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ORIGINAL RESEARCH

Cost-Effectiveness and Clinical Outcomes of Secondary Hyperparathyroidism Treatments in Patients with Chronic Kidney Disease

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Abstract

The study addresses the challenge of treating secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD) patients, focusing on the cost-effectiveness of surgical versus pharmacological interventions. Conducting a retrospective analysis on 152 CKD patients with SHPT at the Third People's Hospital of Chengdu, the study matched 80 patients into two groups: 40 undergoing parathyroidectomy with autotransplantation (PTX + AT) and 40 treated with calcimimetics. PTX + AT was more effective in alleviating symptoms, particularly bodily pain, and demonstrated greater cost-effectiveness over a long-term period compared to calcimimetics. This was especially significant in patients with PTH levels > 1800 pg/mL and hyperphosphatemia. Despite similar initial costs, PTX + AT led to a substantial decrease in expenses during the 2–5 years post-treatment period, PTX + AT results in an ICER of -RMB 26.71/QALY for the first post-treatment year and -RMB-111.9k/QALY for the 2–5 year period, indicating cost-effectiveness with reduced long-term costs. The study also found an increased economic burden in managing patients with hyperphosphatemia. Surgical intervention (PTX + AT) is advocated as the primary treatment strategy for severe SHPT in CKD patients, owing to its long-term economic and clinical advantages. The results underscore the need for a severity-based approach in treating SHPT.

Keywords Secondary hyperparathyroidism · Cost-effectiveness · Calcimimetics · Parathyroidectomy with autotransplantation

Introduction

Secondary hyperparathyroidism (SHPT) is a complication often resulting from renal disease, characterized by the hyperactivity of the parathyroid glands. Two primary treatment strategies are commonly employed: pharmacological intervention with cinacalcet, and surgical treatment via parathyroidectomy. Each strategy presents distinct advantages and challenges, thus the optimal treatment choice should be individualized based on each patient's unique circumstances.

While both cinacalcet and surgical interventions have demonstrated effective therapeutic outcomes in SHPT patients, the costs associated with each vary significantly across different countries and regions. This study aims to investigate the direct medical costs affiliated with SHPT treatments and to identify contributing factors to cost escalation. The insights derived from this study could assist in the informed decision-making process, ensuring that treatment strategies are not only clinically effective but also economically sustainable for the patient and healthcare provider.

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Methods

Study Design

A retrospective study was conducted on the medical records of patients diagnosed with secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD) at the Third People's Hospital of Chengdu. The study reviewed records from January 2016 to January 2021, encompassing 152 patients initially. Established in July 1941, the Third People's Hospital of Chengdu is a national tertiary A-level comprehensive hospital, with 2200 beds and annually serves more than 1.54 million outpatients, admits over 64,000 inpatients, and performs more than 38,000 inpatient surgeries. This retrospective analysis was approved by the Medical Ethics Committee of the Third People's Hospital of Chengdu (Ethical Approval Number: 2022-S-78).

Data Collection

In this study, from an initial pool of 152 chronic kidney disease patients with secondary hyperparathyroidism, we selected 80 patients using propensity score matching, ensuring balanced groups based on demographics, clinical indicators, and disease severity. The patients were divided into two groups: 40 in the PTX + AT (Parathyroidectomy and Autotransplantation) group and 40 in the Calcimimetics group. This matching considered factors such as age, gender, kidney function, PTH levels, and comorbidities. Data on prescriptions and parathyroidectomy procedures were coded according to ICD-9-CM and ICD-10-CM standards. The Calcimimetics group comprised patients who either opted out of or were not recommended for surgery. The balance of baseline characteristics between the groups was verified with standardized mean differences to ensure the study's methodological reliability.

Inclusion Criteria and Exclusion Criteria

The inclusion criteria were as follows:1.iPTH > 800 pg/ml; 2.Patients were required to have at least 2 years of continuous data; 3.Neck ultrasound detect at least one enlarged parathyroid glands; 4.Patients signed the informed contents. Patients were excluded for 1.Complicated with a malignancy, pregnancy, coagulation disorders or serious chronic illnesses; 2.A follow-up period of < 2 years; 3. Incomplete clinical information;4. Patients had received prior ablation therapy.

