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Original Article

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Long-Term Experience of a Reference Center on Autosomal Dominant Polycystic Kidney Disease: Associated Demographics, Clinical Presentation, and Kidney Survival in Turkish Population

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ABSTRACT

Objective: The autosomal dominant polycystic kidney disease is the most common genetic cause of chronic kidney disease. In this context, it was aimed to investigate the demographical, clinical, and laboratory findings of, and the treatment methods implemented on, patients with autosomal dominant polycystic kidney disease, along with the factors that can be associated with kidney survival.

Methods: Hospital records of autosomal dominant polycystic kidney disease patients, who were followed up by our nephrology clinic, were analyzed retrospectively. Demographical, clinical, and laboratory findings, treatments, and kidney survival of patients were recorded. Kidney survival of patients who were either lost to follow-up or followed by another center was learned through phone calls.

Results: The data of 300 patients with a diagnosis of autosomal dominant polycystic kidney disease, 157 of whom were women and 143 men of whom were men, were analyzed within the scope of the study. Been diagnosed at a younger age, female gender, having a high estimated glomerular filtration rate at initial admission, and use of renin–angiotensin system blockers were determined to be significant in better kidney survival. Moreover, the use of renin–angiotensin system blockers was also determined to be significant for longer kidney survival in patients with less than 1 g/day proteinuria.

Conclusion: It was concluded as a result of the study that early diagnosis and treatment management of autosomal dominant polycystic kidney disease patients are of paramount importance. Additionally, the results of the study suggest that the use of renin–angiotensin system blockers in hypertensive patients with autosomal dominant polycystic kidney disease may be a factor for better kidney survival.

Keywords: Autosomal dominant polycystic kidney disease, hypertension, renin–angiotensin system

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a multisystemic genetic disorder that may present with renal and extrarenal manifestations. Kidney manifestations may include hypertension, nephrolithiasis, hematuria, urinary tract infection, and abdominal pain, acute or chronic flank, whereas extrarenal manifestations may include cerebral aneurysms, hepatic and pancreatic cysts, colonic diverticula, cardiac valve disease, abdominal wall, and inguinal hernia.[1] Clinical signs usually occur when the patients are in their thirties.[2]

An algorithm to predict kidney survival in ADPKD is also included in the PROPKD score, which has been recently presented in the literature. A scoring system from 0 to 9 was developed as follows—being male: 1 point; hypertension before 35 years of age: 2 points; first urologic event before 35 years of age: 2 points; PKD2 mutation: 0 points; nontruncating PKD1 mutation: 2 points; and truncating PKD1 mutation: 4 points.[3] It has been suggested that cyst expansion is responsible for the initial elevation in blood pressure to a large extent, as it causes focal areas of kidney ischemia and enhanced

renin release. Increased activity of the renin–angiotensin system (RAS) and extracellular volume expansion often occur prior to having had elevated serum creatinine levels in ADPKD and may lead to elevated blood pressure.[4] Hypertension occurs frequently and early during ADPKD, affecting both kidney and patient outcomes.[5,6]

In this study, the demographical, clinical, and laboratory findings of, and the treatment methods implemented on, patients with ADPKD, along with the factors that can be associated with kidney survival, have been investigated, whereas the primary objective of this study has been to demonstrate the impact of RAS activation on kidney survival.

METHODS

Study Population

Patients with ADPKD who were followed up and treated by our nephrology clinic between January 1990 and January 2015 were included in this retrospective cohort study. The ethics committee approval (12.01.2015/83045809) for the study has been obtained from the Local Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine.

Demographics and Clinical Findings

A total of 300 patients, of whom 52% (n = 157) were female, who were diagnosed with ADPKD, were included in the study. Diagnosis of ADPKD was based on the clinical features of the disease, familial history (familial history was considered to indicate ADPKD in case of at least 3 kidney cysts before the age of 39, at least 2 cysts per kidney from the age of 40 to 59, and at least 4 cysts per kidney after the age of 60), and/or confirmation of the diagnosis by radiological imaging.[7] Baseline demographic characteristics (age at the time of the diagnosis, gender, smoking status, familial history, causes of admission to hospital, blood pressure, body mass index ((weight (kg)/height^2 (m^2)) and laboratory findings (serum urea, creatinine, C-reactive protein, albumin, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, triglycerides, phosphorus, calcium, hemoglobin and hematocrit, 24-hour urine protein), conditions associated with disease during follow-up (macroscopic hematuria, kidney stones demonstrated by ultrasonography and/or a history of passing kidney stones, hernia, cyst in the liver demonstrated with either ultrasonography or computed tomography, intracranial aneurysm, heart valve disease, diverticular disease of colon, urinary tract infection confirmed by positive urine cultures), comorbid conditions (diabetes mellitus, hypertension, ischemic heart disease, malignancy), and treatments implemented on ADPKD patients (the use of RAS blockers; angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) and/or other antihypertensive drugs, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) who were followed up between January 1990 and January 2015, were analyzed retrospectively. All the medical records and findings were recorded and analyzed by the same researcher.

