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A single-center retrospective cohort study of cinacalcet efficacy in uremic hemodialysis patients: Correlations with changes in parathyroid hormone, calcium and phosphorus over 12 months

Jiebo Huang[1], Yuan Fu[1], Lin Chen[1], Yan Liang[1] and Nie Wu[2]*

[1]Blood Purification Center of Nanjing Pukou District Hospital of Traditional Chinese Medicine, No. 18, Gongyuan North Road, Jiangpu Sub-district, Pukou District, Nanjing 211800, Jiangsu Province, China

[2]Department of Nephrology, Nanjing Pukou District Hospital of Traditional Chinese Medicine, No. 18, Gongyuan North Road, Jiangpu Sub-district, Pukou District, Nanjing 211800, Jiangsu Province, China

Abstract: **Background**: Secondary hyperparathyroidism (SHPT) is a common complication in uremic hemodialysis patients, associated with disordered calcium (Ca) and phosphorus (P) metabolism. The long-term efficacy of cinacalcet (Cin) versus calcitriol (Cal) in achieving composite control of parathyroid hormone (iPTH) and Ca × P product remains unclear. **Objectives**: To compare the 12-month efficacy and safety of Cin versus Cal in treating SHPT and to explore correlations between treatment outcomes and changes in iPTH, Ca and P. **Methods**: This retrospective cohort study included SHPT patients on maintenance hemodialysis from June 2023 to June 2025. After propensity score matching (1:1), 75 patients were assigned to each Cin or Cal group. The primary endpoint was the composite response rate (iPTH ≤ 300 pg/mL and Ca × P < 55 mg²/dL²) at 12 months. Correlation analyses assessed associations between achieving the composite endpoint and changes in biochemical parameters. **Results**: At 12 months, the composite response rate was significantly higher in the Cin group than in the Cal group (42.67% vs. 16.00%, P < 0.001). Cin produced greater reductions in iPTH and P and lower Ca and Ca × P levels (all P < 0.05). Achieving the composite endpoint correlated positively with greater reductions in iPTH (r = 0.453) and Ca (r = 0.463). ΔiPTH was moderately correlated with ΔP (r = 0.604, P < 0.001). Hypocalcemia was more frequent with Cin (16.00% vs. 4.00%, P=0.014), but no serious adverse events led to treatment discontinuation. **Conclusion**: Cin is more effective than Cal in helping uremic hemodialysis patients achieve composite control of iPTH and Ca × P. Therapeutic success correlates with reductions in iPTH and Ca and iPTH decline is closely linked to improved P levels, highlighting the importance of integrated management of SHPT.

Keywords: Cin; Cal; Correlation analysis; Hemodialysis; Secondary hyperparathyroidism

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INTRODUCTION

Secondary hyperparathyroidism (SHPT) is a prevalent and clinically consequential complication observed in individuals with stage 5 chronic kidney disease, particularly those on maintenance hemodialysis. Its prevalence is high and increases significantly with longer dialysis duration (Chan *et al*., 2026; Elhadedy *et al*., 2023). SHPT is not only a central component of mineral and bone disorders but also a key independent risk factor for cardiovascular calcification and increased all-cause and cardiovascular mortality, imposing a heavy burden on patient prognosis and healthcare resources (Haffner and Leifheit-Nestler, 2021; Hiramitsu *et al*., 2023; Tuna *et al*., 2025). The underlying pathophysiology is complex, primarily stemming from Ca and P metabolism, skeletal resistance to PTH and hyperplasia and hyperfunction of the parathyroid glands themselves due to renal failure (Dream *et al*., 2022; Iorga *et al*., 2023). Effectively controlling serum iPTH levels while managing the balance of Ca and P metabolism is a core therapeutic goal for improving long-term outcomes in SHPT patients (Brandenburg and Ketteler, 2022; Magagnoli *et al*., 2024).

Current pharmacological management of SHPT primarily targets two key pathways. On one hand, active vitamin D and its analogs [e.g., calcitriol (Cal)] have long served as foundational therapy by activating the vitamin D receptor (VDR) to directly suppress PTH gene transcription and synthesis in the parathyroid glands (Liu *et al*., 2024; Shigematsu *et al*., 2022; Xiang *et al*., 2022). On the other hand, the calcimimetic Cinacalcet (Cin) represents an innovative agent that allosterically activates the calcium-sensing receptor (CaSR) on parathyroid cell membranes, directly inhibiting PTH secretion without raising serum Ca (Alvarado *et al*., 2022; Gulcan-Kersin *et al*., 2020; Ngamkam *et al*., 2021). However, their long-term impact patterns on key biochemical parameters are fundamentally different. While suppressing PTH, active vitamin D enhances intestinal absorption of Ca and P, often leading to or exacerbating hypercalcemia and hyperphosphatemia, which may increase the risk of vascular calcification. In contrast, Cin reduces iPTH while also lowering P and the Ca-P product (Ca × P), though it may induce hypocalcemia (Wang *et al*., 2025). Although the short-term efficacy of both agents is well established, high-level evidence from strictly controlled comparisons on the more stringent composite endpoint of "achieving both

**Corresponding author:* e-mail: WN943513633@hotmail.com

iPTH target and controlled Ca × P" in long-term treatment remains scarce. Furthermore, SHPT management should not focus solely on reducing a single parameter but should also consider the dynamic changes in key indices (iPTH, Ca, P) during therapy and their relationship with ultimate efficacy (Ruifang *et al*., 2025). Currently, few studies investigate the correlation between the magnitude of reductions in iPTH, Ca and P during treatment and the final composite response rate.

To address this, this study aims to conduct a single-center, retrospective cohort study using propensity score matching (PSM) to minimize baseline confounding bias. It systematically compares the 12-month long-term efficacy and safety of Cin versus Cal in maintenance hemodialysis patients with SHPT. The core focus extends beyond assessing the difference between the two groups in achieving the composite endpoint of "iPTH ≤ 300 pg/mL and Ca × P < 55 mg^2/dL^2". It emphasizes analyzing the correlation between the overall treatment efficacy and the magnitude of change in iPTH, Ca and P over the 12-month treatment period. This aims to provide more robust and detailed evidence for optimizing long-term pharmacological management strategies in SHPT patients and achieving a more comprehensive risk-benefit balance.

Through a rigorously PSM-adjusted retrospective cohort study, this research systematically compares the comprehensive efficacy of Cin versus active vitamin D in treating SHPT and associates treatment outcomes with the longitudinal changes in iPTH, Ca and P. The study provides important evidence-based insights for optimizing long-term pharmacologic management strategies for SHPT.

