



Outcomes of end-stage renal disease patients on the waiting list for deceased donor kidney transplantation: A single-center study

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Background: Kidney transplantation is an effective renal replacement therapy for patients with end-stage renal disease (ESRD). In this study, we assessed the impact of the baseline characteristics and comorbidities of ESRD patients on the probability of deceased donor kidney transplantation (DDKT) and evaluated the morbidity and mortality during the time spent waiting.

Methods: The study population consisted of 544 ESRD patients on the waiting list for DDKT at Chungnam National University Hospital in South Korea between February 2000 and October 2015. The patients were observed from the date of transplantation list registration to the date of transplantation. Baseline characteristics and comorbidities were investigated together with new-onset comorbidities that occurred during the waiting time.

Results: Diabetes mellitus (39.0%), hypertension (25.2%), and glomerulonephritis (21.3%) were the three most common causes of ESRD in this study, and coronary artery disease (9.4%) was the most common comorbidity. The 115 patients (19.3%) who underwent DDKT had a mean waiting time of 1,711 days (768–2,654 days or 4.68 years [2.10–7.27]). Blood groups other than type O, peritoneal dialysis, and nondiabetic ESRD were significantly associated with a higher likelihood of DDKT. Infection was the leading cause of death and the most common comorbidity that arose during the waiting time. Patients who experienced cardiovascular events during the waiting time showed a lower transplant rate compared with those who did not.

Conclusion: The prevalence of comorbidities was high in renal transplantation candidates. During the often-long waiting time, new comorbidities may occur, with long-term sequelae limiting access to kidney transplantation or resulting in death.

Keywords: Comorbidity, End-stage renal disease, Kidney transplantation, Waiting lists

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Introduction

Kidney transplantation (KT) is an effective renal replacement therapy that reduces mortality and improves the quality of life of patients with end-stage renal disease (ESRD) [1–4]. However, an increase in the number of ESRD patients along with a chronic shortage of donor kidneys has resulted in an extended waiting time for deceased donor kidney transplantation (DDKT). According to an annual report on KT in Korea, the number

of patients on the waiting list for DDKT grew from 2,309 in 2000 to 16,011 in 2015, with a mean waiting time in 2015 of 1,904 days [5]. The prevalence and incidence of comorbidities in ESRD patients are higher than in the general population. Therefore, KT candidates who wait for a long time are likely to develop new comorbidities, which may impact their suitability for transplantation [6–10]. Typical comorbidities in ESRD patients include cardiovascular disease and infection, both of which can severely aggravate the underlying medical condition and limit access to KT [11–18]. The factors that influence the probability of receiving a transplant in DDKT candidates have not been thoroughly studied. Thus, the aim of this study was to identify the baseline factors that affect the probability of undergoing DDKT and to determine the effects of new comorbidities that develop during the waiting time on the likelihood of KT in waitlisted patients.

Methods

Study design and patients

Dialysis patients with stage 5 chronic kidney disease who were registered on the waiting list for DDKT at Chungnam National University Hospital between February 2000 and October 2015 were included in this study.

Data collection

This study was approved by the Institutional Review Board of Chungnam National University Hospital (IRB approval number: CNUH 2018-09-028). Demographic and clinical data were collected retrospectively through a review of medical records and included age, sex, blood type, dialysis modality, panel reactive antibody, previous history of KT, cause of ESRD, and baseline comorbidities, including coronary artery disease, cerebrovascular disease, peripheral vascular disease, chronic liver disease, and a history of malignancy.

