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Risk of carpal tunnel syndrome after parathyroidectomy in patients with end-stage renal disease

A population-based cohort study in Taiwan

Jie-Sian Wang, MD[a,b], Wei-Shan Chen, MS[c], Cheng-Li Lin, MS[c], I-Kuan Wang, MD, PhD[b,*], Ming-Yi Shen, PhD[a,d,e,*]

Abstract

Carpal tunnel syndrome (CTS) is the most common mononeuropathy in clinical practice. Some patients with end-stage renal disease (ESRD) often associate with tertiary hyperparathyroidism, and ultimately need parathyroidectomy (PTX). However, no studies have definitively demonstrated an effect of PTX on ESRD patients' quality of life. We selected 1686 patients who underwent PTX and 1686 patients who did not receive PTX between 2000 and 2010. These patients were propensity-matched with others by age, sex, and comorbidities at a ratio of 1:1. We used single and multivariable cox proportional hazard models to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). In this study, 116 ESRD patients developed CTS, and the CTS incidences were 7.33 and 12.5 per 1000 person-years for the non-PTX and PTX group. The results reveal that the incidence curve for the PTX group was significantly higher than that for the non-PTX group (log-rank test, $P = .004$). After adjustments were made for sex, age, and baseline comorbidities, the PTX group had a 1.70-fold higher risk of CTS (hazard ratio (HR) = 1.70, 95% confidence intervals (CI) = 1.17–2.47) than the non-PTX group. The results also demonstrated that female patients (HR = 1.60, 95% CI = 1.06–2.42) and patients with one or more comorbidities (HR = 1.79, 95% CI = 1.23–2.60) might have an increased risk of CTS. The subhazard ratio for CTS risk was 1.62 (95% CI = 1.12–2.36) for the PTX group compared with the non-PTX group in the competing risk of death. In conclusion, we revealed that ESRD patients who had undergone PTX may have an increased risk of CTS.

Abbreviations: CHF = congestive heart failure, CI = confidence intervals, COPD = chronic obstructive pulmonary disease, CTS = carpal tunnel syndrome, DM = diabetes mellitus, ESRD = end-stage renal disease, HL = hyperlipidemia, HR = hazard ratio, HTN = hypertension, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHI = National Health Insurance, NHIRD = NHI Research Database, PTH = parathyroid hormone, PTX = parathyroidectomy, RCIPD = Registry of Catastrophic Illness Patient Database, SD = standard deviation, SHPT = secondary hyperparathyroidism, SHR = subhazard ratio.

Keywords: carpal tunnel syndrome, cohort study, end-stage renal disease, parathyroidectomy

1. Introduction

Carpal tunnel syndrome (CTS) refers to the compression of the median nerve as it travels through the carpal tunnel.[1] Patients commonly experience numbness, weakness, and tingling in the near-thumb side of the hand. CTS is the most common mononeuropathy in clinical practice.[2,3] The pathophysiology of CTS is increasing pressure in the intracarpal canal.[4] The

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

[a] Graduate Institute of Biomedical Sciences, [b] Department of Internal Medicine, Division of Nephrology, [c] Management Office for Health Data, [d] Department of Medical Research, China Medical University Hospital, [e] Department of Nursing, Asia University, Taichung, Taiwan.

[*] Correspondence: I-Kuan Wang, Division of Nephrology, Department of Internal Medicine, China Medical University Hospital, No. 2, Yude Road, North District, Taichung City, 404472, Taiwan (e-mail: ikwang@seed.net.tw); Ming-Yi Shen, Graduate Institute of Biomedical Sciences, China Medical University, No. 91, Hsueh-Shih Road, Taichung, 40402, Taiwan (e-mail: shenmy1124@gmail.com).

