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Clinical Features of 167 Inpatients with Autosomal Dominant Polycystic Kidney Disease at a Single Center in China

Anhui Province PKD Center, Institute/Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, P.R. China

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCE **Jialin Meng***
ABCE **Yuchen Xu***
BD **Ao Li**
BDG **Song Fan**
BD **Xufeng Shen**
BD **Dongyue Ma**
F **Li Zhang**
F **Zongyao Hao**
F **Xiansheng Zhang**
AFG **Chaozhao Liang**

* These authors contributed equally to this work

Corresponding Author: Chaozhao Liang, e-mail: liang_chaozhao@ahmu.edu.cn

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Background: The aim of this study was to describe the clinical characteristics of Chinese ADPKD inpatients and to identify the factors associated with disease severity.


Material/Methods: We included 167 hospitalized patients (inpatients) with ADPKD in this study. Multiple regression analyses were conducted to determine factors correlated with estimated glomerular filtration rate (eGFR). Patients were stratified into subgroups according to the presence of symptoms, in which clinical parameters were analyzed and compared.

Results: The mean age of hospitalized ADPKD patients was 48.7 years old, lumbar and/or abdominal pain was seen in 40.12% of patients, following by nephrolithiasis (38.92%), hematuria (30.54%), and urinary tract infection (24.55%). Serum thrombocyte level and hemoglobin exhibited significant positive correlations with eGFR. Symptomatic patients accounted for 71.26% of the studied population. Patients with hypertension had increased risk of presence of symptoms (OR=2.794, 95%CI=1.341–5.822). Low thrombocyte and hemoglobin levels were observed in patients with hematuria.

Conclusions: Thrombocyte level was positively correlated with eGFR but was not associated with presence of PKD-related symptoms, suggesting thrombocyte level might be an independent serum biomarker for disease progression. Hypertension was associated with increased risk of symptom occurrence, indicating the relationship between hypertension and disease progression. This study reveals the clinical characteristics of inpatients with ADPKD in China and provides clinicians with useful insights into this intractable disease.

MeSH Keywords: **Signs and Symptoms • Glomerular Filtration Rate • Polycystic Kidney, Autosomal Dominant • Urologic Surgical Procedures**

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Background

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. Progressively enlarged cysts impair the renal parenchyma, resulting in renal function damage, and ultimately leading to end-stage renal disease (ESRD) [1]. The extrarenal manifestations of ADPKD include hepatic and pancreatic cysts, intracranial aneurysms, cardiac abnormalities, and inguinal hernia [2]. Diverse morbidities (incidence rates from 1/4000 to 1/400) have been reported in different regions of the world, and the European incidence of the disease was recently reported to be 1/2500 [1,3,4]. More than half of ADPKD patients develop ESRD at 50–60 years old, making ADPKD the fourth leading cause of ESRD [3].

ADPKD is caused by mutations in 2 different genes: approximate 85% in *PKD1* and 15% in *PKD2* [5,6]. However, recent Chinese studies reported a lower incidence (<10%) of *PKD2* mutations [7–9]. In addition, approximately 10% of patients diagnosed with ADPKD via clinical features have no mutation detected in either *PKD1* or *PKD2* gene [5,10]. The latest study reported that mutations in the gene encoding the glucosidase II α subunit (*GANAB*) induces ADPKD phenotypes and might be another causal gene [10–12]. *PKD1* mutations lead to more severe symptoms and earlier onset of ESRD compared to *PKD2* mutations [13]. In addition to genetic background, ADPKD progression is also associated with other factors such as ischemic kidney injury [14,15] and nephrotoxicity [16].

ADPKD patients usually do not exhibit obvious symptoms at the early stage of the disease. Along with the disease progression, patients present lumbar/abdominal pain caused by enlarged kidneys or accompanying nephrolithiasis, hematuria induced by vessel aneurysms or endothelial impairment, and fever due to renal cyst infection. Clinical manifestations and prognosis have been well characterized in developed countries, but ADPKD is often clinically overlooked at its early stage in most developing countries. In China, there are 1.5 million people with this life-threatening disease [17]. Although several recent studies have deepened the understanding of ADPKD in China [9,18–21], huge gaps still exist in ADPKD research between Western countries and China, particularly in central China.