MATERIALS AND METHODS

Study design

This research constitutes a single-center, retrospective cohort analysis. Clinical data were extracted from the hospital's electronic medical record system for patients who underwent maintenance hemodialysis at the blood purification center between June 2023 and June 2025, were diagnosed with SHPT and received treatment with either Cin or Cal for at least 12 months. Based on the treatment regimen, patients were categorized into the Cin and the Cal. PSM was employed to balance baseline differences, ultimately including 75 patients in each group for analysis. The design and operational workflow are illustrated in figure 1.

Ethical statement

This investigation received approval from the institutional ethics committee of Nanjing Pukou District Hospital of Traditional Chinese Medicine and was conducted in strict compliance with the ethical guidelines outlined in the Declaration of Helsinki and prevailing international standards for biomedical research. As this retrospective study analyzed archived clinical data, the ethics committee approved an exemption from informed consent. All study data were anonymized and participants' privacy and identity were maintained at all times.

Inclusion and exclusion criteria

Inclusion criteria: (1) Receiving regular maintenance hemodialysis (dialysis duration ≥ 3 months); (2) Age ≥ 18 years; (3) Meeting the diagnostic criteria for SHPT: serum iPTH level > 300 pg/mL; (4) Initiating treatment with Cin or Cal as the primary therapy to lower PTH for the first time and continuing treatment for at least 12 months; (5) Complete clinical medical records.

Exclusion criteria: (1) Suffering from primary hyperparathyroidism or parathyroid cancer; (2) Having undergone parathyroidectomy or parathyroid interventional treatment during the study period; (3) Co-existing with a malignant tumor or severe liver dysfunction; (4) Pregnant or lactating; (5) Allergic to any component of the study medication; (6) Documented treatment interruption for more than 1 month during the study period, as verified by monthly prescription refill records, dialysis nursing notes and pill count assessments. Patients with missing follow-up visits without confirmed medication records were also excluded.

Treatment methods

Both groups received standard maintenance hemodialysis treatment (three times per week, four hours per session), with dietary education and the routine use of phosphate binders (primarily Ca-based binders) (Weng *et al*., 2025). The following dialysis parameters were standardized across both groups: dialysate calcium concentration (1.5 mmol/L), polysulfone high-flux dialyzers (surface area 1.5–1.8 m^2) and individualized ultrafiltration based on interdialytic weight gain. Dialysis adequacy (Kt/V) was monitored regularly and showed no significant difference between groups at baseline or during follow-up.

Cin (Al-Homrany *et al*., 2022; Li *et al*., 2023): On top of background therapy, patients received oral Cin. The initial dose was 25 mg daily, taken after dinner or at bedtime. Dose adjustments followed the product labeling and clinical practice: serum iPTH and corrected Ca levels were monitored every 2 to 4 weeks. If iPTH > 300 pg/mL and serum Ca > 8.4 mg/dL, the daily dose could be increased by 25 mg. If iPTH decreased to 150–300 pg/mL, the current dose was maintained. If symptomatic hypocalcemia (Ca < 8.4 mg/dL with clinical symptoms) or intolerable gastrointestinal side effects occurred, the dose was reduced or temporarily discontinued as appropriate. The maximum daily dose did not exceed 100 mg.

