Estimating Patient Survival and Risk of End-Stage Kidney Disease in Patients With Autosomal Dominant Polycystic Kidney Disease in Iran

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Introduction. Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary kidney disease that can affect several organs. The clinical course of the disease varies among patients; some never become symptomatic, and others reach end-stage kidney disease (ESKD) in the 5th decade of their life.
Methods. This historical cohort study was conducted on ADPKD patients to investigate kidney and patient survival rates and related risk factors in Iran. Survival analysis and risk ratio calculation were performed using the Cox proportional hazards model, Kaplan–Meier method, and log-rank test.
Results. Among the 145 participants, 67 developed ESKD, and 20 died before the end of the study period. Developing chronic kidney disease (CKD) at the age of ≤ 40, baseline serum creatinine level (SCr) of more than 1.5 mg/dL, and cardiovascular disease increased the risk of ESKD by 4, 1.8, and 2.4 times; respectively. Patient survival analysis revealed a fourfold increase in mortality if the glomerular filtration rate (GFR) declined more than 5 cc/min annually and if CKD was diagnosed at the age of ≤ 40. Vascular thrombotic events or ESKD in the course of disease increased the risk of death by approximately 6- and 7-fold, respectively. Kidney survival was 48% by the age of 60 and 28% by the age of 70. Patient survival was 86.05% at the age of 60 and 67.99% at the age of 70. Additionally, men had a significantly better renal function and survival than women.
Conclusion. Elevated baseline SCr and cardiovascular disease can increase ESKD risk in ADPKD patients. A rapid decline in GFR, ESKD development, and vascular thrombotic events increase the risk of death, but early CKD can affect both.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD), the most prevalent hereditary kidney disease, has been identified in all racial and ethnic groups.[1] It is a multisystemic progressive disease, with the manifestations usually appearing at manifests the 3rd and 4th decades of life.[2,3] Approximately, 1 in 1000 people carry a mutant gene for this condition.[4,5,6] ADPKD is predominantly caused by mutations in the PKD1 and PKD2 genes, and patients with mutation in PKD2 have less severe manifestations than patients with PKD1

mutation.[6] The age of onset of renal dysfunction in ADPKD varies widely,[4] typically, the decline in renal function starts after the fourth decade of life,[6] but more than half of the patients remain asymptomatic and are not diagnosed during their life.[5] Cysts appear later in PKD2 mutations, and these patients typically reach end-stage kidney disease (ESKD) at a mean age of 74 compared with 54.3 in PKD1.[7]

Until now, several risk factors have been identified to explain the progression of kidney disease in patients with ADPKD. These risk factors include genetic factors, especially PKD1 mutation, kidney size, number of cysts and rapid kidney growth rate, male sex, early-onset hypertension, early-onset hematuria, especially before the age of 30, recurrent gross hematuria, proteinuria, higher urinary sodium excretion, and history of three or more pregnancies, which are related to more rapid decline in glomerular filtration rate (GFR).[5,8,9,10]

According to previous studies, 55% of ADPKD patients develop ESKD by the age of 50 and 70% by the age of 70.[11] Based on another report from Japan, ESKD occurs in approximately 49% of 65- to 69-year-old patients, and after this age, it declines.[12] In a retrospective study in 2022, it was mentioned that 45 to 70% of patients with ADPKD reached ESKD by the age of 65.[13]

In one study on patients with ADPKD, the most common mortality cause before 1975 was infection (30%), followed by uremia (28%) and cardiac disease (21%), and after 1975, cardiac disease (36%) became more prominent than infection (24%) due to causing death. Infection had equal prevalence before and after 1975, and 94% presented as sepsis and 47% as direct ADPKD-related complications. [14] In another study, infection (42.9%) was the most common cause of mortality, followed by sudden cardiac death (25.0%).[13]

