with respect to incidences of asymptomatic pyuria were created. Results: There were 687 included patients (347 AP, 340 NP). The AP group had more female (65.1% vs 49.4%). Median age at kidney failure was 86 and 80 years in NP and AP groups, respectively (Log-rank, p=0.49) for patients with Mayo Imaging Class (MIC)1A-1B as compared to 59 and 55 years for patients with MIC1C-1D-1E (Log-rank, p=0.02). Compared to NP group, the rate of kidney function decline shifted significantly after detection of asymptomatic pyuria in models including all patients (-1.48, p<0.001), MIC 1A-B patients (-1.79 , p<0.001), MIC 1C-1D-1E patients (-1.18, p<0.001), and PKD1 patients (-1.04, p<0.001). Models evaluating kidney volume rate of growth showed no change after incidence of asymptomatic pyuria as compared to NP group. Conclusions: Asymptomatic pyuria is associated with kidney failure and faster kidney function decline irrespective of the ADPKD gene, cystic burden, and cystic growth. These results support asymptomatic pyuria as an enriching prognostic biomarker for the rate of disease progression.-

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Asymptomatic Pyuria as a Prognostic Biomarker in Autosomal Dominant Polycystic Kidney Disease

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Key Points:

- Asymptomatic pyuria is associated with kidney failure and faster kidney function decline irrespective of the ADPKD gene and cystic growth.
- The eGFR decline occurred after detection of asymptomatic pyuria without significant changes in rate of total kidney volume growth.
- This study supports the use of asymptomatic pyuria as an enriching prognostic biomarker to predict faster disease progression.

Abstract:

Background: Autosomal dominant polycystic kidney disease (ADPKD) has phenotypic variability only partially explained by established biomarkers that do not readily assess pathologically important factors of inflammation and kidney fibrosis. We evaluated asymptomatic pyuria, a surrogate marker of inflammation, as a biomarker for disease progression.

Methods: We performed a retrospective cohort study of adult patients with ADPKD. Patients were divided into asymptomatic pyuria (AP) and no pyuria (NP) groups. We evaluated the effect of pyuria on kidney function and kidney volume. Longitudinal models evaluating kidney function and kidney volume rate of change with respect to incidences of asymptomatic pyuria were created.

Results: There were 687 included patients (347 AP, 340 NP). The AP group had more female (65.1% vs 49.4%). Median age at kidney failure was 86 and 80 years in NP and AP groups, respectively (Log-rank, p=0.49) for patients with Mayo Imaging Class (MIC)1A-1B as compared to 59 and 55 years for patients with MIC1C-1D-1E (Log-rank, p=0.02). Compared to NP group, the rate of kidney function (ml/min/1.73m²/year) decline shifted significantly after detection of asymptomatic pyuria in models including all patients (-1.48, p<0.001), MIC 1A-B patients (-1.79, p<0.001), MIC 1C-1D-1E patients (-1.18,
p<0.001), and PKD1 patients (-1.04, p<0.001). Models evaluating kidney volume rate of growth showed no change after incidence of asymptomatic pyuria as compared to NP group.

**Conclusions:** Asymptomatic pyuria is associated with kidney failure and faster kidney function decline irrespective of the ADPKD gene, cystic burden, and cystic growth. These results support asymptomatic pyuria as an enriching prognostic biomarker for the rate of disease progression.

**Introduction:**

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease and the fourth most common cause of kidney failure.\(^1\)\(^2\) It is a phenotypically variable disease with patients progressing to kidney failure from relentless kidney growth.\(^3\) Disease severity stratification using genetic, clinical, and radiological biomarkers is used to predict the rate of ADPKD progression.\(^4\) Height-adjusted total kidney volume (Ht-TKV) has been recognized as a prognostic biomarker of cystic burden and disease severity. Age-adjusted Ht-TKV, represented by the Mayo Imaging Classification (MIC), estimates the intrinsic rate of kidney cyst growth which translates into various rates of estimated glomerular filtration rate (eGFR) decline.\(^5\)\(^-\)\(^14\) However Ht-TKV explains approximately 42% of the variance for GFR indicating that other non-cystic mechanisms could affect kidney function decline.\(^15\) While fluid secretion and cell proliferation play a major role in cystic severity, mechanisms such as inflammation and fibrosis could affect the renal parenchyma and kidney function without affecting cystic burden.\(^16\) Interstitial inflammation and subsequent fibrosis are pathologic hallmarks of ADPKD.\(^17\)\(^-\)\(^19\) Preclinical studies support an important role of inflammation, such as manipulation of macrophages in PKD animal models resulting in improved renal function.\(^20\)\(^,\)\(^21\) High levels of inflammatory cell migration and upregulation of chemokines and cytokines are described in patients with ADPKD.\(^18\)\(^,\)\(^21\)\(^-\)\(^24\) These observations have driven the evaluation of inflammatory markers for additional prognostication and
targeting inflammatory pathways as potential therapeutic interventions in ADPKD. Asymptomatic pyuria could be used as a surrogate marker of inflammation in the absence of urinary infection.

We sought to evaluate the effect of asymptomatic pyuria on disease progression in ADPKD and hypothesized that the presence of asymptomatic pyuria, as a surrogate marker of inflammation, is associated with faster eGFR decline.

