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Prevalence of Bone Mineral Disease in Children with Acute Kidney Disease on Continuous Renal Replacement Therapy: A Case Control Study

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Abstract

Background

Continuous kidney replacement therapy (CKRT) with regional citrate anticoagulation (RCA) is preferred in critically ill children with acute kidney disease (AKD). It is unclear whether CKRT exacerbates risk of bone mineral disease in AKD. We designed a case-control study to evaluate osteopenia and mineral balance markers in prolonged CKRT with RCA compared to prolonged immobilization.

Methods

Cases were AKD patients on CKRT with RCA and controls immobilized ≥ 28 days, matched with propensity scoring. Data collected at day 0, 14 and 28. Two blinded radiologists independently evaluated for osteopenia/fractures; reliability assessed by kappa statistics.

Results

Osteopenia in cases higher at day 14 (20/53 cases v/s 10/49 controls, p 0.05), and at day 28 (21/53 cases v/s 11/49 controls, p 0.06). Younger age, CKRT, gastrointestinal/liver comorbidity increased odds of osteopenia in cases and controls. Citrate rate adjusted for blood flow had higher odds of day 28 osteopenia. New fractures higher in cases (13/53) than controls (3/49) (p 0.01). Younger age, osteopenia at baseline, day 14, and 28 had higher odds of fractures in cases. Radiologist agreement for osteopenia was moderate (Kappa 0.62).

Conclusions

This is the first comparative study in children with AKD on prolonged CKRT and bone complications. Increased fractures and osteopenia noted in children undergoing prolonged CKRT compared to immobilization. Increased risk of fractures associated with presence/persistence of osteopenia and younger age. Increased osteopenia on CKRT suggested factors beyond immobilization, like age, anticoagulation, metabolic demands, dialytrauma, baseline osteopenia, hyperparathyroidism, and underlying primary disease, may play a significant role.

Background

Acute Kidney Disease (AKD), as defined by the Kidney Disease Improving Global Outcomes (KDIGO), refers to an acute and abrupt decline in kidney function lasting more than 7 days up to 90 days, beyond which persistent kidney dysfunction is classified as chronic kidney disease (CKD) [1], [2], [3]. The severity of AKD and the necessity and duration of kidney replacement therapy in critically ill patients is directly correlated with worse patient outcomes, regardless of etiology [1], [4], [5]. While previous studies on AKD

have mainly focused on all-cause mortality and the development of CKD, recent research has suggested associations between AKD and hypocalcemia, hyperphosphatemia, hyperparathyroidism, and Vitamin D deficiency [6], [7], [8]. AKD likely disrupts bone mineral metabolism, potentially increasing the long-term risk of fractures. However, it remains unclear whether supportive care for AKD, such as continuous kidney replacement therapy (CKRT), exacerbates this risk.

CKRT is the preferred method of dialysis in critically ill children with AKD in resource replete settings, with the majority of pediatric centers utilizing regional citrate anticoagulation (RCA) [9][10]. Citrate acts as a chelator for calcium, disrupting the coagulation cascade. RCA is proven to be highly effective, well-tolerated, and associated with a reduced risk of bleeding compared to heparin [11], [12], [13], [14]. Nevertheless, there are case reports of higher prevalence of hypocalcemia and pathological fractures in critically ill adults undergoing long-term CKRT with RCA [15], [16], [17], [18], [19].

There is however, a scarcity of studies on the effects of prolonged CKRT on bone mineral metabolism in children. In our recently published prospective study, vitamin D insufficiency (serum 25(OH)D levels < 30 ng/mL in 69% patients) and deficiency (serum 25(OH)D levels < 20 ng/mL in 17.2% patients) was noted among patients who required CKRT for ≥ 28 days or longer [18]. Strikingly, 30% of our patients on prolonged CKRT had bone findings of osteopenia or fractures [18]. While the precise driver for these bone findings is unclear, immobilization-associated bone resorption increasing the propensity to fractures could play a role in bone pathologies in children undergoing prolonged CKRT [7], [20], [21], [22].

Our objective was to assess bone and bone mineral marker changes in children undergoing prolonged CKRT with RCA. We designed a case-control study to systematically evaluate osteopenia and mineral balance markers in pediatric AKD patients undergoing prolonged CKRT with RCA and compared them with patients experiencing prolonged immobilization in the pediatric intensive care unit (PICU).

