Kidney Transplantation Outcomes across Autosomal Dominant Polycystic Kidney Disease at Siriraj Hospital

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ABSTRACT

Background: Thailand has a population of 65 million. The estimated incidence of chronic kidney disease (CKD) patients is approximately 17%. Siriraj Hospital has performed kidney transplantations since 1973. With 43 years of experience, a total of 1,150 kidney transplantations (65.5% were deceased donors and 34.5% were living donors) were performed at Siriraj Hospital. Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent, potentially lethal, monogenetic disorder with the prevalence of 1:500-1:1000 worldwide. It is the fourth leading cause of end-stage renal disease (ESRD). The characteristic of ADPKD is the enlargement of kidney from numerous cysts present on the renal tubules which gradually grow resulting in the decline of glomerular filtration rate (GFR) and eventually turning into ESRD.

Objective: We aimed to study the outcome of kidney transplantation in ADPKD recipients at Siriraj Hospital.

Methods: Thirty-one ESRD-ADPKD patients (male 22, female 9) received kidney transplantation at Siriraj Hospital. Twenty-eight patients (90.3%) were deceased donors and 3 patients (9.7%) were living donors. All living donors were performed genetic tests, including linkage study and mutation test, to exclude ADPKD relatives who carried abnormal PKD genes.

Results: The kidney allograft survival at 1-, 5- and 10-years were 81%, 81% and 54%, respectively. The results of patient survival at 1-, 5- and 10-years were 94%, 90% and 75%, respectively.

Conclusion: Kidney transplantation provides excellent patient and graft survival rates and is the preferred treatment option for patients with ADPKD and ESRD.

Keywords: ADPKD; kidney transplantation; outcome; Thailand (Siriraj Med J 2017;69: 194-197)

INTRODUCTION

Thailand has a population of 65 million. The estimated incidence of chronic kidney disease (CKD) is approximately 17% of total population, and presently about 70,000 ESRD patients are receiving dialysis treatments (hemodialysis, HD) or continuous ambulatory peritoneal dialysis, (CAPD). Diabetic kidney disease and hypertensive nephropathy are the two most common causes of ESRD, among dialysis patients.[1] The first renal transplant in Thailand was performed in 1972. The second successful cadaveric renal transplant was performed at the Siriraj Medical School Hospital in 1973. Only living related donors, spouses and deceased donors are legally allowed to donate for kidney transplantation in Thailand.[2] The official brain death criteria were announced by The Thailand Medical Association in 1989. Presently, the Organ Donation Center of the Thai Red Cross Society acts as the center for organ donation and allocation of cadaveric kidneys. Organs are shared among patients on a national waiting list based on HLA matching, anti-HLA antibody titers and waiting time, but the hospital that procured the donor has the right to use one of the kidneys for the best HLA-matched patient on its local list.[3] Prior to the year 2004, only ESRD patients who were working

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for government service could reimburse their costs for kidney transplantation. The Social Security Office and the National Health Security Office launched a program to grant kidney transplantation reimbursement since December 5, 2004 and October 1, 2008 respectively. Ever since all Thais have had health care coverage that included dialysis and kidney transplantation.[3]

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent, potentially lethal, monogenetic disorder with the prevalence of 1:500-1:1,000 all over the world and accounts for approximately 10% of the patients who are on renal replacement therapy. It is the fourth leading cause of end-stage renal disease (ESRD). The characteristic of ADPKD is the enlargement of kidney from numerous cysts present on the renal tubules which gradually grow resulting in the decline of GFR and eventually turning into ESRD. The enlargement of the cysts results from cell proliferation, fluid secretion and the remodeling of the surrounding milieu. Until now, the mechanism underlying this disorder has not been fully understood. Many hypotheses had been proposed. In ADPKD, there is the mutation of PKD1 and/or PKD2 genes, resulting in abnormal formation of polycystin-1 and polycystin-2 protein. Both polycystin proteins have been found in the primary cilium, which is a non-motile microtubule-based structure that extends from the apical membrane of tubular cells into the lumen. These primary cilia composed of abnormal polycystin-1 and polycystin-2 are associated with abnormal intracellular signaling process that leads to increased cell proliferation and increased cell apoptosis. Other than the numerous kidney cysts, ADPKD patients can also develop cysts in other organs such as liver, pancreas, seminal vesicles or arachnoid membrane and can also have other pathologies such as abnormal intracerebral vessels (intracranial aneurysm and intracranial dolichoectasias), aortic root dilatation, aortic root aneurysm, mitral valve prolapse, diverticular disease or abdominal wall hernia. It has been shown that patients with ADPKD are insulin resistant and some patients are hyperinsulinemic, which may indicate that ADPKD patients are at high risk of cardiovascular complications.[4-6]