**Materials and Methods:**

This is a retrospective cohort study that included adult ADPKD patients seen at Mayo Clinic (Minnesota, Florida, and Arizona) from 1/1992 to 1/2020. This study was performed with adherence to the Declaration of Helsinki and was approved by the Mayo Clinic Institutional Review Board.

**Study Patients and Patient Categorization**

Patients were initially included from a query of the Mayo PKD database utilizing the following criteria: 1) age 18-80 years, 2) ADPKD diagnosis based on Ravine-Pei modified criteria (in presence of family history) or ≥20 total bilateral kidney cysts without evidence of alternative cystic disease (in absence of family history), 3) ≥1 available abdominal image (CT/MRI), 4) ≥1 urinalysis (UA), and 5) ≥2 serum creatinines. Patients were excluded if any of the following were true: 1) first available Ht-TKV or UA was obtained after kidney failure, 2) procedures (cyst aspiration, fenestration, nephrectomy, or kidney transplant) that affect kidney volume were performed prior to first available abdominal imaging; 3) renal cystic disease due to GANAB mutation.

Pyuria was defined as the presence of > 3 white blood cells per high power field (WBC/hpf) on UA. Asymptomatic pyuria was defined as the presence of pyuria with no evidence of urinary tract infection (UTI). After review of electronic records, patients were excluded if pyuria was attributed to one of the following: 1) positive urinary culture and/or clinical symptoms of cystitis, prostatitis, pyelonephritis, or kidney cyst infection within the two preceding months of pyuria identification, 2) urinary contamination defined as >10 squamous cells/hpf on UA, 3) recent urinary instrumentation, or
4) bladder tumor. Patients with any available UA before reaching kidney failure that satisfied the criteria for asymptomatic pyuria were categorized in the asymptomatic pyuria group (AP). Patients who had no pyuria on any UA before reaching kidney failure were categorized into the no pyuria group (NP). The classifying UA was the earliest UA for the NP group and the first UA meeting pyuria criteria for the AP group.

Data Collection

Medical records reviews were performed by two medical doctors to obtain demographics, PKD pathologic variant, UA, serum creatinines, Ht-TKV, MIC, kidney failure or transplant dates (if applicable). Data concerning possible confounders was compared at the time of the classifying UA: body mass index (BMI), smoking history, hypertension, number and class of anti-hypertensive agents, and use of medication which could affect pyuria (systemic steroids, proton pump inhibitors (PPI), antibiotics, and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs)). To ascertain other cofounder factors that could affect the occurrence of pyuria, we evaluated the medical records up to the time of the classifying UA for the number of all hospital admissions including those for stroke, acute kidney injury (AKI) or cardiovascular disease (CV), visits for emergency department (ED), prior history of cardiovascular procedures, prior history of preeclampsia, prior history of sepsis, history of inflammatory bowel disease, and history of any malignancy. All available kidney function and volumes have been collected until last follow up or date of ESKD. Baseline kidney function and volume were obtained from earliest serum creatinine and earliest abdominal imaging (CT/MRI), respectively.

Definitions and Standards

The CKD EPI equation was used to calculate eGFR. Serum creatinine measurements were obtained through various standardization methods given the study duration. However, this likely had minimal effect given that calibration error related to non-standardized creatinine measurements is most important when GFR is well preserved and that patients included in this study have low eGFR. Kidney
failure or end-stage kidney disease (ESKD) was defined by the initiation of kidney replacement therapy (dialysis or preemptive kidney transplantation).

Abdominal MRI or CT planimetry or stereology was used to calculate TKV and standardized to height to calculate Ht-TKV (ml/m). Different acquisition sequences can introduce variability in measurement of TKV, however this variability is comparable to the inter-reader differences and not likely to have affected the results. It has been shown that MRI and CT produce comparable measurements of TKV.\textsuperscript{14} Mayo Class was determined using MIC calculator as detailed by Irazabal et al.\textsuperscript{14, 32} Ht-TKV rate of growth was analyzed in patients who had ≥2 abdominal images with ≥1 year interval.

The entire coding and flanking intronic regions of \textit{PKD1} and \textit{PKD2} were screened for pathologic variants by Sanger or next-generation sequencing.\textsuperscript{33-36} Patients were classified as follows: \textit{PKD1} truncating (\textit{PKD1}\textsuperscript{T}), \textit{PKD1} nontruncating (\textit{PKD1}\textsuperscript{NT1} and \textit{PKD1}\textsuperscript{NT2}), \textit{PKD2} and \textit{GANAB}.\textsuperscript{37-39}

\textbf{Statistical Methods:}

Descriptive statistics were performed utilizing Wilcoxon rank-sum tests and Pearson Chi-square tests to compare those and without observed asymptomatic pyuria during follow up for continuous and categorical variables, respectively. Two multivariable longitudinal linear mixed effects models, one for eGFR and another for Ht-TKV were developed. These models included baseline predictors of gender and age along with follow-up years from baseline to subsequent visits. Baseline was defined as data at first available eGFR. The primary exposure variables in the model were time-dependent, updated to reflect pyuria status over time. Follow up time in years from baseline estimates the average annual change in eGFR (annual slope) among patients prior to or without pyuria while a ‘time after pyuria’ variable estimates the change in annual slope following asymptomatic pyuria. The same approach was used for Ht-TKV. Models included a random subject-specific intercept and slope term. Variants of these basic models including genetic information (utilizing patients \textit{PKD1} genotypes as reference for patients with
PKD2 genotypes) and separated by image classification group (1A-1B and 1C-1D-1E) were generated. Kaplan-Meier analysis (log-rank) was used to compare median kidney survival. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results:

