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ORIGINAL ARTICLE

Declining trend of preemptive kidney transplantation and impact of pretransplant dialysis: a Korean nationwide prospective cohort study

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SUMMARY

We evaluated the temporal trend of preemptive kidney transplantation (KT) and the effect of pretransplant dialysis duration on post-transplant outcomes. This was a nationwide cohort study of the first-time 3392 living donor KT (LDKT) recipients (2014–2019). The annual changes in proportion of preemptive KT, factors associated with preemptive KT, and post-transplant outcomes were analyzed. Preemptive KT was performed in 816 (24.1%) patients. Annual trend analysis revealed gradual decrease in preemptive KT over time ($P = 0.042$). Among the underlying causes of preemptive KT, the proportion of diabetes increased and that of glomerulonephritis decreased during the study period. Glomerulonephritis as the primary renal disease was a predictor of preemptive KT. Patients with pretransplant dialysis >6 months showed increased graft failure risk than preemptive KT in the subdistribution of hazard model for competing risk (adjusted hazard ratio [aHR], 2.53; 95% confidence interval [CI], 1.09–5.87; $P = 0.031$) and in propensity score-matched analysis (aHR, 2.45; 95% CI, 1.02–5.92; $P = 0.034$); however, pretransplant dialysis ≤6 months showed comparable graft survival with preemptive KT in both analyses. Preemptive KT declined over successive years, associated with an increase in diabetes and a decrease in glomerulonephritis as underlying causes of KT. Short period of dialysis less than 6 months does not affect graft survival compared with preemptive KT; however, longer dialysis decreases graft survival.

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Introduction

Kidney transplantation (KT) is the treatment of choice for patients with end-stage kidney disease (ESKD) [1–3]. Preemptive KT refers to KT performed before initiation of dialysis. Preemptive KT has been shown to offer advantages with respect to graft and patient survival, quality of life, medical expenses, and return-to-work rates compared with KT after pretransplant dialysis [4–8]. In addition to these advantages, avoiding dialysis lowers the risk of dialysis-associated complications, such as catheter-related infection, sudden cardiovascular events, and progression of heart failure [9–11].

Despite these advantages, there are some limitations of preemptive KT. It requires sufficient time to prepare for transplantation [12]. For example, recipients need to be sufficiently stable to remain off dialysis during undergoing evaluation of immunologic and infection risks [13]. Government permission for transplantation is also needed and takes time. Moreover, some patients with chronic kidney disease may experience unexpected sudden decline in renal function [14].

In the United States, the reported rates of preemptive KT increased significantly from 17.9% in 1995 to 32.1% in 2009; these rates varied depending on the underlying cause of kidney failure [15]. The mean pretransplant estimated glomerular filtration rate (eGFR) in patients undergoing preemptive KT has shown a steady increase, which is indicative of increasing trend of early preemptive KT [15]. However, the changes in the recent trend and outcomes of preemptive KT, especially in the rapidly aging Asian population, are not well characterized. This study aimed to analyze the temporal trend of preemptive KT and evaluate the effects of pretransplant dialysis duration on the post-transplant outcomes.

Materials and methods

Patient population

The Korean Organ Transplant Registry (KOTRY) data were used in this study. The KOTRY collects data from 59 transplant centers. Since 2014, KOTRY prospectively collects nationwide organ transplantation data pertaining to five solid organs (kidney, liver, pancreas, heart, and lung) [16]. Detailed information about the KOTRY has been previously reported [17]. We analyzed data pertaining to all kidney transplant recipients who received living donor KT (LDKT) from 2014 to 2019 in the KOTRY database. The data do not contain personal information and do not infringe on the privacy of patients. This study was approved by the Institutional Review Board of the Kyungpook National University Hospital (2020-11-056). All patients provided written informed consent before participation, and the study was conducted in accordance with the 2000 Declaration of Helsinki and the Declaration of Istanbul 2008.

Data collection

A total of 3458 patients underwent LDKT during the study reference period. Sixty-six patients who had received second kidney transplants were excluded from the analysis; therefore, the remaining the first-time 3392 KT recipients were included in this study. These patients were divided into three groups according to the duration of pretransplant dialysis, that is preemptive KT, early KT (pretransplant dialysis less than 6 months), and late KT (pretransplant dialysis longer than 6 months). We set the cut-off duration of pretransplant dialysis between early KT and late KT as 6 months, referring to the previous studies that showed poor outcome in KT recipients with dialysis for more than 6 months [18,19]. Baseline demographic characteristics of the recipients, primary renal diseases, comorbid diseases, pretransplant desensitization, human leukocyte antigen (HLA) mismatch number, laboratory data, last follow-up date, graft loss, patient death, and occurrence of rejection were collected. In addition, demographic characteristics of donors and data of comorbidities were also collected. eGFR was calculated using the Modification of Diet in Renal Disease equation [20].

Objectives

The study objectives were to evaluate the temporal changes in the trend of preemptive KT, predictors of preemptive KT, and clinical outcomes according to the duration of pretransplant dialysis. Clinical outcomes were graft survival, patient survival, and early biopsy-proven acute rejection (BPAR)-free survival. Early BPAR was defined as the occurrence of BPAR within 3 months from KT. Subgroup analyses of graft survival by dialysis duration were also performed. Graft survival was defined as the time from KT to the initiation of maintenance renal replacement therapy. For patients who died with a functioning graft, the graft survival was censored at the time of death. Patient survival was defined as the time from KT to death from any cause.

