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ORIGINAL ARTICLE

Impact of secondary hyperparathyroidism on disease progression, healthcare resource utilization and costs in pre-dialysis CKD patients*

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ABSTRACT

Background and objectives: Secondary hyperparathyroidism (SHPT) can lead to significant morbidity, mortality, and additional healthcare resource utilization in chronic kidney disease (CKD) stage 5. The objective of this study was to examine healthcare costs and utilization, and the risks of dialysis or mortality, among pre-dialysis CKD patients with and without SHPT.

Research design and methods: This retrospective cohort study examined insurance claims from 66 644 adult, pre-dialysis, CKD patients with and without SHPT during a 72-month period. Annualized estimates of healthcare costs and utilization, and disease progression to dialysis or death following index CKD diagnosis were compared.

Results: Post-index annualized costs and inpatient healthcare resource utilization was higher in those with SHPT in both unadjusted and adjusted (controlling for gender, age, plan type, payer type, geographic region, physician specialty, pre-index co-morbidities, and pre-index total healthcare costs), and unmatched and matched analyses. Kaplan–Meier analysis demonstrated that the rate of progression to dialysis or death was higher for CKD with SHPT compared to CKD without SHPT, and Cox proportional hazard models suggested that CKD patients with SHPT were more than four to five times as likely to initiate dialysis or die as compared to CKD without SHPT.

Conclusion: SHPT in pre-dialysis CKD patients is associated with significantly greater healthcare costs, inpatient hospitalizations, and a faster rate of disease progression compared to pre-dialysis CKD without SHPT. Since observational studies are designed to demonstrate associations rather than causality, further investigation is required to confirm these findings.

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Introduction

Chronic kidney disease (CKD) is defined as a gradual loss of kidney function, which eventually results in end-stage renal disease leading to the need for renal replacement therapy such as dialysis treatment or kidney transplantation. Secondary hyperparathyroidism (SHPT) and 1,25 di-OH vitamin D deficiency invariably occurs in moderate to advanced CKD[1,2].

As CKD progresses and kidney function declines, abnormalities of serum calcium and phosphate become increasingly apparent. These hormonal and mineral disorders result in alteration of the bone matrix, known as renal osteodystrophy, which can lead to bone structure derangement and predisposition to fractures[3–6]. A 2005 report by the United States Renal Data System found that advanced kidney disease (stage 5) quadrupled the risk of fractures[7,8]. The Dialysis Morbidity and Mortality Study reported that the mortality rate after fracture was 2.7 times greater for those with bone disease compared to general dialysis patients[9].

In addition to skeletal abnormalities, SHPT and associated osteodystrophy have been shown to impart significant extra-skeletal disorders, leading to morbidity and mortality, especially in stage 3–5 CKD[9,10]. In fact, cardiovascular disease is the leading cause of death in all stages of CKD. Robbins *et al.*[11] have shown that the per-patient-per-month charges for CKD were $4265 between 6–1 months prior to dialysis, with hospitalization charges representing greater than 50% of the cost. Furthermore, individuals with CKD stage 3 and 4 are more likely to be hospitalized and to die of complications related to cardiovascular disease than to progress to dialysis[12]. A decrease in vitamin D receptor activator (VDRA) increases circulating rennin levels and blood pressure and may lead to left ventricular and vascular calcification[13].

Healthcare costs have been shown to begin to rise 2 years prior to dialysis and peak around the initiation of dialysis[11,13]. Hospitalizations have been shown to be the major component of these costs[14]. While the VDRA therapy costs associated with treating SHPT in CKD patients are understood, little is known about the impact of SHPT on health care utilization and costs[15].

The objective of this study was to compare the rate of resource utilization and costs and risks of dialysis and mortality among pre-dialysis CKD patients with and without SHPT.

Patients and methods

A historically (unmatched) collected administrative claims database was examined to compare clinical and economic outcomes in patients with CKD not on dialysis, with and without comorbid SHPT. A second matched analysis was conducted in which patients with no evidence of SHPT or VDRA therapy were matched to maximize sample size on a 4 : 1 basis to patients with SHPT and no VDRA therapy based on age (5 year age bands), gender, duration of follow-up (60 day intervals) and Charlson Comorbidity Index. Unsuccessfully matched patients were excluded from all matched analyses. The specific objectives of this study were: (1) to compare baseline (pre-CKD) patient demographic and clinical characteristics; (2) to calculate rates of resource utilization and healthcare costs among these individuals (including CKD-related and cardiovascular [CV]-related utilization and costs); and (3) to determine the risk of CKD progression to dialysis or all-cause mortality.

