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Hyperparathyroidism at 1 year after kidney transplantation is associated with graft loss

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ABSTRACT

Background: Hyperparathyroidism persists in many patients after kidney transplantation. The purpose of this study was to evaluate the association between post-transplant hyperparathyroidism and kidney transplantation outcomes.

Methods: We identified 824 participants from a prospective longitudinal cohort of adult patients who underwent kidney transplantation at a single institution between December 2008 and February 2020. Parathyroid hormone levels before and after kidney transplantation were abstracted from medical records. Post-transplant hyperparathyroidism was defined as parathyroid hormone level ≥70 pg/mL 1 year after kidney transplantation. Cox proportional hazards models were used to estimate the adjusted hazard ratios of mortality and death-censored graft loss by post-transplant hyperparathyroidism. Models were adjusted for age, sex, race/ethnicity, college education, parathyroid hormone level before kidney transplantation, cause of kidney failure, and years on dialysis before kidney transplantation. A Wald test for interactions was used to evaluate the risk of death-censored graft loss by age, sex, and race.

Results: Of 824 recipients, 60.9% had post-transplant hyperparathyroidism. Compared with non-hyperparathyroidism patients, those with post-transplant hyperparathyroidism were more likely to be Black (47.2% vs 32.6%), undergo dialysis before kidney transplantation (86.9% vs 76.6%), and have a parathyroid hormone level ≥300 pg/mL before kidney transplantation (26.8% vs 9.5%) (all $P < .001$). Patients with post-transplant hyperparathyroidism had a 1.6-fold higher risk of death-censored graft loss (adjusted hazard ratio = 1.60, 95% confidence interval: 1.02–2.49) compared with those without post-transplant hyperparathyroidism. This risk more than doubled in those with parathyroid hormone ≥300 pg/mL 1 year after kidney transplantation (adjusted hazard ratio = 4.19, 95% confidence interval: 1.95–9.03). The risk of death-censored graft loss did not differ by age, sex, or race (all $P_{interaction} > .05$). There was no association between post-transplant hyperparathyroidism and mortality.

Conclusion: The risk of graft loss was significantly higher among patients with post-transplant hyperparathyroidism when compared with patients without post-transplant hyperparathyroidism.

Introduction

Hyperparathyroidism is present in the majority of patients at the time of kidney transplant (KT) and typically resolves within 1 year of successful KT in many patients.[1–6] However, recent studies have demonstrated that hyperparathyroidism can persist in ≤60% of patients at 1-year post-KT.[7–11] Post-transplant hyperparathyroidism, or elevated parathyroid hormone (PTH) levels >1 year post-KT, is multifactorial and encompasses both secondary and tertiary hyperparathyroidism. Pretransplant risk factors for developing post-transplant hyperparathyroidism include prolonged length of dialysis, obesity, calcimimetic use, pretransplant PTH levels ≥300 pg/mL, and hypercalcemia at the time of KT.[11–14]

Data regarding the impact of post-transplant hyperparathyroidism on KT outcomes are conflicting. Although several studies have found that normalization of PTH levels post-KT may be

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associated with improved graft function,[14–18] others have not identified a relationship between post-transplant hyperparathyroidism and transplant outcomes.[19,20] These mixed results may arise from varying definitions of post-transplant hyperparathyroidism, discrepancies in the timing of PTH measurement post-KT, differing sample sizes, variation in study populations, differentiation of types of hyperparathyroidism, and variations in post-KT outcomes assessed. Finally, limited evidence exists regarding whether the adverse transplant outcomes identified are mediated by calcium, vitamin D deficiency, or PTH.

Recommendations from Kidney Disease: Improving Global Outcomes are vague regarding the length of time post-KT that PTH should be measured.[21] Furthermore, Kidney Disease: Improving Global Outcomes cites a low quality of evidence provided for the guidelines regarding the treatment of hyperparathyroidism post-KT and does not offer recommendations for the management of hyperparathyroidism beyond the first 12 months after transplant.[21] As a result, treatment for post-transplant hyperparathyroidism is often delayed.[22]

Understanding the impact of elevated PTH levels on KT outcomes may help guide treatment for those patients who have post-transplant hyperparathyroidism. Therefore, the purpose of this study was to evaluate the association between post-transplant hyperparathyroidism, irrespective of calcium or vitamin D levels, on both graft loss and mortality. We also sought to identify the subgroups most at risk for these adverse outcomes.