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BPAR was diagnosed based on the Banff 07 classification [21].

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as frequency and percentage (%). The one-way analysis of variance (ANOVA) was applied, and then, the post hoc Bonferroni method was used to compare the continuous baseline characteristics among the three groups. Between-group differences were assessed using Pearson's chi-squared test or Fisher's exact test for categorical variables. Linear regression analysis was used to evaluate the change in the proportion of preemptive KT and other risk factors (diabetes, hypertension, glomerulonephritis, cardiovascular diseases, tumor, hepatitis C, and desensitization) over time. Logistic regression analysis was used to examine the predictors of receiving preemptive KT. Variables that showed a significant association in the univariable analysis were entered in the multivariable logistic regression model. Graft survival, patient survival, and early BPAR-free survival were analyzed using Kaplan–Meier analysis, and between-group differences with respect to survival outcomes were assessed using the log-rank test. Cox regression model was used to identify factors associated with graft failure. To account for patient death as a competing risk, we applied Fine and Gray proportional subdistribution hazard models for graft failure [22]. Variables associated with graft survival in the univariable analysis were entered in the multivariable model, along with age and sex. In addition, to balance the difference in baseline characteristics including age, BMI, comorbid diabetes and cardiovascular disease, and pretransplant desensitization between the preemptive KT and nonpreemptive KT groups (either early KT or late KT), a propensity score matching (PSM) using nearest-neighbor 1:1 matching was performed. Subgroup analyses by age, sex, desensitization, early acute rejection, body mass index, HLA mismatch, donor age, and donor type were performed. To investigate whether the adjusted hazard ratios (aHRs) for mortality differed significantly by dialysis vintage for each selected subgroup, statistical interaction was tested by adding multiplicative term in the Cox regression model. SPSS version 22.0 (IBM Corp., Armonk, NY) and R (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org) were used for statistical analyses. P values <0.05 were considered indicative of statistical significance.

Results

Baseline characteristics

Among 3392 patients with LDKT, 816 patients (24.1%) received preemptive KT; at the time of transplant, the mean age was 47.6 ± 11.6 years and the mean eGFR was 8.0 ± 2.9 mL/min/1.73 m^2 (Fig. 1a). The mean eGFR at the time of preemptive KT was similar during the study period ($P = 0.414$, Fig. 1b). A total of 1350 patients (39.8%) underwent pretransplant dialysis for less than 6 months (early KT), and 1226 patients (36.1%) were dialyzed for longer than 6 months (late KT).

The characteristics of patients in the three groups of LDKT recipients (preemptive, early, and late groups) are shown in Table 1. In the preemptive KT group, the proportion of patients with diabetes or hypertension as the primary renal disease was lower, and that of patients with glomerulonephritis and polycystic kidney disease (PCKD) was higher than other groups ($P < 0.001$). A number of comorbid diseases, such as diabetes, cardiovascular disease, malignancy, and hepatitis C, were also less frequent in the preemptive KT group than nonpreemptive KT groups ($P < 0.05$ for all). The proportion of desensitized patients in the preemptive KT group was significantly lower than that in the other groups ($P < 0.001$). The proportion of patients who had pretransplant DSA was lower in the preemptive KT group compared with the late KT group (7.7% vs. 12.5%; $P < 0.001$). The induction and maintenance immunosuppressants were not different among groups.

Predictors of preemptive KT

Predictors of preemptive KT are shown in Table 2. In the univariable analysis, transplant year, specific primary renal diseases (such as diabetes, hypertension, glomerulonephritis, and PCKD), comorbid diseases (such as cardiovascular disease, malignancy, and hepatitis C), pretransplant desensitization, donor age, and donor BMI showed a significant association with preemptive KT ($P < 0.05$ for all). In the multivariable analysis, transplantation in recent year was associated with less preemptive KT (adjusted odds ratio [aOR], 0.95; 95% confidence interval [CI], 0.89–1.00; $P = 0.046$). Underlying glomerulonephritis or PCKD, comorbid cardiovascular disease, malignancy, pretransplant desensitization, donor age, and donor BMI were also independent predictors of preemptive KT ($P < 0.05$ for all).

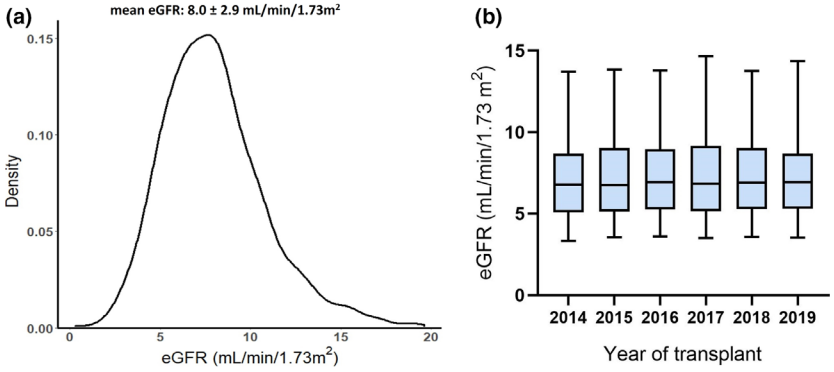

Figure 1 Recipient eGFR at preemptive kidney transplantation. (a) Distribution of eGFR; (b) Annual changes in recipient eGFR at preemptive kidney transplantation. eGFR, estimated glomerular filtration rate.

