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 the 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 (AP), 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 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 AP were created.

Results There were 687 included patients (347 AP, 340 NP). The AP group had more women (65% versus 49%). Median ages at kidney failure were 86 and 80 years in the NP and AP groups (log rank, \( P = 0.49 \)), respectively, for patients in Mayo Imaging Class (MIC) 1A–1B as compared with 59 and 55 years for patients in MIC 1C–1D–1E (log rank, \( P = 0.02 \)). Compared with the NP group, the rate of kidney function (ml/min per 1.73 m\(^2\) per year) decline shifted significantly after detection of AP in the models, including all patients (\(-1.48; P < 0.001\)), patients in MIC 1A–1B (\(-1.79; P < 0.001\)), patients in MIC 1C–1D–1E (\(-1.18; P < 0.001\)), and patients with PKD1 (\(-1.04; P < 0.001\)). Models evaluating kidney volume rate of growth showed no change after incidence of AP as compared with the NP group.

Conclusions AP is associated with kidney failure and faster kidney function decline irrespective of the ADPKD gene, cystic burden, and cystic growth. These results support AP 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 radiologic 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 Class (MIC), estimates the intrinsic rate of kidney cyst growth, which translates into various rates of eGFR decline (5–14). However, Ht-TKV explains approximately 42% of the variance for GFR, indicating that other noncystic mechanisms could affect kidney function decline (15). Although 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 polycystic kidney disease (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 (17,25). Asymptomatic pyuria (AP) could be used as a surrogate marker of inflammation in the absence of urinary infection (26).

We sought to evaluate the effect of AP 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 patients with ADPKD seen at the Mayo Clinic (Minnesota, Florida, and Arizona) from January 1992 to January 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 on the basis of Ravine–Pei modified criteria (in the presence of family history) (27) or ≥20 total bilateral kidney cysts without evidence of alternative cystic disease (in the absence of family history), (3) greater than or equal to one available abdominal image (computed tomography [CT]/magnetic resonance imaging [MRI]), (4) greater than or equal to one urinalysis (UA), and (5) greater than or equal to two serum creatinine values. 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 the first available abdominal imaging, and (3) renal cystic disease due to the glucosidase, alpha; neutral AB (GANAB) mutation.

Pyuria was defined as the presence of more than three white blood cells per high-power field (on UA (28)). AP 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 2 preceding months of pyuria identification, (2) urinary contamination defined as more than ten squamous cells per high-power field on UA (29), (3) recent urinary instrumentation, or (4) bladder tumor (30). Patients with any available UA before reaching kidney failure that satisfied the criteria for AP were categorized in the AP group. Patients who had no pyuria (NP) on any UA before reaching kidney failure were categorized into the NP group. 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 record reviews were performed by two medical doctors to obtain demographics, PKD pathologic variant, UA, serum creatinine, Ht-TKV, MIC, and kidney failure or transplant dates (if applicable). Data concerning possible confounders were compared at the time of the classifying UA: body mass index, smoking history, hypertension, number and class of antihypertensive agents, and use of medication that could affect pyuria (systemic steroids, proton pump inhibitors, antibiotics, and nonaspirin nonsteroidal anti-inflammatory drugs). To ascertain other confounder 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, AKI, or cardiovascular disease; visits to the emergency department; 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 were collected until last follow-up or date of ESKD. Baseline kidney function and volume were obtained from the earliest serum creatinine and earliest abdominal imaging (CT/MRI), respectively.

Definitions and Standards

The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate eGFR (31). 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 nonstandardized creatinine measurements is most important when GFR is well preserved and that patients included in this study have low eGFR (31). Kidney failure or ESKD was defined by the initiation of KRT (dialysis or preemptive kidney transplantation).

