

The Prevalence and Risk Factors for Persistent Hyperparathyroidism in Post-Kidney Transplant Patients: A Single-Center Retrospective Study

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Abstract

Background. Persistent hyperparathyroidism (PHPT) remains a notable challenge among kidney transplant recipients due to its impact on calcium-phosphorus metabolism, potentially hindering recovery and long-term renal function. Understanding its prevalence and risk factors is vital for enhancing patient outcomes.

Objective. To determine the prevalence and identify risk factors for persistent hyperparathyroidism in adult Filipino kidney transplant recipients at a tertiary care hospital.

Methodology. A retrospective chart review was conducted for 80 kidney transplant recipients at Cardinal Santos Medical Center from January 1, 2014, to July 31, 2024. Data included demographics, comorbidities, medications, and laboratory profiles pre- and post-transplant.

Results. Persistent hyperparathyroidism was found in 58.8% of patients. Their mean age was 55.3 years, and 53.8% were male. Hypertension was present in 76.3%, and 60% had diabetes mellitus. Diabetic kidney disease was the leading cause of renal failure (57.5%). Post-transplant use of vitamin D supplements and calcimimetics increased by 31.3% and 26.3%, respectively. Pre-transplant hyperparathyroidism was a key risk factor, with a prevalence of 26.3%.

Conclusion. Regular monitoring and management of hyperparathyroidism are essential to improving long-term outcomes in kidney transplant recipients.

Key words: hyperparathyroidism, kidney transplantation, prevalence, risk factors

INTRODUCTION

Chronic kidney disease (CKD) is frequently complicated by renal hyperparathyroidism (rHPT), driven by imbalances in calcium, phosphate, and vitamin D. This condition causes elevated parathyroid hormone (PTH) levels and is associated with increased cardiovascular complications and bone disease. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend routine screening and management of rHPT in CKD stage 3 patients (eGFR <60 mL/min/1.73 m²). Despite advances in medical treatment such as vitamin D analogues, phosphate binders, and calcimimetics, some patients still require parathyroidectomy to manage long-term effects.¹

Kidney transplantation is the preferred treatment for end-stage renal disease, offering improved long-term survival and quality of life compared to dialysis.^{2,3}

However, post-transplantation persistent hyperparathyroidism (PHPT) remains a significant complication even after successful kidney transplantation (KT). Persistent HPT is linked to adverse outcomes such as renal allograft dysfunction, increased cardiovascular morbidity, bone resorption with a higher fracture risk, and diminished quality of life.⁵⁻¹⁰ Tertiary hyperparathyroidism (THPT), a specific type of PHPT, is associated with nephrolithiasis, pancreatitis, soft tissue calcification, and peptic ulcer disease. The management of PHPT is challenging due to the lack of a universally accepted definition for THPT, ongoing debates over optimal treatment approaches, and unclear treatment goals for this patient population.¹¹

The reported prevalence of persistent hyperparathyroidism (PHPT) and tertiary hyperparathyroidism (THPT) post-KT varies widely (10-70%) due to differences in diagnostic criteria, such as PTH and calcium thresholds,

and the timing of post-transplant assessments.^{5,6,12,13} While PTH levels typically decrease significantly within the first 3 months post-KT, diagnosing PHPT can take up to two years, resulting in increased morbidity due to delayed treatment.^{5,14,15} As a result, the true prevalence of PHPT and THPT, as well as the patient and transplant-related factors contributing to their development, remain largely undetermined.

Several studies suggest a link between the severity of pre-operative secondary hyperparathyroidism (SHPT) and higher rates of post-transplant graft dysfunction and persistent PHPT.¹⁵⁻¹⁷ However, limited data exists on how advancements in SHPT treatment over the past two decades have impacted the development of THPT. Moreover, specific pre-operative PTH and calcium thresholds for reducing THPT risk remain undefined.