The diagnosis of ADPKD is based on a positive family history and imaging findings.[15] Although genetic testing is the most sensitive diagnostic method, it is used only in research studies or in the definitive exclusion of diagnosis in some clinical situations, e.g., in a potential living kidney donor or an atypical presentation of the disease.[6,15] Ultrasound-based diagnosis of ADPKD is based on Ravine criteria, which have a 100% sensitivity in type 1 ADPKD and a lower sensitivity in type 2 ADPKD, especially at the age of less than 30 or in those without a positive family history; therefore, different diagnostic criteria should be considered.[6,15] Computed tomography (CT) and magnetic resonance imaging (MRI) are particularly useful in cases of negative family history, when ADPKD should be diagnosed according to the identification of enlarged kidneys with multiple bilateral cysts, concurrent hepatic cysts, and the absence of symptoms related to other cystic kidney disease. Additionally, they are used to differentiate cyst complications or as a baseline image for future comparison.[15]

Over the past few years, significant advances have been made in genetic diagnosis, pathogenesis, and natural course of the disease, and novel tools have been introduced to estimate prognoses and disease progression, such as predicting renal outcomes in ADPKD (PROPKD) score as well as the introduction of Myo-clinic classification.[16]

In the therapeutic field, identifying the risk factors and predicting the individual outcome of ADPKD would help long-term decision-making for these patients.[1] In addition, early referral to a nephrologist and implementation of newly approved treatments such as V2R antagonists such as Tolvaptan may have a beneficial effects.[16]

MATERIALS AND METHODS

This retrospective cohort study was conducted on 145 eligible adult patients with ADPKD who had come to Hasheminejad Kidney Center, affiliated to Iran university of medical sciences in Tehran between March 2014 and March 2021.

Individuals with a single kidney, other genetic disorders, underlying diseases affecting the kidney, other concurrent kidney disorders, and those with incomplete medical document or inconstant follow up were excluded from the study. Demographic data, family history, the presence of concomitant liver cysts, medication history, age of ADPKD diagnosis, age of reaching ESKD and age of death if it occurs, mortality cause, the amount of salt they consume in teaspoon units and the number of glasses of water they drink each day, a history of hypertension, diabetes mellitus, cardiovascular disease, nephrolithiasis, anemia, gross hematuria, cyst complications, as well as laboratory test results including serum creatinine levels and red blood count (RBC) in urine analysis were collected.

ADPKD was defined according to ultrasound-

based Ravine criteria.[15] ESKD was defined as patients with kidney failure requiring renal replacement therapy (RRT), kidney survival as the time to develop ESKD, and patient survival as the time of death. Chronological age at the time of death or ESKD was also considered as the time of event. CKD staging was considered on the basis of KDIGO classification,[17] and GFR was estimated by applying the CKD-EPI formula.

We also collected the demographic characteristics of the study participants, frequency of renal complications of ADPKD, mortality rate, and the cause of mortality.

The Kaplan–Meier model with log-rank test was applied to estimate overall patient and kidney survival as well as sex differentiation with a 95% confidence limits. The Cox regression method was used to analyze the relationship between prognostic factors and mortality or ESRD events among our study population. In this analysis, apart from the confidence limits of 95% in hazard ratios, a P value of less than 0.05 was considered statistically significant.

In the regression analysis, to facilitate the interpretation of the results, continuous quantitative variables such as age at CKD diagnosis, serum creatinine level, and the amount of annual decline in GFR were recoded to binomial variables. The cutoff values used for this conversion are listed in Table 1 and Table 2. SPSS version 16 and STATA version 14 statistical software were used in Cox regression.

Table 1. Demographics of Patients with Autosomal Dominant Polycystic Kidney Disease

Variables All patients (n = 145)	
Mean Age at Diagnosis, y	53.15 ± 12.38
Male Gender (%)	100 (69)
Female Gender (%)	45 (31)
Family History of ADPKD (%)	124 (85.52)
Hypertension (%)	96 (66.21)
Nephrolithiasis	94 (64.83)
Liver Cyst	56 (38.62)
Anemia	72 (49.65)
Cardiovascular Disease	32 (22.07)
Diabetes Mellitus	15 (10.34)
Cyst Hemorrhage	51 (35.17)
Cyst Infection	17 (11.72)
Gross Hematuria	42 (29)
Vascular Thrombosis	5 (3.45)
Cerebrovascular Events	3 (2.07)
Renal Malignancy	1 (0.69)

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

Table 2. Clinical Outcomes of the Patients with Autosomal Dominant Polycystic Kidney Disease

