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Journal

American Journal of Kidney Diseases, 81(3)

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Publication Date

2023-03-01

DOI

10.1053/j.ajkd.2022.07.015

Peer reviewed

HHS Public Access

Author manuscript

Am J Kidney Dis. Author manuscript; available in PMC 2024 March 01.

Published in final edited form as:

Am J Kidney Dis. 2023 March ; 81(3): 270–280.e1. doi:10.1053/j.ajkd.2022.07.015.

Parathyroidectomy and Cinacalcet Use in Medicare-Insured Kidney Transplant Recipients

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Abstract

Rationale & Objective: Post-transplant hyperparathyroidism is common and treatment practices are poorly characterized. The goal of this study was to examine the incidence, associations, and outcomes of post-transplant parathyroidectomy and calcimimetic use in a cohort of Medicare-insured US kidney transplant recipients.

Study Design: Retrospective observational cohort study.

Setting & Participants: We used the US Renal Data System to extract demographic, clinical, and prescription data from Medicare Parts A, B and D-insured patients who received their first kidney transplant between 2007 and 2013. We excluded patients with pre-transplant parathyroidectomy.

Predictors: Calendar year of transplantation and pre-transplant patient characteristics.

Outcomes: 1) Incidence of and secular trends in parathyroidectomy and cinacalcet use in the 3 years following transplant, 2) 90-day outcomes following post-transplant parathyroidectomy and cinacalcet initiation.

Analytical Approach: Temporal trends and pre-transplant correlates of parathyroidectomy and cinacalcet use were assessed using proportional hazards models and multivariable Poisson regression, respectively.

Results: 30,127 patients met the inclusion criteria. 10,707 used cinacalcet pre-transplant. 551 patients underwent post-transplant parathyroidectomy and 5413 patients filled ≥ 1 prescription for cinacalcet. The rate of post-transplant parathyroidectomy was stable over time. In contrast,

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Authors' Contributions: Study design: AXW, CRL; data abstraction: SL, MEM-R; data analysis: AXW, CRL, SL, MEM-R; mentorship: GMC, CRL. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

The remaining authors declare that they have no relevant financial interests.

cinacalcet use increased during the period studied. Long dialysis vintage and pre-transplant cinacalcet use were strongly associated with post-transplant parathyroidectomy and cinacalcet use. Roughly one in four patients were hospitalized within 90 days of post-transplant parathyroidectomy, with hypocalcemia-related diagnoses being the most common complication. Parathyroidectomy (versus cinacalcet initiation) was not associated with an increase in acute kidney injury.

Limitations: We lacked access to laboratory data to help assess severity of secondary/tertiary hyperparathyroidism. The cohort was limited to Medicare beneficiaries.

Conclusions: Almost one fifth of our study cohort was treated with parathyroidectomy and/or cinacalcet. Further studies are needed to establish the optimal treatment for post-transplant hyperparathyroidism.

Plain Language Summary:

Treatment options for post-kidney transplant hypercalcemic hyperparathyroidism include cinacalcet and surgical parathyroidectomy. Best practice remains unclear. Using a large database of US kidney transplant recipients, we examined cinacalcet and parathyroidectomy treatment practices, associations, and outcomes in the first 3-years after kidney transplant. 18% of patients used cinacalcet and 1.8% underwent parathyroidectomy after transplant. For patients transplanted between 2007 and 2013, the rate of parathyroidectomy remained stable. In contrast, cinacalcet use increased during the study period. Longer time on dialysis and cinacalcet use prior to transplant were strongly associated with both post-transplant parathyroidectomy and post-transplant cinacalcet use. Hypocalcemia was a common early complication of parathyroidectomy.

Keywords

Hyperparathyroidism; ICD-9-CM codes; kidney transplantation; cohort study; mineral metabolism; clinical nephrology; calcium; outcomes; acute renal failure; hospitalization; parathyroid hormone; United States Renal Data System (USRDS)

INTRODUCTION

Kidney transplantation is the best treatment for most patients with end stage kidney disease (ESKD).[1] Preemptive or early kidney transplantation when possible is associated with superior outcomes.[2] However, due to scarcity of kidney donors and prolonged wait times, many patients spend years on dialysis before receiving a kidney transplant and, as a consequence, frequently have advanced secondary or tertiary hyperparathyroidism at time of kidney transplant.[3]

In advanced chronic kidney disease (CKD) and kidney failure, phosphate retention, nutritional vitamin D deficiency, diminished production of 1,25-dihydroxy vitamin D, and hypocalcemia, often resulting from reduced intestinal calcium absorption and/or augmented urinary calcium excretion (with loop diuretic therapy), all contribute to an increase in parathyroid hormone (PTH) secretion and parathyroid gland hyperplasia – commonly referred to as secondary hyperparathyroidism. Over time, PTH synthesis and secretion may no longer respond to negative feedback stimuli, leading to autonomous or

"tertiary" hyperparathyroidism.[4] Following successful kidney transplant and normalization of kidney function, persistent hyperparathyroidism frequently manifests as hypercalcemia due to reduced skeletal resistance to PTH, often accompanied by hypophosphatemia and hypomagnesemia (the latter compounding one of the metabolic effects of calcineurin inhibitors). Post-transplant hyperparathyroidism is associated with an increased risk of fracture, vascular calcification, interstitial graft calcification, graft loss and mortality.[5–9]

Treatment options for post-transplant hyperparathyroidism include vitamin D and vitamin D analogs (typically limited by hypercalcemia), the calcimimetic agent cinacalcet, and parathyroidectomy.[10–15] Transplant providers typically prefer to wait at least one-year before considering surgical intervention as hyperparathyroidism may spontaneously resolve post-transplant. However, while hypercalcemia regresses in most cases, some degree of hyperparathyroidism commonly endures.[8, 16–18]

Current post-transplant hyperparathyroidism treatment practices in the United States (U.S.) are not well understood and are likely evolving, as greater numbers of patients with long dialysis vintage and moderate to severe secondary hyperparathyroidism are being transplanted. The goals of this study were 1) to determine the incidence and secular trends in post-transplant parathyroidectomy (and cinacalcet use) in Medicare-insured kidney transplant recipients in the U.S.; 2) to identify pre-transplant correlates of post-transplant parathyroidectomy (and cinacalcet use); and 3) to examine 90-day post-transplant complications of parathyroidectomy (and cinacalcet use).

METHODS

Data Source

The U.S. Renal Data System (USRDS) contains demographic, clinical, treatment, and survival data for almost all patients with kidney failure in the U.S. Linkage of the USRDS to Medicare Part A, B, and D records allows for the abstraction of detailed inpatient, outpatient and prescription claims data, the vast majority of whom are Medicare beneficiaries.[19] Kidney transplant recipients typically lose Medicare coverage at 3-years following successful transplantation.