Despite successful kidney transplantation leading to normalization of serum calcium, phosphorus, and calcitriol levels within one year, some patients with well-functioning grafts may still exhibit persistent PTH elevation and hypercalcemia,¹⁸⁻²¹ with hyperparathyroidism remaining unresolved in over half of kidney transplant recipients.²²

This persistent issue may result from incomplete normalization of renal function or residual pre-transplant parathyroid gland hyperplasia.¹⁹ Despite some improvements, the risk factors for persistent hyperparathyroidism are not yet fully understood.²³

Effective management of persistent hyperparathyroidism (PHPT) requires a clear understanding of how pre-operative secondary hyperparathyroidism (SHPT) management influences post-transplant outcomes. Furthermore, establishing standardized diagnostic and treatment guidelines is essential.

This research aims to clarify the mechanisms underlying PHPT and its impact on patient health. Specifically, the study investigates the relationship between pre-operative SHPT management and PHPT development in kidney transplant recipients. It also analyzes factors contributing to the persistence of hyperparathyroidism in patients with well-functioning grafts (creatinine <2 mg/dL) receiving immunosuppressive therapy.

Understanding these factors is key to enhancing patient care and refining PHPT management strategies, ultimately leading to better outcomes for kidney transplant recipients.

METHODOLOGY

Study design and ethics

This retrospective, single-center observational cohort study focuses on post-kidney transplant patients at a tertiary hospital. Ethics committee approval was granted for this study prior to data collection (Research Ethics Review

Committee of Cardinal Santos Medical Center, CSMC RERC CODE 2024-054). Participants include Filipino adults who underwent renal transplantation between January 1, 2014, and July 31, 2024. They must have complete records on demographic data, baseline characteristics, pre-transplant tertiary hyperparathyroidism (THPT), pre-transplant treatment for secondary hyperparathyroidism (SHPT), pre-transplant parathyroid hormone (PTH) levels, post-transplant vitamin D deficiency, BMI, cause of kidney failure, dialysis history, and hypertension history. The study specifically considers post-operative laboratory results within 6 to 12 months after transplantation. Patients excluded from the study include pregnant or breastfeeding women, those who underwent parathyroidectomy as treatment for pre-transplant hyperparathyroidism, and those with incomplete medical records on specified data points.

Definitions and criteria

Persistent hyperparathyroidism (PHPT) was defined as PTH ≥ 70 pg/mL measured 6 to 12 months post-transplantation, regardless of calcium status. Pre-transplant PTH levels were identified from records obtained within 6 months prior to kidney transplantation. Patients who underwent parathyroidectomy for pre-transplant hyperparathyroidism were excluded to avoid confounding biochemical trajectories resulting from surgical intervention.

Sampling and sample size

Based on institutional census records indicating approximately 10 KT patients per year, the study target was the entire available transplant population from the last decade. Using OpenEpi version 3, the minimum sample size was computed as 73 patients, assuming a population of 100 KT patients, a 95% confidence level, and an estimated PHPT prevalence of 21.5% based on existing literature.¹¹ The minimum sample size of 73 was met with a final cohort of 80 patients. While the overall sample is powered for primary prevalence, it is acknowledged that subgroup analyses may have limited statistical power due to the cohort size.

Statistical analysis

Summary statistics were collated and tabulated as mean \pm SD for continuous data and frequency (%) for categorical data. Normality of continuous data was first checked via formal statistical tests (Shapiro-Wilk and Kolmogorov-Smirnov) and analysis of z-scores. No data imputation was performed; analyses were conducted only on available cases. Sensitivity analysis was performed by excluding outliers to check the robustness of the correlation between PTH and creatinine. Non-normal data were presented as median and interquartile range. Correlations were assessed via Pearson correlation coefficients. This study is exploratory in nature; therefore, *p*-values should be interpreted cautiously as no formal correction for multiple testing was applied.

