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Vitamin D and metabolic bone disease in prolonged continuous kidney replacement therapy: a prospective observational study

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Abstract

Background Complications of prolonged continuous kidney replacement therapy (CKRT) have not been well described. Our objective was to describe mineral metabolism and bone findings in children who required prolonged CKRT.

Methods In this single center prospective observational study, we enrolled 37 patients who required CKRT for ≥ 28 days with regional citrate anticoagulation. Exposure was duration on CKRT and outcomes were 25-hydroxy vitamin D and osteopenia and/or fractures.

Results The prevalence of vitamin D deficiency and insufficiency was 17.2% and 69.0%, respectively. 29.7% of patients had radiographic findings of osteopenia and/or fractures. There was no association between vitamin D deficiency or insufficiency with age or ethnicity. Time on CKRT and intact PTH levels were not predictive of vitamin D levels. Children with chronic liver disease were more likely to have osteopenia and/or fractures compared children with other primary diagnoses, odds ratio (3.99 (95%CI, 1.58–2.91), $p = 0.003$) after adjusting for age and time on CKRT.

Conclusion Vitamin D deficiency and/or insufficiency, and osteopenia and/or fractures are prevalent among children who require CKRT for a prolonged period. The risk for MBD may be higher with chronic liver disease. Higher doses of vitamin D may be required to maintain normal levels while on CKRT.

Introduction

Chronic kidney disease (CKD) is commonly associated with changes in calcium and phosphate homeostasis [1–4]. These disorders result from dysregulation of 1,25-dihydroxyvitamin D (1, 25 di-$(OH)_2$D), parathyroid hormone (PTH), phosphate metabolism, fibroblast growth factor (FGF)-23, and expression of Klotho. In addition to mineral bone disease (MBD), the resulting metabolic abnormalities are associated with an increased risk of cardiovascular disease, a major cause of morbidity and mortality in individuals with CKD [1–3]. Although these changes are often prominent in advanced stages of CKD, the precise timing of when these events begin to occur remains unclear.

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Acute kidney injury (AKI), an increasingly recognizable risk factor for CKD, could also have dysregulation of the same feedback mechanisms resulting in metabolic derangements similar to those seen in CKD [5–7]. Often, these abnormalities include hypocalcemia, hyperphosphatemia, hyperparathyroidism, decreased 1, 25$(OH)_2$D, increased FGF-23, and decreased renal expression of Klotho. Severe AKI is common among hospitalized patients and is an independent risk factor for morbidity and mortality in the pediatric intensive care unit (PICU) population even after adjusting for primary diagnoses. AKI is also associated with increased risk of cardiovascular mortality and major cardiovascular events in adult patients [8, 9].

Continuous kidney replacement therapy (CKRT) is used in critically ill children with AKI, to prescribe gradual fluid removal and to control hemodynamics while allowing nutritional support. Acute Disease Quality Initiative (ADQI) consensus has recently defined AKI persisting for ≥7 days but less than 90 days as acute kidney disease (AKD). Essentially, AKI, AKD and CKD are a disease continuum differentiated by disease duration. It is not uncommon for some patients with AKD who remain hemodynamically fragile or who have excessive fluid intake needs to require CKRT for a prolonged period to allow adequate nutrition and fluid management, as well as electrolyte and metabolic management [10].

Vitamin D, a crucial hormone for maintaining calcium and phosphorus homeostasis, is also deficient in critically ill children [11–13]. Vitamin D effects are not limited to calcium and phosphorus metabolism and bone health but also include immunomodulation and infection control among other functions [1–3]. Its deficiency increases risk for morbidity and mortality in the PICU [14–17]. One of the mechanisms contributing to deficiency of vitamin D in critically ill children is impaired kidney function [7, 18, 19]. Often very ill children will be on total parenteral nutrition (TPN) with minimal parenteral vitamin D intake. Those that are not able to tolerate any enteral supplementation are at an even increased risk for worsening vitamin D levels in the absence of adequate supplementation.

While MBD in CKD has been widely studied, little is known about MBD in pediatric AKD and prolonged CKRT (pCKRT). pCKRT could cause phosphate and calcium losses via mass transfer; in cases of regional anticoagulation with citrate these changes could be easily missed since calcium is continuously replaced [20, 21].