Study Cohort

1. Main study cohort. We identified all adult patients who received their first kidney transplant between January 1, 2007 and December 31, 2013. For inclusion in the study, we required that patients had uninterrupted Medicare Parts A, B, and D coverage for at least 6 months before undergoing kidney transplantation and evidence of at least one Medicare claim in the 2 years prior to transplantation. We excluded patients with any parathyroidectomy claim (Table S1) prior to transplant.
2. Study sub-cohorts. A) Parathyroidectomy sub-cohort: patients who underwent post-transplant parathyroidectomy and B) cinacalcet sub-cohort: patients who used cinacalcet post-transplant.

Patient Characteristics

From the USRDS patient, treatment history, and transplantation files, we abstracted demographic, dialysis, and transplantation characteristics for each patient at time of transplant: recipient age, sex, self-reported race (White, Black, and other), cause of kidney failure, Quételet (body mass) index (BMI), dialysis modality, dialysis vintage, previous solid organ transplant (heart, lung, or liver), patient blood type, donor type (living and deceased), donor age and sex, human leukocyte antigens (HLA) mismatch, calculated panel-reactive antibody (cPRA, at time of transplant), cold ischemia time, induction immunosuppression, and maintenance immunosuppression at time of post-transplant surgery discharge.

We identified the following pre-transplant comorbid conditions using an inpatient and outpatient International Classification of Diseases, Ninth Revision (ICD-9) claims-based algorithm: diabetes mellitus, cancer, coronary artery disease (CAD), cerebrovascular disease (CVD), arrhythmia, liver disease, tobacco use, alcohol dependence, peripheral arterial disease (PAD), hypertension, valvular heart disease (VHD), and chronic pulmonary disease (COPD) (Table S1). We used a 'look-back' window of at least 6 months and up to 2 years before transplant. To assign a pre-transplant comorbidity we required either ≥1 inpatient or ≥2 outpatient claims separated by at least 1 day. We determined healthcare utilization in the 6 months prior to kidney transplant using the following metrics: days spent at skilled nursing facilities, days spent in hospital and number of non-nephrology outpatient visits. We used Part D prescription data to identify patients who had filled a prescription for cinacalcet in the 6 months prior to transplant.

Outcomes

Main Cohort—The two outcomes of interest were 1) post-transplant parathyroidectomy and 2) post-transplant cinacalcet use. Post-transplant parathyroidectomy was identified by current procedural terminology (CPT) codes 60500 and 60505 (Table S1). Cinacalcet use was identified using Medicare Part D prescription claims. We defined post-transplant cinacalcet use as any post-transplant cinacalcet prescription fill. Patients were followed from transplant to the outcome of interest, death, [graft failure], loss of Medicare coverage (Parts A and B and Parts A, B and D for parathyroidectomy and cinacalcet analyses, respectively), 3 years post-transplant (corresponding to a study period of January 1, 2007 to December 31, 2016), and end of study (December 31, 2016), whichever came first. The outcomes 1) post-transplant parathyroidectomy and 2) post-transplant receipt of cinacalcet were assessed independently of one another. For example, a patient treated with cinacalcet post-transplant could undergo parathyroidectomy and vice versa, in which case, the patient is considered to have both outcomes. For the analysis of temporal trends in parathyroidectomy and cinacalcet use, year of transplant was the exposure of interest.

Parathyroidectomy Sub-Cohort—We examined the following 90-day post-parathyroidectomy outcomes: 1) (re)hospitalization, 2) acute kidney injury (AKI), 3) graft failure, and 4) mortality. To avoid capturing a switch from outpatient observation to inpatient status as a hospitalization complication, we required at least 3 days between outpatient parathyroidectomy claim and an inpatient hospitalization. AKI was defined as any inpatient or outpatient AKI claim within 90 days of parathyroidectomy (Table S1). 90-day post

parathyroidectomy graft failure and mortality were identified from the USRDS patient files. We excluded patients who had graft failure prior to parathyroidectomy or first cinacalcet prescription fill. Patients were followed from parathyroidectomy to the outcomes, death (for non-mortality outcomes), loss of Medicare coverage, 90 days post-parathyroidectomy, 3 years post-transplant, and end of study (December 31, 2016), whichever came first.

Cinacalcet Sub-Cohort—We examined the following 90-day post-cinacalcet initiation outcomes: 1) hospitalization, 2) AKI, 3) graft failure, and 4) mortality. We excluded patients who had graft failure prior to parathyroidectomy or first cinacalcet prescription fill. Patients were followed from cinacalcet initiation to the outcomes, death (for non-mortality outcomes), loss of Medicare coverage 90 days post-cinacalcet initiation, 3 years post-transplant, and end of study (December 31, 2016), whichever came first.

Sensitivity Analyses

1. We examined post-transplant cinacalcet initiation requiring ≥2 cinacalcet prescription fills (rather than ≥1) to define post-transplant cinacalcet use.
2. The majority of cinacalcet was prescribed early post-transplant, while parathyroidectomy was performed later post-transplant. To account for these differences in timing of treatment, we performed a sensitivity analysis that examined 1) 90-day post-parathyroidectomy hospitalization and AKI, and 2) 90-day post-cinacalcet initiation hospitalization and AKI restricted to those patients who underwent parathyroidectomy/initiated cinacalcet ≥1-year post-transplant.

Statistical Analysis

Baseline characteristics were presented stratified by year of transplant. Continuous variables were presented as either mean with standard deviation (SD) or median with interquartile range (IQR) and categorical variables as proportions.

For each transplant year, the incidence of parathyroidectomy and cinacalcet use was determined over the subsequent 3 years. We computed unadjusted incidence rates (IR), defined as the number of events over patient-time observed and examined secular trends by computing unadjusted and incrementally adjusted cause-specific hazard ratios, using cause-specific hazards models, and their corresponding 95% confidence intervals (CI) for incident parathyroidectomy and cinacalcet use by year of transplant: model 1 included only the exposure of interest (year of transplant); model 2 was additionally adjusted for age at time of transplant, sex, and race; model 3 was additionally adjusted for cause of ESKD, dialysis vintage, and most recent dialysis modality, BMI, all comorbidities and healthcare utilization metrics; and model 4 was additionally adjusted for transplant characteristics, baseline cinacalcet use and medications and therefore included all variables listed as baseline characteristics on Table 1. Trend analysis used orthogonal polynomial contrasts.[20] Given our large sample size, we did not perform variable selection for this analysis. Instead, we provided estimates for incrementally adjusted models, allowing the reader to quantify the effect of confounding of the various variables included in the models.

We used multivariable Poisson regression to examine associations between pre-transplant characteristics and receipt of 1) post-transplant parathyroidectomy and 2) post-transplant cinacalcet prescription. Transplant year, age at transplant, sex, dialysis vintage, and dialysis modality were pre-selected for inclusion in the model. Other variables were selected using a backwards elimination method using a likelihood ratio test at a significance level of 0.157 as suggested by Heinze et al.[21] Immunosuppression variables were not included in the models as the goal was to identify pre-transplant associations with post-transplant parathyroidectomy and cinacalcet use. For 90-day post-parathyroidectomy/cinacalcet initiation outcomes, we presented IRs and used unadjusted Poisson regression to compute 95% CIs.

