Observational Study

Medicine

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Clinical characteristics and risk factors for kidney failure in patients with autosomal dominant polycystic kidney disease

A retrospective study

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary and progressive renal disease. By the age of 65 years, 45% to 70% of patients with ADPKD reach end-stage renal disease (ESRD). Although there are various treatments for this condition, no standard therapy exists to delay the progression of ADPKD. Hence, understanding the factors that affect disease progression may be helpful for the treatment of ADPKD. The medical records of 288 patients with ADPKD at Keimyung University Dongsan Medical Center between January 1989 and August 2018 were analyzed retrospectively. Furthermore, we inspected the risk factors involved in the progression of ADPKD and the kidney survival rates of patients using the Cox proportional hazards model and Kaplan–Meier survival analysis. The mean age at the time of diagnosis was 43.1 ± 14.1 years, and there were 146 males (50.7%). In total, 197 patients (68.4%) had hypertension and 11 patients (3.8%) had cerebral aneurysm. Stroke occurred in 35 patients (12.1%), including 11 cases of cerebral hemorrhage and 24 cases of cerebral infarction. Twenty-eight patients (9.7%) died during the follow-up period (117.1 ± 102.1 months). Infection (42.9%) was the most common cause of mortality, followed by sudden cardiac death (25.0%). Overall, 132 patients (45.8%) progressed to ESRD and 104 patients (36.1%) required renal replacement therapy (RRT). The mean duration from diagnosis to RRT was 110.8 ± 93.9 months. Age at diagnosis after 30 years (odd's ratio [OR], 2.737; 95% confidence interval [CI], 1.320–5.675; $P = .007$), baseline serum creatinine levels (OR, 1.326; 95% CI, 1.259–1.396; $P < .001$), and cyst infection (OR, 2.065; 95% CI, 1.242–3.433; $P = .005$) were the independent risk factors for kidney failure in multivariable analysis. To delay the advance of ADPKD to ESRD, early diagnosis and close observation for the onset of cyst infection are crucial.

Abbreviations: ADPKD = autosomal dominant polycystic kidney disease, CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, OR = odd's ratio, RRT = renal replacement therapy, SD = standard deviation, TKV = total kidney volume, TNF-α = tumor necrosis factor-alpha, UTIs = urinary tract infections.

Keywords: autosomal dominant polycystic kidney disease, outcomes, survival

1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited and progressive condition with the formation of numerous fluid-filled kidney cysts resulted from mutations in the PKD1 and PKD2 genes.[1] These cysts press the adjacent renal tissue, and lead to the ongoing loss of kidney function.[2] By the age of 65 years, 45% to 70% of patients with ADPKD proceed to end-stage renal disease (ESRD).[3] In Korea, ADPKD is the fourth principal cause of ESRD.[4] It also involves other organs and manifests as cardiovascular diseases, cerebral aneurysms, or colon diverticula.[5]

In the 1990s, a few studies regarding therapeutic interventions using taxol,[6] methylprednisolone,[7] and lovastatin[8] to delay the progression of ADPKD in animal models were published. Recently, phase 3 clinical trials concerning the effect of tolvaptan on ADPKD progression were conducted.[9–11] These trials demonstrated a sustained disease-modifying effect of tolvaptan on the estimated glomerular filtration rate (eGFR). Hence, an ADPKD outcome model was developed for implementing tolvaptan treatment.[12,13]

The cause and pathogenesis of ADPKD have been well identified, but there is no standard therapy to slow its progression, despite the development of various therapeutic approaches.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Park H, Paek JH, Kim Y, Park WY, Han S, Jin K. Clinical characteristics and risk factors for kidney failure in patients with autosomal dominant polycystic kidney disease: A retrospective study. Medicine 2022;101:47(e31838).

Received: 22 September 2022 / Received in final form: 25 October 2022 / Accepted: 26 October 2022

http://dx.doi.org/10.1097/MD.0000000000031838

Therefore, when treating ADPKD, it is helpful to understand the factors affecting disease progression. The present study discussed the clinical features of patients with ADPKD and the risk factors associated with its progression.