Methods

Study population and design

Under institutional review board approval, we leveraged a longitudinal prospective cohort study of 1,236 adult (age ≥18 years) KT recipients enrolled at admission for KT at the Johns Hopkins Hospital, Baltimore, Maryland (Dec 2008 to Feb 2020). Patient characteristics including age, sex, race, ethnicity, education, body mass index, dialysis pre-KT, and years on dialysis were self-reported, measured, or abstracted from medical records at time of enrollment. All recipients were linked to the Scientific Registry of Transplant Recipients (SRTR) to ascertain post-transplant outcomes of graft loss and death. The SRTR includes data on all donor and transplant recipients in the United States, submitted by members of the Organ Procurement and Transplant Network.[23] Additional characteristics ascertained from SRTR included cause of end-stage renal disease (ESRD) and donor type.

We retrospectively abstracted lab results of PTH, calcium, and vitamin D levels pre-KT and at 1-year post-KT for each recipient from medical records. After a chart review, a total of 845 recipients had a PTH level measured at a median of 1-year post-KT (IQR = 0.9–1.2 years). In order to include only those with functioning grafts at 1-year post-KT, we excluded recipients who had graft loss within 1 year of KT ($n = 21$) for a final sample size of 824 participants. These patients were followed for a median of 6.9 (IQR = 5.2–9.0) years.

Definitions

A PTH level <70 pg/mL is considered normal at the health care system where transplants took place. Therefore, post-transplant hyperparathyroidism was defined as PTH ≥70 pg/mL at 1-year post-KT. This definition encompassed patients with both secondary hyperparathyroidism, defined as PTH ≥70 pg/mL and calcium <10 mg/dL; and tertiary hyperparathyroidism, defined as patients with PTH ≥70 pg/mL and calcium ≥10 mg/dL. Patients with both secondary and tertiary hyperparathyroidism were included to be consistent with nephrology literature. Those without post-transplant hyperparathyroidism were defined as patients with a PTH level <70 pg/mL at 1-year post-KT. This included patients with preoperative hyperparathyroidism who subsequently experienced normalization of PTH levels to <70 pg/mL within 1-year post-KT. Hypercalcemia was defined as calcium level ≥10 mg/dL, and vitamin D deficiency was defined as vitamin D 25-OH level ≤30 ng/mL.

All recipients were followed for graft loss until death or administrative censoring (Oct 2021). The primary exposure was the presence of post-transplant hyperparathyroidism, classified as a binary variable. Because several nephrology guidelines recommend maintaining a pretransplant PTH level <300 pg/mL in patients with ESRD,[24,25] a secondary analysis was performed in which those with post-transplant hyperparathyroidism were further stratified as having a PTH level either 70 to 299 pg/mL or ≥300 pg/mL. The outcomes of interest were all-cause mortality, all-cause graft loss, and death-censored graft loss (DCGL). All-cause graft loss was defined as graft loss for any cause (including return to dialysis, retransplant, and death), and DCGL was defined as graft loss due to any cause other than death. Each of these outcomes was ascertained through SRTR. The time to event was defined as the period from receipt of KT to date of event or end of follow-up.

Statistical analysis

The differences in patient and clinical characteristics by post-transplant hyperparathyroidism were tested using analysis of variance tests for normally distributed continuous variables, Kruskal-Wallis tests for non-normally distributed continuous variables, and Fisher exact tests for the categorical variables.

The cumulative incidence of each outcome of interest was estimated using the Kaplan-Meier method, and the unadjusted survival curves were compared using log-rank tests. After verifying the proportional hazard assumptions by visually inspecting log-log plots, the association between hyperparathyroidism and post-KT outcomes was assessed using adjusted Cox proportional hazard models. Models were adjusted for older age (≥65 years), sex, Black race, college education, high PTH level pre-KT (≥300 pg/mL), cause of ESRD, and years on dialysis. The primary analysis evaluated post-transplant hyperparathyroidism as a binary variable, whereas the secondary analysis evaluated categorical PTH levels <70 pg/mL, 70 to 299 pg/mL, and ≥300 pg/mL. We tested whether associations between post-transplant hyperparathyroidism and transplant outcomes differed by age, sex, or race by including an interaction term between post-transplant hyperparathyroidism and each factor in separate models; a Wald test was used to determine whether these associations were significant. Furthermore, we estimated the association between post-transplant hyperparathyroidism and each outcome within age, sex, and race subgroups.

We imputed the missing values for all covariates using multiple imputation method with 10 iterations for all regression analyses. All analyses were performed using Stata version 15 (StataCorp, College Station, TX).

