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Kidney transplantation waiting times and risk of cardiovascular events and mortality: a retrospective observational cohort study in Taiwan

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ABSTRACT

Objectives Patients with end-stage renal disease (ESRD) are at a high risk of cardiovascular events (CVEs), and kidney transplantation (KT) has been reported to improve risk of CVEs and survival. As the association of KT timing on long-term survival and clinical outcomes remains unclear, we investigated the association of different KT waiting times with clinical outcomes.

Design Retrospective observational cohort study.

Setting We conducted an observational cohort study using data from the National Health Insurance Research Database in Taiwan. Adult patients who initiated KT therapy from 1997 to 2013 were included.

Participants A total of 3562 adult patients who initiated uncomplicated KT therapy were included and categorised into four groups according to KT waiting times after ESRD: group 1 (<1 year), group 2 (1–3 years), group 3 (3–6 years) and group 4 (>6 years).

Primary outcome measures The main outcomes were composite of all-cause death, non-fatal myocardial infarction or non-fatal stroke, based on the primary diagnosis in medical records during hospitalisation.

Results Compared with group 1, the adjusted risk of primary outcome events (all-cause death, non-fatal myocardial infarction or non-fatal stroke) increased by 1.67 times in group 2 (95% CI: 1.40 to 2.00; p<0.001), 2.17 times in group 3 (95% CI: 1.73 to 2.71; p<0.001) and 3.10 times in group 4 (95% CI: 2.21 to 4.35; p<0.001). The rates of primary outcome events were 6.7%, 13.4% and 14.0% within 5 years, increasing to 19.5%, 26.3% and 30.8% within 10 years in groups 1, 2 and 3, respectively.

Conclusions Our results demonstrate that early KT is associated with superior long-term cardiovascular outcomes compared with late KT in selected patients with ESRD receiving uncomplicated KT, suggesting that an early KT could be a better treatment option for patients with ESRD who are eligible for transplantation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The data for this study were collected from patients who initiated kidney transplantation therapy from 1997 to 2013 and were enrolled in the National Health Insurance Research Database in Taiwan.
⇒ Our findings indicated that kidney transplantation should be performed as early as possible in eligible patients with end-stage renal disease to improve their survival and clinical outcomes.
⇒ Limitations include the risk of residual confounding in view of the retrospective study design and inherent limitations of administrative claims data, including the lack of key data on physical and laboratory parameters.

INTRODUCTION

The prevalence and incidence of patients with end-stage renal disease (ESRD) are relatively high in Asian countries such as Japan and Taiwan.[1–3] Patients with ESRD must receive renal replacement therapy (RRT) including kidney transplantation (KT), haemodialysis (HD) treatments and/or peritoneal dialysis (PD) treatments. RRT-dependent patients who wait for KT need to receive dialysis treatments. Studies have revealed that KT was superior to dialysis treatments in terms of improved quality of life,[4 5] survival[6–8] and cardiovascular outcome.[9 10] Therefore, KT is considered a gold-standard RRT; however, KT recipients still exhibit increased cardiovascular events (CVEs), compared with the general population.[4 6] Moreover, several independent risk factors were reported for mortality and CVEs in KT recipients including male sex,[11] older age,[12 13] prior CVEs,[14 15] left ventricular hypertrophy,[16] abnormal myocardial perfusion,[16] low/high-density lipoprotein cholesterol,[17] low physical activity[18] and elevated plasma levels of asymmetrical dimethylarginine.[19]

A proportionally large number of patients with ESRD received late KT due to the shortage of kidney donors. Thus, by early 2017, the KT waitlist in Taiwan exceeded 6000 patients; nevertheless, only 230–325 patients received KTs per year (between 2005 and 2016).[20] While evidence regarding the effect of KT timings on clinical outcomes is very limited,[9] a few national reports have

shown that longer pre-KT dialysis duration is associated with a higher risk of all-cause mortality.[21–25] We hypothesised that longer KT waiting times were associated with poorer clinical and survival outcomes in a selected group of Taiwanese patients with ESRD receiving uncomplicated KT, and vice versa. We highly concerned that several clinical factors related to KT complications possibly influenced the outcomes. We therefore conducted a large-scale retrospective observational study with an exclusion of KT complications to analyse a 17-year sample from the Taiwan National Health Insurance Research Database (NHIRD) to investigate the relationship between KT timing and long-term cardiovascular outcomes; the study results may aid in national policy development for promoting organ donations, clinical practice and further investigations.