SHPT Treatments

All patients were treated with regular hemodialysis (three times a week, four hours each time), and patients with hypercalcemia before dialysis were treated with low-calcium dialysate, while patients with hyperphosphatemia were treated with phosphate binder. Patients in the calcimimetics group were treated with the following protocol according to the iPTH test results: calcimimetics 25 ~ 100mg/qd. Patients in the PTX + AT group received hemodialysis on the day of operation and the second day after operation, total parathyroidectomy and autotransplantation were performed intraoperatively, all the parathyroid glands removed were confirmed histopathologically. Vital signs were routinely monitored after the operation, serum calcium, serum phosphorus and iPTH were detected. Calcitriol/paricalcitol, calcium carbonate and/or calcium gluconate were injected to maintain calcium > 1.8 mmol/l as appropriate. Intravenous calcium supplementation was slowly reduced and then discontinued.

Pain Assessment

We evaluated the impact of the treatment on pain using the 'Bodily Pain' scale of the SF-36 Health Survey, and using a formula to convert SF-36 scores to Short Form 6 Dimensions (SF-6D) utility values. The 'Bodily Pain' scale assesses pain intensity and its interference with normal activities over the past four weeks. The change in scores was analyzed to determine the treatment's effectiveness in pain relief and improvement in daily functioning. A lower score on the 0–100 scale of the SF-36 'Bodily Pain' section indicates greater pain severity and more significant limitations in physical functioning.

Statistical Analysis

We used propensity score matching to create comparable treatment groups and controlled for confounding factors in the statistical analysis. For numerical variables, we applied parametric or non-parametric tests as appropriate after assessing the distribution of the variables. For categorical variables, we used the $\chi 2$ test.

In addition to the primary cost outcome, we conducted a multivariable regression analysis to identify factors associated with higher treatment costs. All tests were two-sided and a P-value < 0.05 was considered statistically significant. The statistical software utilized for data processing was SPSS 20.0.

Result

Table 1 Sample characteristics

Patient characteristics	PTX + AT n = 40	Calcimimetics n = 40	p value
Gender, n (%)			0.502
Men	22(55%)	19(47.5%)	
Women	18(45%)	21(52.5%)	
Age at the basal visit (years), median [Q1, Q3]	45(35,57)	50(39,60)	0.059
Hypertension, n (%)			0.692
No	4(10%)	3(7.5%)	
Yes	36(90%)	37(92.5%)	
Diabetes, n (%)			0.745
No	35(87.5%)	34(85%)	
Yes	5(12.5%)	6(15%)	
hyperlipidemia, n (%)			0.644
No	3(7.5%)	2(5%)	
Yes	37(92.5%)	38(95%)	
Hypercalcemia, n (%)			0.556
No	35(87.5%)	36(90%)	
Yes	5(12.5%)	4(10%)	
Hyperphosphatemia, n (%)			0.502
No	24(60%)	27(67.5%)	
Yes	16(40%)	13(32.5%)	
PTH, n (%)			0.501
< 1800 pg/ml	20(50%)	23(57.5%)	
≥ 1800 pg/ml	20(50%)	17(42.5%)	
Bodily Pain(SF-36)	36.84±17.21	40.10±16.95	0.371
Skin Itching, n			0.101
No	18	10	
Yes	22	30	
Skeletal Deformity, n			0.811
No	26	28	
Yes	14	12	
Calcium (mmol/l, x ± s)	2.53±0.22	2,56±0.20	0.556
iPTH(pg/ml, x±s)	1708±645	1777±566	0.578
phosphorus(mmol/l, x ± s)	1.43±0.37	1.47±0.31	0.630

Characteristics of Patients with SHPT

For the entire study population, the median age at basal visit was 48 years, and 48.8% of the patients were female, Most patients had hypertension (91.3%), hyperlipidemia (93.8%), and less than half had diabetes (13.8%), hypercalcemia (17.5%), hyperphosphatemia (48.8%). Median age at time of parathyroidectomy was 45.0 ([Q1; Q3]:35,57). There was no significant difference in patient characteristics between two groups. (Table 1).

