Hazards of Stroke in Renal Transplant Recipients and Patients With End-Stage Renal Disease

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ABSTRACT

Background. Several comparison studies have suggested that kidney transplant (KT) could reduce stroke risk in patients with end-stage renal disease (ESRD). To avoid the selection criteria bias of using dialysis patients as control groups, we compared the risk of stroke between KT recipients and comparable propensity score-matched dialysis patients.

Methods. We used Taiwan's National Health Insurance Research Database to identify patients with newly diagnosed ESRD between 2000 and 2009. We separated them into 2 groups: a KT group and a non-KT dialysis-only group. To evaluate the stroke outcome, we compared each patient with KT to a patient on dialysis without KT using propensity score matching.

Results. In total, 2735 KT recipients and 10,940 propensity score-matched dialysis patients were identified. The incidence rates of overall stroke were 9.1 and 23.4 per 1000 person-years in KT recipients and non-KT dialysis patients. Compared with the propensity score-matched dialysis patients, the patients who received KT exhibited significantly lower overall stroke risk, hemorrhagic stroke, and ischemic stroke, the adjusted hazard ratios were 0.37 (95% CI, 0.31–0.45), 0.19 (95% CI, 0.12–0.29), and 0.46 (95% CI, 0.37–0.56), respectively (all $P < .001$).

Conclusions. Through a propensity score-matched cohort, this study confirms that KT is associated with a reduced risk of stroke more than dialysis alone in patients with newly diagnosed ESRD.

THE INCIDENCE of stroke is high in end-stage renal disease (ESRD) [1]. In fact, stroke is one of the most important causes of increased morbidity and mortality in patients with ESRD who receive either dialysis or kidney transplant (KT) [2]. Some retrospective studies reported that KT was associated with a lower incidence and mortality rate than patients who underwent regular dialysis [2,3]. The effect of selection bias on stroke risk for patients with ESRD with or without KT remains unclear, especially with respect to age and comorbidities. Compared with the dialysis population, KT recipients are relatively younger and have less comorbidity. A study using the matching method to adjust the common difference between the dialysis population and KT recipients could provide stronger evidence. Propensity score matching is a powerful tool for adjusting

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Table 1. Baseline Characteristics Between Without Renal Transplantation and With Renal Transplantation Among ESRD Patients by Propensity Score Matching

	ESRD			
	All	Without RT	With RT	
	n = 13,675	n = 10,940	n = 2,735	*P* Value
Sex*, n (%)				.36
Female	6881 (50.3)	5483 (50.1)	1398 (51.1)	
Male	6794 (49.7)	5457 (49.9)	1337 (48.9)	
Age, year*, n (%)				.23
20–44	4547 (33.3)	3601 (32.9)	946 (34.6)	
45–64	8588 (62.8)	6909 (63.2)	1679 (61.4)	
≥65	540 (3.9)	430 (3.9)	110 (4.0)	
Age,† mean (SD)	48.7 (9.9)	48.8 (9.9)	48.3 (9.9)	.02
Comorbidity*, n (%)				
Hypertension	12,347 (90.3)	9895 (90.4)	2452 (89.7)	.22
Hyperlipidemia	6092 (44.5)	4906 (44.8)	1186 (43.4)	.17
Diabetes	4865 (35.6)	3914 (35.8)	951 (34.8)	.34
Heart disease	6726 (49.2)	5400 (49.4)	1326 (48.5)	.42
CAD	5700 (41.7)	4576 (41.8)	1124 (41.1)	.50
AF	474 (3.5)	375 (3.4)	99 (3.6)	.67
Propensity Score, mean (SD)	0.16 (0.08)	0.16 (0.08)	0.16 (0.08)	.86
Duration time,† year, mean (SD)	4.11 (3.19)	4.11 (3.24)	4.10 (2.98)	.90

Duration time: the duration between ESRD and index date.
Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; ESRD, end-stage renal disease; KT, kidney transplant.
*χ^2 test
†Student's t-test.

confounding variables and reducing the number of treatment selection biases [4,5]. In the current study, we used an adjusted cohort through propensity score matching to evaluate the risk of stroke in patients with newly diagnosed ESRD with or without KT.

