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Effect of different kidney transplantation waiting times on cardiovascular events and deaths

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Abstract

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

Design: Retrospective observational cohort study.

Setting: An observational cohort study from the National Health Insurance Research Database in Taiwan. Adult patients who initiated kidney transplantation therapy from 1997 to 2013 were enrolled.

Participants: A total of 3571 adult patients who initiated uncomplicated KT therapy were collected and categorized into 4 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 and secondary outcome measures: Primary endpoints were defined as all-cause death, nonfatal myocardial infarction, or nonfatal stroke using the primary diagnosis in medical records during hospitalization.

Results: Compared with Group 1, the adjusted primary events risk (all-cause death, nonfatal myocardial infarction, or nonfatal stroke) increased 1.7 folds in Group 2, 2.15 folds in Group 3, and 3.07 folds in Group 4. The rates of the primary events were 6.7%, 13.4%, and 14.0% within five 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 clinical and survival outcomes compared to late KT in selected ESRD patients receiving uncomplicated KT, suggesting that an early KT is a better treatment option for ESRD patients who are eligible for transplantation.

Keywords: Clinical outcomes; End-stage renal disease; Kidney transplantation; Myocardial infarction; Stroke

Strengths and limitations of this study

- The data for this study were retrospectively collected from patients who initiated kidney transplantation therapy from 1997 to 2013 were enrolled in the National Health Insurance Research Database in Taiwan.
- This study examines the different KT waiting times, which notably affect differences in the long-term clinical and survival outcomes.
- Limitations are that lack of physical and biochemical information because of inherent limitations from administrative claims data.

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), hemodialysis (HD) treatments, and/or peritoneal dialysis (PD) 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 in 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 ESRD patients received late KT due to the shortage of kidney donors. Thus, by early 2017, the KT waitlist in Taiwan exceeded 6,000 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 a longer pre-KT dialysis duration is associated with a higher risk of all-cause mortality.[21-25] We hypothesized 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 complication to analyze a 17-year sample from the Taiwan National Health Insurance Research Database (NHIRD); the study

results may aid in national policy development for promoting organ donations, clinical practice, and further investigations.

Methods

Patient and public involvement

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

Data Source

The data for the analyses were obtained from the NHIRD in Taiwan between 1997 and 2012. 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 ESRD patients (≥18 years old) from the population who had received uncomplicated KT as an RRT between January 1, 1997 and December 31, 2012, that were followed-up until December 31, 2013.

Ethics approval

The Institutional Review Board of Kaohsiung Veterans General Hospital approved the study protocol (VGHKS15-EM10-02).

Study Design and Relevant Variables

Patients with ESRD certificate cards (labeled by the ICD-9-CM code number 585) 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 of dialysis start (the date ESRD certificate card was recoded) and the time at KT (the date the code number V42.0 were recorded). Patients who were not simultaneously coded by the ICD-9-CM code numbers 585 and V42.0, were younger than 18 years, or that had KT complications such as graft infection, rejection, and failure (ICD-9-CM code number 996.81) were excluded. We categorized 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 numbers of 250.X), hypertension (ICD-9-CM code numbers of 401.X–405.X), dyslipidemia (ICD-9-CM code numbers of 272.X), prior ischemic 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.

Primary events included a composite of all-cause mortality, nonfatal MI, and nonfatal ischemic stroke. Death by any cause was identified as withdrawal from the NHI system. A nonfatal MI event after KT was defined as ICD-9-CM codes 410.X and 411.X, and a nonfatal stroke event after KT was defined as ICD-9-CM codes 433–434. The observational period was 1–17 years. The analysis was conducted as described to avoid repetitive counting, as the time to the first event involved composite endpoints.

Statistical Analyses

All variables were analyzed using SPSS software version 20 (SPSS Inc., Illinois, USA). All the categorical data and rates are displayed as numbers and percentages, while the continuous data are shown as means ± standard deviation. The baseline and outcome data were compared among the groups by using the Chi-squared 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 hazard ratio (CHR), adjusted hazard ratio (AHR), and 95% confidence interval (CI) were obtained using a Cox regression model with univariate and multivariate analyses for the primary cardiovascular endpoints, all-cause mortality, nonfatal MI, and nonfatal ischemic stroke among the groups. The method of Schoenfeld residuals were used to test the proportional hazards assumption of the Cox model. A P value <0.05 with a two-sided 95% CI was considered statistically significant for all tests.

Results

Baseline Characteristics

A total of 3,571 eligible ESRD adults 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, 1660 (46.5%) 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 dyslipidemia at the baseline among the groups (all P <0.001), except for the prior acute MI and prior stroke (both P >0.05). Patients in Group 4 were younger and had fewer comorbidities of DM, hypertension, and dyslipidemia 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 70% in Group 2, 115% in Group 3, and 207% in Group 4.

Compared with Group 1, Cox's regression analyses revealed that the event risks significantly increased in Group 2, including the primary events (CHR: 1.44; 95% CI: 1.21–1.71; P <0.001; AHR: 1.70; 95% CI: 1.43–2.03; P <0.001), all-cause mortality (CHR: 1.48; 95% CI: 1.22–1.79; P <0.001; AHR: 1.72; 95% CI: 1.42–2.09; P <0.001), and nonfatal MI (CHR: 1.65; 95% CI: 1.05–2.61; P = 0.031; AHR: 2.16; CI: 1.35–3.44; P = 0.001). The results of the univariate and multivariate Cox regression analyses are summarized 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 trend was observed in the cumulative rates of the nonfatal MI among the groups (P = 0.099 by log-rank test) (Figure 4). No statistical difference was observed in the cumulative rates of the nonfatal ischemic stroke among the groups (P = 0.655 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-fold risks of primary events, and all-cause mortality increased 1.69-2.77-fold risk 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 3-fold 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 one 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 completely intact body has limited organ donation. The organization of Taiwan Organ Registry and Sharing Center has been responsible to manage the organ donation, matching and sharing. Nearly three-fourths of the selected KT recipients received KT over one 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 group; therefore, our study suggests early KT for eligible ESRD adults in order to lower the risks of primary events and mortality. Furthermore, the present study observed high rates of the primary events (11.8% at within five 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 five years. Conflicting results obtained from a retrospective study on KT recipients (n = 4,954) indicated no significant change in the incidence of major CVEs (MI, coronary angioplasty, bypass surgery, and stroke) and death over a three-year observation 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 nonfatal AMI and stroke compared with total (fatal and nonfatal) AMI and stroke were relatively low in the study because the partial numbers of fatal AMI and stroke might be contributed 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 five 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. This finding may be explained by the fact that delayed KT requires a longer pre-KT dialysis duration; however, 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 durations are reversely associated with the survival outcome.[21-25] Furthermore, an 11-year retrospective cohort study on KT recipients (n = 4,654) 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: 1.01–1.81; P = 0.04).[25] Moreover, the documented preemptive KT was associated with a 45% reduction in the hazard of the dialysis or re-KT (HR: 0.55; 95% CI: 0.47–0.64; P <0.001), and a 40% reduction in the hazard of death with a functioning graft (HR: 0.60; 95% CI: 0.50–0.71; P <0.001).[27] In addition, young adults (11–30 year-old) with ESRD who were not listed for KT within five 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 favorable 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 were receiving late uncomplicated KT had an approximately 3-fold higher clinical risk than patients in Group 1 receiving early uncomplicated KT. Second, pre-KT dialysis durations in most patients in Groups 1–4 varied and presumably affected the clinical outcomes. Late KT with longer pre-KT dialysis durations 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 durations may lead to a relatively poorer survival.[21-25] By contrast, early KT with shorter pre-KT dialysis durations may yield more favorable 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, a longer KT duration with a shorter dialysis duration may yield relatively favorable outcomes in early KT recipients. Although the survival rates vary significantly due to the different KT waiting times, the nonimmunologic pairing of kidney donors and recipients deserves serious consideration regarding clinical outcomes.[29]

As conducting a randomized and controlled trial with randomization 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 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. 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 (i.e., cigarette smoking), and achievements of therapeutic goals were not analyzed. We highlight it

should be limited to generalize the results to all KT patients. Fourth, the durations between the KT and ESRD might not be entirely accurate, using the record dates of the medical codes. 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 reveals notable differences in the long-term clinical and survival outcomes among groups with stratified KT waiting times after ESRD in selected patients receiving uncomplicated KT. Compared to late uncomplicated KT, early uncomplicated KT is strongly associated with superior clinical and survival outcomes; therefore, this study suggests that KT should be performed as early as possible in eligible ESRD patients, the shortage of kidney donors should be emphasized and rapidly solved.

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Contributorship statement: HHC and CCL designed the study plan, supervised all parts of this project, interpreted the patient data, and did the final edition of the manuscript. YBC and CCL helped in performing the experiments, gathered and collected the relevant data, and wrote the manuscript draft. CYH and PLT analyzed the data and interpreted the results of the experiments. HHC, YBC and CCL were involved in the grant application, setting the study design and conduction. All authors have read and agreed to the published version of the manuscript.

Competing interests: None declared.

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Patient consent for publication: Not required.

Ethics approval: The National Health Research Institute (NHRI), a non-profit organization 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).