Hypertension was defined as having a blood pressure ≥ 140/90 mm Hg and/or the use of antihypertensive drugs. The estimated glomerular filtration rate (eGFR) was calculated using Chronic Kidney Disease Epidemiology Collaboration formula.[8]

Analysis of Kidney Survival

A patient who had a GFR value <15 mL/min/1.73 m^2 or started dialysis or underwent transplantation was considered to have end-stage kidney disease (ESKD). Demographical, clinical, laboratory, and treatment findings of patients with and without ESKD were compared in order to determine the factors associated with kidney survival. Duration of kidney survival was defined as the time elapsed from birth to the onset of ESKD.

Statistical Analysis

Statistical analysis was performed using Student's *t*-test, chi-square test, Kaplan–Meier survival analysis, log-rank test, Cox regression, and logistic regression analyses. *P* values < .05 were considered to be significant. All computations were conducted using the Statistical Package for Social Sciences for Windows, version 17.0, software (SPSS Inc., Chicago, Ill, USA).

RESULTS

Study Population

Mean age of the patients, of whom 52.3% (n = 157) were female, at the time of the diagnosis was 47.7 ± 19.9 years (min: 15–max: 83). Of these patients, 82.9% had a relevant familial history. The most commonly observed symptom was flank pain, which was experienced by 28.6% of the patients. Of the patients, 17.1% were diagnosed incidentally during the imaging, 11.4% were diagnosed during the assessment of the etiology of hypertension, and 7.1% were diagnosed during family screening. Of the patients, 45.3% were smokers. Demographic characteristics of the patients, the causes of their admission to the hospital, conditions manifested in relation to the disease, laboratory findings of the patients, and the antihypertensive treatments administered to the patients are shown in Table 1.

The most common clinical finding was hypertension, which was observed in 82.8% (231 out of 278) of the patients. Ratios of the patients using ACEI and/or ARBs, calcium channel blockers, beta-blockers, diuretics, and alpha-blockers were

MAIN POINTS

- Early diagnosis and treatment are important in autosomal dominant polycystic kidney disease (ADPKD).
- In our large-scale patient involvement study, which included 300 patients, the factors affecting kidney survival in ADPKD in Turkish population were shown.
- The use of renin–angiotensin system blockade is effective in kidney survival in ADPKD.

Table 1. Baseline Demographic Characteristics aaboratory Findings of the Patients (Data are presented as mean ± SD)

Variables	
Age at the time of diagnosis (years)	47.7 ± 19.9
Female gender (%)	143 (52.3)
Familial history, %	82.9
Mean arterial pressure (mmHg)	101 ± 14.4
Systolic blood pressure (mmHg)	135 ± 21
Diastolic blood pressure (mmHg)	83 ± 12
Body mass index (kg/m^2)	26.5 ± 4.5
Serum urea (mg/dL)	59.5 ± 46.1
Serum creatinine (mg/dL)	2.3 ± 2.5
Serum uric acid (mg/dL)	5.5 ± 1.7
Serum albumin (g/dL)	4.1 ± 0.4
eGFR (mL/min/1.73 m^2)	61.6 ± 39.1
Proteinuria (mg/day), median (IQR 25-75)	182 (100-403)
CRP (mg/L), median (IQR 25-75)	3.2 (1.6-8.4)
Total cholesterol (mg/dL)	196 ± 51.3
HDL cholesterol (mg/dL)	46.2 ± 18.5
LDL cholesterol (mg/dL)	124.0 ± 37.2
Triglyceride (mg/dL)	140.9 ± 83.5
Phosphorus (mg/dL)	3.8 ± 1.0
Calcium (mg/dL)	9.1 ± 0.9
Sodium (mEq/L)	140.0 ± 3.7
Potassium (mEq/L)	4.4 ± 0.6
Hemoglobin (g/dL)	12.3 ± 2.0
Hematocrit (%)	36.8 ± 6.1

CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standart deviation *P* < *.05* means there is a statistically significant difference.

determined as 43.8%, 44.2%, 18.3%, 14.8% and 7.6%, respectively. Echocardiography was performed on 36 patients, and mitral valve prolapse was detected in 6 (16.1%) of them. Colonoscopy was performed on 13 patients, and 3 (23.1%) of the patients were diagnosed with colon diverticular disease.