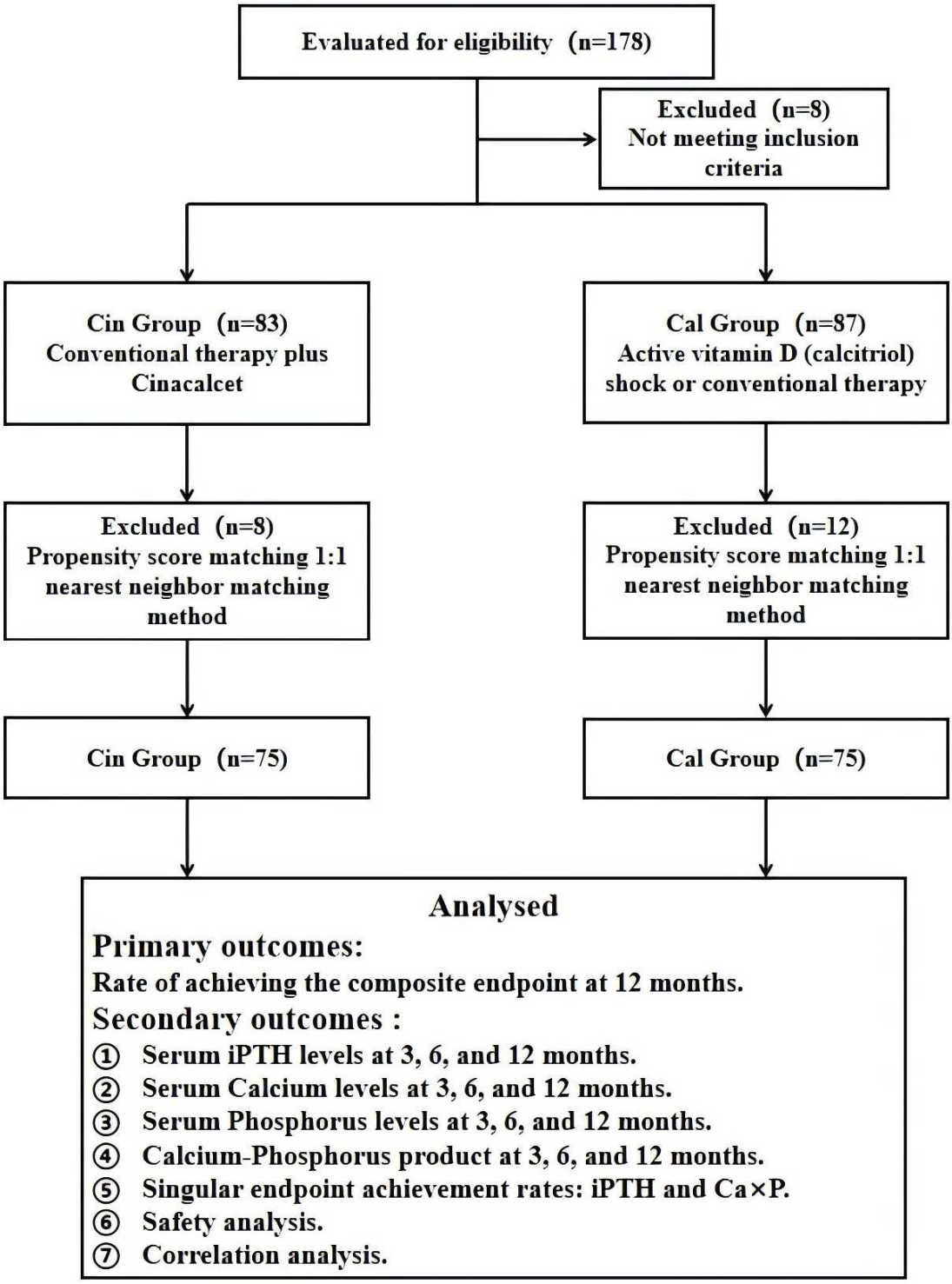

Fig. 1: Research flowchart.
Note: A total of 178 patients with uremic hemodialysis and secondary hyperparathyroidism (SHPT) were initially screened. After applying exclusion criteria (primary hyperparathyroidism or parathyroid cancer, n = 2; parathyroidectomy or interventional treatment during study period, n = 3; malignancy or severe liver dysfunction, n = 1; missing follow-up or treatment interruption >1 month, n = 2), 170 patients were included and divided into the Cin (n = 83) and the Cal (n = 87). Propensity score matching (1:1 nearest-neighbor matching, caliper width = 0.2 SD of the propensity score) was performed to balance baseline characteristics, resulting in 75 patients in each group for final analysis.

Cal (Cardoso *et al*., 2023; Shen *et al*., 2023) (control group): Active vitamin D (Cal) was the primary iPTH-lowering therapy. Dosing was individualized based on the patient's iPTH level and serum Ca. For patients with markedly elevated iPTH (usually > 600 pg/mL), oral Cal was given at 1.0–2.0 μg per dose, 2–3 times per week; or intravenous Cal was administered at 1.0–2.0 μg per dose at the end of each dialysis session. When iPTH decreased to near the target range, a "conventional maintenance" regimen was adopted, consisting of oral Cal 0.25–0.5 μg. In the matched cohort (n=75), 51 patients (68.0%) received oral Cal and 24 (32.0%) received intravenous Cal. Ca and P levels were closely monitored. If hypercalcemia or hyperphosphatemia occurred, the Cal dose was reduced or withheld and P-lowering therapy was intensified.

During the 12-month treatment period, the mean maintenance dose of Cin was 44.67 ± 15.32 mg/day (range: 25–100 mg/day). For Cal, the mean maintenance dose was 1.12 ± 0.54 μg per session (range: 0.25–2.0 μg/session, three times weekly). Standardized treatment was continued for 12 consecutive months. Throughout the study, all relevant medication adjustments (e.g., type or dose of phosphate binders, dose of Cin or Cal) were made by the same team of specialists according to the established protocol and patient response and were fully documented in the medical records.

Assessment measures

Data for all measures were collected retrospectively by reviewing the hospital's electronic medical records, associated communication logs [which contained detailed records of medication dose adjustments, patient-reported adverse events (e.g., gastrointestinal symptoms, hypocalcemia) and dietary or adherence counseling] and standardized nursing documentation.

Baseline data

Patient demographic data (age, gender, body mass index), dialysis characteristics (primary etiology, dialysis vintage), comorbidities (diabetes, cardiovascular disease, history of prior fractures), concomitant medications (use of Ca-based phosphate binders) and baseline laboratory parameters—including hemoglobin, serum albumin and serum ferritin—were collected. All baseline data were sourced from the initial medical records and archived test reports from before the start of treatment.

Efficacy and safety indicators

(1) *Primary efficacy indicator*: The composite response rate at 12 months of treatment, defined as the simultaneous fulfillment of: (1) iPTH ≤ 300 pg/mL; (2) Ca × P < 55 mg²/dL². These thresholds were selected based on the KDIGO 2017 Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD), which recommends an iPTH target of 2 to 9 times the upper normal limit for patients on dialysis (with 300 pg/mL representing a commonly adopted upper bound) and a Ca×P product < 55 mg²/dL² to reduce vascular calcification risk(Group, 2017).

(2) *Secondary efficacy indicators*: (1) iPTH, Ca, P and Ca × P levels at baseline, 3, 6 and 12 months. (2) The individual response rates at 12 months for iPTH ≤ 300 pg/mL and for Ca × P < 55 mg²/dL².

(3) *Safety indicators*: Adverse events occurring during the treatment period were recorded, including nausea, vomiting, upper respiratory tract infections, dizziness/headache, cardiovascular events, etc.

(4) *Correlation analysis indicators*: The analysis examined the correlation between achieving the composite outcome at 12 months and the magnitude of change (Δ values) from baseline to 12 months for the following parameters: iPTH, Ca and P.

Sample size calculation

Based on preliminary experiments and literature data(Platt *et al*., 2024), the estimated composite response rate at 12 months was approximately 16% for the Cal and 42% for the Cin, with $\alpha = 0.05$ (two-sided) and $\beta = 0.10$ (90% power), the minimum required sample size per group was calculated using PASS 15.0 software to be 68 cases. Accounting for potential attrition during the matching process, the sample size was increased by approximately 10%, resulting in a planned enrollment of 75 cases per group.

Statistical analysis

Statistical analysis was conducted with SPSS 26.0. The Shapiro-Wilk test evaluated normality, while Levene's test assessed homogeneity of variance. Normally distributed continuous data are reported as mean ± SD and compared via independent t-tests. Categorical data are shown as number (%) and compared with chi-square or Fisher's exact tests, as appropriate. PSM was performed on baseline variables that could potentially influence efficacy or adherence, including age, sex, body mass index, dialysis vintage, primary etiology, diabetes, cardiovascular disease, history of prior fractures, use of calcium-based phosphate binders, hemoglobin, serum albumin, serum ferritin and baseline iPTH. The matching was performed using a logistic regression model with a caliper width of 0.2 of the standard deviation of the propensity score, applying 1:1 nearest-neighbor matching without replacement. Repeated-measures analysis of variance (ANOVA) was used to compare changes in biochemical parameters over time (baseline, 3, 6 and 12 months) between the two groups, as the data met the assumptions of sphericity and normality. For missing data, complete-case analysis was used given the low proportion (<5%). Effect sizes are reported as partial η^2. Post hoc multiple comparisons were adjusted using the Bonferroni method to control the Type I error rate.

Recurrence rates between groups were compared using the chi-square test. Correlation analyses were conducted using Pearson or point-biserial correlation. All analyses were two-tailed, with statistical significance defined as $P < 0.05$.

