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ORIGINAL RESEARCH

Health Care Costs in Patients with and without Secondary Hyperparathyroidism in Spain

Enrique Alonso-Perez · Carles Forné · Marco Soro · Marta Valls · Anton-Giulio Manganelli · Jose M. Valdivielso

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ABSTRACT

Objective: To analyze the economic burden of secondary hyperparathyroidism (sHPT) in Spain by quantifying differences in costs of pharmacological treatments and associated cardiovascular events (CVE) between renal patients with and without sHPT.

Methods: We used data collected in the NEFRONA cohort study and obtained treatment and CVE costs from the BOT PLUS database and Hospital Discharge Records in the Spanish Health System (CMBD-H), respectively. We examined data from 2445 renal patients followed during 2 years for chronic kidney disease (CKD) progression and 4 years for CVE, stratifying by presence of sHPT. Patient characteristics, administered treatments and CVE were directly extracted from NEFRONA registries. Dosage for each treatment regimen was assumed based on guidelines and multiplied by official unit costs to obtain treatment costs. Costs of CVE were based on ICD-9-CM.

Results: Prevalence of sHPT in the cohort was 65.6% (63.6; 67.6). Average yearly pharmacological costs for patients without sHPT were 610.33€, while costs were 1483.17€ for sHPT patients (average increase of 143.0%). Two hundred three patients registered CVE, resulting in 4-year average costs of 582.57€ for non-sHPT patients compared to 941.87€ for sHPT patients (61.7% average increase). Bivariate analyses considering presence of dialysis, hypercalcemia or hyperphosphatemia and stratified by sHPT showed higher costs for sHPT patients.

Conclusions: These results show that sHPT is associated with substantially higher costs of both, pharmacological treatments and associated CVEs. Preventing the development of sHPT with early management in the course of CKD could possibly lead to better health outcomes

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E. Alonso-Perez · A.-G. Manganelli
CRES, University Pompeu Fabra, Barcelona, Spain

C. Forné
Department of Basic Medical Sciences, University of Lleida, Lleida, Spain

C. Forné
Heorfy Consulting, Lleida, Spain

M. Soro
Vifor Pharma Global HEOR, GPMA, Glattbrugg, Switzerland

M. Valls
Vifor Pharma, Barcelona, Spain

A.-G. Manganelli
EADA Business School, Barcelona, Spain

J. M. Valdivielso (✉)
Vascular and Renal Translational Research Group, IRBLleida, Lleida, Spain
e-mail: josemanuel.valdivielso@udl.cat

and cost balance for health care systems.**Keywords:** Chronic kidney disease; Secondary hyperparathyroidism; Cost analysis; Cardiovascular; NEFRONA cohort

Key Summary Points
Why carry out this study?
Secondary hyperparathyroidism (sHPT) is a common consequence in chronic kidney disease (CKD) patients, leading to potentially higher treatment costs
sHPT is related to a higher risk of suffering cardiovascular events that could increase health care costs
What was learned from the study?
The results from analyzing data in a cohort study suggest that pharmacological costs and cardiovascular events imply a twofold increase in the economic burden for sHPT patients in Spain
Treatments for sHPT patients supposed higher costs consistently across all comorbidity comparisons compared to non-sHPT patients
Early CKD management and avoiding the development of sHPT may imply costs offsets for the healthcare systems

INTRODUCTION

Chronic kidney disease (CKD) is a notable public health problem, recognized as one of the most important chronic non-communicable diseases [1] and identified as a major medical priority in recent years by the World Health Organization [2]. Patients with CKD have a significant risk of health complications that generally contribute to increased disease burden [3–5]. Secondary hyperparathyroidism (sHPT) is a common condition in patients with CKD, and it is characterized by parathyroid gland hyperplasia and excessive secretion of parathyroid hormone (PTH) [6, 7]. Entailing alterations in serum calcium, phosphate, vitamin D and FGF23, sHPT is associated with bone and mineral metabolism disorders, and it is caused by chronic kidney disease [8, 9]. It is a severe condition with a prevalence of 77.9% among the CKD population in Spain and also related to CKD progression [10]. sHPT is typically associated with increased morbidity and mortality in CKD patients, leading to an increased incidence of cardiovascular events (CVEs) [11–14]. These complications result in higher hospitalization rates and a substantial increase in medical costs, with the subsequent economic burden [15, 16]. The surge in health care resource utilization raises concerns about the costs of treating sHPT and the impact on the sustainability of health care systems.