Abdominal MRI or CT planimetry or stereology was used to calculate total kidney volume (TKV) and standardized to the height to calculate Ht-TKV (milliliters per meter). Different acquisition sequences can introduce variability in measurement of TKV; however, this variability is comparable with 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 (14). MIC was determined using the MIC calculator as detailed by Irazabal et al. (14,32). Ht-TKV rate of growth was analyzed in patients who had two or more abdominal images with ≥1-year interval.

The entire coding and flanking intronic regions of PKD1 and PKD2 were screened for pathologic variants by Sanger or next generation sequencing (33–36). Patients were classified as follows: PKD1 truncating, PKD1 nontruncating, PKD2, and GANAB (37–39).

Statistical Methods

Descriptive statistics were performed utilizing Wilcoxon rank sum tests and Pearson chi-squared tests to compare
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

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)

No Pyuria (NP) Group
N = 340

Asymptomatic Pyuria (AP) Group
N = 347

Figure 1. | Overview of the study flow chart and cohort selection depicting patient exclusions and group assignment on the basis of urinalysis (UA) results. ADPKD, autosomal dominant polycystic kidney disease; GANAB, glucosidase, alpha; neutral AB; hpf, high-power field; PKD, polycystic kidney disease; WBC, white blood cell.

Results
Among 1068 adult patients with ADPKD, UA, 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 AP with no evidence of UTI or contamination. For the 681 patients included in analysis, there were 13,209 eGFR measurements (median = 11; interquartile range [IQR], 5–23) per patient), 1918 Ht-TKV measurements (median = 3; IQR, 2–6 per patient), and 2547 UAs (median = 2; IQR, 1–4 per patient). Median follow-up was 3 (IQR, 1–8) years.

Demographic, clinical, and genotypic characteristics comparing the NP and AP groups are summarized in Table 1. The AP group had more women (65% versus 49%) and White patients (92% versus 89%) as compared with the NP group. Median age at classifying UA was not different...
between the NP (48.8 years) and AP (48.8 years) groups. Body mass index, 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 nonurinary infections was seen more in patients with AP (7% versus 4%). Median age at first available eGFR (45.6 versus 45.4 years) and median age at first available Ht-TKV (43.3 versus 44.7 years) were not different between the NP and AP groups, respectively. Median first available eGFR (ml/min per 1.73 m²) was not significantly different between the NP (65.5) and AP (60.9) groups. 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 AP on kidney survival after stratification by MIC. For patients with MIC 1A–1B, the median ages at ESKD were 86 and 80 years in NP and AP groups, respectively (log rank, P = 0.49) (Figure 2A). Interestingly, for patients with MIC 1C–1D–1E, those with AP had significantly worse kidney survival than those who had NP, with median age at ESKD of 59 versus 55 years for NP and AP groups, respectively (log rank, P = 0.02) (Figure 2B). When compared with patients with NP, those with AP had lower eGFR but similar Ht-TKV across all of the age groups (Figure 3, Supplemental Figure 1). Similar trends of eGFR at last follow-up have been noted when patients are

Table 1. Demographic, clinical, and genotypic characteristics of patients with autosomal dominant polycystic kidney disease with or without asymptomatic pyuria

