NEPHROLOGY

Nephrology **23** (2018) 139–147

Original Article

Risk of acute coronary syndrome after parathyroidectomy in patients with end-stage renal disease: A population-based cohort study in Taiwan

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KEY WORDS:

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Accepted for publication 20 October 2016.
Accepted manuscript online 27 October 2016.

doi: 10.1111/nep.12958

ABSTRACT:

Aim: **Patients with end-stage renal disease (ESRD) who received parathyroidectomy (PTX) had persistently reduced levels of parathyroid hormone. This study investigated the risk of acute coronary syndrome (ACS) in patients with ESRD who underwent PTX using a nationwide health insurance claims database.**

Methods: **Of all ESRD patients, we selected 1047 individuals who had undergone PTX between 2000 and 2008 as the PTX group and 4188 patients who did not undergo PTX (non-PTX group) matched by propensity score. Multivariable Cox proportional hazards regression analysis was conducted for assessing the excess ACS risk for the PTX group compared to the non-PTX group.**

Results: **The mean follow-up periods were 4.63 and 4.04 years for the PTX and non-PTX groups, respectively. A significant reduction in the risk of ACS (adjusted hazard ratio = 0.74, 95% confidence interval = 0.57–0.96) was observed for the ESRD patients after PTX.**

Conclusions: **Parathyroidectomy is associated with reduced risk of ACS in patients with ESRD.**

SUMMARY AT A GLANCE

From a national health insurance claims database, this study matched patients receiving dialysis who had a parathyroidectomy to patients who did not, using a propensity score method. They demonstrate that patients who had a parathyroidectomy were less likely to experience an acute coronary syndrome in the ensuing 4 years.

INTRODUCTION

Cardiovascular (CV) disease is the most critical cause of mortality and morbidity in patients undergoing dialysis. The United States Renal Data System (USRDS) indicated that acute myocardial infarction (AMI) and congestive heart failure (CHF) have been recognized as the leading causes of death in elderly patients undergoing dialysis since 1999.[1] In Taiwan, AMI has been the leading cause of hospitalization in patients with end-stage renal disease (ESRD) since 2001.[2] The incidence of acute coronary syndrome (ACS) in patients undergoing dialysis has been reported to be 1.78 per 100 person-years in Taiwan and 10.2% within a 2.2-year follow-up in the United States, respectively.[3,4] Compared to the general population, the survivals of the patients with advanced chronic kidney disease after AMI were much shorter, with a mean survival period of only 22 months.[5] The risk factors for AMI and ACS in ESRD include the male sex, old age, smoking, physical inactivity, hypertension (HTN), diabetes mellitus (DM), hyperlipidaemia (HL), and anaemia.[3,5] The mechanisms underlying

incident ACS episodes included accelerated coronary calcification,[6] platelet-activation factors and thrombosis,[7] and autonomic dysfunction.[8]

Secondary hyperparathyroidism (SHPT) is prevalent in patients undergoing dialysis. Several studies have reported a close relationship between SHPT and the increased risk of CV events, including AMI, stroke, and CV death.[9,10] Only 22% of patients with severe SHPT who received medical therapy may achieve the ideal serum parathyroid hormone (PTH) level.[11] In a multi-centre randomized controlled trial, the investigators concluded, in dialysis patients with moderate to severe SHPT, treatment with calcimimetic failed to reduce the risk of CV events or death.[12] Parathyroidectomy (PTX) is the main treatment for severe SHPT refractory to medical treatment. Conzo *et al*. reported that PTX may effectively reduce the PTH level and maintain appropriate levels up to 5 years.[13] Previous studies have reported a reduced risk of major CV events, including stroke, AMI, peripheral arterial disease and mortality in patients with SHPT who underwent PTX.[14,15]

In spite of the aforementioned sporadic clinical observations favouring PTX in dialysis patients, large scaled studies investigating the changes in the risk of ACS in dialysis patients who underwent PTX are scant. The objective of the present study was to investigate the risk of incident ACS in these patients in a nationally representative cohort. We hypothesized that dialysis-dependent ESRD patients with severe SHPT who have undergone PTX have a reduced risk of ACS.