Pharmacological treatment approaches for sHPT include the use of vitamin D analogs, calcimimetics and phosphate binders to act on resetting the physiological mineral homeostasis [17]. These are mainly categorized as bone and mineral metabolism treatments (BMM) [18]. Looking specifically at active vitamin D analogs, unwanted but common side effects of their use are episodes of hypercalcemia and, less frequently, also hyperphosphatemia, which can lead to serious adverse effects and additional costs [19]. To adequately characterize the economic burden of sHPT in patients with renal disease, it is crucial to consider not only direct pharmacological costs but also the associated costs of managing clinical complications that occur as a consequence of the disease. Previous international studies have analyzed the association of sHPT and increased healthcare costs, estimating treatment costs through literature reviews or administrative claims databases [20–26]. These studies reported worse clinical outcomes and a relevant increase in costs associated with sHPT patients. However, and to the best of our knowledge, the additional economic burden generated by sHPT in CKD patients with real world data has not been described in the literature. Therefore, the current article aims to quantify the health care resource utilization due to health outcomes and treatment patterns in

the Spanish setting, based on data collected in the prospective NEFRONA study.

The main aim of this study was to analyze the economic burden of sHPT by quantifying the differences in costs of pharmacological treatments and associated CVEs between patients with and without sHPT in Spain. Moreover, it also intended to investigate associations between related underlying conditions and the possible magnification effect on health care costs in sHPT population.

METHODS

Data Sources and Study Design

This is a descriptive study on clinical and cost data from a cohort of CKD patients related to the NEFRONA study. This included 2445 CKD patients who were followed during 4 years for CVEs. Additionally, an intermediate follow-up at 2 years collected CKD progression and atheromatosis burden. The NEFRONA study was a multicenter, observational, prospective cohort study based on a primary care registry of nephrological data taken from the Spanish province of Lleida, and its registry methods and results have been properly described in previous publications [27, 28]. In short, patients between 18 and 75 years in different CKD stages were recruited from 2009 to 2012. Demographic characteristics of patients and data related to comorbidities and clinical parameters were recorded at baseline. Patients completed a follow-up period of 4 years, with periodic data collections including CVEs (fatal and non-fatal) and death from other causes. Data on CVEs were collected by physicians using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The study was approved by the local ethics committees, and all included patients signed an informed consent. We selected individuals with a valid response for the variable collecting information on the sHPT condition. Patients with sHPT were defined as subjects with PTH levels over the recommended Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [29] or treated with PTH-reducing agents (cinacalcet or active vitamin D compounds). Similarly, hypercalcemia was defined as blood calcium levels > 10 mg/dl, and hyperphosphatemia was defined as blood phosphate levels > 4.5 mg/dl.

Economic Evaluation and Perspective of the Analysis

To determine the consequences of sHPT in economic terms, the current study included subsequent stratified analyses, comparing costs between sHPT groups regarding differences in CKD stages and presence of related conditions such as hypercalcemia and hyperphosphatemia. Indirect medical costs and productivity losses were not considered since they were outside the scope of this analysis. The analysis was performed from the perspective of the Spanish National Health Service.