Data source

The data used in this analysis were obtained from the PharMetrics Patient-Centric Database, which was comprised of fully adjudicated medical and pharmaceutical claims for over 47 million patients from 86 health plans across the United States (US) at the time of this study. The database includes both inpatient and outpatient diagnoses (The International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] format), and procedures (Current Procedural Terminology [CPT], 4th edition and Healthcare Common Procedural Coding System formats), as well as prescription records (retail and mail order) including the national drug code and quantity dispensed. Both charged and paid amounts are available for all services rendered (net of any patient co-payments or co-insurance), as well as dates of service for all claims. Additional data elements include demographic variables (age, gender, geographic region), plan type (e.g., health maintenance organizations, preferred provider organizations,), payer type (e.g., commercial, self-pay), provider specialty, and patient start and stop dates for plan enrollment.

The data were longitudinal, with an average patient enrollment time of 2 years. Only health plans submitting data for all patients are included in the database; this ensures complete data capture and representative samples. Data contributions are also subjected to a series of quality checks to ensure a standardized format and minimal error rates.

Sample selection

Patients with a diagnosis of CKD based on at least one medical or facility claim during the period January 1, 2000 to December 31, 2004 (inclusive) were identified

initially based on their ICD-9-CM diagnosis codes (Table 1)[16].

Patients needed to be continuously enrolled in a health plan for at least 12 months prior and at least 6 months after the initial CKD medical or facility claim to be included in the analysis. The date associated with the initial medical or facility claim meeting these criteria was the 'index date' assigned to each patient. Follow-up time varied for each patient beyond the minimum 6-months after the index date and was terminated as of the date of health plan disenrollment, the end of available data (defined as no more claims), initiation of dialysis, or the end of the study period (data not included after the study end of June 30, 2005). Pre-index was defined as time prior to this first medical or facility claim for CKD, and post-index was defined as the time after the first medical or facility claim for CKD.

Patients were excluded if they met the following criteria: (1) they were less than 18 years of age at the index date; (2) their health plan did not provide data for pharmacy days supply; (3) they were enrolled less than 12 months prior to the index date; (4) they were enrolled less than 6 months after the index date; (5) they were diagnosed with SHPT during the pre-index period; (6) they were 65 years or older and not enrolled in a 'Medicare Risk' plan (because complete claims histories during intervals of continuous enrollment may not be available for individuals aged 65 years or older whose insurance coverage is not Medicare 'risk' due to issues of coordination of benefits with traditional Medicare or another payer); (7) key variables were missing in their patient record (e.g., missing or invalid values in gender, birth year, or enrollment date variables); or (8) received a prescription for active or activated VDRA therapy.

Table 1. *ICD-9-CM codes to define CKD*

Code	Description
585	Chronic renal failure
586	Renal failure, unspecified
587	Renal sclerosis, unspecified
403.xx	Hypertensive renal disease
404.xx	Hypertensive heart and renal disease
250.4x	Diabetes with renal manifestations
582.x	Chronic glomerulonephritis
583.xx	Nephritis and nephropathy, not specified as acute or chronic
588.xx	Disorders resulting from impaired renal function
593.9	Unspecified disorder of kidney and ureter (e.g., renal disease NOS)
581.xx	Nephrotic syndrome
580.xx	Acute glomerulonephritis
582.xx	Chronic glomerulonephritis
589.xx	Small kidney of unknown cause
593.7	Vesicoureteral reflux
753	Cystic kidney disease
753.1	Congenital anomalies of urinary system
753.3	Other specified anomalies of kidney

CKD = chronic kidney disease; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; NOS = not otherwise specified)

Definition of SHPT

CKD patients were considered to have a diagnosis of SHPT if they had a diagnosis of SHPT (based on at least one medical or facility claim indicative of the diagnosis, ICD-9 code 588.8x), a diagnosis of hyperphosphatemia (based on at least one medical or facility claim indicative of the diagnosis, ICD-9 code 275.3), or evidence of treatment with a phosphate binder (based on at least one pharmacy claim).

In order to examine exclusively pre-dialysis CKD patients, any patient undergoing maintenance dialysis treatment during the follow-up period was censored just prior to initiating dialysis. For these patients their cohort assignment was based on claims present prior to censoring and their follow-up period for evaluating resource utilization, costs, and outcomes measures ended the day prior to the first dialysis claim during the follow-up period.

Patient cohorts

Patients with CKD who met the clinical and enrollment criteria noted above were assigned to one of two mutually exclusive cohorts (Figure 1). Cohort assignment was based on the presence of a post-index diagnosis of SHPT. Patients in neither group were receiving VDRA therapy. CKD patients with no evidence of SHPT or VDRA therapy were assigned to cohort 1. CKD patients with evidence of SHPT but no VDRA therapy were assigned to cohort 2.