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement: Data are available on reasonable request. 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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Tables

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

Variable	Total (n = 3,563)	Waiting Time for Kidney Transplantation				P Value[a]
		< 1 years (n = 853)	1-3 years (n = 1,652)	4-6 years (n = 750)	> 6 years (n = 308)	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
Sex						
Female	1,667 (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[b]
Diabetes						
No	2,804 (78.7)	646 (75.7)	1,262 (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	2,735 (76.8)	673 (78.9)	1,297 (78.5)	559 (74.5)	206 (66.9)	
Dyslipidemia						
No	2,588 (72.6)	557 (65.3)	1,184 (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	3,487 (97.9)	841 (98.6)	1,621 (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	3,592 (98.0)	834 (97.8)	1,613 (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)	

Note: Values for the categorical variables are given as number (percentage); continuous variables as mean ± standard deviation.

[a]*P* value was estimated using the Chi-squared test.

[b]*P* value was estimated using the Kruskal–Wallis one-way analysis of variance test.

Abbreviation: AMI, acute myocardial infarction; KT, kidney transplantation; SD, standard deviation.

The age was measured at the time of KT. The waiting time was calculated from the time of dialysis start (the date ESRD certificate card was recoded) and the time at KT (the date the code number V42.0 were recorded). Diabetes was defined as the ICD-9-CM code numbers of 250.X, hypertension as 401.X–405.X, dyslipidemia as 272.X, history of acute myocardial infarction as 410.X–411.X before KT, history of stroke as 433–434 before KT.

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

Waiting Time for Transplant	Primary Events[a]				All-Cause Death				Nonfatal AMI				Nonfatal Stroke			
	No. of Patients with Events	The Cumulative Incidence Rate (%)		*P* Value[b]	No. of Patients with Events	The Cumulative Incidence Rate (%)		*P* Value[b]	No. of Patients with Events	The Cumulative Incidence Rate (%)		*P* Value[b]	No. of Patients with Events	The Cumulative Incidence Rate (%)		*P* Value[b]
		5-year	10-year			5-year	10-year			5-year	10-year			5-year	10-year	
< 1 years	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	

Note: Values for categorical variables are given as percentage.

[a] "Primary events" indicates a composite of all-cause death, nonfatal AMI, and nonfatal stroke.

[b] *P* value was estimated using log-rank test.

Abbreviation: AMI, acute myocardial infarction; KT, kidney transplantation.

Table 3. Univariate and multivariate Cox regression analyses of clinical events (all-cause death, nonfatal AMI, and nonfatal stroke) among groups with different waiting times for kidney transplantation

Waiting Time for KT	No. (%)	Primary Events[a]		All-Cause Death		Nonfatal AMI		Nonfatal Stroke	
		CHR (95% CI)	*P* Value[b]	CHR (95% CI)	*P* Value[b]	CHR (95% CI)	*P* Value[b]	CHR (95% CI)	*P* Value[b]
< 1 years	853 (23.9)	1.00		1.00		1.00		1.00	
1-3 years	1652 (46.4)	1.41 (1.19-1.68)	<0.001	1.44 (1.19-1.75)	<0.001	1.63 (1.03-2.57)	0.037	1.12 (0.70-1.80)	0.625
4-6 years	750 (21.1)	1.64 (1.32-2.04)	<0.001	1.68 (1.32-2.13)	<0.001	1.84 (1.03-3.31)	0.040	1.03 (0.54-1.95)	0.932
> 6 years	308 (8.6)	1.79 (1.29-2.49)	0.001	1.71 (1.18-2.46)	0.004	2.12 (0.85-5.27)	0.101	1.68 (0.72-3.93)	0.230
	No. (%)	**AHR (95% CI)**	***P* Value[c]**	**AHR (95% CI)**	***P* Value[c]**	**AHR (95% CI)**	***P* Value[c]**	**AHR (95% CI)**	***P* Value[c]**
< 1 years	853 (23.9)	1.00		1.00		1.00		1.00	
1-3 years	1652 (46.4)	1.67 (1.40-2.00)	<0.001	1.69 (1.39-2.05)	<0.001	2.14 (1.34-3.42)	0.002	1.32 (0.82-2.14)	0.256
4-6 years	750 (21.1)	2.17 (1.73-2.71)	<0.001	2.14 (1.68-2.73)	<0.001	3.01 (1.64-5.55)	<0.001	1.46 (0.76-2.82)	0.257
> 6 years	308 (8.6)	3.10 (2.21-4.35)	<0.001	2.77 (1.90-4.05)	<0.001	4.80 (1.87-12.32)	0.001	3.28 (1.35-7.96)	0.009

[a] "Primary events" indicates a composite of all-cause death, nonfatal AMI, and nonfatal stroke.

[b] *P* values were estimated using the Cox's regression analyses.

[c] *P* values were adjusted for sex, age, diabetes, hypertension, dyslipidemia, history of AMI, and history of stroke using multiple Cox`s regression analyses. No statistical significance using the method of Schoenfeld residuals to test the proportional hazards assumption of the Cox model.

Abbreviation: AHR, adjusted hazard ratio; AMI, acute myocardial infarction; CHR, crude hazard ratio; CI, confidence interval; KT, kidney transplantation

Figure Legends

Figure 1. Patient selection flow chart.

Abbreviations: ESRD, end-stage renal disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; KT, kidney transplantation; NHI, National Health Insurance

Figure 2. 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 (<1 year) represented by the black line indicates the most favorable primary outcome during the observational period.

Figure 3. 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 (<1 year) represented by the black line indicates the most favorable survival outcome during the observational period.

Figure 4. Kaplan–Meier survival analysis indicates a statistical trend in the cumulative incidence of nonfatal myocardial infarction among the four KT groups during the 17-year observational period. Early KT (<1 year) represented by the black line indicates the most favorable outcome of nonfatal acute myocardial infarction (AMI) during the observational period. The different lines representing the other three KT groups are not obviously separated for nonfatal AMI.

Figure 5. Kaplan–Meier survival analysis indicates no statistical difference in the cumulative incidence of nonfatal stroke among the four KT groups during the 17-year observational period. Late KT (>6 years) represented by the gray line indicates the least favorable outcome of nonfatal stroke during the late observational years. In addition, the other lines are not separated during the observational period.