Methods

We conducted a single center case-control study. We defined cases as patients with acute kidney disease (AKD) who underwent CKRT for ≥ 28 days between 2010 and 2021. We used continuous venovenous hemodiafiltration (CVVHDF) as our CKRT modality in accordance with the institutional guidelines. All our patients received CKRT with RCA and no other anticoagulation was used in this period. We chose the threshold of ≥ 28 days for prolonged CKRT based on our previous work, aligning with the original pediatric RIFLE (pRIFLE) criteria defining loss of function (pRIFLE category "L") as persistent kidney failure lasting more than 4 weeks [11], [23]. We identified controls from our PICU database as patients who were immobilized on mechanical ventilation for ≥ 28 days without AKD from 2010 to 2021. We employed propensity score matching to select appropriate controls, stratifying patients without AKD by the duration of immobilization on mechanical ventilation ≥ 28 days and performing 1:1 matching using the R package MatchIT. Independent covariates included in the propensity model included primary diagnoses, comorbidities at PICU admission, age, height, weight, gender, ethnicity, ventilator days, and PRISM 3 Risk of Mortality (ROM). A tolerance of +/- 0.3 was

allowed for matching, ensuring patients on mechanical ventilation ≥ 28 days without AKD were matched if they were within 0.3 SD of propensity score from each other. We excluded patients with underlying metabolic bone disease (both cases and controls), cases with underlying chronic kidney disease (CKD) stage 3 or worse (based on estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m²). We excluded controls with any kidney injury or disease as AKD itself can play a role in bone mineral metabolism.

We collected data retrospectively from patients' electronic medical records (EMR). We extracted demographics, primary diagnoses, associated comorbidities, mortality, medication history (including steroids), duration of PICU stay, length of mechanical ventilation. Our CKRT-specific data included indication/s for starting CKRT, blood flow, calcium and citrate infusion rate at day 0, 14 and 28, and duration of CKRT. Day 0 was the day of CKRT initiation in cases and the day of PICU admission for controls. Initial citrate and calcium rate is based on the blood flow and titrated for changes in blood flow and calcium level, as per our institutional policy. For statistical analyses, we used citrate and calcium rate adjusted for blood flow to account for these changes. Our serum bone mineral balance markers included calcium, ionized calcium (iCa), phosphorus, pH, bicarbonate at day 0, 14, and 28; serum parathyroid hormone (PTH), 25-hydroxy vitamin D (Vit D), and 1, 25-dihydroxy vitamin D level at or beyond 28 days on CKRT or immobilization. For patients with multiple PICU admissions, we only included data from the first admission with prolonged CKRT or immobilization (index admission). Two blinded radiologists evaluated chest radiographs (CxR) independently at day 0, 14, and 28 for evidence of osteopenia and/or fractures, with additional review of EMR for documentation of fractures through the index admission. We defined survival as survival to hospital discharge during index admission. We calculated baseline eGFR using baseline serum creatinine (Cr)(mg/dL) at admission or start of CKRT with the modified Schwartz equation ([0.413 * height in cm]/Cr). We defined baseline Cr as the lowest Cr during index admission before CKRT initiation or if available, lowest outpatient Cr within a month of admission.

Our primary outcome was presence of osteopenia and/or fractures at day 14 and 28 compared to baseline on day 0. The secondary outcome was change in bone mineral markers at day 14 and 28 and their association with osteopenia/fracture, if any.

We presented continuous data as medians (interquartile range [IQR]), and categorical data as percentages. We compared our data using Chi-square or Fisher's exact test as appropriate. We utilized a mixed model with fixed effects, along with logistic regression, for comparison of worsening osteopenia and fractures. Predictors included in the multivariate model were based on strength of correlation in univariate model.

We set statistical significance at p-value < 0.05, and reported 95% confidence intervals (CIs) for logistic regression. We used Kappa statistic to assess inter-rater reliability for osteopenia readings. Statistical analysis was performed using STATA 15.0 and R software version 4.2.3. Our study protocol was

reviewed and approved by the Baylor College of Medicine Institutional Review Board, with a waiver of informed consent.

Results

We identified a total of 53 cases meeting our inclusion criteria alongside 49 controls. None of the included patients had underlying metabolic or genetic bone diseases.

Demographics:

The demographic data with clinical variables and outcomes are summarized in Tables 1 and 2, respectively. The median age for cases was 54 months (IQR: 8.5, 182), and that for controls was 50 months (IQR: 8.5, 169), without a significant difference between sexes.

