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ORIGINAL ARTICLE

Short stature in advanced pediatric CKD is associated with faster time to reduced kidney function after transplant

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Abstract

Background Among children who receive a kidney transplant, short stature is associated with a more complicated post-transplant course and increased mortality. Short stature prior to transplant may reflect the accumulated risk of multiple factors during chronic kidney disease (CKD); however, its relationship with post-transplant kidney function has not been well characterized.

Methods In the Chronic Kidney Disease in Children (CKiD) cohort restricted to children who received a kidney transplant, short stature (i.e., growth failure) was defined as age-sex-specific height < 3rd percentile. The outcome was time to estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73 m^2 after transplant. Parametric survival models, including adjustment for disease severity, socioeconomic status (SES), and parental height by inverse probability weighting, described the relative times to eGFR< 45 ml/min/1.73 m^2.

Results Of 138 children (median CKD duration at transplant: 13 years), 20% (28) had short stature before the transplant. The median time to eGFR < 45 ml/min/1.73 m^2 after kidney transplantation was 6.6 years and those with short stature had a significantly faster time to the poor outcome (log-rank *p* value 0.004). Children with short stature tended to have lower SES, nephrotic proteinuria, higher blood pressure, and lower mid-parental height before transplant. After adjusting for these variables, children with growth failure had 40% shorter time to eGFR < 45 ml/min/1.73 m^2 than those with normal stature (relative time 0.60, 95%CI 0.32, 1.03).

Conclusions Short stature was associated with a faster time to low kidney function after transplant. SES, disease severity, and parental height partially explained the association. Clinicians should be aware of the implications of growth failure on the outcome of this unique population, while continued attempts are made to define modifiable factors that contribute to this association.

Keywords Kidney transplantation · Pediatrics · Growth failure · GFR · Graft loss

Introduction

Short stature, also referred to as growth failure, is commonly observed at all levels of impaired kidney function among children with chronic kidney disease (CKD), and the prevalence increases in advanced CKD stages [1]. Similarly, the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) has shown that among pediatric kidney transplant recipients, lower estimated glomerular filtration rate (eGFR) 30 days after transplant was associated with lower height z-scores [2]. Growth failure is associated with increased mortality, hospitalizations, and infections [3, 4] after kidney transplantation. A recent retrospective analysis of 2008 children after their first kidney transplantation in the US Renal Data System (USRDS) database documented a higher risk of all-cause mortality, as well as cardiac- and infection-related death in patients who had short stature [5]. The relationship between short stature prior to transplant and post-transplant kidney function, however, has not been well characterized in previous literature.

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The underlying cause of growth failure in children is multifactorial. Nutritional status and severity of chronic diseases have been well described as important risk factors [6, 7]. In children with CKD, growth can be impaired by various physiological mechanisms, including renal osteodystrophy, metabolic acidosis, and perturbations in the growth hormone axis [8]. Additionally, lower socioeconomic status (SES) is associated with lower height z-score across diverse populations [9–11]. Therefore, we hypothesized that short stature reflects the accumulated risk of overall nutritional status, disease severity, SES, and potential metabolic imbalances during the course of CKD progression and that these same risk factors may, at least partially explain poor graft outcomes in short children after transplantation. Based on this hypothesis, we aimed to evaluate short stature as a marker to identify patients at an increased risk of low kidney function (i.e., time to eGFR < 45 ml/min/1.73 m^2) after transplant in the Chronic Kidney Disease in Children (CKiD) cohort. CKiD is a long-standing and well-characterized cohort that is now empowered to link detailed pre-transplant factors to post-transplant outcome. It provides a unique opportunity to evaluate the risks of a low post-transplant eGFR that is associated with short stature in advanced CKD stages. Understanding this relationship may assist clinicians to distinguish vulnerable patients at high risk and to tailor care and treatment plans.