Direct Pharmacological Costs

Information on pharmacological treatments was collected as dichotomous variables at the time of recruitment for every patient in the NEFRONA study. The database recorded the use of specific drugs. Details about dosage or treatment regimen were not included; hence, posology from each drug's Summary of Product Characteristics (SmPC) was assumed as the dosage for the analysis. To assess the accuracy of the data, we reviewed official guidelines and treatment protocols, although they do not specify use of explicit drugs but provide recommendations on what pharmacological group should be used for each treatment [30–33]. Aligned with this, we proceeded to employ the drug use registries in the NEFRONA study to determine pharmacological costs. Drugs were classified in four treatment groups, with some subgroups for certain diseases: lipid-lowering (statins), antidiabetics (metformin; cost of insulin was insignificant and therefore not added to the total cost), antihypertensives (angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers, calcium antagonists and diuretics) and bone and mineral metabolism (BMM)-related treatments. The latter group constitutes the main treatment for

sHPT, and the stepped approach recommended by Spanish guidelines starts with phosphate binders (calcium and non-calcium based) followed by active vitamin D compounds (including calcitriol and paricalcitol) and cinacalcet in patients with dialysis [34]. Accordingly, BMM was divided into these subgroups.

Unit costs for each treatment were extracted from BOT PLUS, the official drugs database from the General Council of the Official College of Pharmacists in Spain [35]. We used list-prices for retail drugs and ex-factory prices for drugs dispensed in hospital pharmacy services, all in 2019 euros (€). Certain retail drugs are subject to copayment; nonetheless, we did not consider it in our analysis [36]. Unit costs were multiplied by the assumed posology in every drug; hence, we could systematically attribute resource utilization to pharmacological treatments (Supplementary Table 1). After pharmacological costs for each treatment group were measured, they were aggregated to average cost per patient/year for each drug and condition.

Cost of Cardiovascular Events

Cost of events was determined based on the registries of CMBD-H (Spanish acronym for Minimum Basic Hospital Data Set) in the NEFRONA study. These are the standard collection registries for morbidity and hospitalization care data in Spain, which adhere to the ICD-9-CM coding system until 2015 and ICD-10-CM from 2016 onwards, allowing for international comparability [37]. The database includes costs for every CVE reported by the physician's follow-up. In the specific case of some fatal CVE, ICD-9-CM codes for associated costs in dialysis patients were not identified; therefore, the codes were assumed according to fatal CVE from a study on cause of death with reduced kidney function [38]. This analysis was performed with epidemiological data from a Canadian CKD patient registry. Its data source and methodology are similar to the current study, hence resulting in an appropriate comparison. Likewise, the distribution of fatal CVE for non-dialysis patients was obtained from the United States Renal Data System (USRDS) [39] as it is an accurate and detailed public source and considers that the age-standardized rate of disability-adjusted life years for cardiovascular diseases attributable to impaired kidney function is similar between the US and Europe [1]. CMBD-H costs were adjusted by inflation (Spanish Consumer Price Index), since December of the first reported year (2015) until December 2019. We included all the registered CVEs and their costs in the analysis (supplementary table 2).

Costs for CVEs were measured by average cost per patient over the 4 years of follow-up, thus considering the whole follow-up period available in the database.

Statistical Analysis

We used descriptive statistics to examine clinical information and background characteristics of the study population. Quantitative variables were expressed as median values and their first and third quartile (Q1; Q3), whereas qualitative variables were expressed as frequencies and percentages. Group comparisons by presence of sHPT were performed by means of the Mann-Whitney *U* test or the chi-squared test. A significance level of 0.05 was accepted. Mean healthcare costs per patient were estimated by type of resource or treatment group. The analysis was performed with the R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Sample Characteristics

The analysis included 2445 CKD patients of the NEFRONA study population, of which 2175 (89%) had available data to determine the presence or absence of SHPT. Table 1 provides a summary of the patient characteristics in the cohort with a bivariate analysis depending on the presence of sHPT (34.4% of patients without and 65.6% with, respectively). The majority of patients were male, and the median age was

Table 1 Patient characteristics depending on the presence of secondary hyperparathyroidism