Table 1. Baseline characteristics.

	Preemptive KT (n = 816)	Dialysis ≤ 6 mo (n = 1350)	Dialysis > 6 mo (n = 1226)	P
Age, y	47.6 ± 11.6[a, b]	47.3 ± 11.7[a]	48.6 ± 11.8[b]	0.016
Sex, male n, %	474 (58.1)	796 (59.0)	730 (59.5)	0.807
Body mass index, kg/m^2	23.4 ± 3.8[a]	23.0 ± 3.6[a]	23.3 ± 3.6[a]	0.038
Dialysis vintage before KT, mo	0[a]	2.2 ± 1.7[a]	46.1 ± 54.4[b]	<0.001
Primary renal disease, n (%)				<0.001
Diabetes	163 (20.0)	325 (24.1)	337 (27.5)	
Hypertension	91 (11.2)	188 (13.9)	178 (14.5)	
Glomerulonephritis	333 (40.8)	459 (34.0)	369 (30.1)	
Polycystic kidney disease	62 (7.6)	59 (4.4)	48 (3.9)	
Comorbid conditions, n (%)				
Diabetes	203 (24.9)[a]	425 (31.5)[b]	420 (34.3)[b]	<0.001
Hypertension	723 (88.6)	1219 (90.3)	1091 (89.0)	0.384
Cardiovascular disease	37 (4.5)[a]	91 (6.7)[a]	180 (14.7)[b]	<0.001
Tumor	37 (4.5)[a]	74 (5.5)[a]	96 (7.8)[b]	0.004
Hepatitis B	36 (4.5)	70 (5.2)	80 (6.5)	0.108
Hepatitis C	4 (0.5)[a]	12 (0.9)[a]	25 (2.1)[b]	0.003
Desensitization, n (%)	238 (29.2)[a]	489 (36.2)[b]	453 (37.0)[b]	<0.001
Pretransplant DSA, n (%)	63 (7.7)[a]	117 (8.7)[a]	153 (12.5)[b]	<0.001
HLA mismatch number	3.24 ± 1.63	3.21 ± 1.62	3.19 ± 1.60	0.801
Hemoglobin, g/dL	9.9 ± 1.5[a]	10.6 ± 1.6[b]	10.7 ± 1.6[b]	<0.001
Donor age, y	47.7 ± 11.3[a]	46.2 ± 11.8[b]	45.9 ± 12.0[b]	0.003
Donor sex, male n, %	362 (44.4)	581 (43.0)	521 (42.5)	0.701
Donor body mass index, kg/m^2	23.9 ± 3.0[a]	24.2 ± 3.2[a, b]	24.4 ± 3.3[b]	0.005
Donor hypertension, n (%)	77 (9.5)	133 (9.9)	121 (9.9)	0.941
Transplantation type, n (%)				0.239
Living-related	462 (56.6)	781 (57.9)	738 (60.2)	
Living-unrelated	354 (43.4)	569 (42.2)	488 (39.8)	
Induction immunosuppression, n (%)				
Basiliximab	704 (86.3)	1167 (86.4)	1034 (84.3)	0.264
Anti-thymocyte globulin	116 (14.2)	199 (14.7)	195 (15.9)	0.552
Immunosuppressants, n (%)				
Tacrolimus	776 (95.1)	1300 (96.3)	1158 (94.5)	0.080
Mycophenolate	755 (92.5)	1261 (93.4)	1114 (90.9)	0.054
Sirolimus	4 (0.5)	7 (0.5)	11 (0.9)	0.397
Corticosteroid	803 (98.4)	1332 (98.7)	1203 (98.1)	0.547

The different superscripts (a, b, c) denote significant differences between groups not sharing the same superscript at 0.05 level.

HLA, human leukocyte antigen; KT, kidney transplantation; mo, months; y, years.

Table 2. Results of logistic regression analysis showing predictors of preemptive kidney transplantation.

	Univariable OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Age	1.00 (0.99–1.01)	0.554		
Sex (ref: female)	0.95 (0.81–1.12)	0.533		
Body mass index	1.01 (0.99–1.04)	0.202		
Transplantation year	0.94 (0.89–0.99)	0.015	0.95 (0.89–1.00)	0.046
Primary renal disease, *n* (%)				
Diabetes	0.72 (0.59–0.87)	<0.001	1.02 (0.79–1.30)	0.909
Hypertension	0.75 (0.59–0.96)	0.024	0.89 (0.66–1.19)	0.421
Glomerulonephritis	1.46 (1.24–1.72)	<0.001	1.42 (1.14–1.76)	0.002
Polycystic kidney disease	1.92 (1.39–2.65)	<0.001	2.11 (1.46–3.03)	<0.001
Comorbid conditions, *n* (%)				
Cardiovascular disease	0.38 (0.27–0.55)	<0.001	0.43 (0.29–0.62)	<0.001
Tumor	0.63 (0.44–0.92)	0.016	0.67 (0.46–0.98)	0.040
Hepatitis B	0.73 (0.50–1.07)	0.104		
Hepatitis C	0.34 (0.12–0.97)	0.043	0.38 (0.13–1.06)	0.065
Desensitization, *n* (%)	0.72 (0.59–0.87)	<0.001	0.67 (0.56–0.80)	<0.001
HLA mismatch	1.02 (0.97–1.07)	0.513		
Donor age	1.01 (1.01–1.02)	0.001	1.01 (1.01–1.02)	<0.001
Donor sex (ref: female)	1.07 (0.91–1.26)	0.398		
Donor body mass index	0.96 (0.94–0.99)	0.005	0.97 (0.94–0.99)	0.010
Donor hypertension	0.95 (0.72–1.24)	0.685		
Living-unrelated (ref: living-related)	1.11 (0.95–1.31)	0.190		