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population-based annual incidence of CTS ranges from 1.73 per 1000 person-years to 3.76 per 1000 person-years.[5,6] Certain factors, including the following: women, obesity, diabetes, rheumatoid arthritis, osteoarthritis, and pregnancy, have been associated with CTS.[6–8]

Patients with chronic kidney disease (CKD) frequently encountered disorders of mineral and bone metabolism. Secondary hyperparathyroidism (SHPT) begins early in the course of CKD, and its prevalence increases as kidney function declines.[9,10] SHPT is manifested by abnormalities of calcium, phosphorus, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and vitamin D metabolism.[11] Skeletal resistance to the action of PTH appears to contribute to the pathogenesis of extraskeletal calcification in end-stage renal disease (ESRD).[12,13] These vascular calcifications contribute to mortality.[14,15]

Some patients with ESRD often associate with tertiary hyperparathyroidism, which reflects severe parathyroid hyperplasia, with autonomous secretion of PTH.[16,17] Such patients often fail conventional treatment and ultimately need parathyroidectomy (PTX).[18] The clinical presentations of ESRD patients with tertiary hyperparathyroidism are osteoporosis, bone pain, and even bone fracture.[19] Treatments for SHPT in adult patients with ESRD include calcimimetic, synthetic vitamin D analogs, active vitamin D, or PTX.[20] All therapies are for advanced SHPT. However, no studies have definitively demonstrated an effect of PTX on ESRD patients' quality of life. Thus, we choose CTS based on patients with ESRD after the PTX.

2. Materials and methods

2.1. Data sources

The Taiwan National Health Insurance (NHI) program is a universal compulsory health insurance program established in 1995 that covered over 98% of Taiwan's 23 million citizens in 1998. The Taiwanese government established the NHI Research Database (NHIRD), which consists of the claims data of 1 million Taiwan's NHI insurants. This study used a subset of the NHIRD known as the Registry of Catastrophic Illness Patient Database (RCIPD). The RCIPD contains the information of insurants who qualified to obtain catastrophic illness cards (which covers 30 categories of diseases requiring long-term care including ESRD, cancer, chronic mental illness, or one of several autoimmune diseases). The data structure in the RCIPD is the same as that in the NHIRD and contains beneficiaries' data (including sex, occupation, and birth date), outpatient and inpatient care records, catastrophic illness files, and other medical service information. Diagnoses entered in the database were in accordance with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Patient data are encrypted to conform with the release policy for privacy protection. The latest database (RCIPD of the NHIRD) we have is December 31, 2011.

2.2. Study population

The candidate population was patients with ESRD (ICD-9-CM code 585, with a catastrophic illness card) aged 18 years or older who received maintenance dialysis. From 2000 to 2010, we identified PTX and non-PTX in the study cohorts. The PTX group included patients with ESRD who underwent PTX (ICD-9-CM procedure code 06.8) after ESRD was diagnosed. For such patients, the PTX procedure date was set as the index date. The non-PTX group comprised maintenance dialysis patients who did not receive the stated procedure. The assigned index date of non-PTX patients was the same as that of their matched PTX counterparts. In both groups, patients with a history of CTS (ICD-9-CM 354.0) before the index date were excluded. These patients were propensity-matched with others by age, sex, and comorbidities at a ratio of 1:1. The study patients were followed up from the index date until the date of CTS diagnosis, discontinuity of the NHI program, or when the database ended (December 31, 2011). The possible reasons for the discontinuity of national health insurance include death, withdrawal of insurance, immigration, prison sentence, etc. Each subject in the study cohorts was followed by screening the claims data, starting the index date, until the date with CTS diagnosed or the end of 2011 to estimate the follow-up person-years.

Baseline comorbidities were identified. Comorbidities included diabetes mellitus (DM, ICD-9-CM code 250), hyperlipidemia (HL, ICD-9-CM code 272), hypertension (HTN, ICD-9-CM code 401–405), congestive heart failure (CHF, ICD-9 CM codes 398.91, 425, and 428), and chronic obstructive pulmonary disease (COPD, ICD-9-CM codes 491, 492, and 496).

2.3. Statistical analysis

We calculated the number and proportions according to sex and comorbidities between the PTX and non-PTX groups and compared them using Pearson's chi-square test. We measured the mean age and corresponding standard deviation (SD) and analyzed differences by using Student's *t* test. For each group, we calculated the incidence density of CTS and plotted the cumulative incidence curve by using the Kaplan–Meier method. Differences were determined using the log-rank test. To clarify the association between PTX and CTS, we used single and multivariable cox proportional hazard models to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). A sensitivity analysis was also conducted and applied in the competing risk analysis. Because death might result in study bias, the competing risk model, developed from the standard Cox model, was used to estimate subhazard ratios (SHRs) and 95% CIs to compare the risk of CTS between maintenance dialysis patients with and without PTX. SAS statistical package (version 9.4; SAS Institute Inc., Cary, NC) was used to analyze all data. The cumulative incidence curve was plotted using the R software platform (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was determined for two-tailed *P* values lower than .05.