Patient characteristics	sHPT no *n* = 748	sHPT yes *n* = 1427	*p* value
Gender, *n* (%)			0.032
Men	478 (63.9%)	843 (59.1%)	
Women	270 (36.1%)	584 (40.9%)	
Age at the basal visit (years), median [*Q*1; *Q*3]	60.7 [49.6; 67.7]	61.3 [48.9; 68.2]	0.967
Hypertension, *n* (%)			
No	75 (10.0%)	120 (8.4%)	
Yes	673 (90.0%)	1307 (91.6%)	0.240
CKD stage, *n* (%)			< 0.001
CKD-3	341 (45.6%)	411 (28.8%)	
CKD 4–5	196 (26.2%)	555 (38.9%)	
Dialysis	211 (28.2%)	461 (32.3%)	
Hypercalcemia, *n* (%)			0.329
No	644 (86.6%)	1246 (88.1%)	
Yes	100 (13.4%)	168 (11.9%)	
Hyperphosphatemia, *n* (%)			< 0.001
No	556 (75.1%)	932 (66.6%)	
Yes	184 (24.9%)	467 (33.4%)	
Treatment with calcitriol/paricalcitol, *n* (%)			< 0.001
No	748 (100.0%)	981 (68.7%)	
Yes	0 (0.0%)	446 (31.3%)	
Treatment with cinacalcet, *n* (%)			< 0.001
No	748 (100.0%)	1,185 (83.0%)	
Yes	0 (0.0%)	242 (17.0%)	
Treatment with phosphate binders, *n* (%)			< 0.001
No	508 (67.9%)	817 (57.3%)	
Yes	240 (32.1%)	610 (42.7%)	
Observed event, *n* (%)			< 0.001
Censored	501 (67%)	824 (57.7%)	
CV	49 (6.6%)	134 (9.4%)	
Non-CV death	28 (3.7%)	68 (4.8%)	
Kidney transplant	170 (22.7%)	401 (28.1%)	

sHPT secondary hyperparathyroidism, *Q*1 (3) quartile 1 (3), *CKD* chronic kidney disease, *CV* cardiovascular

Table 2 Annual average pharmacological costs of treatment, characterized by presence of secondary hyperparathyroidism, hypercalcemia or hyperphosphatemia

Pharmacological costs	Secondary hyperparathyroidism				Hypercalcemia				Hyperphosphatemia			
	No		Yes		No		Yes		No		Yes	
	Cost	%	Cost	%	Cost	%	Cost	%	Cost	%	Cost	%
(a) Antidiabetic	1.09€	0.2%	0.71€	0.1%	0.89€	0.1%	1.26€	0.1%	1.12€	0.2%	0.47€	0.0%
(b) Statins	21.26€	3.5%	22.52€	1.5%	21.68€	1.9%	23.27€	2.6%	22.63€	3.2%	19.96€	1.0%
(c) Antihypertensives	135.49€	22.2%	145.97€	9.8%	142.05€	12.6%	139.55€	15.3%	137.49€	19.7%	152.13€	7.2%
(d) Bone and mineral metabolism	452.49€	74.1%	1313.97€	88.6%	960.98€	85.4%	746.38€	82.0%	535.52€	76.9%	1925.13€	91.8%
Calcitriol/paricalcitol	0.00€		223.62€		135.27€		109.30€		97.24€		217.94€	
Cinacalcet	0.00€		389.65€		238.75€		182.60€		133.47€		475.61€	
Phosphate binders	452.49€		700.70€		586.96€		454.49€		304.80€		1231.58€	
Total pharmacological costs ((a) + (b) + (c) + (d))	610.33€	100.0%	1483.17€	100.0%	1125.60€	100.0%	910.46€	100.0%	696.76€	100.0%	2097.69€	100.0%

very similar in both groups. Patients with sHPT were also more likely to present hyperphosphatemia, while no statistical differences were found regarding incidence of hypercalcemia. In addition, the sHPT group had more patients treated with calcitriol/paricalcitol, cinacalcet and phosphate binders. Furthermore, patients in the sHPT group were more likely to suffer a CVE.

Direct Pharmacological Costs

Table 2 displays direct pharmacological costs stratified by presence of sHPT and the additional stratification by presence of hypercalcemia or hyperphosphatemia. Results show that average annual costs of treatments for patients with sHPT were more than double (143.0% higher) compared to patients without sHPT. In both groups the main components of costs were BMM treatments to a great extent, representing a larger share in the sHPT group. Specifically, in the latter group phosphate binders accounted for more than half of the BMM treatment costs (53.3%), followed by cinacalcet (29.7%) and calcitriol/paricalcitol (17.0%). On the other hand, patients with hypercalcemia exhibited 19.1% lower pharmacological costs than those without hypercalcemia. Finally, annual average cost was three times larger (201.1%) in patients with hyperphosphatemia compared to those without the disease.