CI, confidence interval; HLA, human leukocyte antigen; OR, odds ratio.

Changes in annual trend of preemptive KT

The temporal trend of change in preemptive KT is shown in Fig. 2. Among the LDKT, the proportion of preemptive KT showed a gradual decrease over time ($P = 0.042$). Patients who had diabetes as the underlying cause of renal failure increased, while patients with glomerulonephritis decreased ($P = 0.013$ and $P < 0.001$, respectively). Patients with cardiovascular disease also showed a steady increase ($P = 0.037$). However, the proportion of patients who received pretransplant desensitization did not change significantly over the entire period ($P = 0.090$).

Comparison of clinical outcomes according to the duration of pretransplant dialysis

Development of delayed graft function, graft failure, patient death, and BPAR was summarized in Table 3, and there was no significant difference in the frequency of outcomes among the three groups (all $P > 0.05$). However, early BPAR was less frequent in preemptive KT group ($P = 0.020$).

Comparison of clinical outcomes, such as graft survival, patient survival, and early BPAR-free survival, is displayed in Fig. 3. Patients with preemptive KT showed the highest survival rate, whereas the late KT group showed the lowest survival rate with borderline significance (log-rank $P = 0.049$, Fig. 3a). Patient survival did not differ significantly among the three groups (log-rank $P = 0.057$), but the preemptive KT patients had longer survival than the late KT patients ($P = 0.032$, Fig. 3b). To mitigate the lead time bias on patient survival, we additionally performed survival analysis using the initial diagnosis time of ESKD (transplantation day for preemptive KT recipients and initiation of maintenance dialysis day for nonpreemptive KT recipients). There was no significant difference in patient survival among groups (Fig. 4). On comparing early BPAR-free survival, the preemptive KT group had the lowest rate of BPAR, and the late KT group had the highest rate of BPAR (log-rank $P = 0.010$) (Fig. 3c).

We investigated the predictors of graft failure in LDKT using proportional hazards model for subdistribution of a competing risk (Table 4). In multivariable analysis, late KT was an independent predictor of graft failure compared with preemptive KT (aHR, 2.53; 95% CI 1.09–5.87; $P = 0.031$); however, the risk of graft failure in the early KT group was comparable to that in the preemptive KT group ($P > 0.05$). The occurrence of early BPAR was also identified as independent predictors of graft survival (aHR, 4.22; 95% CI 2.14–8.33;