Among 1,068 adult patients with ADPKD, urinalysis, abdominal imaging and sequential GFR, 807 had data before interventions affecting kidney volume and reaching kidney failure (Figure 1). Of these, 340 patients had no evidence of pyuria (NP) and 466 were identified to have at least one UA with pyuria. Of the 466 patients with pyuria, 347 had asymptomatic pyuria (AP) with no evidence of UTI or contamination. For the 681 patients included in analysis, there were 13,209 eGFR measurements [median(IQR) = 11(5,23) per patient], 1,918 Ht-TKV measurements [median(IQR) = 3(2,6) per patient], and 2,547 UAs [median(IQR) = 2(1,4) per patient]. Median (IQR) follow up was 3(1,8) years.

Demographic, clinical, and genotypic characteristics comparing the NP and AP groups are summarized in Table 1. The AP group had more female (65.1% vs. 49.4%) and white (91.9% vs. 88.8%) patients as compared to the NP group. Median age at classifying UA was not different between the NP (48.8 years) and AP (48.8 years) groups. BMI, smoking history, hypertension prevalence, count of antihypertensive agents and use of medications that could cause or treat interstitial nephritis were not different between the groups, however antibiotics use for non-urinary infections was seen more in AP patients (7.2% vs. 3.5%). Median age at first available eGFR (45.6 vs 45.4 years) and median age at first available Ht-TKV (43.3 vs. 44.7 years) were not different between the NP and AP groups, respectively. Median first available eGFR (ml/min/1.73m²) was not significantly different between the NP (65.5) and AP (60.9). When evaluating additional possible confounders that could affect occurrence of pyuria, the AP group did not have increased occurrences of various hospitalizations, conditions, or malignancies (Supplemental Table 1). We assessed the effect of asymptomatic pyuria on kidney survival after stratification by the MIC. For patients with MIC1A-1B, the median age at ESKD was 86 and 80 years in NP
and AP groups, respectively (Log-Rank, p=0.49) (Figure 2A). Interestingly, for patients with MIC1C-1D-1E, those with asymptomatic pyuria had significantly worse kidney survival than those who had no pyuria with median age at ESKD of 59 vs. 55 years for NP and AP groups, respectively (Log-Rank p=0.02) (Figure 2B). When compared to patients with NP, those with AP had lower eGFR but similar Ht-TKV across all the age groups (Figure 3, Supplemental Figure 1). Similar trends of eGFR at last follow up have been noted when patients are subcategorized by sex and MIC groups (Supplemental Figure 2-3).

**Effect of pyuria on rate of kidney function decline**

After adjusting for age and gender in a longitudinal multivariate model (n=687), occurrence of asymptomatic pyuria was associated with worsening in annual eGFR rate of decline (ml/min/1.73m^2/year) as compared to NP patients (-3.81 vs. -2.33), representing a shift of -1.48 following identification of asymptomatic pyuria, p<0.001 (Table 2, Figure 4A). When the patients were stratified into separate models for slow (MIC1A-1B) and rapid progressors (MIC1C-1D-1E), a similar shift was observed (Table 2). Patients with MIC1A-1B had an eGFR rate of decline (ml/min/1.73m^2/year) of -1.27 prior and -3.06 after identification of asymptomatic pyuria representing with a shift of -1.79 (p<0.001) (Table 2). Patients with MIC1C-1D-1E had an eGFR rate of decline (ml/min/1.73m^2/year) of -3.04 prior and -4.22 after detection of asymptomatic pyuria with a shift of -1.18 (p<0.001) (Table 2, Supplemental Figure 4A). The eGFR slopes for individual patients have been plotted in Supplemental Figure 5.

We then evaluated for additional effect of PKD genotype on the association of asymptomatic pyuria with kidney function decline. Patients with *PKD1* pathologic variants (n=257) had an annual eGFR rate of decline (ml/min/1.73m^2/year) of -2.87 prior and -3.91 after detection of pyuria, representing an additional shift of -1.04, p<0.001 (Supplemental Table 2). Patients with *PKD2* pathologic
variants (n=44) lost kidney function at a rate of -1.92 ml/min/1.73m²/year which is slower by 0.95 as compared to patients with PKD1 pathologic variants, p=0.02. Asymptomatic pyuria continued to be associated with faster rate of eGFR decline (-3.06 vs -1.92 ml/min/1.73m², p<0.001) in patients with PKD2 pathologic variants. PKD genotype had no additional effect on how asymptomatic pyuria detection affected eGFR rate of decline (p=0.83) (Supplemental Table 2). To evaluate the effect of medications that could affect the occurrence of pyuria, we performed a longitudinal multivariate random effect model for all patients excluding those who were exposed to the medications of interest (n=463) (Supplemental Table 3). The effect of pyuria on the rate of eGFR change remained unchanged after excluding the patients who were exposed to medications such as systemic steroids, PPI, antibiotics, or NSIADS (Supplemental Table 3). Furthermore, we evaluated the effect of the various clinical factors that could be confounders in occurrence of pyuria on the rate of eGFR change after detection of pyuria (Supplemental Table 4). After adjusting for these various clinical factors in the longitudinal multivariate model, occurrence of asymptomatic pyuria continued to be associated with worsening in annual eGFR rate of decline (ml/min/1.73m²/year) as compared to NP patients (-3.79 vs. -2.33), representing a shift of -1.46 following identification of asymptomatic pyuria, p<0.001 (Supplemental Table 4).