Missing Data

24,453 patients (81%) had at least one variable missing. The percentage of missing values was low, in the order of <1% for most variables with records missing, with exception of the variables BMI (8%), HLA mismatch (8%), PRA (9%), and cold ischemia time (11%). We assumed that the data was missing at random given the observed characteristics. Missing data were handled using multiple imputation by fully conditional specification (FCS) as implemented in SAS. Nineteen imputed datasets were obtained for the parathyroidectomy study and cinacalcet analyses, respectively. [22, 23] We included all covariates, the Nelson-Aalen estimate of the cumulative hazard, and event indicator in the imputation model.[24–26] Model parameters were estimated by applying the appropriate analysis model (Cause-specific hazards models or Poisson regression) to each imputed data set separately. These estimates and their standard errors were combined using Rubin's rules.[27] For the analysis looking at associations between pre-transplant characteristics and receipt of post-transplant parathyroidectomy or post-transplant cinacalcet prescription, we fitted a final Poisson regression model to each imputed dataset that included the pre-selected variables plus any variable selected through the backward elimination algorithm, applied to each imputed dataset separately.

We conducted statistical analyses using SAS software, version 9.4 (SAS institute, Inc., Cary, NC, USA), Stata MP, version 16 (StataCorp, College Station, TX). The Institutional Review Board at Stanford University (IRB-17904) approved the study and granted a waiver of informed consent.

RESULTS

30,127 kidney transplant recipients met the study's inclusion criteria (Figure 1). Patient characteristics at the time of transplant are shown for the cohort as a whole and stratified by baseline cinacalcet use in Table 1. About one-third of patients (n=10,707) had filled a prescription for cinacalcet before transplant. Pre-transplant cinacalcet users were younger, more likely to be female, Black, and of longer dialysis vintage than non-users.

551 parathyroidectomies were observed over 70,883 patient-years of follow-up, yielding an unadjusted IR of 78 (95% Cl: 72–84) parathyroidectomies per 10,000 patient-years. The median time from transplant to parathyroidectomy was 13.9 months. 319 parathyroidectomies were performed as inpatient and 232 as outpatient procedures, in total

accounting for 1.8% of the entire study cohort. 5413 patients filled at least one prescription for cinacalcet over 58,326 patient-years follow-up, yielding an unadjusted IR of 928 (95% Cl: 904–953) post-transplant cinacalcet users per 10,000 patient-years. The median time from transplant to first-post-transplant cinacalcet prescription fill was 6.8 weeks. When we defined post-transplant cinacalcet use as ≥2 post-transplant cinacalcet prescription fills, we identified 4458 patients over 60,807 person-years follow-up yielding an unadjusted rate of 733 (95% Cl: 712–755) post-transplant cinacalcet users per 10,000 patient-years.

The incidence of parathyroidectomy in the 3 years following kidney transplant did not change significantly between 2007 and 2013 (trend p-value ≥ 0.1 for all models; Figure 2A and Table S2). In contrast, post-transplant cinacalcet use did increase significantly (trend p-value ≤ 0.002 for all models). The unadjusted and Model 4-adjusted hazard ratio (HR) for cinacalcet use in patients transplanted in 2013 (vs 2007) were 1.4 (95% CI: 1.3–1.5) and 1.2 (95% CI: 1.1–1.3) respectively (Figure 2B and Table S3).

Tables 2 and 3 show pre-transplant characteristics associated with receipt of post-transplant parathyroidectomy and cinacalcet use, respectively. Unsurprisingly, longer pre-transplant dialysis vintage and pre-transplant cinacalcet use were most strongly associated with both. The risk of parathyroidectomy and cinacalcet use was approximately 2.9- and 3.7-fold higher, respectively in those patients on dialysis for 5 or more years (versus less than 2 years). Figure 3 shows the percent of transplant recipients who received parathyroidectomy only, cinacalcet and parathyroidectomy, and cinacalcet only in the entire cohort and then stratified by pre-transplant cinacalcet user status.

Finally, we examined 90-day hospitalization, AKI, graft failure, and mortality following post-transplant parathyroidectomy and cinacalcet initiation. Of the 551 patients who underwent post-transplant parathyroidectomy, 25% were hospitalized within 90 days of parathyroidectomy yielding an IR of 12 (95% CI: 10–15) events per 10 person-years. The mean time from parathyroidectomy to hospitalization was 27 days. A hypocalcemia/hypoparathyroidism-related diagnosis was present in 44% of post-parathyroidectomy hospitalizations. 9.4% were diagnosed with AKI within 90 days post-parathyroidectomy yielding an IR of 4 (95% CI: 3–5) events per 10 person-years. There was one death (0.2%) and three graft failures (0.5%). Of the 5413 patients who initiated cinacalcet, 27.7% were hospitalized within 90 days of their first post-transplant prescription for IR of 14 (95% CI: 13–15) events per 10 person-years. The mean time from first post-transplant prescription to rehospitalization was 31 days. 20.4% were diagnosed with AKI yielding an IR of 9 (95% CI: 8–10) of events per 10 person-years. There were 39 deaths (0.7%) and 94 graft failures (1.7%). In the sensitivity analyses, where we restricted to patients who underwent parathyroidectomy or received their first cinacalcet prescription 1 year or more after transplant, we found that for the 319 patients who underwent parathyroidectomy 1 year or more (median 1.7 years) after transplant, 23.5% and 7.8% were hospitalized and had an AKI claim within 90 days, respectively. For the 692 patients who were first prescribed cinacalcet 1 year or more (median 1.6 years) after transplant, 14.7% and 10.8% were hospitalized and had an AKI claim within 90 days, respectively. Tables 4 and 5 summarize 90-day post parathyroidectomy and 90-day post-cinacalcet initiation outcomes, respectively. Data are shown for the cohort as a whole and restricted to those who underwent parathyroidectomy/

initiated cinacalcet ≥1-year post-transplant. 90-day post parathyroidectomy hospitalization and AKI rates appeared similar in patients who had and had not used cinacalcet post-transplant prior to undergoing parathyroidectomy (Table S4).

DISCUSSION

We used a nationwide registry of Medicare-insured U.S. kidney transplant recipients to examine parathyroidectomy and cinacalcet use in the first 3-years following kidney transplantation. The rate of parathyroidectomy in the first 3-years post-transplant remained stable from 2007 to 2016 while post-transplant cinacalcet use increased. Among factors associated with post-transplant parathyroidectomy and cinacalcet use, the most striking associations were dialysis vintage and pre-transplant cinacalcet use for both.