Table 1
Demographics

Patient Demographics		**Cases (n = 53)**	**Controls (n = 49)**	**P value**
Age in months (Median, IQR)		54 (IQR 8.5, 182)	50 (IQR 8.5, 169)	0.1
Female		57%	47%	0.3
Primary diagnosis	Acute Liver failure	26%	11%	0.04
	Acute Respiratory Failure	21%	65%	< 0.001
	Sepsis	32%	12%	0.01
	Other	31%	12%	0.27
GI-liver comorbidity		32%	31%	0.9
Medications	Steroids	98%	84%	0.02
	Antimicrobials	98%	92%	0.3
	Vitamin D supplementation	19%	16%	0.1
Days on CKRT (Median, IQR)		43 (38, 59)	N/A	
Baseline eGFR (mL/min/1.73m2) (Median, IQR)		107 (82, 137)	162 (123, 193)	< 0.001
eGFR at start of CKRT (mL/min/1.73m2) (Median, IQR)		28 (17, 42)	N/A	

Table 2
Patient outcomes

Outcome	Cases (n = 53)	Controls (n = 49)	p value
Days in PICU (Median, IQR)	72 (45, 117)	48 (37, 71)	0.004
Days on mechanical ventilation (Median, IQR)	38 (26, 64)	43 (31, 61)	0.77
Mortality	62%	23%	< 0.001
Kidney Outcome in survivors at end of hospitalization (Cases n = 20; Controls n = 37)	Kidney Recovery/normal function: 15% CKD 5*: 40% CKD 1–2**: 25% CKD 3–4***: 20%	Kidney Recovery/normal function: 95% CKD 5*: 0% CKD 1–2**: 5% CKD 3–4***: 0%	
*CKD 5/kidney failure defined as dependence on KRT or eGFR < 16 ml/min/1.73m2 at ≥ 90 days			
** CKD 1–2: eGFR > 60 ml/min/1.73m2			
*** CKD 3–4:eGFR 16 to 60 ml/min/1.73m2			

A quarter of cases (26%) had liver failure (including acute and acute-on-chronic liver failure) as the primary diagnosis compared to 11% in controls. A majority of controls (65%) and 21% of cases had respiratory failure as the primary diagnosis. On PICU admission, although eGFR was normal in both groups, eGFR in cases was lower than controls (Table 1).

CKRT was initiated in cases for multiple indications; all the patients had stage 3 AKD with either fluid overload, refractory electrolyte abnormalities, hyperammonemia and/or oligo-anuria. Median CKRT duration was 43 days (IQR: 38, 59). Steroids and antimicrobials were the most commonly used medications in both groups; steroid use was higher in cases than controls (cases 98% vs. controls 84%, p 0.02) (Table 1).

Cases had significantly longer median PICU stay of 72 days compared to 48 days in controls (p 0.004), and a higher mortality rate (62% v/s 23%, p < 0.001) *(*Table 2*)*. Among the cases who survived hospitalization and prolonged CKRT (n = 20), 40% (8/20) developed kidney failure and remained on kidney replacement therapy whereas 20% (4/20) developed severe kidney disease (>/= CKD Stage 3) at discharge. Amongst the controls, 95% who survived their PICU stay (n = 37) retained normal kidney function and 5% had mild kidney disease (stage 1 CKD) at discharge (Table 2).

Bone Mineral Markers:

We noted no difference in serum phosphorus and iCa levels between the groups at baseline, day 14 or 28. Cases had higher total calcium levels at day 14 ($p < 0.001$) and day 28 ($p < 0.001$) compared to controls *(*Table 3*)*. Cases presented with lower serum pH ($p = 0.007$) and lower serum bicarbonate levels ($p = 0.02$) at baseline *(*Table 3*)*. Although the difference in pH did not persist at day 14 or 28, cases continued to exhibit lower bicarbonate levels than controls at day 14 ($p = 0.02$) and 28 ($p = 0.015$) (Table 3). Interestingly, cases had higher total calcium/iCa ratio (mg/dL:mmol/L) than controls at day 14 (cases 11 vs controls 9, $p < 0.001$) and 28 (cases 11 vs controls 9, $p < 0.001$). Another notable finding is the significant increase in the citrate infusion rate, and citrate rate corrected for blood flow from baseline to day 14 to day 28 without a corresponding change in calcium infusion rate or calcium rate corrected for blood flow *(*Table 4*)*.