Measurements and definitions

The primary cause of ESRD was divided into groups of diabetes mellitus, hypertension, glomerulonephritis, polycystic kidney disease, and others. Diabetes mellitus and hypertension were defined as being present follow-

ing a physician diagnosis or based on a current prescription for medication to treat each disease. The dialysis modality was defined as the type of renal replacement therapy that each patient was receiving at enrollment. All patients except those who underwent living donor kidney transplant (LDKT) or died were grouped according to whether they received a DDKT or remained on dialysis; the baseline characteristics and the baseline prevalence of comorbidities were compared between these groups. Cardiovascular disease, infection, and malignancy that occurred during the waiting time were also noted. Cardiovascular disease was defined as hospitalization for coronary artery disease, cerebrovascular disease, or peripheral vascular disease. Cardiomyopathy, arrhythmia, and congestive heart failure cases diagnosed during outpatient treatment in numerous cases were not included in this category. Regarding infection, only severe cases that required hospitalization were included in the analysis. Patients whose waiting time was shorter than the 90th percentile of the waiting time of the transplanted group were divided into those who developed each new onset comorbidity and those who did not, and the transplantation rates were then compared.

Statistical analysis

Fisher's exact test was used to compare the baseline characteristics and comorbidities between patients who underwent DDKT and those who remained on dialysis. Logistic regression analysis was used to identify independent factors affecting the probability of DDKT by adjusting for potential confounders. Blood type, dialysis modality, cause of ESRD, duration of dialysis before kidney transplantation, and waiting time were included in the logistic regression analysis to calculate adjusted odds ratios (ORs). These ORs express the likelihood of undergoing DDKT for patients with risk factors compared with those without risk factors.

Cox regression analysis was used to compare patients who developed a new-onset comorbidity with those who did not with respect to the transplant rate. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software (ver. 22.0; IBM Corp., Armonk, NY, USA). A *P* value < 0.05 was considered to indicate statistical significance.

Results

Baseline characteristics and comorbidities of DDKT candidates

Between February 2000 and October 2015, 544 patients were registered on the waiting list for DDKT at Chungnam National University Hospital. The mean age at registration was 48.4 ± 12.0 years, and the female-to-male ratio was 0.57. Among them, 426 (78.3%) patients were on hemodialysis, and 118 (21.7%) were on peritoneal dialysis. Twenty-five (4.6%) patients had a previous history of KT. Diabetes mellitus ($n = 212$, 39.0%), hypertension ($n = 137$, 25.2%), and glomerulonephritis ($n = 116$, 21.3%) were the three most common causes of ESRD (Table 1). The most common comorbidity in waitlisted patients was coronary artery disease ($n = 51$, 9.4%) (Table 2).

Comparison of the baseline characteristics and comorbidities of patients who underwent DDKT and those who remained on dialysis

During the study period, 123 patients (22.6%) underwent KT (Table 3), 52 (9.6%) died, and 51 (9.4%) were

transferred to another hospital for KT. Of the 123 patients who underwent transplantation, DDKT was performed in 105 (85.4%) patients, while 18 (14.6%) received LDKT. The mean waiting time for DDKT was 4.68 years (2.10–7.27 years). The proportions of patients 60 years of age and older, and of male patients, were not significantly different between patients who underwent DDKT and those who remained on dialysis. Fewer patients in the transplanted group had blood type O than in the non-transplanted group ($P = 0.006$). The proportion of patients on peritoneal dialysis was larger in the transplanted group ($P = 0.009$), while the proportion of diabetic ESRD patients was smaller

Table 1. Baseline characteristics of the study population

Characteristic	Data (n = 544)
Age (yr)	48.4 ± 11.7
Sex, male:female	347 (63.8):197 (36.2)
Blood type	
A	187 (34.4)
B	155 (28.5)
O	140 (25.7)
AB	62 (11.4)
Type of RRT	
Hemodialysis	426 (78.3)
Peritoneal dialysis	118 (21.7)
Previous kidney transplantation	25 (4.6)
Primary causes of ESRD	
Diabetes	212 (39.0)
Non-diabetes	332 (61.0)
Hypertension	137 (25.2)
Glomerulonephritis	116 (21.3)
Polycystic kidney disease	21 (3.9)
Other	58 (10.7)

Data are presented as mean \pm standard deviation or number (%).