Variables	Frequency (%)	Total Numbers
ESKD (%)	67 (46.21)	145
Hemodialysis (%)	62 (42.76)	145
Peritoneal Dialysis (%)	0 (0)	145
Preemptive Kidney Transplantation (%)	5 (3.45)	145
Mortality (%)	20 (13.79)	145
Sepsis	6 (30)	20
COVID-19	6 (30)	20
Cardiovascular Events	2 (10)	20
ESKD Complications	1 (5)	20
Kidney Transplant Rejection	1 (5)	20
Extra-renal Malignancies	1 (5)	20
Others	2 (10)	20

Abbreviations: ESKD, end-stage kidney disease

RESULTS

Our study population included 100 males (69%) and 45 females (31%), with a mean age of 53.15 ± 12.38 (22 to 87 years). The mean and median ages at diagnosis were 37.46 ± 12.38 and 36 years, respectively. A positive family history of ADPKD was identified in 124 cases (85.5%).

Hypertension was found in 96 patients (66.21%), nephrolithiasis in 94 patients (64.83%), and anemia in 72 patients (49.65%). Liver cysts were detected in 56 patients (38.62%). Renal cyst complications developed in 68 patients, including 51 cases (35.17%) of cyst hemorrhage and 17 cases (11.72%) of cyst infection. Cardiovascular disease occurred in 32 patients (22.7%). Table 1 displays the demographic data of patients with ADPKD.

Population distribution is illustrated in Figure 1, according to different CKD stages, at two-time points of ADPKD diagnosis and CKD diagnosis. As it is shown most patients have normal kidney function at the time of ADPKD diagnosis, and most cases of CKD are at stages 2 and 3. Overall, in the course of the disease, 71 patients (48.97%) progressed to different stages of CKD, 67 patients (46.21%) reached ESKD and required RRT, and only 7 patients maintained their normal kidney function (4.82%) (Figure 2). The mean duration of progression from ADPKD diagnosis to CKD was 15.84 ± 11.86 years, and the rate of GFR decline per year was estimated at 3.36 ± 2.55 cc/min, by

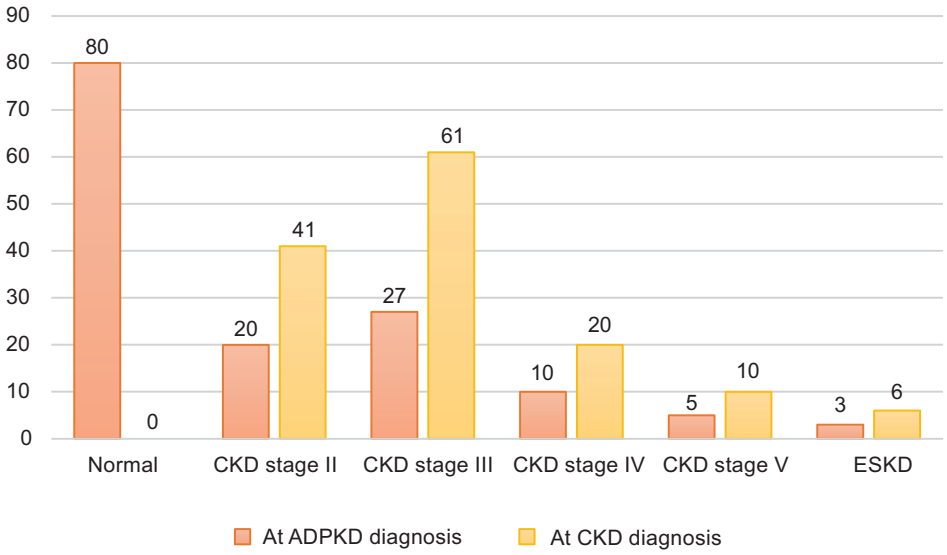

Figure 1. Population Distribution According to Kidney Function, at the Time of ADPKD Diagnosis and CKD Diagnosis in the Course of the Disease.

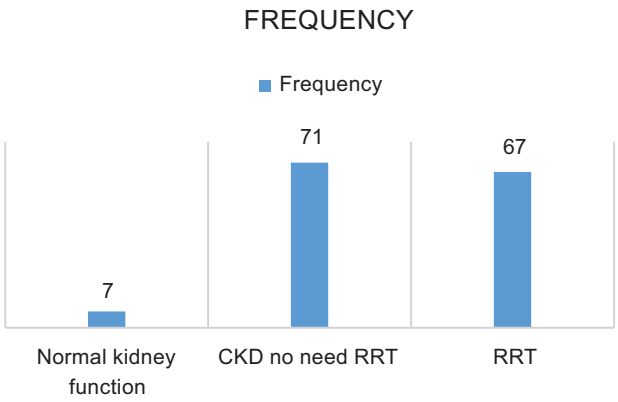

Figure 2. Population Distribution According to Kidney Status During the Study.

using the CKD-EPI formula.