Materials and methods

Study design and population

The CKiD study is a multicenter, prospective cohort study conducted at 54 pediatric nephrology centers across North America since 2003. Eligible children were between 1 and 16 years with mild to moderate CKD based on an eGFR of 30–90 ml/min/1.73 m^2 at enrollment. Details of the study visits have been previously described [12]. Briefly, data collected at the regular visits included kidney function, growth, socioeconomic status, cardiovascular health, and neurocognitive development. These in-person study visits ceased after documented initiation of renal replacement therapy (RRT), either dialysis or transplantation. After RRT, participants were followed by annual short data collection protocols (interviews) completed over phone, in person, or online. Data collected were self-reported RRT status, health care utilization status, mediation use, physical symptoms, and quality of life. In parallel, clinical coordinators extracted serum creatinine and anthropometric data from medical charts corresponding to clinical visits.

Our study sample comprised children who received a first kidney transplant before age 21 with available serum creatinine data after kidney transplantation. Since the primary aim of the study was to investigate growth and kidney function after kidney transplant, children who did not have anthropometric data collected within 3 years prior to receiving a kidney transplant were excluded from this analysis.

Outcome

The primary outcome of interest was time from kidney transplant to serum creatinine-based eGFR < 45 ml/min/1.73 m^2. The CKiD bedside equation [13] was used since external studies have demonstrated its validity in a post-transplant population [14]. To account for variability in eGFR immediately after kidney transplant, we excluded observations within 3 months after kidney transplant. For participants with any observed eGFR value less than 45 ml/min/1.73 m^2, the event time was estimated by linear interpolation between two post-transplant eGFR data points. In our study sample, there were 18 children with the first observed eGFR after transplant below 45 ml/min/1.73 m^2 (i.e., "prevalent event"). For these participants, these eGFR values were measured several years after transplant (median 3.5, IQR 3.2-4.1 years) compared to the rest of the study sample (median 0.9, IQR 0.4-2.0 years). To address this missing data problem, eGFR at 3 months after transplant was imputed based on their pre-transplant characteristics using a single imputation model informed by the observed participants. We assessed the robustness of our simple imputation model against multiple imputation with consistent results. To investigate potential differences between those with a "prevalent event" ($n = 18$) and an "incident event" ($n = 25$ with an observed GFR < 45 ml/min/1.73 m^2), pre-transplant characteristics were compared and no significant differences were found between these subgroups. For the 18 children, imputed eGFR was the anchor for linear interpolation to their first observed data point when eGFR < 45 ml/min/1.73 m^2. Participants free of the event were censored at the last post-transplant visit.

Exposures

Height and weight were based on the mean of two repeated measurements using a stadiometer and standing scale at regular study visits before kidney transplant. After kidney transplant, height and weight data were obtained from medical chart review. We calculated age-sex-specific height percentile and z-score using US Centers for Disease Control and Prevention (CDC) growth charts with the US general population as the reference [15]. Since participants should have attained adult height at around age 20, we used the CDC reference for 20-year-olds to calculate height z-score for participants who were older than 20 years ($n = 5$, maximum age

20.6 years) at the time of transplant. In this study, short stature was defined as the last height prior to kidney transplant below the third percentile of general population with same age and sex (i.e., height z-score < −1.88).

Pre-transplant characteristics

At the baseline visit, demographic, SES, kidney disease characteristics, birth history, and medication use of the study participants were collected. SES characteristics included maternal education, household income, private health insurance, and enrollment in federal food assistance program. Birth history included gestational age, low birth weight (< 2500 g), and small for gestational age. Kidney disease characteristics included CKD diagnoses (glomerular vs. non-glomerular), duration of CKD, having dialysis before transplant, duration of the dialysis, and urine protein and creatinine ratio (uP/C). Proteinuria (urine protein/creatinine) was categorized as minimal (< 0.2 mg/mg), elevated (0.2–2 mg/mg), or nephrotic (> 2 mg/mg). Pre-transplant GFR was estimated by height (ht, in meter), serum creatinine (Scr), cystatin C, and blood urea nitrogen (BUN) using the equation: $eGFR = 39.8 \times (ht(m)/Scr)^{0.456}(1.8/cystatin\ C)^{0.418}(30/BUN)^{0.079}1.076^{male}(ht(m)/1.4)^{0.179}$ [16]. Longitudinal eGFR was used to calculate average annual percent of change as a metric of pre-transplant kidney function decline [17]. Additionally, systolic and diastolic blood pressure were measured at regular visits and standardized by age, gender, and height to the normal population [18]. Pre-transplant urine protein/creatinine ratio, GFR level and rate of change, and blood pressure were used as indicators of disease severity in this analysis. At each pre-transplant study visit, participants were asked whether they were "currently taking growth hormone/vitamin D supplements/alkali therapy." Any use of growth hormone/vitamin D supplements/alkali therapy was defined as ever reported use from baseline to when the last height was measured before transplant. Self-reported heights of children's biological parents were collected at baseline. Mid-parental height was calculated by the equation [19] as a predictor of children's projected adult height.