Measures and statistical analysis

Demographic and clinical characteristics (age, gender, number of comorbid conditions, and mean total health care costs during the 12-month pre-index period) were compared for the two CKD patient cohorts. In addition, the baseline comorbidity profile was defined for each patient using the Dartmouth–Manitoba modification of the Charlson Comorbidity Index[17]. This weighted index identifies prevalent conditions associated with a relatively high mortality risk. Index scoring is applied prospectively and has been adapted

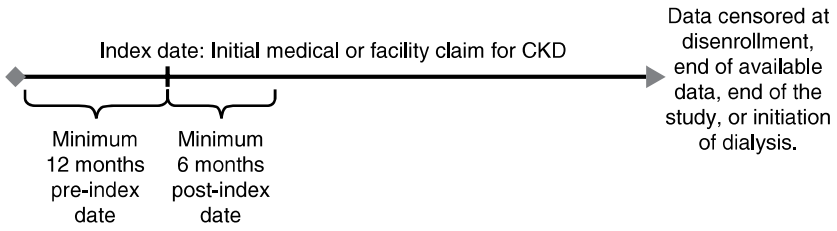

Figure 1. *Study design. CKD = chronic kidney disease*

Groups	Historic cohorts	Matched cohorts*	Percent of matches in cohorts
CKD without SHPT and no VDRA	65 352	2422	3.7%
CKD with SHPT and no VDRA	667	645	96.7%

*Matching based on age in 5-year bands, gender, Charlson comorbidity index (exact match), and follow-up in 60-day intervals
CKD = chronic kidney disease; SHPT = secondary hyperparathyroidism; VDRA = vitamin D receptor activator

and validated for use with longitudinal data. Univariate comparisons between cohorts were conducted using chi-square for categorical variables and Wilcoxon rank-sum tests for continuous variables.

Resource utilization and direct health care costs were reported for each of the cohorts during the follow-up period up to the time of censoring. CKD-related care was categorized based on the presence of a relevant clinical code on the claim of interest. All other utilization and costs were categorized as non-CKD related health care. CV-related care was also categorized based on the presence of a relevant clinical code on the claim of interest, and all other utilization and costs categorized as non CV-related (Table 2). Because follow-up time was variable, all total, CKD-related and CV-related utilization measures and costs were annualized. Patients undergoing dialysis had a dialysis censoring flag created to indicate the time of the first dialysis-related claim and the analysis was conducted up to the day before the first dialysis claim.

Costs (i.e., plan payments for services rendered) were expressed in 2004 US dollars as the amount paid by the health plan, and were adjusted as necessary using the medical care component of the US Consumer Price Index. Descriptive statistics and general linear models (GLM) multivariate modeling were employed to assess observed differences between cohorts in CKD-related, non CKD-related, CV-related, and non CV-related utilization and follow-up health care while adjusting for potential confounders. The patterns of observed data guided the selection of model specification (e.g., gamma for cost and negative binomial for resource use).

Dialysis, death and combined dialysis and death analyses using Kaplan–Meier and Cox proportional hazard

Table 2. *ICD-9-CM codes to define CV disease*

Code	Description
401.xx	Essential hypertension
402.xx	Hypertensive heart disease
403.xx – excluding 403.x1	Hypertensive renal disease
404.xx – excluding 404.x2 and 404.x3	Hypertensive heart and renal disease
410.xx–414.xx	Ischemic heart disease
420.xx–429.xx	Other forms of heart disease (including pericarditis, endocarditis, myocarditis, valvular disorders, cardiomyopathy, conduction disorders, cardiac dysrhythmias, heart failure)
430.xx–438.xx	Cerebrovascular disease (includes hypertensive encephalopathy)
441.3, 441.4	Abdominal aortic aneurysm
443.x	Peripheral vascular disease
405.xx	Secondary hypertension
583.xx, 585, 403.x1, 404.x2, 404.x3	Chronic renal failure
584.x	Acute renal failure
272.x	Hyperlipidemia
786.50	Chest pain NOS
786.51	Precordial pain
786.59	Chest pain NEC
780.2	Syncope and collapse
785.1	Palpitations

CV = cardiovascular; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification

models were conducted. Death was determined using the methods described by Joyce and others[18]. Death or death proxy was defined as patients with claims for defibrillation, cardiac arrest/failure (ICD-9-CM 427.5x), hospitalization (Revenue Center Codes 100–219), emergency room visit (point of service [POS] 23; CPT-4 99271–99288; Revenue Center Codes 450–459, 981), ambulance service (CPT-4 99289–99290, Revenue Center Codes 540–549), cerebral death (CPT-4 95824), thoracostomy (CPT-4 32160), aneurism repair (CPT-4 35002, 35013, 35022, 35082, 35092, 35103, 35112, 35122, 35132, 35142, 35152), or an organ or kidney transplant complication (ICD-9-CM 996.80, 996.81) during the last month in which medical and pharmacy claims were available prior to disenrollment were assumed to have died.

Results

Baseline characteristics

A total of 66 019 patients with CKD meeting the study inclusion criteria were identified. In the historic analysis, 99% ($n = 65\,352$) of the study sample had CKD with no evidence of SHPT, while 1% ($n = 667$) had CKD with SHPT. The age and gender of the two cohorts did not differ significantly. However, CKD with SPHT had more comorbidities, and greater total health care costs at baseline (12-month prior to the CKD diagnosis). The mean pre-index number of comorbidities was 4.51 and 4.85 ($p = 0.0007$) for CKD and CKD with SHPT, respectively. Mean total health care costs during the 12-month pre-index period were \$13 918 and \$21 344 for CKD and CKD with SHPT respectively, $p < 0.0001$ (Table 3).