MATERIALS AND METHODS

Data Source

We performed a retrospective nationwide cohort study by analyzing the Registry for Catastrophic Illness Patients Database (RCIPD) of Taiwan's National Health Insurance (NHI) program, which covers 99% of the 23 million inhabitants of Taiwan and was launched on March 1, 1995. The RCIPD contains the medical records for each patient diagnosed as having a catastrophic illness between 1997 and 2011. The catastrophic illnesses were defined by the Taiwan government, and patients with catastrophic illness can get free health care for their illness or related conditions. The application of the catastrophic illness card should be inspected by sufficient medical records and the process of equal reviews. Therefore, the diagnoses from the RCIPD are even more convincing compared with the use of clinical diagnosis only. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH104-REC2-115-CR3).

Study Population

We identified patients first listed in the RCIPD from 2000 to 2009 with catastrophic illness registration cards for ESRD who underwent regular dialysis by International Statistical Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 585 (N = 167,373). We separated these patients into 2 groups: a KT group (ICD-9-CM Code V42.0) and a comparison group of patients receiving dialysis without KT (non-KT). Stroke (ICD-9-CM codes 430–438) is classified into 2 categories. The ICD-9-CM 430–432 was hemorrhagic stroke; the ICD-9-CM 433–438 was classified in the group with ischemic stroke. The study index date was defined as the date on which the patient first received KT. Patients with stroke before the index date and those younger than 20 years old or with missing demographic data were excluded. Patients in KT and non-KT groups were selected by 1:4 matching by propensity scores to minimize selection bias. Propensity scores were calculated using logistic regression to estimate the probability of receiving a KT based on the baseline variables of age, sex, index date, and comorbidities. The comorbidities were hypertension (ICD-9-CM Codes 401–405), hyperlipidemia (ICD-9-CM Codes 272), diabetes mellitus (ICD-9-CM Codes 250), heart disease (ICD-9-CM Codes 420–429), coronary artery disease (ICD-9-CM Codes 410–414), and atrial fibrillation (ICD-9-CM Codes 427.31, 427.32). All patients were followed until the diagnosis of stroke, withdrawal from the National Health Insurance (NHI) program, censorship because of death, loss to follow-up, or December 31, 2011 (whichever occurred first).

Statistical Analysis

Demographic characteristics and the prevalence of comorbidities were compared between the groups using the χ^2 test for categorical variables and a *t* test for the continuous variables. The incidence rate (per 1000 person-years) of stroke was estimated by age, sex, and comorbidity in the KT and non-KT groups. The multivariable Cox proportional hazards model assessed the risk of stroke (including overall stroke, hemorrhagic stroke, and ischemic stroke) between the KT and non-KT groups presented by the incidence rate ratio (IRR), hazard ratio (HR), and 95% CI. All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, United States) and the 2-tailed statistical significance level was set at $P < .05$.

Table 2. Hazard Ratios of Stroke, Hemorrhagic Stroke and Ischemic Stroke Between Kidney Transplantation and Non-Kidney Transplantation Cohorts by Propensity Score Matching

	Non-KT			KT			Compared to Non-KT	
Variables	Event	PY	Rate	Event	PY	Rate	IRR (95% CI)	aHR* (95% CI)
Overall Stroke	1324	56,700	23.4	148	16,260	9.1	0.39 (0.34–0.45)†	0.37 (0.31–0.45)†
Hemorrhagic Stroke	415	56,700	7.3	26	16,260	1.6	0.22 (0.18–0.27)†	0.19 (0.12–0.29)†
Ischemic Stroke	909	56,700	16.0	122	16,260	7.5	0.47 (0.41–0.54)†	0.46 (0.37–0.56)†

Rate: incidence rate (per 1000 person-years).
Abbreviations: aHR, adjusted hazard ratio; IRR, incidence rate ratio; KT, kidney transplantation; PY, person-year.
*aHR: multivariable analysis including age, sex, hypertension, hyperlipidemia, diabetes, coronary artery disease, atrial fibrillation, and heart disease.
†$P < .001$.