3. Results

This study analyzed 1686 and 1686 dialysis patients with and without PTX, respectively, from 2000 to 2010 (Table 1). The characteristics, such as age, sex, diabetes, hyperlipidemia, hypertension, CHF, and COPD, were not statistically significant between the PTX and non-PTX group ($P > .05$ for all).

Table 2 presents the incidence density and risk of CTS between dialysis patients with and without PTX. In this study, 116 dialysis patients developed CTS, and the CTS incidences were 7.33 and 12.5 per 1000 person-years for the non-PTX and PTX group, respectively. Figure 1 shows the cumulative incidence of CTS between the PTX and non-PTX group. The results reveal that the

Table 1

Demographic characteristics and comorbidities of patients with end-stage renal disease according to PTX status.

Variables	PTX group, N = 1686		Non-PTX group, N = 1686		*P*-value
	n	%	n	%	
Sex					0.91
Female	1061	62.9	1058	62.8	
Male	625	37.1	628	37.3	
Age at baseline, yr					0.88
18–64	1442	85.5	1439	85.4	
≥65	244	14.5	247	14.7	
Mean (SD)*	53.2	11.2	52.9	11.3	0.62
Comorbidity					
Diabetes	458	27.2	460	27.3	0.94
Hyperlipidemia	846	50.2	820	48.6	0.37
Hypertension	1575	93.4	1585	94.0	0.48
CHF	539	32.0	533	31.6	0.82
COPD	342	20.3	341	20.2	0.97

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; PTX = parathyroidectomy; SD = standard deviation.
* Student's *t* test.

aforementioned incidence curve for the PTX group was significantly higher than that for the non-PTX group (log-rank test, $P = .004$). After adjustments were made for sex, age, and baseline comorbidities, the PTX group had a 1.70-fold higher risk of CTS (hazard ratio (HR) = 1.70, 95% CI = 1.17–2.47) than the non-PTX group. The results also demonstrated that female patients (HR = 2.46, 95% CI = 1.54–3.92) and patients with COPD (HR = 1.59, 95% CI = 1.04–2.42) might have an increased risk of CTS.

Table 3 presents the risk of CTS for the study groups stratified by sex, age, and comorbidities. Female patients with dialysis who underwent PTX had a 1.60-fold higher risk of CTS than did female patients with dialysis who did not receive this treatment (HR = 1.60, 95% CI = 1.06–2.42). In patients who were aged 18–64 years, those in the PTX group had a 1.74-fold higher risk of CTS than this age group who did not receive PTX (HR = 1.74, 95% CI = 1.17–2.58). In patients with one or more comorbidities, the HR of CTS risk was 1.79 (95% CI = 1.23–2.60) for the PTX group compared with the non-PTX group.

Table 4 reveals the sensitivity analysis results for CTS between the PTX and non-PTX groups in considering the competing risks of death. After adjustments were made for all confounders, the subhazard ratio (SHR) for CTS risk was determined to be 1.62 (95% CI = 1.12–2.36) for the PTX group compared with the non-PTX group.