For the matched analyses, 2422 patients with CKD and no evidence of SHPT or VDRA treatment were matched with 645 patients with CKD with non-VDRA treated SHPT. The mean age was 54 years for both matched cohorts (CKD without SHPT: 53.90; CKD with SHPT: 54.42, $p = 0.5162$) and 48% of each matched cohort was female (CKD without SHPT: 47.73%; CKD with SHPT: 47.60%; $p = 0.9523$). The mean number of comorbidities per patient was 4.75 for the CKD without SHPT and 4.79 for the CKD with SHPT cohorts ($p = 0.8609$), and the mean Charlson Comorbidity Index was 1.51 (CKD w/o SHPT) and 1.65 (CKD w/SHPT, $p = 0.2101$).

Univariate analysis

The post-index duration of the historic follow-up time was not significantly different between the two groups (521 vs. 529 days, $p = 0.3451$, for CKD without and CKD with SHPT respectively), while the duration of the matched follow-up was 596 days for CKD without SHPT and 523 days for CKD with SHPT ($p < 0.0001$). A higher proportion of CKD with SHPT remained enrolled in their health plan at 1 year as compared to CKD without SHPT for both the historic and matched analyses (historic: 85% vs. 65% and matched: 85% vs. 77%) (Table 4). For CKD with SHPT, the mean time to initial SHPT diagnosis was 221 days (from the date of CKD diagnosis) for the historic analysis, and 219 days for the CKD with SHPT for the matched analysis.

In the historic analysis, the mean annual number of prescriptions filled was higher for CKD with SHPT versus CKD without SHPT, as was the mean number of CKD-related and CV-related prescriptions filled annually. Similar results were found with the matched analysis. The CKD with SHPT cohort also had the higher mean number of annual CKD-related and CV-related outpatient claims compared to those CKD patients that did not develop SPHT (Table 5).

The historic analysis showed the CKD with SHPT cohort also had a greater number of CKD-related inpatients claims (both days in hospital and number of hospitalizations). Mean annual CKD-related hospital days were 56.47 and 9.80 ($p < 0.0001$) for those with and without SHPT, respectively. Likewise, the mean number of annual CV-related hospital days (59.94 vs. 11.86, $p < 0.0001$) and hospitalizations (3.08 vs. 0.98, $p < 0.0001$) was higher in those with SHPT. The matched CKD with SHPT patients had a mean of 3.23 inpatient admissions, 57.98 CKD-related days in hospital, and 61.40 CV-related days in hospital, as compared with 1.05 inpatient admissions, 8.37 CKD-related and 10.61 CV-related days in hospital for the matched CKD without SHPT group (all $p < 0.0001$) (Table 5).

The historic analyses mean annual healthcare costs were higher for the CKD with SHPT cohort (\$195 814 vs. \$54 422, $p < 0.0001$) compared to those without SHPT. Likewise both CKD-related costs (\$170 287 vs. \$40 935, $p < 0.0001$) and CV-related costs (\$180 415 vs. \$46 408, $p < 0.0001$) were higher in CKD with SHPT versus CKD. The matched analyses mean annual healthcare costs remained higher in the CKD with SHPT cohort (\$200 531 vs. \$38 767; CKD-related: \$175 205 vs. \$23 734; CV-related: \$185 074 vs. \$30 199; all $p < 0.0001$). Post-index costs are summarized in Table 6.

Multivariate results

Adjusting for potential confounder via multivariate modeling resulted in similar findings when comparing CKD-related and CV-related costs controlled for gender, age, insurance type, physician specialty, geographic region, pre-index comorbidities, and pre-