Table 3
Serum bone mineral markers: calcium, ionized calcium (iCa), phosphorus, bicarbonate, and pH in cases v/s controls

Serum Biomarkers		Cases Median (IQR)	Controls Median (IQR)	P value
Serum calcium (mg/dL)	Baseline	8.9 (7.8, 9.9)	8.6 (8.1, 9.1)	0.09
	Day 14	10.6 (10.1, 11.2)	8.9 (8.3, 9.3)	< 0.001
	Day 28	10.6 (10.4, 11.2)	9.2 (8.6, 9.6)	< 0.001
Serum iCa (mg/dL)	Baseline	4.69 (4.25, 5.17)	4.97 (4.73, 5.21)	0.3
	Day 14	4.81 (4.65, 4.93)	4.93 (4.81, 5.01)	0.5
	Day 28	4.89 (1.18, 1.27)	4.97 (4.65, 5.25)	0.4
Serum phosphorus (mg/dL)	Baseline	4.7 (3.8, 6.4)	4.5 (3.5, 5.5)	0.14
	Day 14	5 (4.2, 5.7)	4.4 (4, 5.3)	0.13
	Day 28	4.6 (4.1, 5.1)	4.7 (3.9, 5.3)	0.4
Serum bicarbonate (mmol/L)	Baseline	23 (20, 27)	26 (22, 30)	0.02
	Day 14	31 (26, 35)	33 (29, 37)	0.03
	Day 28	28 (26, 33)	32 (29, 37)	0.015
Serum pH	Baseline	7.28 (7.25, 7.37)	7.35 (7.27, 7.41)	0.007
	Day 14	7.38 (7.31, 7.44)	7.4 (7.35, 7.44)	0.1
	Day 28	7.37 (7.31, 7.41)	7.38 (7.34, 7.4)	0.55

Table 4
Blood flow, calcium infusion rate, citrate infusion rates over time from baseline to Day 28

	Baseline (IQR)	Day 14 (IQR)	Day 28 (IQR)	P value
Blood flow Rate (mL/min)	97 (94, 100)	102 (99, 105)	103 (101, 106)	0.004
Citrate Infusion rate (mL/hr)	126 (116, 136)	166 (156, 175)	170 (161, 180)	< 0.001
Calcium infusion rate (mL/hr)	59 (53, 65)	70 (64, 75)	65 (59, 71)	0.06
Citrate infusion rate corrected for blood flow	1.2	1.55	1.6	< 0.001
Calcium infusion rate corrected for blood flow	0.64	0.68	0.59	0.2
Citrate infusion rate and citrate infusion rate corrected for blood flow significantly increased over time from baseline to Day 28 of CKRT whereas no difference in calcium infusion rate or calcium infusion rate corrected for blood flow over time.				

On day 28, the median PTH level in cases (n = 38) was 182 pg/mL, and the median Vit D level (n = 40) was 24 ng/mL. PTH and Vit D levels were not available for controls at day 28. 1, 25 dihydroxy vitamin D levels were not available for a sufficient number of patients in either group, preventing a valid comparison.

Osteopenia and Fractures:

There was no difference in osteopenia at baseline between cases and controls. However, a greater number of cases had osteopenia at day 14 and at day 28 as compared to controls (Table 5), though it did not reach statistical significance. Inter-rater agreement for osteopenia was moderate among radiologists (Kappa 0.62). CxR was missing for two cases and one control at baseline, four controls at day 14, and 5 controls at day 28. An analysis of risk factors for day 28 osteopenia across all patients (both cases and controls) revealed that younger age, CKRT, or GI/liver comorbidity were associated with increased odds of developing osteopenia (Fig. 1). We then analyzed risk factors associated with osteopenia in the cases. Univariate logistic regression for day 28 osteopenia in cases showed that younger age, GI/liver comorbidity, and citrate rate adjusted for blood flow had higher odds of day 28 osteopenia *(Fig. 2)*. However, in multivariate regression, GI/liver comorbidity (OR 3.2, 95% CI 1.48, 6.86) and younger age (OR 0.99, 95% CI 0.86, 0.99) had higher odds of osteopenia in cases.