When performing stratified analyses with sHPT presence and dialysis, hypercalcemia or hyperphosphatemia, pharmacological costs were always higher in the patient groups with sHPT (Fig. 1). Overall, the largest costs were for patients with dialysis and presence of sHPT and for patients with hyperphosphatemia and also sHPT. Patients on dialysis, which involved 30.9% of the study population, had higher costs than the group without dialysis. Furthermore, stratified analyses in groups with and without hypercalcemia also showed higher costs for sHPT patients, particularly the largest difference across all groups (63.9% patients with hypercalcemia). When compared by presence of hyperphosphatemia, both groups showed higher costs for patients with sHPT (61.7%

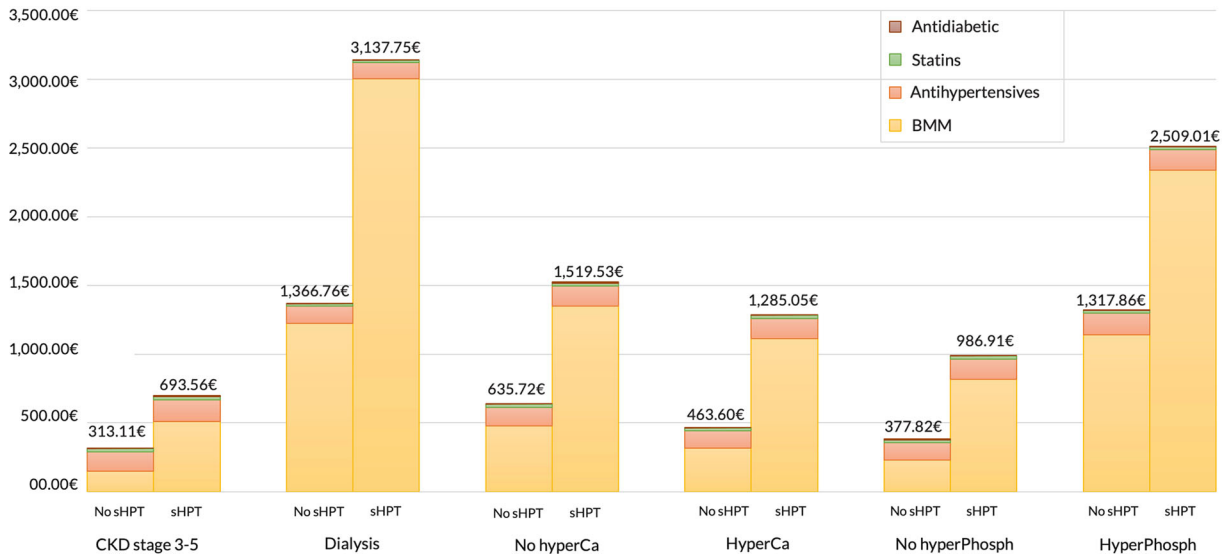

Fig. 1 Distribution of annual average pharmacological costs in groups with and without CKD dialysis, hypercalcemia and hyperphosphatemia, stratified by sHPT. The purpose of this figure is to compare the differences in costs considering the presence of sHPT across several comorbidities. *CKD* Chronic Kidney Disease, *sHPT* secondary Hyperparathyroidism, *HyperCa* hypercalcemia, *HyperPhosph* hyperphosphatemia, *BMM* Bone and Mineral Metabolism

Table 3 Average costs for CVEs in 4 years, depending on the presence of dialysis, hypercalcemia and hyperphosphatemia, stratified by sHPT

Secondary hyperparathyroidism	Dialysis		Hypercalcemia		Hyperphosphatemia		Total average
	No	Yes	No	Yes	No	Yes	
No	519.72€	742.52€	559.30€	427.10€	434.97€	875.29€	582.57€
Yes	902.56€	1,024.25€	992.39€	640.09€	905.33€	1,060.13€	941.87€
Total average	719.57€	927.84€	811.84€	539.64€	706.77€	974.79€	

hyperphosphatemia and 47.5% non-hyperphosphatemia).