| Characteristics | No Pyuria, N=340 | Asymptomatic Pyuria, N=347 |
|-----------------|-----------------|---------------------------|
| Women, n (%)    | 168 (49.4%)     | 226 (65.1%)               |
| White, n (%)    | 302 (88.8%)     | 320 (92%)                 |
| Age at classifying UA, yr, median (Q1, Q3) | 48.8 (39.8, 57.0) | 48.8 (40.5, 58.0) |
| No. of UAs per patient, median (Q1, Q3) | 2 (1, 3) | 3 (2, 6) |
| Positive leukocyte esterase, n (%) | 21 (6.2%) | 37 (10.7%) |
| Positive nitrite, n (%) | 21 (6.2%) | 28 (8.1%) |
| BMI, kg/m², median (Q1, Q3) | 26.8 (23.7, 30.3) | 27.4 (23.7, 30.9) |
| History of smoking, n (%) | 17 (5%) | 25 (7%) |
| Hypertension, n (%) | 255 (75.2%) | 274 (79%) |
| Count of antihypertensives, median (Q1, Q3) | 2.0 (1.0, 3.0) | 2.0 (1.0, 2.0) |
| Other medication use, n (%) | | |
| PPI | 52 (15.3%) | 45 (13%) |
| Systemic steroids | 7 (2.1%) | 10 (3%) |
| NSAIDs | 19 (5.6%) | 25 (7%) |
| Antibiotics | 12 (3.5%) | 25 (7%) |
| Baseline eGFR, ml/min per 1.73 m², median (Q1, Q3) | 65.5 (36.7, 83.4) | 60.6 (36.9, 79.0) |
| Age at baseline eGFR, yr, median (Q1, Q3) | 45.6 (36.6, 53.9) | 45.5 (36.5, 54.3) |
| No. of eGFR measurements per patient, median (Q1, Q3) | 9.0 (5.0, 20.0) | 13.0 (6.0, 27.5) |
| CKD stage at classifying UA, n (%) | | |
| 1 | 67 (19.7%) | 48 (13.8%) |
| 2 | 122 (35.9%) | 125 (36%) |
| 3 | 87 (25.6%) | 106 (31%) |
| 4 | 44 (12.9%) | 46 (13%) |
| 5 | 20 (5.9%) | 23 (7%) |
| Kidney failure, n (%) | 111 (33%) | 141 (41%) |
| Age at kidney failure, yr, median (Q1, Q3) | 55.8 (49.5, 63.1) | 53.4 (44.6, 61.0) |
| Baseline Ht-TKV, ml/m, median (Q1, Q3) | 600.4 (342.2, 1093.0) | 616.7 (358.5, 990.1) |
| Age at baseline Ht-TKV, yr, median (Q1, Q3) | 43.3 (33.4, 52.9) | 44.8 (36.8, 54.3) |
| Mayo Imaging Class, n (%) | | |
| 1A | 41 (12%) | 58 (17%) |
| 1B | 88 (26%) | 83 (24%) |
| 1C | 105 (31%) | 91 (26%) |
| 1D | 69 (20%) | 66 (19%) |
| 1E | 37 (11%) | 49 (14%) |
| No. of Ht-TKV measurements per patient, median (Q1, Q3) | 3.0 (2.0, 5.0) | 3.0 (2.0, 6.0) |
| Genotype, n (%) | | |
| PKD1 | 144 (43%) | 158 (46%) |
| PKD1NT1 | 74 (21%) | 76 (22%) |
| PKD1NT2 | 24 (7%) | 30 (9%) |
| PKD2 | 22 (6%) | 31 (10%) |
| No pathologic variant detected | 0 (0%) | 1 (0.6%) |

UA, urinalysis; Q, quartile; BMI, body mass index; PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug; No., Number; Ht-TKV, height-adjusted total kidney volume; PKD1T, PKD1 truncating; PKD1NT1, PKD1 nontruncating 1; PKD1NT2, PKD1 nontruncating 2.
Figure 2. | Patients at risk of rapid progression had worse kidney survival when asymptomatic pyuria was present. (A) Kidney survival of patients with Mayo Imaging Class (MIC) 1A–1B on the basis of the presence of asymptomatic pyuria (AP) or the absence of AP (no pyuria [NP]). There was no significant difference in kidney survival between the two groups. (B) Kidney survival of patients with MIC 1C–1D–1E on the basis of AP or NP. There was a significant difference in kidney survival between patients with or without pyuria, with median survival of 55 and 59 years, respectively (log rank, \( P = 0.02 \)). 95% CI, 95% confidence interval.