We aimed to describe metabolic and bone findings of pediatric patients with AKD who required CKRT with regional citrate anticoagulation for greater than 28 days. We hypothesized that vitamin D deficiency would be prevalent in pediatric AKD and control of serum calcium and phosphorus with regional citrate anticoagulation would impact vitamin D and PTH levels. Our secondary outcome was radiographic bone findings observed among these patients.

Methods

We conducted a prospective observational study of patients who required CKRT for greater than 28 days at our institution between 2015 and 2017. Prolonged CKRT (pCKRT) was defined as being on uninterrupted CKRT for ≥28 day (pCKRT). Children with a prior diagnosis of CKD or end-stage kidney disease (ESKD), children receiving CKRT while on extracorporeal membrane oxygenation were excluded from this study. Data including patient demographics (age, gender and body weight), primary diagnosis, CKRT indication, duration on CKRT; calcium, phosphorus, serum hydroxy vitamin D (25 (OH) D), serum 1, 25 di-$(OH)_2$D, parathyroid hormone (PTH) were collected from the electronic health record or the institutional CKRT database. Data on both enteral and parenteral vitamin D supplementation were obtained. We have a care bundle recommendation that includes monitoring of clinically available bone health parameters at 4 weeks and every 4 weeks thereafter, however, the laboratory testing was ordered by the clinical ICU team and adherence to the clinical practice bundle was incomplete. Testing was at the discretion of the clinicians. Our study was purely observational and no study related laboratory sampling was mandated. As per our institutional nutrition protocol, patients on parenteral nutrition received standard vitamin D supplementation based on weight as follows: (1.5 mL/day (120 units) for <1 kg, 3.25 mL/day (260 units) for ≥1–3 kg, 5mL (400 units) if≥3 kg – 11 years, and 10 mL/day (800 units) for ≥11 kg).

Our center utilizes pre-dilution continuous veno-venous hemodiafiltration (CVVHDF) with regional citrate anticoagulation (RCA) per institutional protocol for CKRT. The minimum dose of CKRT prescribed is 2000mL/1.73m^2/hour and 50% of the dose is prescribed as convection via hemofiltration and 50% is prescribed as diffusion via dialysis. With RCA, calcium is infused post-filter to keep serum ionized calcium levels in the normal range. Patients are routinely assessed for readiness for CKRT discontinuation or transitioning to intermittent hemodialysis.

The primary outcome was the prevalence of vitamin D deficiency and insufficiency among children on pCKRT. Vitamin D deficiency was defined as a serum 25 (OH)D less than 20 ng/mL and vitamin D insufficiency defined as serum 25 (OH)D between 20 and 30 ng/mL. The secondary outcomes were (1) association between vitamin D levels and PTH and (2) radiographic bone findings.

Continuous variables were expressed as median and inter-quartile ranges (IQR), and categorical variable as percentages. Univariate and multivariable modeling was

done to assess for associations. For repeated measures analyses, generalized lineral models were used with patient level set as random effects. Statistical analyses were carried out using Stata™ 15.1 (StataCorp, 2020 College Station, TX) software.

Institutional review board (IRB)/Ethics approval was obtained with a waiver of consent due to the observational nature of the study.

Table 1 Patient demographics and characteristics

Variable	*N* = 37
Male, n (%)	21 (57)
Ethnicity, n (%)	
White	13 (35)
Hispanic	15 (41)
Black	7 (19)
Other	2 (5)
Age in years at CKRT start, median (IQR)	6 (1–13)
Age category (years)	
<1	11 (29.7)
1–5	7 (18.9)
>5	19 (51.4)
Primary diagnosis, n (%)	
Malignancy	14 (38)
Biliary atresia	10 (27)
Heart failure	6 (16)
Hemophagocytic lymphohistiocytosis	2 (5)
Other†	5 (14)
Length of CKRT days, median (IQR)	51 (38–84)
Mineral parameters during CKRT	
Calcium mg/dL, median (IQR)	9.1 (9.5–10.5)
Ionized calcium, mmol/L, median (IQR)	1.23 (1.15–1.27)
Phosphorus, mg/dL, median (IQR)	4.0 (3.4–4.5)
Hypophosphatemia by age cutoffs‡	8 (21)
Vitamin 25(OH)D ng/mL, median (IQR)	24.9 (20.6–29.2)
Vitamin D deficiency n (%)	5 (17.2)
Vitamin D insufficiency n (%)	20 (69.0)
PTH (pg/mL), median, IQR	82 (45.0-235.6)
% with high PTH levels for age (years)	
<1	6/7 (85.7)
1–8	2/3 (66.7)
9–17	1/7 (14.3)
>17	1/3 (33.3)
Osteopenia and/or fractures while on CKRT, **n(%)**	11 (29.7)