RESULTS

Comparison of baseline characteristics

This study initially included a total of 178 patients. After exclusions, 170 patients were included and divided into the Cin and the Cal. Following PSM, 75 cases were included in each group. As shown in table 1, before matching, a significant imbalance existed between the Cin and the Cal regarding dialysis vintage ($P < 0.001$). After matching, all characteristics were balanced ($P > 0.05$). Specifically, there were no statistically significant differences between the two groups in terms of age ($P = 0.801$), gender distribution ($P = 0.624$), body mass index ($P = 0.879$), distribution of primary etiology ($P = 0.964$), prevalence of comorbidities such as diabetes ($P = 0.726$) and cardiovascular disease ($P = 0.697$), usage rate of Ca-based phosphate binders ($P = 0.675$), or key laboratory indicators including hemoglobin ($P = 0.785$), serum albumin ($P = 0.936$) and serum ferritin ($P = 0.746$). These results indicate that PSM effectively balanced baseline characteristics across groups, providing a comparable basis for subsequent efficacy and safety comparisons.

Changes in serum iPTH levels

Changes in iPTH levels before and after treatment in both groups are presented in table 2. A significant main effect of time was observed ($F = 154.762$, $P < 0.001$), indicating that iPTH levels decreased significantly over the treatment period in both groups. The main effect of group ($F = 714.919$, $P < 0.001$) and the group × time interaction ($F = 18.394$, $P < 0.001$) were also significant, suggesting differences in both the overall iPTH levels and their patterns of reduction between the two groups. Intergroup comparisons revealed no statistically significant difference in baseline iPTH levels between the groups ($t = -0.251$, $P = 0.802$). Starting from the third month of treatment, iPTH levels in the Cin were already significantly lower than those in the Cal ($t = -7.530$, $P < 0.001$). This advantage became more pronounced at 6 and 12 months (both $P < 0.001$). These results indicate that Cin demonstrates a faster onset and stronger effect in reducing iPTH and its efficacy advantage continues to increase over the course of treatment.

Changes in serum Ca levels

In table 3, significant main effects of time ($F = 58.838$, $P < 0.001$) and group ($F = 20.784$, $P < 0.001$), along with a significant interaction effect ($F = 8.931$, $P < 0.001$). Between-group comparisons showed no difference in baseline Ca levels ($t = -1.192$, $P = 0.234$). By the third month of treatment, Ca in the Cin was already lower than that in the Cal ($t = -6.794$, $P < 0.001$) and this difference persisted at 6 and 12 months (all $P < 0.05$). At the 12-month mark, Ca in the Cin remained lower than those in the Cal ($t = -2.446$, $P = 0.016$). These results indicate that Cin exerts a clear Ca-lowering effect, while Cal treatment is associated with higher serum Ca.

Changes in serum P levels

In table 4, repeated measures analysis of variance indicated significant main effects of time ($F = 29.305$, $P < 0.001$) and group ($F = 13.092$, $P < 0.001$), as well as a significant interaction effect ($F = 2.957$, $P = 0.032$). Between-group comparisons showed no difference in baseline P levels ($t = -0.370$, $P = 0.712$). At the 3-, 6- and 12-month treatment time points, P in the Cin group was consistently lower than that in the Cal group (all $P < 0.01$). These findings demonstrate that Cin is more effective in lowering serum P, providing a clear advantage in improving hyperphosphatemia in SHPT patients.

Changes in Ca × P

The changes in Ca × P for the two patient groups are detailed in table 5. Repeated-measures analysis of variance showed significant main effects of time ($F = 62.469$, $P < 0.001$) and group ($F = 22.759$, $P < 0.001$), along with a significant interaction ($F = 7.787$, $P < 0.001$). Between-group comparisons indicated no difference in baseline Ca × P ($t = -0.453$, $P = 0.651$). Starting from the third month of treatment, Ca × P in the Cin was significantly lower than that in the Cal (all $P < 0.001$). At the 12-month treatment point, Ca × P in the Cin remained lower than that in the Cal ($t = -2.918$, $P = 0.004$). These results suggest that Cin reduces Ca × P earlier and more effectively, which is crucial for lowering the risk of vascular calcification.

Response rate for the primary efficacy endpoint

The achievement of the primary efficacy endpoint at 12 months of treatment is shown in table 6. In the Cin, 53 patients (70.67%) met the individual criterion of iPTH ≤ 300 pg/mL, which was significantly higher than in the Cal, where 23 patients (30.67%) met the Criterion ($\chi^2 = 24.004$, $P < 0.001$). Regarding the individual response rate for Ca × P < 55 mg^2/dL^2, the rates were 64.00% (48/75) and 65.33% (49/75) for the two groups, respectively, with no significant difference ($\chi^2 = 0.029$, $P = 0.864$). However, for the composite response rate of simultaneously achieving iPTH ≤ 300 pg/mL and Ca × P < 55 mg^2/dL^2, the Cin was higher than the Cal, with a highly significant difference ($\chi^2 = 12.864$, $P < 0.001$). These results clearly demonstrate that, compared to Cal, Cin significantly improves the rate of achieving dual control of PTH and Ca-P metabolism in SHPT patients, with its key advantage being superior iPTH control.

Table 1: Comparison of baseline characteristics before and after PSM.

Characteristic	Before PSM				After PSM			
	Cin (n = 83)	Cal (n = 87)	t/χ^2	*P*	Cin (n = 75)	Cal (n = 75)	t/χ^2	*P*
Demographics and dialysis characteristics								
Age ($\bar{x}\pm s$, years)	56.12 ± 10.87	58.89 ± 11.34	-1.625	0.106	57.33 ± 10.24	56.89±11.07	0.253	0.801
Male (n, %)	43 (51.81)	46 (52.87)	0.019	0.889	41 (54.67)	38 (50.67)	0.241	0.624
BMI ($\bar{x}\pm s$, kg/m^2)	23.15 ± 3.52	23.78 ± 3.81	-1.118	0.265	23.45 ± 3.12	23.53±3.29	-0.153	0.879
Dialysis vintage ($\bar{x}\pm s$, years)	5.62 ± 2.01	4.65 ± 1.41	3.656	< 0.001	5.16 ± 1.34	4.89±1.17	1.301	0.195
Primary etiology (n, %)			0.135	0.987			1.000	0.964
Chronic glomerulonephritis	41 (49.40)	43 (49.43)			35 (46.67)	36 (48.00)		
Diabetic nephropathy	29 (34.94)	29 (33.33)			27 (36.00)	26 (34.67)		
Hypertensive nephropathy	10 (12.05)	12 (13.79)			10 (13.33)	11 (14.67)		
Others	3 (3.61)	3 (3.45)			3 (4.00)	2 (2.67)		
Comorbidities and medical history (n, %)								
Diabetes	32 (38.55)	26 (29.89)	1.420	0.233	25 (33.33)	23 (30.67)	0.123	0.726
Cardiovascular disease	19 (22.89)	21 (24.14)	0.037	0.848	18 (24.00)	16 (21.33)	0.152	0.697
History of prior fractures	7 (8.43)	5 (5.75)	0.467	0.494	6 (8.00)	5 (6.67)	0.098	0.754
Concomitant medications (n, %)								
Use of Ca-based phosphate binders	71 (85.54)	69 (79.31)	1.135	0.287	62 (82.67)	60 (80.00)	0.176	0.675
Baseline laboratory parameters								
Hemoglobin ($\bar{x}\pm s$, g/L)	106.89 ± 14.12	107.95 ± 13.45	-0.501	0.617	106.76 ± 13.19	107.33±12.55	-0.273	0.785
Serum albumin ($\bar{x}\pm s$, g/L)	37.89 ± 4.23	38.47 ± 4.05	-0.913	0.362	38.31 ± 3.98	38.25 ± 4.11	0.081	0.936
Serum ferritin ($\bar{x}\pm s$, μg/L)	298.34 ± 46.78	285.67 ± 48.92	1.724	0.087	285.23 ± 42.33	287.45 ± 41.67	-0.325	0.746