Table 3. *Historic cohort pre-index demographics and clinical characteristics*

Baseline characteristics	Cohort 1:CKD without SHPT	Cohort 2:CKD with SHPT	*p*-value*
Total patients, *n* (%)	65 352 (1.00)	667 (1.00)	
Mean age, years (mean, SD)	53.14 (15.03)	54.42 (15.05)	0.0310
Female gender, *n* (%)	32 566 (49.83)	315 (47.23)	0.1806
Plan type, *n* (%)			
Health maintenance organization	39 637 (60.65)	415 (62.22)	0.5271
Indemnity plan	2283 (3.49)	17 (2.55)	
Preferred provider organization	16 229 (24.83)	168 (25.19)	
Point of service	6566 (10.05)	63 (9.45)	
Unknown	637 (0.97)	4 (0.6)	
Payer type, *n* (%)			
Commercial plan	48 695 (74.51)	449 (67.32)	<0.0001
Medicaid	1554 (2.38)	48 (7.20)	
Medicare risk	11 379 (17.41)	139 (20.84)	
Self-insured	1808 (2.77)	10 (1.50)	
Unknown	1916 (2.93)	21 (3.15)	
Geographic region, *n* (%)			
Northeast	5089 (7.79)	31 (4.65)	0.0010
Midwest	32 498 (49.73)	376 (56.37)	
South	19 861 (30.39)	189 (28.34)	
West	7904 (12.09)	71 (10.64)	
Physician specialty, *n* (%)			
General/family practice	9544 (14.60)	76 (11.39)	<0.0001
Internal medicine	10 375 (15.88)	107 (16.04)	
Endocrinology	2218 (3.39)	13 (1.95)	
Nephrology	5618 (8.60)	162 (24.29)	
Cardiology	3005 (4.60)	40 (6.00)	
Other	19 993 (30.59)	198 (29.69)	
Unknown	14 599 (22.34)	71 (10.64)	
Pre-index comorbidities, *n* (%)			
Infectious and parasitic diseases	12 078 (18.48)	150 (22.49)	0.0080
Neoplasms	15 480 (23.69)	135 (20.24)	0.0371
Endocrine/metabolic/immune disorders	39 690 (60.73)	465 (69.72)	<0.0001
Blood and blood-forming organ disorders	10 563 (16.16)	173 (25.94)	<0.0001
Mental disorders	13 549 (20.73)	134 (20.09)	0.6838
Nervous system and sense organ disorders	27 255 (41.70)	306 (45.88)	0.0297
Circulatory system disorder	39 857 (60.99)	493 (73.91)	<0.0001
Respiratory system disorders	29 542 (45.20)	317 (47.53)	0.2307
Digestive system disorders	22 529 (34.47)	216 (32.38)	0.2585
Genitourinary system disorders	31 453 (48.13)	317 (47.53)	0.7567
Pregnancy/childbirth/puerperium disorders	1148 (1.76)	9 (1.35)	0.4251
Skin/subcutaneous tissue disorders	17 351 (26.55)	183 (27.44)	0.6061
Musculoskeletal system disorders	34 457 (52.73)	337 (50.52)	0.2574
Pre-index total health care costs†			
Mean (SD)	$13 918 (41 637)	$21 344 (45 093)	<0.0001

*Differences between cohorts were analyzed using chi-square for categorical variables and Wilcoxon rank-sum tests for continuous variables

†For 12 month pre-index period

CKD = chronic kidney disease; SD = standard deviation; SHPT = secondary hyperparathyroidism

Table 4. Attrition of study sample by cohort

Follow-up	Cohort 1:CKD without SHPT		Cohort 2:CKD with SHPT	
Historic				
N	65 352		667	
At 180 days, *n* (%)	65 352	100	667	100
At 360 days, *n* (%)	42 602	65	567	85
At 500 days, *n* (%)	30 780	47	506	76
At 750 days, *n* (%)	16 908	26	377	57
At 1000 days, *n* (%)	8968	14	299	45
Matched				
N	2422		645	
At 180 days, *n* (%)	2422	100	645	100
At 360 days, *n* (%)	1877	77	546	85
At 500 days, *n* (%)	1534	63	485	75
At 750 days, *n* (%)	865	36	360	56
At 1000 days, *n* (%)	400	17	284	44

CKD = chronic kidney disease; SHPT = secondary hyperparathyroidism

index total healthcare costs analyses. Multivariate adjustment using the foregoing covariates was also carried out for medications, outpatient and inpatient annualized service utilization, and costs, which yield similar differences as unadjusted results.

The historic analysis total outpatient resource utilization was 215% higher in the cohort with SHPT compared to the cohort without SHPT ($p < 0.0001$) (Table 7). Those with CKD who developed SHPT experienced 407% higher CKD-related, 255% higher CV-related outpatient resource utilization ($p < 0.0001$ for all comparisons). As shown in Table 7, total annual inpatient resource utilization was 279% higher for the CKD with SPHT cohort ($p < 0.0001$); and CV-related inpatient resource utilization was 297% higher for the CKD with SHPT ($p < 0.0001$) compared to CKD patients without SHPT. Overall, total costs were 427% higher for the cohort with SHPT compared to the cohort without SHPT ($p < 0.0001$). Least-squares mean estimates (exponentiated) confirmed the differences between the groups. The total annualized CKD-related costs were $139 707 for CKD with SHPT versus $23 517 for CKD without SHPT ($p < 0.0001$). CKD-related and CV-related total costs were higher in the cohort with SHPT ($p < 0.0001$ for all comparisons).

Results of the GLM models for the matched cohorts showed that CKD-related, CV-related, and total outpatient resource utilization and total, CV-related, and non CV-related pharmacy, outpatient and inpatient resource utilization were higher for the CKD with SHPT matched cohort than for the CKD without SHPT group. Annualized total, CV-related and non-CV-related costs were also higher for the CKD with SHPT matched cohort.