METHODS

Data source

Taiwan's National Health Insurance (NHI) programme, which was established in 1995, offers comprehensive, universal health insurance coverage for all residents of Taiwan and covered more than 99.9% of the population in 2014.[16] The National Health Insurance Research Database (NHIRD) is managed, maintained, and released by Taiwan's National Health Research Institutes (NHRI). To protect individual privacy, patients' data are encrypted. In this study, we used the Registry for Catastrophic Illness Patient Database (RCIPD), which is a subset of the NHIRD. The RCIPD contains medical claims data from the insured suffering from any of the 30 categories of major diseases (e.g., cancer, chronic mental illness, ESRD, and autoimmune diseases) requiring long-term care. The entitlement of the registry for catastrophic illness exempts patients from the healthcare copayment.[17] The NHIRD contains patient information, such as demographic data, all records of clinical visits and hospitalization, prescribed drugs and dosages, and disease diagnoses. Diseases were coded based on the International Classification of Disease Diagnoses, Ninth Revision, of Clinical Modification (ICD-9-CM).

Ethics statement

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfil the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2–115). The IRB also specifically waived the consent requirement.

Study population

Figure 1 illustrates the study framework. We enrolled patients aged ≥18 years, diagnosed with ESRD (defined as those who had catastrophic illness registration cards for ESRD, ICD-9-CM 585), and received long-term renal replacement therapy (i.e., dialysis or renal transplant) for more than 90 days during 2000–2007. We conducted a population-based retrospective cohort study in which we assigned patients with ESRD who underwent PTX (ICD-9 codes for procedure 06.8) for the first time during 2000–2008 to the PTX group. The date of the first PTX was considered the index date. We identified the non-PTX group by propensity score (PS) matching. We applied a multivariate logistic regression model for the probability of receiving PTX for the PTX group.[18] We incorporated sex, age, insured amount, urbanization, diabetes, HL, HTN, atrial fibrillation (AF), CHF, stroke, chronic obstructive pulmonary disease (COPD), obesity, alcohol-related disease, years since ESRD diagnosis, and year of index date in the PS model. The exclusion criteria for both groups included ACS (ICD-9-CM 410, 411.1, and 411.8), renal transplantation (ICD-9-CM V42.0 and 996.81), parathyroid tumour (ICD-9 CM 194.1 and 227.1), or a parathyroid disorder (ICD-9 CM code 252.8) before the index date or missing information on sex or age.

Covariates and outcomes

Demographic factors included sex, age (groups aged 18–34, 35–49, 50–64, and ≥65 years), premium-based income, and urbanization. Premium-based income was classified into three levels: <15 000, 15 000–29 999, and ≥30 000 (NT$/month). City districts and townships where patients registered for insurance were grouped into four urbanization levels according to the population density (people/km^2), ratio of people whose education level is a college degree or higher, ratio of people aged older than 65 years, ratio of agricultural workers, and the number of physicians per 100 000 persons.[19] Level 1 indicates the most urbanized area, and level 4 represents the least urbanized area. Considering the fact that over 90% of patients with ESRD in Taiwan received haemodialysis,[20] we did not include dialysis modality (haemodialysis versus peritoneal dialysis) in the adjustment variables.