Effect of pyuria on the rate of kidney volume growth

To assess whether asymptomatic pyuria worsen kidney function through cystic enlargement mechanisms, we evaluated the effect of asymptomatic pyuria on the rate of kidney growth (n=439). After adjusting for age and gender, occurrence of asymptomatic pyuria was not associated with worsening in annual Ht-TKV rate of growth, 59.02 vs 61.87 ml/m/year prior to identification of pyuria. This represented a non-significant shift of -2.86 following identification of pyuria, p=0.66 (Table 3, Figure 4B). When the patients were stratified into separate models for slow (MIC1A-1B) and rapid progressors (MIC1C-1D-1E), the effect of pyuria on kidney growth remained neutral (Table 3). Patients with MIC1A-B had an annual Ht-TKV rate of growth of 17.40 compared with 13.59 ml/m/year after detection of
asymptomatic pyuria, a non-significant shift of -3.82, p=0.21 (Table 3). Similarly, detection of pyuria in patients with MIC1C-1D-1E was not associated with significantly faster growth of kidney volume. These patients had an annual Ht-TKV rate of growth of 93.57 compared with 96.78 ml/m/year after detection of asymptomatic pyuria, a non-significant shift of 3.21, p=0.77 (Table 3, Supplemental Figure4B). The Ht-TKV slopes for individual patients have been plotted in Supplemental Figure 6.

Discussion:

In this large cohort study of patients with ADPKD, asymptomatic pyuria is associated with faster kidney function decline irrespective of PKD genotype, cystic burden, or cystic growth. This decline occurred after detection of asymptomatic pyuria without significant changes in rate of Ht-TKV growth. Furthermore, this decline persisted after adjusting for several clinical confounders that could affect the occurrence of pyuria. Moreover, patients with asymptomatic pyuria reached kidney failure at younger age compared to those with no pyuria. These results support the use of asymptomatic pyuria as an enriching prognostic biomarker to predict faster disease progression.

There is growing evidence supporting the role of inflammation in modulating disease progression in ADPKD. Cysts are surrounded by immune cells with complex interaction between those that promote (M2-like macrophages) and others that inhibit cyst growth (CD8+ cytotoxic T cells). Monocyte chemoattractant protein-1 (MCP-1) expression promote macrophage accumulation and cystic dilation. Depleting macrophages in PKD mice lowered their cystic index and improved their kidney function as compared to controls. Urinary MCP-1 concentrations were higher in patients with ADPKD before appreciable increase in serum creatinine. Increase in tubular MCP-1 excretion is an early event in pediatric ADPKD population and an early marker of disease severity. Furthermore, urinary MCP-1 in adult patients with ADPKD provided a predictive prognostic value when added to other biomarkers that reflect tubular damage such as β2-microglobulin. Urinary T cells correlated moderately with renal
function decline in a small cohort of ADPKD patients providing further evidence that this novel marker could be a candidate of disease activity in ADPKD. 49

Advancements in urinary biomarkers, such as urinary MCP-1, in combination with imaging biomarkers, would empower clinicians to individualize ADPKD prognosis based on the activity of various signaling pathways involved in cellular proliferation, cyst secretion, and inflammation. However, these urinary biomarkers are not readily accessible in clinical practice. On the other hand, microscopic evaluation of urine for white blood cell count (pyuria) is universally accessible, simple, reproducible, and relatively inexpensive as compared to other urinary biomarkers.

Urological complications at an age younger than 35, including cyst infection and cyst bleeding, are associated with worse kidney prognosis in patients with ADPKD and have been incorporated in the PROPKD prognostic score.50 Pyuria has been commonly described in patients with ADPKD in the context of a genitourinary infection,50-53 with UTI linked to faster progression of disease in small retrospective studies.54,55 Pyuria has also been associated with increased risk of kidney failure in non-ADPKD patients with chronic kidney disease stage 3-5.57

In our study, pyuria (independent of infection) continued to be a negative prognostic marker of kidney function supporting its use as a marker of disease-related inflammatory processes. Patients without pyuria had GFR change and Ht-TKV rate of growth comparable to expected rates for patients with similar cystic burden and PKD pathologic variants with significantly faster kidney function decline identified after detection of asymptomatic pyuria. Notably, this shift in rate of decline persisted in patients with low cystic burden. Patients with MIC1A-1B are thought to be slow progressors who might benefit less from treatments modifying mechanisms of cystic growth. However, a subcategory of patients with MIC1A-1B and inflammatory predictors, might benefit from treatments modulating inflammation. This further illustrates how biomarkers may allow an individualized and mechanism-specific treatment of ADPKD using disease-modifying therapies.
However, it is critical to note that presence of asymptomatic pyuria should not be used in isolation but rather to enhance prognostication provided by current available tools such as imaging-based (MIC) or genetic-based (PROPKD score) prognosticators. While this study could not causally link pyuria with faster eGFR decline, the statistical modeling provides some indication that the shift in GFR decline occurs after the detection of pyuria. Moreover, the detection of pyuria did not affect the rate of cystic volume growth, which could be explained by the role of inflammation on interstitial parenchyma rather than on cystic growth mechanisms. Additionally, this study highlights the importance of several mechanisms contributing to ADPKD progression, some of which are possibly independent of the cystic burden represented by the age-adjusted TKV.