METHODS

Data source

The data for the analyses were obtained from the NHIRD in Taiwan between 1997 and 2012. The observation period ended in 2013. The NHIRD contains numerous inpatient and outpatient medical data for almost 23 million residents. All RRT strategies, including KT and maintenance dialysis (PD and/or HD) treatments, are covered by the NHI system. The database contains patients' identification number, age, sex, details of outpatient and inpatient services, as well as diagnoses and procedures. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code system has been used for reimbursement in the healthcare system. Numerous studies have been published based on this valuable medical database. This observational cohort study collected data of all adult patients with ESRD (≥18 years old) from the population who had received uncomplicated KT as an RRT between 1 January 1997 and 31 December 2012, who were followed up until 31 December 2013.

Study design and relevant variables

Patients with ESRD certificate cards (labelled by the ICD-9-CM code number 585) indicating RRT-dependent patients, who had received KT, defined as the ICD-9-CM code number V42.0, were eligible for inclusion. The relevant data were accumulated from the code numbers of the selected patients. The date of receipt of the ESRD diagnosis was defined as the date the ESRD certificate card was recorded. Dialysis treatments, regardless of the HD and/or PD treatments, were allowed both before and after the KT. The waiting time was calculated from the time the dialysis started (the date ESRD certificate card was recoded) and the time of KT (the date the code number V42.0 was recorded). Patients who were not simultaneously coded by the ICD-9-CM code numbers 585 and V42.0, were younger than 18 years or had KT complications such as graft infection, rejection and failure (ICD-9-CM code number 996.81) were excluded. We categorised the selected patients into four groups according to the different KT waiting times after ESRD: group 1 (<1 year), group 2 (1–3 years), group 3 (3–6 years) and group 4 (>6 years).

The diagnostic codes were linked to inpatient and outpatient claims from the NHIRD including age, sex, patient demographics, baseline comorbidities, survival status and date of death. Comorbidities at the baseline were diabetes mellitus (DM) (ICD-9-CM code number of 250.X), hypertension (ICD-9-CM code numbers of 401.X–405.X), dyslipidaemia (ICD-9-CM code number of 272.X), prior ischaemic stroke (ICD-9-CM code numbers 433–434) before KT and prior myocardial infarction (MI) (ICD-9-CM code numbers of 410.X–411.X) before KT. The primary outcomes were composite of all-cause mortality, non-fatal MI and non-fatal ischaemic stroke. We also analysed these three outcomes separately. Death by any cause was identified as withdrawal from the NHI system. A non-fatal MI event after KT was defined as ICD-9-CM codes 410.X and 411.X, and a non-fatal stroke event after KT was defined as ICD-9-CM codes 433–434. The observational period was 1–17 years.

Statistical analyses

All variables were analysed using SPSS software V.20. All the categorical data and rates are displayed as numbers and percentages, while the continuous data are shown as means±SD. The baseline and outcome data were compared among the groups by using the X^2 or Fisher's exact test for categorical variables; analysis of variance was used for continuous variables. Kaplan-Meier analysis with the log-rank test was used to detect differences in the cumulative event-free survival among groups during the observational period. Crude HR (CHR), adjusted HR (AHR) and 95% CI were obtained using a Cox regression model with univariate and multivariate analyses for the primary cardiovascular endpoints, all-cause mortality, non-fatal MI and non-fatal ischaemic stroke among the groups. The method of Schoenfeld residuals was used to test the proportional hazards assumption of the Cox