CKRT: continuous kidney replacement therapy, AKI: acute kidney injury, SD: standard deviation, IQR: inter-quartile range, PTH: parathyroid hormone. †Other diagnoses include sepsis (1), Alagille syndrome (1), acute liver failure of unclear etiology (1), sickle cell anemia (1), inborn error of metabolism (1)

‡Phosphate age-specific values (mg/dL): <1y: 4.8–7.4, 1-5y: 4.5–6.5, 6-12y: 3.6–5.8, and 13-20y: 2.3–4.5

PTH reference values (pg/mL): <1y: 6.4–88.6, ≤1-<9y: 16.2–63.0, ≥9-≤17y: 21.9–87.6, and > 17y: 16-60.4

(NKF KDOQI guidelines)

Results

We enrolled 37 patients in this study, 57% were male. The median age was 6 years (interquartile range (IQR) 1–13 years). 32% of patients were one year or younger (Table 1). The most common primary diseases were malignancy and biliary atresia. These were all critically ill children with stage 3 AKI with hemodynamic instability, diuretic-resistant fluid retention and/or oligoanuria, and need for optimization of nutrition among children with persistent oliguria or hemodynamically unstable.

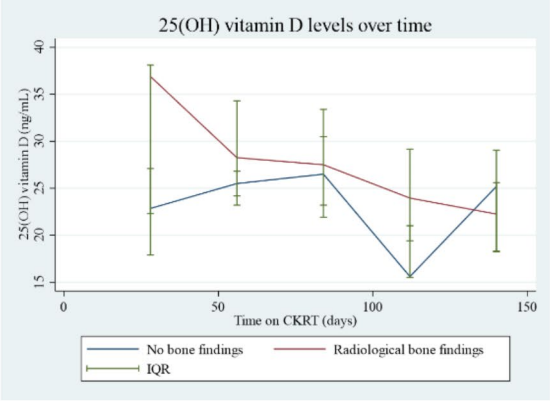
Patients were assessed for readiness for CKRT discontinuation or transitioning to intermittent hemodialysis on a daily basis. Indications to continue CKRT included hemodynamic instability, oligoanuria with diuretic-resistant fluid retention, and need for optimization of nutrition in patients with persistent oliguria or hemodynamically unstable. Daily fluid balance (intake and output) was reviewed, and residual kidney function assessed by urine output with or without diuretic challenge and/or trial off CKRT.

The median duration on CKRT was 51 days (IQR 38–84). Thirty-four patients (97%) were receiving some form of vitamin D supplementation during CKRT. Thirty-two (94%) patients received standard vitamin D supplementation in parenteral nutrition based on weight. Two patients were on ergocalciferol in addition to parenteral nutrition and another two patients on only ergocalciferol supplements. Only 8% (3/37) of patients were on calcitriol during pCKRT. The median total serum calcium level was 9.1 mg/dL (IQR 9.5–10.5), ionized calcium 1.23 (IQR 1.15–1.27) and phosphorus, 4.0 mg/dL (IQR 3.4–4.5). As serum calcium was tightly controlled by continuous calcium infusions, frequent measurements, and immediate titration, we did not observe hypocalcemia. 21% (8 of 37) patients had mild transient hypophosphatemia while on pCKRT as patients had chemistries at least daily and frequently more often. The median nadir serum phosphorus level in this cohort was 3.3 mg/dL (IQR 2.7–3.8). Only one patient had a serum phosphorus < 2 mg/dL during the study time. Phosphate was supplemented routinely in the dialysate and the replacement solutions, and the composition of the dialysate fluids was changed when needed.