Results

Participant characteristics

The 824 KT recipients had a mean age of 53.2 years (SD = 13.6) at the time of KT. Of these patients, 39.8% were female, 41.5% were Black, 2.8% were Hispanic, and 68.6% had a college education. The most common cause of ESRD was hypertension (31.9%), followed by glomerulonephritis (26.2%). A majority of the cohort (82.9%) underwent dialysis pre-KT with a median time on dialysis of 2.7 years

Table I
Characteristics of KT recipients at admission for KT by post-KT post-transplant HPT

Characteristic	Overall ($n = 824$)	HPT status 1-year post-KT		P value
		No post-transplant HPT ($n = 322$)	Post-transplant HPT ($n = 502$)	
Age at KT, mean (SD)	53.2 (13.6)	53.0 (14.1)	53.4 (13.3)	.69
Female, %	328 (39.8%)	137 (42.5%)	191 (38.0%)	.20
Race/ethnicity, %				
White	405 (49.2%)	177 (55.0%)	228 (45.4%)	< .001
Black	342 (41.5%)	105 (32.6%)	237 (47.2%)	
Hispanic	23 (2.8%)	9 (2.8%)	14 (2.8%)	
Other	54 (6.6%)	31 (9.6%)	23 (4.6%)	
College education, %	565 (68.6%)	217 (67.4%)	348 (69.3%)	.56
BMI, mean (SD)	27.2 (5.5)	26.4 (5.2)	27.7 (5.6)	< .001
Cause of ESRD, %				
Glomerulonephritis	215 (26.2%)	90 (28.0%)	125 (25.0%)	.005
Diabetes mellitus	136 (16.5%)	51 (15.9%)	85 (17.0%)	
Hypertension	262 (31.9%)	82 (25.5%)	180 (35.9%)	
Other	209 (25.4%)	98 (30.5%)	111 (22.2%)	
Pre-KT dialysis, %	682 (82.9%)	246 (76.6%)	436 (86.9%)	< .001
Years on dialysis, median (IQR)	2.7 (0.6, 5.5)	1.6 (0.1, 4.1)	3.6 (1.2, 6.2)	< .001
Deceased donor KT, %	537 (65.2%)	201 (62.4%)	336 (66.9%)	.18
Pre-KT PTH level, %				
<100 pg/mL	118 (15.3%)	70 (23.1%)	48 (10.2%)	< .001
100–299 pg/mL	355 (46.0%)	155 (51.2%)	200 (42.6%)	
300–599 pg/mL	203 (26.3%)	57 (18.8%)	146 (31.1%)	
≥600 pg/mL	96 (12.4%)	21 (6.9%)	75 (16.0%)	
Pre-KT hypercalcemia,* %	132 (16.4%)	43 (13.4%)	89 (18.4%)	.061
Pre-KT vitamin D deficiency,† %	152 (71.4%)	58 (64.4%)	94 (76.4%)	.056
Pre-KT parathyroidectomy, %	25 (3.0%)	6 (1.9%)	19 (3.8%)	.12
Post-KT hypercalcemia,* %	243 (29.5%)	63 (19.6%)	180 (35.9%)	< .001
Post-KT vitamin D deficiency,† %	448 (56.5%)	135 (43.1%)	313 (65.2%)	< .001
Post-KT treatment for HPT, %				
None	673 (81.8%)	302 (93.8%)	371 (74.1%)	< .001
Calcimimetics	132 (16.0%)	16 (5.0%)	116 (23.2%)	
Parathyroidectomy	10 (1.2%)	3 (0.9%)	7 (1.4%)	
Both	8 (1.0%)	1 (0.3%)	7 (1.4%)	

Post-transplant HPT was defined as PTH level ≥70 pg/mL at 1-year post-KT.
BMI, body mass index; *ESRD*, end-stage renal disease; *HPT*, hyperparathyroidism; *KT*, kidney transplant; *PTH*, parathyroid hormone.
* Post-KT hypercalcemia was defined as calcium level ≥10 mg/dL at 1-year post-KT.
† Post-KT vitamin D deficiency was defined as vitamin D level ≤30 ng/mL at 1-year post-KT.

(IQR = 0.6–5.5). Most of the patients (65.2%) received a deceased donor KT. Pre- KT, 15.3% of patients had PTH levels <100 pg/mL, and 36.2% had PTH levels ≥300 pg/mL (Table I).