Cinacalcet and parathyroidectomy are the chief treatments for post-transplant hypercalcemic hyperparathyroidism. Cinacalcet allosterically modulates the parathyroid calcium sensing receptor to increase its sensitivity to extracellular calcium. Treatment with cinacalcet decreases PTH transcription and secretion and reduces parathyroid gland hyperplasia.[28, 29] Parathyroid surgical interventions include total parathyroidectomy with or without auto-transplantation, subtotal parathyroidectomy and adenomectomy. High quality data on post-transplant cinacalcet use and parathyroidectomy are limited. A small placebo-controlled randomized clinical trial (RCT) (n=57 per treatment arm) showed that post-transplant cinacalcet was safe and more efficacious than placebo at correcting hypercalcemia.[12] Another RCT (n=15 per treatment arm) compared post-transplant parathyroidectomy with cinacalcet use and found that parathyroidectomy was more likely to result in sustained normocalcemia and, after 14 months, was more cost-effective. The study also hinted at an improvement in bone mineral disease (BMD) associated with parathyroidectomy over cinacalcet use.[30] The paucity of data for the treatment of post-transplant hypercalcemic hyperparathyroidism is additionally reflected in the Kidney Disease: Improving Global Outcomes (KDIGO) Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder guidelines, which state that ‘cinacalcet is not approved for the treatment of hyperparathyroidism in kidney transplant recipients; however, it is clinically used, especially in patients with significant hypercalcemia. While efficiently correcting hypercalcemia, cinacalcet so far has failed to show a beneficial impact on bone mineralization in the transplant population’.[31] More recent KDIGO transplant guidelines suggest that patients requiring ‘PTH-lowering therapy should first receive medical therapy in the form of calcimimetic, calcitriol, or vitamin D analogs’, favoring ‘parathyroidectomy before transplantation’.[32]

We found that post-transplant cinacalcet use was common and prescribed with increasing frequency over the period studied. There is no guidance on when to initiate cinacalcet post-transplant or what serum calcium and PTH concentrations to target as its use is off-label. In our practice, cinacalcet is used as first line therapy for patients with moderate to severe post-transplant hypercalcemia secondary to hyperparathyroidism. Absent refractory severe hypercalcemia, we usually defer parathyroidectomy for at least 12 months post-transplant. Median time to parathyroidectomy in our study was nearly 14 months, reflecting a broad adherence to this practice in the U.S.

A decline in allograft function following parathyroidectomy is well described [30, 33, 34] and cited as a rationale for favoring pre-transplant parathyroidectomy in the KDIGO guidelines.[24] A potential mechanism includes altered renal hemodynamics due to loss of PTH-mediated vasodilation.[33, 35] Higher pre-parathyroidectomy PTH concentrations appear to increase the risk of post-parathyroidectomy GFR decline.[36] A reduction in allograft function has also been reported following cinacalcet initiation, an effect that seems to be reversible with cinacalcet discontinuation.[37, 38] In our study, we found that nearly one in 10 patients who underwent parathyroidectomy had an AKI claim within 90 days of his or her surgery. However, when we restricted our analysis to patients who were either prescribed cinacalcet or underwent parathyroidectomy 1 year or later after transplant, we observed numerically more AKI claims in the cinacalcet group. Awareness of this phenomenon is vital as even small decrements in GFR early post-transplant typically trigger kidney biopsy or empiric treatment for rejection.

Cinacalcet treatment was initiated early post-transplant (median 6.8 weeks) while most parathyroidectomies were performed after 1 year (median 13.9 months). We suspect that most hospitalizations occurring after cinacalcet initiation were unrelated to the medication. When the analysis was restricted to patients who initiated cinacalcet 1 year or more after transplant, the 90-day hospitalization rate fell from 27.7% to 14.7%. Hypocalcemia related hospital claims following cinacalcet initiation were rare.

90-day post-parathyroidectomy hospitalization rates were 25% and 23.5% in the group as a whole and in a cohort restricted to those undergoing parathyroidectomy more than 1 year post transplant. Hypocalcemia-related claims were associated with 40% of post-parathyroidectomy hospitalization. Hypocalcemia following parathyroidectomy is a common and potentially life-threatening complication. Unlike patients on dialysis, kidney transplant recipients do not have the safety net of a high calcium dialysate and/or calcitriol or active vitamin D analogs to help prevent hypocalcemia associated with “hungry-bone syndrome.”

About one-third of our cohort was treated with cinacalcet prior to transplantation. Pre-transplant cinacalcet use was strongly associated with both post-transplant cinacalcet use and parathyroidectomy. This was not surprising, as studies have shown that patients receiving dialysis who are initiated on cinacalcet have higher baseline PTH concentrations than those not initiated [39, 40] and in the absence of laboratory data we assume pre-transplant cinacalcet use (vs non-use) is a proxy for the presence of more severe secondary hyperparathyroidism at time of transplant. Whether the use of cinacalcet pre-transplant directly alters the risk of post-transplant parathyroid-related complications, either by allowing pre-transplant parathyroid surgery to be deferred or through altering the natural history of secondary hyperparathyroidism by other means (e.g., attenuation of parathyroid hyperplasia) cannot be answered by this study. Given the nature of deceased donor kidney transplantation, it may not be possible to arrange pre-transplant parathyroidectomy for patients with severe secondary hyperparathyroidism. However, in the setting of planned living donor transplantation, a trial of calcimimetic withdrawal may help to identify patients who might benefit from pre-transplant parathyroidectomy or ongoing therapy with

cinacalcet to maintain control of CKD-MBD through the dialysis-to-functioning-allograft transition.

Our study has several strengths. The sample size was relatively large, and diverse by age, sex, self-reported race/ethnicity, and primary cause of kidney disease. We had comprehensive data on each kidney transplant and hospitalization for all Medicare beneficiaries. There are several key limitations. In order to capture hospital claims (for parathyroidectomy and other events) we had to restrict our sample to Medicare beneficiaries. As such, we may have missed parathyroidectomy and other events in patients younger than 65 who were within their first three years of ESKD (when they may have had employer group health or other insurance to cover costs of hospitalization). Our claims-based algorithmn did not allow us to classify the type of parathyroidectomy procedure that was performed. Moreover, vis-à-vis cinacalcet prescription, we needed to restrict our sample to patients with Medicare Part D for drug coverage. In some instances, patients might have filled a prescription for cinacalcet, but stopped the drug after just a few days because of adverse effects. Lack of laboratory data such as parathyroid hormone level, serum calcium and serum phosphate limits our ability to assess the severity of pre- and post-transplant hyperparathyroidism. Finally, our study was not designed to compare the outcomes of those patients treated with cinacalcet versus parathyroidectomy.

In conclusion, we examined early post-transplant parathyroidectomy and cinacalcet prescription practices in a large and diverse cohort of US kidney transplant recipients. Almost 20% of our study cohort received a cinacalcet prescription (18%) or underwent parathyroidectomy (1.8%) in the first three years following their transplant. With ever-lengthening wait times for kidney transplantation, the frequency and severity of post-transplant hyperparathyroidism have steadily increased. Unfortunately, current management is based on rather sparce data. Prospective studies are urgently needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial Disclosure:

Support: This work was supported by grant number 1R25Al147369-01 (Wang) from the National Institute of Allergy and Infectious Diseases (NIAID) and K24DK085446 (Chertow) from the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK). The funders of this study had no role in study design, collection, analysis, interpretation of data, writing, and/or the decision to submit for publication.