Clinical Signs and Symptoms

After treatment, both groups of patients showed varying degrees of improvement in bodily pain, skin itching, and reduction or deformity in height. The analysis reveals a significant difference in post-treatment bodily pain reduction between calcimimetics group and PTX + AT group. PTX + AT group is notably higher than that of calcimimetics group, indicating greater pain alleviation. This difference is statistically significant ($t = 4.87$, $P < 0.001$). Table 2

Test Indicators

One month, six months, and twelve months after treatment, the levels of iPTH and blood calcium in both groups of patients decreased to a certain extent compared to before treatment. One month, six months, and twelve months after treatment, the iPTH and blood calcium levels in the PTX + AT group were significantly lower than those in the calcimimetics group, with a statistically significant difference ($P < 0.001$). Table 3.

Direct Medical Cost

Table 4 summarizes the total direct healthcare costs associated with SHPT in the first postoperative year. Overall, costs amounted to RMB 45.9k (IQR: 28.9k, 69.3k). The distribution of costs across different comorbidities was as follows: diabetes (RMB 1.8k, IQR: 1.1k, 2.4k), hyperlipidemia (RMB 1.1k, IQR: 0.7k,1.8k), hypertension (RMB 6.1k, IQR: 3.3k, 10.0k), and SHPT cost (RMB 3.63k, IQR:

Table 2 Comparison of Clinical Symptom Improvement Post-Treatment in Three Groups of Patients with SHPT

Variability	Bodily pain (SF-36)		Skin itching [Cases (%)]		Skeletal deformity [Cases (%)]	
	before	after Pain Relief	before	after	before	after
calcimimetics	40.10±16.95	66.13±15.54	30	12 (45.0%)	12	6 (15.0%)
PTX + AT	36.84±17.21	80.48±11.37	22	3 (47.5%)	14	8 (15.0%)
t/X^2	4.87		1.61		0.000	
P	0.000		0.204		1.000	

Table 3 Comparison of Post-Treatment Indicators in Two Groups of Patients (x ± s)

	iPTH (pg/ml)			Calcium (mmol/l)		
	1 M Post-Tr	6 M Post-Tr	12 M Post-Tr	1 M Post-Tr	6 M Post-Tr	12 M Post-Tr
calcimimetics	888.00 ± 514.15	815.69 ± 469.45	736.38 ± 508.27	2.34 ± 0.14	2.33 ± 0.12	2.31 ± 0.13
PTX + AT	129.18 ± 96.32	163.54 ± 109.79	247.62 ± 120.91	2.07 ± 0.13	2.17 ± 0.10	2.23 ± 0.11
t	11.22	10.41	7.20	10.23	7.16	3.40
P	0.000	0.000	0.000	0.000	0.000	0.001

1 M Post-Op = one month treatment, 6 M Post-Op = six month treatment, 12 M Post-Op = twelve month post-treatment

Table 4 The cost of two groups during the first year postoperation[Median (IQR)]

Cost	PTX + AT	Calcimimetics
Diabetic	2.2 k(1.5 k,2.5 k)	1.4 k(3.5 k,2.6 k)
hyperlipidemia	1.2 k(0.6 k,1.7 k)	1.1 k(0.7 k,1.8 k)
Hypertension	7.1 k(3.2 k,10.4 k)	5.4(3.5 k,9.3 k)
*SHPT cost	33.9 k(25.1 k,57.0 k)	36.3(25.1 k,57.2 k)
Totle	41.4 k(28.8 k,70.0 k)	45.9(28.9 k,70.8 k)

*SHPT cost included surgical treatment (PTX + AT) or calcimimetics (cinacalcet), calcitriol/paricalcitol, or phosphate binders (calciumacetate, calciumcarbonate, sevelamer hydrochloride/carbonate, or lanthanum carbonate)

25.1k, 57.2k). However, the comparison between different patient groups did not yield a statistically significant difference in the cost (all P > 0.05).

