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Reduced Stroke Risk After Parathyroidectomy in End-Stage Renal Disease

A 13-Year Population-Based Cohort Study

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Abstract: Research information on the risk of stroke in patients with dialysis-dependent end-stage renal disease (ESRD) who have undergone parathyroidectomy (PTX) is scant.

We used a nationwide health insurance claims database to select all patients with dialysis-dependent ESRD age 18 years and older for the study population. Of the patients with ESRD, we selected 1083 patients who had undergone PTX between 1998 and 2006 as the PTX group and frequency-matched 1083 patients with ESRD by sex, age, years since the disease diagnosis, and the year of undergoing PTX as the non-PTX group.

We used a multivariate Cox proportional hazards regression analysis to measure the risk of stroke for the PTX group compared with the non-PTX group after adjusting for sex, age, premium-based income, urbanization, and comorbidity.

The mean follow-up periods were 6.08 and 5.38 years for the PTX and non-PTX groups, respectively. After adjusting for previously mentioned variables, significant risk reductions of stroke (adjusted hazard ratio = 0.57, 95% confidence interval = 0.41–0.79), particularly those of hemorrhagic stroke (adjusted hazard ratio = 0.34, 95% confidence interval = 0.20–0.57), with PTX were observed. Chronologically, the risk of stroke in the PTX group decreased in the second year after PTX and persisted for >3 years.

PTX reduces the risk of stroke, particularly that of hemorrhagic stroke, in patients with dialysis-dependent ESRD. Other factors for risk reduction include sex (females), an age <65 years, and the presence of comorbidity.

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Abbreviations: CI = confidence interval, ESRD = end-stage renal disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, PTH = parathyroid hormone, PTX = parathyroidectomy, RCIPD = Registry for Catastrophic Illness Patient Database, SHPT = secondary hyperparathyroidism.

INTRODUCTION

The incidence of stroke in dialysis-dependent patients with end-stage renal disease (ESRD) is up to 10 times greater than that in the general population and is associated with a poor prognosis.[1,2] Patients on dialysis have a 3-fold higher risk of death following acute stroke, independent of traditional risk factors.[1,3,4] The risk of hemorrhagic stroke is significantly higher in patients on dialysis who have had a stroke.[5,6] Cerebral hemorrhage occurs 10 years earlier in patients on chronic dialysis.[7] More than two-thirds of patients with cerebral hemorrhage die within 3 months of the onset of a cerebrovascular event.[8] The risks of stroke are similar in patients regardless of dialysis modality.[9] Other risk factors for stroke in dialysis-dependent patients include the initiation of dialysis,[2,7] an older age, hypertension (HTN), diabetes mellitus (DM), a previous stroke, and atrial fibrillation (AF).[8,9]

Secondary hyperparathyroidism (SHPT) is one of the major problems for patients on long-term dialysis and is associated with increased vascular calcification, cardiovascular (CV) risk, and mortality.[10–12] Levels of serum parathyroid hormone (PTH) >600 pg/mL are associated with a 21% increase in

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all-cause mortality risk.[11] An elevated PTH level predicts a greater likelihood of prevalent and incident CV events, including myocardial infarction (MI), stroke, and CV death.[12,13]

Parathyroidectomy (PTX) reduces the risk of CV death and all-cause mortality.[10,14–16] Sharma et al[14] reported a 33% reduced risk of CV death after PTX. Iwamoto et al[17] reported that the CV death-free survival rate is significantly improved in the PTX group than in the non-PTX group (94.6% vs 76.3%). Kestenbaum et al[18] demonstrated that the long-term relative risk of death among patients undergoing PTX was 10% to 15% lower than that among patients not undergoing PTX. However, in a report by Conzo et al,[19] PTX did not alter CV morbidity and mortality rates among patients on hemodialysis with SHPT; delayed treatment was considered a possible factor.