GMC reports having served as consultants to Akebia, Amgen, Ardelyx, Astra Zeneca, Baxter, Cricket, DiaMedica, Gilead, Miromatrix, Reata, Sanifit, Unicycive, Vertex; having ownership interest in Ardelyx, CloudCath, Durect, DxNow, Eliaz Therapeutics, Outset, Physiowave, PuraCath; and having served as scientific advisor to or membership in Board of Directors, Satellite Healthcare, Co-Editor, Brenner & Rector's The Kidney (Elsevier); and other interests/relationships in DSMB service, Angion, Bayer, ReCor.

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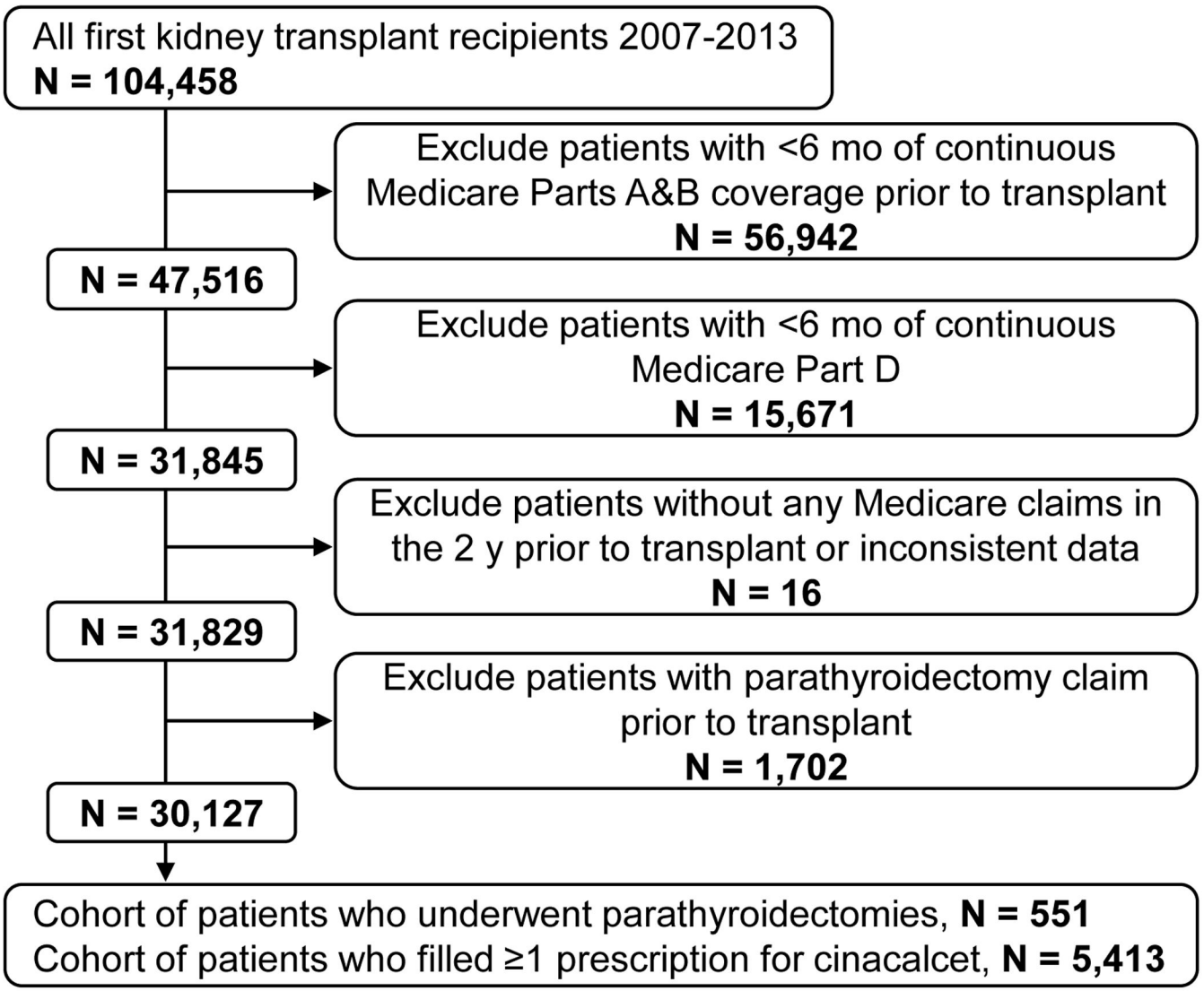