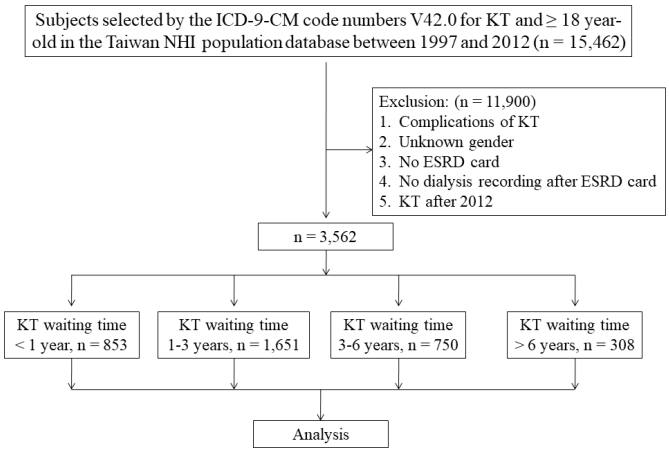


Figure 1 Patient selection flow chart. ESRD, end-stage renal disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; KT, kidney transplantation; NHI, National Health Insurance.

model. The analysis was conducted as described to avoid repetitive counting, as the time to the first event involved composite endpoints. A p value of <0.05 with a two-sided 95% CI was considered statistically significant for all tests.

Patient and public involvement

Patients and the public were not involved in the design, conduct or reporting of our study.

RESULTS

Baseline characteristics

A total of 3562 eligible adults with ESRD receiving uncomplicated KT between January 1997 and December 2012 were selected (figure 1). The average follow-up time was 8.1±4.3 years. Of the selected patients, 853 (23.9%) constituted group 1, 1651 (46.4%) group 2, 750 (21.0%) group 3 and 308 (8.6%) group 4. Significant differences were observed in the classic risk factors such as sex, age, presence of DM, hypertension and dyslipidaemia at the baseline among the groups (all p<0.001), except for the prior acute MI (AMI) and prior stroke (both p>0.05). Patients in group 4 were younger and had fewer comorbidities of DM, hypertension and dyslipidaemia at the baseline. The characteristics at the baseline are outlined among the four groups, stratified by the KT waiting times (table 1).

Primary outcome and KT waiting times

Primary events and all-cause mortality significantly increased in groups 2, 3 and 4 when compared with group 1 (all p<0.001), regardless of the unadjusted or adjusted statistical models (table 2). Compared with group 1, the adjusted risk of primary events significantly increased by 67% in group 2, 117% in group 3 and 210% in group 4 (table 3). Compared with group 1, Cox regression analyses revealed that the event risks significantly increased

Table 1 Characteristics at baseline among groups of patients with different waiting times for kidney transplantation (KT)

		Waiting time for KT				
	Total (n=3562)	<1 year (n=853)	1–3 years (n=1651)	4–6 years (n=750)	>6 years (n=308)	
Variable	No (%)	No (%)	No (%)	No (%)	No (%)	P value*
Sex						
Female	1667 (46.8)	362 (42.4)	766 (46.4)	365 (48.7)	174 (56.5)	<0.001
Male	1896 (53.2)	491 (57.6)	886 (53.6)	385 (51.3)	134 (43.5)	
Age (years, mean±SD)	43.2±11.2	45.5±11.1	43.4±11.5	42.2±10.4	38.2±9.6	<0.001†
Diabetes						
No	2804 (78.7)	646 (75.7)	1262 (76.4)	619 (82.5)	277 (89.9)	<0.001
Yes	759 (21.3)	207 (24.3)	390 (23.6)	131 (17.5)	31 (10.1)	
Hypertension						
No	828 (23.2)	180 (21.1)	355 (21.5)	191 (25.5)	102 (33.1)	<0.001
Yes	2735 (76.8)	673 (78.9)	1297 (78.5)	559 (74.5)	206 (66.9)	
Dyslipidaemia						
No	2588 (72.6)	557 (65.3)	1184 (71.7)	582 (77.6)	265 (86.0)	<0.001
Yes	975 (27.4)	296 (34.7)	468 (28.3)	168 (22.4)	43 (14.0)	
History of AMI						
No	3487 (97.9)	841 (98.6)	1621 (97.7)	733 (97.7)	300 (97.4)	0.400
Yes	76 (2.1)	12 (1.4)	39 (2.3)	17 (2.3)	8 (2.6)	
History of stroke						
No	3592 (98.0)	834 (97.8)	1613 (97.6)	739 (98.5)	306 (99.4)	0.151
Yes	71 (2.0)	19 (2.2)	39 (2.4)	11 (1.5)	2 (0.6)	