The relationship between PTX and incident stroke in patients with ESRD receiving regular dialysis warrants further attention; however, no previous study has addressed this topic. This study aimed to investigate the impact of PTX on the risk of incident stroke in patients with dialysis-dependent ESRD in a retrospective cohort study by using a nationwide health insurance database. We hypothesized that undergoing PTX reduces the risk of incident stroke in patients with ESRD.

METHODS

Data Sources

The National Health Insurance (NHI) program of Taiwan is a single-payer and compulsory health care program introduced in 1995. By 2008, the NHI program provided coverage for >99% of the population of Taiwan, and >92% of health care organizations in Taiwan had signed health service contracts.[20]

The data analyzed in this study were retrieved from the Taiwan NHI Research Database (NHIRD), a database maintained by the Taiwan National Health Research Institutes, and containing comprehensive outpatient and inpatient information, such as demographic data, dates of visits, *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes, and complete prescription details. Dialysis-dependent ESRD is included in the list of catastrophic illnesses of the NHI program. Patients with dialysis-dependent ESRD can apply for a catastrophic illness certificate, with which they can have all ESRD-related health care copayments waived; therefore, >99% of patients with dialysis-dependent ESRD are included in the data sets of the Registry for Catastrophic Illness Patient Database (RCIPD), which was used in this study to select all patients with dialysis-dependent ESRD as the study population. The data sets of the study consisted of the registry of beneficiaries, ambulatory and inpatient care claims, and the RCIPD from 1996 to 2011 from the NHIRD. To protect patient privacy, all personal identification numbers were encrypted before electronic files were released. This study was approved by the institutional review board of China Medical University (CMU-REC-101-012).

Study Patients

Figure 1 depicts the study framework. We included all patients with incident ESRD age 18 years and older, based on the records of ESRD in the RCIPD (ICD-9-CM code 585) and who began regular renal replacement therapy (ie, dialysis or renal transplant) for >90 days from January 1, 1998, to December 31, 2004. All the patients with ESRD who newly underwent PTX were selected and constituted the PTX group. The exclusion criteria included a previous history of stroke (ICD-9-CM code 430–438), renal transplantation (ICD-9-CM code V42.0), parathyroid tumor (ICD-9-CM code 194.1 and 227.1), or other parathyroid disorders (ICD-9-CM code 252.8) during 1998–2006. The date of first PTX was considered the index date. We selected patients with ESRD who did not undergo PTX to form the non-PTX group, based on identical exclusion criteria, by conducting 1:1 random frequency matching by sex, age (in 5-year bands), years since ESRD diagnosis, and the year of undergoing PTX.

The demographic factors studied included sex, age, monthly income surrogated as premium-based income, and urbanization. The amount of premium-based income was categorized into 3 levels: <NT$15,000, NT$15 000–29 999, and

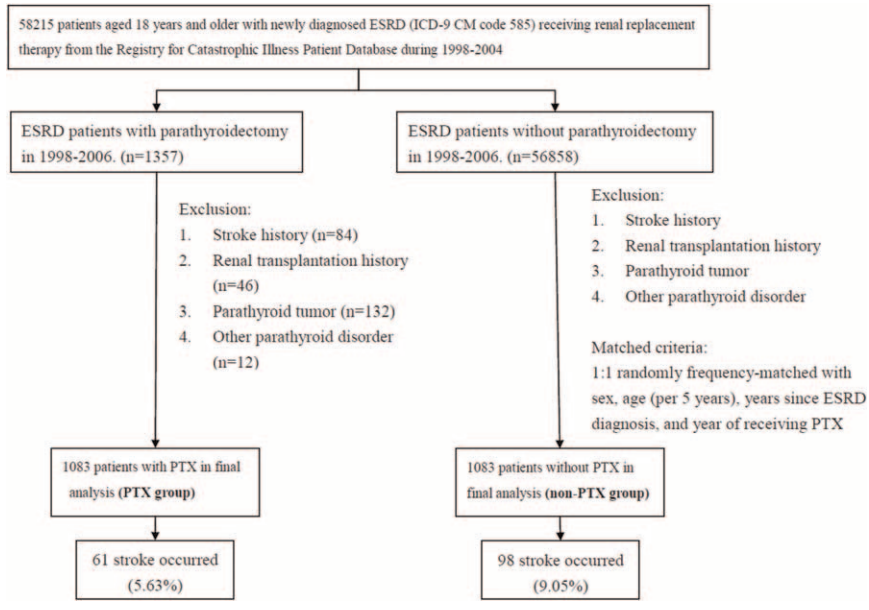

FIGURE 1. Flow chart showing selection of study subjects. ESRD = end-stage renal disease; PTX = parathyroidectomy.