One of the major strengths of this study is the size of the cohort and granularity and depth of individual patient chart review. To our knowledge, this is the first study analyzing the effect of asymptomatic pyuria on kidney function decline in the context of risk stratification by genotype and disease severity. More importantly, this study provides an additional tool in prognostication. Patients with MIC1A-1B and asymptomatic pyuria might develop faster kidney function decline than otherwise predicted. Therapeutics targeting inflammation are likely to benefit all ADPKD patients, particularly those with distinct inflammatory biomarkers. This provides an opportunity to use combination therapy in ADPKD targeting multiple mechanisms synergistically.

There are several limitations to our study given the retrospective nature of the study design. Firstly, our study might have underdiagnosed the occurrence of asymptomatic pyuria if it occurred outside the medical care at Mayo Clinic or AP occurring during gaps between measured UA. Genetic analysis was not available for the entire cohort. Despite all the efforts in excluding other factors that could affect pyuria, asymptomatic pyuria is not specific and could be affected by other factors that could have been elusive to chart review. Most patients in this cohort are Caucasian, therefore the generalizability of this study’s results to other ethnic and racial groups may be limited. Although a
referral bias could be present, given that Mayo Clinic is a tertiary center, almost two-thirds of the patients are from Minnesota and surrounding states. The cohort is representative of the general ADPKD population except for the race limitation. While the reported outcomes from this single-center study have not been demonstrated in an independent cohort, the concept of pyuria or urinary T cells as a prognostic biomarker has been supported by several previously published studies in 2 small cohorts of ADPKD patients and a large non-ADPKD cohort.\textsuperscript{49, 56, 57} These studies support potential generalizability of the association of pyuria with rapid eGFR decline. Additionally, MIC may change over time. However, MIC remained stable in most patients over time in both the Mayo and CRISP cohort with only 11-22% of patients progressing to an immediate higher class.\textsuperscript{12, 14} Lastly, the statistical model associated pyuria with a significant acceleration of kidney function decline, however, the models are not validated as a predictive model of eGFR or TKV.

In conclusion, microscopic examination of urine for WBC is a readily available and inexpensive tool that can be used to assess for inflammation in the form asymptomatic pyuria. If identified, asymptomatic pyuria portends a worse prognosis in terms of faster decline in kidney function. Identification of pyuria did not affect Ht-TKV rate of change. These results suggest that inflammation plays a role in ADPKD disease progression and warrants future prospective studies to evaluate more specific urinary inflammatory biomarkers. Therapeutics targeting inflammation might be effective in slowing disease progression in all patients with ADPKD irrespective of their disease severity.

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**Author Contributions:**
Brian Jones: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Visualization; Writing - original draft; Writing - review and editing. Yaman Mkhaimer: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing - original draft; Writing - review and editing. Laureano Rangel: Data curation; Formal analysis; Investigation; Writing - original draft; Writing - review and editing. Maroun Chedid: Data curation; Formal analysis. Phillip Schulte: Data curation; Formal analysis; Writing - review and editing. Alaa Mohamed: Data curation; Formal analysis. Reem Neal: Data curation; Formal analysis. Dalia Zubidat: Data curation; Formal analysis. Amarjyot Randhawa: Data curation; Formal analysis. Christian Hanna: Writing - review and editing. Adriana Gregory: Data curation; Formal analysis. Timothy Kline: Data curation; Formal analysis. Ziad Zoghby: Writing - review and editing. Sarah Senum: Data curation; Formal analysis; Writing - review and editing. Peter Harris: Data curation; Formal analysis; Funding acquisition; Writing - review and editing. Vicente Torres: Funding acquisition; Writing - review and editing. Fouad Chebib: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing - original draft; Writing - review and editing.

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5. **Supplemental Figure 5:** eGFR slopes for individual patients by presence of asymptomatic pyuria, age, sex, and MIC category
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7. **Supplemental Table 1:** Additional clinical characteristics of ADPKD patients with (AP) or without (NP) asymptomatic pyuria.
8. **Supplemental Table 2:** Longitudinal multivariable random effects model evaluating effect of PKD genotype on kidney function rate of change before and after detection of asymptomatic pyuria in ADPKD patients.
9. **Supplemental Table 3:** Longitudinal multivariable random effects model evaluating kidney function rate of change before and after detection of asymptomatic pyuria in ADPKD patients with or without medications that could affect occurrence of pyuria
10. **Supplemental Table 4:** Longitudinal multivariable random effects model evaluating kidney function rate of change before and after detection of asymptomatic pyuria in ADPKD patients with slow and rapidly progressing disease including additional clinical factors that could confound occurrence of pyuria.

**References:**


19.