Material and Methods

Study population

From January 2012 to December 2016, 178 inpatients at the First Affiliated Hospital of Anhui Medical University who were clinically diagnosed with ADPKD were included in this study. The diagnosis was based on the Japanese criteria for patients with

unknown genotype (*PKD1* or *PKD2*) [22]. Data of patients at admission time were extracted from medical records of the hospital, including general information, laboratory tests, imaging examinations, and clinical features. We excluded 12 patients because of incomplete clinical information. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation to evaluate renal function [23]. Patients with PKD-related symptoms at admission, including lumbar and/or abdominal pain, hematuria, urinary tract infection, and nephrolithiasis, were regarded as symptomatic. Surgical treatments for PKD included cyst decortication and cyst puncture. All clinical data were anonymized before use.

Statistical analysis

The data were statistically evaluated using SPSS V.22.0 (Chicago, IL, USA). Means, standard deviation, and percentage were used to describe the distribution of demographic and clinical parameters. To investigate the correlations between eGFR and major clinical parameters, Spearman's rho test and partial correlation analysis were performed between eGFR and each parameter, then multiple linear regression analysis was performed to verify the correlation between eGFR and clinical parameters that had statistical significance ($P < 0.05$) in the preceding partial correlation analysis. Shapiro-Wilk analysis was performed to determine normality of variables. Numerical variables with normal distribution and equal variance were evaluated by the *t* test, while those with non-normal distribution were compared by the Mann-Whitney U test. For multiple statistical tests using the same dataset as in Figure 1A and 1B, thrombocyte and hemoglobin levels in the 3 groups of ADPKD patients with impaired eGFR were compared with those in patients with eGFR over 90 mL/min/1.73 m². *P* value was adjusted by Bonferroni correction with $P_{\text{Adjust}} = P \text{ value} * 3$ (number of independent tests). Categorical variables were assessed by chi-square test. Correlation between the presence of related symptoms and clinical parameters was assessed by logistic regression analysis. With 95% confident interval, $P < 0.05$ was considered to be statistically significant.

Results

General characteristics of the ADPKD patients

In total, 167 ADPKD inpatients (72 males and 95 females) with evaluable clinical information were analyzed in the study. Clinical features of the patients are shown in Table 1. Patients admitted to hospital had an average age of 48.7 (16–78) years. Hypertension and polycystic liver disease were found in 84 (50.30%) and 88 (52.69%) cases, respectively. There were 119 (71.26%) who patients exhibited 1 or more PKD-related symptoms. Lumbar and/or abdominal pain was the most frequent symptom and was seen in 40.12% of patients, followed