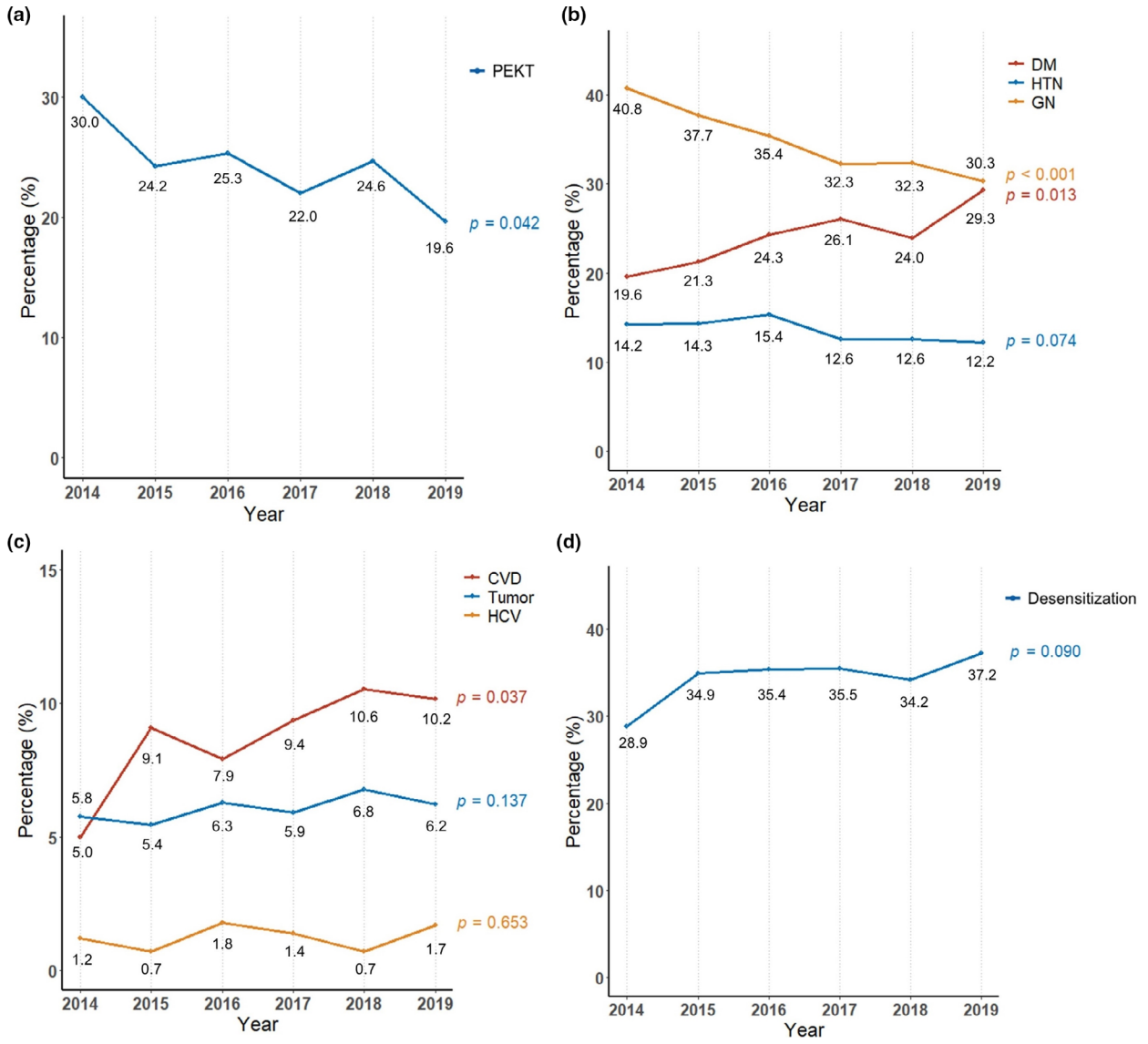

Figure 2 Trend analysis of the proportion of factors associated with preemptive kidney transplantation. DM, diabetes; HTN, hypertension; GN, glomerulonephritis; CVD, cardiovascular disease; HCV, hepatitis C virus.

Table 3. Incidences of clinical outcomes.

	Preemptive KT	Dialysis ≤ 6 mo	Dialysis > 6 mo	*P*
Patient death, *n* (%)	4 (0.5)	10 (0.7)	17 (1.4)	0.079
Graft failure, *n* (%)	7 (0.9)	20 (1.5)	26 (2.1)	0.075
BPAR, *n* (%)	81 (9.9)	156 (11.6)	131 (10.7)	0.485
Early BPAR, *n* (%)	31 (3.8)	76 (5.6)	82 (6.7)	0.020
Delayed graft function, *n* (%)	1 (0.1)	8 (0.6)	10 (0.8)	0.118

BPAR, biopsy-proven acute rejection.

$P < 0.001$). To compensate for the confounding variables and sensitivity analysis, we created PSM groups using baseline characteristics. Table S1 shows the baseline characteristics for the PSM populations before and after matching. In the Cox proportional hazard regression analysis using PSM groups, the late KT group

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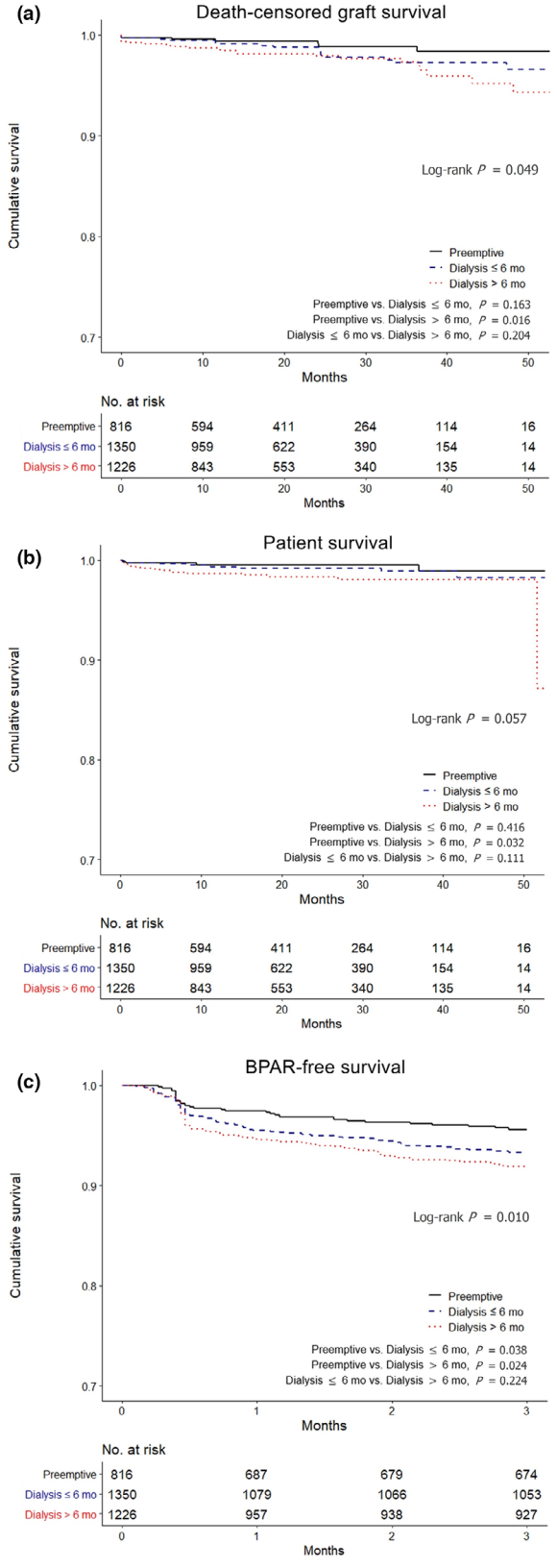

Figure 3 Graft, patient, and BPAR-free survival after living donor kidney transplantation according to preemptive status. BPAR, biopsy-proven acute rejection.