![Graph of kidney survival for MIC 1A-1B](image1)

![Graph of kidney survival for MIC 1C-1D-1E](image2)

**Patients at risk**

|            | NP (n = 129) | AP (n = 141) |
|------------|--------------|--------------|
| NP (n = 129) | 127 119 96 56 18 6 | 139 133 118 82 43 6 |
| AP (n = 141) | 139 133 118 82 43 6 | 18 43 6 |

**Figure 3. | Patients with asymptomatic pyuria had lower eGFR in all age groups.** Patients are divided into age groups on the basis of the age at the time of eGFR. Patients have multiple eGFR values in one or more age group. Q, quartile.

| Age group, years | <35 | 35–44 | 45–54 | 55–64 | ≥65 |
|------------------|-----|-------|-------|-------|-----|
|                   | NP  | AP    | NP    | AP    | NP  |
| Median eGFR (Q1–Q3), ml/min/1.73m² | 91.5 (73.4–104.6) | 68 (27–93.3) | 67.8 (47.0–82.4) | 55.3 (24.3–78.9) | 49.1 (28.4–73.0) |
| Mean eGFR ± SD, ml/min/1.73m² | 86.1 ± 28.9 | 64.5 ± 26.9 | 65.6 ± 26.9 | 55.1 ± 31.3 | 52.7 ± 27.6 |
| N of eGFR values | 706 | 541 | 1207 | 1160 | 1903 |
| N of unique patients | 101 | 58 | 174 | 114 | 220 |
Effect of Pyuria on Rate of Kidney Function Decline

After adjusting for age and sex in a longitudinal multivariate model ($n=687$), occurrence of AP was associated with worsening in annual eGFR rate of decline (ml/min per 1.73 m² per year) as compared with patients with NP ($-3.81$ versus $-2.33$), representing a shift of $-1.48$ following identification of AP ($P<0.001$) (Figure 4A, Table 2). When the patients were stratified into separate models for slow (MIC 1A–1B) and rapid progressors (MIC 1C–1D–1E), a similar shift was observed (Table 2). Patients with MIC 1A–1B had an eGFR rate of decline (ml/min per 1.73 m²) of $-1.27$ prior and $-3.06$ after identification of AP, representing with a shift of $-1.79$ ($P<0.001$) (Table 2). Patients with MIC 1C–1D–1E had an eGFR rate of decline (ml/min per 1.73 m²) of $-3.04$ prior and $-4.22$ after detection of AP, with a shift of $-1.18$ ($P<0.001$) (Table 2, Supplemental Figure 4A). The eGFR slopes for individual patients are plotted in Supplemental Figure 5.

We then evaluated for additional effect of PKD genotype on the association of AP with kidney function decline. Patients with PKD1 pathologic variants ($n=257$) had an annual eGFR rate of decline (ml/min per 1.73 m² per 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 per 1.73 m² per year, which is slower by 0.95 as compared with patients with PKD1 pathologic variants ($P=0.02$). AP continued to be associated with a faster rate of eGFR decline ($-3.06$ versus $-1.92$ ml/min per 1.73 m²; $P<0.001$) in patients with PKD2 pathologic variants. PKD genotype had no additional effect on how AP 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, proton pump inhibitors, antibiotics, or non-steroidal anti-inflammatory drugs (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 AP continued to be associated with worsening in annual eGFR rate of decline (ml/min per 1.73 m² per year) as compared with patients with NP ($-3.79$ versus $-2.33$), representing a shift of $-1.46$ following identification of AP ($P<0.001$) (Supplemental Table 4).