As mentioned earlier, death and ESKD occurrence were considered the primary outcomes. The frequencies of primary outcomes are displayed in Table 2. During the follow-up period, 20 patients (13.79%) died, with a median age of 64.2 ± 12.96. The most common cause of death was infection, especially sepsis (30%) and COVID-19 (30%), and the second most common cause was cardiac events (10%). Cerebrovascular events, extra renal malignancies, and surgical or medical complications of kidney transplantation were less common causes of death.

Patient and kidney survival analysis and risk ratio calculation were performed for 145 ADPKD patients. The Kaplan–Meier method estimated an overall patient survival ratio of 99.06% by the age of 45 (95% CI: 0.93 to 0.99), 86.05% at the age of 60, and 67.99% at the age of 70. As illustrated in Figure 3, the slope of the curve decreased. Furthermore, the patient mean and median survival times were 76.76 (95% CI: 73.35 to 80.16) and 83 years, respectively.

Kidney survival, as demonstrated in Figure 4, decreases more steeply by the age of 44 and is reduced to 48% by the age of 60 and 28% by the age of 70, which can be interpreted as the probability of reaching ESKD being 52% and 72% by these ages, respectively (95% CI: in all results). Additionally, the mean and median kidney survival were 61.81 (95% CI: 58.65 to 64.97) and 58 years, respectively, in 145 participants of the study. The log-rank test showed that men had significantly better kidney or patient survival than women ($P < .05$).

In the Cox regression model, as reported in Table 3, CKD diagnosis at the age of 40 years or less and a GFR reduction of more than 5 cc/min per year, increases the risk of death in patients by more than four times.

In addition, reaching ESKD in the course of the disease increased the risk of death more than seven times. Although vascular thrombosis was observed in only five of the participants, this complication, as an independent risk factor, increased the risk of death by nearly six folds.

Considering the significant correlation between the patient's serum creatinine level at the first visit and the probability of ESKD occurrence (Pearson