Table 2: Comparison of serum iPTH levels (pg/mL).

Time	Cin (n = 75)	Cal (n = 75)	*t*	*P*
Baseline	605.41 ± 78.32	608.57 ± 75.87	-0.251	0.802
Month 3	330.28 ± 67.94	415.36 ± 70.41	-7.530	<0.001
Month 6	265.19 ± 58.46	378.36 ± 61.17	-11.584	<0.001
Month 12	247.44 ± 60.04	316.85 ± 57.58	-7.226	<0.001
Main effect of group	$F = 714.919$, $P < 0.001$, $\eta^2 = 0.728$			
Main effect of time	$F = 154.762$, $P < 0.001$, $\eta^2 = 0.053$			
Interaction effect time × group	$F = 18.394$, $P < 0.001$, $\eta^2 = 0.019$			

Table 3: Comparison of serum Ca levels (mg/dL).

Time	Cin (n = 75)	Cal (n = 75)	*t*	*P*
Baseline	9.98 ± 0.95	10.04 ± 0.92	-1.192	0.234
Month 3	9.25 ± 0.87	10.32 ± 1.06	-6.794	<0.001
Month 6	9.08 ± 0.77	9.89 ± 0.94	-5.705	<0.001
Month 12	9.04 ± 0.96	9.41 ± 0.88	-2.446	0.016
Main effect of group		$F = 20.784$, $P < 0.001$, $\eta^2 = 0.084$		
Main effect of time		$F = 58.838$, $P < 0.001$, $\eta^2 = 0.080$		
Interaction effect time × group		$F = 8.931$, $P < 0.001$, $\eta^2 = 0.036$		

Table 4: Comparison of serum P levels (mg/dL).

Time	Cin (n = 75)	Cal (n = 75)	*t*	*P*
Baseline	5.82 ± 0.97	5.87 ± 0.98	-0.370	0.712
Month 3	5.06 ± 0.92	5.65 ± 1.04	-3.692	<0.001
Month 6	4.87 ± 0.85	5.52 ± 1.01	-4.301	<0.001
Month 12	5.13 ± 0.94	5.54 ± 0.97	-2.666	0.009
Main effect of group		$F = 13.092$, $P < 0.001$, $\eta^2 = 0.059$		
Main effect of time		$F = 29.305$, $P < 0.001$, $\eta^2 = 0.044$		
Interaction effect time × group		$F = 2.957$, $P = 0.032$, $\eta^2 = 0.013$		

Table 5: Comparison of serum Ca × P (mg^2/dL^2).

Time	Cin (n = 75)	Cal (n = 75)	*t*	*P*
Baseline	58.04 ± 11.53	58.86 ± 10.64	-0.453	0.651
Month 3	46.83 ± 9.94	58.31 ± 12.24	-6.304	<0.001
Month 6	44.22 ± 8.62	54.71 ± 11.50	-6.303	<0.001
Month 12	46.86 ± 11.65	52.11 ± 10.34	-2.918	0.004
Main effect of group		$F = 22.759$, $P < 0.001$, $\eta^2 = 0.092$		
Main effect of time		$F = 62.469$, $P < 0.001$, $\eta^2 = 0.084$		
Interaction effect time × group		$F = 7.787$, $P < 0.001$, $\eta^2 = 0.031$		

Table 6: Comparison of primary efficacy endpoint achievement [n (%)].

Indicator	Cin (n = 75)	Cal (n = 75)	χ^2	*P*
iPTH ≤ 300 pg/mL	53 (70.67)	23 (30.67)	24.004	<0.001
Ca × P < 55 mg^2/dL^2	48 (64.00)	49 (65.33)	0.029	0.864
Composite response rate	32 (42.67)	12 (16.00)	12.864	<0.001

Safety analysis

Regarding safety, the two treatment regimens exhibited similar profiles of adverse events. As shown in table 7, there were no statistically significant differences between the Cin and the Cal in the incidence of nausea (P = 0.440), vomiting (P = 0.513), upper respiratory tract infection (P = 0.675), dizziness/headache (P = 0.575), or cardiovascular events (P = 0.547). Notably, hypocalcemia occurred in 12 patients (16.00%) in the Cin group, compared with 3 patients (4.00%) in the Cal group (P = 0.014). All recovered after calcium supplementation and dose adjustment. No patient in the Cal group required treatment modification for hypocalcemia. All adverse events were managed symptomatically or resolved spontaneously and none led to treatment discontinuation. These results suggest that over the 12-month treatment period, the overall safety and tolerability profiles of Cin and Cal are comparable.

Correlation analysis

The correlation analysis between achieving the composite endpoint at 12 months and the changes in various parameters from baseline to 12 months is presented in table 8. Achieving the composite endpoint showed a significant positive correlation with ΔiPTH (r = 0.453, P < 0.001) and a significant positive correlation with ΔCa (r = 0.463, P < 0.001). It also showed a positive correlation with ΔP (r = 0.203, P = 0.013). Furthermore, there were significant positive correlations among changes in these parameters. Specifically, ΔiPTH demonstrated moderate positive correlations with both ΔCa (r = 0.644, P < 0.001) and ΔP (r = 0.604, P < 0.001). Similarly, ΔCa and ΔP showed a moderate positive correlation with each other (r = 0.624, P < 0.001).

Table 7: Comparison of adverse between the two groups [n (%)].