2. Methods

This study enrolled 350 adult patients with ADPKD who received medical care at Keimyung University Dongsan Medical Center between January 1989 and August 2018. ADPKD was defined as more than two cysts in an unilateral kidney or a single cyst in each kidney in patients aged < 30 years, more than two cysts in each kidney in patients aged 30 to 59 years, and more than four cysts in each kidney in patients older than 60 years.[14] Subjects who had insufficient data regarding certain factors were excluded from the analysis. Finally, the medical records of 288 patients with ADPKD who received care at the center were analyzed retrospectively.

Demographic information that included age at diagnosis, sex, family history of ADPKD, hypertension, diabetes mellitus, cerebral aneurysm, stroke, and cardiovascular disease were collected. Furthermore, clinical outcomes, such as cyst complication, which included infection and hemorrhage, number of patients that progressed to ESRD, number of patients receiving renal replacement therapy (RRT), duration from diagnosis to RRT, mortality, and the cause of mortality were investigated. Kidney failure was defined as ESRD requiring RRT, and the primary outcome was the kidney survival rates. The criterion for the age at diagnosis was selected as 30 years because studies regarding the linkage between the PKD1 gene and ultrasonography results found a 100% penetrance of renal cysts after the age of 30 years.[14,15] The baseline serum creatinine levels over the upper normal limit were considered >1.3 mg/dL according to the reference value of the center.

Numerical values are marked as mean ± standard deviation (SD), and categorized variates are represented by numbers and percentages. Overall and kidney survival rates were calculated with Kaplan–Meier survival analysis. In addition, log rank test made a comparison between the survival curves. Clinical risk factors for kidney failure were investigated using the Cox proportional hazards model. Furthermore, multivariable analysis was performed as forward conditional method, using the variables that showed significant results in univariable analysis. Statistical analyses were conducted with the version 28 of the IBM SPSS Statistics for Windows. A *P* value of <.05 was regarded as statistical significance.

The institutional review board of Dongsan Medical Center approved the present study in accordance with the Declaration of Helsinki (DSMC 2022-03-008).

3. Results

The mean age at the time of diagnosis was 43.1 ± 14.1 years, and there were 146 males (50.7%). A family history of ADPKD was identified in 113 cases (39.2%). Overall, Hypertension was found in 197 patients (68.4%) and 11 patients (3.8%) had cerebral aneurysm. Stroke was detected in 35 patients (12.1%), which included 11 cases of cerebral hemorrhage and 24 cases of cerebral infarction. Cardiovascular disease developed in 17 patients (5.9%). Table 1 displays the demographic data of patients with ADPKD.

During the follow-up period, 28 patients (9.7%) died. The most common cause of death was infection (42.9%), and the second most common cause was sudden cardiac death (25.0%). Cyst complications such as cyst infection and hemorrhage developed in 43 patients (14.9%). In total, 132 patients (45.8%) advanced to ESRD and 104 patients (36.1%) required RRT. The mean duration from diagnosis to RRT was 110.8 ± 93.9 months. Table 2 shows the clinical outcomes of the patients.

There were 104 cases of kidney failure, which indicated the cases of ESRD requiring RRT. In univariable Cox analysis, age at diagnosis after 30 years (odd's ratio [OR], 3.648; 95% confidence interval [CI], 1.771–7.517; *P* < .001), baseline serum creatinine levels (OR, 1.347; 95% CI, 1.281–1.418; *P* < .001), hypertension (OR, 1.596; 95% CI, 1.008–2.525; *P* = .046), cardiovascular disease (OR, 2.106; 95% CI, 1.095–4.049; *P* = .026), and cyst infection (OR, 2.671; 95% CI, 1.618–4.411; *P* < .001) significantly increase the risk for kidney failure. In multivariable Cox test, the independent risk factors for kidney failure were age at diagnosis after 30 years (OR, 2.737; 95% CI, 1.320–5.675; *P* = .007), baseline serum creatinine levels (OR, 1.326; 95% CI, 1.259–1.396; *P* < .001), and cyst infection (OR, 2.065; 95% CI, 1.242–3.433; *P* = .005). Table 3 shows the clinical risk factors for kidney failure in patients with ADPKD.