Statistical analyses

Pre-transplant characteristics including demographics, SES, CKD characteristics, birth history, and medication use were summarized by short stature. Differences in pre-transplant characteristics between the two groups was assessed using *t* tests and chi-square tests. To account for imbalances in pre-transplant characteristics between the two groups, propensity scores were used to construct stabilized inverse probability weights [20]. Specifically, multivariate logistic regression was used to determine the propensity for short stature (as the dependent variable) with SES factors, baseline uP/C, blood pressure, low birth weight, and mid-parental height being predictors. The cumulative incidence of eGFR < 45 ml/min/1.73 m^2 after transplant among children with and without short stature were estimated using non-parametric methods in the unweighted and weighted study samples. To estimate relative times between the two groups, parametric survival methods using a conventional log-normal distribution were fit to the unweighted and weighted populations, respectively. In the adjusted model, 95% confidence intervals of parameter estimates were obtained from 1000 bootstrapped samples [21]. All analyses were performed using SAS 9.4 (SAS Institute, Inc.) and R 3.4.3.

Results

Of 891 CKiD participants enrolled with CKD, a total of 192 reported receiving a kidney transplant as of September 2016. Of these, 152 provided serum creatinine data during their post-transplant period. Fourteen children were excluded because they either received a transplant after 21 years of age or did not have growth data collected within 3 years before transplant. Thus, 138 children were included in the present analysis. These study participants have a median of 13 years [IQR 9-16] of CKD duration at the time when they received kidney transplantation. The estimated median time to eGFR< 45 ml/min/1.73m^2 was 6.6 years after kidney transplantation.

Table 1 describes pre-transplant characteristics stratified by short stature. Of 138 eligible participants, 28 children had short stature prior to receiving their kidney transplant. Among the short stature group, 74% had lower maternal education, 36% reported a low household income, and 36% did not have any private health insurance. In contrast, in the normal stature group, the corresponding proportions were 67%, 29%, and 28%, respectively. Additionally, children having short stature reported higher proportion of low birth weight and had higher blood pressure at baseline. Other demographic and CKD characteristics, as well as BMI z-scores prior to transplant, did not differ between exposure groups. Mid-parental height was lower in the short stature group, indicating the effect of genetics. Thirty-nine percent of children having short stature received growth hormone prior to the transplant, whereas only 28% with normal stature received growth hormone. Similarly, more children received alkali therapy in the short stature group. Table 2 presents the summary statistics in the respective study groups after we applied inverse probability weights to achieve balance in potentially confounding variables. The application of inverse probability weights demonstrated no significant differences in the pre-transplant characteristics including SES, disease characteristics, and mid-parental height and allowed for a comparison of time-to-event that is not confounded by these factors.

Table 1 Descriptive statistics of pre-transplant characteristics by short stature in study population ($N = 138$) [a]