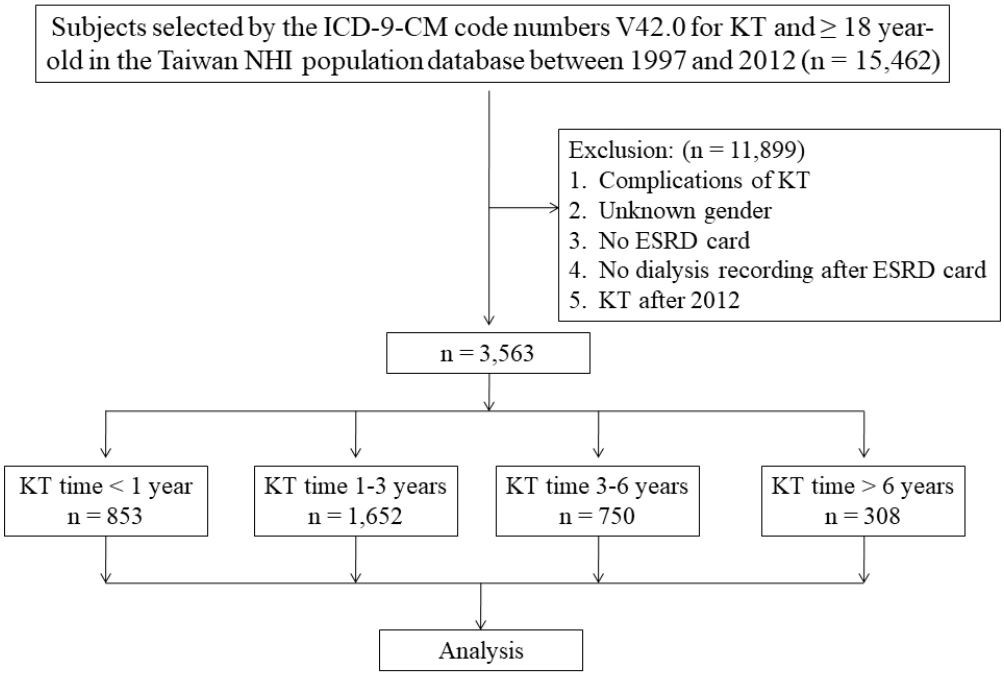

Figure 1

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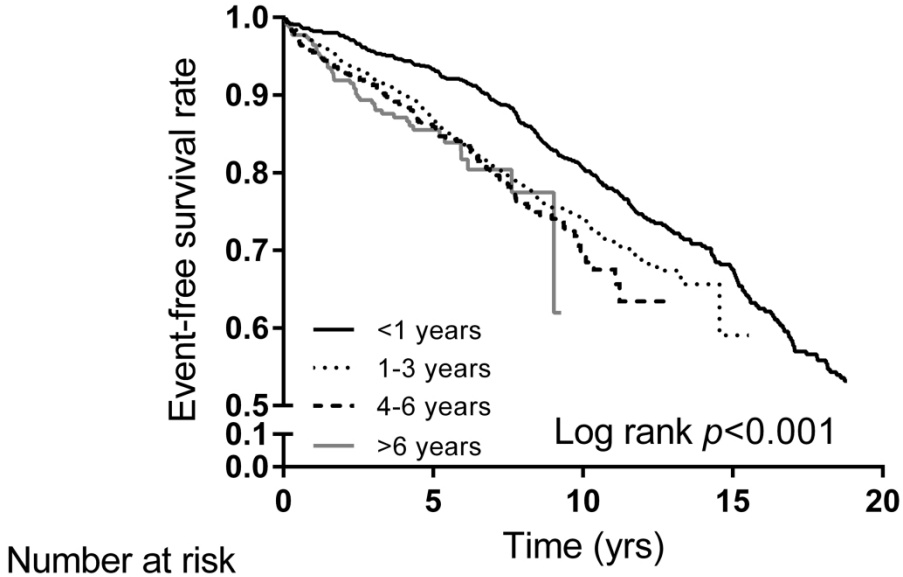
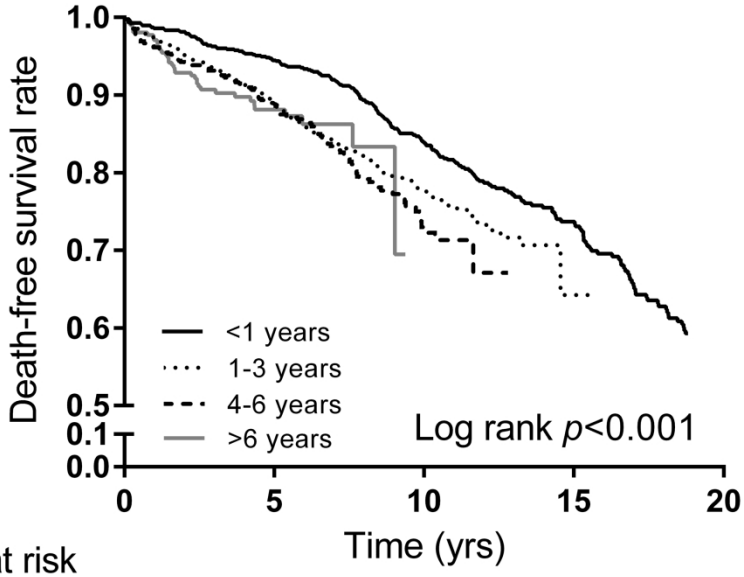


Number at risk

<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

133x118mm (600 x 600 DPI)

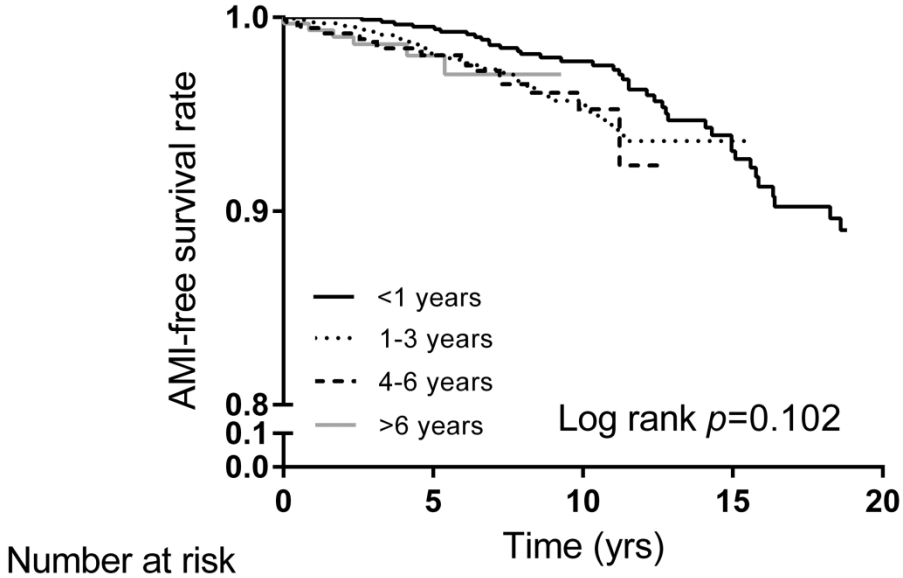


Number at risk

<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

133x118mm (600 x 600 DPI)

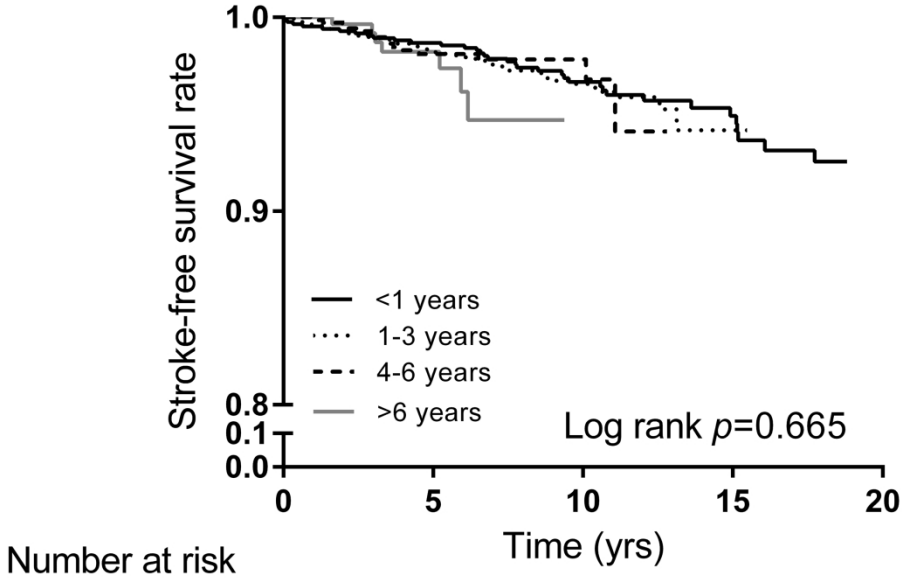


Number at risk

<1 years	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

133x118mm (600 x 600 DPI)



Number at risk

<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

133x118mm (600 x 600 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 or 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not applicable
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	7

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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: While patients with end-stage renal disease (ESRD) are at a high risk of cardiovascular events (CVEs), kidney transplantation (KT) has been reported to improve 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 on clinical outcomes.

Design: Retrospective observational cohort study.

Setting: An observational cohort study from the National Health Insurance Research Database in Taiwan. Adult patients who initiated kidney transplantation therapy from 1997 to 2013 were enrolled.

Participants: A total of 3562 adult patients who initiated uncomplicated KT therapy were collected and categorized into 4 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 and secondary outcome measures: Primary endpoints were defined as all-cause death, nonfatal myocardial infarction, or nonfatal stroke using the primary diagnosis in medical records during hospitalization.

Results: Compared with Group 1, the adjusted primary events risk (all-cause death, nonfatal myocardial infarction, or nonfatal stroke) increased 1.67 folds in Group 2 (95% CI: 1.40–2.00; *P* <0.001), 2.17 folds in Group 3 (95% CI: 1.73–2.71; *P* <0.001), and 3.10 folds in Group 4 (95% CI: 2.21–4.35; *P* <0.001). The rates of the primary events were 6.7%, 13.4%, and 14.0% within five 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 clinical and survival outcomes compared to late KT in selected ESRD patients receiving

uncomplicated KT, suggesting that an early KT could be a better treatment option for ESRD patients who are eligible for transplantation.

Keywords: Clinical outcomes; End-stage renal disease; Kidney transplantation; Myocardial infarction; Stroke

Strengths and limitations of this study

- The data for this study were retrospectively collected from patients who initiated kidney transplantation therapy from 1997 to 2013 were enrolled in the National Health Insurance Research Database (NHIRD) in Taiwan.
- This study examines the different KT waiting times, which notably affect differences in the long-term clinical and survival outcomes.
- Limitations are that lack of physical and biochemical information because of inherent limitations from administrative claims data.
- Some crucial variables and confounders were not available and not totally considered. For example, the NHIRD did not contain laboratory details and all patients' characteristics, and factors affecting waitlisting.

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), hemodialysis (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 in 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 ESRD patients received late KT due to the shortage of kidney donors. Thus, by early 2017, the KT waitlist in Taiwan exceeded 6,000 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 a longer pre-KT dialysis duration is associated with a higher risk of all-cause mortality.[21-25] We hypothesized 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 analyze 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

Patient and public involvement

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

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 ESRD patients (≥18 years old) from the population who had received uncomplicated KT as an RRT between January 1, 1997 and December 31, 2012, that were followed-up until December 31, 2013.

Ethics approval

The Institutional Review Board of Kaohsiung Veterans General Hospital approved the study protocol (VGHKS15-EM10-02).

Study Design and Relevant Variables

Patients with ESRD certificate cards (labeled 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 of dialysis start (the date ESRD certificate card was recoded) and the time at KT (the date the code number V42.0 were recorded). Patients who were not simultaneously coded by the ICD-9-CM code numbers 585 and V42.0, were younger than 18 years, or that had KT complications such as graft infection, rejection, and failure (ICD-9-CM code number 996.81) were excluded. We categorized 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 numbers of 250.X), hypertension (ICD-9-CM code numbers of 401.X–405.X), dyslipidemia (ICD-9-CM code

numbers of 272.X), prior ischemic 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.