Figure 1.
Cohort Assembly

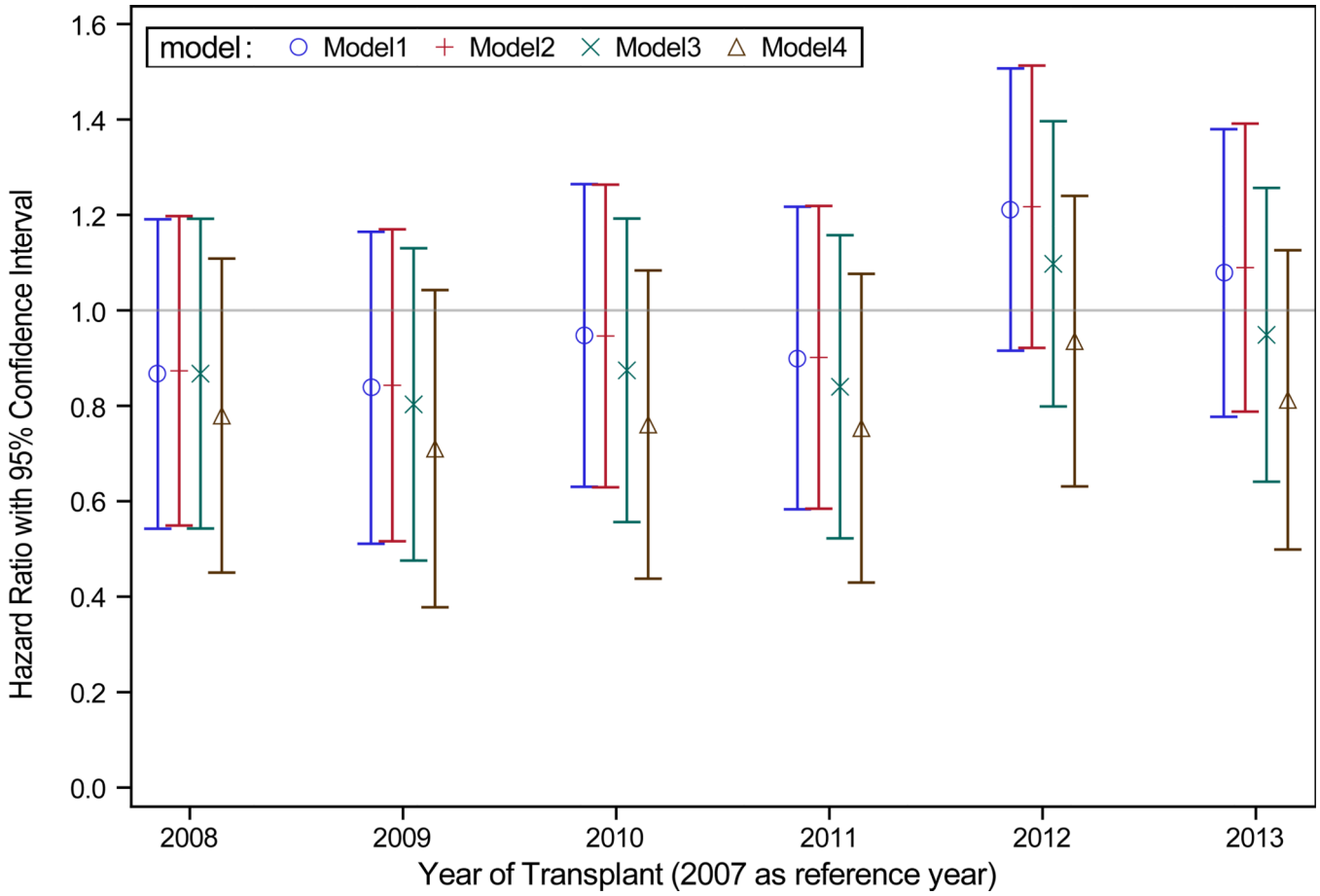

Figure 2A.
Trends in post-transplant parathyroidectomy by year of transplant

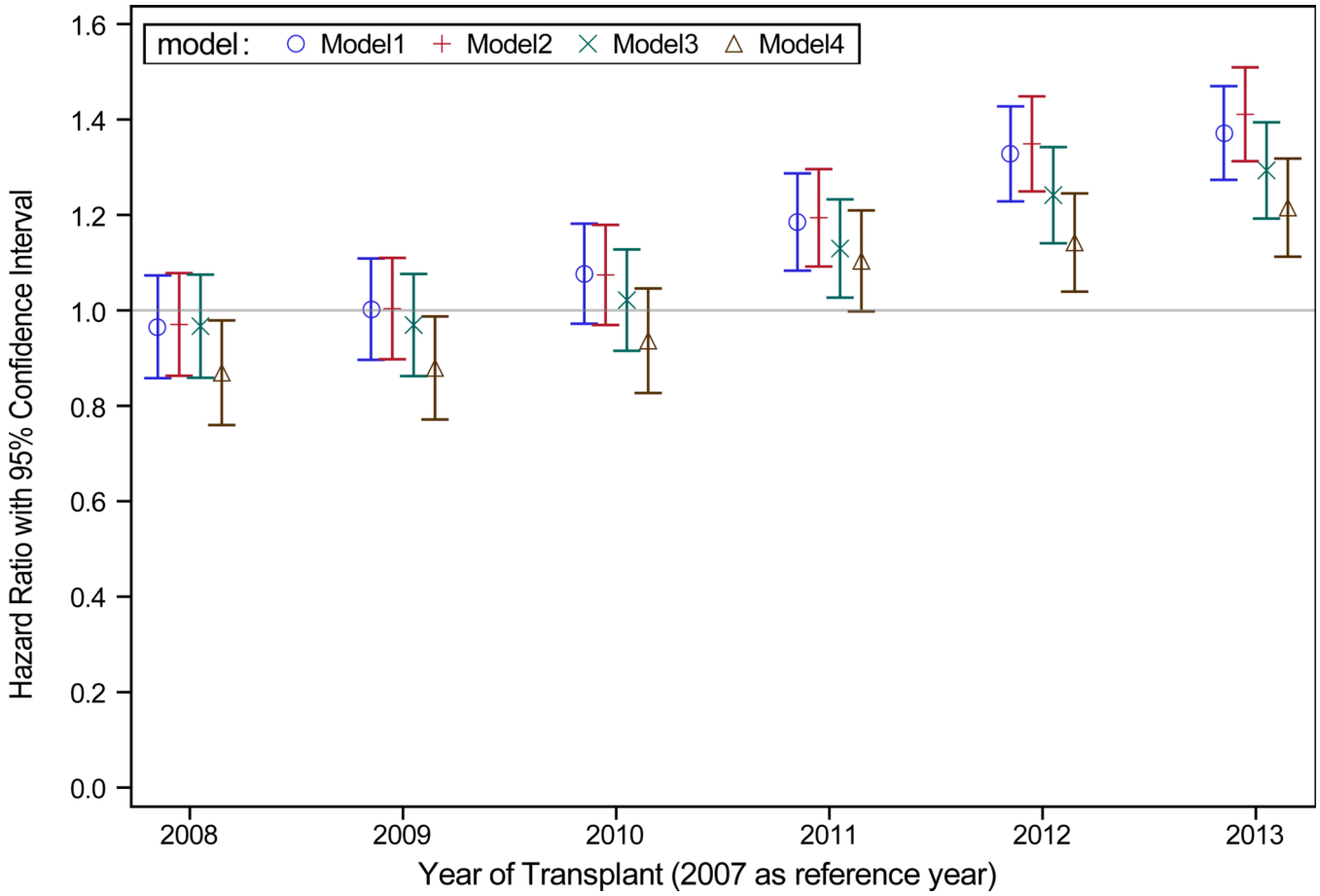

Figure 2B.
Trends in post-transplant cinacalcet use by year of transplant

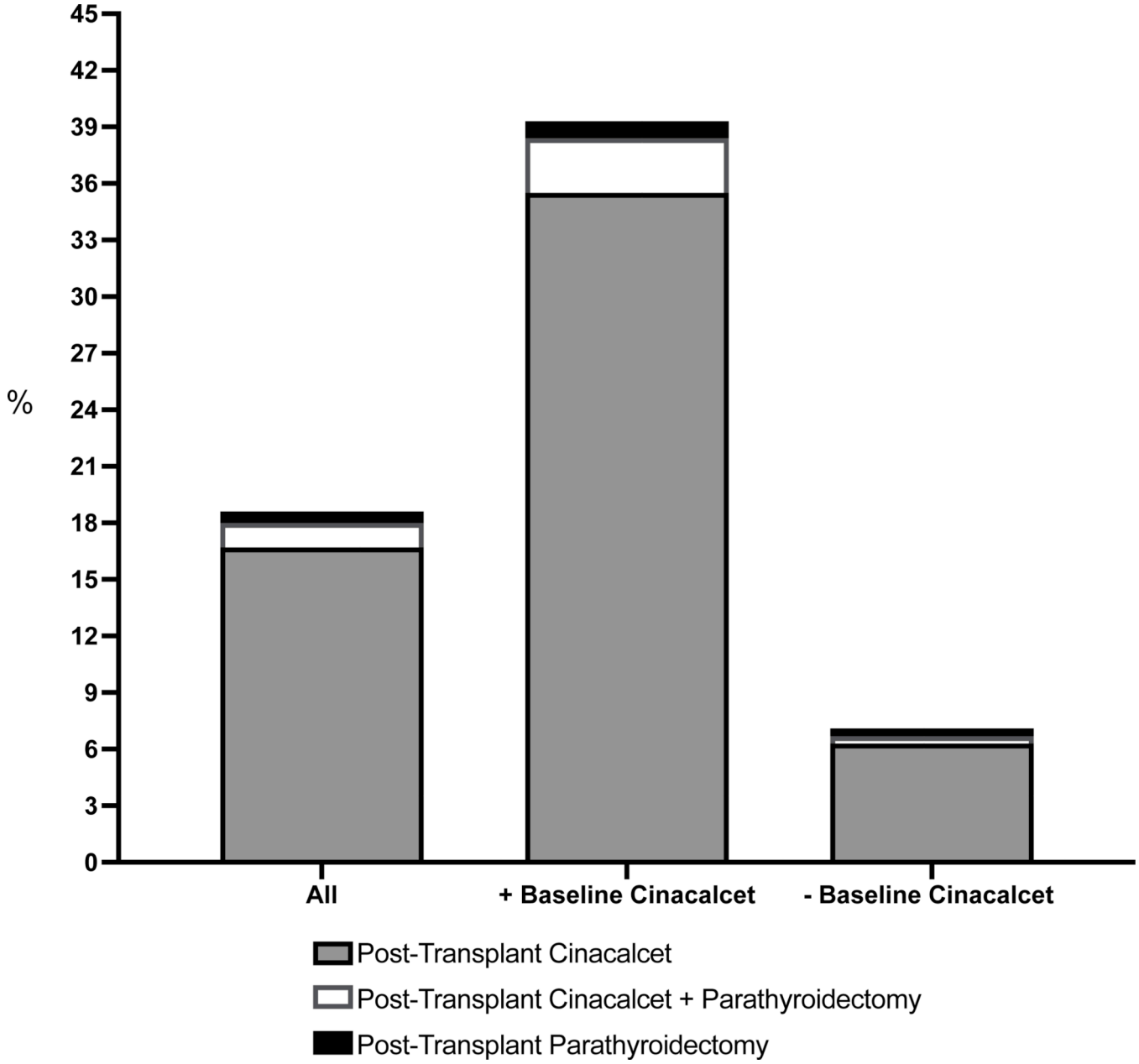

Figure 3.

Percentage of patients who underwent parathyroidectomy only, underwent parathyroidectomy and used cinacalcet, and used cinacalcet only in the first 3 years following kidney transplant for the cohort as 1) a whole (All) (N=30,127), 2) pre-transplant cinacalcet users (+ Baseline Cinacalcet) (N=10,707), and 3) pre-transplant cinacalcet non-users (- Baseline Cinacalcet) (N=19,420)

Table 1.

Baseline characteristics for the cohort as a whole and stratified by pre-transplant cinacalcet use

Baseline Characteristics	All N=30,127	Pre-Transplant Cinacalcet Users N=10,707	Pre-Transplant Cinacalcet Non-users N=19,420
Male (%)	61.3	60.1	62
Age (years ± SD)	50.9 ± 13.8	48.8 ± 13.3	52 ± 14.0
Race (%)			
White	57.6	49.7	62.0
Black	34.6	42.9	30
Other	7.8	7.4	8
Cause of ESKD (%)			
Diabetes	35.6	28.8	39.3
Hypertension	25.6	29.2	23.6
Glomerulonephritis	20.6	22.7	19.5
Other	17.9	19	17.3
Missing	0.4	0.4	0.3
BMI at Transplant (kg/m^2 ± SD)	28 ± 5.2	28.4 ± 5.3	27.8 ± 5.1
≥30	32.1	35.7	30.1
Missing	7.4	5.8	8.2
Dialysis Modality (%)			
Hemodialysis	85.8	86.5	85.4
Missing	0.7	0.6	0.8
Dialysis Vintage Years, median (IQR)	3.8 (2.3–5.6)	4.7 (3.2–6.7)	3.3 (1.9–4.9)
Comorbidities (%)			
Diabetes mellitus	56.2	50.0	59.5
Alcohol dependence	1.7	1.4	1.8
CAD	35.1	32.7	36.4
COPD	18.4	18.4	18.4
CVD	10.3	9.2	10.8
Cerebral bleed	0.8	0.6	0.9
Cancer	5.8	5.5	6
Hypertension	94.8	94.4	95
VHD	18.8	19.5	18.4
PVD	23.5	23.1	23.8
