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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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.

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, platelet-activation factors and thrombosis, and autonomic dysfunction.

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 AML, stroke, and CV death. Only 22% of patients with severe SHPT who received medical therapy may achieve the ideal serum parathyroid hormone (PTH) level. 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. 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. Previous studies have reported a reduced risk of major CV events, including stroke, AML, peripheral arterial disease and mortality in patients with SHPT who underwent PTX.

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. 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. 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 fulfill 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 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. 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 (NTS/month). City districts and townships where patients registered for insurance were grouped into four urbanization levels according to the population density (people/km²), 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. 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, we did not include dialysis modality (haemodialysis versus peritoneal dialysis) in the adjustment variables.
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 χ² 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

| Variables                      | Non-PTX group | PTX group | P-value |
|-------------------------------|---------------|-----------|---------|
| | n = 55917 | n = 1335 |       |       |
| Year of ESRD diagnosis        |               |           |       |
| 2000                          | 6006          | 331       | 0.001  |
| 2001                          | 6271          | 298       | 0.001  |
| 2002                          | 6619          | 200       | 0.001  |
| 2003                          | 6847          | 207       | 0.001  |
| 2004                          | 6959          | 131       | 0.001  |
| 2005                          | 7574          | 84        | 0.001  |
| 2006                          | 7517          | 58        | 0.001  |
| 2007                          | 8124          | 26        | 0.001  |
| Year of index date            |               |           | 0.09   |
| 2000                          | 1477          | 2         | 0.001  |
| 2001                          | 3135          | 17        | 0.001  |
| 2002                          | 4051          | 17        | 0.001  |
| 2003                          | 4922          | 44        | 0.001  |
| 2004                          | 5903          | 93        | 0.001  |
| 2005                          | 6848          | 180       | 0.001  |
| 2006                          | 8192          | 281       | 0.001  |
| 2007                          | 10463         | 317       | 0.001  |
| Sex                           |               |           | 0.95   |
| Women                         | 28634         | 907       | 0.001  |
| Men                           | 27283         | 428       | 0.001  |
| Age at receiving PTX, years   |               |           | 0.74   |
| 18–34                         | 2032          | 123       | 0.001  |
| 35–49                         | 8286          | 455       | 0.001  |
| 50–64                         | 18565         | 589       | 0.001  |
| ≥65                           | 27034         | 168       | 0.001  |
| Mean (SD)                     | 62.9 (14.1)   | 51.3 (11.6) | 0.001   |
| Insured amount (NT$/ month)   |               |           | 0.74   |
| < 15 000                      | 32448         | 595       | 0.001  |
| 15 000–29999                  | 19564         | 534       | 0.001  |
| ≥ 30 000                      | 3905          | 206       | 0.001  |
| Urbanization                  |               |           | 0.84   |
| Level 1 (highest)             | 14411         | 246       | 0.001  |
| Level 2                       | 16584         | 416       | 0.001  |
| Level 3                       | 9481          | 285       | 0.001  |
| Level 4 (lowest)              | 15438         | 288       | 0.001  |
| Comorbidity                   |               |           |        |
| Diabetes                      | 28744         | 245       | 0.001  |
| Hyperlipidemia                | 27815         | 652       | 0.03   |
| Hypertension                  | 52040         | 1248      | 0.59   |
| AF                            | 2562          | 57        | 0.03   |
| CHF                           | 19919         | 336       | 0.001  |
| Stroke                        | 11277         | 59        | 0.001  |
| COPD                          | 14719         | 209       | 0.001  |
| Obesity                       | 429           | 21        | 0.001  |
| Alcohol-related disease       | 1582          | 16        | 0.001  |

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 (0.75–1.20) |
| ≥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)
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, HTN, 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 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, 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. In our study, the ACS incidence was 17.9 and 14.2 per 1000 person-years for the non-PTX and PTX

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**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.

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

| Follow-up period, years | Event no. | Person-years | IR   | Compared to non-PTX group |
|-------------------------|-----------|--------------|------|----------------------------|
|                         |           |              |      | HR† (95% CI)               |
| ≤ 2                     | 139       | 7529         | 18.5 |                           |
| 2–4                     | 99        | 5939         | 16.7 |                           |
| 4–6                     | 52        | 2683         | 19.4 |                           |
| > 6                     | 13        | 785          | 16.6 |                           |

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Risk of ACS after PTX in ESRD

| Risk of ACS | HR (95% CI) | p for interaction |
|-------------|-------------|------------------|
| Sex         |             | 0.8              |
| Women       | 0.78 (0.56-1.0) |                 |
| Men         | 0.70 (0.46-1.06) |                 |
| Age, years  |             | 0.78             |
| 18-64       | 0.73 (0.54-0.98)* |                 |
| 65+         | 0.95 (0.52-1.73) |                 |
| Diabetes    |             | 0.58             |
| No          | 0.72 (0.51-1.01) |                 |
| Yes         | 0.80 (0.52-1.21) |                 |
| Hyperlipidemia |     | 0.67             |
| No          | 0.84 (0.55-1.28) |                 |
| Yes         | 0.73 (0.52-1.03) |                 |
| Hypertension |         | 0.96             |
| No          | 0.86 (0.16-4.62) |                 |
| Yes         | 0.77 (0.59-1.01) |                 |
| AF          |             | 0.17             |
| No          | 0.80 (0.61-1.04) |                 |
| Yes         | 0.12 (0.01-1.27) |                 |
| CHF         |             | 0.64             |
| No          | 0.82 (0.59-1.15) |                 |
| Yes         | 0.64 (0.42-0.99)* |               |
| Stroke      |             | 0.06             |
| No          | 0.83 (0.63-1.09) |                 |
| Yes         | 0.31 (0.10-0.94)* |               |
| COPD        |             | 0.86             |
| No          | 0.76 (0.56-1.03) |                 |
| Yes         | 0.86 (0.50-1.47) |                 |
| Obesity     |             | 0.27             |
| No          | 0.75 (0.57-0.98)* |               |
| Yes         | 1.12 (0.07-18.3) |                 |
| Alcohol-related disease | | 0.83             |
| No          | 0.77 (0.59-0.99)* |               |
| Yes         | -            |                 |

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, hyperlipidemia, 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 AML. 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. 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 and might further reduce the ACS incidence; while intradialytic hypotension has been a known risk factor for mortality for patients on HD. 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. For patients with ESRD, calcium deposition occurs in both the intimal and medial layers or in the medial layer alone. London et al. reported that medial layer calcification increases the risk of mortality. PTX decreases the calcium score of the coronary artery and improves ACS risk factors including blood pressure, total cholesterol, and low-density lipoprotein cholesterol in kidney transplant recipients. Third, platelet activity and thrombosis also play critical roles in the development of ACS; a previous study reported that the blood level of platelet-activating factor decreased after PTX in HD patients. 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. Patients with ESRD who underwent PTX exhibited improved heart rate variability. 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, 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.\textsuperscript{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\textsuperscript{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,\textsuperscript{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 \textit{et al.} reported higher rates of PTX were noted in women, younger patients, and in patients without history of DM or HTN.\textsuperscript{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 \textit{et al.}\textsuperscript{33} included radio-nuclide 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 enrollee; 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.

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CONFLICT OF INTEREST STATEMENT

All authors report no conflict of interest.

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