Figure 1 presents the overall survival rates wherein the 1-year survival rate was 97.3%, 5-year survival rate was 89.9%, and 10-year survival rate was 87.8%. Figure 2 shows the kidney survival rates according to age at diagnosis. Patients diagnosed with ADPKD after 30 years old showed worse kidney survival rates than those diagnosed before 30 years old (*P* < .001). Figure 3 shows the kidney survival rates according to the baseline serum creatinine levels. Patients with baseline serum creatinine levels over the upper normal limit showed worse kidney survival rates compared with those having baseline serum creatinine levels below the upper normal limit (*P* < .001). Figure 4 shows the kidney survival rates according to cyst infection. Patients with cyst infection showed worse kidney survival rates compared with those who had no cyst infection (*P* < .001).

4. Discussion

ADPKD is the most common inherited kidney disease with a single gene mutation.[16] The major problem of this condition is the inevitably decreasing renal function of the patients, which ultimately results in ESRD requiring RRT. However, standard treatments have not yet been established. Hence, it is important to predict the kidney outcomes and outline the clinical risk factors for such patients. Age at diagnosis after 30 years, baseline serum creatinine levels, and cyst infection are the independent risk factors for kidney failure, as found in this study.

The demographics of the current study group were similar to that of another Korean cohort study that enrolled 364 patients with ADPKD from 9 hospitals.[17] In the present study, the mean age at the time of diagnosis was 43.1 ± 14.1 years, whereas in the other Korean cohort study, it was 37.9 ± 10.6 years. In both the studies, the male-to-female ratio was almost equal. A large

Table 1

Demographics of patients with autosomal dominant polycystic kidney disease.

Variables	All patients (n = 288)
Age at diagnosis (years)	43.1 ± 14.1
Male gender (%)	146 (50.7)
Family history of ADPKD (%)	113 (39.2)
Hypertension (%)	197 (68.4)
Diabetes mellitus (%)	21 (7.3)
Cerebral aneurysm (%)	11 (3.8)
Cerebral vascular accident (%)	35 (12.1)
Cerebral hemorrhage	11 (31.4)
Cerebral infarction	24 (68.6)
Cardiovascular disease (%)	17 (5.9)

Values are expressed as mean ± SD, n (%).
ADPKD = autosomal dominant polycystic kidney disease.

Table 2

Clinical outcomes of the patients with autosomal dominant polycystic kidney disease.

Variables	All patients (n = 288)
Cyst complication (%)	43 (14.9)
Cyst infection	28 (65.1)
Cyst hemorrhage	15 (34.9)
ESRD (%)	132 (45.8)
RRT (%)	104 (36.1)
Hemodialysis	74 (71.1)
Peritoneal dialysis	2 (1.9)
Kidney transplantation	28 (26.9)
Duration from diagnosis to RRT (months)	110.8 ± 93.9
Follow-up duration (months)	117.1 ± 102.1
Mortality (%)	28 (9.7)
Causes of mortality (%)	
Infection	12 (42.9)
Cyst infection	3 (10.7)
Urinary tract infection	2 (7.1)
Pneumonia	2 (7.1)
Catheter-related infection	2 (7.1)
Bacterial meningitis	1 (3.6)
Pseudomembranous colitis	1 (3.6)
Colitis	1 (3.6)
Cerebral hemorrhage	1 (3.6)
Sudden cardiac death	7 (25.0)
Pulmonary thromboembolism	2 (7.1)
Others	6 (21.4)

Values are expressed as mean ± SD, n (%).
ESRD = end-stage renal disease, RRT = renal replacement therapy.

proportion of patients had hypertension: 68.4% in this study versus 87.6% in the other Korean cohort study.