Survival analysis

As shown in the Kaplan–Meier plots (Figures 2 and 3), the rate of dialysis or death was higher for CKD patients with SHPT compared to CKD patients without SHPT patients in both the historic and matched analysis. Accordingly, for the combined risk of death or dialysis, the results of the historic analysis of the Cox proportional hazard models suggested that CKD patients with SHPT were more than four times as likely to initiate dialysis or die as compared to CKD patients without SHPT (hazard ratio [HR] = 4.19, 95% confidence interval [CI] = 3.68–4.78). The risk of dialysis in the historic cohort analysis of Cox proportional hazard models suggests CKD patients with SHPT were more than five times as likely to initiate dialysis as compared to CKD without SHPT (HR = 5.76, 95% CI = 4.99–6.66). The results of the matched analysis of the Cox models also demonstrated that patients in the CKD with SHPT cohort had a significantly higher risk of dialysis or death (HR = 5.05; 95% CI = 4.08–6.24) than patients in the CKD without SHPT. The risk of dialysis in the matched cohort analysis of Cox proportional hazard models suggests CKD patients with SHPT were more than six times as likely to initiate dialysis as compared to CKD without SHPT (HR = 6.52, 95% CI = 5.07–8.39).

Discussion

The results suggest that CKD patients with SHPT who are not treated with VDRA therapy are associated with higher average annual utilization of medication and higher use of both inpatient and outpatient medical services compared with CKD patients with no evidence of SHPT or VDRA therapy. This is the case even when the data are adjusted for a variety of known confounders. Further, CKD patients with SPHT progress more quickly to dialysis or death compared to CKD patients without SPHT. A recent study by Khan[19] demonstrated higher parathyroid hormone levels were associated with a higher prevalence of congestive heart failure and acute myocardial infarction/ischemic heart disease. To the best of our knowledge this is the first study to investigate disease progression associated with SHPT in pre-dialysis patients, and also provides the repeat validity to Kahn's results of increased hospitalizations and healthcare costs in patients with SHPT.

Table 5. *Post-index descriptive annual number of prescriptions, outpatient services and inpatient services**

Prescriptions or medical service utilization	Cohort 1: CKD without SHPT, mean (SD)	Cohort 2: CKD with SHPT, mean (SD)	*p*-value*
Historic analysis			
Medications			
CV-related medications	9.92 (12.85)	19.75 (49.00)	<0.0001
CKD-related medications	19.78 (22.77)	37.22 (30.56)	<0.0001
Total medications	33.87 (35.08)	58.92 (44.69)	<0.0001
Outpatient services			
CV-related outpatient services	19.28 (53.56)	53.16 (71.10)	<0.0001
CKD-related outpatient services	6.61 (39.79)	33.29 (60.69)	<0.0001
Total outpatient services	63.36 (102.21)	143.09 (245.20)	<0.0001
Inpatient services			
Total hospitalizations	1.07 (12.05)	3.19 (15.77)	<0.0001
CV-related hospitalizations	0.98 (11.96)	3.08 (15.76)	<0.0001
CKD-related hospitalizations	0.71 (11.49)	2.66 (15.74)	<0.0001
CV-related hospital days	11.86 (263.01)	59.94 (951.16)	<0.0001
CKD-related hospital days	9.80 (262.62)	56.47 (951.24)	<0.0001
Matched analysis			
Medications			
CV-related medications	10.91 (13.01)	19.81 (19.40)	<0.0001
CKD-related medications	21.89 (23.19)	37.15 (30.83)	<0.0001
Total medications	36.76 (35.38)	58.71 (44.84)	<0.0001
Outpatient services			
CV-related outpatient services	22.07 (51.96)	53.58 (72.03)	<0.0001
CKD-related outpatient services	8.29 (47.15)	34.07 (61.49)	<0.0001
Total outpatient services	69.16 (96.73)	143.93 (248.86)	<0.0001
Inpatient services			
Total hospitalizations	1.05 (11.12)	3.23 (16.03)	<0.0001
CV-related hospitalizations	0.97 (11.11)	3.12 (16.03)	<0.0001
CKD-related hospitalizations	0.70 (11.08)	2.70 (16.00)	<0.0001
CV-related hospital days	10.61 (174.17)	61.40 (967.23)	<0.0001
CKD-related hospital days	8.37 (173.77)	57.98 (967.31)	<0.0001

*Differences between cohorts were analyzed using Wilcoxon rank-sum tests for continuous variables.
CKD = chronic kidney disease; CV = cardiovascular; SD = standard deviation; SHPT = secondary hyperparathyroidism

Since patients could not be classify based upon their CKD stage, both cohorts had the same index date definition. The index date was defined as of their first diagnosis of CKD in a real world setting. Based on this methodology, these cohorts should theoretically have a similar level of CKD at the start of the study. Multivariate analyses were conducted adjusting for differences in gender, age, insurance type, physician specialty, geographic region, pre-index comorbidities, and pre-index total health care costs between cohorts to enhance confidence in the data. Finally, additional analyses were conducted using matched cohorts to further ensure the similarity of these cohorts. While this analysis decreased the sample size, it may be viewed as a sensitivity analysis to analyze the impact of larger samples size in the CKD without SHPT cohort.