Variable	Normal stature ($n = 110$)	Short stature ($n = 28$)	p value[b]
Demographic			
Male	62% (68)	57% (16)	.81
White race	71% (78)	75% (21)	.85
Age at transplant (year)	14 (3.4)	15 (2.8)	.69
Socioeconomic status			
Maternal education: less than college degree	67% (72)	74% (20)	.66
Annual household income < $30,000	29% (31)	36% (10)	.63
No private health insurance	28% (29)	36% (8)	.56
Enrolled in federal food assistance program	16% (18)	18% (5)	1
Chronic kidney disease characteristics			
Glomerular diagnosis	29% (32)	32% (9)	.93
CKD duration at transplant (year)	12.2 (5.3)	12.3 (4.9)	.93
Having dialysis before transplant	51% (56)	57% (16)	.71
Duration of dialysis before transplant (year)	0.8 (0.6)	0.9 (0.9)	.59
eGFR at baseline (ml/min/1.73 m^2)	39 (12.2)	37 (13.6)	.45
Average annual eGFR % change prior to renal replacement therapy	− 20.0 (17.6)	− 16.1 (17.4)	.33
Proteinuria at baseline [c]			.09
Minimal (< 0.2 mg/mg of Cr)	36% (39)	15% (4)	
Elevated (0.2 to 2 mg/mg of Cr)	32% (34)	35% (9)	
Nephrotic(> 2 mg/mg of Cr)	32% (34)	50% (13)	
Blood pressure			
Systolic BP z-score at baseline[c]	0.53 (0.99)	0.99 (1.24)	.04
Diastolic BP z-score at baseline[c]	0.59 (0.99)	0.93 (0.96)	.10
Birth history			
Gestational age (week)	38.7 (1.8)	38.1 (2.6)	.13
Low birth weight	12% (12)	30% (8)	.05
Small for gestational age	16% (16)	31% (8)	.15
Anthropometric			
Height z-score at the last visit	− 0.41 (0.89)	− 2.40 (0.45)	< .001
Weight z-score at the last visit	− 0.05 (1.11)	− 1.24 (1.26)	< .001
BMI z-score at the last visit	0.14 (1.14)	0.10 (1.17)	.87
Body surface area at the last visit (m^2)	1.47 (0.35)	1.29 (0.27)	.01
Mid-parental height (cm)	173 (6)	168 (5)	< .01
Medication use[d]			
Any use of growth hormone before transplant	28% (31)	39% (11)	.36
Any use of vitamin D before transplant	85% (93)	89% (25)	.74
Any use of alkali therapy before transplant	65% (69)	75% (21)	.32
Proportion (number) with post-transplant eGFR < 45 ml/min/1.73 m^2	26% (29)	50% (14)	.03

SES socioeconomic status, *CKD* chronic kidney disease, *Cr* Creatinine, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *BMI* body mass index

[a] Mean (SD) for continuous variables and % (*N*) for categorical variables, based on non-missing values for each variable. Normal stature was defined as height z-score > = − 1.88. Short stature was defined as height z-score < − 1.88

[b] *P* values were based on Student's *t* test for continuous variables and chi-square test for categorical variables

[c] Median [IQR] duration from baseline to transplant were 3.5 [1.7, 6.2] and 3.5 [2.3, 4.7] years in normal and short stature groups, respectively

[d] Any reported use of medication from baseline to when the last height was measured before transplant

Table 2 Descriptive statistics of pre-transplant characteristics by short stature in the pseudo-population after applying stabilized weights [a]

Variable	Normal stature ($n = 110$)	Short stature ($n = 28$)	p value[b]
Demographic			
Male	62% (68)	56% (16)	.47
White race	70% (77)	77% (22)	.51
Age at transplant (year)	14 (3.4)	15 (2.8)	.43
SES measured at baseline			
Maternal education: less than college degree	70% (77)	75% (21)	.53
Annual household income < $30,000	33% (36)	34% (10)	.89
No private health insurance	32% (35)	32% (9)	.95
Enrolled in federal food assistance program	18% (20)	21% (6)	.72
Chronic kidney disease characteristics			
Glomerular diagnosis	32% (35)	35% (9)	.79
CKD duration at transplant (year)	11.9 (5.4)	12.3 (4.5)	.70
Having dialysis before transplant	54% (59)	50% (14)	.89
Duration of dialysis before transplant (year)	0.9 (0.6)	0.9 (1.0)	.82
eGFR at baseline (ml/min/1.73 m^2)	39 (12.0)	36 (13.6)	.37
Average annual eGFR % change prior to renal replacement therapy	− 20.2 (17.3)	− 14.6 (18.6)	.19
Proteinuria at baseline [c]			.29
Minimal (< 0.2 mg/mg of Cr)	33% (36)	17% (5)	
Elevated (0.2 to 2 mg/mg of Cr)	30% (33)	39% (11)	
Nephrotic (> 2 mg/mg of Cr)	36% (40)	44% (12)	
Blood pressure			
Systolic BP z-score at baseline[c]	0.64 (1.02)	0.77 (1.23)	.61
Diastolic BP z-score at baseline[c]	0.67 (1.00)	0.83 (0.97)	.47
Birth history			
Gestational age (week)	38.6 (1.9)	38.6 (2.2)	.86
Low birth weight	16% (18)	15% (4)	.95
Small for gestational age	18% (20)	25% (7)	.48
Anthropometric			
Height z-score at the last visit	− 0.47 (0.88)	− 2.37 (0.45)	< .001
Weight z-score at the last visit	− 0.10 (1.10)	− 1.34 (0.96)	< .001
BMI z-score at the last visit	0.11 (1.12)	0.01 (0.93)	.63
Body surface area at the last visit (m^2)	1.47 (0.35)	1.29 (0.22)	.001
Mid-parental height (cm)	171 (6)	170 (5)	.28
Medication use[d]			
Any use of growth hormone before transplant	28% (31)	39% (11)	.30
Any use of vitamin D before transplant	84% (92)	88% (25)	.61
Any use of alkali therapy before transplant	63% (69)	75% (21)	.25