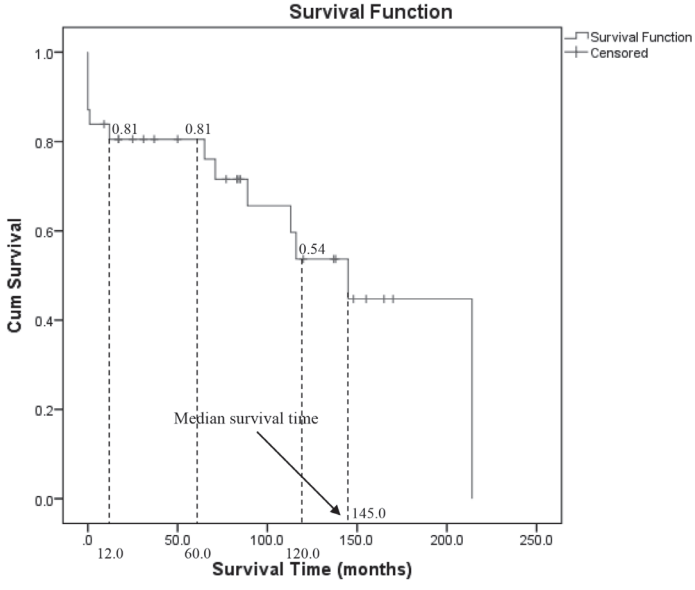
MATERIALS AND METHODS

We reviewed all patients who underwent kidney transplantation (KT), from both living and deceased donors, at our center between June 27, 1973 and September 30, 2016. With 43 years of experience, a total of 1,150 kidney transplantations (65.5% were deceased donors and 34.5% were living donors) were performed at Siriraj Hospital. The initial immunosuppressive regimen was azathioprine (AZA) and prednisolone. Cyclosporine (CsA) was introduced in 1985, mycophenolate mofetil (MMF) was introduced in 1999 and have been a part of standard regimen since 2003. Our current standard regimen includes calcineurin inhibitor (CNI), MMF and prednisolone. Tacrolimus (FK 506) became available in 2000. Maintenance immunosuppression consisted of prednisolone (P) (40 mg/day tapered to 10 mg/day and CNI [CsA (3-5 mg/kg BW/day) or FK (0.06-0.08 mg/kg BW/day)] and/or MMF (1.5-2 g/day). The dose of MMF was adjusted according to complete blood counts. Doses of CNI were adjusted as per trough levels.[7] Amongst all 1,150 kidney transplants, 31 patients were ADPKD. The diagnosis of ADPKD had been established before kidney transplantation by display of enlarged polycystic kidneys using ultrasound techniques and, in some ADPKD patients, it was further confirmed by the demonstration of liver cysts and/or a family history of ADPKD. All living donors were performed genetic tests, including linkage study and mutation test, to exclude ADPKD relatives who carried abnormal PKD genes. Deceased donors were allocated by the Organ Donation Center of the Thai Red Cross Society using the allocation score. After kidney transplantation, all ADPKD patients were followed at weekly intervals for the first three months, fortnightly for the next three months, monthly for the next six months and three-monthly intervals thereafter. On every visit, complete blood counts, renal function tests including urinalysis and blood trough levels on CNI were monitored. Kidney graft biopsy was performed in the event of graft dysfunction, and rejection was diagnosed according to the modified Banff classification and patients were treated with standard anti-rejection therapy. Acute T-cell mediated rejections were treated with methylprednisolone (MP) 500 mg x 3 doses in combination with or without r-ATG 1.5 mg/kg BW, single dose. Acute B-cell mediated rejections were treated with MP 500 mg for three doses, plasmapheresis (1.5 x plasma volume per session for three sessions), intravenous immunoglobulin (IVIG) 2 g/kg divided in 2 days in combination with Rituximab 375 mg/m^2 BSA. The 1-, 5- and 10-year actuarial graft survival rates and patient survival rates were calculated according to the Kaplan-Meier method. Graft survival was defined as time from transplant to requirement for hemodialysis or peritoneal dialysis. Patient survival was defined as time from transplantation to death. Statistical analysis was performed using SPSS version-12 (Statistical Package of Social Sciences). Continuous data were presented as mean ± SD and Student's t tests were used to compare two groups and ANOVA was used for more than two

groups. Categorical data were compared using χ2 tests or Fisher's exact tests. Kaplan-Meier curves and log-rank tests were used to describe and compare the patient and graft survival rates. $P < 0.05$ was taken to indicate statistical significance.