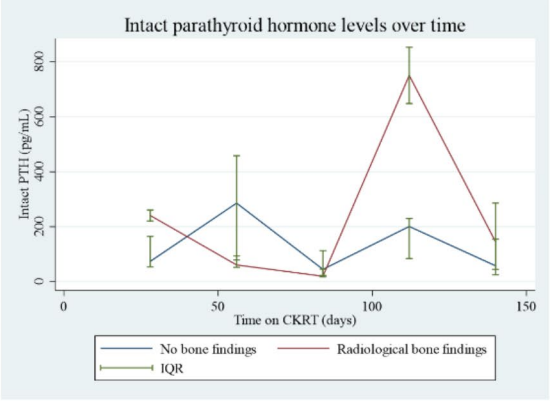
Prevalence of Vitamin D Insufficiency and Deficiency

Of the cohort, 78% (29 of 37) and 54% (20 of 37) of patients had 25 (OH)D and PTH levels obtained at or after 28 days of being on CKRT respectively. The median time for vitamin D and intact PTH testing was 62 (IQR 33–96) days and 68 (IQR 37–101) days, respectively.

The median serum 25 (OH)D while on pCKRT was 24.9 (IQR 20.6–29.2) ng/mL. The prevalence of vitamin D deficiency was 17.2% and that of vitamin D insufficiency was 69%. 62% of patients had 25 (OH)D levels that were



Time interval (days on CKRT)	0-15	16-30	31-45	46-60	61-75	76-90	91-105	106-120	>120
Number of patients with 25-OH vitamin D levels	2	4	8	4	6	2	5	4	3



Time interval (days on CKRT)	0-15	16-30	31-45	46-60	61-75	76-90	91-105	106-120	>120
Number of patients with intact PTH levels	4	4	5	3	5	5	3	5	3

Fig. 1 1**a** and **b**: 25-hydroxy vitamin D and intact parathyroid hormone levels during CKRT

Table 2 Metabolic parameters by bone changes

Variable	Osteopenia/ Fractures (*n* = 11)	No osteopenia/Fractures (*n* = 26)	*p*-value
Age (years)	1.00 (0.80, 11.20)	9.50 (1.90, 13.60)	0.062
Chronic liver disease‡, n(%)	6 (54.5)	5 (19.2)	0.042
Duration on CKRT (days)	84 (57, 146)	51 (40, 109)	0.236
Metabolic parameters			
Serum phosphorus (mg/dL)‡	4.2 (4.1, 4.9)	4.15 (3.8, 4.9)	0.163
Hypophosphatemia in pCKRT	4 (36%)	4 (15.4%)	0.157
Serum calcium (mg/dL) ‡	9.9 (9.6–10.3)	9.6 (9.2–10.2)	0.335
Ionized calcium (mmol/L) ‡	1.22 (1.16–1.27)	1.22 (1.15–1.26)	
Vitamin D-25(OH) (ng/mL) ‡			
During CKRT	27.4 (21.9, 29.7)	24.1 (20.4, 26.1)	0.4927
Intact PTH (pg/mL) ‡			
During CKRT	81.7 (38.5, 368)	67.0 (54.0, 229.6)	0.3369

‡Median and interquartile ranges

‡ Includes biliary atresia (10) and Alagille syndrome (1)

persistently below 30 ng/mL despite being on enteral or parenteral supplemental vitamin D. Children with liver disease were more likely to be vitamin D deficient, odds ratio (OR) 8.17 (CI, 1.86–33.12) on bivariate analysis. However, this association was lost in multivariate analyses after adjusting for age, ethnicity, primary diagnosis, and time on CKRT. Median intact PTH during pCKRT was 82 (IQR 45.0-235.6) pg/mL.Intact PTH levels were not predictive of 25 (OH)D levels. Figure 1a. and 1b. show 25-hydroxy vitamin D and intact parathyroid hormone levels during CKRT. With only 27% (10/37) of the patients having vitamin 1, 25 di$(OH)_2$D levels checked more than once, this data was not used in the analyses.