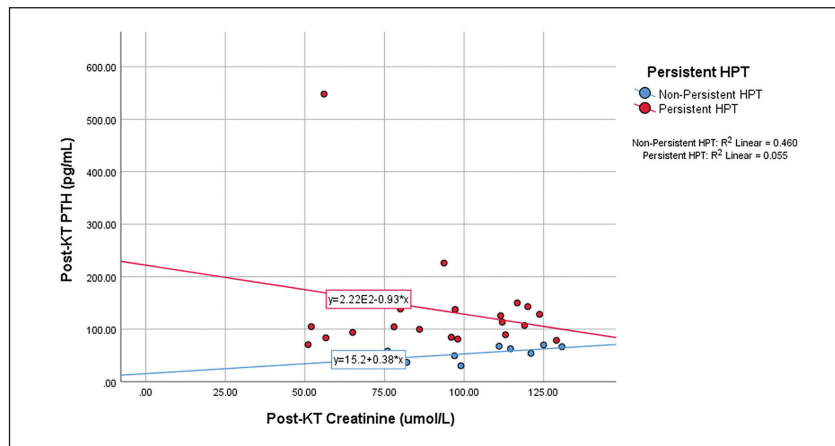


Figure 1. Scatterplot of Post-KT creatinine and PTH levels stratified according to presence of persistent hyperparathyroidism.

Post-transplant PTH measurements, when available, were also used to classify individuals with and without persistent hyperparathyroidism. Tabulations of demographics, independent variables and dependent variables were made as well using these groups.

Statistics were computed using SPSS version 26.

RESULTS

The average age of kidney transplant recipients was 55.3 years (SD = 13.5), with a range of 23 to 79 years (Table 1). Pre-transplant, 26.3% (n = 21) of the sample had secondary hyperparathyroidism (SHPT) (Table 1). Medications taken prior to transplant included calcium supplements (n = 15; 18.8%), various Vitamin D supplements (n = 12; 15.0%), and cinacalcet (a calcimimetic) (n = 2; 2.5%). However, the majority of patients were recorded as not taking any medications or supplements. Available pre-transplant laboratory values for at least five patients each included total serum calcium (n = 11) and serum ionized calcium (n = 6).

Following kidney transplant, medication use increased, particularly for Vitamin D supplements (n = 25; 31.3%) and calcimimetics (n = 21; 26.3%) (Table 2). Other post-transplant medications included alendronic acid (n = 1) and denosumab (n = 1), while calcium supplement use decreased (n = 12; 15.0%). Post-transplant laboratory data were available for serum creatinine (n = 76), serum ionized calcium (n = 70), parathyroid hormone (PTH) (n = 34), and Vitamin D (n = 13). Vitamin D levels and serum creatinine followed a normal distribution. However, serum ionized calcium and PTH levels were both right-skewed, with several outliers exhibiting extremely high values. Of the 34 PTH measurements, 20 (58.8%) exceeded the cutoff of 70 pg/mL, indicating persistent hyperparathyroidism (PHPT) (Table 2).

An initial correlation analysis between PTH levels and serum creatinine revealed a weak, inverse, but statistically

non-significant relationship (r = -0.15, R² = 2.3%, p = 0.404) (Figure 1). A sensitivity analysis, excluding two outliers (one with a significantly high PTH level and another with a significantly high creatinine level), showed a weak, positive correlation with a slightly improved fit to the data, but it remained non-significant (r = 0.24, R² = 5.6%, p = 0.192).

Table 1. Pre-kidney transplant factors abstracted from charts of post-kidney transplant patients

Pre-Kidney Transplant Factors	Post-KT Patients (n = 80)
Age at Kidney Transplant (M, SD)	55.3 (13.5)
History of Hemodialysis (n, %)	
Yes	30 (37.5)
No	50 (62.5)
Secondary Hyperparathyroidism (n, %)	
Yes	21 (26.3)
No	59 (73.8)
Medications Taken (n, %)	
Calcium Supplements	15 (18.8)
Vitamin D Supplements	12 (15.0)
Calcimimetics	2 (2.5)
Others	0 (0)
Laboratory Values (M, SD)	
Serum calcium (mg/dL)	9.2 (0.5)
Serum ionized calcium (mmol/L)	1.2 (0.1)

n = 78 for age, n = 11 for pre-KT serum Ca, n = 6 for pre-KT serum iCa

Table 2. Post-kidney transplant factors abstracted from charts of post-kidney transplant patients