≥NT$30,000. The urbanization level was defined according to a Taiwan National Health Research Institutes report (levels 1 and 4 were the highest and lowest levels of urbanization, respectively). The information and characteristics (ICD-9-CM code) of comorbidity, including DM (ICD-9-CM 250), hyperlipidemia (HL; ICD-9-CM 272.0–272.4), HTN (ICD-9-CM 401–405), ischemic heart disease (IHD; ICD-9-CM 410–414), AF (ICD-9-CM 427.31), congestive heart failure (CHF; ICD-9-CM 398.91, 425, and 428), chronic obstructive pulmonary disease (COPD; ICD-9-CM 491–494 and 496), obesity (ICD-9-CM 278), and alcohol-related diseases (ICD-9-CM 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, and V11.3), were collected from the NHIRD.

The main outcome was the occurrence of stroke during the follow-ups, which was defined by at least once admission record of stroke by ICD-9 disease code in the discharge diagnosis, including hemorrhagic stroke (ICD-9-CM 430–431), ischemic stroke (ICD-9-CM 433–434), transient ischemic attack (ICD-9-CM 435), and unspecified acute stroke (ICD-9-CM 436). Participants were followed from the index date to the date of stroke diagnosis, withdrawal from the insurance program, death, or the end date of the database (December 31, 2011).

Statistical Analyses

First, we compared the distributions of demographic variables and comorbidities between the PTX and non-PTX groups. The chi-square test was used to determine the differences between the 2 groups regarding the distribution of categorical variables. Differences in mean age between the 2 groups were examined using a Student *t* test. The incidence density rate (per 1000 person-years) of stroke was calculated by dividing the number of incident strokes by person-years at risk in both the groups. The follow-up person-years were calculated for each patient since the index date until the stroke diagnosis, at the end of 2011, or until withdrawal from the insurance system. The cumulative incidence of stroke was computed using the Kaplan–Meier method, and differences in cumulative incidences between the 2 groups were tested using a log-rank test. We used a multivariable Cox proportional hazards regression analysis to measure the adjusted hazard ratio of stroke for the PTX group compared with the non-PTX group after adjusting for sex, age, premium-based income, urbanization, and comorbidity (DM, HL, HTN, IHD, AF, CHF, COPD, obesity, and alcohol-related diseases). All statistical analyses were

TABLE 1. Demographic Factors and Comorbidity of Patients With End-Stage Renal Disease According to PTX Status

	PTX Group N = 1083		Non-PTX Group N = 1083		
Variables	**n**	**%**	**n**	**%**	***P***
Sex					0.99
Women	717	66.20	717	66.20	
Men	366	33.80	366	33.80	
Age at receiving PTX, y					0.99
18–34	97	8.98	97	8.96	
35–49	433	39.98	433	39.98	
50–64	452	41.74	452	41.74	
≥65	101	9.33	101	9.33	
Mean (SD)	50.03	(11.17)	50.22	(11.29)	0.69
Premium-based income (NT$/mo)					<0.001
<15,000	466	43.03	530	48.94	
15,000–29,999	419	38.69	432	39.89	
≥30,000	198	18.28	121	11.17	
Urbanization					0.91
Level 1 (highest)	293	27.05	291	26.87	
Level 2	348	32.13	360	33.24	
Level 3	187	17.27	176	16.25	
Level 4 (lowest)	255	23.55	256	23.64	
Comorbidity					
Diabetes	170	15.70	312	28.81	<0.001
Hyperlipidemia	446	41.18	367	33.89	<0.001
HTN	956	88.27	926	85.50	0.06
IHD	392	36.20	428	39.52	0.12
AF	23	2.12	24	2.22	0.99
CHF	234	21.61	301	27.79	0.001
COPD	202	18.65	220	20.31	0.36
Obesity	9	0.83	5	0.46	0.42
Alcohol-related disease	7	0.65	10	0.92	0.62
Follow-up time, mean (SD), y	6.08	(2.52)	5.38	(2.58)	