SES socioeconomic status, *CKD* chronic kidney disease, *Cr* Creatinine, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *BMI* body mass index

[a] Mean (SD) for continuous variables and % (*N*) for categorical variables. *N* was calculated by weighted percentage * number (rounded to the nearest integer) of children in each group. Normal stature was defined as height z-score > = − 1.88. Short stature was defined as height z-score < − 1.88

[b] *P* values were based on weighted t-test for continuous variables and the chi-square test for categorical variables

[c] Median [IQR] duration from baseline to transplant were 3.5 [1.7, 6.2] and 3.5 [2.3, 4.7] years in normal and short stature groups, respectively

[d] Any reported use of medication from baseline to when the last height was measured before transplant

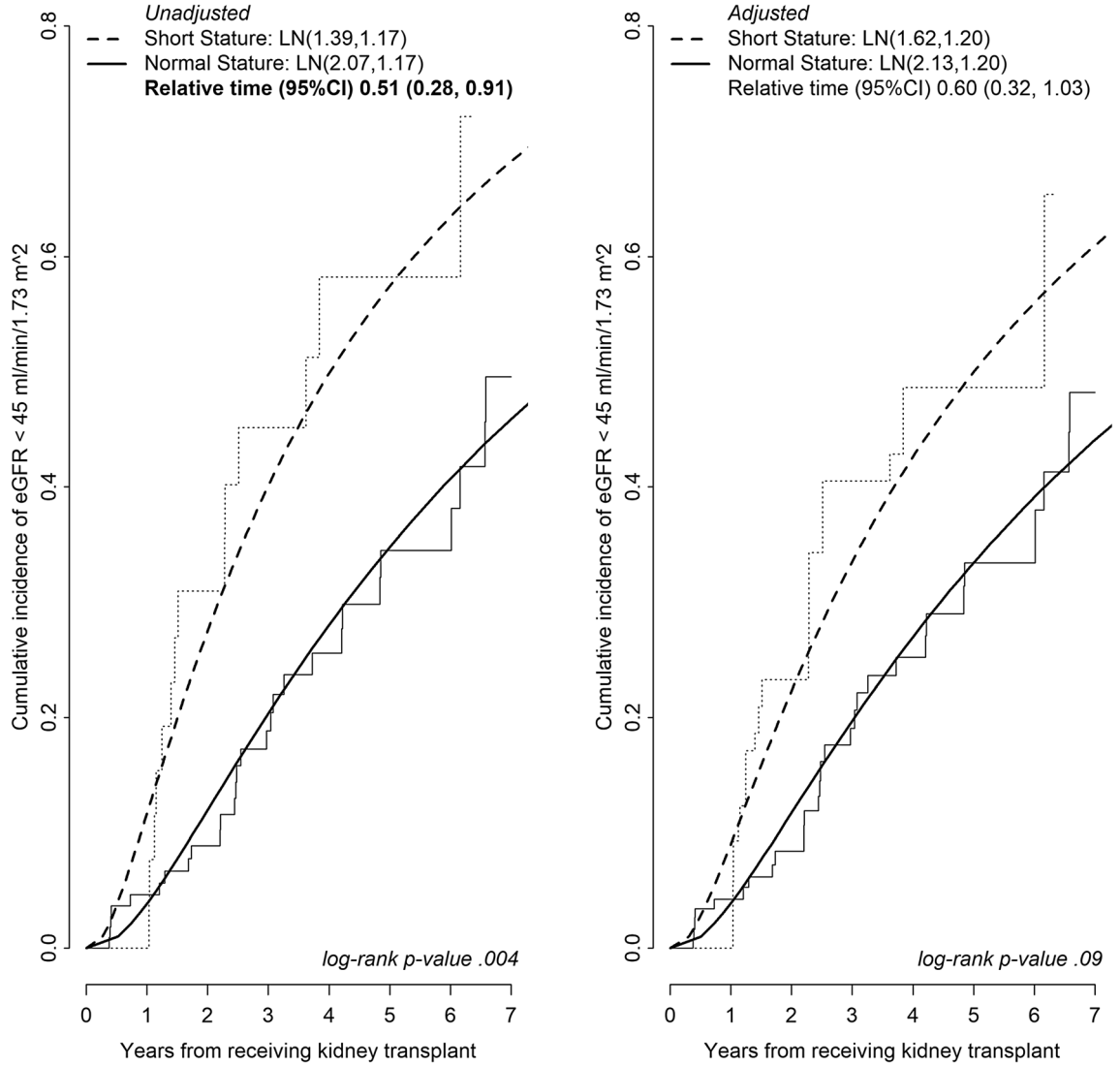

Fig. 1 Unweighted (left panel) and inverse probability weighted (right panel) step functions of the time to estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73 m^2 after kidney transplant, by short stature ($N = 138$). Cumulative incidence curves were based on parametric survival models with log-normal distribution for each group with location (β) and scale (σ) and denoted as LN(β,σ)

Figure 1 displays times to eGFR < 45 ml/min/1.73 m^2 by non-parametric step functions and parametric survival curves, in the unweighted (left panel) and weighted (right panel) samples. Twenty-five percent of children with short stature experienced eGFR < 45 ml/min/1.73 m^2 by 1.5 years; among children with normal stature, 25% experienced the outcome by 3.7 years (log-rank *p* value 0.004).

Parametric survival models were fit without and with inverse probability weights (i.e., naïve and adjusted) to evaluate the relationship between time to eGFR < 45 ml/min/1.73 m^2 and short stature. In the naïve analysis, those with growth failure had a relative time of 0.51 (95%CI 0.28, 0.91). This is interpreted as participants with growth failure prior to transplant had a 49% shorter time to the low eGFR outcome, and this effect was