Values for the categorical variables are given as number (percentage); continuous variables as mean±SD.
The age was measured at the time of KT. The waiting time was calculated from the time the dialysis started (the date ESRD certificate card was recoded) and the time of KT (the date the code number V42.0 was recorded). Diabetes was defined as the ICD-9-CM code numbers of 250.X, hypertension as 401.X–405.X, dyslipidaemia as 272.X, history of AMI as 410.X–411.X before KT, history of stroke as 433–434 before KT.
*P value was estimated using the X^2 test.
†P value was estimated using the Kruskal-Wallis one-way analysis of variance test.
AMI, acute myocardial infarction; ESRD, end-stage renal disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Table 2 Cumulative incidence rates of clinical events (all-cause death, non-fatal AMI and non-fatal stroke) in KT groups with different waiting times

Waiting time for KT	Primary events*				All-cause death				Non-fatal AMI				Non-fatal stroke			
	No of patients with events	Cumulative incidence rate (%)		P value†	No of patients with events	Cumulative incidence rate (%)		P value†	No of patients with events	Cumulative incidence rate (%)		P value†	No of patients with events	Cumulative incidence rate (%)		P value†
		5 years	10 years			5 years	10 years			5 years	10 years			5 years	10 years	
<1 year	244	6.7	19.5	<0.001	205	5.5	16.2	<0.001	39	0.6	2.3	0.101	35	1.3	3.3	0.664
1–3 years	389	13.0	26.0		330	11.0	22.2		59	1.9	4.5		47	1.8	3.4	
4–6 years	155	14.0	30.8		131	11.2	27.7		21	2.0	4.8		15	1.9	3.2	
>6 years	47	14.5	–		37	11.9	–		6	2.0	–		7	1.8	–	
All KT	835	11.8	25.2		703	9.8	21.4		125	1.6	3.9		104	1.7	3.4	

Values for categorical variables are given as percentage.
*'Primary events' indicate a composite of all-cause death, non-fatal AMI and non-fatal stroke.
†P value was estimated using log-rank test.
AMI, acute myocardial infarction; KT, kidney transplantation.

in group 2, including the primary events (CHR: 1.41; 95% CI: 1.19 to 1.68; p<0.001; AHR: 1.67; 95% CI: 1.40 to 2.00; p<0.001), all-cause mortality (CHR: 1.44; 95% CI: 1.19 to 1.75; p<0.001; AHR: 1.69; 95% CI: 1.39 to 2.05; p<0.001) and non-fatal MI (CHR: 1.63; 95% CI: 1.03 to 2.57; p=0.037; AHR: 2.14; CI: 1.34 to 3.42; p=0.002). The results of the univariate and multivariate Cox regression analyses are summarised in table 3.

Kaplan-Meier analysis of clinical outcomes

Kaplan-Meier analysis confirmed the superiority of early uncomplicated KT over late uncomplicated KT, with regard to the primary outcome during the long-term follow-up period (p<0.001 by log-rank test) (figure 2). Considering all-cause mortality, a significant difference in the cumulative rates was illustrated among the four groups (p<0.001 by log-rank test) (figure 3). A non-significant result was observed in the cumulative rates of the non-fatal MI among the groups (p=0.102 by log-rank test) (figure 4). No statistical difference was observed in the cumulative rates of the non-fatal ischaemic stroke among the groups (p=0.665 by log-rank test) (figure 5).