AF = atrial fibrillation, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, HTN = hypertension, IHD = ischemic heart disease, PTX = parathyroidectomy, SD = standard deviation.

TABLE 2. Incidence Density Rates and Hazard Ratios of Stroke Between PTX and Non-PTX Groups

	PTX Group			Non-PTX Group			HR (95% CI)	
Stroke	Event No.	Person-Years	IR	Event No.	Person-Years	IR	Unadjusted	Adjusted[†]
All stroke	61	6589.52	9.26	98	5829.39	16.81	0.55 (0.40–0.76)***	0.57 (0.41–0.79)***
Hemorrhagic stroke	20		3.04	51		8.75	0.35 (0.21–0.58)***	0.34 (0.20–0.57)***
Ischemic stroke	32		4.86	34		5.83	0.84 (0.52–1.35)	0.88 (0.54–1.45)
TIA	5		0.76	5		0.86	0.92 (0.27–3.17)	0.99 (0.28–3.51)
Unspecified acute stroke	4		0.61	8		1.37	0.46 (0.14–1.53)	0.60 (0.18–2.04)

ICD-9-CM: hemorrhagic stroke, 430–431; ischemic stroke, 433–434; TIA, 435; unspecified acute stroke, 436. CI = confidence interval, HR = hazard ratio, HTN = hypertension, IR = incidence density rate, per 1000 person-years, PTX = parathyroidectomy, TIA = transient ischemic attack.

[†] Adjusted for sex, age (continuous), premium-based income, urbanization, diabetes, hyperlipidemia, HTN, ischemic heart disease, atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease, obesity, and alcohol-related disease in Cox proportional hazards regression.

*** $P < 0.001$.

performed using the SAS 9.3 statistical package (SAS Institute, Cary, NC). The 2-sided level of significance was set at 0.05.

RESULTS

There were 58,215 patients with incident ESRD during 1998–2004. After exclusion and matches, as detailed in Figure 1, the PTX and matched non-PTX groups consisted of 1083 patients each between 1998 and 2006. Women accounted for 66.20% of the patients in both the groups. The mean age in both the groups was 50.03 versus 50.22 years ($P = 0.69$) (Table 1). Compared with the non-PTX group, the PTX group was less likely to have a low income, diabetes, and CHF, but more likely to have HL.

The average time from incident ESRD to undergoing PTX for the PTX group was 4.65 ± 1.97 years; the mean follow-up periods from undergoing PTX to the stroke event were 6.08 ± 2.52 and 5.38 ± 2.58 years for the PTX and matched non-PTX groups, respectively.

The risk of stroke (hazard ratio [HR] = 0.55), particularly that of hemorrhagic stroke (HR = 0.35), was lower in the PTX group compared with that in the non-PTX group (9.26 vs 16.81 per 1000 person-years, respectively; Table 2). After adjusting for sex, age, premium-based income, urbanization, and comorbidity, the risks of stroke in the PTX group were 43% lower than those in the non-PTX group (adjusted HR = 0.57, 95% confidence interval [CI] = 0.41–0.79); the risk reduction of hemorrhagic stroke was even higher, up to 66%, in the PTX group (adjusted HR = 0.34, 95% CI = 0.20–0.57). The Kaplan–Meier analysis revealed that the non-PTX group had a higher cumulative incidence rate of stroke than the PTX group did (log-rank test, $P < 0.001$) (Figure 2).