Among the entire cohort, 60.9% of patients had post-transplant hyperparathyroidism, or PTH level ≥70 pg/mL at 1-year post-KT. Compared to those without post-transplant hyperparathyroidism, patients with post-transplant hyperparathyroidism were more likely to be Black (47.2% vs 32.6%, $P < .001$), have a higher body mass index (27.7 vs 26.4 kg/m^2, $P < .001$), receive dialysis pre-KT (86.9% vs 76.6%, $P < .001$), and have hypertension as the cause of ESRD (35.9% vs 25.5%, $P = .005$). Additionally, 3.8% of patients with post-transplant hyperparathyroidism and 1.9% of patients without post-transplant hyperparathyroidism underwent parathyroidectomy pre-KT ($P = .12$). Patients with post-transplant hyperparathyroidism had higher PTH levels pre-KT and were more likely to have hypercalcemia (35.9% vs 19.6%, $P < .001$) and vitamin D deficiency (65.2% vs 43.1%, $P < .001$) at 1-year post-KT. Compared to patients without post-transplant hyperparathyroidism, patients with post-transplant hyperparathyroidism were more likely to undergo treatment with calcimimetics (23.3% vs 5.0%), parathyroidectomy (1.4% vs 0.9%), or both (1.4% vs. 0.3%) post-KT (all $P < .001$) (Table I).

Mortality

Among the entire cohort, 19.1% ($n = 157$) of patients died during the follow-up period. The cumulative incidence of mortality was similar when comparing patients with and without post-transplant hyperparathyroidism (log-rank $P = .13$) (Figure 1, *A*). After adjusting for all covariates, post-transplant hyperparathyroidism was not associated with all-cause mortality (aHR = 1.35, 95% CI: 0.96–1.91) (Table II).

All-cause graft loss

Among the entire cohort, the incidence of all-cause graft loss during the follow-up period was 29.4% ($n = 242$). The cumulative incidence of all-cause graft loss was higher among recipients with post-transplant hyperparathyroidism compared with those without hyperparathyroidism (log-rank $P = .02$) (Figure 1, *B*).

Compared with those without post-transplant hyperparathyroidism, patients with post-transplant hyperparathyroidism had a 1.37-fold higher risk of all-cause graft loss (aHR = 1.37, 95% CI: 1.04–1.82) (Table II). This association did not differ by age ($P_{interaction} = .85$), sex ($P_{interaction} = .67$), or race ($P_{interaction} = .43$). When stratified by PTH level at 1-year post-KT, patients with a PTH 70 to 299 pg/mL did not have an increased risk of all-cause graft loss. However, the risk of all-cause graft loss was 2.46-fold higher among patients with a PTH level ≥300 pg/mL when compared to those with a PTH <70 pg/mL (aHR = 2.46, 95% CI: 1.38–4.40) (Table III).

Death-censored graft loss

Among the entire cohort, the incidence of DCGL during the follow-up period was 12.6% ($n = 104$). The cumulative incidence of DCGL was higher among recipients with post-transplant