RESULTS

Among 167,373 patients with newly diagnosed ESRD in the RCIPD from 2000 to 2009, we selected a cohort of 2,735 patients in the KT group and 10,940 patients in the non-KT group by propensity score matching. Table 1 shows the baseline characteristics, comorbidity, duration years between ESRD, index date, and propensity score of the KT group and non-KT group. The mean age was 48.3 (SD, 9.9) years and 48.8 (SD, 9.9) years in the KT group and the comparison non-KT group, respectively. Propensity score matching successfully balanced the distributions of comorbidities across the KT group vs non-KT group. The patients in the groups matched by age, sex, index date, and comorbidities were predominately between the ages 45 and 64 years (range, 61.4%-63.2%). The most common comorbidities in our study patients were hypertension (range, 89.7%-90.4%), heart disease (range, 48.5%-49.4%), and hyperlipidemia (range, 43.4%-44.8%), while diabetes mellitus was less prevalent in our study cohort (range, 34.8%-35.8%). The mean duration time between ESRD and index date was 4.10 (SD, 2.98) years and 4.11 (SD, 3.24) years in the KT group and non-KT group, respectively.

The incidence rates of overall stroke, hemorrhagic stroke, and ischemic stroke were 9.1, 1.6, and 7.5 per 1000 person-years, respectively, in KT recipients. In the non-KT group, the incidence rates of overall stroke, hemorrhagic stroke, and ischemic stroke were 23.4, 7.3, and 16.0 per 1000 person-years, respectively. Table 2 shows the HRs of stroke, hemorrhagic stroke, and ischemic stroke between the RT group and the propensity score-matched non-KT control group. The overall incidence density for stroke was significantly lower in the KT recipients than in the non-KT patients (9.10 vs 23.4 per 1000 person-years). Compared with non-KT patients, the KT recipients had a significantly lower IRR of 0.39 (95% CI, 0.34–0.45; $P < .001$). The IRR was 0.22 and 0.47 in hemorrhagic stroke and ischemic stroke, respectively. Moreover, the adjusted HR was also significantly lower in the KT group at 0.37 (95% CI, 0.31–0.45; $P < .001$). The risks of both ischemic stroke and hemorrhagic stroke were significantly lower in the KT patients than in the non-KT patients, with adjusted HR of 0.46 (95% CI, 0.37–0.56) and 0.19 (95% CI, 0.12–0.29), respectively, all with $P < .001$.

DISCUSSION

We previously reported that a lower mortality rate was observed in the ESRD patients who received KT than in those propensity score-matched dialysis patients [5]. Here, this 12-year population-based record linkage cohort study provides strong evidence to support a significantly reduced risk of stroke in KT recipients when compared with a propensity score-matched dialysis cohort. The incidence rate of stroke could be reduced from 23.4 to 9.1 per 1000 person-years (Table 2), especially in hemorrhagic stroke (from 7.3 to 1.6 per 1000 person-years).

Unlike in the report from Oliveras and colleagues [6], the incidence rate of hemorrhagic stroke is lower than ischemic stroke in a Taiwanese cohort. In fact, the pattern of stroke is similar to the general population in Taiwan. Between 2006 and 2008, the Taiwan Stroke Registry reported that the most common type of stroke was the ischemic stroke, accounting for almost 74% of all strokes [7].

There are several limitations in this present study. The data compiled in the RCIPD limited what could be done in our study. For example, the dataset could not distinguish between deceased donor and living donor KT. The information about the condition of the donor's kidney is also not available.

CONCLUSION

This propensity score-matched cohort study provides strong evidence to support that KT was associated with a reduced hazard of stroke in patients with newly diagnosed ESRD.

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