The median follow-up period of the patients was 43.1 (interquartile range 15.7-97.1) months. During follow-up, 22.3% of patients had developed macroscopic hematuria, 18.8% of them had urinary tract infection, and 28.3% of them had nephrolithiasis. In terms of other non-renal organ involvements detected during the follow-up, the liver cyst was detected in 54.7% of the patients, other non-liver cysts were detected in 1.6% of the patients, hernia was detected in 8.2% of the patients, heart valve disease was detected in 16.7% of the patients, and diverticular disease was detected in 23.1% of the patients.

Table 2. Factors Associated with Kidney Survival (Data are Presented as Mean ± SD)

Variables	Non-ESKD Patients, n = 151 (%)	ESKD Patients, n = 88 (%)	*P*
Female gender, %	59	44	*.02*
Smoking, %	44.4	50	NS
Familial history, %	83.5	77.4	NS
Macroscopic hematuria, %	18	26.5	NS
Nephrolithiasis, %	24.2	29.4	NS
Systolic blood pressure (mmHg)	132 ± 19	137 ± 22	NS
Diastolic blood pressure (mmHg)	83 ± 11	83 ± 12	NS
Mean arterial pressure (mmHg)	99 ± 13	101 ± 14	NS
Body mass index (kg/m^2)	26.5 ± 5.06	26.2 ± 3.6	NS
Urinary tract infection, %	21.6	14.8	NS
Kidney stone, %	24.2	29.4	NS
Cyst in the liver, %	48.4	50	NS
Hernia, %	4.1	15.7	.002
Diabetes mellitus, %	9	9.5	NS
Hypertension, %	76.9	90.2	*.012*
Ischemic heart disease, %	16.6	34.1	*.002*
Serum urea (mg/dL)	40.5 ± 30.5	91 ± 51	*<.001*
Serum creatinine (mg/dL)	1.16 ± 0.92	4.32 ± 3.23	*<.001*
Serum uric acid (mg/dL)	5.1 ± 1.7	6.3 ± 1.8	*<.001*
Serum albumin (g/dL)	4.2 ± 0.3	3.9 ± 0.4	*<.001*
eGFR (mL/min/1.73m^2)	83.2 ± 32.6	28.0 ± 24.3	*<.001*
Proteinuria (mg/day)*	163 (95-255)	684 (289-2184)	*<.001*
CRP (mg/L)*	3.3 (3-8.5)	4.8 (3-9)	NS
Total cholesterol (mg/dL)	193.4 ± 55.2	194 ± 46	NS
HDL cholesterol (mg/dL)	46.5 ± 10.7	45 ± 28	NS
LDL cholesterol (mg/dL)	124.2 ± 42.4	121 ± 32	NS
Triglyceride (mg/dL)	133.1 ± 76.6	156 ± 97	NS
Sodium (mEq/L)	140 ± 3	139 ± 4	NS
Potassium (mEq/L)	4.4 ± 0.6	4.5 ± 0.7	NS
Phosphorus (mg/dL)	3.4 ± 0.8	4.2 ± 1.1	*<.001*
Calcium (mg/dL)	9.3 ± 0.6	8.8 ± 1.1	*<.001*
Hemoglobin (g/dL)	12.8 ± 1.9	11.5 ± 2.0	*<.001*
Hematocrit (%)	38.1 ± 5.7	34.3 ± 6.2	*<.001*
RAS blockage, %	5-Ü.7	33.3	*.018*

CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; RAS, renin–angiotensin system; SD, standart deviation
*Median (interquartile range 25-75).*P* < *.05* means there is a statistically significant difference.

Additionally, intracranial aneurysm was detected in 6 (16.2%) of the 37 patients who underwent cranial magnetic resonance angiography due to a suspected cranial aneurysm. In terms of comorbidities, 10% of the patients were found to have diabetes

mellitus, 24.9% of the patients were found to have ischemic heart disease, and 2.1% of the patients were found to have malignancy.