Cost of Cardiovascular Events

A total of 203 (8.3%) patients were registered with a CVE (fatal and non-fatal). Acute myocardial infarction, angina pectoris and stroke represented the most common ones, accounting for 16.7%, 13.8% and 13.8% of the total CVEs, respectively. However, events with the highest unit costs were stent/bypass without pain, subarachnoid hemorrhage and abdominal aortic aneurysm.

Results on average costs of CVEs showed that patients suffering sHPT consumed 61.7% more health care resources than those without sHPT (Table 3). The bivariate analysis regarding CKD stage shows that CVE costs were 28.9% larger for dialysis than non-dialysis patients. Furthermore, the stratified analysis resulted in higher costs for sHPT compared to non-sHPT in all CKD stages. On the contrary, average costs were 33.5% lower for patients with hypercalcemia compared to patients without it. Nevertheless, when stratifying by sHPT, both groups sustained higher costs when sHPT was present. Finally, presence of hyperphosphatemia

resulted in 37.9% higher CVE costs for the sHPT compared to non-sHPT group.

DISCUSSION

Presence of sHPT, a common condition in CKD, leads to an increase in mortality and morbidity in CKD patients, leading to an increased incidence of cardiovascular events (CVEs). Together with the increased disease burden, the presence of sHPT also contributes to elevated costs for health care systems. Consequently, in this study we investigated the potential economic consequences of sHPT by quantifying the health care resource utilization in a cohort of CKD patients in Spain. In addition, we not only estimated total treatment costs for sHPT patients, but also compared them to costs for other CKD patients without sHPT, providing a new perspective in terms of quantifying the additional economic burden with observational cohort data.

Our analysis reveals a high prevalence of sHPT in CKD patients without past cardiovascular events, which is consistent with results in previous studies [10, 40, 41]. The main result of our study is that presence of sHPT entails a twofold increase of health care resource utilization compared to patients in absence of sHPT. Specifically, direct pharmacological costs were more than double for patients with sHPT. These results are consistent across different analyses, repeatedly reporting higher costs for sHPT patients comparing presence of dialysis and hyperphosphatemia considered as aggravating factors, the latter causing a threefold increase. Contrarily, patients with hypercalcemia (another complication often associated with some of the treatments used for sHPT) had lower pharmacological costs, basically due to a potential decrease in some treatments related to BMM. This might be due to the known effect of cinacalcet, which decreases calcium levels [42], and the reluctance of nephrologists to administer active vitamin D compounds to patients with high calcium levels as the these treatments can further increase them [43]. The decrease in phosphate binder expenses in the hypercalcemia group is due to a lower incidence of hyperphosphatemia (26.9% vs. 29.2% in the normocalcemia group), the main indicator for prescribing them. In any case, when stratifying hypercalcemia groups by the presence of sHPT, we observe that costs of treatments are always higher in patients with sHPT compared with patients without it. Our findings are consistent with previous studies in the US [20, 21, 24, 26], Italy [22, 23], Ecuador [25] and UK [16]. Moreover, results reveal substantial differences regarding BMM drug costs, particularly phosphate binders, probably due to the recommendation of its use in the Spanish guidelines if control of phosphatemia cannot be achieved by dietary restrictions [34]. These cause a large increase in pharmacological costs in sHPT patients, suggesting that earlier control of sHPT could significantly reduce health care costs.

Overall, a number of publications have provided similar amounts in terms of unit costs for CVEs; hence, data from the NEFRONA study can be considered robust and our results consistent [16, 21, 44, 45]. Our findings reveal that the averaged CVE cost after 4 years is > 60% higher for patients with sHPT compared to those without sHPT in Spain. Likewise, associated CVE costs were considerably higher for sHPT groups, since all analyses stratifying by dialysis, hypercalcemia and hyperphosphatemia resulted in more than doubled costs compared to absence of sHPT. Previous evidence shows that sHPT is associated with incremented cardiovascular risk [46, 47]. Moreover, a recent study with the exact same NEFRONA cohort found clinically relevant independent effects of sHPT presence on CVE incidence while controlling for known risk factors as potential confounders [48]. The consistency of these results, together with our findings, suggest that development of sHPT is a steady independent contribution to healthcare costs, posing it as a threat in terms of economic burden.