During the follow-up period ranging from 2 to 5 years postoperatively (mean duration: 3.1 ± 0.8 years), a statistically significant reduction in costs was noted in PTX + AT group. The costs associated with the PTX + AT group were RMB 19.9k (IQR: 8.6k, 49.5k), which was significantly lower than the costs incurred by the calcimimetics group RMB 37.8k (IQR: 28.4k,61.2k) (z = -3.531, P < 0.05). Figure 1.

Cost-Effectiveness

Base-case results for the incremental cost-effectiveness between two groups are listed in Table 5. For patients who are the first year post-treatment, PTX + AT conferred a slight increase in quality-adjusted life expectancy (0.09 QALYs), but cost a lower cost RMB-2.4k, resulting in an ICER of RMB -26.71/QALY gained. For patients who are from 2 to 5yr post-treatment, PTX + AT resulted in a significant improvement in clinical outcomes, along with a lower lifetime costs. The incremental costs and QALYs were RMB-17.9k and 0.16, respectively, yielding an ICER of RMB-111.9k/QALY gained.

Table 6 presents a stratified analysis of direct costs according to PTH levels, further divided based on the presence of hypercalcemia or hyperphosphatemia. The data

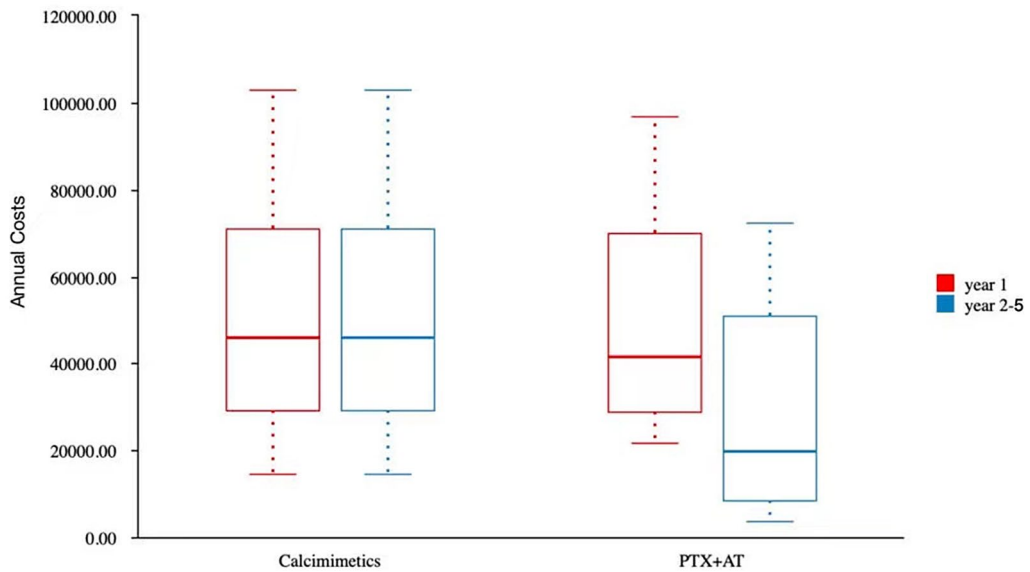

Fig. 1 The cost of two groups during the follow-up period (from 2 to 5yr)

Table 5 Base-Case Cost-Effectiveness Results

	Cost(RMB)	QALYs	Incremental Costs	Incremental QALYs	ICER(RMB/QALY)
1yr post-treatment					
calcimimetics	36.3k	0.70	-2.4k	0.09	-26.7k
PTX + AT	33.9k	0.79			
2yr-5yr post-treatment					
calcimimetics	37.8k	0.71	-17.9k	0.16	-111.9k
PTX + AT	19.9k	0.87			

ICER incremental cost-effectiveness ratio; *QALY* quality-adjusted life-year; Incremental Costs, Cost(PTX + AT) -Cost(calcimimetics); Incremental QALYs, QALYs(PTX + AT) -QALYs(calcimimetics)

Table 6 Direct costs by PTH, hypercalcemia and hyperphosphatemia [Median (IQR)]