Tables:

**Table 1:** Demographic, clinical and genotypic characteristics of ADPKD patients with (AP) or without (NP) asymptomatic pyuria.

<table>
<thead>
<tr>
<th></th>
<th>No Pyuria (N=340)</th>
<th>Asymptomatic Pyuria (N=347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>168 (49.4%)</td>
<td>226 (65.1%)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>302 (88.8%)</td>
<td>320 (92%)</td>
</tr>
<tr>
<td>Age at classifying UA (yr), median (Q1, Q3)</td>
<td>48.8 (39.8, 57.0)</td>
<td>48.8 (40.5, 58.0)</td>
</tr>
<tr>
<td>Number of UAs per patient, median (Q1, Q3)</td>
<td>2 (1, 3)</td>
<td>3 (2, 6)</td>
</tr>
<tr>
<td>Positive leukocyte esterase, n (%)</td>
<td>21 (6.2%)</td>
<td>37 (10.7%)</td>
</tr>
<tr>
<td>Positive nitrite, n (%)</td>
<td>21 (6.2%)</td>
<td>28 (8.1%)</td>
</tr>
<tr>
<td>BMI (kg/m^2), median (Q1, Q3)</td>
<td>26.8 (23.7, 30.3)</td>
<td>27.4 (23.7, 30.9)</td>
</tr>
<tr>
<td>History of smoking, n (%)</td>
<td>17 (5%)</td>
<td>25 (7%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>255 (75.2%)</td>
<td>274 (79%)</td>
</tr>
<tr>
<td>Count of antihypertensives, median (Q1, Q3)</td>
<td>2.0 (1.0, 3.0)</td>
<td>2.0 (1.0, 2.0)</td>
</tr>
<tr>
<td>Other medication use, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI</td>
<td>52 (15.3%)</td>
<td>45 (13%)</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>7 (2.1%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>19 (5.6%)</td>
<td>25 (7%)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>12 (3.5%)</td>
<td>25 (7%)</td>
</tr>
<tr>
<td>Baseline eGFR (ml/min/1.73m^2), median (Q1, Q3)</td>
<td>65.5 (36.7, 83.4)</td>
<td>60.6 (36.9, 79.0)</td>
</tr>
<tr>
<td>Age at baseline eGFR (yr), median (Q1, Q3)</td>
<td>45.6 (36.6, 53.9)</td>
<td>45.5 (36.5, 54.3)</td>
</tr>
<tr>
<td>Number of eGFR measurements per patient, median (Q1, Q3)</td>
<td>9.0 (5.0,20.0)</td>
<td>13.0 (6.0,27.5)</td>
</tr>
<tr>
<td>CKD Stage at classifying UA, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>67 (19.7%)</td>
<td>48 (13.8%)</td>
</tr>
<tr>
<td>2</td>
<td>122 (35.9%)</td>
<td>125 (36%)</td>
</tr>
<tr>
<td>3</td>
<td>87 (25.6%)</td>
<td>106 (31%)</td>
</tr>
<tr>
<td>4</td>
<td>44 (12.9%)</td>
<td>46 (13%)</td>
</tr>
<tr>
<td>5</td>
<td>20 (5.9%)</td>
<td>23 (7%)</td>
</tr>
<tr>
<td>Kidney Failure, n (%)</td>
<td>111 (33%)</td>
<td>141 (41%)</td>
</tr>
<tr>
<td>Age at kidney failure (yr), median (Q1, Q3)</td>
<td>55.8 (49.5, 63.1)</td>
<td>53.4 (44.6, 61.0)</td>
</tr>
<tr>
<td>Baseline Ht-TKV (ml/m), median (Q1, Q3)</td>
<td>600.4 (342.2, 1093.0)</td>
<td>616.7 (358.5, 990.1)</td>
</tr>
<tr>
<td></td>
<td>No Pyuria (N=340)</td>
<td>Asymptomatic Pyuria (N=347)</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Age at baseline Ht-TKV (yr), median (Q1, Q3)</td>
<td>43.3 (33.4, 52.9)</td>
<td>44.8 (36.8, 54.3)</td>
</tr>
<tr>
<td>Mayo Imaging Class, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>41 (12%)</td>
<td>58 (17%)</td>
</tr>
<tr>
<td>1B</td>
<td>88 (26%)</td>
<td>83 (24%)</td>
</tr>
<tr>
<td>1C</td>
<td>105 (31%)</td>
<td>91 (26%)</td>
</tr>
<tr>
<td>1D</td>
<td>69 (20%)</td>
<td>66 (19%)</td>
</tr>
<tr>
<td>1E</td>
<td>37 (11%)</td>
<td>49 (14%)</td>
</tr>
<tr>
<td>Number of Ht-TKV measurements per patient, median (Q1, Q3)</td>
<td>3.0 (2.0, 5.0)</td>
<td>3.0 (2.0, 6.0)</td>
</tr>
<tr>
<td>Genotype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKD1</td>
<td>74 (51%)</td>
<td>76 (48%)</td>
</tr>
<tr>
<td>PKD1NT1</td>
<td>24 (17%)</td>
<td>30 (19%)</td>
</tr>
<tr>
<td>PKD2NT2</td>
<td>22 (15%)</td>
<td>31 (20%)</td>
</tr>
<tr>
<td>PKD2</td>
<td>24 (17%)</td>
<td>20 (13%)</td>
</tr>
<tr>
<td>No pathologic variant detected</td>
<td>0 (0%)</td>
<td>1 (0.6%)</td>
</tr>
</tbody>
</table>
**Table 2**: Longitudinal multivariable random effects model evaluating kidney function rate of change before and after detection of asymptomatic pyuria in ADPKD patients with slow and rapidly progressing disease.