DISCUSSION

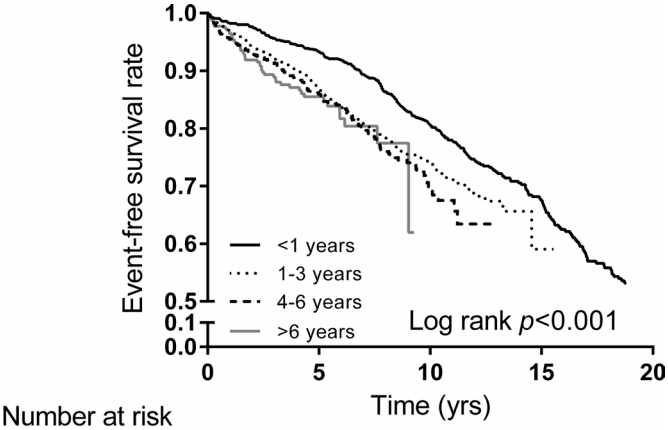
This study generated four major findings; first, significant differences in the primary events and all-cause mortality were exhibited among the four groups with stratified KT waiting times of <1, 1–3, 3–6 and >6 years. The KT waiting time is an independent predictor for primary events and all-cause mortality in uncomplicated KT recipients. Second, the late uncomplicated KT groups (>1 years) versus the early uncomplicated KT group (<1 year) exhibited significantly increased (1.67–3.10 times) risks of primary events and all-cause mortality (1.69–2.77 times) during the long-term observational period. Third, patients in group 4 receiving the latest uncomplicated KT (>6 years), who were younger and presented fewer comorbidities had an approximately three times increased risk of primary events; therefore, compared with an earlier uncomplicated KT, a later uncomplicated KT may increase the risk of primary events and reduce the clinical benefits. Fourth, only one-fourth of the domestic KT recipients received KT within 1 year after they had been diagnosed with ESRD, despite early KT being strongly recommended.

The key problem of delayed KT is lack of kidney donors in Taiwan. A cultural concept of keeping a completely intact body has limited organ donation. The organisation of Taiwan Organ Registry and Sharing Center has been responsible for managing the organ donation, matching and sharing. Nearly three-fourths of the selected KT recipients received KT over 1 year after ESRD diagnosis. The results indicated that the early uncomplicated KT group (<1 year) was significantly associated with lower risks of primary events and mortality, compared with those in the late uncomplicated KT groups. This clearly points out that when the waiting times for the KT are shorter, the primary and mortality risks are further reduced in the selected

Table 3 Univariate and multivariate Cox regression analyses of clinical events (all-cause death, non-fatal AMI and non-fatal stroke) among groups with different waiting times for KT

Waiting time for KT	No (%)	Primary events*		All-cause death		Non-fatal AMI		Non-fatal stroke	
		CHR (95% CI)	P value†	CHR (95% CI)	P value†	CHR (95% CI)	P value†	CHR (95% CI)	P value†
<1 year	853 (23.9)	1.00		1.00		1.00		1.00	
1–3 years	1651 (46.4)	1.41 (1.19 to 1.68)	<0.001	1.44 (1.19 to 1.75)	<0.001	1.63 (1.03 to 2.57)	0.037	1.12 (0.70 to 1.80)	0.625
4–6 years	750 (21.1)	1.64 (1.32 to 2.04)	<0.001	1.68 (1.32 to 2.13)	<0.001	1.84 (1.03 to 3.31)	0.041	1.03 (0.54 to 1.95)	0.932
>6 years	308 (8.6)	1.79 (1.29 to 2.49)	0.001	1.71 (1.18 to 2.46)	0.004	2.12 (0.85 to 5.27)	0.105	1.68 (0.72 to 3.93)	0.230
	No (%)	**AHR (95% CI)**	**P value‡**	**AHR (95% CI)**	**P value‡**	**AHR (95% CI)**	**P value‡**	**AHR (95% CI)**	**P value‡**
<1 year	853 (23.9)	1.00		1.00		1.00		1.00	
1–3 years	1651 (46.4)	1.67 (1.40 to 2.00)	<0.001	1.69 (1.39 to 2.05)	<0.001	2.14 (1.34 to 3.42)	0.002	1.32 (0.82 to 2.14)	0.256
4–6 years	750 (21.1)	2.17 (1.73 to 2.71)	<0.001	2.14 (1.68 to 2.73)	<0.001	3.01 (1.64 to 5.55)	<0.001	1.46 (0.76 to 2.82)	0.257
>6 years	308 (8.6)	3.10 (2.21 to 4.35)	<0.001	2.77 (1.90 to 4.05)	<0.001	4.80 (1.87 to 12.32)	0.001	3.28 (1.35 to 7.96)	0.009

No statistical significance using the method of Schoenfeld residuals to test the proportional hazards assumption of the Cox model.
*'Primary events' indicate a composite of all-cause death, non-fatal AMI and non-fatal stroke.
†P values were estimated using the Cox regression analyses.
‡P values were adjusted for sex, age, diabetes, hypertension, dyslipidaemia, history of AMI and history of stroke using multiple Cox regression analyses.
AHR, adjusted HR; AMI, acute myocardial infarction; CHR, crude HR; KT, kidney transplantation.