Cost	PTH		Hypercalcemia		Hyperphosphatemia	
	< 1800 pg/ml	≥ 1800 pg/ml	No	Yes	No	Yes
PTX + AT	28.9k(27.3k,32.1k)	69.4k(55.0k,81.4k)	33.0k(28.1k,68.8k)	54.8k(49.7k,79.7k)	40.7k(28.9k,68.0k)	68.2k(53.3k,80.1k)
Calcimimetics	31.1k(24.7k,39.98k)	71.6k(61.9k,81.5k)	35.8k(26.0k,55.7k)	74.5k(62.4k,81.0k)	31.1k(24.7k,45.6k)	71.2k(58.3k,81.5)k

revealed that the mean annual costs for patients with PTH levels ≥ 1800 pg/ml were significantly higher, amounting to RMB 71.2k (IQR: 58.0k, 81.5k), than those for patients with PTH levels < 1800 pg/ml, which were RMB 29.1k (IQR: 25.8k, 33.1k). This represented a substantial increase of 245.0%. Additionally, patients diagnosed with hypercalcemia and hyperphosphatemia incurred significantly elevated annual costs compared to those without these conditions ($P < 0.05$).

Cost of Bone and Mineral Metabolism

Upon further stratified analysis of the costs related to bone and mineral metabolism, we identified significant differences in the costs of phosphate binding agents based on PTH levels. It was found that patients with PTH levels ≥ 1800 pg/ml had markedly higher costs [RMB 33.0k (IQR: 26.0k, 41.1k)] compared to those with PTH levels < 1800 pg/ml [RMB 1.1k (IQR: 0.9k, 1.3k)] ($p < 0.05$). Likewise, patients diagnosed with hypercalcemia incurred significantly higher phosphate binding agent costs [RMB 27.3k (IQR: 18.8k, 39.4k)] in comparison to patients without hypercalcemia [RMB 1.3k (IQR: 0.9k, 3.0k)] ($p < 0.05$). A similar pattern was observed among patients with hyperphosphatemia, who experienced increased phosphate binding agent costs [RMB 32.9k (IQR: 22.5k, 40.4k)] relative to those without hyperphosphatemia [RMB 1.0k (IQR: 0.9k, 1.3k)] ($p < 0.05$), but no significant differences were seen in other treatment costs, such as calcimimetics or PTX + AT agent, and calcitriol/paricalcitol agent ($P > 0.05$). Figures 2, 3, and 4.

Multivariable Logistic Regression Analysis

A multivariable logistic regression model was implemented to evaluate the impact of pre-treatment serum calcium, pre-treatment serum phosphate, PTH, gender, treatment group, and payment source on cost (Table 7). Pre-treatment serum phosphate and PTH levels were positively associated with cost. Each unit increase in pre-treatment serum phosphate was associated with an increase in the odds of higher cost by a factor of 33.742 (95% CI: 1.499—759.458, $p = 0.027$). In tandem, each unit increase in PTH amplified the odds of higher costs by a factor of 1.002 (95% CI: 1.001—1.004, $p = 0.004$). There were indications of a relationship between gender, payment source, and cost, although not statistically significant at a conventional level ($p > 0.05$). Females exhibited higher odds of incurring greater costs by a factor of 3.937 (95% CI: 0.902—17.182, $p = 0.068$). Similarly, patients who self-financed treatment demonstrated increased odds of higher costs by a factor of 4.168 (95% CI: 0.975—17.820, $p = 0.054$).(Table 8).

Discussion

The main findings of our study on secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD) patients are as follows: First, we observed that in CKD patients with severe SHPT (PTH > 800), surgical treatment (PTX + AT) was not only more effective in alleviating symptoms, particularly bodily pain, but also proved to be more cost-effective over a long-term period compared to pharmacological management with calcimimetics. Notably, we found that