statistically significant. The effect estimate was attenuated in the weighted sample, suggesting that SES factors, CKD characteristics, and mid-parental height (as a proxy for genetic influence) partially explained the observed association of short stature with low eGFR after transplant. The association persisted after the adjustment and was borderline significance with a relative time of 0.60 (95% CI 0.32, 1.03). In other words, those with short stature had a 40% shorter time to eGFR < 45 ml/min/1.73 m^2 after transplant, compared to children with normal stature, when both groups had the same distribution of observed pre-transplant characteristics (i.e., adjusted for covariates).

Discussion

In this unique pediatric population in which anthropometric and socioeconomic data were collected prior to kidney

transplant during the CKD phase, we explored the association of short stature with outcome after transplant. Kidney transplant outcomes were based on longitudinal post-transplant eGFR data, with poor outcome defined as eGFR < 45 ml/min/1.73 m^2. Our results showed that short stature was associated with faster time to the poor outcome and can be potentially used as an indicator to identify high-risk patients.

Informed by previous publications [22–25], we hypothesized that short stature was an indicator reflecting the composite effect of low SES, disease severity, over all nutritional status, disturbances in mineral homeostasis, and chronic inflammation prior to kidney transplant. The attenuated association comparing the adjusted model with the crude model suggests that SES, CKD characteristics, and parental height explain, at least in part, the faster time to low eGFR after transplant for those with growth failure. Importantly, after the adjustment, the association persisted and children with short stature had a 40% faster progression to the poor outcome. We thus speculate that mineral metabolic disorder, chronic inflammation, and poor nutrition may also contribute to the increased risk of poor transplant prognosis among children with growth failure.