Bone findings on pCRRT

All patients had imaging studies done at the discretion of the primary physicians during CKRT. 30% (11 of 37) of patients had bone findings of osteopenia or fractures incidentally identified on x-rays obtained for clinical reasons other than metabolic bone disease evaluation (e.g., chest xray, endotracheal tube placement or localization among other). Duration on CKRT, patient age, calcium, phosphorus, 25 (OH)D, and intact PTH levels were comparable among patients with and without osteopenia and/or fractures (Table 2). Children with chronic liver disease (defined by primary team) were more likely to have osteopenia and/or fractures compared children with other primary diagnoses, odds ratio (3.99 (95%CI, 1.58–2.91), $p = 0.003$) after adjusting for age and time on CKRT. The median age of children with chronic liver disease was 0.7 (0.6-1.0) years compared with 11.6 (5.0-14.7) years in children without chronic liver disease. Three patients had osteopenia and/or fractures prior to CKRT initiation and all three demonstrated worsening of the preexisting metabolic bone disease while on pCKRT. Patients who had phosphorus levels below the lower limit for age at some point were more likely to have osteopenia and/or fractures, 36.4% vs. 15.4% (Table 2). Neither intact PTH levels nor presence of osteopenia and/or fractures fully explained the change in vitamin D values over time in GLM analyses (Fig. 1a and b). However, the number of observations after the first few weeks were very few, limiting our ability to draw conclusions.

Discussion

In this prospective observational cohort study, we demonstrated that vitamin D insufficiency and deficiency are prevalent in critically ill children with AKD requiring CKRT for a prolonged time. The prevalence of vitamin D insufficiency (serum 25(OH)D levels < 30 ng/mL)

was 69% and deficiency (serum 25(OH)D levels < 20 ng/mL) was 17.2% among patients who required CKRT for ≥ 28 days. Additionally, we observed that 30% (11 of 37) of these patients had bone findings of osteopenia or fractures while on CKRT with citrate anticoagulation, and that children with chronic liver disease were more likely to have these radiological osteopenia and/or fractures. Neither time spent of CKRT nor intact parathyroid hormone levels were predictors of vitamin D levels or osteopenia and/or fractures. It is possible that longer duration of chronic liver disease prior to CKRT could predispose patients to develop deranged metabolic profile.

As reported in previous studies [11–13, 22], we demonstrated a high prevalence of vitamin D insufficiency and deficiency among critically ill children. We observed a decreasing levels of 25(OH)D levels over time among children with bone findings while on CKRT. Czarnik et al., also demonstrated a rapid decline in vitamin D levels during the course of CKRT [23]. In another study, Czarnik et al., demonstrated a variation in PTH trends during CKRT, with a decrease in levels initially. They observed increasing levels especially when the clinical course was complicated by sepsis [24]. In our study, there was no identifiable trend in the intact PTH levels.

Our study is unique in that the study population focused on children with severe AKI/AKD on CKRT with prolonged citrate exposure. While MBD in CKD has been widely studied, little is known about MBD in pediatric AKD and pCKRT. Prolonged exposure to citrate during CKRT with CVVHDF with prefilter hemodilution and RCA may have unforeseen metabolic effects on bone through mass transfer of calcium during CVVHDF. To our knowledge, this is the first study on vitamin D levels and osteopenia and/or fractures in children who require CKRT for a prolonged period.

The literature contains only two adult case reports on mineral and bone disorders associated with prolonged CKRT with citrate anticoagulation. In these two case reports, the two patients were on CKRT for 120 days and 254 days [25]. Both of these case reports found a decreasing calcium requirement, bone resorption, and spontaneous fractures over time [25]. Total serum calcium levels remained normal without much exogenous calcium infusion suggesting endogenous mobilization of calcium. Klingele et al. also demonstrated decreasing vitamin D levels over time despite supplementation [20]. In our study, we demonstrate variations in 25(OH)D and intact PTH levels during CKRT despite tight control and maintenance of normal serum calcium and phosphorus levels. These findings suggest that traditional markers of mineral bone disease (25(OH)D, 1, 25 di-$(OH)_2$D), and PTH) may not be reliable in patients on prolonged CKRT. It is possible that vitamin D insufficiency or deficiency and not low ionized calcium or high phosphorus is the trigger for PTH release in these patients. However, the lack of association between high PTH and sufficient vitamin D may suggest other molecules such as FGF-23 and/or Klotho could have a role in the vitamin D and PTH dysregulation. In addition, pCKRT could cause phosphate and calcium losses via mass transfer which could be easily missed because calcium is continuously replaced when regional anticoagulation with citrate is used [20, 21] and phosphate typically added to the solutions used.