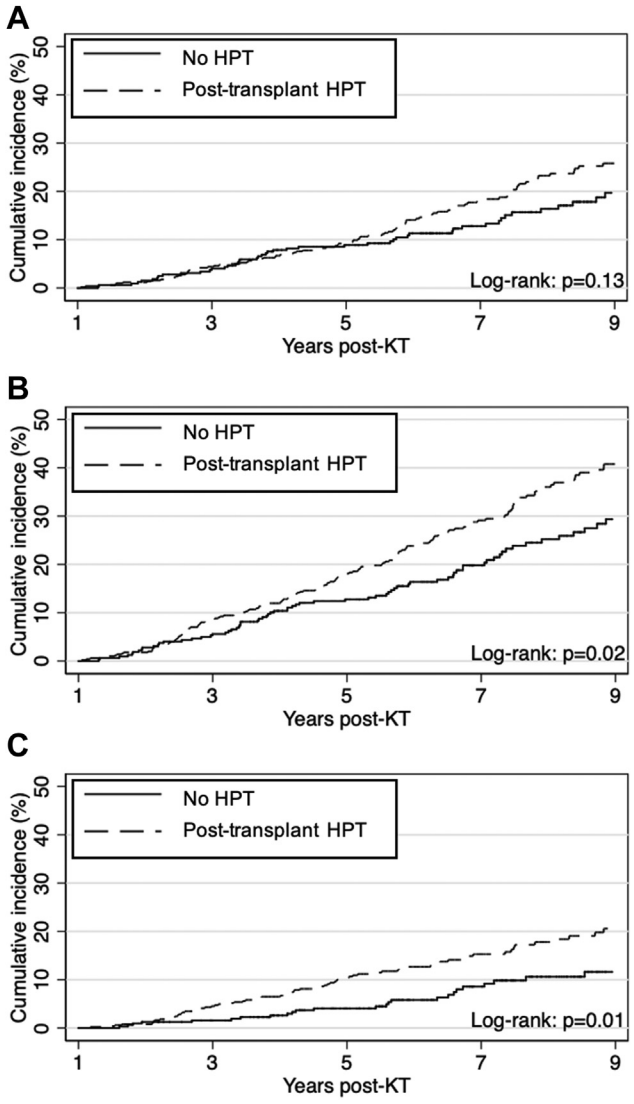

Figure 1. Cumulative incidence of (A) all-cause mortality, (B) all-cause graft loss, and (C) death-censored graft loss by post-transplant hyperparathyroidism among kidney transplant recipients (n = 824). Post-transplant hyperparathyroidism was defined as parathyroid hormone level ≥70 pg/mL at 1-year post-KT; as such, the cumulative incidence was calculated starting at 1-year post-KT. *KT*, kidney transplant; *HPT*, hyperparathyroidism.

hyperparathyroidism compared with those without hyperparathyroidism (log-rank $P = .01$) (Figure 1, *C*).

Compared with those without post-transplant hyperparathyroidism, patients with post-transplant hyperparathyroidism had a 1.6-fold higher risk of DCGL (aHR = 1.60, 95% CI: 1.02–2.49) (Table II). This association did not differ by age ($P_{interaction} = .80$), sex ($P_{interaction} = .06$), or race ($P_{interaction} = .20$). When stratified by PTH level at 1-year post-KT, patients with a PTH 70 to 299 pg/mL did not have an increased risk of DCGL. However, the risk of all-cause graft loss was 4.21-fold higher among patients with a PTH ≥300 pg/mL compared to those with a PTH <70 pg/mL (aHR = 4.21, 95% CI: 1.90–9.30) (Table III).

Sensitivity analyses

Because our definition of post-transplant hyperparathyroidism encompassed patients with both secondary and tertiary hyperparathyroidism, several sensitivity analyses were carried out to better evaluate the impact that hypercalcemia may have on transplant outcomes. Three sensitivity analyses were performed in which patients with pretransplant hypercalcemia, post-transplant hypercalcemia, and either pre- or post-transplant hypercalcemia were excluded from the main analysis. When excluding patients with hypercalcemia pre-KT, those with post-transplant hyperparathyroidism had a 1.45-fold higher risk of all-cause graft loss and a 1.90-fold higher risk of DCGL compared with those without post-transplant hyperparathyroidism (aHR = 1.45, 95% CI: 1.07–1.97 and aHR = 1.90, 95% CI: 1.16–3.11). When excluding patients with hypercalcemia post-KT, those with post-transplant hyperparathyroidism had a 1.50-fold higher risk of all-cause graft loss and a 1.77-fold higher risk of DCGL compared with those without post-transplant hyperparathyroidism (aHR = 1.50, 95% CI: 1.08–2.08 and aHR = 1.77, 95% CI: 1.08–2.90). Finally, when excluding patients with hypercalcemia either pre- or post-KT, those with post-transplant hyperparathyroidism had a 1.51-fold higher risk of all-cause graft loss and a 2.13-fold higher risk of DCGL compared to those without post-transplant hyperparathyroidism (aHR = 1.51, 95% CI: 1.07–2.14 and aHR = 2.13, 95% CI: 1.25–3.64). Similar to the primary analysis, there was no association between post-transplant hyperparathyroidism and mortality in any of the three sensitivity analyses (Table IV).

Six additional sensitivity analyses were also performed in which patients with pretransplant hypercalcemia, post-transplant hypercalcemia, and either pre- or post-transplant hypercalcemia were excluded when stratifying patients with post-transplant hyperparathyroidism by a PTH level either 70 to 299 pg/mL, or ≥300 pg/mL at 1-year post-KT. When excluding those with hypercalcemia, patients with a PTH 70 to 299 pg/mL at 1-year post-KT had a significantly increased risk of graft loss. Additionally, the risk of graft loss remained significant in those with a PTH ≥300 pg/mL at 1-year post-KT when patients with hypercalcemia were excluded (Table V).

Discussion

In this single-institution retrospective study of 824 KT recipients followed for a median of 6.9 years, we found that patients with post-transplant hyperparathyroidism, or PTH ≥70 pg/mL at 1-year post-KT, had a 1.37-fold higher risk of all-cause graft loss and a 1.6-fold higher risk of DCGL compared with patients without post-transplant hyperparathyroidism. When stratified by PTH levels at 1-year post-KT, this risk roughly doubled among those with a PTH level ≥300 pg/mL. The association between post-transplant hyperparathyroidism and graft loss persisted even when excluding patients with hypercalcemia. Our findings suggested that KT recipients with hyperparathyroidism after transplant should be closely monitored to optimize graft viability.