Kidney Survival

A total of 61 patients were excluded from the survival analysis. Of these patients, 23 were excluded because of insufficient data, 22 of these patients were excluded due to having been followed up for less than 3 months, and 16 of these patients were excluded since they died without ESKD after having been followed up for at least 3 months. As a consequence, 239 patients were included in the kidney survival analysis. The mean kidney survival period was 542 ± 189 months. During the follow-up of 239 patients, 88 patients received kidney replacement therapy (hemodialysis in 77 patients, peritoneal dialysis in 9 patients, and transplantation in 9 patients). Three peritoneal dialysis and hemodialysis patients each had switched to transplantation. Six patients switched between hemodialysis and peritoneal dialysis. The comparison of the data related to the patients with kidney outcome (n = 88) and without (n = 151) is given in Table 2.

Age at the time of the diagnosis, gender, the concomitant presence of hypertension, baseline serum albumin, eGFR, hemoglobin levels, and RAS blockade use were included in the binary logistic regression analysis to determine the factors associated with the kidney outcome of the patients. The use of RAS blockades, eGFR hypertension, and age at the time of the diagnosis were determined as independent factors that affect the kidney outcome (Table 3).

Table 3. Binary Logistic Regression Analysis Results (Factors Affecting Kidney Survival)

	B	Standard Error	*P*	95% CI	
Fixed variates	**12.659**	**4.531**	**.005**	**Lower**	**Upper**
eGFR (mL/min/m²)	−0.073	0.015	*<.001*	0.90	0.95
RAS blockage use	−1.596	0.659	*.016*	0.05	0.73
Female gender	0.973	0.696	.162	0.67	10.36
Hypertension	2.902	1.005	*.004*	2.54	130.4
Hemoglobin (g/dL)	−0.297	0.167	.075	0.53	1.03
Age at the time of diagnosis (years)	−0.067	0.024	*.005*	0.89	0.98
Albumin (g/dL)	−0.936	0.873	.284	0.07	2.17

eGFR, estimated glomerular filtration rate; RAS: renin–angiotensin system. *P* < .05 means there is a statistically significant difference.

Kidney survival in patients who received RAS blockers and who did not is shown in Figure 1. Cox regression analysis of the factors predicting the progression of ESRD revealed that age, gender, baseline eGFR, hemoglobin level, and use of ACEIs and/or ARBs were independent variables (Table 4).

DISCUSSION

The ADPKD may present renal and/or extrarenal manifestations.[9] In this single-center study, the mean age at the time of diagnosis was found as 47.7 ± 19.9 years. In comparison, the mean age at the time of diagnosis in a multicenter study conducted by

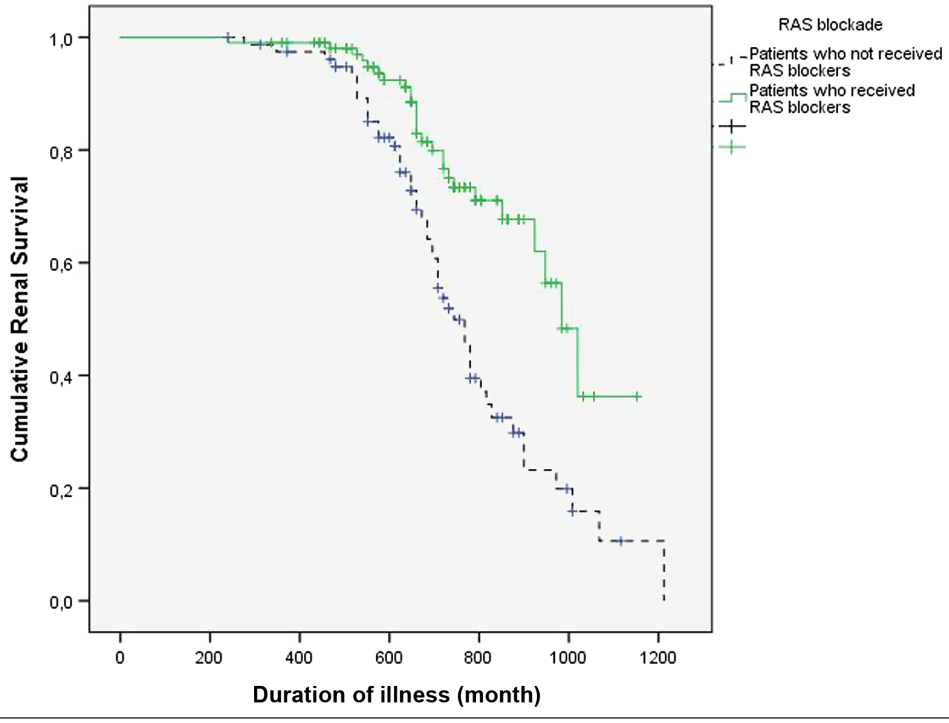

Figure 1. Kidney survival of patients separated lines for the usage of renin–angiotensin system blockage (log-rank *P* = .006).