To investigate the potential role of mineral metabolic disorders and outcomes in this population, we conducted an ad hoc analysis and found that those with short stature had higher levels of C-terminal FGF23 (median level 408 vs. 272 RU/mL, $p < 0.001$). This is consistent with the known CKD and ESRD related risks associated with these biomarkers [26–30] and provide preliminary evidence of pre-transplant levels conferring risk post-transplant. It should be noted that the FGF23 measurements occurred at heterogeneous time prior to transplant and should be considered exploratory data. Future studies should incorporate laboratory biomarkers to describe pre-transplant mineral disturbances in the context of post-transplant outcomes.

In our population, there was a higher proportion of children who received growth hormone therapy before transplant among those with short stature (39% vs. 28%), but 61% were untreated. This may indicate suboptimal treatment and poor growth outcomes after therapy, and information in regard of GH therapy compliance and the impact of therapy on a monthly or yearly basis are needed for further investigation. Nevertheless, since growth hormone therapy is an efficacious and safe treatment for growth failure in children with CKD, increasing its utilization and effectiveness early in the course of CKD may lead to better outcomes after transplantation. Furthermore, this also provides hints that chronic inflammation might serve as the underlying link since it can exacerbate perturbations in the growth hormone/insulin-like growth factor 1 axis [31, 32] and it too can accelerate deterioration of graft function [33, 34].

There were several strengths of this study that identified short stature as a potentially meaningful risk factor for poor transplant prognosis in children. Firstly, SES, disease severity, and parental height were relatively strong confounders and were taken into account by inverse probability weighting. After the adjustment, a persistent association of growth failure with the outcome remained. Our analysis was also strengthened by the CKiD study design which collected longitudinal data during both the CKD stage and post-transplant phase of pediatric kidney disease in order to prospectively link exposures to outcomes. Lastly, we developed an applied methodology to estimate poor kidney transplant outcomes based on longitudinal GFR data after transplant. This method allows us to define a subclinical study endpoint (i.e., time to eGFR < 45 ml/min/1.73m^2) and incorporate prevalent events into our analysis.

There were several limitations to our analysis. First, the study population was a subset of a CKD cohort and detailed transplant data were not available. We acknowledge that the relationship between short stature and post-transplant kidney function may be influenced by major transplantation characteristics which were not available in this analysis, including allograft mismatch, donor source, delayed graft function, non-adherence to transplant medication, and rejection episodes. As a sensitivity analyses, we considered height percentile less than the 25th percentile, as well as a continuous variable (height z-scores) and the results were consistent, but attenuated, compared to using the more typical definition of height less than the third percentile. Secondly, the subclinical endpoint of eGFR < 45 ml/min/1.73 m^2 was considered a reasonable and clinically meaningful proxy for poor graft outcome, but graft failure may not be imminent for these individuals. In addition, the event time was estimated based on a combination of observed and imputed eGFR values and may not be precise. Nevertheless, this subclinical study endpoint is helpful for clinicians to identify patients at a higher risk in a preemptive manner and consider interventions to improve prognosis. To address how the event time was estimated, we compared more complex models using multiple imputation by chained equations and found very similar outcomes as our simple approach. Lastly, this subset of the CKiD study was relatively small compared to kidney transplant registries in which outcomes are typically assessed. Therefore, to establish short stature as a risk factor for kidney transplant prognosis, future studies should validate the relationship in an independent cohort where sufficient number of clinical events, donor's source, body size, as well as other important transplant characteristics, are available.

In summary, this analysis suggested that short stature prior to kidney transplant was associated with a higher risk of lower kidney function after transplant among pediatric recipients. This relationship was partially, but not entirely, explained by pre-transplant SES, disease severity, and parental height. Clinicians should be aware of the implications of

growth failure on transplant outcomes in this unique population. Future research should continue to identify modifiable factors that contribute to poor transplant outcomes and effective interventions to minimize or delay risk.

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Compliance with ethical standards

The study protocol was approved by the institutional review board of each participating center. All participants and their families provided informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

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