Similar to our findings, others have demonstrated an association between post-transplant hyperparathyroidism and adverse transplant outcomes. Lou et al found that normalization of PTH within 1 year of KT was associated with improved overall graft survival on Kaplan-Meier analysis compared to those with post-transplant hyperparathyroidism.[14] Araujo et al found that ionized calcium >5.3 mg/dL or PTH >100 pg/mL at 1-year post-KT was associated with a shorter median time to graft loss compared with non-hyperparathyroidism patients.[15] In addition, Isakov et al reported that PTH >150 pg/mL at 3-months post-KT was an independent predictor for decreased GFR in KT recipients ≤3 years post-transplant.[17] Our study was built on each of these previous findings by examining PTH thresholds at 1-year post-KT; we found that higher PTH levels were associated with a greater risk of graft loss.

In contrast to our study, Wolf et al found no association between post-transplant hyperparathyroidism and graft loss; however, the

Table II
Risks of all-cause mortality, all-cause graft loss, and death-censored graft loss by post-transplant HPT among the entire cohort ($n = 824$)

Post-transplant HPT	All-cause mortality	All-cause graft loss	Death-censored graft loss
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
No	Reference	Reference	Reference
Yes	1.35 (0.96–1.91)	1.37 (1.04–1.82)	1.60 (1.02–2.49)

Post-transplant HPT was defined as PTH level ≥70 pg/mL at 1-year post-KT.
The aHRs with 95% CIs are presented from Cox proportional hazards models adjusted for older age (≥65 years), sex, Black race, college education, high pre-KT PTH level (≥300 pg/mL), cause of ESRD, and years on dialysis.
ESRD, end-stage renal disease; *HPT*, hyperparathyroidism; *KT*, kidney transplant; *PTH*, parathyroid hormone.

Table III
Risks of all-cause graft loss and death-censored graft loss among KT recipients by PTH level at 1-year post-KT ($n = 824$)

PTH level at 1-year post-KT (pg/mL)	All-cause graft loss	Death-censored graft loss
	aHR (95% CI)	aHR (95% CI)
<70	Reference	Reference
70–299	1.33 (1.00–1.76)	1.50 (0.96–2.36)
≥300	2.46 (1.38–4.40)	4.21 (1.90–9.30)

Post-transplant PTH was stratified into 3 categories: <70, pg/mL, 70 to 299 pg/mL, and ≥300 pg/mL.
The aHRs with 95% CIs are presented from Cox Proportional Hazards models adjusted for older age (≥65 years), sex, Black race, college education, high preKT PTH level (≥300 pg/mL), cause of ESRD, and years on dialysis.
ESRD, end-stage renal disease; *HPT*, hyperparathyroidism; *KT*, kidney transplant; *PTH*, parathyroid hormone.

Table IV
Risks of all-cause mortality, all-cause graft loss, and death-censored graft loss by post-transplant HPT when excluding patients with pretransplant hypercalcemia, post-transplant hypercalcemia, and pre- or post-transplant hypercalcemia

Post-transplant HPT	All-cause graft loss	Death-censored graft loss
	aHR (95% CI)	aHR (95% CI)
No	Reference	Reference
Patients with pretransplant hypercalcemia excluded	1.45 (1.07–1.97)	1.90 (1.16–3.11)
Patients with post-transplant hypercalcemia excluded	1.50 (1.08–2.08)	1.77 (1.08–2.90)
Patients with either pre- or post-transplant hypercalcemia excluded	1.51 (1.07–2.14)	2.13 (1.25–3.64)

Post-transplant HPT was defined as PTH level ≥70 pg/mL at 1-year post-KT. Hypercalcemia was defined as calcium ≥10 mg/dL.
The aHRs with 95% CIs are presented from Cox proportional hazards models adjusted for older age (≥65 years), sex, Black race, college education, high pre-KT PTH level (≥300 pg/mL), cause of ESRD, and years on dialysis.
ESRD, end-stage renal disease; *HPT*, hyperparathyroidism; *KT*, kidney transplant; *PTH*, parathyroid hormone.

time interval at which PTH levels were collected post-KT was variable.[19] Similarly, Marcén et al found no association between post-transplant hyperparathyroidism and graft loss on univariate analysis, although this study did not use a multivariate analysis to control for any potential confounding effects.[20] Pihlstrøm et al reported an association between post-transplant hyperparathyroidism and all-cause mortality, a finding that was not seen in our study.[16] However, unlike our study, Pihlstrøm et al used PTH levels that were collected at an average of 5.1 years from KT, suggesting that a longer exposure to elevated PTH levels post-KT may result in an increased risk of mortality.