RRT, renal replacement therapy; ESRD, end-stage renal disease.

Table 2. Comorbidities of end-stage renal disease patients on the waiting list for deceased donor kidney transplantation

Comorbidity	Data (n = 544)
Coronary artery disease	51 (9.4)
Cerebrovascular accident	20 (3.7)
Chronic liver disease	14 (2.6)
HBV	9 (1.7)
HCV	4 (0.7)
Alcoholic	1 (0.2)
Malignancy	11 (2.0)
Colorectal cancer	2 (0.4)
Renal cell carcinoma	2 (0.4)
Breast cancer	2 (0.4)
Lung cancer	1 (0.2)
Stomach cancer	1 (0.2)
Thyroid cancer	1 (0.2)
Hematologic malignancy	1 (0.2)
Sarcoma	1 (0.2)
Peripheral vascular disease	8 (1.5)

Data are presented as number (%).

HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 3. Outcomes of end-stage renal disease patients on the waiting list for deceased donor kidney transplantation

Outcome	Data (n = 544)
Kidney transplantation	123 (22.6)
Deceased donor KT	105 (85.4)
Living donor KT	18 (14.6)
Death	52 (9.6)
Transfer	51 (9.4)
Still waiting	318 (58.4)

Data are presented as number (%).

Mean \pm standard deviation of waiting time for DDKT = $1,711 \pm 943$ days (4.68 \pm 2.58 years).

DDKT, deceased donor kidney transplantation; KT, kidney transplantation.

($P = 0.013$). The baseline prevalence of each comorbidity did not significantly differ between the two groups (Table 4). Independent factors affecting the likelihood of undergoing DDKT were O blood type (OR, 0.470; 95% confidence interval [CI], 0.265–0.833; $P = 0.010$), peritoneal dialysis (OR, 1.756; 95% CI, 1.052–2.932; $P = 0.031$), and diabetic ESRD (OR, 0.609; 95% CI, 0.374–0.991; $P = 0.046$), even after adjustment for the duration of dialysis before kidney transplantation and the waiting time (Table 5).

Comparison of new-onset comorbidities between the transplanted and non-transplanted groups during the waiting time

Infection was the most common cause of death in

waitlisted patients (2.2%), followed by cerebrovascular disease (1.3%). Infection was also the most common comorbidity during the waiting time. Infection developed in 95 (17.5%) patients, cardiovascular disease in 32 (5.9%), and malignancy in 19 (3.5%). Infection occurred at a median of 553 days after registration on the waiting list, with

Table 5. Multivariate logistic regression analysis for predicting deceased donor kidney transplantation

Variable	OR (95% CI)	P value
Blood type, type O	0.470 (0.265–0.833)	0.010
Type of RRT, peritoneal dialysis	1.756 (1.052–2.932)	0.031
Primary cause of ESRD, DM	0.609 (0.374–0.991)	0.046

CI, confidence interval; ESRD, end-stage renal disease; DM, diabetes mellitus; OR, odds ratio; RRT, renal replacement therapy.

Table 4. A comparison of characteristics between patients who underwent deceased donor kidney transplantation and those who remained on dialysis