Table 5
Osteopenia in cases v/s controls

	Cases (n = 53)	Controls (n = 49)	P value
Baseline	32% (n = 17)	24% (n = 12)	0.4
Day 14	38% (n = 20)	20% (n = 10)	0.05
Day 28	40% (n = 21)	22%(n = 11)	0.06

New fractures during index admission were noted in 24.5% (13/53 cases) and 6.1% (3/49) controls (p = 0.01). We excluded one control with fracture as the patient had sustained fracture 34 days prior to PICU admission. The median age of patients with fracture was 6 months (IQR: 4, 11) in cases and 50 months (IQR: 29, 125) in controls. Baseline osteopenia was present in 8/13 cases (61.5%) and 2/3 controls (66.7%) with fractures. The median time for onset of fracture in cases was 31 days from CKRT initiation (IQR: 21, 85). In univariate logistic regression, younger age, osteopenia at baseline, day 14, and day 28 had higher odds of fracture. Younger age and day 28 osteopenia had higher odds of fracture in the multivariable analysis *(*Table 6*)*.

Table 6
Multivariate logistic regression analysis of risk factors for fractures in cases

Risk Factor	Odds Ratio	95% CI
Young Age in months	0.98	0.97, 1.0
GI/Liver comorbidity	1.4	0.28, 7.29
Day 28 Osteopenia	9.3	1.54, 56.65

Higher PTH at day 28 was associated with a higher prevalence of osteopenia (PTH 207 vs. 99, p = 0.03). Vit D levels were not significantly different at day 28 from baseline (Vit D 38 vs 24, p = 0.12). However, several patients had missing values; therefore, we did not include PTH and vitamin D in the mixed model.

Discussion

We demonstrated a higher incidence of fractures and osteopenia in children undergoing prolonged CKRT with RCA compared solely to immobilization. Baseline osteopenia was noted in 17 cases as compared to 12 controls. However, at day 14 and 28, osteopenia was noted in 20 and 21 cases respectively, whereas the number of controls having osteopenia decreased to 10 at day 14 and 11 at day 28, respectively. This is the first comparative study examining the association between prolonged CKRT and bone complications in children with AKD. Notably, the presence and persistence of osteopenia, and younger age, were associated with an increased risk of fractures. More than 60% of cases with fractures had baseline osteopenia and the fractures were noted as early as day 7 of CKRT with a median of 31 days in cases. Median age of cases with fractures was 6 months (IQR: 4, 11).

Studies in adults looking at the effects of prolonged CKRT on bone metabolism indicate a need for lower exogenous calcium infusion on CKRT with RCA after 4 weeks [8], [20], [15], [19]. In these studies, immobilization was presumed to be central to the pathogenesis of bone demineralization increasing endogenous calcium secretion [7], [19]. We used age-matched controls who were immobilized on prolonged intubation to study the effect of immobilization. We noted higher incidence of osteopenia in children receiving CKRT, suggesting that factors in addition to immobilization might play a role in bone mineral disease associated with severe AKD.

There are a multitude of factors that lead to dialytrauma in patients on CKRT. Water soluble mineral deficiencies and amino acid loss has been well described in children [24]. As calcium citrate complexes are filtered and removed in the effluent, prolonged CKRT could lead to negative calcium balance from calcium loss in effluent [15], [17]. Similar to adult studies, our study suggested ongoing endogenous calcium release from bone, when we saw an increase in citrate infusion rates from initiation to day 28 of CKRT without an accompanying increase in calcium infusion rate. The increase in citrate rate was significant even when corrected for blood flow. A randomized controlled trial in adults comparing negative calcium balance in low and high citrate infusion on CKRT found that supplementing calcium to maintain ionized calcium levels (>/= 4 mg/dL) resulted in a positive calcium balance and lower parathyroid hormone (PTH) and 25-hydroxy vitamin D levels [17]. Our study, however, suggests that supplemental calcium and maintaining iCal >/= 4 mg/dL may not be sufficient in children since all our patients received supplemental calcium to maintain ionized calcium levels in a tightly controlled interval (4.4 to 5.17 mg/dL).