Primary events included a composite of all-cause mortality, nonfatal MI, and nonfatal ischemic stroke. Death by any cause was identified as withdrawal from the NHI system. A nonfatal MI event after KT was defined as ICD-9-CM codes 410.X and 411.X, and a nonfatal 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 analyzed using SPSS software version 20 (SPSS Inc., Illinois, USA). All the categorical data and rates are displayed as numbers and percentages, while the continuous data are shown as means ± standard deviation. The baseline and outcome data were compared among the groups by using the Chi-squared 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 hazard ratio (CHR), adjusted hazard ratio (AHR), and 95% confidence interval (CI) were obtained using a Cox regression model with univariate and multivariate analyses for the primary cardiovascular endpoints, all-cause mortality, nonfatal MI, and nonfatal ischemic stroke among the groups. The method of Schoenfeld residuals were used to test the proportional hazards assumption of the Cox model. The analysis was conducted as described to avoid repetitive counting, as the time to the first event involved composite endpoints. A *P* value <0.05 with a two-sided 95% CI was considered statistically significant for all tests.

Results

Baseline Characteristics

A total of 3,562 eligible ESRD adults 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 dyslipidemia at the baseline among the groups (all P <0.001), except for the prior acute MI and prior stroke (both P >0.05). Patients in Group 4 were younger and had fewer comorbidities of DM, hypertension, and dyslipidemia 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's regression analyses revealed that the event risks significantly increased in Group 2, including the primary events (CHR: 1.41; 95% CI: 1.19–1.68; P <0.001; AHR: 1.67; 95% CI: 1.40–2.00; P <0.001), all-cause mortality (CHR: 1.44; 95% CI: 1.19–1.75; P <0.001; AHR: 1.69; 95% CI: 1.39–2.05; P <0.001), and nonfatal MI (CHR: 1.63; 95% CI: 1.03–2.57; P = 0.037; AHR: 2.14; CI: 1.34–3.42; P = 0.002). The results of the univariate and multivariate Cox regression analyses are summarized 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 trend was observed in the cumulative rates of the nonfatal MI among the groups (P = 0.102 by log-rank test) (Figure 4). No statistical difference was observed in the cumulative rates of the nonfatal ischemic 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-fold risks of primary events, and all-cause mortality increased 1.69-2.77-fold risk 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 3-fold 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 one 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 completely intact body has limited organ donation. The organization of Taiwan Organ Registry and Sharing Center has been responsible to manage the organ donation, matching and sharing. Nearly three-fourths of the selected KT recipients received KT over one 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 group; therefore, our study suggests early KT for eligible ESRD adults in order to lower the risks of primary events and mortality. Furthermore, the present study observed high rates of the primary events (11.8% at within five 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 five years. Conflicting results obtained from a retrospective study on KT recipients (n = 4,954) indicated no significant change in the incidence of major CVEs (MI, coronary angioplasty, bypass surgery, and stroke) and death over a three-year observation 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 nonfatal AMI and stroke compared with total (fatal and nonfatal) AMI and stroke were relatively low in the study because the partial numbers of fatal AMI and stroke might be contributed 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 five 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. RRT dependent patients who waited for KT needed to receive dialysis treatments. This finding may be explained by the fact that delayed KT requires a longer pre-KT dialysis 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 durations are reversely associated with the survival outcome.[21-25] Furthermore, an 11-year retrospective cohort study on KT recipients (n = 4,654) 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: 1.01–1.81; P = 0.04).[25] Moreover, the documented preemptive KT was associated with a 45% reduction in the hazard of the dialysis or re-KT (HR: 0.55; 95% CI: 0.47–0.64; P <0.001), and a 40% reduction in the hazard of death with a functioning graft (HR: 0.60; 95% CI: 0.50–0.71; P <0.001).[27] In addition, young adults (11–30 year-old) with ESRD who were not listed for KT within five 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 favorable 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 3-fold 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 durations in most patients in Groups 1–4 varied and presumably affected the clinical outcomes. Late KT with longer pre-KT dialysis durations 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 durations may lead to a relatively poorer survival.[21-25] By contrast, early KT with shorter pre-KT dialysis durations may yield more favorable 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, a longer KT duration with a shorter dialysis duration may yield relatively favorable outcomes in early KT recipients. Although the survival rates vary significantly due to the different KT waiting times, the nonimmunologic pairing of kidney donors and recipients deserves serious consideration regarding clinical outcomes.[29]

As conducting a randomized and controlled trial with randomization 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 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. 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 (i.e., cigarette smoking), and achievements of therapeutic goals were not analyzed. We highlight it should be limited to generalize the results to all KT patients. Fourth, the durations 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 reveals notable differences in the long-term clinical and survival outcomes among groups with stratified KT waiting times after ESRD in selected patients receiving uncomplicated KT. Compared to late uncomplicated KT, early uncomplicated KT is strongly associated with superior clinical and survival outcomes; therefore, this study suggests that KT should be performed as early as possible in eligible ESRD patients, the shortage of kidney donors should be emphasized and rapidly solved.

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Contributorship statement: HHC and CCL designed the study plan, supervised all parts of this project, interpreted the patient data, and did the final edition of the manuscript. YBC and CCL helped in performing the experiments, gathered and collected the relevant data, and wrote the manuscript draft. CYH and PLT analyzed the data and interpreted the results of the experiments. HHC, YBC and CCL were involved in the grant application, setting the study design and conduction. All authors have read and agreed to the published version of the manuscript.

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Ethics approval: The National Health Research Institute (NHRI), a non-profit organization 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 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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Tables

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

Variable	Total (n = 3,562)	Waiting Time for Kidney Transplantation				P Value[a]
		< 1 years (n = 853)	1-3 years (n = 1,651)	4-6 years (n = 750)	> 6 years (n = 308)	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
Sex						
Female	1,667 (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[b]
Diabetes						
No	2,804 (78.7)	646 (75.7)	1,262 (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	2,735 (76.8)	673 (78.9)	1,297 (78.5)	559 (74.5)	206 (66.9)	
Dyslipidemia						
No	2,588 (72.6)	557 (65.3)	1,184 (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	3,487 (97.9)	841 (98.6)	1,621 (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	3,592 (98.0)	834 (97.8)	1,613 (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)	

Note: Values for the categorical variables are given as number (percentage); continuous variables as mean ± standard deviation.

[a]*P* value was estimated using the Chi-squared test.

[b]*P* value was estimated using the Kruskal–Wallis one-way analysis of variance test.

Abbreviation: AMI, acute myocardial infarction; KT, kidney transplantation; SD, standard deviation.

The age was measured at the time of KT. The waiting time was calculated from the time of dialysis start (the date ESRD certificate card was recoded) and the time at KT (the date the code number V42.0 were recorded). Diabetes was defined as the ICD-9-CM code numbers of 250.X, hypertension as 401.X–405.X, dyslipidemia as 272.X, history of acute myocardial infarction as 410.X–411.X before KT, history of stroke as 433–434 before KT.

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

Waiting Time for Transplant	Primary Events[a]				All-Cause Death				Nonfatal AMI				Nonfatal Stroke			
	No. of Patients with Events	The Cumulative Incidence Rate (%)		*P* Value[b]	No. of Patients with Events	The Cumulative Incidence Rate (%)		*P* Value[b]	No. of Patients with Events	The Cumulative Incidence Rate (%)		*P* Value[b]	No. of Patients with Events	The Cumulative Incidence Rate (%)		*P* Value[b]
		5-year	10-year			5-year	10-year			5-year	10-year			5-year	10-year	
< 1 years	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	

Note: Values for categorical variables are given as percentage.

[a] "Primary events" indicates a composite of all-cause death, nonfatal AMI, and nonfatal stroke.

[b] *P* value was estimated using log-rank test.

Abbreviation: AMI, acute myocardial infarction; KT, kidney transplantation.

Table 3. Univariate and multivariate Cox regression analyses of clinical events (all-cause death, nonfatal AMI, and nonfatal stroke) among groups with different waiting times for kidney transplantation

Waiting Time for KT	No. (%)	Primary Events[a]		All-Cause Death		Nonfatal AMI		Nonfatal Stroke	
		CHR (95% CI)	*P* Value[b]	CHR (95% CI)	*P* Value[b]	CHR (95% CI)	*P* Value[b]	CHR (95% CI)	*P* Value[b]
< 1 years	853 (23.9)	1.00		1.00		1.00		1.00	
1-3 years	1651 (46.4)	1.41 (1.19-1.68)	<0.001	1.44 (1.19-1.75)	<0.001	1.63 (1.03-2.57)	0.037	1.12 (0.70-1.80)	0.625
4-6 years	750 (21.1)	1.64 (1.32-2.04)	<0.001	1.68 (1.32-2.13)	<0.001	1.84 (1.03-3.31)	0.042	1.03 (0.54-1.95)	0.932
> 6 years	308 (8.6)	1.79 (1.29-2.49)	0.001	1.71 (1.18-2.46)	0.004	2.12 (0.85-5.27)	0.101	1.68 (0.72-3.93)	0.230
	No. (%)	**AHR (95% CI)**	***P* Value[c]**	**AHR (95% CI)**	***P* Value[c]**	**AHR (95% CI)**	***P* Value[c]**	**AHR (95% CI)**	***P* Value[c]**
< 1 years	853 (23.9)	1.00		1.00		1.00		1.00	
1-3 years	1651 (46.4)	1.67 (1.40-2.00)	<0.001	1.69 (1.39-2.05)	<0.001	2.14 (1.34-3.42)	0.002	1.32 (0.82-2.14)	0.256
4-6 years	750 (21.1)	2.17 (1.73-2.71)	<0.001	2.14 (1.68-2.73)	<0.001	3.01 (1.64-5.55)	<0.001	1.46 (0.76-2.82)	0.257
> 6 years	308 (8.6)	3.10 (2.21-4.35)	<0.001	2.77 (1.90-4.05)	<0.001	4.80 (1.87-12.32)	0.001	3.28 (1.35-7.96)	0.009

[a] "Primary events" indicates a composite of all-cause death, nonfatal AMI, and nonfatal stroke.