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N= 687)</th>
<th>MIC 1A-1B (N=270)</th>
<th>MIC 1C-1D-1E (N=417)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimate (95 % CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept, ml/min/1.73m²</td>
<td>122.25 (115.01, 129.49)</td>
<td>141.51 (132.46, 150.56)</td>
<td>127.14 (118.04, 136.24)</td>
</tr>
<tr>
<td>Age at baseline, by year of age</td>
<td>-1.27 (-1.42, -1.12)</td>
<td>-1.44 (-1.61, -1.26)</td>
<td>-1.62 (-1.82, -1.42)</td>
</tr>
<tr>
<td>Male gender (reference is female)</td>
<td>-7.16 (-11.14, -3.19)</td>
<td>2.07 (-3.08, 7.22)</td>
<td>-4.80 (-9.64, -0.04)</td>
</tr>
<tr>
<td>Rate of eGFR change without pyuria, ml/min/1.73m²/year</td>
<td>-2.33 (-2.58, -2.09)</td>
<td>-1.27 (-1.60, -0.94)</td>
<td>-3.04 (-3.37, -2.71)</td>
</tr>
<tr>
<td>Shift in rate of eGFR change after detection of pyuria, ml/min/1.73m²/year</td>
<td>-1.48 (-1.76, -1.19)</td>
<td>-1.79 (-2.23, -1.35)</td>
<td>-1.18 (-1.55, -0.81)</td>
</tr>
<tr>
<td>Rate of eGFR change after detection of pyuria, ml/min/1.73m²/year*</td>
<td>-3.81 (-4.11, -3.51)</td>
<td>-3.06 (-3.46, -2.66)</td>
<td>-4.22 (-4.62, -3.81)</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI – confidence interval, eGFR – estimate glomerular filtration rate, MIC – Mayo Imaging Class

*This is calculated as an addition of the two prior rows and not a unique variable in the model.*
### Table 3: Longitudinal multivariable random effects model evaluating Total Kidney Volume Rate of change before and after detection of asymptomatic pyuria in ADPKD patients with slow and rapidly progressing disease.

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N= 437)</th>
<th>MIC 1A-1B (N=190)</th>
<th>MIC 1C-1D-1E (N= 247)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (95% CI)</td>
<td>Estimate</td>
<td>Estimate (95% CI)</td>
</tr>
<tr>
<td>Intercept, ml/m</td>
<td>287.63 (83.04, 492.22)</td>
<td>121.05 (39.53, 202.58)</td>
<td>-157.58 (-464.63, 149.46)</td>
</tr>
<tr>
<td>Age at baseline, by year of age</td>
<td>11.78 (7.56, 15.99)</td>
<td>5.12 (3.51, 6.73)</td>
<td>32.55 (25.57, 39.53)</td>
</tr>
<tr>
<td>Male gender (reference is female)</td>
<td>52.22 (-57.72, 162.15)</td>
<td>34.87 (-13.60, 83.33)</td>
<td>17.22 (-138.28, 172.73)</td>
</tr>
<tr>
<td>Rate of Ht-TKV change without pyuria (ml/m/yr)</td>
<td>61.87 (52.95, 70.79)</td>
<td>17.40 (12.92, 21.89)</td>
<td>93.57 (80.24, 106.90)</td>
</tr>
<tr>
<td>Shift in rate of Ht-TKV change after detection of pyuria (ml/m/yr)</td>
<td>-2.86 (-15.49, 9.77)</td>
<td>-3.82 (-9.79, 2.16)</td>
<td>3.21 (-17.98, 24.40)</td>
</tr>
<tr>
<td>Rate of Ht-TKV change after detection of pyuria (ml/m/yr)*</td>
<td>59.02 (46.85, 71.18)</td>
<td>13.59 (7.86, 19.32)</td>
<td>96.78 (76.66, 116.90)</td>
</tr>
</tbody>
</table>

CI – confidence interval, Ht-TKV – height-adjusted total kidney volume, MIC – Mayo Imaging Class, ml/m – milliliter per meter

*This is calculated as an addition of the two prior rows and not a unique variable in the model
Figure Legends:

**Figure 1:** Overview of study flow chart and cohort selection depicting patient exclusions and group assignment based on urinalysis results. ADPKD – autosomal dominant polycystic kidney disease, GFR – glomerular filtration rate, hpf – high power field, UA – urinalysis, WBC – white blood cell.

**Figure 2:** A) Kidney survival of patients with MIC Class 1A-1B based on presence (AP) or absence (NP) of asymptomatic pyuria. There was no significant difference in kidney survival between the two groups. B) Kidney survival of patients with MIC Class 1C-1D-1E based on presence (AP) or absence (NP) of asymptomatic pyuria. Significant difference in kidney survival between patient with or without pyuria with median survival of 55 and 59 years, respectively (log-rank p<0.02). MIC: Mayo Imaging Class. NP: No pyuria group, AP: Asymptomatic pyuria.