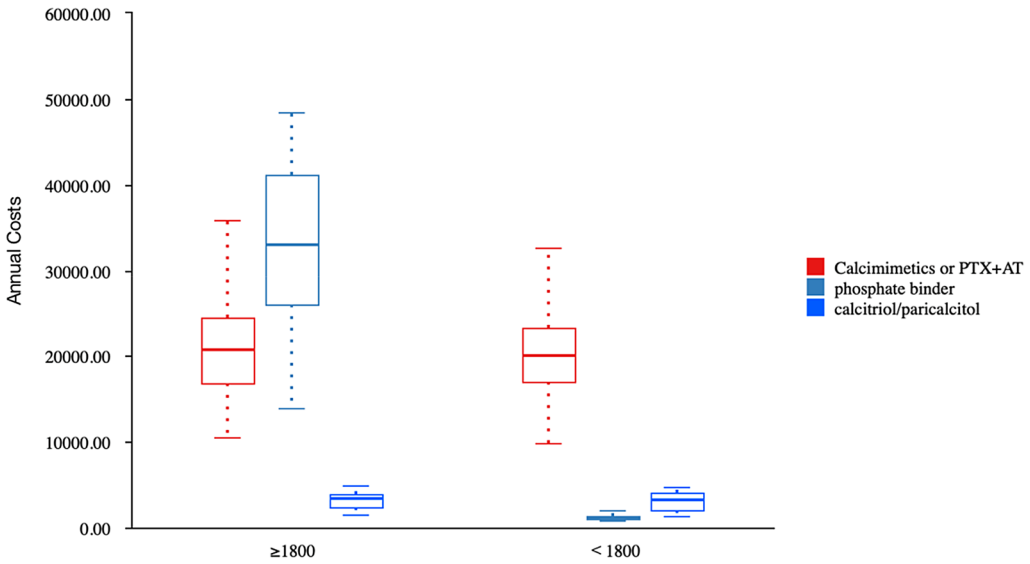

Fig. 2 Differential annual costs of patients: PTH Levels

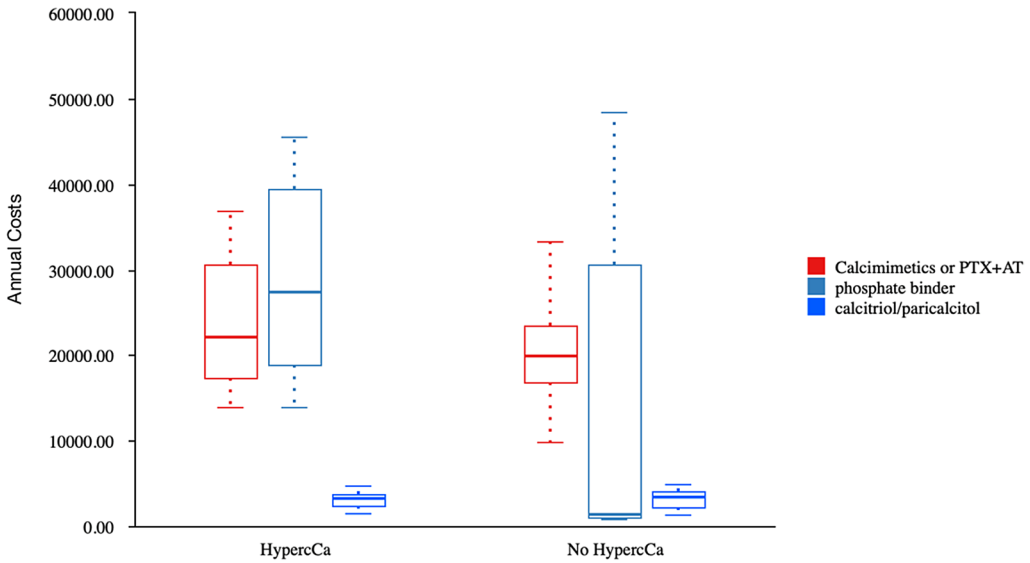

Fig. 3 Differential annual costs of patients: hypercalcemia and non-hypercalcemia

patients with extremely high PTH levels (> 1800 pg/mL) and hyperphosphatemia incurred significantly higher treatment costs, underscoring the efficacy of PTX + AT in such severe cases. The PTX + AT group, despite higher initial costs, experienced a significant reduction in expenses during the 2–5 years postoperative period, in contrast to the sustained costs in the calcimimetics group. Second, our study highlighted the importance of categorizing SHPT patients based on the severity of their condition. This distinction was crucial, as it revealed that the benefits of surgical treatment, both in terms of symptom relief and cost-effectiveness, were particularly pronounced in patients with severe SHPT. This finding provides new insights into the management of SHPT, contrasting with other studies that did not differentiate outcomes based on SHPT severity. Third, the results suggested that for severe SHPT in CKD patients, surgical intervention should be considered as a primary treatment strategy, offering long-term economic and clinical advantages. This represents a significant shift from the common practice of prioritizing medical management for SHPT in CKD, marking a pivotal point in treatment approach considerations. Fourth, our findings indicate that the severity of