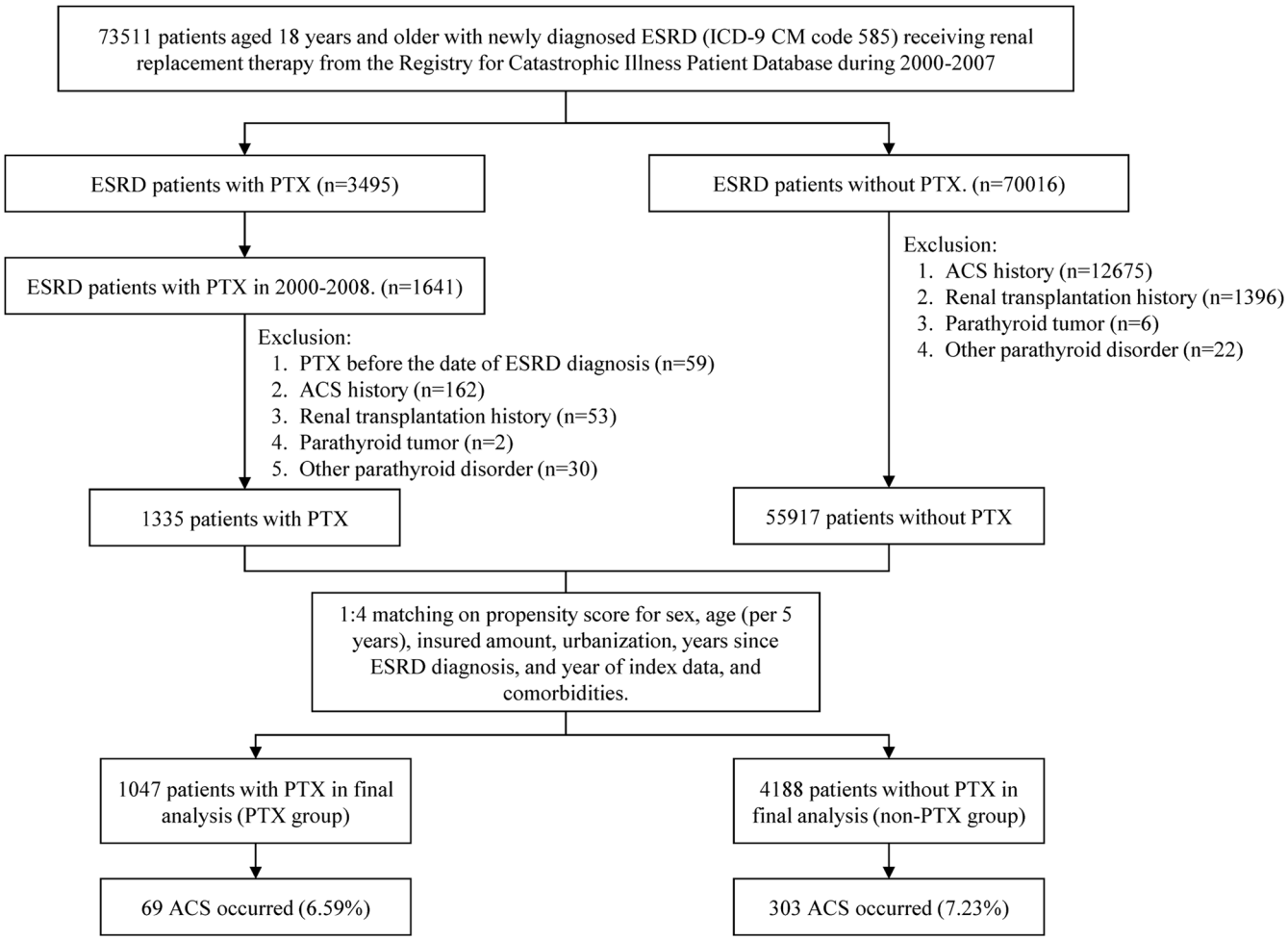

Fig. 1 Flowchart of the recruitment procedure.ACS, acute coronary syndrome; ESRD, end stage renal disease; PTX, parathyroidectomy.

Comorbidity records were determined for each patient before the index date. The records included DM (ICD-9-CM 250), HL (ICD-9-CM 272.0–272.4), HTN (ICD-9-CM 401–405), AF (ICD-9-CM 427.31), CHF (ICD-9-CM 398.91, 425, and 428), stroke (ICD-9-CM 430–438), 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).

The definition of ACS included ST-elevation and Non-ST elevation myocardial infarction but not unstable angina. The recorded outcome was ACS (ICD-9-CM 410, 411.1, and 411.8). Both groups were followed from the index date to the first diagnosis date of ACS, withdrawal from the NHI program, or the end of 2011, whichever occurred first.

Statistical analyses

Continuous variables were expressed as means and standard deviation (SD), whereas categorical variables were expressed as numbers and percentages. We used Student's *t*-test and Pearson's ^{2} test for continuous and categorical variables, respectively, for comparing the differences between the PTX and non-PTX groups in terms of sex, age, premium-based income, urbanization, and comorbidities. The incidence density rate (per 1000 person-years) of ACS was calculated as the incidence of ACS during follow-up divided by person-years at risk for each group according to sex, age, and comorbidities. Multivariable Cox proportional hazards regression models were used to assess the risk of ACS. The covariates adjusted in the multivariable models included sex, age, premium-based income, urbanization, diabetes, HL, HTN, AF, CHF, stroke, COPD, obesity, alcohol-related disease, year of ESRD diagnosis, and year of index date. We also evaluated the association of PTX on the risk of ACS in various subgroups according to sex, age, comorbidities, and the follow-up period. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for quantifying the ACS risk. The interactions of PTX with sex, age, diabetes, HL, HTN, AF, CHF, stroke, COPD, obesity, and alcohol-related disease were further examined by adding their product terms into the full model and the likelihood ratio test was used to test its significance. $P < 0.05$ was considered significant for 2-sided tests. All analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 1 Demographic factors and comorbidity of patients with end stage renal disease according to parathyroidectomy (PTX) status