[b] *P* values were estimated using the Cox's regression analyses.

[c] *P* values were adjusted for sex, age, diabetes, hypertension, dyslipidemia, history of AMI, and history of stroke using multiple Cox`s regression analyses. No statistical significance using the method of Schoenfeld residuals to test the proportional hazards assumption of the Cox model.

Abbreviation: AHR, adjusted hazard ratio; AMI, acute myocardial infarction; CHR, crude hazard ratio; CI, confidence interval; KT, kidney transplantation

Figure Legends

Figure 1. Patient selection flow chart.

Abbreviations: ESRD, end-stage renal disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; KT, kidney transplantation; NHI, National Health Insurance

Figure 2. 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 favorable primary outcome during the observational period.

Figure 3. 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 favorable survival outcome during the observational period.

Figure 4. Kaplan–Meier survival analysis indicates a statistical trend in the cumulative incidence of nonfatal 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 favorable outcome of nonfatal acute myocardial infarction (AMI) during the observational period.

The different lines representing the other three KT groups are not obviously separated for nonfatal AMI.

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

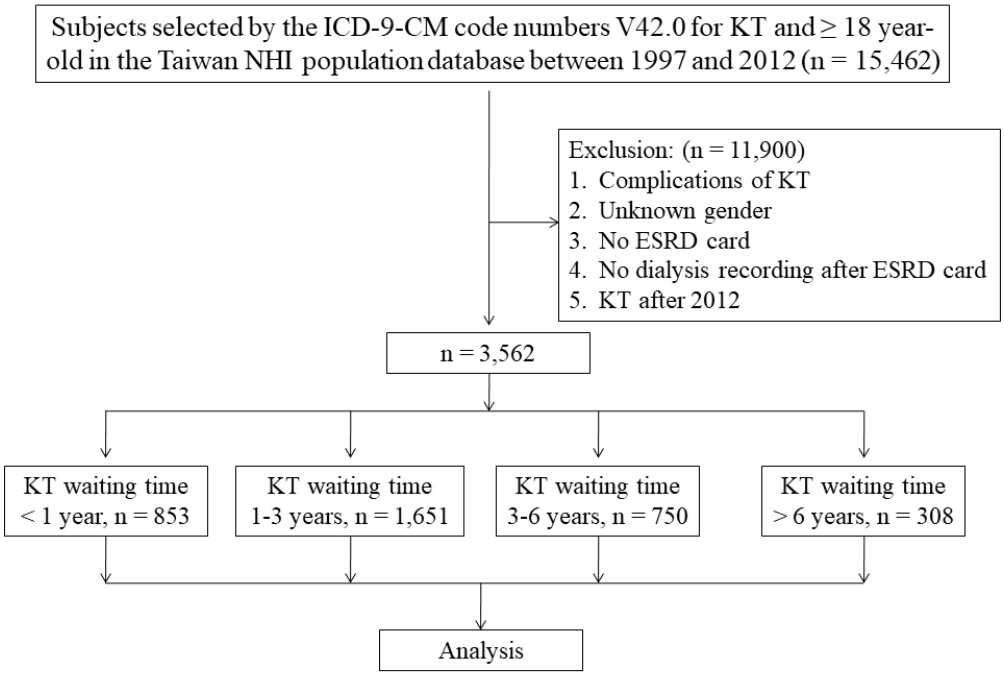
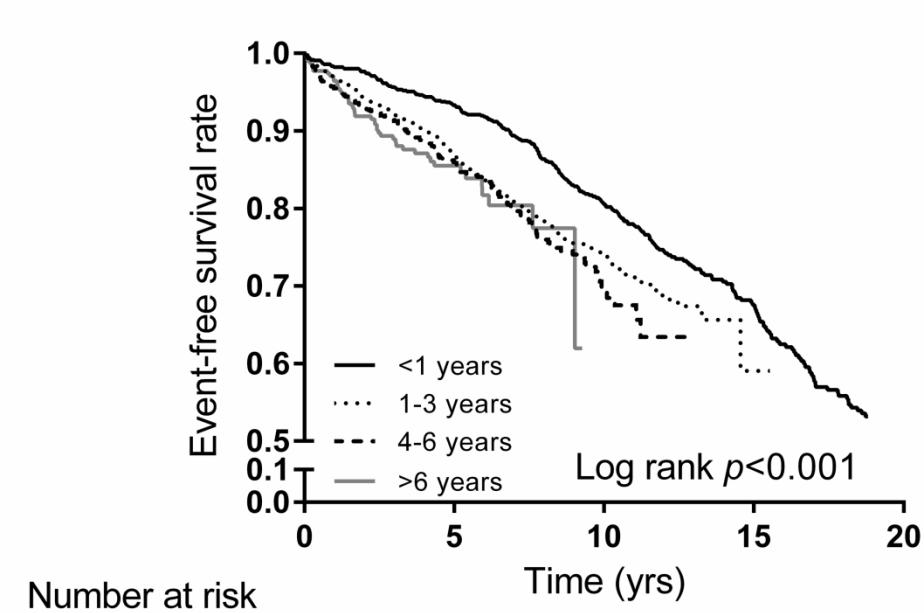


Figure 1

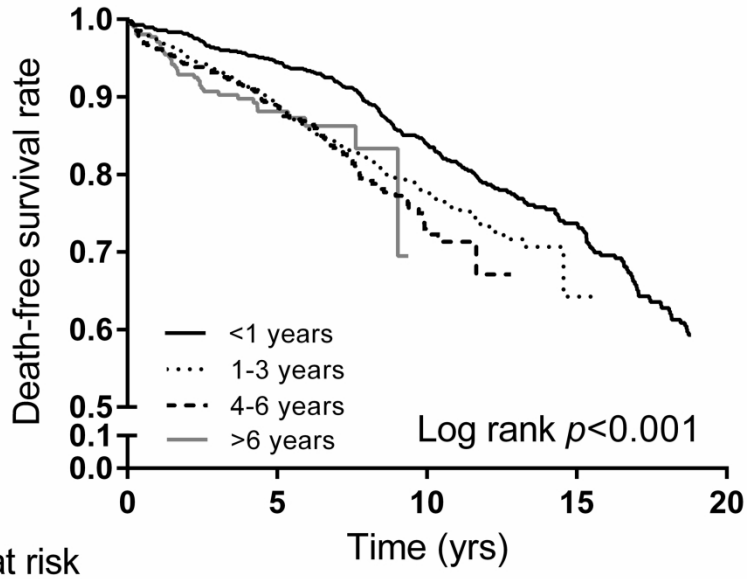
254x190mm (96 x 96 DPI)



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

133x120mm (600 x 600 DPI)