Effect of Pyuria on the Rate of Kidney Volume Growth

To assess whether AP worsens kidney function through cystic enlargement mechanisms, we evaluated the effect of AP on the rate of kidney growth ($n=439$). After adjusting for age and sex, occurrence of AP was not associated with worsening in annual Ht-TKV rate of growth: 59.02 versus 61.87 ml/m per year prior to identification of pyuria. This represented a nonsignificant shift of $-2.86$ following identification of pyuria ($P=0.66$) (Figure 4B, Table 3). When the patients were stratified into separate models for slow (MIC 1A–1B) and rapid progressors (MIC 1C–1D–1E), the effect of pyuria on kidney growth remained neutral (Table 3).
Table 2. Longitudinal multivariable random effects model evaluating kidney function rate of change before and after detection of asymptomatic pyuria in patients with autosomal dominant polycystic kidney disease with slow and rapidly progressing disease

|                      | All Patients, N=687 | Mayo Imaging Class 1A–1B, N=270 | Mayo Imaging Class 1C–1D–1E, N=417 |
|----------------------|---------------------|----------------------------------|-----------------------------------|
| **Intercept, ml/min per 1.73 m²** | 122.25 (115.01 to 129.49) | 141.51 (132.46 to 150.56) | 127.14 (118.04 to 136.24) |
| **Age at baseline, yr** | −1.27 (−1.42 to −1.12) | −1.44 (−1.61 to −1.26) | −1.62 (−1.82 to −1.42) |
| **Men (reference is women)** | −7.16 (−11.14 to −3.19) | 2.07 (−3.08 to 7.22) | 0.43 |
| **Rate of eGFR change without pyuria, ml/min per 1.73 m² per year** | −2.33 (−2.58 to −2.09) | −1.27 (−1.60 to −0.94) | −3.04 (−3.37 to −2.71) |
| **Shift in rate of eGFR change after detection of pyuria, ml/min per 1.73 m² per year** | −1.48 (−1.76 to −1.19) | −1.79 (−2.23 to −1.35) | −1.18 (−1.55 to −0.81) |
| **Rate of eGFR change after detection of pyuria, ml/min per 1.73 m² per year** | −3.81 (−4.11 to −3.51) | −3.06 (−3.46 to −2.66) | −4.22 (−4.62 to −3.81) |

*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 patients with autosomal dominant polycystic kidney disease with slow and rapidly progressing disease

|                      | All Patients, N=437 | MIC 1A–1B, N=190 | MIC 1C–1D–1E, N=247 |
|----------------------|---------------------|------------------|---------------------|
| **Intercept, ml/m**  | 287.63 (83.04 to 492.22) | 121.05 (39.53 to 202.58) | −157.58 (−464.63 to 149.46) |
| **Age at baseline, yr of age** | 11.78 (7.56 to 15.99) | 5.12 (3.51 to 6.73) | 32.55 (25.57 to 39.53) |
| **Men (reference is women)** | 52.22 (−57.72 to 162.15) | 34.87 (−13.60 to 83.33) | 17.22 (−138.28 to 172.73) |
| **Rate of Ht-TKV change without pyuria, ml/m per yr** | 61.87 (52.95 to 70.79) | 17.40 (12.92 to 21.89) | 93.57 (80.24 to 106.90) |
| **Shift in rate of Ht-TKV change after detection of pyuria, ml/m per yr** | −2.86 (−15.49 to 9.77) | −3.82 (−9.79 to 2.16) | 3.21 (−17.98 to 24.40) |
| **Rate of Ht-TKV change after detection of pyuria, ml/m per yr** | 50.02 (46.85 to 71.18) | 13.59 (7.86 to 19.32) | 96.78 (76.66 to 116.90) |

*Ht-TKV, height-adjusted total kidney volume.

*This is calculated as an addition of the two prior rows and not a unique variable in the model.
Patients with MIC 1A–1B had an annual Ht-TKV rate of growth of 17.40 compared with 13.59 ml/m per year after detection of AP, a nonsignificant shift of −3.82 (P=0.21) (Table 3). Similarly, detection of pyuria in patients with MIC 1C–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 ml/m per year compared with 96.78 ml/m per year after detection of AP, a nonsignificant shift of 3.21 (P=0.77) (Table 3, Supplemental Figure 4B). The Ht-TKV slopes for individual patients are plotted in Supplemental Figure 6.