Several studies have been conducted for predicting kidney survival in patients with ADPKD. Gall et al proposed a predicting renal outcome in ADPKD scoring system ranging from 0 to 9 points: being male as 1 point, hypertension before 35 years old as 2 points, first urologic event (gross hematuria, flank pain, and cyst infection) before 35 years old as 2 points, PKD2 mutation as 0 point, non-truncating PKD1 mutation as 2 points, and truncating PKD1 mutation as 4 points. There are 3 risk groups for the progression of ESRD: 0 to 3 points as low risk, 4 to 6 points as intermediate risk, and 7 to 9 points as high risk, with corresponding median ages for the onset of ESRD as 70.6, 56.9, and 49 years, respectively.[18] Another study presented the total kidney volume (TKV) as a powerful and independent predictor for developing advance of chronic kidney disease (CKD).[19] Moreover, Johnson et al suggested age at diagnosis before 30 years, male gender, PKD1 gene mutation, hypertension before 35 years old, gross hematuria before 30 years old as risk factors for ESRD in patients with ADPKD.[20]

The accurate age at diagnosis that can be considered a risk factor remains controversial, with different studies presenting contrary results. Johnson et al reported that individuals diagnosed with ADPKD before the age of 30 years are diagnosed with ESRD at an earlier age than those diagnosed with ADPKD after the age of 30 years (risk ratio, 3.2; 95% CI, 2.3–4.5; $P < .0001$).[20] Since seven tenths of young patients with ADPKD are symptomatic, the symptoms are often likely to provoke the diagnosis. Therefore, these patients diagnosed with ADPKD earlier can experience a more severe course of disease. On the contrary, Ozkok et al suggested age as a significant and independent factor for predicting the progression of CKD (hazard ratio, 1.05; 95% CI, 1.01–1.09; $P = .01$).[21] Similar to the latter study, the risk for kidney failure was greater in the patients who were diagnosed later in the present study. Owing to good medical accessibility in Korea, the progression of ADPKD to ESRD may be slow because of close monitoring and management following early diagnosis. However, further researches are needed to clarify the influence of age on kidney prognosis.

Recently, a number of studies have reported that baseline TKV is the most important predictor of the disease progression.[22–24] Numerous researches have suggested an inverse relationship between TKV and eGFR.[25,26] eGFR is inversely proportional to serum creatinine levels in accordance with the Modification of Diet in Renal Disease study equation. Therefore, a direct proportional relationship between TKV and serum creatinine levels exists. In the current study, multivariable analysis revealed that baseline serum creatinine levels are a significant and independent risk factor for kidney failure. There are no data regarding the TKV of the study group, but the relationship between baseline serum creatinine levels, TKV, and kidney prognosis may be established.

During the lifetime, 30% to 50% of patients with ADPKD experience urinary tract infections (UTIs), with cyst infection and acute pyelonephritis being the most common causes of upper UTIs in such patients.[27] In a retrospective study, the fast progressor group defined by the doubling of serum creatinine levels within 36 months showed a greater prevalence of UTIs than the slow progressor group.[28] Another study presented that chronic asymptomatic pyuria and overt UTIs were related to a rapid decline in kidney function. The researchers proposed that UTIs might be a direct cause of cystogenesis.[29] When renal tubular epithelial cells were subjected to ischemic damage or nephrotoxic injury, abnormal cell proliferation and cyst formation appeared.[30,31] Furthermore, other studies have reported the influence of tumor necrosis factor-alpha (TNF-α) on cyst formation and lipopolysaccharide on peritubular capillary dysfunction.[32,33] Hence, inflammation provoked by UTIs may result in cell proliferation, cyst formation, fibrosis, and renal function deterioration. Similar to the results of former studies, cyst

Table 3

Clinical risk factors for kidney failure in patients with autosomal dominant polycystic kidney disease.