Post-Kidney Transplant Factors	Post-KT Patients (n = 80)
Medications Taken (n, %)	
Calcium Supplements	12 (15.0)
Vitamin D Supplements	25 (31.3)
Calcimimetics	21 (26.3)
Others	2 (2.5)
Laboratory Values (M, SD)	
Serum ionized calcium (mmol/L)*	1.3 (1.2 – 1.4)
Serum creatinine (umol/L)	92.3 (26.9)
Parathyroid hormone (pg/mL)*	82.2 (52.8 – 116.5)
Vitamin D (ng/mL)	27.7 (11.7)

n = 76 for serum creatinine, n = 70 for serum iCa, n = 34 for serum PTH, n = 13 for Vitamin D

*values presented as median and interquartile range

Stratified results

Patients with persistent hyperparathyroidism (PHPT) post-transplant had a higher baseline prevalence of pre-transplant secondary hyperparathyroidism compared to the non-PHPT group (30.0%, n = 6 vs. 14.3%, n = 2; Table 3), though this difference was not statistically significant ($p = 0.42$). Regarding pre-transplant medications, a higher percentage of PHPT patients used calcium supplements (30.0%, n = 6), while Vitamin D supplementation was more frequent in the non-PHPT group (21.4%, n = 3). Post-transplant, PHPT patients showed higher rates of Vitamin D supplement (45.0%, n = 9) and calcimimetic use (85.0%, n=17) (Table 4). While pre-transplant calcium and post-transplant calcium and creatinine levels were comparable between groups, PTH levels were significantly higher in the PHPT subset (Mdn = 105.95, IQR = 52.34). Mean Vitamin D levels were similar across groups, but the PHPT group exhibited much lower variability (SD = 4.15). Stratified correlation analysis revealed that in the non-PHPT group, PTH levels correlated moderately and positively with serum creatinine ($r = 0.68$, $R^2 = 46.0\%$, $p = 0.011$). Conversely, the correlation in the PHPT group remained non-significant, even after excluding the high-PTH outlier.

Table 3. Pre-kidney transplant factors abstracted from charts of post-kidney transplant patients with persistent hyperparathyroidism

Pre-Kidney Transplant Factors	PHPT Patients (n = 20)	Non-PHPT Patients (n = 14)
Age at Kidney Transplant (M, SD)	54.5 (12.9)	56.3 (13.1)
History of Hemodialysis (n, %)		
Yes	6 (30.0)	5 (35.7)
No	14 (70.0)	9 (64.3)
Secondary Hyperparathyroidism (n, %)		
Yes	6 (30.0)	2 (14.3)
No	14 (70.0)	12 (85.7)
Medications Taken (n, %)		
Calcium Supplements	6 (30.0)	0 (0)
Vitamin D Supplements	1 (5.0)	3 (21.4)
Calcimimetics	1 (5.0)	1 (7.1)
Laboratory Values (M, SD)		
Serum calcium (mg/dL)	9.18 (0.57)	9.66 (0.23)
Serum ionized calcium (mmol/L)	–	1.25 (0.13)

Table 4. Post-kidney transplant factors abstracted from charts of post-kidney transplant patients with persistent hyperparathyroidism

Post-Kidney Transplant Factors	PHPT Patients (n = 20)	Non-PHPT Patients (n = 14)
Medications Taken (n, %)		
Calcium Supplements	2 (10.0)	1 (7.1)
Vitamin D Supplements	9 (45.0)	4 (28.6)
Calcimimetics	17 (85.0)	4 (28.6)
Others	1 (5.0)	0 (0)
Laboratory Values (M, SD)		
Serum ionized calcium (mmol/L)*	1.3 (1.3–1.4)	1.3 (1.3–1.4)
Serum creatinine (umol/L)	92.7 (25.9)	94.9 (23.8)
Parathyroid hormone (pg/mL)*	105.9 (85.7–138.0)	47.2 (37.2–63.6)
Vitamin D (ng/mL)	29.8 (4.2)	31.9 (10.0)