	Before PS matching					After PS matching				
	Non-PTX group *n* = 55917		PTX group *N n* = 1335			Non-PTX group *n* = 4188		PTX group *n* = 1047		
Variables	*n*	%	*n*	%	*P*-value	*n*	%	*n*	%	*P*-value
Year of ESRD diagnosis					<0.001					0.96
2000	6006	10.7	331	24.8		785	18.7	214	20.4	
2001	6271	11.2	298	23.3		797	19.0	199	19.0	
2002	6619	1.8	200	15.0		722	17.2	174	16.6	
2003	6847	12.2	207	15.5		763	18.2	186	17.8	
2004	6959	12.5	131	9.81		478	11.4	118	11.3	
2005	7574	13.6	84	6.29		330	7.88	79	7.55	
2006	7517	13.4	58	4.34		206	4.92	53	5.06	
2007	8124	14.5	26	1.95		107	2.55	24	2.29	
Year of index date					<0.001					0.99
2000	1477	2.64	2	0.15		10	0.24	2	0.19	
2001	3135	5.61	17	1.27		58	1.38	14	1.34	
2002	4051	7.24	17	1.27		52	1.24	15	1.43	
2003	4972	8.89	44	3.30		153	3.65	40	3.82	
2004	5903	10.6	93	6.97		322	7.69	84	8.02	
2005	6848	12.3	180	13.5		618	14.8	158	15.1	
2006	8192	14.7	281	21.1		857	20.5	217	20.7	
2007	10463	18.7	317	23.8		970	23.2	241	23.0	
2008	10876	19.5	384	28.8		1148	27.4	276	26.4	
Sex					<0.001					0.95
Women	28634	51.2	907	67.9		2739	65.4	683	65.2	
Men	27283	48.8	428	32.1		1449	34.6	364	34.8	
Age at receiving PTX, years					<0.001					0.74
18–34	2032	3.63	123	9.21		349	8.33	87	8.31	
35–49	8286	14.8	455	34.1		1259	30.1	333	31.8	
50–64	18565	33.2	589	44.1		1934	46.2	469	44.8	
≥65	27034	48.4	168	12.6		646	15.4	158	15.1	
Mean (SD)	62.9	(14.1)	51.3	(11.6)	<0.001	53.6	(12.8)	52.1	(11.8)	< 0.001
Insured amount (NT$/ month)					<0.001					0.74
< 15 000	32448	58.0	595	44.6		1954	46.7	481	45.9	
15 000–29999	19564	35.0	534	40.0		1664	39.7	414	39.5	
≥ 30 000	3905	6.98	206	15.4		570	13.6	152	14.5	
Urbanization					<0.001					0.84
Level 1 (highest)	14414	25.8	346	25.9		1045	25.0	270	25.8	
Level 2	16584	30.0	416	31.2		1329	31.7	339	32.4	
Level 3	9481	17.0	285	21.4		869	20.8	207	19.8	
Level 4 (lowest)	15438	27.6	288	21.6		945	22.6	231	22.1	
Comorbidity										
Diabetes	28744	51.4	245	18.4	<0.001	875	20.9	225	21.5	0.70
Hyperlipidemia	27815	49.7	652	48.8	0.53	2052	49.0	508	48.5	0.81
Hypertension	52040	93.1	1248	93.5	0.59	3886	92.8	970	92.7	0.93
AF	2562	4.58	27	2.02	<0.001	93	2.22	24	2.29	0.98
CHF	19919	35.6	336	25.2	<0.001	1009	24.1	276	26.4	0.14
Stroke	11277	20.2	79	5.92	<0.001	236	5.64	71	6.78	0.18
COPD	14719	26.3	209	15.7	<0.001	680	16.2	182	17.4	0.40
Obesity	429	0.77	21	1.57	0.002	47	1.12	17	1.62	0.24
Alcohol-related disease	1582	2.83	16	1.20	<0.001	43	1.03	15	1.43	0.34