Liver disease	27.1	26.7	27.3
Tobacco use	9.8	10	9.6
Arrhythmia	7.8	7.7	7.9
Previous Solid Organ Transplant (%)	3.5	2.4	4.2
Patient Blood Type (%)			
O	46.5	48.3	45.5
A	34.1	31.9	35.2

Baseline Characteristics	All N=30,127	Pre-Transplant Cinacalcet Users N=10,707	Pre-Transplant Cinacalcet Non-users N=19,420
B	14.2	15.3	13.7
AB	4.6	3.8	5.0
Missing	0.6	0.6	0.6
Donor Type (%)			
Living donor	17.8	13.2	20.3
Missing	6.6	4.8	7.6
Donor Characteristics			
Age (years ± SD)	39.0 ± 15.8	38.3 ± 15.8	39.3 ± 15.8
Missing	0.6	0.7	0.6
Male donor (%)	56.3	57.3	55.8
Missing	0.6	0.6	0.6
HLA Mismatch			
0	5.7	4.6	6.3
1–3	21.3	19	22.5
4–6	65.3	70.5	62.4
Missing	7.7	5.9	8.7
Panel-Reactive Antibody (%)	14.2 ± 28.2	15.1 ± 29.1	13.7 ± 27.7
Missing	9	6.7	10.3
Cold Ischemia Time (hours ± SD)	15.3 ± 10.9	16.1 ± 10.9	14.9 ± 10.9
Missing	11.2	8.5	12.7
Nursing Home Stay (%)	1.3	1.1	1.4
Hospital Days, median (IQR)	2.0 (1–3)	2.0 (1–3)	2.0 (1–3)
Non-Nephrology Clinic Visits, median (IQR)	12.0 (6–20)	11.0 (5–19)	12.0 (6–21)
Pretransplant Cinacalcet Use (%)	35.5	100	0
Induction Immunosuppression (%)			
Thymoglobulin	46.7	49.4	45.1
Alemtuzumab	12.5	13.5	12.0
IL2 RA	23.3	22.4	23.9
Maintenance Immunosuppression			
Tacrolimus	83.4	85.7	82.1
Cyclosporine	5.1	4.4	5.5
mTOR	2.9	2.7	5.1
Mycophenolate	86.4	88.5	85.3
Azathioprine	0.4	0.4	0.4
Steroid	87.1	89	86

Data for categorical values are percentages; data for continuous variables are given as mean ± standard deviation (SD) or median (interquartile range, IQR). Abbreviations: BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; ESKD, end stage kidney disease; PVD, peripheral vascular disease; VHD, valvular heart disease; IL2 RA, Interleukin-2 receptor antagonist; mTOR, mammalian target of rapamycin.