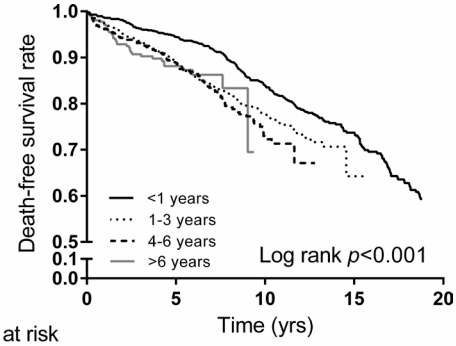


Number at risk KT waiting time					
<1 years	853	774	464	220	0
1-3 years	1651	1233	509	4	0
4-6 years	750	474	98	0	0
>6 years	308	125	0	0	0

Figure 2 Kaplan-Meier analysis for the primary composite outcome. Kaplan-Meier survival analysis illustrates a significant difference in the cumulative incidence of primary events among the four groups with stratified KT waiting times during the 17-year observational period (p<0.001 by log-rank test). Early KT (KT waiting time <1 year) represented by the black line indicates the most favourable primary outcome during the observational period. KT, kidney transplantation.

group; therefore, our study suggests early KT for eligible adults with ESRD in order to lower the risks of primary events and mortality. Furthermore, the present study observed high rates of the primary events (11.8% within 5 years and 25.2% within 10 years) among the overall uncomplicated KT recipients (table 2). In groups 1, 2 and 3, the rates were 6.7%, 13.0% and 14.0% within 5 years, increasing to 19.5%, 26.0% and 30.8% within 10 years, respectively. The results reveal that the rates of the primary events in the uncomplicated KT recipients were high, approximately doubling within the following 5 years. Conflicting results obtained from a retrospective study on KT recipients (n=4954) indicated no significant change in the incidence of major CVEs (MI, coronary angioplasty, bypass surgery and stroke) and death over a 3-year observational period (p=0.41 and p=0.92, respectively).[26] Different characteristics of the selected patient groups, primary endpoints and observational periods may partially account for the inconsistent results. It was reasonable that the rates of non-fatal AMI and stroke compared with total (fatal and non-fatal) AMI and stroke were relatively low in the study because the partial numbers of fatal AMI and stroke might contribute to the numbers of all-cause death.

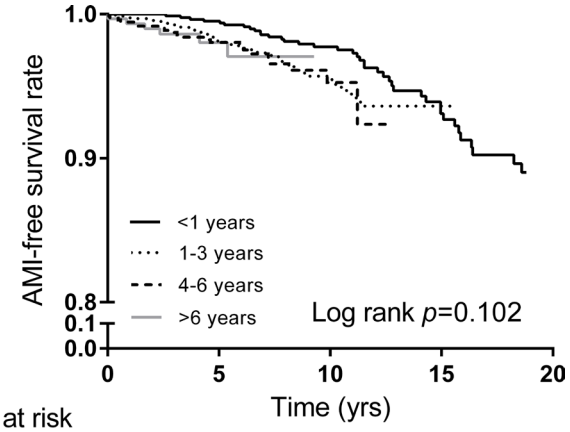
All-cause mortality rates were increased in the late uncomplicated KT groups over 15 years. Compared with group 1, group 2 had all-cause mortality rates of 11.0% (vs 5.5%) within 5 years, 22.2% (vs 16.2%) within 10 years and 35.8% (vs 26.3%) within 15 years, respectively. The adjusted mortality risk was considerably augmented by 69% in group 2 during the long-term observational period.



Number at risk KT waiting time					
<1 years	853	784	481	237	0
1-3 years	1651	1262	536	5	0
4-6 years	750	487	100	0	0
>6 years	308	129	0	0	0

Figure 3 Kaplan-Meier analysis for all-cause mortality. Kaplan-Meier survival analysis illustrates a significant difference in the cumulative incidence of all-cause mortality among the four KT groups during the 17-year observational period (p<0.001 by log-rank test). Early KT (KT waiting time <1 year) represented by the black line indicates the most favourable survival outcome during the observational period. KT, kidney transplantation.