The results should not be surprising since the clinical consequences of unmanaged SHPT can manifest itself in a myriad of deleterious ways, including renal bone disease[14,20–22], cardiovascular complications[23–26], and parathyroid gland hyperplasia[27,28]. Increased and prolonged mobilization of calcium and phosphorus from the skeletal system can lead to significant bone loss and fragility. Excess calcium and phosphorus released from the bone subsequently can lead to extraskeletal deposition of calcium and phosphorus and calcification of cardiovascular tissue and blood vessels. Elevated

Table 6. *Post-index descriptive annual costs of prescriptions, outpatient services and inpatient services**

Prescriptions or medical service costs	Cohort 1: CKD without SHPT,mean (SD)	Cohort 2: CKD with SHPT,mean (SD)	*p*-value*
Historic analysis			
Medication costs			
CV-related medications	$390 ($619)	$756 ($938)	< 0.0001
CKD-related medications	$1010 ($1950)	$2316 ($3513)	< 0.0001
Total medications	$1993 ($3762)	$4206 ($6822)	< 0.0001
Outpatient costs			
CV-related outpatient services	$1714 ($11 549)	$4806 ($12 583)	< 0.0001
CKD-related outpatient services	$749 ($10 554)	$3543 ($12 211)	< 0.0001
Total outpatient services	$7091 ($20 341)	$14 972 ($30 676)	< 0.0001
Inpatient costs			
CV-related hospitalizations	$44 304 ($1 866 656)	$174 852 ($2470.811)	< 0.0001
CKD-related hospitalizations	$39 176 ($1 886 375)	$164 427 ($2 470 904)	< 0.0001
Total hospitalizations	$45 338 ($1 866 722)	$176 637 ($2 470 804)	< 0.0001
Matched analysis			
Medication costs			
CV-related medications	$444 ($660)	$754 ($945)	< 0.0001
CKD-related medications	$1164 ($2132)	$2324 ($3562)	< 0.0001
Total medications	$2274 ($4295)	$4209 ($$6910)	< 0.0001
Outpatient costs			
CV-related outpatient services	$1909 ($8111)	$4858 ($12 781)	< 0.0001
CKD-related outpatient services	$830 ($6498)	$3640 ($12 403)	< 0.0001
Total outpatient services	$7816 ($17 817)	$15 034 ($31 031)	< 0.0001
Inpatient costs			
CV-related hospitalizations	$17 846 ($448 852)	$179 462 ($2 512 517)	< 0.0001
CKD-related hospitalizations	$21 741 ($447 335)	$169 241 ($2 512 807)	< 0.0001
Total hospitalizations	$28 677 ($448 852)	$181 287 ($2 512 507)	< 0.0001

*Differences between cohorts were analyzed using Wilcoxon rank-sum tests for continuous variables
CKD = chronic kidney disease; CV = cardiovascular; SD = standard deviation; SHPT = secondary hyperparathyroidism

Table 7. *Generalized linear models* comparing CKD with SHPT healthcare resource utilization versus CKD without SHPT*

Prescriptions or medical service	Historic analysis CKD with SHPT	*p*-value	Matched analysis CKD with SHPT	*p*-value
Medication				
CV-related medications	208%	< 0.0001	179%	< 0.0001
Total medications	176%	< 0.0001	168%	< 0.0001
Outpatient services				
CV-related outpatient services	255%	< 0.0001	236%	< 0.0001
Total outpatient services	215%	< 0.0001	207%	< 0.0001
In-patient services				
CV-related Hospitalizations	297%	< 0.0001	409%	< 0.0001
Total hospitalizations	279%	< 0.0001	368%	< 0.0001

*Adjusted for gender, age, plan type, payer type, geographic region, physician specialty, pre-index co-morbidities, and pre-index total healthcare costs
CKD = chronic kidney disease; CV = cardiovascular; SHPT = secondary hyperparathyroidism

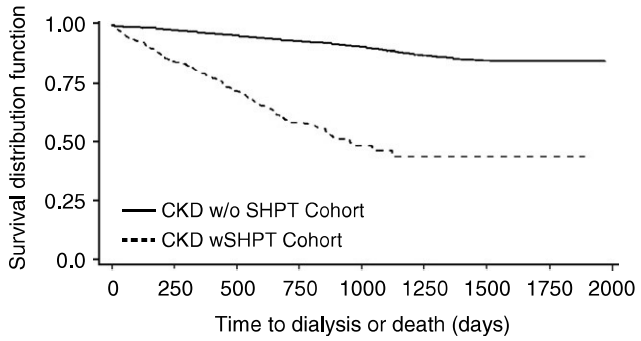

Figure 2. *Historic analysis: Kaplan–Meier analysis for time to dialysis or death. CKD = chronic kidney disease*