4. Discussions

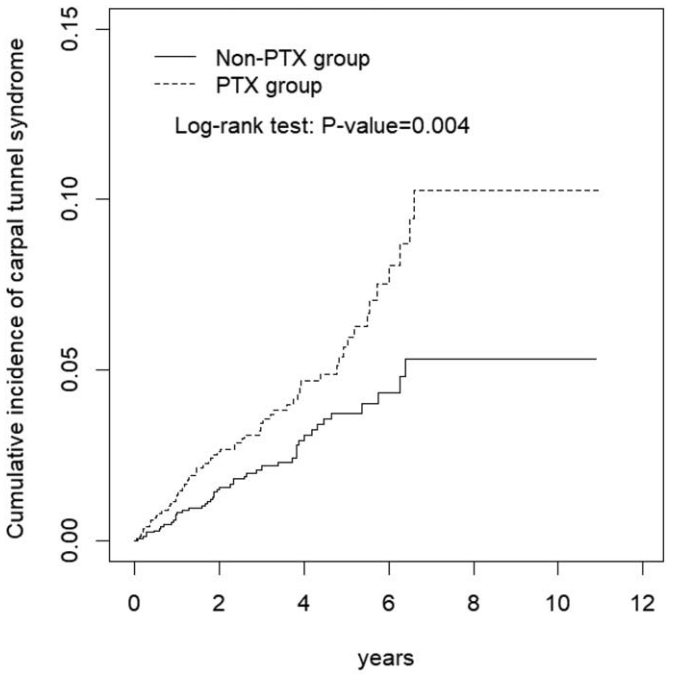
We conducted this nationwide population-based retrospective cohort study in Taiwan. In this study, 116 ESRD patients developed CTS, and the CTS events were 47 and 69 for the non-PTX and PTX group, respectively. After regression models were adjusted to control for the effects of age, sex, and baseline comorbidities (diabetes, hyperlipidemia, hypertension, CHF, and COPD), the PTX group had a 1.70-fold higher risk of CTS than the non-PTX group (HR = 1.70, 95% CI = 1.17–2.47). The incidence curve for the PTX group was significantly higher than that for the non-PTX group (Fig. 1). Female sex and the presence of COPD were associated with an increased risk of CTS in dialysis patients who had undergone PTX. Female patients with

Table 2

Risk of CTS associated with PTX and covariates according to a Cox proportional hazard model.

Variables	Event no.	Person-years	Incidence density*	Crude HR (95% CI)	Adjusted HR (95% CI)
PTX					
No	47	6410	7.33	ref	ref
Yes	69	5502	12.5	1.71 (1.18, 2.49)	1.70 (1.17, 2.47)
Sex					
Female	94	7529	12.5	2.47 (1.55, 3.93)	2.46 (1.54, 3.92)
Male	22	4383	5.02	ref	ref
Age, yr					
18–64	103	10,383	9.92	1.16 (0.65, 2.06)	1.27 (0.71, 2.29)
≥65	13	1529	8.50	ref	ref
Comorbidity					
Diabetes					
No	85	8963	9.48	ref	ref
Yes	31	2949	10.5	1.12 (0.74, 1.69)	1.14 (0.74, 1.76)
Hyperlipidemia					
No	57	6274	9.09	ref	ref
Yes	59	5638	10.5	1.15 (0.80, 1.66)	1.03 (0.70, 1.51)
Hypertension					
No	8	860	9.30	ref	ref
Yes	108	11,052	9.77	1.04 (0.51, 2.14)	0.98 (0.47, 2.04)
CHF					
No	84	8432	9.96	ref	Ref
Yes	22	3480	9.19	0.93 (0.62, 1.39)	0.87 (0.57, 1.32)
COPD					
No	85	9678	8.78	ref	ref
Yes	31	2234	13.9	1.56 (1.05, 2.39)	1.59 (1.04, 2.42)

CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CTS = carpal tunnel syndrome; HR = hazard ratio; PTX = parathyroidectomy.
* Per 1000 person-years.



PTX, No.							
At risk	1686	1144	524	174	34	7	7
Carpal tunnel syndrome events	0	40	16	9	4	0	0
Non-PTX, No.							
At risk	1686	1254	618	206	37	6	0
Carpal tunnel syndrome events	0	25	13	7	2	0	0

Figure 1. Cumulative incidence curves of carpal tunnel syndrome for PTX and non-PTX groups. PTX, parathyroidectomy.

dialysis who underwent PTX had a 1.60-fold higher risk of CTS than who did not receive this PTX (HR = 1.60, 95% CI = 1.06–2.42). In patients with one or more comorbidities, the HR of CTS risk was 1.79 for the PTX group compared with the non-PTX group (HR = 1.79, 95% CI = 1.23–2.60). These significant results persisted in the competing risk analysis model, the SHR for CTS risk was determined to be 1.62 (95% CI = 1.12–2.36) for the PTX group compared with the non-PTX group.