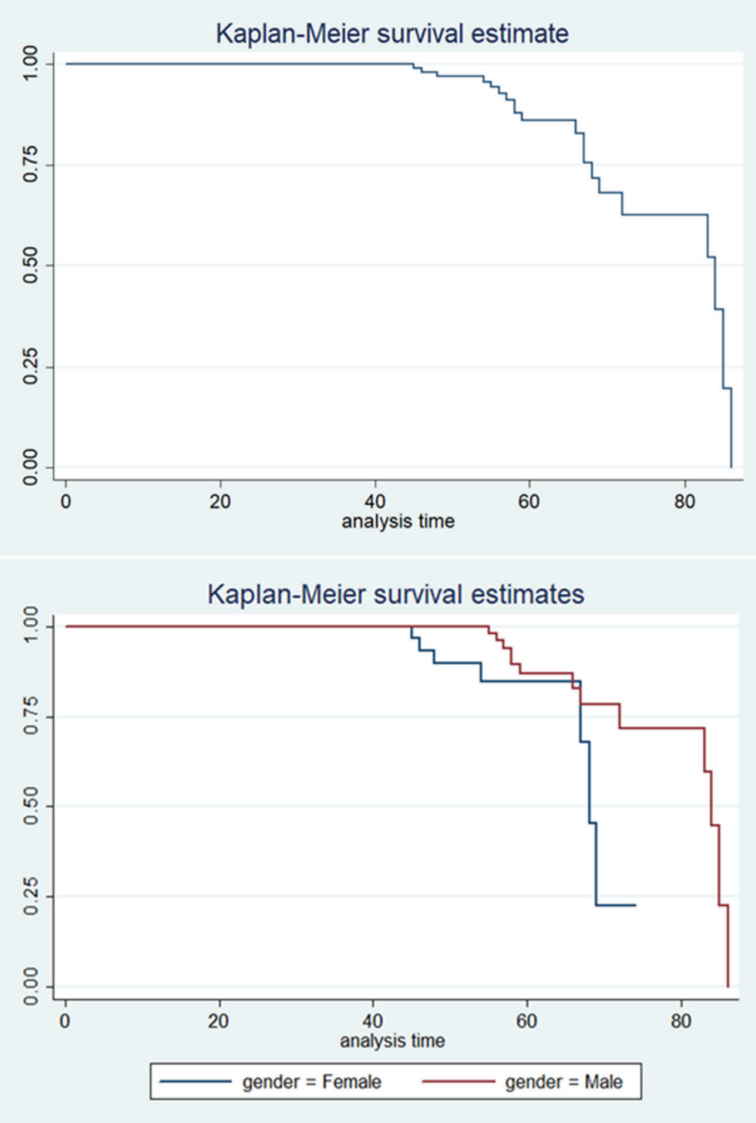

Figure 3. Overall patient survival rates in ADPKD (above), and comparison by gender shows better survival in males than females (P = .0326), note that the difference increases by age (below). The horizontal axis shows time in years and the vertical axis shows the patients' survival ratio.

correlation coefficient = 0.364, $P < .001$) and the collinearity associated with this correlation, this variable was regressed separately, and if the creatinine level at the initial investigation was higher than 1.5 mg/dL, the risk of death increased approximately three times.

We found that an age of 40 years or less at the time of CKD diagnosis increased the risk of ESKD by approximately four times. A baseline serum creatinine level of more than 1.5 mg/dL and underlying ischemic heart disease increased the ESKD risk ratio by 1.8- and 2.4-fold, respectively (Table 4).

Among other factors, including gross hematuria, hypertension, the amount of water and salt in diet, and antihypertensive drugs, no significant role in patient or kidney survival was detected.

DISCUSSION

Up to 12 million people are affected by ADPKD, making it the fourth most common cause of renal replacement therapy (RRT) worldwide.[18] There is no shadow of doubt that a definitive diagnosis of ADPKD based on the genetic study is generally out of reach. Regarding the lack of broadly accepted practical guidelines for the care of ADPKD, it is crucial to predict kidney outcomes and identify the clinical risk factors for these patients in Iran.