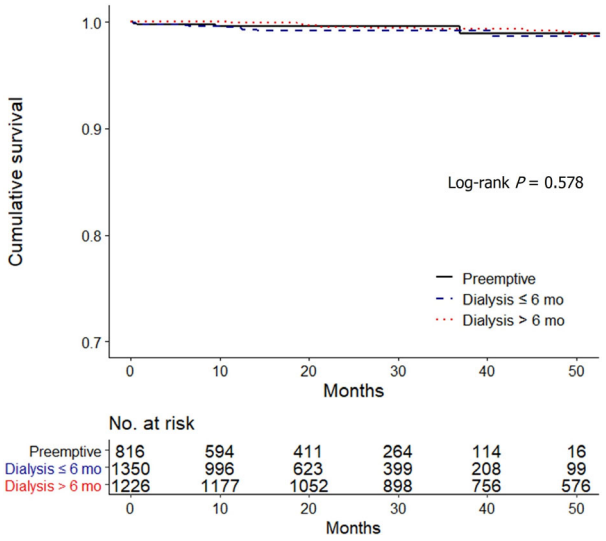

Figure 4 Patient survival after diagnosis of end-stage kidney disease.

also had a higher risk of graft failure than the preemptive KT group (aHR, 2.45; 95% CI, 1.02–5.92; $P = 0.034$), but the early KT group did not have increased risk of graft failure (Table 5).

On subgroup analysis, the following subgroups in the late KT were associated with a higher risk of graft failure compared to preemptive KT: older than mean age of 49.0 years, pretransplant desensitization, BMI < 25.0 m^2/kg, HLA mismatch number <4, and living-related KT ($P < 0.05$ for all, Table 6).

Discussion

In this prospective nationwide study, we evaluated the recent changes in trends related to preemptive KT. Although the well-known advantages such as better graft survival and improved quality of life, we observed a steady decrease in the proportion of preemptive KT among LDKT patients. Among the underlying causes of renal failure in patients undergoing preemptive KT, the proportion of diabetic kidney disease has increased, whereas the proportion of glomerulonephritis has decreased. Patients with preemptive KT had better graft survival than patients who were dialyzed longer than 6 months. Still, graft survival was not different from those with pretransplant dialysis for less than 6 months. Therefore, even if dialysis has been initiated, clinicians need to emphasize the benefits of early KT and encourage the patients on dialysis to identify the potential living donors in order to receive KT within 6 months after dialysis initiation.

In Korea, LDKT increased by 49.8% from 2014 to 2019 (1001 cases to 1499 cases) [23]. However, during

Table 4. Fine and Gray competing risk regression analysis for graft failure in living donor kidney transplantation.

	Univariable HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
Age	0.99 (0.97–1.01)	0.990	0.99 (0.96–1.01)	0.256
Sex (ref: female)	0.94 (0.55–1.62)	0.829	1.12 (0.65–1.94)	0.679
Dialysis vintage before KT	Reference: preemptive		Reference: preemptive	
≤6 mo	1.84 (0.78–4.35)	0.168	1.73 (0.72–4.18)	0.223
>6 mo	2.66 (1.16–6.15)	0.022	2.53 (1.09–5.87)	0.031
Body mass index	1.05 (0.97–1.14)	0.195		
Primary renal disease				
Glomerulonephritis	Reference			
Diabetes	0.97 (0.51–1.84)	0.924		
Hypertension	1.10 (0.52–2.32)	0.811		
Polycystic kidney disease	0.80 (0.19–3.28)	0.754		
Comorbid conditions, *n* (%)				
Cardiovascular disease	0.63 (0.20–2.03)	0.438		
Tumor	2.03 (0.86–4.76)	0.106		
Hepatitis B	2.25 (0.96–2.30)	0.063		
Hepatitis C	1.69 (0.23–12.39)	0.608		
Desensitization, *n* (%)	1.63 (0.95–2.79)	0.077		
HLA mismatch	1.24 (1.02–1.52)	0.034	1.23 (0.98–1.53)	0.072
Early BPAR	5.02 (2.66–9.49)	<0.001	4.22 (2.14–8.33)	<0.001
Donor age	1.03 (1.00–1.05)	0.035	1.02 (0.99–1.05)	0.168
Donor sex	0.74 (0.43–1.30)	0.296		
Donor body mass index	1.00 (0.93–1.08)	0.990		
Donor hypertension	2.09 (1.02–4.27)	0.044	1.79 (0.83–3.86)	0.136
Living-unrelated (ref: living-related)	1.25 (0.73–2.15)	0.420		

BPAR, biopsy-proven acute rejection; CI, confidence interval; HLA, human leukocyte antigen; HR, hazards ratio; KT, kidney transplantation.