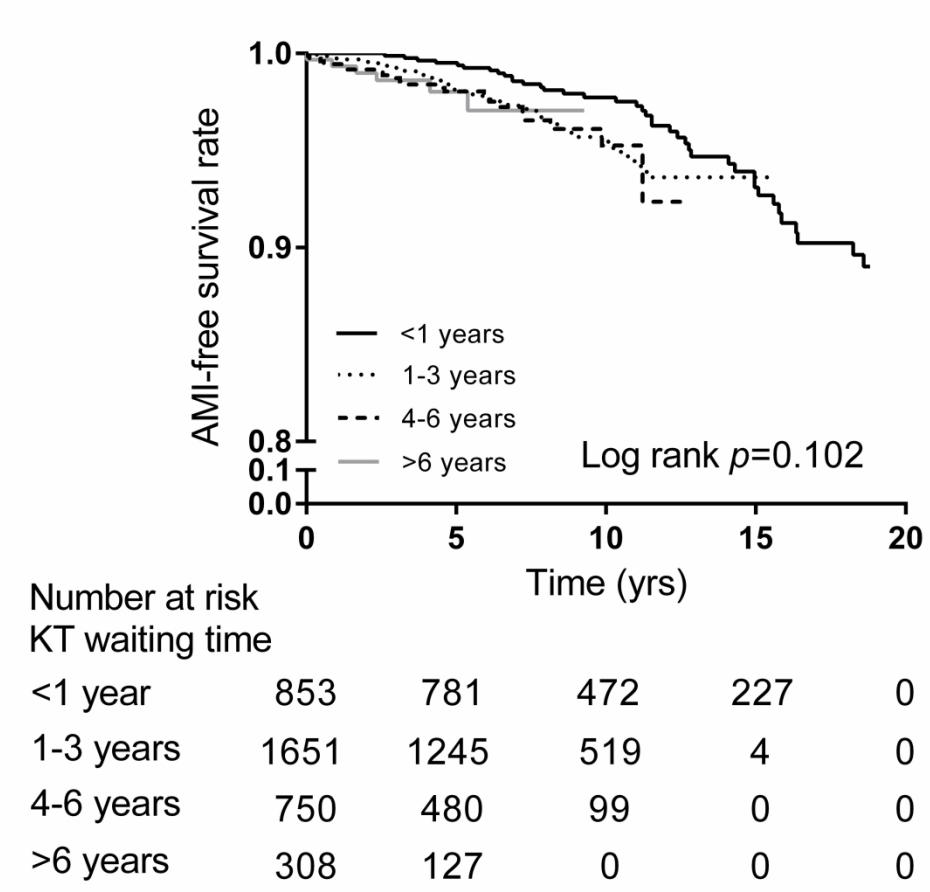


Number at risk

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

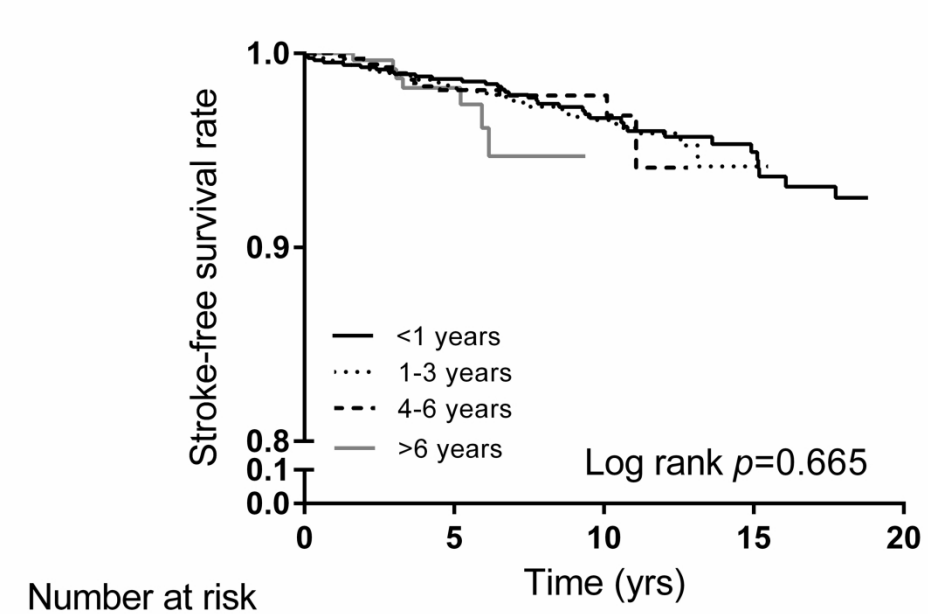
133x120mm (600 x 600 DPI)



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

133x121mm (600 x 600 DPI)



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

133x120mm (600 x 600 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 or 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not applicable
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	7

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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 on 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 kidney transplantation therapy from 1997 to 2013 were included.

Participants: A total of 3562 adult patients who initiated uncomplicated KT therapy were included and categorized 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 measure: The main outcome was a composite of all-cause death, nonfatal myocardial infarction, or nonfatal stroke, based on the primary diagnosis in medical records during hospitalization.

Results: Compared with Group 1, the adjusted risk of primary outcome events (all-cause death, nonfatal myocardial infarction, or nonfatal stroke) increased by 1.67 times in Group 2 (95% CI: 1.40–2.00; P <0.001), 2.17 times in Group 3 (95% CI: 1.73–2.71; P <0.001), and 3.10 times in Group 4 (95% CI: 2.21–4.35; P <0.001). The rates of primary outcome events were 6.7%, 13.4%, and 14.0% within five 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 to late KT in selected ESRD patients receiving

uncomplicated KT, suggesting that an early KT could be a better treatment option for ESRD patients who are eligible for transplantation.

Keywords: Clinical outcomes; End-stage renal disease; Kidney transplantation; Myocardial infarction; Stroke

Strengths and limitations of this study

- The data for this study were collected from patients who initiated kidney transplantation therapy from 1997 to 2013 were enrolled in the National Health Insurance Research Database (NHIRD) in Taiwan.
- Our findings indicated that kidney transplantation should be performed as early as possible in eligible end-stage renal disease (ESRD) patients 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), hemodialysis (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 in 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 ESRD patients received late KT due to the shortage of kidney donors. Thus, by early 2017, the KT waitlist in Taiwan exceeded 6,000 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 a longer pre-KT dialysis duration is associated with a higher risk of all-cause mortality.[21-25] We hypothesized 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 analyze 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 ESRD patients (≥18 years old) from the population who had received uncomplicated KT as an RRT between January 1, 1997 and December 31, 2012, that were followed-up until December 31, 2013.

Ethics approval

The Institutional Review Board of Kaohsiung Veterans General Hospital approved the study protocol (VGHKS15-EM10-02).

Study design and relevant variables

Patients with ESRD certificate cards (labeled 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 of dialysis start (the date ESRD certificate card was recoded) and the time at KT (the date the code number V42.0 were recorded). Patients who were not simultaneously coded by the ICD-9-CM code numbers 585 and V42.0, were younger than 18 years, or that had KT complications such as graft infection, rejection, and failure (ICD-9-CM code number 996.81) were excluded. We categorized 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 numbers of 250.X), hypertension (ICD-9-CM code numbers of 401.X–405.X), dyslipidemia (ICD-9-CM code numbers of 272.X), prior ischemic 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 outcome was a composite of all-cause mortality, nonfatal MI, and nonfatal ischemic stroke. We also analysed these three outcomes separately. Death by any cause was identified as withdrawal from the NHI system. A nonfatal MI event after KT was defined as ICD-9-CM codes

410.X and 411.X, and a nonfatal 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 analyzed using SPSS software version 20 (SPSS Inc., Illinois, USA). All the categorical data and rates are displayed as numbers and percentages, while the continuous data are shown as means ± standard deviation. The baseline and outcome data were compared among the groups by using the Chi-squared 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 hazard ratio (CHR), adjusted hazard ratio (AHR), and 95% confidence interval (CI) were obtained using a Cox regression model with univariate and multivariate analyses for the primary cardiovascular endpoints, all-cause mortality, nonfatal MI, and nonfatal ischemic stroke among the groups. The method of Schoenfeld residuals were used to test the proportional hazards assumption of the Cox model. The analysis was conducted as described to avoid repetitive counting, as the time to the first event involved composite endpoints. A *P* value <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 3,562 eligible ESRD adults 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 dyslipidemia at the baseline among the groups (all P <0.001), except for the prior acute MI and prior stroke (both P >0.05). Patients in Group 4 were younger and had fewer comorbidities of DM, hypertension, and dyslipidemia 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's regression analyses revealed that the event risks significantly increased in Group 2, including the primary events (CHR: 1.41; 95% CI: 1.19–1.68; P <0.001; AHR: 1.67; 95% CI: 1.40–2.00; P <0.001), all-cause mortality (CHR: 1.44; 95% CI: 1.19–1.75; P <0.001; AHR: 1.69; 95% CI: 1.39–2.05; P <0.001), and nonfatal MI (CHR: 1.63; 95% CI: 1.03–2.57; P = 0.037; AHR: 2.14; CI: 1.34–3.42; P = 0.002). The results of the univariate and multivariate Cox regression analyses are summarized 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 nonfatal MI among the groups (P = 0.102 by log-rank test) (Figure 4). No statistical difference was observed in the cumulative rates of the nonfatal ischemic 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 3-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 one 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 completely intact body has limited organ donation. The organization of Taiwan Organ Registry and Sharing Center has been responsible to manage the organ donation, matching and sharing. Nearly three-fourths of the selected KT recipients received KT over one 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 group; therefore, our study suggests early KT for eligible ESRD adults in order to lower the risks of primary events and mortality. Furthermore, the present study observed high rates of the primary events (11.8% at within five 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 five years. Conflicting results obtained from a retrospective study on KT recipients (n = 4,954) indicated no significant change in the incidence of major CVEs (MI, coronary angioplasty, bypass surgery, and stroke) and death over a three-year observation 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 nonfatal AMI and stroke compared with total (fatal and nonfatal) AMI and stroke were relatively low in the study because the partial numbers of fatal AMI and stroke might be contributed 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 five 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. RRT dependent patients who waited for KT needed to receive dialysis treatments. This finding may be explained by the fact that delayed KT requires a longer pre-KT dialysis 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 durations are reversely associated with the survival outcome.[21-25] Furthermore, an 11-year retrospective cohort study on KT recipients (n = 4,654) 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: 1.01–1.81; P = 0.04).[25] Moreover, the documented preemptive KT was associated with a 45% reduction in the hazard of the dialysis or re-KT (HR: 0.55; 95% CI: 0.47–0.64; P <0.001), and a 40% reduction in the hazard of death with a functioning graft (HR: 0.60; 95% CI: 0.50–0.71; P <0.001).[27] In addition, young adults (11–30 year-old) with ESRD who were not listed for KT within five 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 favorable 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 3-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 durations in most patients in Groups 1–4 varied and presumably affected the clinical outcomes. Late KT with longer pre-KT dialysis durations 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 durations may lead to a relatively poorer survival.[21-25] By contrast, early KT with shorter pre-KT dialysis durations may yield more favorable 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, a longer KT duration with a shorter dialysis duration may yield relatively favorable outcomes in early KT recipients. Although the survival rates vary significantly due to the different KT waiting times, the nonimmunologic pairing of kidney donors and recipients deserves serious consideration regarding clinical outcomes.[29]

As conducting a randomized and controlled trial with randomization 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 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 be

resulted 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 (i.e., cigarette smoking), and achievements of therapeutic goals were not analyzed. We highlight it should be limited to generalize the results to all KT patients. Fourth, the durations 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 reveals notable differences in the long-term cardiovascular outcomes among groups with stratified KT waiting times after ESRD in selected patients receiving uncomplicated KT. Compared to 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 ESRD, and that the shortage of kidney donors needs to be addressed with urgency.