AF, atrial fibrillation; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

RESULTS

In all, we have 1047 patients in the PTX group and 4188 patients in the non-PTX group (Table 1). Both groups had similar distributions of sex, age, insured amount, urbanization, diabetes, HL, HTN, AF, CHF, stroke, COPD, obesity and alcohol-related disease. Women dominated the study groups (65.2%) and about 84.9% of patients were younger than 64 years old. The mean ages of the non-PTX and PTX groups were 53.6 (SD = 12.8) and 52.1 (SD = 11.8) years, respectively.

Table 2 Cox model measured hazard ratios and 95% confidence interval of acute coronary syndrome (ACS) associated with parathyroidectomy (PTX) and covariates

Variables	Event no.	Person-years	IR	HR† (95% CI)
Year of ESRD diagnosis				
2000	101	4474	22.6	1.32 (0.59–2.93)
2001	68	4561	14.9	0.99 (0.44–2.20)
2002	50	3699	13.5	0.84 (0.37–1.89)
2003	63	3880	16.2	1.04 (0.47–2.31)
2004	37	2321	15.9	0.98 (0.43–2.22)
2005	29	1536	18.9	1.19 (0.52–2.74)
2006	17	884	19.2	1.06 (0.44–2.59)
2007	7	418	16.7	1.00
Year of index date				
2000	2	34	58.3	1.74 (0.41–7.38)
2001	8	394	20.3	1.26 (0.57–2.78)
2002	6	403	14.9	0.70 (0.29–1.71)
2003	19	990	19.2	1.11 (0.63–1.94)
2004	24	2230	10.8	0.62 (0.37–1.01)
2005	66	3886	17.0	1.02 (0.71–1.45)
2006	75	4812	15.6	0.80 (0.58–1.12)
2007	88	4608	19.1	1.05 (0.77–1.43)
2008	84	4418	19.0	1.00
PTX				
No	303	16926	17.9	1.00
Yes	69	4848	14.2	0.74 (0.57–0.96)*
Sex				
Women	219	14422	15.2	1.00
Men	153	7353	20.8	1.53 (1.24–1.90)***
Age, years				
18–34	13	2087	6.23	1.00
35–49	86	7392	11.6	1.96 (1.09–3.53)*
50-64	206	9717	21.2	2.75 (1.55–4.87)***
≥65	67	2579	26.0	2.92 (1.58–5.39)***
Insured amount (NT$/ month)				
<15000	197	9658	20.4	1.00
15 000–29 999	140	8701	16.1	0.95 (0.76–1.20)
≥30 000	35	3416	10.2	0.57 (0.40–0.83)**
Urbanization				
Level 1 (highest)	85	5658	15.0	1.00
Level 2	120	6918	17.4	1.15 (0.87–1.53)
Level 3	73	4409	16.6	1.09 (0.79–1.49)
Level 4 (lowest)	94	4790	19.6	1.20 (0.89–1.62)
Comorbidity				
Diabetes				
No	233	18015	12.9	1.00
Yes	139	3759	37.0	1.92 (1.53–2.41)***
Hyperlipidaemia				
No	136	11691	11.6	1.00
Yes	236	10083	23.4	1.52 (1.21–1.91)***
Hypertension				
No	11	1824	6.03	1.00
Yes	361	19950	18.1	1.82 (0.99–3.35)
AF				
No	359	21415	16.8	1.00
Yes	13	360	36.1	1.61 (0.92–2.82)
CHF				
No	235	16973	13.9	1.00
Yes	137	4802	28.5	1.66 (1.33–2.06)***
Stroke				
No	337	20782	16.2	1.00
Yes	35	993	35.3	1.45 (1.01–2.07)*

(*Continues*)

Table 2 (Continued)

Variables	Event no.	Person-years	IR	HR† (95% CI)
COPD				
No	293	18601	15.8	1.00
Yes	79	3174	24.9	1.18 (0.92–1.53)
Obesity				
No	362	21538	16.8	1.00
Yes	10	237	42.2	2.21 (1.16–4.21)*
Alcohol-related disease				
No	369	21540	17.1	1.00
Yes	3	235	12.8	0.69 (0.22–2.16)

AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IR, incidence density rate, per 1,000 person-years; PTX, parathyroidectomy. †Multivariable analysis including year of end-stage renal disease (ESRD) diagnosis, year of index date, PTX, sex, age(categorical), insured amount, urbanization, diabetes, hyperlipidaemia, hypertension, atrial fibrillation, congestive heart failure, stroke, chronic obstructive pulmonary disease, obesity, and alcohol-related disease. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

During an average follow-up of 4.16 years, 69 and 303 patients from the PTX and non-PTX groups, respectively, developed ACS. The incidence density rates of ACS were 14.2 and 17.9 per 1000 person-years for the PTX and non-PTX groups, respectively. After adjustments for sex, age, premium-based income, urbanization of residency, comorbidities, year of ESRD diagnosis, and year of index date, the PTX group demonstrated a significantly lower risk of ACS than did the non-PTX group (adjusted HR [aHR] = 0.74, 95% CI = 0.57–0.96). Several traditional cardiovascular risk factors such as diabetes, HL, CHF, stroke and obesity appeared to be strong predictors of ACS (Table 2).

Table 3 and Figure 2 showed risk of ACS for PTX and non-PTX group by stratification of age, sex, comorbidities and follow-up period. Age stratification showed that the PTX group were associated with reduced risk of ACS compared with the non-PTX in the age group of 18–64 years (aHR = 0.73, 95% CI = 0.54–0.98). In participants with CHF and with stroke, the PTX group had reduced risk of ACS than did the non-PTX group (aHR = 0.64, 95% CI = 0.42–0.99 for those with CHF; and aHR = 0.31, 95% CI = 0.10–0.94 for those with stroke). Similarly, in participants without obesity and without alcohol-related disease, the PTX group had lower risk of ACS than did the non-PTX group (aHR = 0.75, 95% CI = 0.57–0.98 for those without obesity; and aHR = 0.77, 95% CI = 0.59–0.99 for those without alcohol-related disease; Fig. 2). In addition, the PTX group was associated with a null risk of ACS than in the non-PTX group in all groups of follow-up period (Table 3).

DISCUSSION

In this retrospective nationwide cohort study, we observed that Taiwanese patients with ESRD who had undergone PTX had a 25% lower risk of ACS after adjustments for sex, age, premium-based income, urbanization, and comorbidities (DM, HTN, HL, AF, CHF, stroke, COPD, obesity, and alcohol-related diseases). The significant results persisted in the competing risk analysis model. Traditional CV risk factors such as male gender, increasing age, DM, HL, CHF, stroke and obesity were significantly associated with higher risk of ACS. Conversely, a premium-based income of NT$ 30 000 or more was a protective factor against the development of ACS. Subgroup analysis showed PTX was associated with reduced risk of ACS in dialysis patients with age under 65, with stroke, without obesity and without alcohol-related disease.

No study has focused on the association of PTX with ACS in patients with ESRD, though certain research reported a reduced overall CV risk after PTX,[15] supporting our findings. The ACS incidence was 29 per 1000 person-years according to the data of Wave II of the USRDS Dialysis Morbidity and Mortality study.[21] In our study, the ACS incidence was 17.9 and 14.2 per 1000 person-years for the non-PTX and PTX

Table 3 Incidence density rates and hazard ratios of acute coronary syndrome (ACS) according to parathyroidectomy (PTX) status stratified by follow-up period.

	Non- PTX group			PTX group			Compared to non-PTX group
Follow-up period, years	Event no.	Person-years	IR	Event no.	Person-years	IR	HR† (95% CI)
≤ 2	139	7529	18.5	29	2008	14.4	0.77 (0.52–1.16)
2–4	99	5930	16.7	24	1712	14.0	0.80 (0.51–1.25)
4–6	52	2683	19.4	10	837	11.9	0.58 (0.29–1.15)
> 6	13	785	16.6	6	291	20.6	1.12 (0.39–3.22)

CI, confidence interval; HR, hazard ratio; IR, incidence density rate, per 1,000 person-years. †Adjusting for sex, age (continuous), premium-based income, urbanization, diabetes, hyperlipidaemia, hypertension, atrial fibrillation, congestive heart failure, stroke, chronic obstructive pulmonary disease, obesity, alcohol-related disease, year of end-stage renal disease (ESRD) diagnosis, and year of index date.