Women in the PTX group had a lower risk of stroke than those in the non-PTX group did (adjusted HR = 0.54, 95% CI = 0.36–0.81) (Table 3). Younger patients in the PTX group, age 18 to 64 years, exhibited a lower risk of stroke than those in the non-PTX group with the same age range did (adjusted HR = 0.59, 95% CI = 0.41–0.84). Regarding comorbidity, patients with a comorbidity in the PTX group had a significantly reduced risk of stroke than those with a comorbidity in the non-PTX group did (adjusted HR = 0.52, 95% CI = 0.38–0.72). When stratified by follow-up periods, the risk of stroke began to decrease significantly in the PTX group in the second year after PTX, and the risk reduction persisted for >3 years (Table 3).

Compared with the patients age 18 to 64 years, those age 65 years and older had a 1.94-fold higher risk of stroke development (95% CI = 1.24–3.02) (Table 4). Other risk factors for stroke, demonstrated by the multivariate Cox proportional hazard model, included diabetes (2.19, 95% CI = 1.54–3.13), HTN (3.08, 95% CI = 1.42–6.66), and COPD (1.58, 95% CI = 1.10–2.26).

DISCUSSION

Principal Findings

This nationwide population-based retrospective cohort study was conducted in an area with the highest prevalence of ESRD. After matching for sex, age, years since ESRD

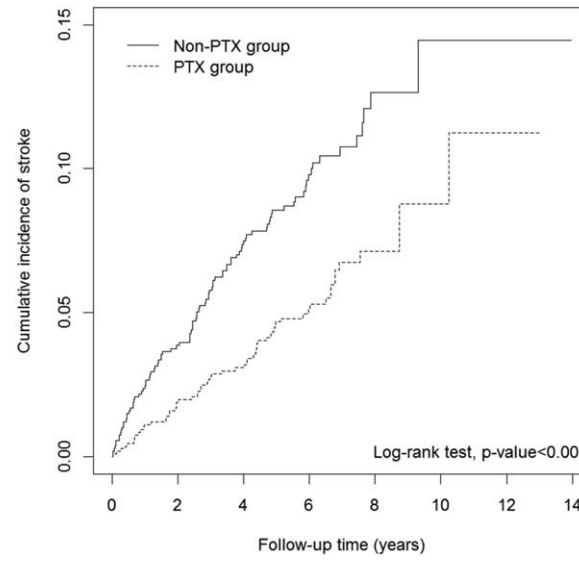

FIGURE 2. Cumulative incidence curves of stroke for PTX and no PTX groups. PTX = parathyroidectomy.

TABLE 3. Incidence Density Rates and Hazard Ratios of Stroke According to PTX Status Stratified by Sex, Age, Comorbidities, and Follow-Up Periods

	PTX Group			Non-PTX Group			HR (95% CI)	
Variables	**Event No.**	**Person-Years**	**IR**	**Event No.**	**Person-Years**	**IR**	**Unadjusted**	**Adjusted†**
Sex								
Women	39	4409.88	8.84	64	3918.64	16.33	0.55 (0.37–0.81)**	0.54 (0.36–0.81)**
Men	22	2179.64	10.09	34	1910.75	17.79	0.57 (0.33–0.97)*	0.57 (0.33–1.00)
Age, y								
18–64	51	6083.33	8.38	81	5454.63	14.85	0.57 (0.40–0.80)**	0.59 (0.41–0.84)**
≥65	10	506.18	19.76	17	374.76	45.36	0.45 (0.21–0.99)*	0.50 (0.21–1.18)
Comorbidity‡								
No	2	505.13	3.96	1	624.16	1.60	2.56 (0.23–28.18)	4.01 (0.23–70.63)
Yes	59	6084.39	9.70	97	5205.23	18.64	0.52 (0.38–0.72)***	0.52 (0.38–0.72)***
Follow-Up, y#								
<1	12	1067.70	11.24	25	1038.41	24.08	0.47 (0.24–0.93)*	0.58 (0.29–1.18)
1–3	17	2029.29	8.38	33	1852.04	17.82	0.47 (0.26–0.84)*	0.47 (0.26–0.86)*
>3	32	3492.53	9.16	40	2938.95	13.61	0.67 (0.42–1.07)	0.62 (0.39–0.99)*