Adverse events	Cin (n = 75)	Cal (n = 75)	χ^2	*P*
Nausea	10 (13.33)	7 (9.33)	0.597	0.440
Vomiting	6 (8.00)	4 (5.33)	0.429	0.513
Upper respiratory tract infection	13 (17.33)	15 (20.00)	0.176	0.675
Dizziness/headache	8 (10.67)	6 (8.00)	0.315	0.575
Cardiovascular events	5 (6.67)	7 (9.33)	0.362	0.547
Hypocalcemia	12 (16.00)	3 (4.00)	6.000	0.014

Table 8: Correlations between composite endpoint achievement and changes in parameters.

Indicator	Composite endpoint achievement	ΔiPTH	ΔCa	ΔP
Composite endpoint achievement	1	0.453**	0.463**	0.203*
ΔiPTH		1	0.644**	0.604**
ΔCa			1	0.624**
ΔP				1

Note: *$P < 0.05$, **$P < 0.001$.

These results indicate that a significant reduction in both iPTH and Ca levels is a key factor associated with achieving the composite treatment endpoint. Concurrently, the magnitude of iPTH reduction is closely linked to the degree of improvement in both Ca and P levels and the changes in Ca and P exhibit a synergistic relationship. This collectively underscores the importance of integrated intervention in the management of SHPT.

DISCUSSION

This PSM-based retrospective cohort study systematically compared the 12-month efficacy and safety of Cin versus Cal in treating SHPT among MHD patients. The core finding is that Cin achieves a significantly higher composite response rate in dual control of iPTH and Ca × P than Cal, with the advantage primarily reflected in more effective iPTH control. Furthermore, achieving the composite endpoint shows significant positive correlations with ΔiPTH and ΔCa and ΔiPTH is closely associated with ΔP. These findings provide important data to support precise clinical management of SHPT and the optimization of treatment strategies.

While the statistical differences in Ca and P between the two groups reached significance, the clinical implications of these absolute differences warrant careful interpretation. In this study, the mean serum Ca difference between groups at 12 months was approximately 0.37 mg/dL and the mean serum P difference was approximately 0.41 mg/dL. Whether such modest biochemical changes translate into meaningful long-term clinical benefits—such as reduced progression of vascular calcification, cardiovascular events, or mortality—cannot be directly inferred from the data presented. Previous studies suggest that larger reductions in Ca × P may be required to alter hard outcomes significantly. Therefore, the findings should be interpreted primarily as evidence of biochemical efficacy rather than definitive proof of long-term clinical benefit.

The findings demonstrate that the composite response rate at 12 months in the Cin was 2.67 times that in the Cal, a difference of significant clinical and statistical importance. Analysis suggests this advantage is primarily attributable to Cin's superior efficacy in reducing iPTH levels (Nakamura *et al*., 2021). Starting from the third treatment month, iPTH concentrations in the Cin were already markedly lower than in the Cal and this advantage continued to increase over time. This is closely related to Cin's unique pharmacological mechanism, which directly activates the CaSR (Chavez-Abiega *et al*., 2020; Fung *et al*., 2023; Okada *et al*., 2025). The CaSR serves as a critical "sensor" regulating PTH secretion. By mimicking a high-Ca state to activate this receptor continuously, Cin potently and directly suppresses PTH synthesis and secretion. This mechanism is particularly advantageous for patients with severe SHPT who have developed resistance to vitamin D therapy(Goodman *et al*., 2022; Liu *et al*., 2022; Nakai *et al*., 2024). In contrast, Cal acts through the VDR pathway and its PTH-lowering effect may be limited by VDR downregulation and the risk of inducing hypercalcemia.

At the level of Ca and P metabolism, this study clearly reveals distinct metabolic patterns between the two groups, which influenced the achievement of the composite endpoint. The Cin demonstrated a more desirable profile of "reducing P with moderate Ca reduction." The effect on lowering P is partly attributable to the indirect improvement in bone P release and renal P excretion following the decrease in PTH and may also be related to its direct pharmacological action (Koiwa *et al*., 2021; Sun *et al*., 2020). Meanwhile, the moderate reduction in Ca induced by Cin, while requiring clinical monitoring and management, avoids hypercalcemia and creates favorable conditions for controlling Ca × P (Alpay and Yıldız, 2023; Eddington *et al*., 2021). In contrast, Cal significantly increased Ca levels while suppressing PTH and exhibited limited ability to control P, resulting in a

smaller improvement in Ca × P and ultimately making it difficult to simultaneously meet the dual criteria for both iPTH and Ca × P control. This finding highlights that in the management of SHPT, solely focusing on PTH reduction while neglecting its concomitant effects on Ca and P metabolism may lead to a deviation from therapeutic goals.

Correlation analysis provides statistical support for the mechanisms described above. The significant positive correlations between achieving the composite endpoint and both ΔiPTH and ΔCa suggest that substantial reductions in iPTH and Ca during treatment may represent a key pathway to therapeutic success (Guo *et al*., 2025). Furthermore, the moderate positive correlation between ΔiPTH and ΔP reasonably reflects the central regulatory role of PTH in P metabolism and explains the superior P-lowering performance observed in the Cin (Warady *et al*., 2020). The positive correlation between ΔCa and ΔP likely indicates coordinated changes within the Ca-P metabolic system under pharmacological intervention.

In terms of safety, the two groups exhibited adverse event profiles with distinct characteristics but overall comparable incidence rates, consistent with the known properties of each drug. The gastrointestinal reactions and risk of hypocalcemia observed in the Cin highlight the clinical need to initiate treatment at a low dose, administer with meals, closely monitor serum Ca levels and promptly supplement with Ca and vitamin D as necessary (Ni *et al*., 2023). The hypercalcemia risk associated with the Cal necessitates more frequent Ca monitoring and flexible dose adjustments (Pan *et al*., 2025). The absence of significant differences in serious adverse events between the groups indicates that, with standardized management, both regimens provide a foundation for safe long-term application.

Several limitations are present in this investigation. First, despite the use of PSM to balance observed confounders, the retrospective single-center design still carries a risk of residual confounding due to unmeasured or unknown variables (e.g., dietary phosphate intake, medication adherence, socioeconomic status), as well as potential selection bias. Second, medication doses were adjusted individually rather than fixed, which may introduce variability in efficacy comparisons. Third, the Cal included both oral (68.0%) and intravenous (32.0%) regimens with different dosing schedules; intravenous Cal may provide more potent PTH suppression but also a higher risk of hypercalcemia, potentially affecting the composite endpoint and complicating direct comparisons with Cin. Fourth, the study primarily focused on biochemical outcomes. Future research could draw on study models, such as those examining the relationship between sleep quality and anemia treatment, to further explore whether biochemical improvements achieved with Cin translate into enhanced patient-reported outcomes—such as sleep quality, pruritus symptoms and fatigue levels (Elif and Cihan, 2025).