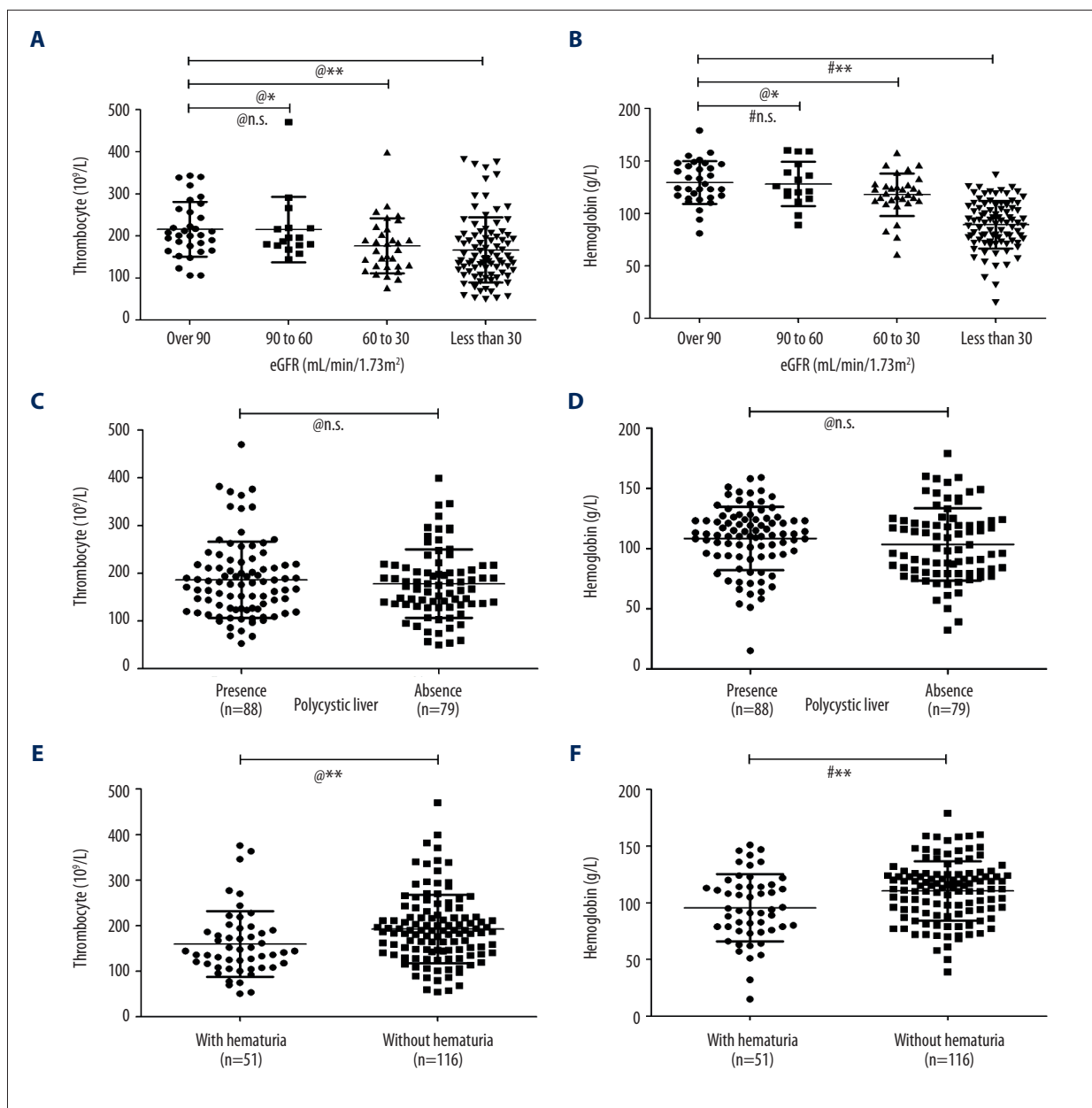


Figure 1. Thrombocyte and hemoglobin levels in the ADPKD inpatients. **(A, B)** Thrombocyte and hemoglobin levels in 3 groups of ADPKD patients with impaired eGFR were compared with those in patients with eGFR over 90 mL/min/1.73 m², P_{adjust} was calculated by 3* P value according to Bonferroni correction. **(C, D)** Comparison of thrombocyte and hemoglobin levels in ADPKD patients with and without polycystic liver. **(E, F)** Comparison of thrombocyte and hemoglobin levels in ADPKD patients with and without hematuria. # t test; @ Mann-Whitney U test; * $P < 0.05$; ** $P < 0.01$.

by hematuria (30.54%) and urinary tract infection (24.55%). Nephrolithiasis was found in 65 (38.92%) ADPKD patients. The remaining 48 (28.74%) patients without symptoms were hospitalized for further investigation because of an accidental finding of polycystic kidney via physical examination. Blood tests showed that the patients had an average leukocyte count of $6.75 \times 10^9/L$, thrombocyte count of $182.58 \times 10^9/L$, and hemoglobin level of 10^6 g/L. Mean serum creatinine level of ADPKD

patients was $308.56 \mu\text{mol/L}$ and calculated eGFR was $42.81 \text{ mL/min/1.73 m}^2$, indicating impaired renal function. In addition, 43 (25.75%) patients received surgical treatment during hospitalization.

Table 1. Clinical features of the ADPKD patients in this study (mean ±SD or percentage).