RRT-dependent patients who waited for KT needed to receive dialysis treatments. This finding may be explained by the fact that delayed KT requires longer pre-KT dialysis



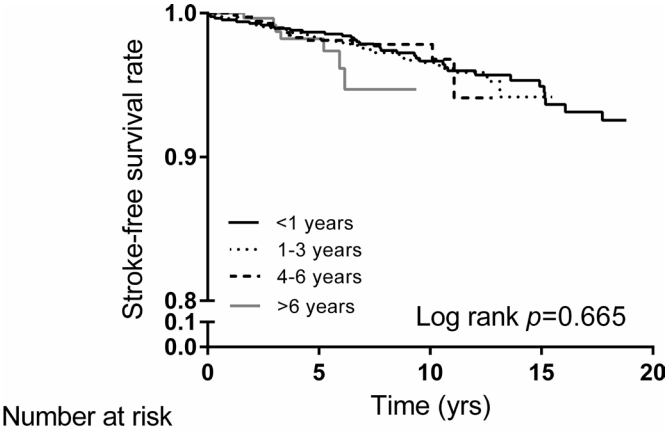
Number at risk KT waiting time					
<1 year	853	781	472	227	0
1-3 years	1651	1245	519	4	0
4-6 years	750	480	99	0	0
>6 years	308	127	0	0	0

Figure 4 Kaplan-Meier analysis for non-fatal myocardial infarction. Kaplan-Meier survival analysis indicates a non-significant result in the cumulative incidence of non-fatal myocardial infarction among the four KT groups during the 17-year observational period. Early KT (KT waiting time <1 year) represented by the black line indicates the most favourable outcome of non-fatal acute myocardial infarction (AMI) during the observational period. The different lines representing the other three KT groups are not obviously separated for non-fatal AMI. KT, kidney transplantation.

duration; that is, the prolonged duration of dialysis while awaiting KT may worsen the prognosis. Consistent results obtained from several studies have exhibited that pre-KT and post-KT dialysis duration is reversely associated with the survival outcome.[21–25] Furthermore, an 11-year retrospective cohort study on KT recipients (n=4654) revealed a marginal increase in mortality in patients with a delay of >1 year, as well as bridge pre-KT HD treatments, compared with patients without delay (HR: 1.36; 95% CI: 1.01 to 1.81; p=0.04).[25] Moreover, the documented pre-emptive KT was associated with a 45% reduction in the hazard of the dialysis or pre-KT (HR: 0.55; 95% CI: 0.47 to 0.64; p<0.001), and a 40% reduction in the hazard of death with a functioning graft (HR: 0.60; 95% CI: 0.50 to 0.71; p<0.001).[27] In addition, young adults (11–30 years old) with ESRD who were not listed for KT within 5 years and received dialysis treatments were 16.6 times more at risk of mortality than those who received transplantation, according to the report of UK renal registry data between 1999 and 2008.[28] Together, the findings strongly support that KT waiting time is an independent predictor for primary events, as well as all-cause mortality, while early KT generates more favourable clinical outcomes.

We propose several possible reasons for the superior clinical outcomes of early uncomplicated KT. First, the patient selection bias and the baseline heterogeneity should have been considered in the present study. Patients in group 4 who were younger, presented with fewer comorbidities and received late uncomplicated KT had an approximately three times higher clinical risk than patients in group 1 receiving early uncomplicated KT. We explained the finding that younger patients in group 4 were with possibly more detrimental factors to result in earlier development of ESRD and need longer dialysis treatments, which might lead to poorer clinical outcomes. Second, pre-KT dialysis duration in most patients in groups 1–4 varied and presumably affected the clinical outcomes. Late KT with longer pre-KT dialysis duration may worsen the clinical and survival outcomes, thus increasing the risks of infections and malignancies. Compatible results from relevant studies have depicted that late KTs with longer pre-KT dialysis duration may lead to a relatively poorer survival.[21–25] By contrast, early KT with shorter pre-KT dialysis duration may yield more favourable outcomes. Third, KT provides a relatively complete RRT with comprehensive physiological functions that may be superior to dialysis treatments in the form of a partial RRT. Therefore, longer KT duration with shorter dialysis duration may yield relatively favourable outcomes in early KT recipients. Although the survival rates vary significantly due to the different KT waiting times, the non-immunological pairing of kidney donors and recipients deserves serious consideration regarding clinical outcomes.[29]