Discussion

In this large cohort study of patients with ADPKD, AP is associated with faster kidney function decline irrespective of PKD genotype, cystic burden, or cystic growth. This decline occurred after detection of AP without significant changes in the 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 AP reached kidney failure at younger age compared with those with NP. These results support the use of AP 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 (40). Cysts are surrounded by immune cells with complex interactions between those that promote (M2-like macrophages) and others that inhibit cyst growth (CD8+ cytotoxic T cells) (24,41). Monocyte chemoattractant protein-1 (MCP-1) expression promoted macrophage accumulation and cystic dilation (42–44). Depleting macrophages in PKD mice lowered their cystic index and improved their kidney function as compared with controls (20). Urinary MCP-1 concentrations were higher in patients with ADPKD before an appreciable increase in serum creatinine (45). Increase in tubular MCP-1 excretion is an early event in the pediatric ADPKD population and an early marker of disease severity (46). 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 (47,48). Urinary T cells correlated moderately with renal function decline in a small cohort of patients with ADPKD, 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 on the basis of 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 with other urinary biomarkers.

Urologic 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 APDKD in the context of a genitourinary infection (50–53), with UTI linked to faster progression of disease in small retrospective studies (54–56). Pyuria has also been associated with increased risk of kidney failure in patients without APDKD with CKD stages 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 with expected rates for patients with similar cystic burden and PKD pathologic variants with significantly faster kidney function decline identified after detection of AP. Notably, this shift in rate of decline persisted in patients with low cystic burden. Patients with MIC 1A–1B are thought to be slow progressors who might benefit less from treatments modifying mechanisms of cystic growth. However, a subcategory of patients with MIC 1A–1B and inflammatory predictors might benefit from treatments modulating inflammation. This further illustrates how biomarkers may allow an individualized and mechanism-specific treatment of APDKD using disease-modifying therapies.

However, it is critical to note that the presence of AP should not be used in isolation but rather, to enhance prognostication provided by currently available tools, such as imaging-based (MIC) or genetic-based (PROPKD score) prognosticators. Although 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 AP 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 MIC 1A–1B and AP might develop faster kidney function decline than otherwise predicted. Therapeutics targeting inflammation are likely to benefit all patients with APDKD, 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. First, our study might have underdiagnosed the occurrence of AP if it occurred outside the medical care at Mayo Clinic or if AP occurred during gaps between measured UA. Genetic analysis was not available for the entire cohort. Despite all of the efforts in excluding other factors that could affect pyuria, AP is not specific and could be affected by other factors that could have been elusive to chart review. Most patients in this cohort were White; 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 the 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. Although 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 is supported by several previously published studies in two small cohorts of patients with ADPKD and a large non-ADPKD cohort (49,56,57). These studies support the 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 cohorts, with only 11%–22% of patients progressing to an immediate higher class (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 white blood cells is a readily available and inexpensive tool that can be used to assess for inflammation in the form AP. If identified, AP 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.

Disclosures

C. Hanna reports consultancy agreements with Horizon Therapeutics and honoraria from Horizon Therapeutics. P.C. Harris reports consultancy agreements with Mitobridge, Otsuka, Regulus, and Vertex; research funding from Acceleron, Jemincare, Navitor, Otsuka Pharmaceuticals, and Palladio Biosciences; patents and inventions with Amgen, Bayer, Genzyme, GlaxoSmithKline, Millipore, Mitobridge, and Vertex; honoraria from Otsuka Pharmaceuticals and Vertex Pharmaceuticals; and serving on the clinical advisory board of Mironid. P.J. Schulte reports other interests/relationships with OxThera. S.R. Senum reports ownership interest in companies targeting in inflammation with the presence of asymptomatic pyuria, age, sex, and MIC category. P.J. Schulte, S.R. Senum, and D. Zubidat were responsible for formal analysis; F.T. Chebib, B.E. Jones, and Y.G. Mkhaimer were responsible for methodology; F.T. Chebib, B.E. Jones, and Y.G. Mkhaimer were responsible for project administration; F.T. Chebib, was responsible for resources; F.T. Chebib and B.E. Jones were responsible for visualization; P.C. Harris and V.E. Torres were responsible for funding acquisition; F.T. Chebib, B.E. Jones, and Y.G. Mkhaimer provided supervision; F.T. Chebib, B.E. Jones, Y.G. Mkhaimer, and I.J. Rangel wrote the original draft; and F.T. Chebib, C. Hanna, P.C. Harris, B.E. Jones, Y.G. Mkhaimer, I.J. Rangel, P.J. Schulte, S.R. Senum, V.E. Torres, and Z.M. Zoghby reviewed and edited the manuscript.