CONCLUSION

In summary, during the 12-month treatment period, Cin demonstrated greater efficacy than Cal in helping hemodialysis patients with uremic SHPT achieve dual control of both iPTH and Ca × P. The ultimate therapeutic success was correlated with ΔiPTH, ΔCa and ΔP. These findings suggest that when formulating pharmacologic strategies for SHPT, consideration should be given to selecting regimens that synergistically improve iPTH and Ca-P metabolism, with personalized adjustments based on the patient's specific biochemical changes and tolerance, so as to explore more effective long-term management pathways.

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Authors' contributions
Jiebo Huang: Conceived and designed the research and analyzed data, drafted and revised the manuscript critically for important intellectual content; Yuan Fu, Lin Chen and Yan Liang: Contributed to the acquisition, analysis and interpretation of data and provided substantial intellectual input during the drafting and revision of the manuscript; Nie Wu: Participated in the conception and design of the study and played a key role in data interpretation and manuscript preparation. All authors have read and approved the final version of the manuscript.

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Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
This investigation received approval from the institutional ethics committee of Nanjing Pukou District Hospital of Traditional Chinese Medicine (Approval No. 20250008) and was conducted in strict compliance with the ethical guidelines outlined in the Declaration of Helsinki and prevailing international standards for biomedical research. This study was performed in adherence with the RECORD guidelines. See supplementary file for the RECORD checklist.

Conflict of interest
The authors declare no conflict of interest.

Supplementary data
https://pjps.pk/uploads/2026/08/SUP1787227137.pdf

REFERENCES

Al-Homrany M, Saeed M, Ali F, Al-Ghamdi S, Mousa D and Alharbi A (2022). The effectiveness of alternate-day cinacalcet therapy for secondary hyperparathyroidism in noncompliant hemodialysis patients. *Saudi J. Kidney Dis. Transpl.,* **33**(4): 503-508.

Alpay N and Yildiz A (2023). Effects of cinacalcet on post-transplantation hypercalcemia and hyperparathyroidism in adult kidney transplant patients: A single-center experience. *Cureus,* **15**(3): e36248.

Alvarado L, Sharma N, Lerma R, Dwivedi A, Ahmad A, Hechanova A, Payan-Schober F, Nwosu A and Alkhalili E (2022). Parathyroidectomy versus cinacalcet for the treatment of secondary hyperparathyroidism in hemodialysis patients. *World J. Surg.,* **46**(4): 813-819.

Brandenburg V and Ketteler M (2022). Vitamin D and secondary hyperparathyroidism in chronic kidney disease: A critical appraisal of the past, present and the future. *Nutrients,* **14**(15): 3009.

Cardoso MMA, Machado-Rugolo J, Lima SAM andrade, LGM, Curado DSP and Ponce D. (2023). Cost-effectiveness analysis of intravenous paricalcitol vs. oral calcitriol in the treatment of hyperparathyroidism secondary to chronic kidney disease. *J. Bras. Nefrol.,* **45**(1): 95-101.

Chan WH, Chan YY, Chen YF, Kou HW, Chen MY, Tsai CY, Wang SY, Tian YC and Yeh CN (2026, 0101). 4D CT-guided parathyroidectomy: Improving operative efficiency in end-stage renal disease patients with medically refractory secondary hyperparathyroidism. *Int. J. Surg.,* **112**(1): 1417-1424.

Chavez-Abiega S, Mos I, Centeno PP, Elajnaf T, Schlattl W, Ward DT, Goedhart J and Kallay E (2020). Sensing extracellular calcium - An insight into the structure and function of the calcium-sensing receptor (CaSR). *Adv. Exp. Med. Biol.,* **1131**: 1031-1063.

Dream S, Kuo LE, Kuo JH, Sprague SM, Nwariaku FE, Wolf M, Olson JA, Moe SM, Lindeman B and Chen H (2022). The American association of endocrine surgeons guidelines for the definitive surgical management of secondary and tertiary renal hyperparathyroidism. *Ann. Surg.,* **276**(3): e141-e176.

Eddington H, Chinnadurai R, Alderson H, Ibrahim ST, Chrysochou C, Green D, Erekosima I, Hutchison A, Bubtana A, Hegarty J and Kalra PA (2021). A randomised controlled trial to examine the effects of cinacalcet on bone and cardiovascular parameters in haemodialysis patients with advanced secondary hyperparathyroidism. *BMC Nephrol.,* **22**(1): 106.

Elhadedy MA, El-Kannishy G, Refaie AF, Sheashaa HA and Halawa A (2023). Management of pre-renal transplant secondary hyperparathyroidism: Parathyroidectomy versus cinacalcet. *Drugs Context,* **12**(11): 5.

Elif B and Cihan U (2025). Sleep quality in hemodialysis patients according to renal anemia treatment outcomes. *Adv. Mod. Biomed.,* **1**(3): 1-10.

Fung MM, Tam DS, Lui DT and Lang BH (2023). Pre-operative cinacalcet administration reduces immediate post-operative hypocalcemia following total parathyroidectomy in severe renal hyperparathyroidism. *World J. Surg.,* **47**(8): 1986-1994.

Goodman WG, Ward DT, Martin KJ, Drayer D, Moore C, Xu J, Lai J, Chon Y and Nemeth EF (2022). Activation of the calcium receptor by calcimimetic agents is preserved despite modest attenuating effects of hyperphosphatemia. *J. Am. Soc. Nephrol.,* **33**(1): 201-212.

Group KDIGOKCMUW (2017). KDIGO 2017 Clinical practice guideline update for the diagnosis, evaluation, prevention and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int. Suppl (2011),* **7**(1): 1-59.

Gulcan-Kersin S, Kirkgoz T, Eltan M, Rzayev T, Ata P, Bilgen H, Ozek E, Bereket A and Turan S (2020, 0615). Cinacalcet as a first-line treatment in neonatal severe hyperparathyroidism secondary to calcium sensing receptor (CaSR) mutation. *Horm. Res. Paediatr.,* **93**(5): 313-321.

Guo S, Liu L, Zou C, Liang P, Wang Y, Sun C, Gan X, Tian X and Yuan L (2025). Correlation between parathyroid volume and calcium and phosphorus metabolism in maintenance hemodialysis patients based on Doppler ultrasound technology. *Int. Urol. Nephrol.,* **57**(11): 3799-3809.

Haffner D and Leifheit-Nestler M (2021). CKD-MBD post kidney transplantation. *Pediatr. Nephrol.,* **36**(1): 41-50.