	Univariable			Multivariable		
Variables	OR	95% CI	*P* value	OR	95% CI	*P* value
Age at diagnosis after 30 years	3.648	1.771–7.517	<.001	2.737	1.320–5.675	.007
Baseline serum creati-nine levels	1.347	1.281–1.418	<.001	1.326	1.259–1.396	<.001
Male gender	0.878	0.593–1.301	.517			
Hypertension	1.596	1.008–2.525	.046	1.064	0.660-1.716	.799
Diabetes mellitus	1.832	0.979–3.428	.058			
Cerebral aneurysm	2.012	0.976–4.147	.058			
Cardiovascular disease	2.106	1.095–4.049	.026	0.852	0.410-1.767	.666
Cyst infection	2.671	1.618–4.411	<.001	2.065	1.242–3.433	.005
Cyst hemorrhage	0.907	0.369–2.230	.832			

OR = odds ratio, CI = confidence interval.

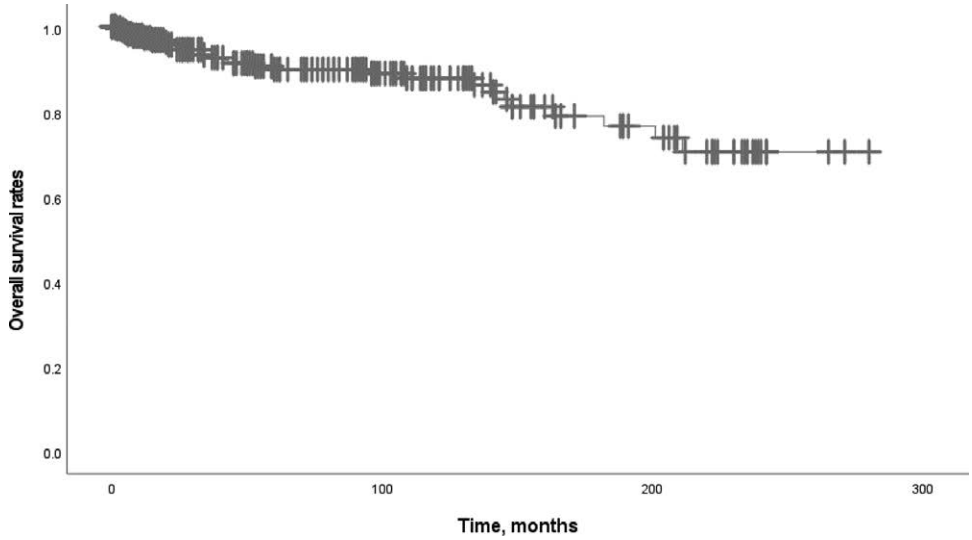
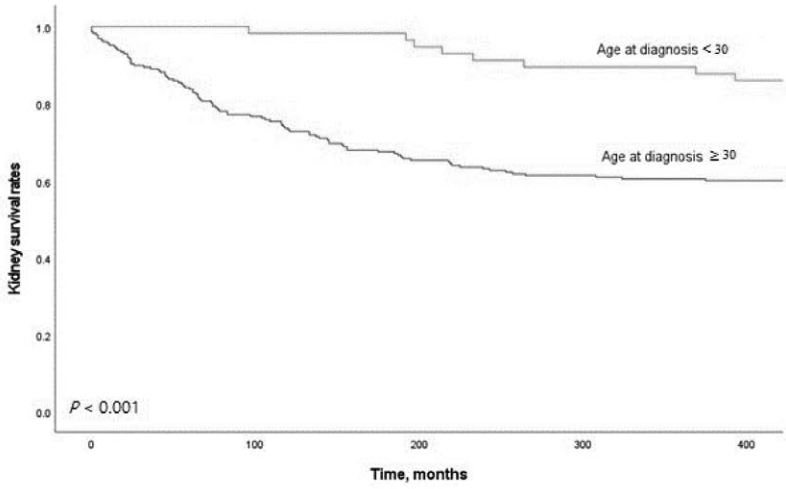
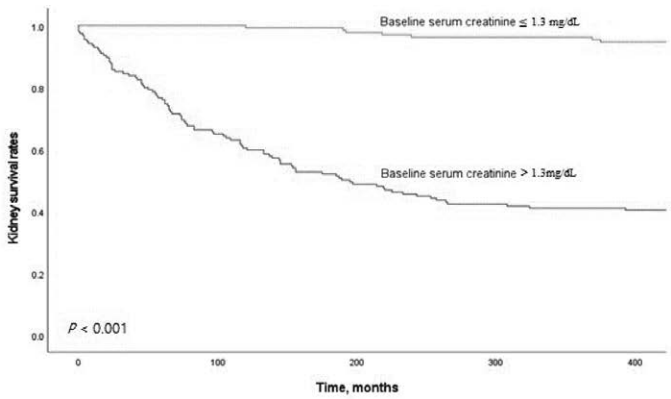