Characteristic	DDKT		OR (95% CI)	P value
	Yes (n = 105)	No (n = 378)		
Age, > 60 yr	11 (10.5)	58 (15.3)	0.646 (0.326–1.280)	0.269
Sex, male:female	72 (68.6):33 (31.4)	230 (60.8):148 (39.2)	1.404 (0.886–2.226)	0.172
Blood type				
A	43 (41.0)	128 (33.9)	1.355 (0.869–2.111)	0.205
B	32 (30.5)	105 (27.8)	1.140 (0.711–1.828)	0.625
O	17 (16.2)	111 (29.4)	0.465 (0.264–0.817)	0.006
AB	13 (12.4)	34 (9.0)	1.430 (0.725–2.820)	0.351
Peak PRA > 20%	15 (14.3)	70 (18.5)	0.733 (0.400–1.343)	0.385
Type of RRT				
Hemodialysis	74 (70.5)	312 (82.5)	0.505(0.307–0.829)	0.009
Peritoneal dialysis	31 (29.5)	66 (17.5)	1.980 (1.206–3.253)	0.009
Previous KT	5 (4.8)	20 (5.3)	1.003 (0.367–2.736)	1.000
Primary cause of ESRD				
Diabetes	30 (28.6)	159 (42.1)	0.551 (0.344–0.882)	0.013
Hypertension	32 (30.5)	89 (23.5)	1.423(0.882–2.297)	0.162
Glomerulonephritis	23 (21.9)	84 (22.2)	0.982 (0.582–1.655)	1.000
Polycystic kidney disease	4 (3.8)	13 (3.4)	1.112 (0.355–3.484)	0.771
Others	16 (15.2)	33 (8.7)	1.879(0.990–3.568)	0.066
Comorbidity				
Cardiovascular disease	13 (12.4)	46 (12.2)	1.020 (0.528–1.968)	0.953
Coronary artery disease	8 (7.6)	35 (9.3)	0.801 (0.360–1.784)	0.701
Peripheral vascular disease	2 (1.9)	4 (1.1)	1.801 (0.325–9.971)	0.616
Cerebrovascular accident	3 (2.9)	12 (3.2)	0.890 (0.246–3.213)	1.000
Cancer	1 (1.0)	9 (2.4)	0.391 (0.049–3.122)	0.698
Chronic liver disease	1 (1.0)	10 (2.7)	0.351 (0.044–2.773)	0.470

Data are presented as number (%).

CI, confidence interval; ESRD, end-stage renal disease; DDKT, deceased donor kidney transplantation; KT, kidney transplantation; PRA, panel reactive antibody; RRT, renal replacement therapy; OR, odds ratio.

Table 6. Cause of death in end-stage renal disease patients awaiting deceased donor kidney transplantation

Cause of death	Data
Infection	11 (25.6)
Cerebrovascular accident	6 (14.0)
Malignancy	3 (7.0)
Coronary artery disease	3 (7.0)
Others	5 (11.6)
Bleeding gastric ulcer	1 (2.3)
Aortic aneurysm rupture	1 (2.3)
Drug intoxication	1 (2.3)
Traffic accident	1 (2.3)
Seizure	1 (2.3)
Unknown	15 (34.9)
Total	43 (100)

Data are presented as number (%).

Median (interquartile range) of time to death = 2.23 (0.84–6.19) years.

Table 7. New-onset comorbidities in end-stage renal disease patients awaiting deceased donor kidney transplantation

New-onset comorbidities	Data (n = 544)
Infection	95 (17.5)
Respiratory	32 (5.9)
CAPD peritonitis	22 (4.0)
Musculoskeletal	14 (2.6)
Genitourinary	9 (1.7)
Gastrointestinal	7 (1.3)
Vascular access-related	6 (1.1)
Other	5 (0.9)
Cardiovascular disease	32 (5.9)
Coronary artery disease	19 (3.5)
Cerebrovascular accident	12 (2.2)
Peripheral artery disease	1 (0.2)
Malignancy	19 (3.5)
Renal cell carcinoma	5 (0.9)
Colorectal cancer	3 (0.6)
Lung cancer	2 (0.4)
Stomach cancer	2 (0.4)
Cholangiocarcinoma	2 (0.4)
Breast cancer	1 (0.2)
Thyroid cancer	1 (0.2)
Hematologic malignancy	1 (0.2)
Sarcoma	1 (0.2)
Hepatocellular carcinoma	1 (0.2)

Data are presented as number (%).

Median (interquartile range) of time to cardiovascular disease = 2.04 (0.62–3.66) years; time to infection = 1.52 (0.81–3.08) years; and time to malignancy = 3.02 (1.22–5.58) years.

respiratory infection being the most common type of infection (n = 32, 5.9%). Cardiovascular disease occurred at a median of 745 days after registration, with coronary artery disease being the most frequent form (n = 19, 3.5%) (Table 6, 7).