CI = confidence interval, HR = hazard ratio, HTN = hypertension, IR = incidence density rate, per 1000 person-years, PTX = parathyroidectomy.
† Mutually adjusting for sex, age (continuous), insured amount, urbanization, and comorbidity.
‡ Patients with any 1 of diabetes, hyperlipidemia, HTN, ischemic heart disease, atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease, obesity, and alcohol-related disease were classified as the comorbidity group.
# Adjusting for sex, age (continuous), premium-based income, urbanization, and comorbidity.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

diagnosis, and the year of undergoing PTX and adjusting the regression models to control the effects of age, sex, premium-based income, urbanization, and comorbidity (DM, HL, HTN, IHD, AF, CHF, COPD, obesity, and alcohol-related disease), we observed that patients with ESRD who had undergone PTX had a 43% reduced risk of developing stroke compared with those who did not undergo PTX. The risk reduction in developing hemorrhagic stroke was even higher, up to 66%. Female sex, an age <65 years, and the presence of comorbidity were factors associated with reduced risk of stroke in patients with ESRD who had undergone PTX. With the mean follow-up period of 6.08 years after PTX and 5.38 years in the matched non-PTX group, the risk of stroke decreased in the second year after PTX and continued to decrease for >3 years. The other crucial risk factors associated with developing stroke included an age >65 years, diabetes, HTN, and COPD.

Comparison With the Literature

No previous research has investigated stroke in patients with ESRD who had undergone PTX; our findings are complementary to those of previous studies, whereby decreased CV events and a more favorable prognosis were observed in patients on dialysis who had undergone PTX.[21–24] Bleyer et al[21] reported improvements in vascular calcification after PTX in a small series of patients on dialysis. Shih et al[22] reported a series of 21 patients on hemodialysis with severe SHPT who achieved a normotensive and euvolemic status after PTX. Nanasato et al[23] reported a restored left ventricular function and an improved cardiac fatty acid metabolism after PTX in a patient on hemodialysis. In a cohort study conducted by Lin et al[24] with 53 nondiabetic patients with hemodialysis-dependent ESRD who had intact PTH levels of >800 pg/mL, PTX was associated with improved outcomes in major CV events, including death, cerebrovascular accidents, and MI. Several other investigations have confirmed that PTX improves survival in patients with ESRD. In the retrospective matched study between 88 patients who had undergone PTX and 88 control patients on dialysis with no indication of PTX, conducted by Iwamoto et al,[17] the CV death-free survival rate was significantly improved in the PTX group. A retrospective study conducted by Goldenstein et al[10] with a cohort of 251 patients with chronic kidney disease with severe SHPT confirms the benefit of PTX on mortality. Sharma et al[14] reported that near-total PTX in patients on dialysis was associated with a significant reduction in the long-term risk of death. However, in a systematic review evaluating the evidence for the association between mineral metabolism disturbances and the risk of all-cause mortality, CV mortality, and CV events in chronic kidney disease, none of the studies independently assessed stroke, transient ischemic attack, or acute coronary syndrome.[25] In this study, we provided evidence from a nationwide investigation of 1083 cases with matched controls, and for the first time, reported that stroke was the primary outcome in patients with ESRD with a history of previous PTX treatment versus those without a history of previous PTX treatment.