Figure 1. Overall survival rates in patients with autosomal dominant polycystic kidney disease.



No. at risk					
Age at diagnosis < 30	57	55	53	50	48
Age at diagnosis ≥ 30	231	173	147	138	135

Figure 2. Kidney survival rates according to age (years) at diagnosis.



No. at risk					
Baseline serum creatinine ≤ 1.3 mg/dL	130	129	126	124	122
Baseline serum creatinine > 1.3 mg/dL	158	99	74	64	61

Figure 3. Kidney survival rates according to baseline serum creatinine levels (mg/dL).

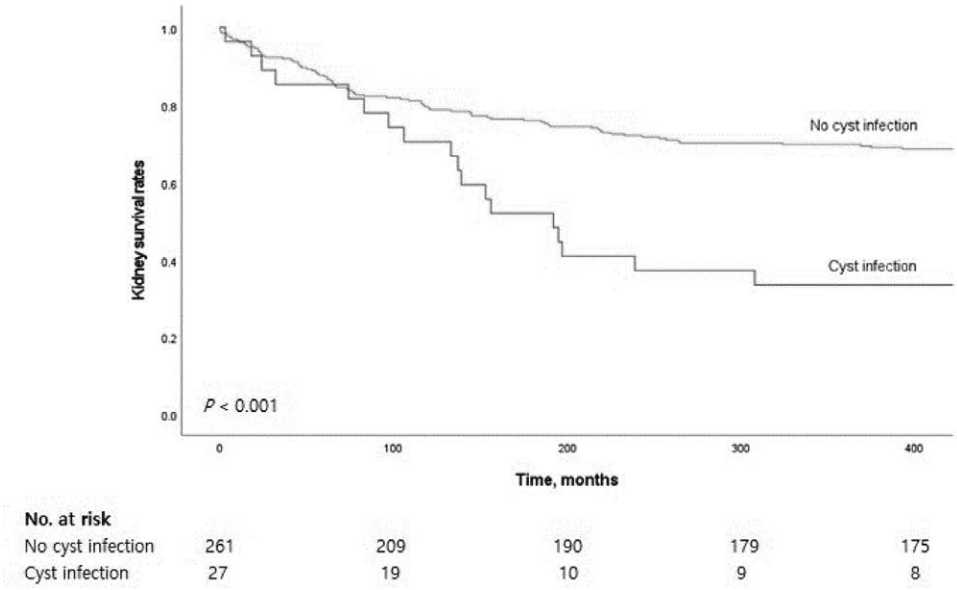


Figure 4. Kidney survival rates according to cyst infection.

infection appeared to be an independent risk factor for kidney failure in this study.

The present study has few limitations. TKV has been suggested as a significant predictor of the disease progression in several studies.[19,34,35] However, in the absence of magnetic resonance imaging stereology and automated methods for TKV determination, data regarding TKV cannot be collected. In addition, PKD1 and PKD2 gene mutations have frequently been presented as a risk factor for ADPKD in various studies.[20,36,37] Since genetic testing is rarely performed, this could not be further analyzed. Moreover, data regarding the treatment of patients with ADPKD have not been investigated.

In conclusion, age at diagnosis after 30 years, baseline serum creatinine levels, and cyst infection were found to be the significant and independent risk factors for kidney failure. Early diagnosis and close observation for the onset of cyst infection may be helpful in delaying the advance to ESRD in patients with ADPKD.

Acknowledgments

Not applicable.

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