DISCUSSION

This retrospective, single-center observational study assessed the prevalence and clinical correlates of PHPT one year after KT. Analysis revealed a 58.8% prevalence of PHPT among the study cohort. The majority of participants (76.3%) had hypertension and diabetes (60%). Predominant etiologies of end-stage renal disease necessitating KT were diabetic kidney disease (57.5%) and hypertensive nephrosclerosis (26.3%). While these findings suggest a link or association between pre-transplant SHPT and post-transplant PHPT, the retrospective nature of the study precludes the determination of causation.

Previous studies report prevalence of PHPT one-year post-KT ranged from 10% to 70%.¹¹ This variability is likely attributable to inconsistencies in definitions, diagnostic thresholds, and monitoring protocols for PHPT. For instance, a study defined post-transplant PHPT as the concurrent presence of elevated parathyroid hormone (PTH) levels (≥ 70 pg/mL) regardless of calcium levels at 1 year post-KT.¹¹ Variations in PTH and calcium monitoring practices across different chronic kidney disease (CKD) stages may also contribute to these disparate rates.²⁴ The prevalence of 58.8% observed in this Philippine cohort, suggests a higher burden of PHPT compared to global averages, likely driven by several contributing factors.

A high baseline prevalence of pre-transplant secondary hyperparathyroidism (SHPT) often predisposes individuals to post-KT PHPT, while Vitamin D deficiency may further exacerbate both secondary and tertiary hyperparathyroidism. Additionally, genetic predispositions within certain populations may influence the development of severe hyperparathyroidism.¹¹ Moreover, post-transplant management – including the use of immunosuppressive medications affecting calcium metabolism, calcium and vitamin D supplementation protocols, and monitoring practices – play a significant role in of post-KT PHPT prevalence.¹¹

In this study, patient-specific factors likely contributed to the higher observed PHPT prevalence. Most PHPT cases occurred in individuals with pre-transplant hyperparathyroidism, with advanced age, diabetes, and vitamin D deficiency identified as additional risk factors. Consistent with previous data, an increased pre-KT PTH level was associated with a higher likelihood of PHPT post-KT,^{11,25} highlighting the importance of pre-transplant PTH levels as a key predictor of post-transplant PHPT.²⁵

Notably, only 37.5% of the study population underwent pre-transplant renal replacement therapy, with the majority receiving preemptive kidney transplantation. Although there is no clear association regarding PHPT post-KT and early transplantation, studies have proven that preemptive KT provides a lower risk of allograft failure and acute rejection. Potential risks from hemodialysis such as catheter-related infection, cardiovascular adverse

effects, intradialytic complications are also avoided in such patients.²⁶ Stratification by PHPT status revealed no significant differences between groups in terms of sex, hypertension prevalence, or age at kidney transplant. Pre-transplant, calcium supplement use was higher among PHPT patients, whereas vitamin D supplementation was more common in non-PHPT patients. Post-transplant, PHPT patients exhibited higher rates of both vitamin D supplement and calcimimetic use. Previous data suggest that pre-transplant calcium supplement intake may lead to a falsely high rate of hypercalcemia at the time of KT. Additionally, intake of calcimimetics pre-KT may also cause lowering of serum calcium levels, thereby masking patients with true hypercalcemia.²⁷ Data has also shown that there may also be a “rebound” effect of cessation of calcimimetics at the time of KT, which may lead to subsequent hyperparathyroidism and hypercalcemia, but the exact mechanism is not fully understood.¹¹