Table 5. Cox regression analysis for graft failure in propensity-matched cohort groups.

Dialysis vintage before KT	Univariable HR	*P*	Multivariable HR*	*P*
≤6 mo (ref: preemptive)	2.21 (0.90–5.42)	0.083	1.99 (0.80–4.93)	0.137
>6 mo (ref: preemptive)	2.76 (1.15–6.62)	0.023	2.45 (1.02–5.92)	0.034

BPAR, biopsy-proven acute rejection; CI, confidence interval; HLA, human leukocyte antigen; HR, hazards ratio; KT, kidney transplantation.

*Adjusted for sex, HLA mismatch numbers, and early BPAR.

this period, the proportion of preemptive KT declined by 10% and showed a decreasing trend over successive years. Owing to ethical constraints, it is difficult to conduct randomized trials to identify the advantages of preemptive KT [24]. Instead, many observational studies have reported various advantages of preemptive KT. These studies emphasized that preemptive KT should be a goal of ESKD care [12,24]. Our data show a steady declining trend of preemptive KT, suggesting that efforts are needed to identify the causes of the current decline and promote preemptive KT.

On detailed analysis of the trend of preemptive KT, the proportion of patients with diabetic kidney disease as the cause of renal failure increased by 10% among preemptive KT patients. However, the overall proportion of diabetic kidney disease among LDKT recipients has remained almost unchanged (13.1% in 2014 to 13.8% in 2019) [23]. This increase in preemptive KT among diabetics with ESKD is desirable and may have helped reduce the cardiovascular complications and improve clinical outcomes of preemptive KT demonstrated in previous studies [25–27]. The increasing trend in the proportion of patients who had cardiovascular disease in the preemptive KT group supports this hypothesis. Previous studies conducted in the United States have also reported similar results wherein

Table 6. Subgroup analysis of graft failure according to dialysis vintage.

Variables	Dialysis ≤ 6 mo aHR (95% CI)	*P of interaction*	Dialysis > 6 mo aHR (95% CI)	*P of interaction*
Age		0.130		0.198
<49.0 years	0.93 (0.31–2.81)	0.903	1.54 (0.54–4.35)	0.420
≥49.0 years	3.96 (0.88–17.91)	0.074	5.08 (1.14–22.57)	0.033
Sex		0.829		0.882
Male	1.55 (0.41–5.88)	0.521	2.72 (0.76–9.71)	0.123
Female	1.88 (0.60–5.84)	0.277	2.40 (0.79–7.30)	0.124
Desensitization		0.122		0.162
Yes	6.05 (0.78–47.09)	0.085	8.07 (1.05–62.28)	0.045
No	0.99 (0.35–2.78)	0.980	1.61 (0.62–4.22)	0.329
Early BPAR		0.982		0.635
Yes	1.80 (0.20–16.33)	0.601	3.92 (0.48–31.79)	0.201
No	1.75 (0.68–4.48)	0.243	2.25 (0.89–5.68)	0.086
Body mass index		0.894		0.595
<25.0	1.66 (0.53–5.17)	0.385	2.99 (1.00–8.92)	0.049
≥25.0	1.87 (0.49–7.06)	0.358	1.88 (0.51–7.01)	0.346
HLA mismatch		0.242		0.080
<4	4.71 (0.59–37.73)	0.144	9.78 (1.29–74.17)	0.027
≥4	1.19 (0.45–3.20)	0.725	1.30 (0.48–3.54)	0.607
Donor age		0.496		0.603
<48.0 yrs	1.18 (0.30–4.60)	0.811	1.88 (0.51–6.98)	0.344
≥48.0 yrs	2.18 (0.71–6.70)	0.175	2.96 (0.99–8.81)	0.052
Donor type		0.378		0.146
Living-related	2.84 (0.62–13.02)	0.178	5.22 (1.20–22.68)	0.027
Living-unrelated	1.23 (0.42–3.62)	0.706	1.34 (0.45–4.02)	0.600

aHR, adjusted hazards ratio; BPAR, biopsy-proven acute rejection; CI, confidence interval; HLA, human leukocyte antigen; KT, kidney transplantation; mo, months; y, years.

comorbid diabetes was found to be a factor that inhibits preemptive KT [27,28]. Patients with diabetic kidney disease usually have other systemic comorbid diseases and are unlikely to regain renal function; therefore, the advantage of preemptive KT is likely to be greater in these patients [5,26,27]. It is still uncertain why comorbid diabetes hinders preemptive KT; however, preemptive KT should be actively encouraged in these patients.

In contrast, the proportion of patients with glomerulonephritis as the cause of renal failure declined by approximately 10% during the study reference period. Patients with glomerulonephritis usually experience gradual decrease in renal function and do not have many comorbid diseases that impede transplantation. This is consistent with our result and that of a previous study in which glomerulonephritis was found to be an independent predictor of preemptive KT [28]. Nevertheless, the annual trend of the proportion of glomerulonephritis has shown a steady decline. Considering that a considerable proportion of patients with glomerulonephritis (40%) among the LDKT recipients underwent early KT, nephrologists should pay more attention to ensure that these early transplant recipients receive preemptive KT. In addition, we observed an increasing trend in the donor age; this may be attributable to the increase in the number of healthy older people and to the advances in desensitization treatment and surgical techniques. The increase is a positive sign, which indicates that the living donor pool can expand.