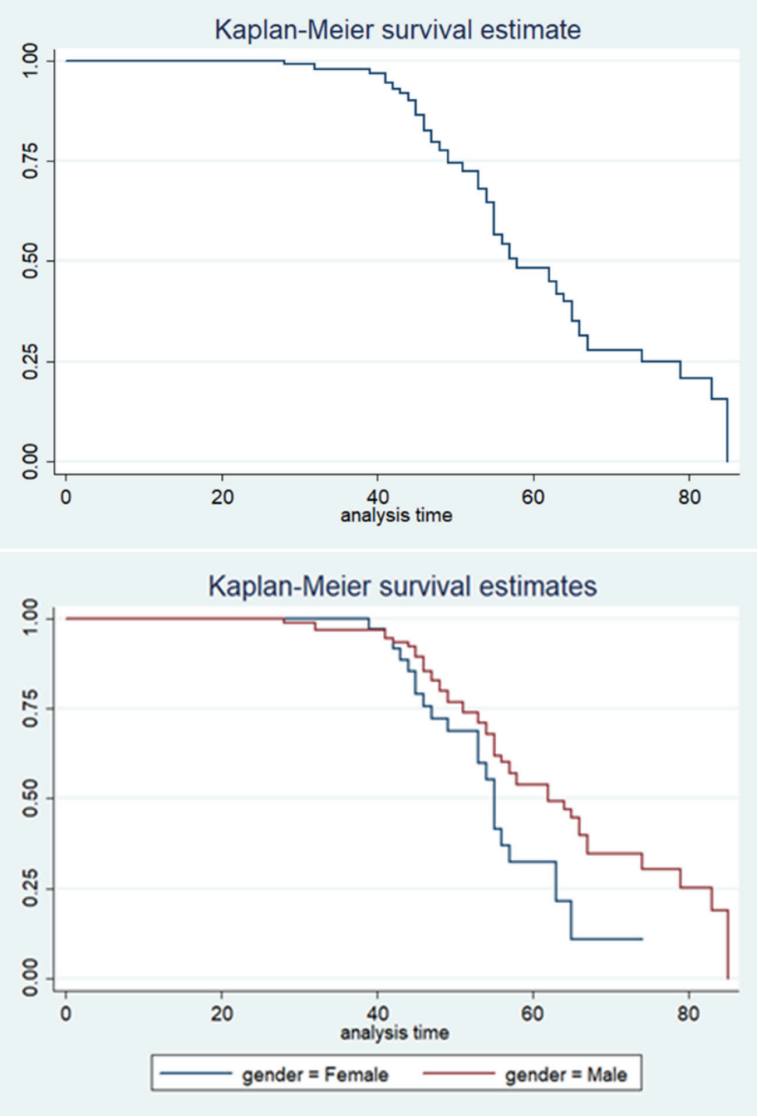

Figure 4. Overall kidney survival rates with autosomal dominant polycystic kidney disease (above), comparison by gender shows better survival in males than females (*P* = .0256) note that the difference increases by age (below). The horizontal axis shows time in years and the vertical axis shows the patients' survival ratio.

Table 3. Clinical Risk Factors for Death in Patients with Autosomal Dominant Polycystic Kidney Disease

Variables	OR (HZ)*	95% CI	*P*
Diagnosis of CKD ≤ 40 y/o	4.66	1.66 to 13.1	.004
Annual GFR Decline of more than 5 cc/min	4.33	1.27 to 14.81	.019
Reach ESKD in the Course of the Disease	7.31	1.51 to 35.36	.013
First SCr Detected above 1.5 mg/dL**	3.09	1.14 to 8.41	.027

Abbreviations: SCr, serum creatinine
*Results of Cox Proportional Hazard Regression Model (outcome: death, analysis time: Death age)
**Level of serum creatinine at diagnosis was fitted in another model containing only this variable and the age at diagnosis of CKD to avoid collinearity between it and the occurrence of ESR.

Because symptoms do not typically manifest before the age of 30, [19] ADPKD is generally diagnosed in adults over this age; accordingly, the mean age of ADPKD diagnosis was approximately 37 years in our study, and around 43 and 38 years in two Korean studies.[13]

In most patients, the renal function remains intact until the fourth decade of life, as reported

Table 4. Clinical Risk Factors for ESKD in Patients with Autosomal Dominant Polycystic Kidney Disease

Variables	OR (HZ)*	95% CI	*P*-value < 0.05
Age at Diagnosis of CKD ≤ 40 y/o	3.99	2.29 to 6.95	.000
First SCr Detected above 1.5 mg/dL	1.82	1.10 to 3.02	.019
Cardiovascular Disease Events	2.41	1.31 to 4.41	.005
Hypertension	0.22	0.07 to 0.63	.005

Abbreviations: SCr, serum creatinine
*Results of Cox Proportional Hazard Regression Model (outcome: ESKD, analysis time: ESKD age)

previously. [6] In line with this, the mean age at CKD diagnosis was approximately 45 years in our study population. Additionally, it has been reported that ESKD develops in ADPKD patients at a mean age of 54.3 and 74 years based on PKD1 and PKD2 mutations.[7] According to our research, the frequency of ESKD was 46.2%, with a mean age of 51 years. Comparable figures were 45.8% in Korea and 49% in Japan.[12,13] Based on our findings, GFR declined by a mean of 3.36 cc/min annually, which was close to the range of 4.4 to 5.9 cc/min found in other studies.[6]

Hypertension is present in the majority of ADPKD patients.[6] It was observed in 66.2% of our cases, and the frequency has been reported to range between 68.4 to 87.6% in some studies.[13] Kidney stones occur in up to 25% of these patients,[20] while, it was detected in 64.8% in our study participants. Anemia is uncommon in ADPKD due to acceptable erythropoietin levels in polycystic kidney disease.[21] Nevertheless, it was found in 49.65% of our study population, even though it was mild; the mean hemoglobin was 12.1 g/dL, and more than half of the patients received renin-angiotensin-aldosterone system (RAAS) inhibitor therapy. The frequency of gross hematuria was 29% based on our results, although in another research, it ranged from 35 to 50%.[20] Liver cysts were detected in 56 out of 145 study participants of our study with a frequency of 38.62%, regardless of age, while other studies reported increasing prevalence of liver cysts with increasing age, from approximately 20% in the third decade to 70% in the seventh decade of life.[22]