Patients undergoing prolonged CKRT with RCA are exposed to citrate for extended periods, which can lead to hypocalcemia due to chelation of calcium [8], [14]. We maintained strict ionized calcium as noted above to prevent hypocalcemia. Interestingly, we observed higher total calcium level thereby translating to higher total calcium to iCa ratio. This indicated mild citrate accumulation, defined as total calcium (mg/dL): iCa (mmole/L) > 10. Citrate is primarily metabolized in the liver, and conditions like primary liver failure or lactic acidosis can affect its metabolism causing citrate accumulation and toxicity in severe cases [12], [13], [14]. In addition, chronic and acute liver disease is associated with altered bone metabolism through pathways like increased production of interleukin-6 which in turn directly or indirectly stimulates osteoclastic resorption, decreased bone production, and altered Vitamin D metabolism [25], [26]. A higher prevalence of liver disease in our cases could partly explain mild citrate accumulation and its likely contribution to the altered mineral metabolism. While liver failure could contribute to altered mineral metabolism, none of our patients with primary liver disease developed overt citrate toxicity characterized by low iCa, elevated total serum calcium, metabolic acidosis, and increased anion gap.

AKD in itself impairs acid base balance leading to metabolic acidosis [6], [27], [28], [29]. Prolonged RCA exposure in liver failure has been reported to worsen metabolic acidosis in some instances [30], [31], [32]. Acidotic states cause bone resorption through cellular pathways inhibiting osteoblasts and stimulating osteoclasts [33]. This theoretical concern of metabolic acidosis did not seem to play a

significant role in our patient population. Cases and controls did not demonstrate a significant difference in serum pH levels at day 14 or 28. Similarly, hyperphosphatemia, commonly seen in advanced CKD [34], [35], was not observed in our cases, as phosphorus level was strictly regulated by adding phosphate to dialysis fluids and supplementing orally or intravenously as needed.

We demonstrated that younger age was associated with a higher risk of osteopenia. Infancy is the period of fastest growth in children and has highly dynamic bone development. Suboptimal bone mineral disease control in CKD is highly prevalent in infancy [36], [37] and our study has shown this to be true for AKD as well. In our previous study [18], we observed Vit D insufficiency/deficiency on prolonged CKRT (Vit D < 30 ng/mL). In the current study, Vit D insufficiency was noted at 28 days with a median Vit D level of 24 ng/mL, but there was no significant difference in Vit D level from baseline to day 28. Additionally, we observed higher than normal PTH level in our cases, which may indicate secondary hyperparathyroidism, a well-recognized risk factor for bone changes in CKD [35], [37], [38]. A similar risk could exist in AKD but needs further validation in larger studies. Fibroblast growth factor (FGF)-23 has been shown to be the earliest marker of bone mineral change in childhood CKD [39], [40], [41], [42]. Its role in AKD associated bone mineral disease has not been studied. It is not routinely monitored at our institution. We routinely monitor PTH and Vit D levels after 28 days on CKRT and at least monthly thereafter as an institutional policy. Because of our findings in this case control study, we suggest that close monitoring start after 14 days instead.

Cases and controls in our study were both exposed to steroids/glucocorticoids during hospitalization. Steroids can affect bone regeneration by various direct and indirect pathways affecting all cell lines including chondrocytes, osteoblasts, and osteoclasts. Steroids cause loss of bone strength resulting in fragility fractures due to osteoporosis [43]. Additionally, steroids alter Vit D metabolism by decreasing its synthesis and increasing catabolism [43]. We did not find an association between steroids or low Vit D levels with development of osteopenia in cases.

Our study had limitations. It is retrospective in nature and from a single center. Our sample size was smaller, being a single center study. Further studies comparing different forms of anticoagulation, such as heparin or prostacyclin, may provide additional insight into prolonged CKRT-associated osteopenia. We recognize that chest radiographs are not a gold standard for evaluating bone density. This was a retrospective study in critically sick children often with multiple comorbidities, on mechanical ventilation and other life support therapies limiting their mobility for further studies like skeletal survey, DEXA scan or CT scan. Additionally this being a pediatric study we want to acknowledge the additional challenges of these imaging studies in critically sick children on various extracorporeal therapies. Therefore, we utilized chest radiographs as they were readily available in both controls and cases. Despite limited by chest radiographs as our best available tool for osteopenia detection, we were able to identify higher number of cases on prolonged CKRT with osteopenia/fracture as compared to controls immobilized on mechanical ventilation alone. A smaller sample size from a single center could be one of reasons why the difference in osteopenia in cases and controls did not reach statistical significance. We had two independent radiologists blinded to cases and controls interpret the chest radiographs for osteopenia

and moderate agreement amongst the radiologists. Though we had propensity matched controls from our administrative database, higher incidence of liver failure as the primary diagnosis in our cases was noted despite our best efforts, but we were able to match them for GI/liver comorbidity. We did not have Vit D and PTH readings in our controls for comparison as they are not routinely done in patients on mechanical ventilation.