Our study results have three clinical implications. First, the risk of CTS increased significantly in female dialysis patients. The risk of CTS was not different between male patients who had undergone or had not undergone PTX. This implied that female gender is still a strong predictor of CTS. One possible explanation for the female predominance is the cross-sectional area of the proximal carpal tunnel is smaller in female than in male.[21] This might play a key role in the development of clinical CTS.[22] However, not all studies support the relationship. A twin study found that up to one-half of the liability for CTS in women was genetic.[23] The genetic change may responsible for increased pressure in the intracarpal canal. Second, there are limited and

Table 3

Incidence density and HRs of CTS according to PTX stratified by sex, age, and comorbidities.

	PTX group			Non-PTX group			Compared to non-PTX group HR (95% CI)	
Variables	**Event no.**	**Person-years**	**Incidence density***	**Event no.**	**Person-years**	**Incidence density***	**Unadjusted**	**Adjusted**
Sex								
Female	55	3496	15.7	39	4033	9.67	1.62 (1.07,2.44)	1.60 (1.06,2.42)
Male	14	2006	6.98	8	2378	3.37	2.14 (0.90, 5.12)	2.17 (0.91, 5.18)
Age, yr								
18–64	62	4841	12.8	41	5542	7.40	1.74 (1.17, 2.58)	1.74 (1.17, 2.58)
≥65	7	661	10.6	6	868	6.92	1.50 (0.50, 4.49)	1.36 (0.45, 4.12)
Comorbidity status								
No	0	253	0.00	2	263	7.61		
Yes	69	5250	13.1	45	6147	7.32	1.80 (1.24, 2.62)	1.79 (1.23, 2.60)

CTS = carpal tunnel syndrome; PTX = parathyroidectomy; HR = hazard ratio; CI = confidence interval.
* Per 1000 person-years.

Table 4

SHRs (95% CI) of CTS using Cox proportional hazard regression with competing risk of death.

	Non-PTX group	PTX group
Crude SHR (95% CI)	1.00	1.63 (1.13–2.36)
Adjusted SHR* (95% CI)	1.00	1.62 (1.12–2.36)

CTS = carpal tunnel syndrome; PTX = parathyroidectomy; SHR = subhazard ratio; CI = confidence interval.

* Adjustments for sex, age (categorical), diabetes, hyperlipidemia, hypertension, congestive heart failure, and chronic obstructive pulmonary disease.

conflicting data with regard to the potential association of age with CTS.[24,25] No study had previously investigated CTS in adult dialysis patients; to our knowledge, this is the first study to describe the relationship between age and CTS of dialysis patient. Third, we identified COPD as a risk factor for CTS in dialysis patients, possibly because COPD is a result of chronic systemic inflammation. Other conditions, including women, obesity, diabetes, rheumatoid arthritis, osteoarthritis and pregnancy, have been linked inflammation with CTS.[6–8]

5. Limitations

This study needs to be interpreted within the context of three limitations. First of all, significant indication bias might exist for the ESRD patient receiving PTX. However, the NHI Bureau randomly samples a fixed percentage of claims from every hospital each year. Any hospital with outlier charges or outlier patterns for any diagnosis group faces the risk of audit and subsequent heavy penalties by the NHI Bureau. With approved NHI reimbursements for PTX in patients with ESRD, we believe that the PTX group would represent ESRD patients with SHPT accurately. Our second limitation is that we could not access to laboratory data, including the levels of calcium, phosphate, PTH, and beta2-microblogulin, which may compromise our findings. Third, some variables such as dietary habits, cigarette smoking and body mass index, were not available in the dataset. Obesity, defined as increased body mass index, is a probable risk factor for CTS.[26–28] In order to ensure the validity of this study, we adjusted for the potential confounding effect by including HTN, DM, HL, CHF, and COPD in multivariate models. And we need further randomized controlled trials to ascertain the effects of PTX on CTS risk in patients undergoing dialysis.

6. Conclusions

In this nationwide cohort study, we revealed that ESRD patients who had undergone PTX may have an increased risk of CTS.

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Author contributions

Methodology: Cheng-Li Lin.
Project administration: Jie-Sian Wang.
Resources: Wei-Shan Chen.
Software: Cheng-Li Lin.
Writing – original draft: Jie-Sian Wang.
Writing – review & editing: I-Kuan Wang, Ming-Yi Shen.

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