We found COPD to be a risk factor for stroke in patients with ESRD who are on dialysis, possibly because COPD is a result of chronic systemic inflammation and has a close relationship with CV diseases.[26] Our findings are consistent with those of a previous report by Yin et al.[27]

Potential Mechanisms

Accelerated atherosclerosis is the key factor for the high prevalence of CV diseases in patients with renal dysfunction.[28] Several studies indicated that high PTH levels could be causally involved in the process leading to the manifestation of CV

TABLE 4. Cox Model Measured Hazard Ratios and 95% Confidence Interval of Stroke Associated With PTX and Covariates

Variables	Event No.	IR	Unadjusted HR (95% CI)	Adjusted HR† (95% CI)
PTX				
No	98	16.81	1.00	1.00
Yes	61	9.26	0.55 (0.40–0.76)***	0.57 (0.41–0.79)***
Sex				
Women	103	12.37	1.00	1.00
Men	56	13.69	1.01 (0.80–1.53)	1.15 (0.83–1.61)
Age, y				
18–64	132	11.44	1.00	1.00
≥65	27	30.65	2.63 (1.73–3.98)***	1.94 (1.24–3.02)**
Premium-based income (NT$/mo)				
<15,000	87	15.72	1.00	1.00
15,000–29,999	52	10.59	0.68 (0.48–0.95)*	0.79 (0.55–1.13)
≥30,000	20	10.14	0.65 (0.40–1.05)	0.93 (0.56–1.54)
Urbanization				
Level 1 (highest)	40	11.60	1.00	1.00
Level 2	50	12.26	1.05 (0.70–1.60)	1.09 (0.72–1.66)
Level 3	28	14.00	1.20 (0.74–1.95)	1.23 (0.76–2.00)
Level 4 (lowest)	41	14.17	1.22 (0.80–1.89)	1.24 (0.79–1.93)
Comorbidity				
Diabetes				
No	98	9.50	1.00	1.00
Yes	61	28.96	3.00 (2.17–4.14)***	2.19 (1.54–3.13)***
Hyperlipidemia				
No	86	10.79	1.00	1.00
Yes	73	16.42	1.51 (1.11–2.06)**	1.13 (0.81–1.58)
HTN				
No	7	3.60	1.00	1.00
Yes	152	14.51	3.97 (1.86–8.49)***	3.08 (1.42–6.66)**
IHD				
No	88	10.83	1.00	1.00
Yes	71	16.55	1.52 (1.11–2.07)**	1.01 (0.72–1.42)
AF				
No	155	12.69	1.00	1.00
Yes	4	19.51	1.50 (0.56–4.05)	1.07 (0.39–2.94)
CHF				
No	115	11.75	1.00	1.00
Yes	44	16.74	1.40 (0.99–1.99)	0.98 (0.67–1.42)
COPD				
No	114	11.09	1.00	1.00
Yes	45	21.00	1.87 (1.33–2.64)***	1.58 (1.10–2.26)*
Obesity				
No	157	12.71	1.00	1.00
Yes	2	28.39	2.21 (0.55–8.92)	1.58 (0.38–6.42)
Alcohol-related disease				
No	159	12.90	1.00	1.00
Yes	0	0.00	—	—

AF = atrial fibrillation, CHF = congestive heart failure, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, HTN = hypertension, IHD = ischemic heart disease, IR = incidence density rate, per 1000 person-years, PTX = parathyroidectomy.

† Multivariable analysis including PTX, gender, age (categorical), premium-based income, urbanization, diabetes, hyperlipidemia, HTN, ischemic heart disease, atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease, obesity, and alcohol-related disease.

* $P < 0.05$

** $P < 0.01$.

*** $P < 0.001$.

diseases in patients both normal or impaired renal function.[12,29,30] In an animal study, PTH2 receptor messenger RNA was abundantly expressed in the arterial and cardiac endothelium, which supported the close relationships between PTH and CV risk.[31] Patients on hemodialysis had advanced atherosclerosis in the carotid arteries compared with matched nondialysis patients.[32] A clinical study showed that high PTH levels are closely associated with coronary calcification.[33] The serum PTH level was reported to be independently associated with the intima-media thickness of the femoral artery in patients

on hemodialysis.[34] Iwamoto et al[17] found that in the PTX group, both PTH and calcium levels fell significantly, and the prognosis was improved. Bleyer et al[21] reported that after PTX in patients with ESRD, the calcification progression slowed down.