Conclusion

Our study highlights the increased risk of osteopenia and fractures in patients undergoing prolonged CKRT with RCA, particularly those with GI/liver comorbidity and younger in age. Persistent or worsening osteopenia over time increased the odds of fractures. Younger patients with GI/liver comorbidity may require closer monitoring of metabolic parameters including serum PTH and vitamin D level and objective assessments of bone disease with skeletal survey or DEXA scan along with targeted interventions, which may help mitigate bone mineral disease in this population. Further research is needed to elucidate underlying mechanisms and optimize management strategies for osteopenia and fracture in patients receiving prolonged CKRT.

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Figures

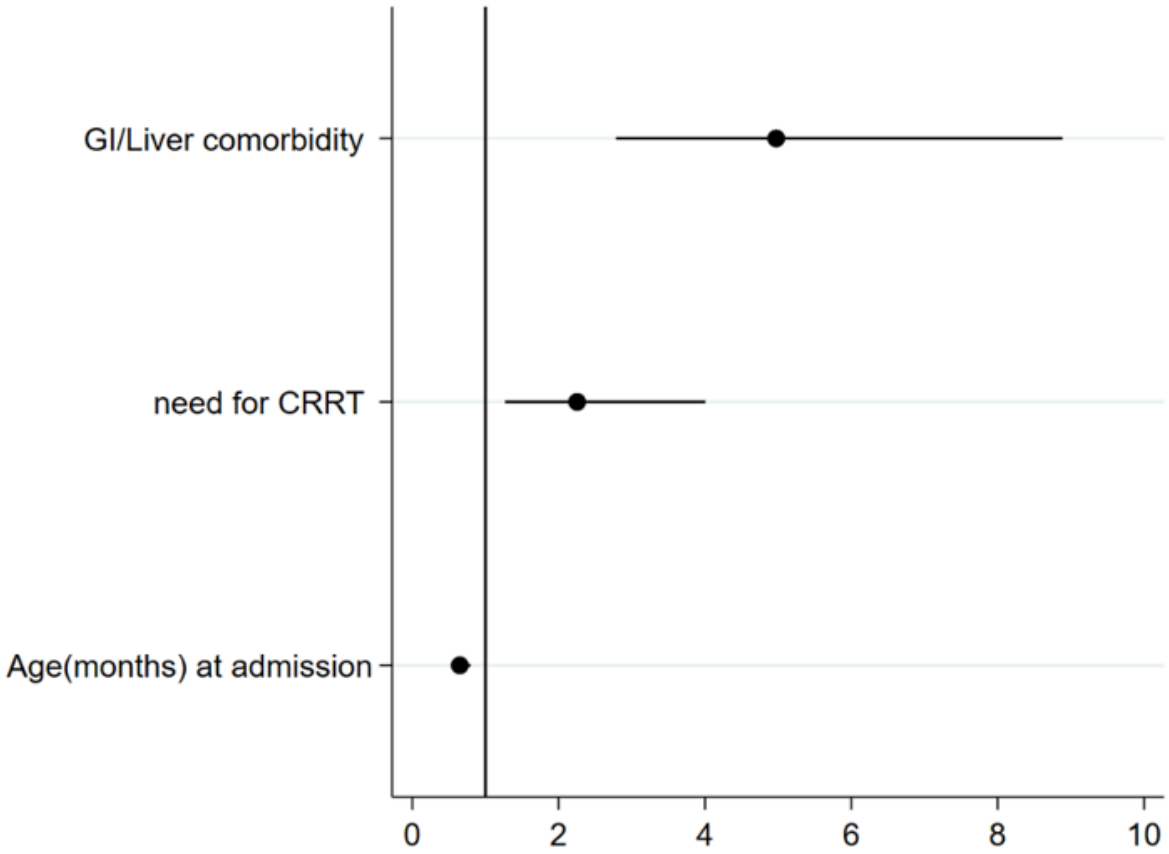


Figure 1: Multivariate longitudinal mixed logistic regression of risk factors for Day 28 osteopenia in both cases and controls

Gastrointestinal (GI) /liver comorbidity: Odds Ratio (OR) 0.9 (95% CI: 2.77, 8.86)

Need for CRRT: OR 0.9 (95% CI 1.28, 4.03)

Age (months) at admission to PICU: OR 0.9 (95% CI 0.98-0.99)

Figure 1

See image above for figure legend.