**Figure 3:** Comparison of all available eGFR by presence of asymptomatic pyuria (AP) or absence of pyuria (NP). Patients are divided into age groups based on the age at time of eGFR. Patients have multiple eGFR values in one or more age group.

**Figure 4:** A) Representative kidney function rate of change plotted longitudinally based on the statistical model. The rate of change in kidney function before pyuria identification (and with persistence absence of pyuria) is depicted as the green line while the rate of change after asymptomatic pyuria identification is depicted as the red line. The star represents time of pyuria identification. After this point a shift in eGFR rate of change (ml/min/1.73m$^2$/yr) (95% CI) of -1.48 (-1.76, -1.19), p<0.001 was noted. B) Representative height-adjusted total kidney volume (Ht-TKV) rate of change plotted longitudinally based on the statistical model. The rate of change in Ht-TKV before pyuria identification (and with persistence absence of pyuria) is depicted as the green line while the rate of change after asymptomatic pyuria identification is depicted as the red line. The star represents time of pyuria identification. After this point a shift in Ht-TKV rate of change (ml/m/yr)(95% CI) of -2.86 (-15.49, 9.77), p=0.66 was noted.
Included from initial Mayo PKD database query
Adult patients with ADPKD and available urinalysis, abdominal imaging, and sequential GFR
N=1068

Imaging post kidney failure (N=62)
UA post kidney failure (N= 109)
Imaging post cyst intervention (N= 90)

Remaining patients for detailed clinical and urinalysis review
N = 807

Patient without pyuria
WBC ≤ 3/hpf on UA
N = 341

GANAB mutation (N=1)

No Pyuria (NP) Group
N = 340

Patients with pyuria
WBC > 3/hpf on UA
N= 466

Infection (N=82)
Bladder tumor (N=3)
Catheterization (N=10)
Contamination (N= 23)
GANAB mutation (N=1)

Asymptomatic Pyuria (AP) Group
N = 347
Figure 2

(A) MIC 1A-1B

Median age at ESKD (95% CI)

NP  86 years (71 - n/a)
AP  80 years (76 - n/a)

Log-Rank, p=0.49

Patients at risk
NP (n= 129)  127  119  96   56   18   6
AP (n= 141)  139  133  118  82   43   6

(B) MIC 1C-1D-1E

Median age at ESKD (95% CI)

NP  59 years (56 - 62)
AP  55 years (54 - 58)

Log-Rank, p=0.02

Patients at risk
NP (n= 211)  200  171  113  48   13   2
AP (n= 206)  196  169  102  35   11   1
Figure 3

![Box plot of eGFR by age group and gender](image)

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>&lt;35</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>≥65</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP Median eGFR (Q1-Q3), ml/min/1.73m²</td>
<td>91.5 (73.4-104.6)</td>
<td>67.8 (47.0-82.4)</td>
<td>55.3 (24.3-78.9)</td>
<td>49.1 (28.4-73.0)</td>
<td>47.9 (27.6-68.0)</td>
</tr>
<tr>
<td>AP Median eGFR (Q1-Q3), ml/min/1.73m²</td>
<td>68 (27-93.3)</td>
<td>55.3 (24.3-78.9)</td>
<td>49.1 (28.4-73.0)</td>
<td>47.9 (27.6-68.0)</td>
<td>41.9 (23.3-64.9)</td>
</tr>
<tr>
<td>NP Mean eGFR ± SD, ml/min/1.73m²</td>
<td>86.1 ± 28.9</td>
<td>64.5 ± 26.9</td>
<td>55.1 ± 31.3</td>
<td>52.7 ± 27.6</td>
<td>49.9 ± 26.8</td>
</tr>
<tr>
<td>AP Mean eGFR ± SD, ml/min/1.73m²</td>
<td>65.6 ± 26.9</td>
<td>55.1 ± 31.3</td>
<td>52.7 ± 27.6</td>
<td>49.9 ± 26.8</td>
<td>46.0 ± 26.3</td>
</tr>
<tr>
<td>N of eGFR values</td>
<td>706</td>
<td>541</td>
<td>1207</td>
<td>1160</td>
<td>1903</td>
</tr>
<tr>
<td>N of unique patients</td>
<td>101</td>
<td>58</td>
<td>174</td>
<td>114</td>
<td>220</td>
</tr>
</tbody>
</table>
Figure 4

Panel A: Graph showing a linear relationship between kidney function (ml/min/1.73m²) and time from baseline eGFR (years). The graph demonstrates a significant decline in kidney function over time for patients with and without pyuria. The dashed line represents patients with asymptomatic pyuria, the solid line represents patients without pyuria. The star symbol indicates the identification of pyuria and its impact on kidney function decline. The p-value is less than 0.001.

Panel B: Graph showing a linear relationship between height-adjusted total kidney volume (ml/m²) and time from baseline Ht-TKV (years). The graph demonstrates an increase in height-adjusted total kidney volume over time for patients with pyuria. The solid line represents patients without pyuria, the dashed line represents patients with asymptomatic pyuria. The star symbol indicates the identification of pyuria and its impact on Ht-TKV growth. The p-value is 0.66.