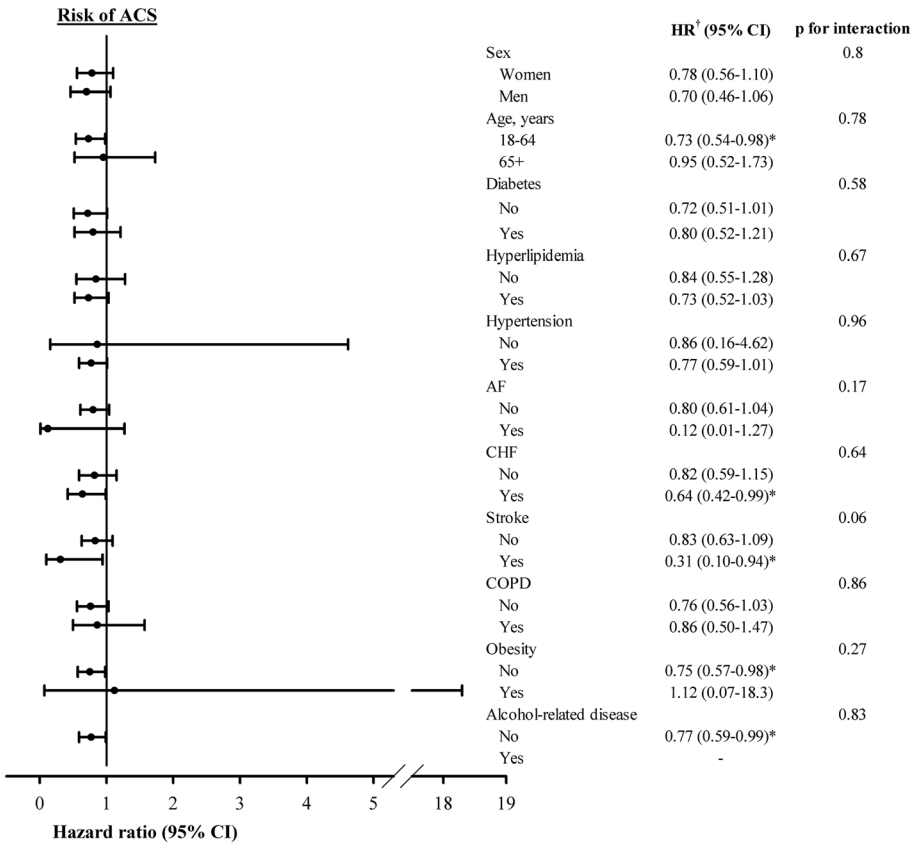

Fig. 2 Risk of ACS according to PTX status stratified by sex, age, and each comorbidity.HR, hazard ratio; CI, confidence interval.† Mutually adjusted for sex, age (continuous), premium-based income, urbanization, diabetes, hyperlipidaemia, hypertension, atrial fibrillation, congestive heart failure, stroke, chronic obstructive pulmonary disease, obesity, alcohol-related disease, year of ESRD diagnosis, and year of index date.* $P < 0.05$.

groups, respectively. Cardiac arrest and in-hospital deaths of dialysis patients were approximately twice higher than those of non-dialysis patients with AMI.[22] A recent large Japanese registry study also used propensity score match method to compare mortality between PTX and non-PTX patients undergoing dialysis, and reported lower cardiovascular mortality in PTX group.[23] Our observation is unequivocal because ESRD itself is a well-accepted high-CV-risk condition.

Parathyroidectomy might decrease the incidence density of ACS in dialysis patients by the following mechanisms: first, HD patients with SHPT who underwent PTX demonstrated an improved left and right ventricular ejection fraction and reduced intradialytic hypotension[24] and might further reduce the ACS incidence; while intradialytic hypotension has been a known risk factor for mortality for patients on HD.[25] Second, SHPT has been reported to accelerate atherosclerosis, particularly to enhance coronary calcification through increased insulin resistance, vascular smooth muscle cells proliferation, calcium–phosphorus deposition in vessel walls, and altered lipoprotein metabolism.[26] For patients with ESRD, calcium deposition occurs in both the intimal and medial layers or in the medial layer alone. London *et al.*[6] reported that medial layer calcification increases the risk of mortality. PTX decreases the calcium score of the coronary artery[27] and improves ACS risk factors including blood pressure, total cholesterol, and low-density lipoprotein cholesterol in kidney transplant recipients.[28] Third, platelet activity and thrombosis also play critical roles in the development of ACS[7]; a previous study reported that the blood level of platelet-activating factor decreased after PTX in HD patients.[29] Fourth, cardiac autonomic dysfunction, manifested by low indices of heart rate variability, was observed in patients with ACS and predicted future coronary events in patients with a history of MI.[8] Patients with ESRD who underwent PTX exhibited improved heart rate variability.[30] Our findings are consistent with the aforementioned studies.