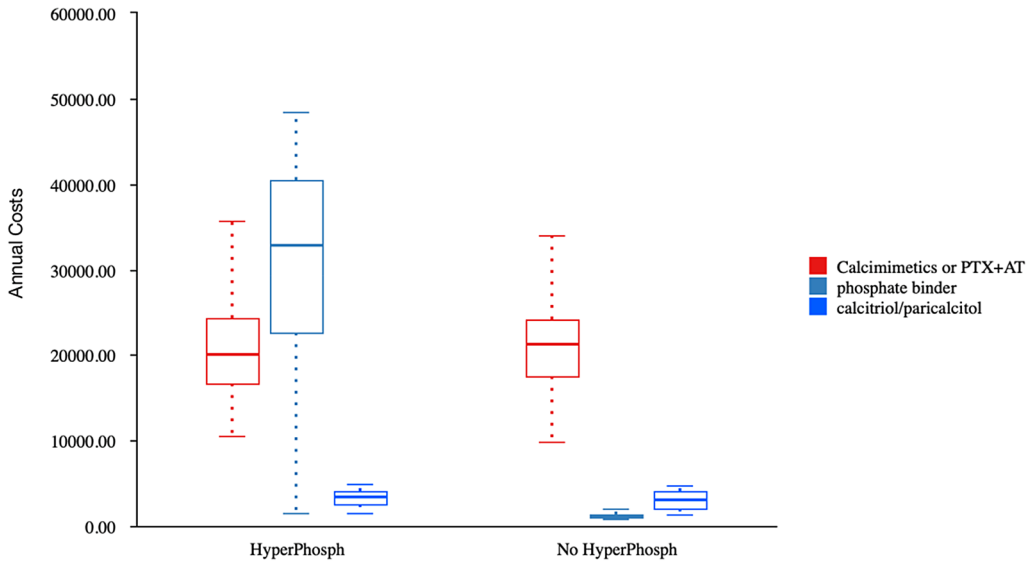

Fig. 4 Differential annual costs of patients: hyperphosphatemia and non-hyperphosphatemia

Table 7 Assignment of variables for factors affecting treatment costs

Variables	Assignment
gender	1 = women; 2 = men
treatment group	1 = PTX + AT; 2 = Calcimimetics
payment source	1 = medical insurance, 2 = self-financed

SHPT should be a key factor in the decision-making process for treatment strategies, underscoring the need for a more tailored approach in managing SHPT in CKD patients. This approach is likely to optimize patient outcomes and resource utilization in healthcare settings.

Previous studies have confirmed that secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) leads to various adverse outcomes, such as bone disease and cardiovascular issues [1–4]. These problems not only affect the quality of life of patients but also increase medical expenses and the risk of mortality. Currently, the treatment methods for SHPT mainly include pharmacological treatment (such as calcimimetics) and surgical procedures (parathyroidectomy) [5–8]. Although drug treatments have lower short-term costs, surgical treatments may be more cost-effective in the long-term. Research indicates that surgical treatment can effectively alleviate symptoms and reduce long-term medical expenses in CKD patients with severe SHPT [7, 8]. However, these studies have not delved deeply into the economic benefits in cases of extremely severe SHPT (such as PTH ≥ 1800 pg/mL). Our study corroborates these findings and adds to them in at least 3 ways: first, we have detailed the economic burden of SHPT patients of varying severity, especially in those with extremely severe SHPT (PTH ≥ 1800 pg/mL),while a 100 pg/mL rise in PTH corresponded to a RMB1,932 increment in annual treatment cost. We found that compared to the current prevalent drug treatments, surgical treatment (PTX + AT) is more cost-effective in the long-term for patients with extremely severe SHPT. Second, our study also highlights the significant increase in treatment costs for patients with hyperphosphatemia, providing new insights into the treatment strategies for this specific group.In our study, we observed that each 1 mg/dL increase in serum phosphate led to a RMB3,279 increment in annual treatment cost.Third, we explored the unique advantage of surgical