In 90% of patients who received a KT during the study period, transplantation was performed within 2,704 days after the patient had been waitlisted. In patients with the waiting time less than 2,704 days, the group that developed new-onset cardiovascular disease during the waiting time showed a lower transplant rate compared with the group that did not ($P = 0.021$) (Fig. 1). In contrast, the transplant rates of patients who developed infection or malignancy were similar to those of patients who did not have these comorbidities.

Discussion

The aim of this study was to identify the factors influencing the probability of DDKT in ESRD patients registered on the renal transplant waiting list of a single center. For this purpose, we compared the baseline characteristics and comorbidities of patients who underwent DDKT and of those who remained on dialysis. The results showed higher proportions of blood type O ($P = 0.006$), hemodialysis ($P = 0.009$), and diabetes-related ESRD ($P = 0.030$) patients in the non-transplanted than in the transplanted group. New-onset comorbidities that developed after registration of the patient on the waiting list were also evaluated. Patients who developed new-onset

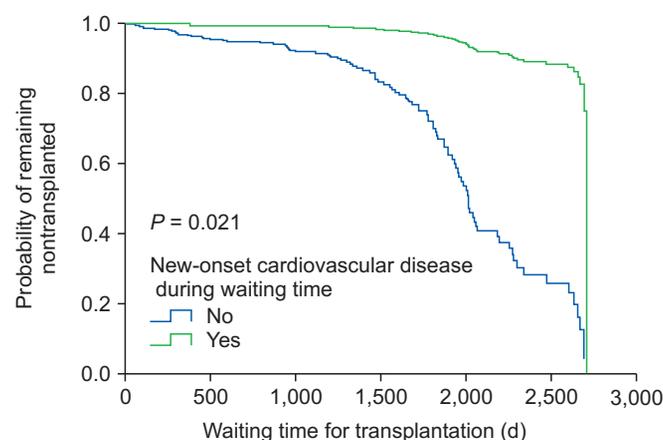


Figure 1. A comparison of the probability of remaining nontransplanted in patients who developed new-onset cardiovascular disease and patients who did not.

cardiovascular disease during the waiting time showed a lower transplant rate compared with those who did not.

The proportion of patients with blood type O was higher in the non-transplanted than in the transplanted group. This difference can be accounted for by the longer waiting time of these patients, as noted in an annual report on KT in Korea [5].

In the transplanted group, the proportion of patients on peritoneal dialysis was higher than in the non-transplanted group. Stel et al [19] found that, compared to patients on hemodialysis, those on peritoneal dialysis as their first therapy had a higher likelihood of receiving their first KT within four years. The authors suggested that the tendency for sicker patients to receive hemodialysis could explain these results [20]. In another study, Chalem et al [21] found that the median waiting time for KT was shorter in peritoneal dialysis patients than in hemodialysis patients, but they attributed this difference to a center effect. Snyder et al [22] reported a 1.39-fold greater likelihood of KT in peritoneal dialysis versus hemodialysis patients, even after adjusting for demographic and clinical characteristics, such as sex, race, age, body mass index (BMI), and comorbidities; however, the authors could not provide an explanation for the difference in the likelihood of KT between the two groups. In this study, likewise, the difference of the probability of transplantation between peritoneal dialysis patients and hemodialysis patients was maintained even after adjusting for baseline characteristics and comorbidities. As a result, we could not discern why the probability of DDKT in peritoneal dialysis patients was higher than in hemodialysis patients. It is possible that this difference may be due to the difference in longitudinal change in comorbid conditions during the waiting time between these two groups; further research on this topic will be needed.