Patients with chronic liver disease were more likely to have radiological osteopenia and/or fractures. This increased risk could be due to a combination of kidney and hepatic osteodystrophy.

Hepatic osteodystrophy is a well described entity in chronic liver disease [25] as vitamin D undergoes 25-hydroxylation in the liver while the kidney is responsible for 1α-hydroxylation process. For this reason, presence of both chronic liver diease and prolonged AKI and its effect on mineral metabolism could lead to more severe bone disease. Whether immobilization and/or prolonged citrate exposure with pCKRT pose an additional risk for fractures needs to be studied further.

In this study, we demonstrate persistently low 25(OH)D levels throughout CKRT despite vitamin D supplementation enterally for patients that would tolerate enteral supplements or through TPN at a standard weight-based supplementation for patients who required parenteral nutrition. This observation is similar to that of Czarnik et al. [23], and may suggest that supplementation was suboptimal and that higer doses may be required to maintain sufficient vitamin D levels and prevent complications. There is an ongoing study on vitamin D3 supplementation in critically ill patients on CKRT. This study should provide further insight on this issue [].

Patients requiring pCKRT, especially those with chronic liver disease need regular monitoring of CKD-MBD parameters as well as screening skeletal surveys to identify MBD as early as possible. Our findings, while compelling, are by no means conclusive and should be viewed as hypothesis generating for further research.

The limitations of our study include those inherent in the study design. First, being an observational study, laboratory tests were not systematically obtained and some patients had fewer data points. Specifically, we did not have pre-CKRT baseline vitamin D and PTH levels on many of the subjects, and even while on CKRT, tests were obtained at varying time points and we did not collect data on timing of, or duration of vitamin D supplementation. As a result, we were unable to determine the degree of change in vitamin D levels after starting CKRT. Second, the absence of a control group makes it challenging to attribute our findings solely to prolonged CKRT. Third, we did not look at the potential effects of bilirubin and albumin on metabolic bone profiles in this

study. Lastly, we were not able to measure calcium levels in the CKRT effluent fluids to better assess mass transfer of calcium and dialysis related loss. The actual CKRT dose delivered was not considered in these analyses. We recorded the initial prescription dose but were not able to track dynamic dose changes over time. It is possible that higher delivered dose is associated with increased dialysis-related morbidity due to removal of macronutrient as well as other mediators of bone health [26]. Prescribed and delivered dose should be investigated in future studies of bone health in patients with AKD receiving CKRT.

In conclusion, vitamin D insufficiency and deficiency are prevalent in pediatric patients with AKD receiving CKRT and may worsen despite standard supplementation. Higher doses of vitamin D supplementation may be required for patients requiring prolonged CKRT to maintain sufficient levels and prevent MBD. Serum 25(OH) D, 1, 25 di-$(OH)_2D$, and PTH should be closely monitored. Children with biliary atresia or other chronic liver disease (defined by the patient's primary team) maybe at a particularly higher risk for developing bone disease or worsening of underlying bone disease with pCKRT and would warrant regular assessment for bone disease. Maintenance of normal ionized calcium, a stimulant for PTH release in setting of regional citrate anticoagulation and immobilization hypercalcemia, which may be masked on pCKRT could result in bone mineral disease through non-conventional mechanisms. It is unclear how much prolonged immobilization plays a role in the osteopenia and/or fractures and whether prolonged citrate exposure has untoward metabolic effects on bone in this setting. Further studies should evaluate the mechanisms of metabolic bone disease in severe acute kidney disease requiring pCKRT, including role of immobilization hypercalcemia, calcium clearance, FGF23 and Klotho in this phenomenon.

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Author contributions
PDI, AAA and PS designed the study. PDI and NTP extracted and cleaned the data. Data analysis was jointly performed by PDI, AAA and PS. PDI wrote the manuscript. All authors read, edited, and approved the final manuscript. All authors provided intellectual content of critical importance to the work described herein. All authors reviewed and approved the final manuscript.

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Data availability
The datasets used for this study are not publically available for the privacy of the participants and to comply with regulations of the ethics approval. The datasets will however be available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Approval was obtained with a waiver of consent from the Baylor College of Medicine institutional review board (IRB) and Baylor College of Medicine ethics committee (IRB #H-43577) due to the observational nature of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors of this manuscript have no conflicts of interest to disclose.

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