The mechanism of graft loss in those with post-transplant hyperparathyroidism is unclear. Some data has suggested that hyperparathyroidism may indirectly lead to graft failure by causing hypercalcemia, which in turn may lead to calcium deposition in renal vasculature, nephrocalcinosis, and subsequent graft loss.[26] An association between elevated circulating calcium-phosphate product and graft loss has been reported previously.[27] In addition, PTH-mediated hypercalcemia may lead to systemic calciphylaxis, a rare complication that has devastating effects on both graft survival and overall mortality.[28] Conversely, there is some evidence to suggest that PTH levels may influence KT outcomes independent of calcium. Parathyroid hormone receptors have been found on cardiomyocytes, vascular smooth muscle cells, and endothelial cells, suggesting that PTH has a direct impact on vasculature.[29,30] Elevated PTH levels have been shown to cause structural changes to arteries, making them less responsive to vasodilatory changes.[31,32] This has led some to believe that PTH-mediated structural changes within the renal vasculature may lead to micro- and macrovascular complications within the renal allograft, placing KT recipients with hyperparathyroidism at higher risk for graft loss.[33]

Table V
Risks of all-cause graft loss and death-censored graft loss among KT recipients by PTH level at 1-year post-KT when excluding patients with pretransplant hypercalcemia, post-transplant hypercalcemia, or both

PTH level at 1-year post-KT (pg/mL)	All-cause graft loss	Death-censored graft loss
	aHR (95% CI)	aHR (95% CI)
<70	Reference	Reference
70–299	1.33 (1.00–1.76)	1.50 (0.96–2.36)
≥300	2.46 (1.38–4.40)	4.21 (1.90–9.30)
Patients with pretransplant hypercalcemia excluded		
70–299	1.39 (1.02–1.90)	1.79 (1.09–2.96)
≥300	2.88 (1.52–5.45)	5.19 (2.14–12.58)
Patients with post-transplant hypercalcemia excluded		
70–299	1.45 (1.04–2.02)	1.67 (1.01–2.76)
≥300	2.48 (1.24–4.93)	4.07 (1.62–10.22)
Patients with either pre or post-transplant hypercalcemia excluded		
70–299	1.46 (1.03–2.07)	2.01 (1.16–3.46)
≥300	2.56 (1.23–5.31)	5.35 (2.05–13.95)

Post-transplant PTH was stratified into 3 categories: <70, pg/mL, 70 to 299 pg/mL, and ≥300 pg/mL. Hypercalcemia was defined as calcium ≥10 mg/dL.
The aHRs with 95% CIs are presented from Cox proportional hazards models adjusted for older age (≥65 years), sex, Black race, college education, high pre-KT PTH level (≥300 pg/mL), cause of ESRD, and years on dialysis.
aHR, adjusted hazard ratios; *ESRD*, end-stage renal disease; *HPT*, hyperparathyroidism; *KT*, kidney transplant; *PTH*, parathyroid hormone.

To be consistent with the nephrology literature, our definition of post-transplant hyperparathyroidism did not differentiate between the various etiologies of elevated PTH; as such, our analyses included patients with both secondary and tertiary hyperparathyroidism. To better evaluate the role of hypercalcemia in adverse KT outcomes, multiple additional sensitivity analyses were performed in which the relationship between post-transplant hyperparathyroidism and graft loss was determined when excluding patients with pretransplant hypercalcemia, post-transplant hypercalcemia, and either pre- or post-transplant hypercalcemia. When excluding hypercalcemic patients, the association between post-transplant hyperparathyroidism and graft loss did not change significantly when compared with the primary and secondary analyses. Additionally, in the group of patients with a post-transplant PTH 70 to 299 pg/mL, the risk of graft loss increased significantly, a finding that was not seen when patients with hypercalcemia were included. These findings suggested that graft loss in those with post-transplant hyperparathyroidism may be a PTH-mediated phenomena. However, further research is needed to elucidate the mechanisms between hyperparathyroidism and graft loss.