Table 2.

Multivariable associations between pre-transplant characteristics and receipt of post-transplant parathyroidectomy using imputed data, N=30,127

Variables	IRR (99% CI)	*P*-value
Year of Transplant (referent is 2007)		0.8
2008	0.8 (0.5–1.2)	
2009	0.8 (0.5–1.2)	
2010	0.8 (0.5–1.2)	
2011	0.8 (0.5–1.2)	
2012	1.0 (0.7–1.5)	
2013	0.9 (0.6–1.3)	
Age (vs 18–44)		0.003
45–64	1.4 (1.0–1.8)	
≥65	1.5 (1.0–2.1)	
Female	1.3 (1.0–1.6)	0.003
Race (white is referent)		0.005
Black	0.7 (0.6–0.9)	
Other	0.7 (0.4–1)	
Dialysis Vintage, years (vs <2)		<0.001
2 to <5	2.1 (1.4–3.2)	
≥5	2.9 (1.8–4.7)	
Hemodialysis (vs peritoneal dialysis)	0.8 (0.6–1.1)	0.09
Arrhythmia	0.7 (0.4–1.2)	0.9
Coronary Artery Disease	0.8 (0.6–1)	0.02
Lung Disease	0.8 (0.6–1)	0.003
Liver Disease	0.8 (0.6–1.1)	0.09
Previous Solid Organ Transplant	1.5 (0.8–2.9)	0.10
Donor Blood Type (O is referent)		0.2
A	0.9 (0.7–1.2)	
B	1.0 (0.7–1.4)	
AB	0.5 (0.2–1.1)	
Pre-Transplant Cinacalcet Use	4.2 (3.2–5.4)	<0.001

Preselected variables = transplant year, age at transplant, sex, dialysis vintage, and dialysis modality. Other variables were selected using backward selection. Abbreviations: IRR, incident rate ratio; CI, confidence interval

Table 3.

Multivariable associations between pre-transplant characteristics and post-transplant cinacalcet use using imputed data, N=30,127

Variables	IRR (99% CI)	*P*-value
Year of Transplant (referent is 2007)		0.2
2008	0.8 (0.8–1)	
2009	0.7 (0.8–1.1)	
2010	0.8 (0.9–1.2)	
2011	0.8 (1–1.4)	
2012	1.1 (1.1–1.5)	
2013	1 (1.2–1.6)	
Age (vs 18–44)		0.001
45–64	1.5 (1.2–2)	
≥65	1.5 (1–2.1)	
BMI, kg/m^2 (vs <18.5)		0.2
18.5–25	1.5 (0.6–3.9)	
25–30	1.4 (0.5–3.5)	
≥30	1.2 (0.5–3.2)	
Female	1.3 (1.1–1.6)	0.002
Race (white is referent)		0.02
Black	0.8 (0.6–1)	
Other	0.7 (0.5–1.1)	
Dialysis Vintage, years (vs <2)		<0.001
2 to <5	2.2 (1.5–3.3)	
≥5	3.7 (2.5–5.6)	
Hemodialysis (vs peritoneal dialysis)	0.8 (0.6–1.1)	0.1
Cause of ESKD (glomerulonephritis is referent)		0.002
Diabetes	1.3 (0.9–1.9)	
Hypertension	1.1 (0.8–1.7)	
Other	1.7 (1.1–2.4)	
Cerebrovascular Disease	1.2 (0.8–1.8)	0.2
Coronary Artery Disease	0.7 (0.4–1.2)	0.1
Lung Disease	0.8 (0.6–1.1)	0.1
Alcohol	0.8 (0.6–1.1)	0.07
Hypertension	1.1 (0.7–1.8)	0.5
Valvular Disease	1.1 (0.7–1.7)	0.7
Diabetes Mellitus	0.8 (0.6–1.1)	0.09
Peripheral Vascular Disorder	1.1 (0.8–1.5)	0.4
Previous Solid Organ Transplant	1.3 (0.7–2.5)	0.3
Donor blood type (O is referent)		0.09
A	0.9 (0.7–1.1)	
B	1 (0.7–1.3)	
AB	0.5 (0.2–1.1)	

Variables	IRR (99% CI)	*P*-value
Donor Age, years	1 (1–1)	1.0
Cold Ischemia, hours	1 (1–1)	0.4
Pre-Transplant Cinacalcet Use	6 (4.7–7.8)	<0.001

Preselected variables = transplant year, age at transplant, sex, dialysis vintage, and dialysis modality. Other variables were selected using backward selection. Abbreviations: BMI, body mass index; ESKD, end stage kidney disease; IRR, incident rate ratio; CI, confidence interval

Table 4.

Hospitalization and acute kidney injury within 90 days of post-transplant parathyroidectomy

All Post-Transplant Parathyroidectomies (N=551)	**Percent**
Hospitalization within 90 days	25
Principal Hospitalization Diagnoses with Frequencies >5%	
Hypocalcemia	16.6
Complications of Transplant Kidney	12.1
Abnormal Reaction Organ Transplant	8.3
Hungry Bone Syndrome	7.6
Hypocalcemia (hospitalization claim in any position)	44
Acute Kidney Injury	9.4
Parathyroidectomy After 1-Year Post-Transplant (N=319)	
Hospitalization within 90 days	23.5
Principal Hospitalization Diagnoses with Frequencies >5% *Hypocalcemia*	16
Abnormal Reaction Organ Transplant	10
Complications of Transplanted Kidney	9
Hungry Bone Syndrome	5.6
Hypocalcemia (hospitalization claim in any position)	43.9
Acute Kidney Injury	7.8

Table 5.

Hospitalization and acute kidney injury within 90 days of post-transplant cinacalcet initiation

All Post-Transplant Cinacalcet Users (N=5413)	**Percent**
Hospitalization within 90 days	27.7
Principal Hospitalization Diagnoses with Frequencies >5%	
Complications of Transplant Kidney	25.2
Abnormal Reaction Organ Transplant	10.5
Hypocalcemia (hospitalization claim in any position)	2
Acute Kidney Injury	20.4
Initiated Cinacalcet After 1-Year Post-Transplant (N=692)	
Hospitalization within 90 days	14.7
Principal Hospitalization Diagnoses with Frequencies >5% *Complications of Transplanted Kidney*	12.1
Abnormal Reaction Organ Transplant	8.6
Acute Kidney Injury	10.8