Total(n=167)	
Demographic features	
Age (years)	48.66±10.57
Age at diagnosis (years)	41.60±12.34
Gender(male/female)	72/95
Positive family history	65 (38.92%)
Blood test parameters	
Leukocytes (10 ⁹ /L)	6.75±3.03
Thrombocytes (10 ⁹ /L)	182.58±75.74
Hemoglobin (g/L)	105.97±28.15
Total protein (g/L)	67.43±7.98
Albumin (g/L)	39.81±6.90
Globulin (g/L)	27.63±4.35
Creatinine (μmol/L)	308.56±290.47
eGFR (mL/min/1.73 m ²)	42.81±38.12
Clinical features	
Hypertension (%)	84 (50.30%)
Polycystic liver (%)	88 (52.69%)
Presence of related symptoms (%)	119 (71.25%)
Nephrolithiasis (%)	65 (38.92%)
Flank pain (%)	67 (40.12%)
Hematuria (%)	51 (30.54%)
Urinary tract infection (%)	41 (24.55%)
Surgical treatment (%)	43 (25.75%)

eGFR – estimated glomerular filtration rate.

Correlation between eGFR and clinical parameters in the ADPKD patients

eGFR is the fundamental indicator in assessment of renal disease progression and therapeutic effects. We therefore analyzed the correlations between eGFR and diverse clinical parameters in the ADPKD patients (Table 2). No correlation was found between eGFR and polycystic liver, leukocytes, albumin, globulin, or presence of related symptoms in the patients. Partial correlation analysis showed that age ($P=0.029$) and hypertension ($P=0.021$) were negatively correlated with eGFR, while female gender ($P=0.035$), thrombocyte ($P=0.001$), and hemoglobin ($P<0.001$) were positively correlated with eGFR. To further validate these 5 clinical parameters, multiple linear regression analysis was performed. The result revealed that the associations between eGFR and these parameters were still

statistically significant (Table 2, right column), suggesting that hypertension, thrombocyte, and hemoglobin are independent correlation factors of eGFR in ADPKD patients.

Hypertension increased risk of PKD-related symptoms

In a total of 167 patients, 48 (28.74%) were admitted to hospital for further investigation because of physical examination-detected renal cysts while without symptoms. All of the other 119 (71.26%) patients presented PKD-related symptoms, including lumbar and/or abdominal pain, hematuria, urinary tract infection, and nephrolithiasis. Because symptoms are the main cause of hospitalization, we then evaluated the correlations between symptoms and clinical parameters in ADPKD patients (Table 3). The results showed that patients with hypertension account for the largest proportion of patients with related symptoms ($P=0.017$). Compared to patients without hypertension, patients with hypertension were more likely to have symptoms (OR=2.794, 95% CI=1.341–5.822). It is not surprising that leukocyte and hemoglobin levels were also correlated with presence of symptoms, because these symptoms are usually associated with inflammation and hemorrhage. Interestingly, thrombocyte count did not correlate with presence of symptoms, indicating that thrombocyte count is barely influenced by PKD-related events. Combined with the result that thrombocyte count is positively correlated with eGFR, thrombocyte count might be an independent serum biomarker related to disease progression.

Thrombocyte count is correlated with hematuria but not polycystic liver

Both thrombocyte and hemoglobin levels exhibited negative correlations with eGFR; therefore, we divided the patients into 4 groups according to eGFR to further assess correlations (Figure 1A, 1B). Patients with eGFR in the range of 60–30 and less than 30 mL/min/1.73 m² had significantly lower hemoglobin levels compared to patients with eGFR over 60 mL/min/1.73 m² ($P_{\text{Adjust}(60 \text{ to } 30 \text{ vs. over } 90)}=0.041$, $P_{\text{Adjust}(less \text{ than } 30 \text{ vs. over } 90)}=0.001$), which may be attributed to renal anemia. Thrombocyte showed a similar pattern to that of hemoglobin in ADPKD patients ($P_{\text{Adjust}(60 \text{ to } 30 \text{ vs. over } 90)}<0.001$, $P_{\text{Adjust}(less \text{ than } 30 \text{ vs. over } 90)}<0.001$). However, thrombocyte and hemoglobin levels showed no difference between patients with and without cystic liver (Figure 1C, $P=0.749$; Figure 1D, $P=0.169$). To assess potential effects of decreased thrombocytes, thrombocyte levels between patients with and without hematuria were analyzed. Although thrombocyte level showed no correlation with presence of overall symptoms, it did decline in patients with hematuria (Figure 1E, $P=0.002$), suggesting decreased thrombocyte level might associate with hemorrhagic complications. Hemoglobin level showed the same change in patients with hematuria (Figure 1F, $P=0.001$).