According to previous studies, 55% of ADPKD patients developed ESKD by the age of 50 years and 70% by the age of 70.[11] Based on another report in Japan, ESKD was detected in 49% of 65- to 69-year-old patients and then declined [12]. Additionally, a retrospective study in 2022 mentioned that 45% to 70% of patients with ADPKD reach ESKD by the age of 65.[13] We calculated the probability of ESKD to be 52% by the age of 60, and 72% by the age of 70; these findings are consistent with overall kidney survival in our population. The median kidney survival time was 58 years in 145 participants of our study.

Patient survival was 86.05% at the age of 60 and 67.99% at the age of 70, with a median survival time of 83 years. While the overall mortality rate was 13.79% in our study population, Ebadur Rahman and his colleagues, in their retrospective, observational analysis, mentioned that the mortality rate in patients with ADPKD ranged between 1.6- and 2.88-fold in comparison with the general population, with a median death age of 60.5 years in that study. [23] however, the median death age was 62.5 in our study.

According to a global research, risk factors for ADPKD progression include PKD1 mutation, kidney size, number of cysts and rapid kidney growth rate, early onset of hypertension, early symptoms, especially before the age of 30, male sex, proteinuria, recurrent gross hematuria, higher urinary sodium excretion and, three or more pregnancies, which are associated with a more rapid decline in glomerular filtration rate.[6] We investigated some of these parameters, as described above, and found prognostic factors that affect patient or kidney survival. Patients serum creatinine levels above 1.5 mg/dL at the time of diagnosis and underlying coronary vascular disease were identified as risk factors for progressive kidney disease in ADPKD patients, while an annual GFR decline of more than 5 cc/min and a history of vascular thrombosis increase the risk of death in these patients. CKD diagnosis at the age of 40 or less increased the risk for both ESKD and death. According to our findings, females were more prone to ESKD and death than males, contradicting previous research. However, it should be noted that the number of women (45 people) in our study population was less than half of the number of men (100 people)

and this smaller sample size can be a reason for the insufficient variety of all possible conditions for women. Therefore, more studies with larger sample sizes of females are needed to clear any doubt regarding these cases.

Despite the strong association that has been reported between hypertension and deterioration of kidney function, [24] the presence of hypertension did not significantly affect kidney survival in our study. This is likely because almost all 96 hypertensive patients in our study were taking one of the RAAS inhibitor medications, suggesting that the protective effect of these agents obscured the effect of hypertension in the progression of CKD and kidney survival. According to earlier studies, the use of antihypertensive medications and strict control of hypertension increase the survival of ADPKD patients.[25] According to the nephrology societies, the renin-angiotensin-aldosterone system plays a crucial role in the pathophysiology of hypertension, and early detection and management of the condition can improve renal and cardiovascular prognoses.[26]

Despite the fact that numerous studies have been published regarding the prognosis of ADPKD and the risk of progression to ESKD worldwide, there has not been much research on ADPKD in Iran. These reports are undoubtedly helpful to our understanding, but there is still a great deal of uncertainty and ambiguity regarding many aspects of care and management of ADPKD patients. Clinical trials must be conducted with special focus on improving outcomes and quality of life in patients with ADPKD.

CONCLUSION

In patients with ADPKD, the first creatinine level at the time of diagnosis and underlying coronary vascular disease were identified as risk factors for progressive kidney disease, and a decline in GFR of more than 5 ml/min per year was associated with the risk of mortality. A diagnosis of CKD at the age of 40 or less increases the risk of ESKD and death, and females seem to be more prone to ESKD and death than males.

LIMITATIONS OF THE STUDY

Although the literature is certainly valuable to our understanding of ADPKD, there is still considerable uncertainty in many areas of these patients' care and management. A specific focus on more precise data collection and conducting clinical trials to enhance outcomes and quality of life for individuals with ADPKD are suggested.

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ETHICAL CONSIDERATIONS

All procedures performed in this study were according to the ethical standards of the Iran University of Medical Sciences Research Committee (Code: IR.IUMS.FMD.REC.1401.090) and with the 1964 Helsinki Declaration and its later amendments. All participants signed informed consent form before the study.

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