The present study also revealed the clinical advantages of preemptive KT. Patients with preemptive KT showed better graft survival and early BPAR-free survival than the late transplant recipients. Furthermore, early BPAR-free survival in preemptive KT was longer than that in early KT and late KT. Pretransplant dialysis exposure may affect the immune system to potentiate the risk of BPAR [4,29], and the low incidence of early BPAR in preemptive KT may be associated with improved graft prognosis. In addition, our data showed that the patients with longer dialysis duration prior to KT had greater risk of sensitization, which might be associated with the

increased rates of acute rejection. Previous studies conducted in Western countries found a dose-response association between pretransplant dialysis duration and graft survival in KT recipients; in these studies, longer pretransplant dialysis exposure was found to confer a higher risk of graft failure [10,30]. Some studies have also emphasized a safe threshold of dialysis exposure, such as less than 6 or 12 months [12,18,28]. In the present Asian cohort, graft survival rates in patients with pretransplant dialysis exposure less than 6 months were not inferior to that in preemptive KT.

There is a possibility of lead time bias when estimating patient survival, so we analyzed patient survival since the time of initiation of renal replacement therapy to reduce the lead time bias. Our study did not show the advantages of preemptive KT with respect to patient survival. Contrary to our results, Meier-Kriesche *et al*. reported the pretransplant dialysis up to 6 months appeared safe with respect to post-transplant patient survival, but 6 to 12 months of pretransplant dialysis exposure was enough to increase the mortality risk by 21% [9]. This needs to be confirmed by future studies controlling the lead time bias.

Interestingly, on subgroup analysis of graft survival according to the pretransplant dialysis duration, preemptive KT showed a better prognosis than late KT not only in high-risk transplant groups such as older recipients and those receiving desensitization, but also in the low-risk groups such as low BMI, lower HLA mismatch number, and living-related donor. This suggests that the advantages of preemptive KT are not limited to specific high-risk patients. Therefore, if possible, preemptive KT should be encouraged in all patients with impending renal replacement therapy regardless of their risk profile. In addition, graft survival was comparable between all subgroups of patients with preemptive KT and early KT. In that sense, early KT should be implemented as soon as possible if preemptive KT is not feasible.

This prospective cohort study is the first study to identify the trend changes and clinical outcomes of preemptive KT in an Asian nationwide cohort. Although the number of patients who require KT is liable to increase, there is a limit to increasing deceased donors. Therefore, there is a need for national policies and strategies to increase LDKT, especially preemptive KT. This requires characterization of the current trends and advantages of preemptive KT. Based on this, systems for patient and clinician education, early referral to transplant centers, and incentive provision should be supported.

Some limitations of this study should be acknowledged. First, this was an observational study; therefore, there is a possibility of lead time bias and selection bias. Preemptive KT recipients receive transplants at a time when the residual native kidney function is relatively good, resulting in better graft survival. However, previous studies have shown a rapid decline in residual native kidney function after KT because of calcineurin inhibitor toxicity [31,32]. A study found no correlation between pretransplant eGFR and 6-month eGFR after KT in preemptive transplant recipients [31]. In addition, the mortality rate has been reported to peak in the second month after initiation of dialysis [28,33]; therefore, ESKD patients who died early after dialysis would already have been excluded from the pretransplant dialysis group. However, the present study applied statistics considering lead time bias and used national cohort data to minimize the selection bias. Second, we did not consider the factor that there was a possibility of nonpreemptive KT recipients who missed opportunities for preemptive KT because of the length or timing of the recipient and donor evaluation process. Preemptive KT requires a suitable living kidney donor and a recipient with chronic kidney disease sufficiently stable to remain off dialysis during both recipient and donor go through a transplant evaluation process. The third limitation is that this study did not consider the possible disadvantages of preemptive KT. Preemptive KT may cause waste of native kidney function and early exposure to immunosuppressive risk, which increases the risk of complications such as new-onset diabetes after transplant and infection, and lesser adherence than patients with pretransplant dialysis [5,31,34–36]. However, despite some probable disadvantages, several multicenter studies have consistently demonstrated the beneficial effects of preemptive KT with respect to graft survival and patient survival [4,10,18,29].

In conclusion, among patients who underwent LDKT during the study reference period, the proportion of patients who underwent preemptive KT showed a declining trend over successive years. The proportion of diabetic kidney disease as the cause of renal failure showed an increase, while that of glomerulonephritis showed a decrease. Preemptive KT offers advantage over pretransplant dialysis longer than 6 months with respect to graft survival and patient survival; however, short period of dialysis less than 6 months does not significantly affect graft survival and patient survival compared with preemptive KT.

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Authorship

J.H.L. and J.H.C. were participated in research design. J.H.L. and Y.J. were participated in data analysis. S.H.L., Y.H.L., J.P.L., J.Y. and M.S.K. were participated in the performance of the research. J.H.L., H.Y.J., J.Y.C., S.H.P., C.D.K., Y.L.K. and J.H.C. were participated in the writing of the paper. J.H.L. and J.H.C. were participated in the review of the paper.

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Conflicts of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Demographics before and after propensity score matching.

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