While parathyroidectomy is the established gold standard treatment for tertiary hyperparathyroidism (THPT), its role in managing normocalcemic hyperparathyroidism (HPT) in kidney transplant recipients remains less clear. In the study conducted, 45% of patients with PHPT were treated with vitamin D supplementation, 85% were treated with calcimimetics, and none underwent surgical intervention. Studies have demonstrated that early surgical intervention for persistent hyperparathyroidism (PHPT) prior to one-year post-kidney transplantation has been shown to improve long-term allograft function compared to medical management. A study has shown that at 1-year-post-KT, THPT had a 1.37-fold higher risk of all-cause graft loss and 1.6-fold higher risk of death-censored graft loss due to promotion of vascular calcification and renal interstitial fibrosis. Other studies have shown significant worsening of allograft function as early as 3 months post-KT.^{11,28} However, the optimal timing for intervention remains a subject of debate, with considerable variation observed across different clinical practices.²⁸

Limitations

This study acknowledges several limitations. Primarily, the retrospective, single-center observational nature of this research restricts the generalizability of the findings. The relatively restricted sample size, particularly for subgroup analyses, may limit the statistical power and accuracy of the analysis. The relatively limited sample size, particularly when conducting subgroup analyses, may introduce bias and reduce the statistical power of the study. Furthermore, the reliance on retrospective chart review for data collection may have led to incomplete patient information, potentially influencing the accuracy and comprehensiveness of the analysis. Moreover, the sample size precluded the use of multivariable models to adjust for all potential confounders. Future research should prioritize prospective, multi-center study designs with larger, more diverse cohorts to enhance

generalizability and statistical power for subgroup analyses. Implementing standardized data collection protocols would also improve the completeness and accuracy of patient information, thereby increasing the reliability and validity of the research.

Beyond methodological considerations, this study highlights the need for standardized clinical practices in managing post-transplant THPT. The development and implementation of evidence-based guidelines for the screening, diagnosis, and treatment of this condition could significantly improve patient outcomes. Such guidelines would serve to standardize care across different centers, ensuring timely and appropriate intervention to minimize the risk of allograft complications and optimize long-term graft function. This proactive approach to patient management would ultimately contribute to improved quality of life for kidney transplant recipients. Despite the limitations of this study, valuable insights into the prevalence and clinical correlates of persistent hyperparathyroidism (PHPT) following kidney transplantation have been gained. The findings underscore the need for vigilant monitoring of parathyroid hormone (PTH) levels both pre- and post-transplantation and emphasize the critical importance of optimizing therapeutic strategies to effectively manage PHPT. This is particularly crucial in the Philippines, where the high burden of chronic kidney disease, potential limitations in access to specialized nephrology care, nutritional factors, and potential genetic predispositions within the Filipino population may contribute to an elevated prevalence of PHPT.

Further investigation is warranted to fully determine the specific factors driving this elevated prevalence. This may involve analyzing patient records, comparing findings with other Filipino studies, and conducting further research to explore risk factors for PHPT within this specific demographic. Ensuring consistency between diagnostic criteria used in data collection and international standards is also crucial for accurate comparisons. A comprehensive understanding of these factors will facilitate the development of targeted strategies for improved prevention and management of PHPT in the Philippines, ultimately mitigating its potential adverse effects on graft function and overall patient outcomes.

CONCLUSION

This single-center observational study revealed a significant prevalence (58.8%) of persistent hyperparathyroidism (PHPT) among post-kidney transplant patients. Pre-transplant hyperparathyroidism was identified as a key risk factor for the development of PHPT. These findings underscore the need for close monitoring and optimized management of hyperparathyroidism in this population to improve long-term outcomes.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement (based on Author Form)

PAG: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Funding Acquisition; **HHC:** Conceptualization, Validation, Resources, Writing – review and editing, Visualization, Supervision, Project Administration; **MJF:** Investigation, Resources, Writing – review and editing, Supervision, Project Administration; **JC:** Resources, Writing – review and editing, Supervision, Project Administration

Data Availability Statement

Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Authors Disclosure

The authors declared no conflict of interest.

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