Clinical Implication

The prevention of stroke in patients with dialysis-dependent ESRD is challenging. Although antiplatelet therapy, particularly aspirin, is reported to be a safe and effective treatment for ischemic stroke prevention in patients with ESRD undergoing dialysis,[35] other studies have claimed that antiplatelet or warfarin treatment cannot lower the risk of ischemic stroke in patients with ESRD.[36] In addition, lipid-lowering regimens, which have proven effective in reducing the risks of MI and major cardiac events, failed to provide positive evidence for stroke in patients with dialysis-dependent ESRD.[37] Furthermore, few studies have reported an effective regimen for reducing the risk of hemorrhagic stroke in patients with ESRD. Our data provided the first positive evidence that PTX may reduce the risk of stroke, particularly that of hemorrhagic stroke. We considered that PTH represents a new CV risk factor for patients with ESRD, supporting the suggestions by Anderson et al.[12] Additional studies may be required to compare the risk reduction of stroke by PTX versus medical treatments for patients with ESRD with SHPT.

LIMITATIONS

Several limitations must be discussed. First, the study was conducted on a health insurance claims database and lacked information on personal health behaviors and certain crucial CV risk factors, such as smoking, body mass index, alcoholism, exercise, and dietary habits. We were unable to control certain residual confounding factors. However, we included alcohol-related disease to adjust for the influence of alcohol intake. We also included HTN, DM, HL, and obesity to adjust for the influence of body mass index. In addition, we used an alternative method to adjust for smoking-related diseases (including IHD and COPD) to minimize the potential confounding effect of smoking. We understood that neither IHD nor COPD could represent detrimental CV effects of smoking; besides, COPD might result from other causes including alpha 1 antitrypsin deficiency. Nevertheless, alpha 1 antitrypsin deficiency is very rare in Chinese population; in addition, similar methods had been accepted in certain previous study.[38] Second, limited by the characteristics of the NHIRD, we had no access to lab data (including PTH levels) and details of medical treatment with vitamin D analogs or calcimimetics for patients on hemodialysis, which made it difficult to include SHP patients indicated for PTX. Nevertheless, NHI claims undergo strict review, which provides a reliable method for including ESRD patients with SHPT who are indicated for the operation. Third, patients with ESRD without an indication for PTX might have been included in the non-PTX group, which may have attenuated the potential effects of PTX; therefore, we might have underestimated the risk reduction of stroke with PTX. However, the significant results may suggest a strengthened relationship between PTX and a reduced risk of stroke. Fourth, Study designs comparing the PTX and non-PTX groups might have incurred a selection bias. Female sex, a younger age, the absence of diabetes, and HTN were factors associated with higher rates of PTX.[39,40] However, all these factors were matched (age, sex) or adjusted for (diabetes, HTN) in our study design. Finally, the event number in our study was small; hence, we could not further divide our study patients into different modalities of renal replacement therapy. Further research with larger case series and longer follow-up periods might be required.

The major strengths of this research include the following: first, we adopted novel approaches to analyze the relationship between PTX and the risk of stroke, to divide the category of stroke into detailed subgroups, and to confirm higher risks of hemorrhagic stroke in patients with ESRD but with a greater risk reduction after undergoing PTX. Second, we conducted a comprehensive adjustment to control for multiple confounding factors, including traditional CV risk factors and AF, CHF, IHD, and COPD. Third, a large research sample (1083 patients in the PTX group and 1083 matched controls out of 56,858 patients with ESRD) and long follow-up period (mean $= 6.08 \pm 2.52$ and 5.38 ± 2.58 years for the PTX and non-PTX groups, respectively) increased the validity of the data.

CONCLUSION

PTX reduces the risk of stroke, particularly that of hemorrhagic stroke. Other significant factors for risk reduction in patients undergoing PTX include female sex, an age below 65 years, and the presence of comorbidity. Patients aged $\geq$65 years and with DM, HTN, and COPD are at a higher risk of developing stroke. The risk reduction of stroke in patients with ESRD who have undergone PTX becomes significant after the second year of follow-up and persists thereafter. Thus, PTH may be considered a new CV risk factor for patients with ESRD.

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