Table 2. Correlation analysis between eGFR and major clinical parameters in ADPKD patients.

Parameters	eGFR		Multiple linear regression	
	Adjust R	P	β	P
Age	-0.172	0.029*	-0.504	0.020*
Female gender	0.167	0.035*	9.259	0.045*
Hypertension	-0.182	0.021*	-10.497	0.018*
Polycystic liver	0.041	0.601		
Leukocyte	-0.037	0.643		
Thrombocyte	0.261	0.001**	0.084	0.005*
Hemoglobin	0.547	<0.001**	0.823	<0.001**
Albumin	0.052	0.507		
Globulin	-0.138	0.080		
Related symptoms	0.082	0.305		

Correlations between eGFR and major clinical parameters were assessed by Spearman rho test and adjusted by partial correlation analysis. Multiple linear regression was performed to validate these identified parameters. * P<0.05; ** P<0.01.

Table 3. Correlation analysis between symptoms and clinical parameters in ADPKD patients.

	With related symptoms	Without related symptoms	P	Logistic regression	
				P	OR
Total	119	48			
Age (years)	48.98±10.05	47.85±11.85	#0.658	0.286	
Gender (male/female, %)	45/74	27/21	§0.038*	0.161	
Hypertension (%)					
Yes	67 (56.3)	17 (35.4)	§0.017*	0.006**	2.794
No	52 (43.7)	31 (64.6)			
Polycystic liver (%)					
Yes	60 (50.4)	28 (58.3)	§0.395	0.354	
No	59 (49.6)	20 (41.7)			
Leukocyte (10 ⁹ /L)	7.05±3.35	5.98±1.87	#0.126	0.027*	1.194
Thrombocyte (10 ⁹ /L)	184.35±80.42	178.79±63.22	#0.997	0.867	
Hemoglobin (g/L)	102.65±26.39	114.21±30.86	#0.022*	0.013*	0.983
Albumin (g/L)	39.42±7.20	40.77±6.04	#0.106	0.938	
Globulin (g/L)	28.08±4.78	26.50±3.84	®0.034*	0.342	
eGFR (mL/min/1.73m ²)	42.16±3.56	44.43±5.31	#0.728	0.260	

Correlations between the presence of related symptoms and clinical parameters were assessed by Student's T-test, Mann-Whitney U test or Chi-Square test. Logistic regression was performed to validate these identified parameters. ® Student's T-test; # Mann-Whitney U test; § Chi-Square test. * P<0.05; ** P<0.01.

Discussion

ADPKD is now the fourth leading cause of ESRD, leading to poor outcomes and imposing a great economic burden on society [3]. It is usually asymptomatic at the early stage, and the number and volume of renal cysts increase with age in an exponential manner [24]. The progression of renal cysts results in a variety of clinical symptoms and complications, including abdominal pain, hematuria, urinary tract infection, and nephrolithiasis [25]. Our study found that approximately 40% of ADPKD patients had abdominal or lumbar pain as the chief complaint, and the incidence rate of hematuria and urinary tract infection were 30% and 25%, respectively, generally agreeing with the results of other global studies of ADPKD patients [21,26,27]. Hypertension is a common complication and often occurs early in ADPKD patients. It is also associated with disease progression to end-stage renal disease [28]. Although recent HALT-PKD studies showed that rennin-angiotensin-aldosterone system blockade does not alter the declining rate of eGFR [28,29], blood pressure control may be associated with reduced mortality in ADPKD patients [30]. In the present study, hypertension occurred in half of the patients and increased the risk of specific symptoms, including pain, hematuria, infection, and nephrolithiasis. In addition, the average age of ADPKD patients at diagnosis in HALT-PKD trials was 30 years old [31]. However, the average diagnosis age in our study was approximately 42 years old, indicating that many Chinese patients with ADPKD are diagnosed relatively late. Since early diagnosis and managements might benefit ADPKD patients, it should be encouraged and taught that all ADPKD patients in China need early clinical attention and diagnosis.