Hiramitsu T, Hasegawa Y, Futamura K, Okada M, Goto N, Narumi S, Watarai Y, Tominaga Y and Ichimori T (2023). Treatment for secondary hyperparathyroidism focusing on parathyroidectomy. *Front. Endocrinol. (Lausanne),* **14**: 1169793.

Iorga C, Iorga CR andreiana I, Bengulescu I, Constantin T and Strambu V (2023). Advantages of total parathyroidectomy in patients with secondary hyperparathyroidism induced by end stage renal disease. *Front. Endocrinol (Lausanne),* **14**: 1191914.

Koiwa F, Tokunaga S, Asada S, Endo Y, Fukagawa M and Akizawa T (2021). Efficacy of evocalcet in previously cinacalcet-treated secondary hyperparathyroidism patients. *Kidney Int. Rep.,* **6**(11): 2830-2839.

Li X, Ding W and Zhang H (2023). Cinacalcet use in secondary hyperparathyroidism: A machine learning-based systematic review. *Front. Endocrinol. (Lausanne),* **14**: 1146955.

Liu X, Liu Y, Zheng P, Xie X, Li Z, Yang R, Jin L, Mei Z, Chen P and Zhou L (2024). Effects of active vitamin D analogs and calcimimetic agents on PTH and bone mineral biomarkers in hemodialysis patients with

SHPT: A network meta-analysis. *Eur. J. Clin. Pharmacol.,* **80**(10): 1555-1569.

Liu Y, Yang Q, Chen G and Zhou T (2022). A systematic review and meta-analysis of efficacy and safety of calcimimetic agents in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease. *Curr. Pharm. Des.,* **28**(40): 3289-3304.

Magagnoli L, Ciceri P and Cozzolino M (2024). Secondary hyperparathyroidism in chronic kidney disease: Pathophysiology, current treatments and investigational drugs. *Expert Opin. Investig. Drugs,* **33**(8): 775-789.

Nakai K, Kono K, Yamada S, Taniguchi M, Hamano T and Fukagawa M (2024). Calcimimetics treatment strategy for serum calcium and phosphate management in patients with secondary hyperparathyroidism undergoing dialysis: A systematic review and meta-analysis of randomized studies. *Ther. Apher. Dial.,* **28**(4): 557-571.

Nakamura H, Tokumoto M, Anayama M, Kurihara S, Makino Y, Tamura K and Nagasawa M (2021). A case of a hemodialysis patient with secondary hyperparathyroidism who was resistant to etelcalcetide treatment but not to cinacalcet hydrochloride. *CEN Case Rep.*, **11**(2): 254-258.

Ngamkam J, Vadcharavivad S, Areepium N, Auamnoy T, Takkavatakarn K, Katavetin P, Tiranathanagul K, Praditpornsilpa K, Eiam-Ong S and Susantitaphong P (2021). The impact of CASR A990G polymorphism in response to cinacalcet treatment in hemodialysis patients with secondary hyperparathyroidism. *Sci. Rep.,* **11**(1): 18006.

Ni Z, Liang X, Wu CC, Jin K, Kim YL, Lu KC, Chan TM, Fukagawa M, Kinoshita J, Nagai C, Kojima M and Yu X (2023). Comparison of the oral calcimimetics evocalcet and cinacalcet in East Asian patients on hemodialysis with secondary hyperparathyroidism. *Kidney Int. Rep.,* **8**(11): 2294-2306.

Okada K, Tashiro M, Yamaguchi S, Inoue T, Kuragano T and Minakuchi J (2025). Lower mortality in calcimimetic users compared to non-users in dialysis patients with serum parathyroid hormone levels within the target range. *Sci. Rep.,* **16**(1): 241.

Pan Y, Zhu J, Wu Z and Wu D (2025, 0615). Efficacy and safety of prophylactic intravenous calcium supplementation in patients with secondary hyperparathyroidism after parathyroidectomy: A retrospective study. *Front. Endocrinol. (Lausanne),* **16**: 1652418.

Platt A, Wilson J, Hall R, Ephraim PL, Morton S, Shafi T, Weiner DE, Boulware LE, Pendergast J and Scialla JJ (2024). Comparative effectiveness of alternative treatment approaches to secondary hyperparathyroidism in patients receiving maintenance hemodialysis: An observational trial emulation. *Am. J. Kidney Dis.,* **83**(1): 58-70.

Ruifang S, Fadong C, Zengqi X and Xiaozhen L (2025). Clinical value of serum iPTH, ALP and serum markers levels in patients with secondary hyperparathyroidism receiving paricalcitol combined with cinacalcet. *J. Med. Biochem.,* **44**(4): 759-769.

Shen J, Feng X and Li X (2023). Effect of hemodialysis combined with calcitriol on cardiac function and BNP in patients with hyperparathyroidism secondary to nephropathy. *Am. J. Transl. Res.,* **15**(4): 2757-2764.

Shigematsu T, Asada S, Endo Y, Kawata T, Fukagawa M and Akizawa T (2022). Evocalcet with vitamin D receptor activator treatment for secondary hyperparathyroidism. *PLoS One,* **17**(2): e0262829.

Sun Y, Tian B, Sheng Z, Wan P, Xu T and Yao L (2020). Efficacy and safety of cinacalcet compared with other treatments for secondary hyperparathyroidism in patients with chronic kidney disease or end-stage renal disease: A meta-analysis. *BMC Nephrol.,* **21**(1): 316.

Tuna K, Ilkun O, Dziegielewski PT and Sharma A (2025). Uremic leontiasis ossea due to resistant secondary hyperparathyroidism. *AACE Clin Case Rep,* **11**(1): 5-9.

Wang Z, Wang Y, Han S, Chen P, Wu R, Fang C, Cheng J, Wu Y, Guo T, Wen X and Li L (2025). Pharmacodynamic modeling of cinacalcet in secondary hyperparathyroidism: Efficacy and influencing factors analysis. *J. Endocr. Soc.,* **9**(5): bvaf021.

Warady BA, Ng E, Bloss L, Mo M, Schaefer F and Bacchetta J (2020). Cinacalcet studies in pediatric subjects with secondary hyperparathyroidism receiving dialysis. *Pediatr. Nephrol.,* **35**(9): 1679-1697.

Weng W, Li Y, Lin Y, Wang J, Chen X and Zhou T (2025). Cinacalcet improves erythropoietin resistance in patients with secondary hyperparathyroidism receiving dialysis treatment. *Curr. Pharm. Des.,* **31**(16): 1299-1306.

Xiang Z, Wang M, Miao C, Jin D and Wang H (2022). Mechanism of calcitriol regulating parathyroid cells in secondary hyperparathyroidism. *Front. Pharmacol.,* **13**: 1020858.