Table 4. Cox Regression Analysis Results (Factors Affecting Kidney Survival)

Fixed Variates	*B*	Standard Error	*P*	95% CI	
				Lower	Upper
Female gender	0.729	0.289	*.012*	1.17	3.65
Age at the time of diagnosis	−0.104	0.013	*<.001*	0.87	0.92
eGFR (mL/min/m^2)	−0.014	0.006	*.016*	0.97	0.99
RAS blockers use	−0.820	0.312	.009	0.23	0.81
Hypertension	0.798	0.418	.056	0.97	5.04
Hemoglobin (g/dL)	−0.193	0.073	.008	0.71	0.95

eGFR, estimated glomerular filtration rate; RAS, renin–angiotensin system.*P* < *.05* means there is a statistically significant difference.

Kazancioglu et al[1] was found as 37.1 ± 16.3. Late age diagnosis of ADPKD was found to be a risk factor for ESKD in this study contrary to the findings reported in the study of Gabow et al.[10,11] In our study 56.5% of the patients were diagnosed with ADPKD while being examined for symptoms (abdominal pain, flank pain) or complications (nephrolithiasis, urinary tract infection, hypertension examination). Those diagnosed due to family history constituted 7.1% of the patients. The difference in the results of the literature data and our study; may be related to differences of "diagnosis at a younger age" and "presentation of findings at a younger age" are different.

In this study, female patients were determined to have longer kidney survival than male patients, which is consistent with the results reported in other studies available in the literature.[10,12] On the other hand, it was found in an animal study that testosterone constitutes a risk factor for ESKD in rats.[13] Accordingly, it may be speculated that male gonadal hormones may be a risk factor for ESKD in ADPKD patients. Gabow PA et al[10] attributed this result to the effect of gender differences in the prevalence of hypertension, which is a well-known risk factor for ESKD. However, we could not find any difference between male and female patients in terms of rate of hypertension, which was determined to be the most common clinical finding in our study. Blood pressure control may seem to be achieved in about half of the patients at the most, which may be due to certain lifestyles, diet modifications, and compliance with treatments.

Previous studies indicated that RAS is more active among ADPKD patients. The RAS is known to cause cyst enlargement and parenchymal damage. Additionally, angiotensin-2 in relation to RAS activity may cause cardiac and kidney complications.[5] In this study, patients treated with RAS blockers had better kidney survival. Despite the fact that it has been demonstrated in some studies available in the literature that kidney progression slows down with RAS blockade in ADPKD patients,[14,15] there are also a few other studies, which demonstrated that kidney progression does not decrease with RAS blockade.[16] Patients who received RAS blocker treatment with proteinuria less than 1 g/day were also found to have better kidney survival compared to the individuals that did not receive RAS blocker treatment. This result may be attributed to the RAS blockade, which has been likely to be effective in slowing down the progression of kidney disease before the onset of hypertension in ADPKD patients. As expected, the amounts of proteinuria and microalbuminuria were found to be related to the progression to ESKD, which is consistent with the results reported in other studies available in the literature.[17,18]

Macroscopic hematuria has been accepted as a risk factor for ESKD progression in ADPKD patients.[9] Single-variable analysis revealed that macroscopic hematuria was a risk factor for ESKD progression, contrary to the results of the multivariable analysis.

The fact that higher eGFR values were detected during the first admission was concluded to be related to lower ESKD progression rates and longer kidney and patient survival. This finding reinforces the importance of early diagnosis and management of the disease.

The retrospective design of this study constituted an important limitation of this study. Other limitations were only the clinical and laboratory data at the time of admission have been investigated for the effect of kidney survival, lack of total kidney volume, and the genetic mutation information. Since our study examined patient data up to 2015, tolvaptan was not included in our treatment protocol at that time, so routine magnetic resonance imaging, kidney volume, and genetic examination were not performed in our patients.

CONCLUSION

Early diagnosis and treatment management of ADPKD patients were determined to be of prime importance. Additionally, predicting the risk factors associated with ESKD progression and mortality may be helpful in stratifying the patients who are at high risk.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine (Approval no: 83045809, Date: 12.01.2015).

Informed Consent: Verbal inform consert was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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