The strengths of the study included the large sample size, the leverage of an ongoing longitudinal prospective cohort, and the close follow-up of each patient using data from SRTR. Our study had several limitations inherent to database and electronic medical record abstraction, including missing values and human error in data collection. In addition, the PTH levels may naturally fluctuate over the course of several years after transplant, and the type of PTH assay used may have differed across patients, both of which may have led to inaccurate PTH levels and misclassification of hyperparathyroidism. Similarly, PTH levels may vary based on renal function, and because data regarding renal function is not available in SRTR, we were not able to control for this in our model. However, all grafts were deemed to be functioning by each patient's nephrologist. The current study did not address risk factors for post-transplant hyperparathyroidism that can be addressed pre-KT, as previous studies have suggested that improved control of secondary hyperparathyroidism before surgery may help mitigate post-transplant hyperparathyroidism post-KT.[34–36] Although we found an association between post-transplant hyperparathyroidism and graft loss, this study was not designed to determine the most appropriate treatment for post-transplant hyperparathyroidism or to determine the timing of such treatment. Because KT recipients were managed by a wide range of transplant nephrologists after surgery, we were not able to comment on the specific rationale for choosing calcimimetics for treatment of post-transplant hyperparathyroidism in 23% of these patients. Finally, these data were collected from patients who underwent transplant at a single institution, which may limit the generalizability of our findings.

In conclusion, post-transplant hyperparathyroidism post-KT was associated with an increased risk of graft loss compared with patients without post-transplant hyperparathyroidism, and higher PTH levels at 1-year post-KT were associated with an even greater risk of graft loss. This association persisted even when excluding patients with hypercalcemia. These findings suggested that KT recipients should undergo close monitoring of PTH levels after transplant to optimize graft viability. Future studies are warranted to better understand the mechanism of graft loss in patients with post-transplant hyperparathyroidism and to determine the most appropriate treatment for these patients.

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Conflict of interest/Disclosure

The authors have no conflicts of interests or disclosures to report.

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Discussion

Dr Bradford Mitchell (Dover, DE): You are suggesting causation given the fact that kidney dysfunction is likely to lead to vitamin D deficiency. Are you suggesting that it is the elevated parathyroid hormone (PTH) level that is responsible for the graft loss?

Dr Philip Crepeau: To clarify, this study did not show any causation between hyperparathyroidism and graft loss. We can speculate that there may be an association between elevated PTH levels and graft loss, although we do not fully understand the underlying mechanism. There are prior studies that have identified PTH receptors on vascular endothelial cells. Those studies have shown that higher levels of PTH can cause structural changes within the vasculature, making those vessels less responsive to changes in blood flow and blood pressure. So, we can hypothesize that patients with hyperparathyroidism may have PTH-related vascular changes within the renal allografts, leading to decreased areas of perfusion and potential ischemia within the kidney graft. That may explain the higher rates of graft loss in patients with persistently elevated PTH levels; however, that mechanism is not completely clear.

Dr Rongzhi Wang (Birmingham, AL): You noticed that patients have worsening allograft function associated with an elevated PTH level. I was wondering, at 1-year follow-up, did you adjust the baseline allograft function and adjust the kidney donor type?

Dr Philip Crepeau: We did identify the type of transplant that these patients had. There were similar rates of deceased donor kidney transplants among the 2 cohorts. That difference was not significant. To answer your first question regarding kidney graft function, we agree that kidney graft function certainly plays a role in levels of PTH in these patients. Unfortunately, with our current data set, we were not able to identify graft function, so that certainly was a limitation of this study.

Dr Rachel Slotcavage (Little Rock, AK): Why are we still fighting this battle with our nephrology colleagues? Why are more of these

patients not being referred for surgical care either before or even after transplantation?

Dr Philip Crepeau: I cannot speculate on that. I can speak about our specific institution in saying that understanding the adverse impact that elevated PTH levels have on kidney transplant has allowed for greater communication between endocrine surgeons and transplant nephrologists.

Dr Eyas Alkhalili (El Paso, TX): I was wondering if you could do an inflection point analysis on the preoperative level of PTH and patients who underwent transplant to see which level the preoperative PTH was associated with graft loss? How many patients had a protective effect from parathyroidectomy after transplant?

Dr Philip Crepeau: We are certainly looking into preoperative PTH levels, which are important to understand the outcomes in these patients. We know that patients with persistently elevated PTH levels after kidney transplant had higher rates of post-transplant parathyroidectomy; however, we did not investigate whether that had a protective effect on the grafts. This will be an important area to study in the future.

Dr Jesse Pasternak (Toronto, Ontario, Canada): What if you were able to control the hypercalcemia but had an elevated PTH? How is that relevant? Do you think that would erase the effect, or do you think that it is an underlying issue that is not related to the actual PTH level?

Dr Philip Crepeau: That is a great question. We did not control for cinacalcet levels in this analysis to see if that had any sort of artificial effect on lowering parathyroid hormone levels in this study. But, certainly, that is something we can look to in the future to see if that has any sort of confounding impact.