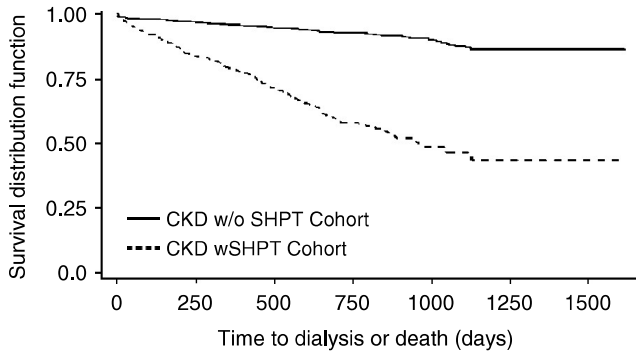

Figure 3. *Matched analysis: Kaplan–Meier analysis for time to dialysis or death. CKD = chronic kidney disease; SHPT = secondary hyperparathyroidism*

parathyroid hormone (PTH) itself, has been identified as a cardiovascular toxin, contributing to myocardial hypertrophy and associated morbidities and mortality. Therefore, it is not unanticipated that the baseline costs of unmanaged SHPT costs would be greater than those without the disease.

The results of this study may have major implications given the prevalence of CKD in the US. There are approximately 8 million patients in the US with pre-dialysis CKD (stages 3 and 4)[29]. A previous study investigating the prevalence of SHPT found that 38% of stage 3 CKD and 68% of stage 4 CKD patients had SHPT without VDRA therapy[30]. However, our study, based on actual claims data, found only 1% of pre-dialysis CKD patients with a diagnosis of SHPT not on VDRA therapy. This may suggest profound under-diagnosis, under-reporting or under-coding of SHPT in pre-dialysis patients. Nevertheless, applying the 1% prevalence of SHPT would suggest that there are at least 80 000 pre-dialysis CKD patients with SHPT in the US without VDRA therapy. Extrapolating the results of our study would suggest that the additional costs incurred by SHPT in pre-dialysis CKD patients exceed 11 billion dollars annually ([$195 818 – $54 422] × 80 000). Selective VDRA therapy has shown a benefit in both morbidity and mortality in CKD stage 5. However, additional analyses are needed to confirm the benefits of selective VDRA therapy in CKD stages 3 and 4.

Among the study limitations, CKD patients were considered to have comorbid SHPT if they had a specific diagnosis of SHPT, a diagnosis of hyperphosphatemia, or were receiving phosphate binder treatment during the post-index (CKD diagnosis) period. The rationale for the use of a surrogate for a diagnosis of SHPT can be justified by the pathophysiology of the disease. A decline in the kidney function results in a fall in serum 1,25-dihydroxyvitamin D and an increase in PTH with changes in serum phosphate and calcium[14]. Hypocalcemia is compensated through release of calcium from the bone. Therefore, the first sign of SHPT in pre-dialysis patients may be an abnormal serum phosphate level, based on a common laboratory test. From a prospective, community-based, non-interventional, cohort study designed to examine SHPT in CKD patients with an estimated glomerular filtration rate of less than 60 mL/min, the prevalence of SHPT was 38% of stage 3 CKD and 68% of stage 4 CKD patients[30]. However, this study demonstrated that less than 1% of pre-dialysis CKD patients have a diagnosis of SHPT. The literature has demonstrated similar results, concluding that SHPT is under-diagnosed[11] and under-treated[11,14]. This definition of SHPT may not be adequately inclusive. However, all relevant ICD-9 codes were screened to reach this diagnosis.

Selection bias, bias from censoring of data (biased toward lower utilization), and measurement error are other potential sources of miscalculation. Nevertheless, there is no reason to suspect that selection bias influenced our results. Data were censored to ensure internal consistency of patients included and for interpretability of our results. This study was largely dependent on the accuracy of the data contained in the medical and pharmacy claims. The accuracy of such coding is known to be variable, particularly with respect to diagnoses. Recall bias or 'upcoding' (biased towards higher costs) may both influence results of these types of studies.

Since the claims database did not provide an indicator of death, a previously published proxy for death in end-stage renal disease patients was used[18]. The use of this proxy indicator may be subject to misclassification error. However, this method has been validated and used frequently[31,32]. Further, one other study has demonstrated statistically significant increases in mortality with elevated PTH levels (>110 pg/mL) in CKD stage 3 and 4 patients, which is consistent with our results[10].

Observational studies such as this are designed to demonstrate associations rather than causality.

Among pre-dialysis CKD patients without VDRA therapy, SHPT appears to be associated with significantly higher health care resource utilization and total health care costs and higher risk of initiation of dialysis or death compared with the CKD patients without SHPT. Further investigation is required to validate these associations and to determine the impact of early treatment of selective VDRA therapy in pre-dialysis CKD patients with SHPT.

Conclusion

SHPT in pre-dialysis CKD patients is associated with significantly greater healthcare costs, inpatient hospitalizations, and a faster rate of disease progression compared to pre-dialysis CKD without SHPT. Since observational studies are designed to demonstrate associations, further investigation is required to confirm these findings.

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