Supplemental Material

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Supplemental Figure 1. Ht-TKV by the presence of asymptomatic pyuria and age group.

Supplemental Figure 2. eGFR by the presence of asymptomatic pyuria, age group, and MIC category.

Supplemental Figure 3. Ht-TKV by the presence of asymptomatic pyuria, age group, and MIC category.

Supplemental Figure 4. Kidney function and Ht-TKV rate of change by MIC and effect of pyuria.

Supplemental Figure 5. eGFR slopes for individual patients by the presence of asymptomatic pyuria, age, sex, and MIC category.

Supplemental Figure 6. Ht-TKV slopes for individual patients by the presence of asymptomatic pyuria, age, sex, and MIC category.

Supplemental Table 1. Additional clinical characteristics of patients with ADPKD with or without asymptomatic pyuria.

Supplemental Table 2. Longitudinal multivariable random effects model evaluating the effect of the PKD genotype on kidney function rate of change before and after detection of asymptomatic pyuria in patients with ADPKD.

Supplemental Table 3. Longitudinal multivariable random effects model evaluating kidney function rate of change before and after detection of asymptomatic pyuria in patients with ADPKD with or without medications that could affect the occurrence of pyuria.

Supplemental Table 4. Longitudinal multivariable random effects model evaluating kidney function rate of change before and after detection of asymptomatic pyuria in patients with ADPKD with slow and rapidly progressing disease, including additional clinical factors that could confound occurrence of pyuria.

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F.T. Chebib, B.E. Jones, and Y.G. Mkhaimer conceptualized the study; F.T. Chebib, M. Chedid, A.V. Gregory, P.C. Harris, B.E. Jones, T.L. Kline, Y.G. Mkhaimer, A.K. Mohamed, R.M. Neal, A.K. Randhawa, L.J. Rangel, P.J. Schulte, S.R. Senum, and D. Zubidat were responsible for data curation; F.T. Chebib, B.E. Jones, Y.G. Mkhaimer, and L.J. Rangel were responsible for investigation; F.T. Chebib, M. Chedid, A.V. Gregory, P.C. Harris, B.E. Jones, T.L. Kline, Y.G. Mkhaimer, A.K. Mohamed, R.M. Neal, A.K. Randhawa, L.J. Rangel, P.J. Schulte, S.R. Senum, and D. Zubidat were responsible for formal analysis; F.T. Chebib, B.E. Jones, and Y.G. Mkhaimer were responsible for project administration; F.T. Chebib, was responsible for resources; F.T. Chebib and B.E. Jones were responsible for visualization; P.C. Harris and V.E. Torres were responsible for funding acquisition; F.T. Chebib, B.E. Jones, and Y.G. Mkhaimer provided supervision; F.T. Chebib, B.E. Jones, Y.G. Mkhaimer, and I.J. Rangel wrote the original draft; and F.T. Chebib, C. Hanna, P.C. Harris, B.E. Jones, Y.G. Mkhaimer, I.J. Rangel, P.J. Schulte, S.R. Senum, V.E. Torres, and Z.M. Zoghby reviewed and edited the manuscript.

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