The main strength of our analysis is the completeness of the data achieved by analyzing clinical data collected in the NEFRONA cohort study. The characteristics of the study, based on a multicentric registry with a high number of patients, provide enough robustness to consider our results externally valid. To the best of our knowledge, no other studies have yet provided a comparative analysis of healthcare resource

utilization for sHPT patients with observational data in Spain; hence, our study complements previous findings by quantifying cost differences in sHPT patients vs. non-sHPT patients.

The findings of this study have to be seen in light of some limitations. First, we did not have actual dosing patterns of the medications, so we assumed the dose used was in line with the recommended package leaflet throughout the whole treatment. This assumption does not consider non-adherence to treatment; nonetheless, applying adherence percentages would imply adding more assumptions that could complicate calculations. Moreover, our methodology estimates the maximum costs for the system, providing crucial information for decision-makers. Second, pharmacological costs were measured in cost/year, which could lead to potential bias regarding differences in treatment periods between patients. Although multiplying treatment costs by the follow-up time was considered, this would generate a heterogeneous sum of costs with differences in follow-up periods across patients and not capturing treatment changes. Similarly, CVE costs were measured in cost for the 4-year study period. A measure of event costs divided by the follow-up time was considered; however, this method would lead to higher costs for patients suffering an event shortly after the start of the follow-up. Consequently, and assuming the implied limitations, it was considered that reporting annual pharmacological costs and 4-year CVE costs was the best approach. Third, this analysis did not consider parathyroidectomy. Although it is indicated for refractory sHPT [49], in Spain it is a marginal procedure seldom implemented anymore. As it was not performed in patients from the NEFRONA cohort, we lacked data in our study. Fourth, we did not have the ICD-9 for the fatal cardiovascular events, so the type of event was estimated based on the incidence of events on another database. Similarly, we lacked data on medical visits. Fifth, in the CVE costs analysis we did not test the independent effect of sHPT, where there could be risk factors acting as confounders in the sHPT group such as CKD stage, diabetes or smoking status. Nevertheless, previous research proved sHPT independence on increasing CVE risk in the same NEFRONA cohort [48], which can be assumed to be similar in our analysis since the same data were used. Despite the limitation, we assumed that sHPT presence has an independent effect on increasing CVE costs. Finally, our study only includes the short-term perspective of the National Health Service. This scope focuses on direct costs but excludes other categories such as indirect treatment costs, follow-up costs or productivity loss. Our analysis was restricted to the cost availability in the NEFRONA study, albeit further studies with the inclusion of indirect costs, a societal perspective and future treatment costs would provide additional valuable information on cost-effectiveness and potential money-saving.

CONCLUSIONS

This study shows that sHPT is associated with twofold higher costs of pharmacological treatments as well as larger costs for associated CVEs. Our analysis is consistent with previous findings in international studies, demonstrating the same results in Spain. Notably, findings suggest that preventing the development of sHPT with early management in the course of CKD could possibly lead to better health outcomes and cost balance for health care systems, since patients without sHPT consistently seem to have lower health care costs. Furthermore, this research is a contribution in terms of comparative cohort analysis, by providing exact quantifications of cost differences between patients with and without sHPT with observational data. Nonetheless, although showing that resource utilization is higher in sHPT patients, it is crucial to evaluate these higher costs jointly with health outcomes to assess cost-effectiveness of treatments. Hence, in addition to quantifying the economic burden of sHPT, future studies are needed to determine the effectiveness of these treatments and their associated costs.

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Compliance with Ethics Guidelines. The NEFRONA study received protocol approval from the local ethics committee of the Hospital Arnau de Vilanova (Lleida, Spain). All subjects provided informed consent to participate in the study. The study and our subsequent analysis were performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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