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Contributors

HHC and CCL designed the study plan, supervised all parts of this project, interpreted the patient data, and did the final edition of the manuscript. YBC and CCL helped in performing the experiments, gathered and collected the relevant data, and wrote the manuscript draft. CYH and PLT analyzed the data and interpreted the results of the experiments. HHC, YBC and CCL were involved in the grant application, setting the study design and conduction. All authors have read and agreed to the published version of the manuscript.

Competing interests

None declared.

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Patient consent for publication

Not required.

Ethics approval

The National Health Research Institute (NHRI), a non-profit organization 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).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi.org/10.5061/dryad.rfj6q57d1

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Tables

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

Variable	Total (n = 3,562)	Waiting Time for Kidney Transplantation				P Value[a]
		< 1 years (n = 853)	1-3 years (n = 1,651)	4-6 years (n = 750)	> 6 years (n = 308)	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
Sex						
Female	1,667 (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[b]
Diabetes						
No	2,804 (78.7)	646 (75.7)	1,262 (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	2,735 (76.8)	673 (78.9)	1,297 (78.5)	559 (74.5)	206 (66.9)	
Dyslipidemia						
No	2,588 (72.6)	557 (65.3)	1,184 (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	3,487 (97.9)	841 (98.6)	1,621 (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	3,592 (98.0)	834 (97.8)	1,613 (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)	

Note: Values for the categorical variables are given as number (percentage); continuous variables as mean ± standard deviation.

[a]*P* value was estimated using the Chi-squared test.

[b]*P* value was estimated using the Kruskal–Wallis one-way analysis of variance test.

Abbreviation: AMI, acute myocardial infarction; KT, kidney transplantation; SD, standard deviation.

The age was measured at the time of KT. The waiting time was calculated from the time of dialysis start (the date ESRD certificate card was recoded) and the time at KT (the date the code number V42.0 were recorded). Diabetes was defined as the ICD-9-CM code numbers of 250.X, hypertension as 401.X–405.X, dyslipidemia as 272.X, history of acute myocardial infarction as 410.X–411.X before KT, history of stroke as 433–434 before KT.

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

Waiting Time for Transplant	Primary Events[a]				All-Cause Death				Nonfatal AMI				Nonfatal Stroke			
	No. of Patients with Events	The Cumulative Incidence Rate (%)		*P* Value[b]	No. of Patients with Events	The Cumulative Incidence Rate (%)		*P* Value[b]	No. of Patients with Events	The Cumulative Incidence Rate (%)		*P* Value[b]	No. of Patients with Events	The Cumulative Incidence Rate (%)		*P* Value[b]
		5-year	10-year			5-year	10-year			5-year	10-year			5-year	10-year	
< 1 years	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	

Note: Values for categorical variables are given as percentage.

[a] "Primary events" indicates a composite of all-cause death, nonfatal AMI, and nonfatal stroke.

[b] *P* value was estimated using log-rank test.

Abbreviation: AMI, acute myocardial infarction; KT, kidney transplantation.

Table 3. Univariate and multivariate Cox regression analyses of clinical events (all-cause death, nonfatal AMI, and nonfatal stroke) among groups with different waiting times for kidney transplantation

Waiting Time for KT	No. (%)	Primary Events[a]		All-Cause Death		Nonfatal AMI		Nonfatal Stroke	
		CHR (95% CI)	*P* Value[b]	CHR (95% CI)	*P* Value[b]	CHR (95% CI)	*P* Value[b]	CHR (95% CI)	*P* Value[b]
< 1 years	853 (23.9)	1.00		1.00		1.00		1.00	
1-3 years	1651 (46.4)	1.41 (1.19-1.68)	<0.001	1.44 (1.19-1.75)	<0.001	1.63 (1.03-2.57)	0.037	1.12 (0.70-1.80)	0.625
4-6 years	750 (21.1)	1.64 (1.32-2.04)	<0.001	1.68 (1.32-2.13)	<0.001	1.84 (1.03-3.31)	0.040	1.03 (0.54-1.95)	0.932
> 6 years	308 (8.6)	1.79 (1.29-2.49)	0.001	1.71 (1.18-2.46)	0.004	2.12 (0.85-5.27)	0.101	1.68 (0.72-3.93)	0.230
	No. (%)	**AHR (95% CI)**	***P* Value[c]**	**AHR (95% CI)**	***P* Value[c]**	**AHR (95% CI)**	***P* Value[c]**	**AHR (95% CI)**	***P* Value[c]**
< 1 years	853 (23.9)	1.00		1.00		1.00		1.00	
1-3 years	1651 (46.4)	1.67 (1.40-2.00)	<0.001	1.69 (1.39-2.05)	<0.001	2.14 (1.34-3.42)	0.002	1.32 (0.82-2.14)	0.256
4-6 years	750 (21.1)	2.17 (1.73-2.71)	<0.001	2.14 (1.68-2.73)	<0.001	3.01 (1.64-5.55)	<0.001	1.46 (0.76-2.82)	0.257
> 6 years	308 (8.6)	3.10 (2.21-4.35)	<0.001	2.77 (1.90-4.05)	<0.001	4.80 (1.87-12.32)	0.001	3.28 (1.35-7.96)	0.009

[a] "Primary events" indicates a composite of all-cause death, nonfatal AMI, and nonfatal stroke.

[b] *P* values were estimated using the Cox's regression analyses.

[c] *P* values were adjusted for sex, age, diabetes, hypertension, dyslipidemia, history of AMI, and history of stroke using multiple Cox`s regression analyses. No statistical significance using the method of Schoenfeld residuals to test the proportional hazards assumption of the Cox model.

Abbreviation: AHR, adjusted hazard ratio; AMI, acute myocardial infarction; CHR, crude hazard ratio; CI, confidence interval; KT, kidney transplantation

Figure Legends

Figure 1. Patient selection flowchart

Abbreviations: ESRD, end-stage renal disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; KT, kidney transplantation; NHI, National Health Insurance.

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 favorable primary outcome during the observational period.

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 favorable survival outcome during the observational period.

Figure 4. Kaplan–Meier analysis for nonfatal myocardial infarction

Kaplan–Meier survival analysis indicates a non-significant result in the cumulative incidence of nonfatal 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 favorable outcome of nonfatal acute myocardial infarction (AMI) during the observational period. The different lines representing the other three KT groups are not obviously separated for nonfatal AMI.

Figure 5. Kaplan–Meier analysis for nonfatal stroke

Kaplan–Meier survival analysis indicates no statistical difference in the cumulative incidence of nonfatal stroke among the four KT groups during the 17-year observational period. Late KT (KT waiting time >6 years) represented by the gray line indicates the least favorable outcome of nonfatal stroke during the late observational years. In addition, the other lines are not separated during the observational period.