As conducting a randomised and controlled trial with randomisation according to the KT waiting times is challenging and against ethics, this retrospective observational study provides long-term, real-world data; nevertheless, inherently, it has several limitations. First, some crucial variables and confounders were not totally considered, as the



Number at risk KT waiting time					
<1 years	853	777	470	229	0
1-3 years	1651	1249	524	5	0
4-6 years	750	481	99	0	0
>6 years	308	127	0	0	0

Figure 5 Kaplan-Meier analysis for non-fatal stroke. Kaplan-Meier survival analysis indicates no statistical difference in the cumulative incidence of non-fatal stroke among the four KT groups during the 17-year observational period. Late KT (KT waiting time >6 years) represented by the grey line indicates the least favourable outcome of non-fatal stroke during the late observational years. In addition, the other lines are not separated during the observational period. KT, kidney transplantation.

NHIRD did not contain laboratory details and all patients' characteristics, and as factors affecting waitlisting. The baseline heterogeneity and the unmeasured confounders may have affected the outcomes, despite the use of statistically adjusted analyses. For example, confounders in retrospective observational studies may result from selection bias, inaccurate and unavailable data, unfair allocation, unequal baseline characteristics and unrecorded events. Second, we did not separate domestic and overseas KTs for the analysis[30]; at the time of this study, we were unaware of the overseas KT failures in some patients. Third, factors such as post-KT complications, immunosuppressive drugs, lifestyle conditions (ie, cigarette smoking) and achievements of therapeutic goals were not analysed. We highlight it should be limited to generalise the results to all KT patients. Fourth, the duration between the KT and ESRD might not be entirely accurate, using the record dates of the medical codes. Dialysis treatments were warranted during the waiting time for KT. Finally, the causes of mortality were not fully obtained (for example, some patients died of cancers, infections or cardiovascular diseases).

In conclusion, the present data reveal notable differences in the long-term cardiovascular outcomes among groups with stratified KT waiting times after ESRD in selected patients receiving uncomplicated KT. Compared with late uncomplicated KT, early uncomplicated KT is strongly associated with superior clinical and survival outcomes; if this association is assumed to be causal, these data suggest that KT should be performed as early

as possible in eligible patients with ESRD, and that the shortage of kidney donors needs to be addressed with urgency.

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Contributors H-HC and C-CL contributed equally to this work. H-HC and C-CL designed the study plan, supervised all parts of this project, interpreted the patient data and did the final edition of the manuscript. Y-BC and C-CL helped in performing the experiments, gathered and collected the relevant data, and wrote the manuscript draft. C-YH and P-LT analysed the data and interpreted the results of the experiments. H-HC, Y-BC and C-CL were involved in the grant application, setting and conducting the study design. C-CL is a guarantor of this work. All authors have read and agreed to the published version of the manuscript.

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Patient consent for publication Not required.

Ethics approval The National Health Research Institute (NHRI), a non-profit organisation for medical research and in charge of the administration of NHIRD, has encrypted the identifiable personal information into anonymous identification numbers of the relevant information in the NHIRD. The researchers could reach the database of NHIRD after approval by the NHRI without patient consent. In addition, the Institutional Review Board of Kaohsiung Veterans General Hospital approved the study protocol (VGHKS15-EM10-02).

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Data availability statement Data may be obtained from a third party and are not publicly available. Data are available on reasonable request. Data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi.org/10.5061/dryad.rfj6q57d1.Data are available from the National Health Insurance Research Database (NHIRD) published by Taiwan National Health Insurance (NHI) Bureau. The data used in this study cannot be made available in the manuscript, online supplemental files or in a public repository due to the Personal Information Protection Act executed by Taiwan's government, starting from 2012. Requests for data can be sent as a formal proposal to the NHIRD (http://nhird.nhri.org.tw).

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