Our study also indicated that diabetes mellitus reduced the probability of DDKT. This result was in accordance with the findings reported by Gaylin et al [23] that patients with diabetes were less likely to undergo KT than those without diabetes. Wolfe et al [1,24] and Villar et al [25] reported that the reduced access of diabetic patients to KT was mainly due to the lower likelihood of being waitlisted, rather than to a lower likelihood of KT after being waitlisted. However, in their study of diabetic ESRD patients, Akolekar et al [7] found that diabetes reduced not only access to the waiting list but also the chance of

receiving an allograft after the patient was waitlisted. Patibandla et al [26] demonstrated that the lower probability of KT associated with diabetes was due to the higher BMI of diabetic patients and their higher likelihood of comorbidities. In our study, however, the association between diabetes and a lower probability of DDKT was maintained even after adjusting for baseline characteristics and comorbidities. As discussed in the next paragraph, we thought this association might be due to the higher incidence of new-onset cardiovascular disease in diabetic patients than in the general population during the waiting time.

In our study, patients who developed cardiovascular disease during the waiting time showed a lower transplant rate compared with those who did not. Cardiovascular disease is the most common cause of death among ESRD patients and, in many cases, reduces the probability of KT in waitlisted patients. Schold et al [27] reported that the rate of removal of patients from the waiting list for being “too sick” was 24.9 per 1,000 person-years, with diabetic patients being more likely to be removed for this reason; cardiovascular events were the predominant cause of removal from the waiting list. Ningyan et al [11] found that 21.6% of KT candidates were dropped from the waiting list due to medical reasons or death, with 38.8% of both reasons being associated with cardiovascular events. Increased operative risk, a reduced willingness to receive a transplant, and increased mortality are all also possible causes of the lowered likelihood of KT in patients who experienced cardiovascular events during the waiting time [28,29]. Baseline cardiovascular disease was not a significant factor affecting the probability of DDKT in this study, while new onset cardiovascular disease was. We thought that this difference was because patients with severe baseline cardiovascular disease were excluded from enrollment on the renal transplant waiting list. In addition, we suspected that the lower likelihood of DDKT in diabetic patients registered on the waiting list was more likely associated with new-onset cardiovascular disease rather than baseline cardiovascular disease.

In this study, the mean waiting time for DDKT was 1,711 days, which was shorter than the 1,904 days reported by a Korean national survey. The difference may have been due to differences in the incidence of brain death and the number of candidates per jurisdiction. Furthermore, while cardiovascular disease was the most common

cause of death in ESRD patients, most of the deaths were due to infection, a discrepancy perhaps explainable by the small size of the sample and the possibility of unreported deaths [30].

A limitation of this study was that the sample size was relatively small; moreover, even patients with an extremely short observation period were included in the analysis, which may have affected the results. Large-scale studies are needed to identify other factors that influence the probability of undergoing DDKT, as well as strategies for the prevention and management of comorbidities in KT candidates.

This study compared the baseline characteristics and comorbidities of transplanted and non-transplanted patients and identified several factors affecting the probability of DDKT. In addition, the proportion of patients in each group who developed new-onset comorbidities during the waiting time was compared to determine the effects of specific comorbidities on KT. Our results led to the following conclusions:

1) The mean waiting time for DDKT among our patients was 1,711 days; in the Korean national survey, it was 1,904 days. This difference may reflect differences in the brain death incidence and the number of transplant candidates by jurisdiction.

2) The proportion of patients with blood type O and that of diabetic ESRD patients were smaller in the transplanted group than in the non-transplanted group, while the number of patients on peritoneal dialysis was larger in the transplanted group.

3) Patients who developed new-onset cardiovascular disease during the waiting time showed a lower transplant rate compared with those who did not have new comorbidities.

The prevalence of comorbidities is high in renal transplantation candidates. During the often-long transplant waiting time, new comorbidities may occur, with long-term sequelae limiting access to KT or resulting in death. Measures to ameliorate the negative impact of comorbidities on KT include regular follow-up.

Conflicts of interest

All authors have no conflicts of interest to declare.

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