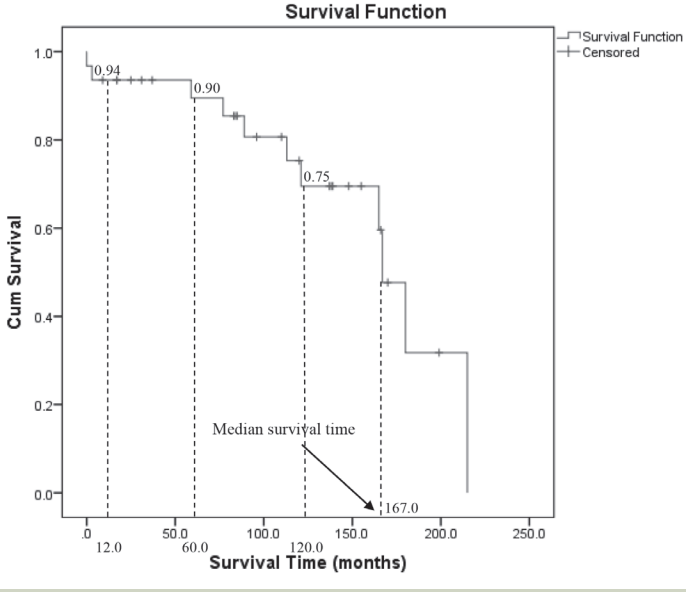
RESULTS

Of 1,150 kidney transplants (KTx) performed at our center between June 27, 1973 and September 30, 2016, 31 (2.7%) KTx were performed for ADPKD. Twenty eight patients (90.3%) were deceased donors and 3 patients (9.7%) were living donors. Mean age of ADPKD transplant patients was 48.7 ± 9.2 years old. One-, five- and ten-year patient survival rates among post-transplant ADPKD patients were 94%, 90% and 75%, respectively Fig 1. One-, five- and ten-year graft survivals amongst ADPKD transplant patients were 81%, 81% and 54%, respectively. Survival rates are shown by Kaplan Meier graphs Fig 2.



	Survival time	Standard error	95% Confidence interval
Mean	134.2	17.7	(99.5, 168.8)
Median	145.0	26.4	(93.2, 196.8)

Fig 1. Kaplan-Meier curve- Patient survival rates of ADPKD transplant patients.



	Survival time	Standard error	95% Confidence interval
Mean	156.1	14.1	(128.5, 183.7)
Median	167.0	7.9	(151.5, 182.5)

Fig 2. Kaplan-Meier curve- Kidney allograft survival rates of ADPKD transplant patients.

DISCUSSION

Our study has demonstrated similar patient and graft survival between ADPKD transplants and overall transplants performed at our hospital. Regarding kidney transplants performed in Siriraj Hospital, overall transplant patient survivals at 1-, 5- and 10-years were 83.8%, 71.5% and 56.5%, respectively for deceased donor transplants and were 97.3%, 90.0% and 83.1%, respectively for living donor transplants. Kidney allograft survival at 1-, 5- and 10-years were 76.3%, 61.2% and 40.9%, respectively for deceased donor transplants and were 95.4%, 84.2% and 65.3%, respectively for living donor transplants.[3] However, in this study, there were only 3 ADPKD patients who were living donor transplants, while 28 ADPKD patients were deceased donor transplants. Thus, it could be concluded that the results of patient and kidney allograft survival of ADPKD transplants were better than deceased donor transplants. Kidney transplantation has become the treatment of choice for ESRD in ADPKD. It has been shown in several studies that the results of kidney transplantation from living donors are better than from deceased donors.[8-12] Because ADPKD is a genetic disease, living relatives of ADPKD recipients may avoid donating a kidney because of fear of a future appearance of polycystic disease. Living related transplants are undertaken for ADPKD recipients with concern about the inaccuracy of pre-symptomatic diagnosis or decreased availability of asymptomatic donors in these families. DNA linkage analysis is also not available in every transplant hospital. As compared with ultrasound imaging, genetic linkage analysis including DNA mutation study is a highly sensitive method of donor screening, with 99% accuracy in the diagnosis of ADPKD and negative predictive value of almost 100%, but currently this is not practical for donor screening in most transplantation centers in Thailand. Therefore, deceased donor is a better or, sometimes, the only option for ADPKD patients in most transplantation centers. However, in our hospital, we can perform genetic linkage including DNA mutation study in our ADPKD patients and use this as a method to screen living relatives who would like to donate their kidneys to their ADPKD recipients.[13]

CONCLUSION

Both decreased and living kidney transplantations are safe approaches of renal replacement therapy in ADPKD patients with ESRD. Our results have shown that kidney transplantation in ADPKD patients provides a low morbidity and high graft and patient survival rates. Genetic linkage analysis including DNA mutation study is the best method to screen the potential living donation in relatives of ADPKD recipients.

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