Renal anemia is a common complication in patients with chronic kidney disease. In our study, hemoglobin was significantly decreased in patients with low eGFR. We also found that thrombocyte count was correlated with eGFR, similar to hemoglobin. Patients with low eGFR showed declined thrombocyte levels, and mean thrombocyte levels of these ADPKD patients were lower than the mean value in a Chinese population, as reported by Li et al. [32]. Furthermore, there was a significant positive correlation between thrombocyte count and eGFR, consistent with a previous study [21]. It has been reported that ADPKD patients have decreased thrombocyte levels [33], but the underlying mechanism and its effect on the progression of ADPKD remains unclear. Recently, Setyapranata et al. [34] found that dialysis-treated ADPKD patients had lower thrombocyte levels than those dialysis-treated non-ADPKD patients with CKD. Because ADPKD is characterized by lesions in renal tubules and biliary ducts, while other CKDs mostly affect glomeruli, we speculate that thrombopoietin (TPO), the major thrombocyte regulator produced in the liver, kidneys, and skeletal muscle [35], might be involved in the low thrombocyte counts of ADPKD patients with exacerbated renal-hepatic cysts. However, we did

not find any differences in thrombocyte counts between patients with and without polycystic liver, suggesting that renal lesions are the main pathological change in ADPKD patients and may have a dominant effect on thrombocyte counts and hemoglobin levels. In addition, thrombocyte count was significantly lower in patients with hematuria, suggesting that thrombocyte count is not only an independent correlative factor of renal function, but may also be associated with hemorrhagic complications of ADPKD. Treatments for renal anemia that focus on erythropoietin (EPO) have become more common in the new age of gene therapy [36], and further research on thrombocyte count might have clinical relevance, such as in preventing hemorrhagic events and improving quality of life.

Currently, treatment options for this incurable disease remain limited. As the most widely used surgical procedure, renal cyst decortication has only been shown to be effective in pain relief and it cannot delay the progression of ADPKD [37]. Several drugs (e.g., mTOR inhibitors, somatostatin analogues, and tyrosine kinase inhibitor) identified in animal models were shown to be ineffective in clinical trials [38–42]. Tolvaptan is the only drug approved for ADPKD treatment [26,43], but its clinical use is challenged by reports of adverse effects [44]. Other drugs, such as metabolism modulators [45–47], autophagy modulators [48], and roscovitine [49], were also assessed in preclinical trials. These promising drugs need further investigation and clinical assessment to develop effective therapeutics with minimal adverse effects for ADPKD patients.

Conclusions

We described the clinical features and manifestations of ADPKD inpatients in a single center in China. As the essential indicator of disease progression, eGFR is positively correlated with blood thrombocyte and hemoglobin levels. Furthermore, thrombocyte count was not associated with presence of PKD-related symptoms, and patients with hematuria exhibited a lower thrombocyte level, suggesting that thrombocyte count might be an independent serum biomarker related to disease progression and complications. But owing to the limitation of this observational study, the role of thrombocyte count in ADPKD needs to be confirmed in prospective studies, and the underlying mechanism needs further investigation. In addition, hypertension was found to increase the risk of symptom occurrence, highlighting the association between hypertension and disease progression. Recent studies revealed that TKV is a valuable clinical biomarker to predict disease progression [20,24,50,51], prompting us to perform the present study. Further investigations on other systemic manifestations such as cardiac abnormalities or intracranial aneurysms are needed, as is increased focus on comprehensive family history or screening of relatives.

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Conflict of interest

None.

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