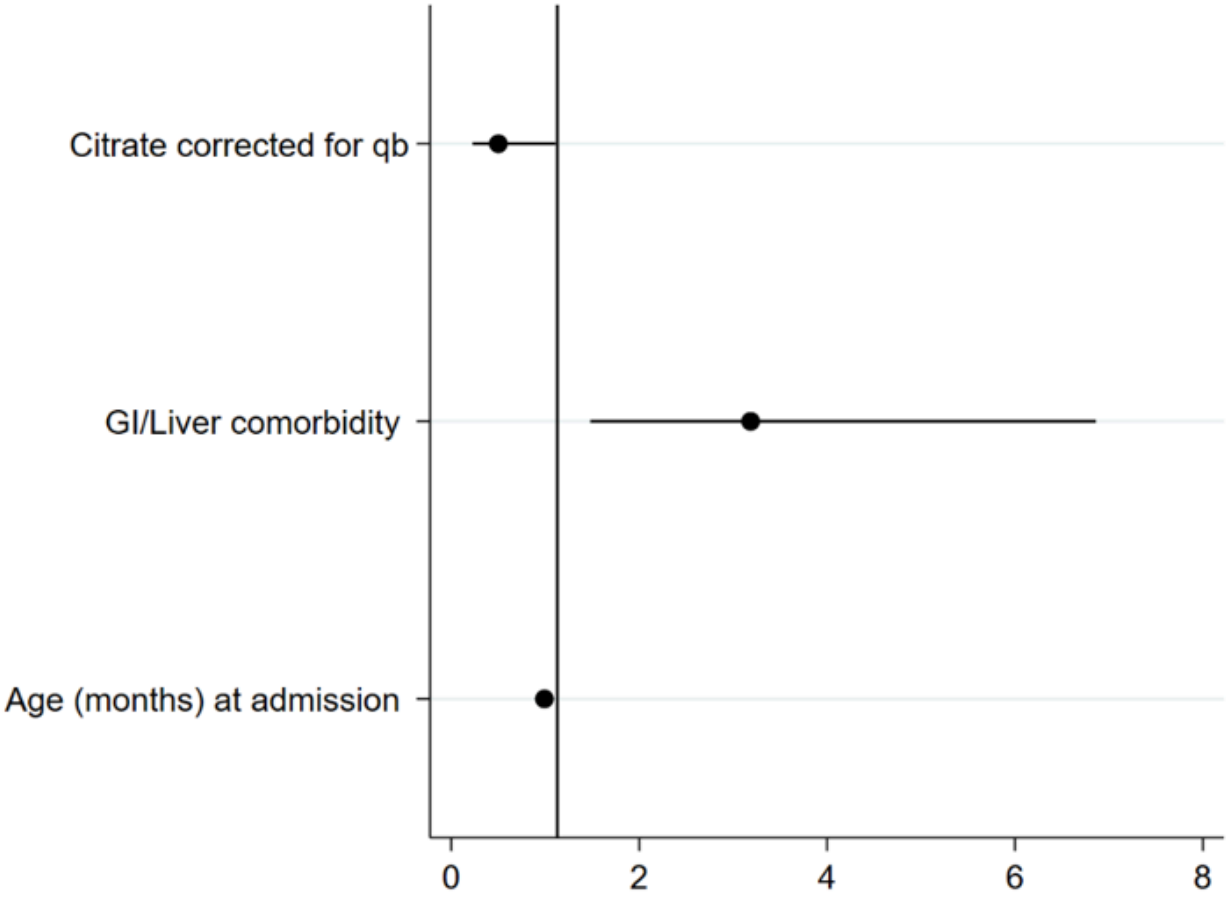


Figure 2: Univariate longitudinal mixed logistic regression analysis of risk factors for Day 28 osteopenia in cases only

Citrate infusion rate corrected for blood flow (qb): Odds Ratio 0.5 (95% CI 0.22, 1.1)

Gastrointestinal (GI)/liver comorbidity: Odds ratio 3.2 (95% CI 1.48, 6.86)

Age (months) at admission to PICU: Odds Ratio 0.99 (95% CI 0.86, 0.99)

Figure 2

See image above for figure legend.