Table 8 Results of multivariable logistic regression analysis of factors influencing treatment cost

Model	β	SEx	*z*	Wald χ^2	*p*	OR	95% CI
serum calcium	-2.755	2.094	-1.316	1.731	0.188	0.064	0.001 ~ 3.856
serum phosphate	3.519	1.589	2.215	4.905	0.027	33.742	1.499 ~ 759.458
PTH	0.002	0.001	2.873	8.256	0.004	1.002	1.001 ~ 1.004
Women	1.370	0.752	1.823	3.322	0.068	3.937	0.902 ~ 17.182
PTX + AT	-0.053	0.687	-0.078	0.006	0.938	0.948	0.246 ~ 3.647
self-financed	1.427	0.741	1.925	3.707	0.054	4.168	0.975 ~ 17.820

treatment in alleviating symptoms such as bodily pain, and PTX + AT led to a substantial decrease in expenses during the 2–5 years post-treatment period, PTX + AT results in an ICER of -RMB 26.71/QALY for the first post-treatment year and -RMB 111.9k/QALY for the 2–5 year period, indicating cost-effectiveness with reduced long-term costs. an aspect less discussed in the existing literature.

The lack of significant cost difference between different comorbidities found in this study is an intriguing observation. One might expect different comorbidities to significantly impact treatment costs due to variations in complexity and resource needs.For example, some studies[1, 9] found that comorbidities such as diabetes, hypertension, and hyperlipidemia contribute to increased costs in patients with SHPT, However, our findings suggest otherwise[10–12] [234]. Considering our statistical data, the cost of treatment for patients with SHPT remained relatively stable regardless of the presence of varying comorbidities. This could be attributed to the following possible reasons:1.Comprehensive Treatment Regime: Since SHPT often coexists with other comorbidities in CKD patients, the treatment regimen may have already been optimized to manage these conditions simultaneously, which may result in a negligible difference in treatment cost.2.Effective Management of SHPT: The efficiency of SHPT treatment, be it pharmacological (cinacalcet) or surgical (PTX + AT), could be so high that it could potentially offset the cost incurred by different comorbidities. 3.Lack of Costly Comorbidities: It's also possible that our sample didn't include patients with significantly cost-inflating comorbidities. It's crucial to note that this lack of cost difference doesn't undermine the importance of effective comorbidity management. A patient's quality of life, disease progression, and survival rates are heavily influenced by the management of comorbid conditions.

This study's limitations include its retrospective nature and potential selection bias. Results may not generalize to all SHPT patients due to regional cost variations. Future research should focus on prospective studies, exploring other cost variables, and devising optimal treatment strategies balancing both health outcomes and costs.

In conclusion, the study highlights the significant direct medical costs associated with treating SHPT in CKD patients and identifies specific factors that contribute to increased costs. By understanding these factors, healthcare providers and policymakers can make informed decisions to improve patient outcomes and healthcare cost-effectiveness.

Authors Contributions WenJie Zhang: Formal analysis, Investigation, Methodology, Writing—original draft, Jian Wu: Conceptualization, Writing—review & editing, Hailiang Ren: Data curation, Software, Qianxiu Liao: Data curation, Investigation.

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Data Availability The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Conflict of interest No financial conflicts of interest were reported by the authors WenJie Zhang, Hailiang Ren,Qianxiu Liao,Jian Wu.

Human and Animal Rights and Informed Consent This study was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All procedures performed in this study involving human participants were in line with the ethical standards of the institutional research committee at the Third Hospital of Chengdu and the national research council. Informed consent was obtained from all individual participants involved in the study. Participant data were de-identified and confidentiality was ensured throughout the study and subsequent data analysis process. This study did not involve any animals.

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