Our study results have several important clinical implications. First, the risk of ACS decreased significantly in the PTX group only in patients with age under 65, with stroke, without obesity and without alcohol-related disease. No significant reduction of ACS was observed in patients with other traditional risk factors such as DM, HTN and HL. This implied that, first, traditional CV risk factors were still strong predictors of events in dialysis patients; second, in addition to traditional CV risk factors, there might be other complicated pathogenetic factors of ACS in ESRD, such as atherosclerosis, vascular calcification, and bone-mineral disease. Further studies are needed to confirm this hypothesis. Second, preventing ACS in dialysis

patients is challenging. Although hyperparathyroidism is correlated with a high overall CV risk,[9] little research addressed the direct relationship of ACS risk reduction in patients with ESRD. Our findings provided valuable evidence. However, we had no intention to promote PTX for patients with ESRD with SHPT; but would like to emphasize the importance of controlling SHPT to avoid ominous CV outcomes. Third, the effective treatments to reduce the ACS risk in non-dialysis patients, including antiplatelet agents, statins, and beta-blockers, were found ineffective for patients with ESRD.[20,31] We reported previously that PTX might reduce the risk of stroke and recommended that hyperparathyroidism be considered as a new CV risk factor for dialysis patients[14]; the present findings support this recommendation. Additional randomized controlled studies are needed to evaluate the effects of PTX and medical treatments on CV risk in dialysis patients complicated with SHPT.

This study has several limitations. First, this study was a secondary data analysis of a health insurance claims database, which lacks information on several crucial CV risk factors such as smoking, body mass index, alcohol use, physical activity, and dietary habits. Nevertheless, we used alcohol-related diseases as a proxy to adjust for the effect of alcohol intake. We adjusted for the potential confounding effect of body mass index by including HTN, DM, and HL in multivariable models. Moreover, the potential confounding effect of smoking was adjusted by including smoking-related diseases, namely stroke and COPD. Modification under these restrictions has been accepted previously,[14] though, markers of nutritional status such as serum albumin and creatinine levels (as a marker for muscle volume) were also unavailable. Multivariate analysis with adjustment of several chronic diseases could not completely compensate this limitation. Second, limited by the characteristics of the NHIRD, we have no access to any laboratory data including the levels of PTH, calcium, phosphate, nor calcium-phosphate products. Besides, the treatment records of vitamin D analogue or calcimimetics treatment had been unavailable because they were either included in the bundled HD payment package or self-paid. However, the NHI strictly reviews the reimbursement of surgical claims. With approved NHI reimbursements for PTX in ESRD patients on maintenance dialysis (either HD or PD), we believe the PTX group represent ESRD patients with severe SHPT indicated for the operation. Third, there might be significant indication bias in receiving PTX. Chuang *et al*. reported higher rates of PTX were noted in women, younger patients, and in patients without history of DM or HTN.[32] We conducted PS matches to minimize the bias. Patients with ESRD without SHPT might also be included in the non-PTX group. A recent study by Ho et at.[33] included radionuclide parathyroid scanning as the enrolling criteria for patients with SHPT and reported reduced mortality in ESRD patients who received PTX, which increased the specificity of the enrolees; however, the exclusion percentage seemed high.

In conclusion, in this nationwide cohort study, we found that PTX is associated with reduced risk of ACS in dialysis patients after adjustment for comorbidities. Further prospective randomized studies are needed to delineate the relationship between PTX and the changes of the risk of ACS.

ACKNOWLEDGMENTS

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10501010037), NRPB Stroke Clinical Trial Consortium (MOST 105-2325-B-039-003), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan; and CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study.

CONFLICT OF INTEREST STATEMENT

All authors report no conflict of interest.

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