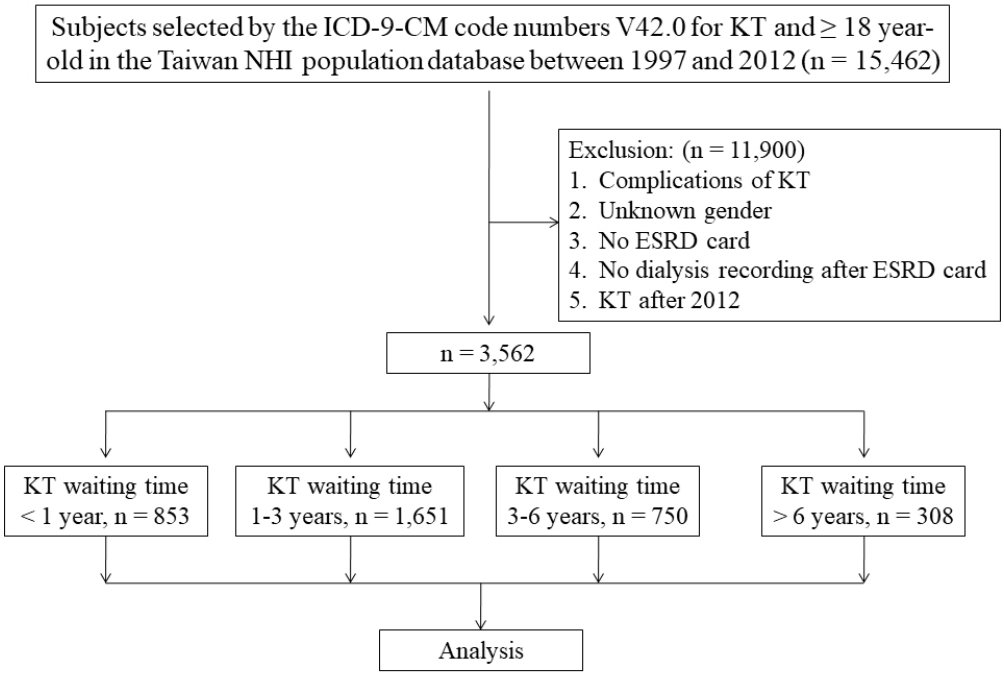

Figure 1

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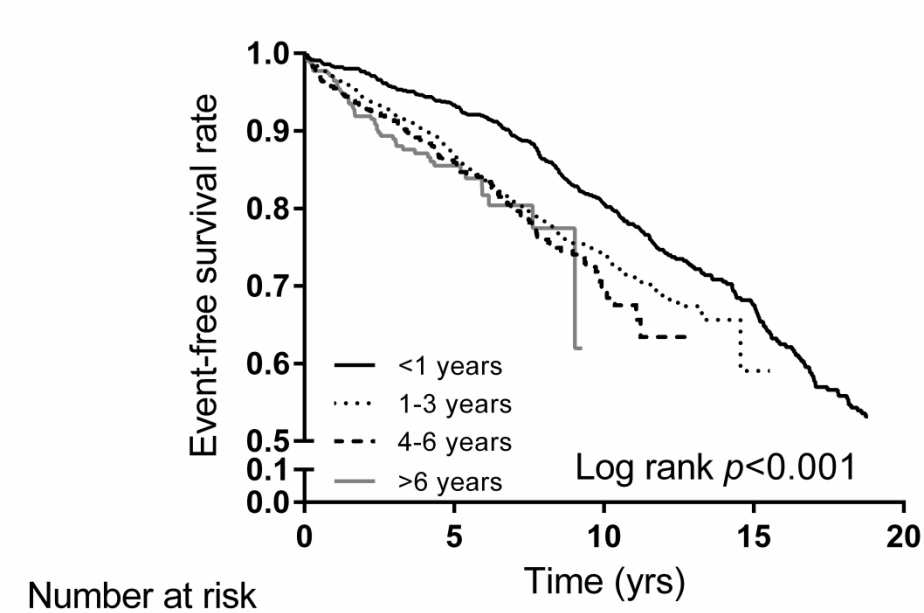
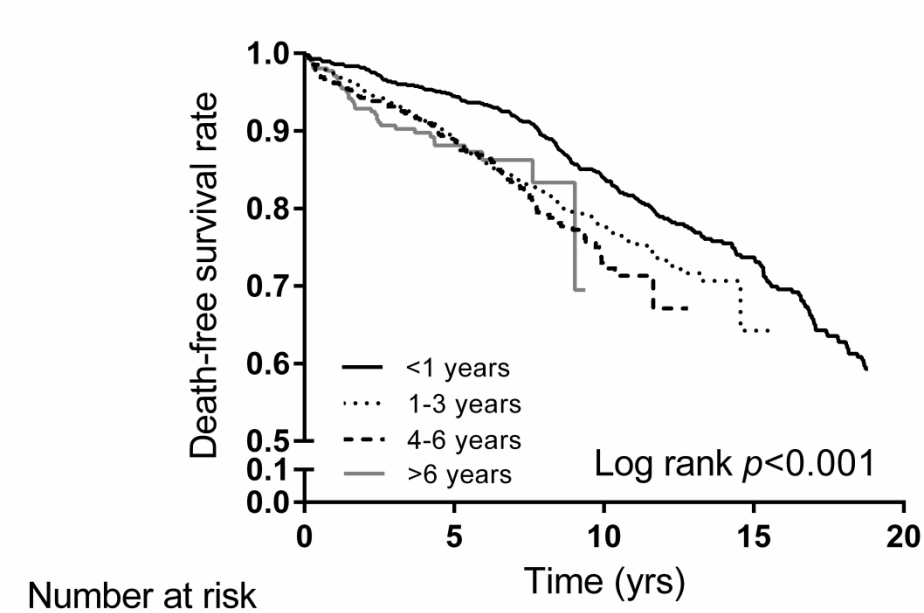


Number at risk

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

133x120mm (1200 x 1200 DPI)



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

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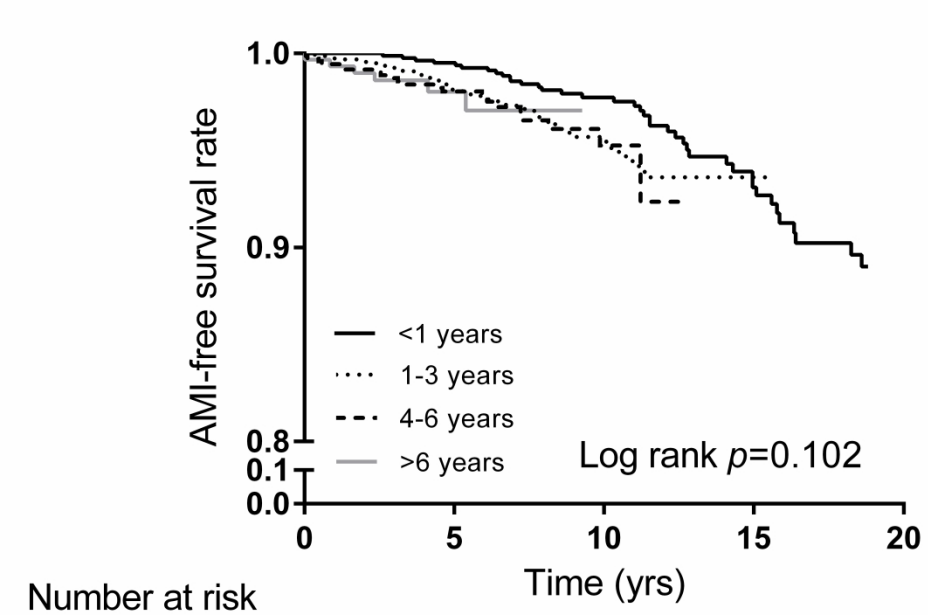

Number at risk
KT waiting time

<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

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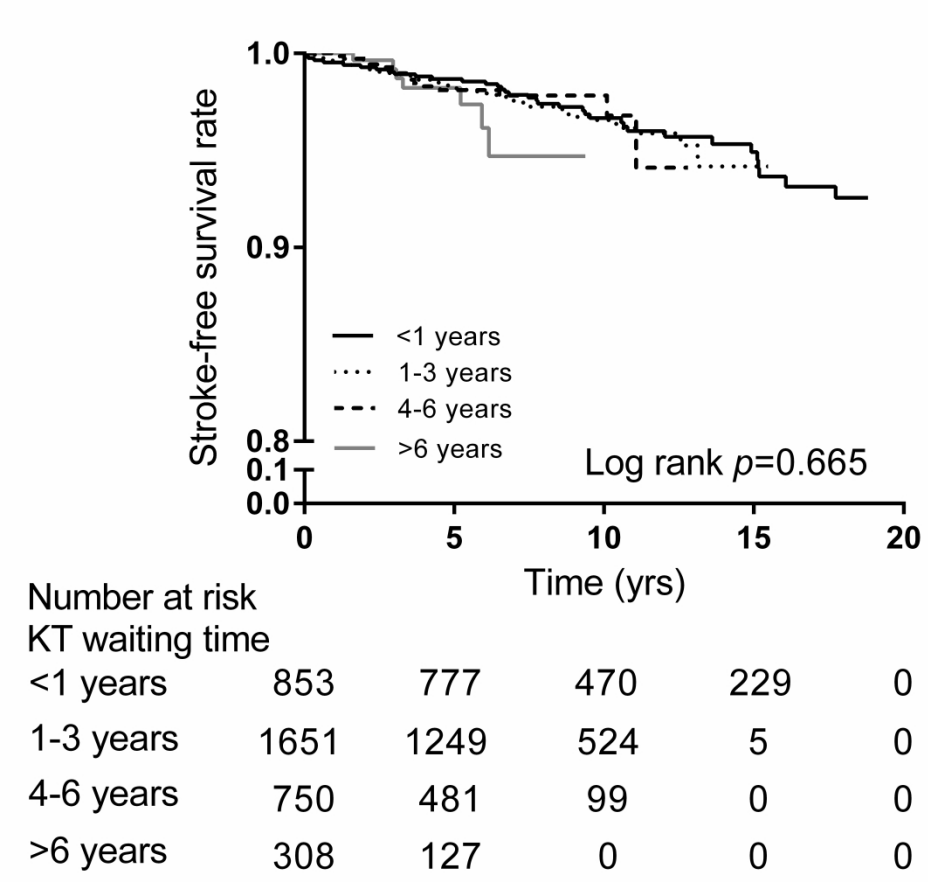

Number at risk

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

133x120mm (1200 x 1200 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 or 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not applicable
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	7

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.