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Original Research Article

Cardiovascular Consequences in Children with Chronic Kidney Disease: A Hospital Based Cross-Sectional Study

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Abstract:

Objectives: To determine the proportion of children with chronic kidney disease requiring dialysis; and to determine the factors associated with children with CKD requiring or not requiring dialysis.

Methods: This was a hospital based cross-sectional study with prospective enrolment of patients (children 1 to 18 years of age with chronic kidney disease (CKD, glomerular filtration rates less than 60 ml/min/1.73 m^2)) conducted in the Department of Paediatrics, in a tertiary healthcare facility in central India between June 2020 and December 2021.

Results: The majority of participants were males (81.3%), and three-quarters were aged ten or older. CKD stages varied, with 38.7% at stage 3, 40.0% at stage 4, and 21.3% at stage 5 and/or requiring dialysis. Several nutritional and hematologic abnormalities were observed, with 72.0% of children being underweight, 52.0% having anemia, and 42.7% presenting with proteinuria. Additionally, 46.7% exhibited abnormal calcium-phosphorus (Ca x PO4) product. The study reported a high prevalence of hypertension, with 22.7% having clinical hypertension and 90.7% having ambulatory hypertension. Metabolic disturbances were notable, including hyperkalaemia (17.3%) and acidosis (60.0%). Among children not requiring dialysis (76.0%), a lower mean (SD) Ca x PO4 product was observed (37.2, SD 2.3) compared to those requiring dialysis (41.5, SD 4.7; $p<0.001$). Hyperphosphatemia and hyperparathyroidism were more common in the dialysis group (66.7%) than in those not requiring dialysis (28.1% and 35.1%, respectively; $p<0.05$). Proteinuria was more prevalent in non-dialysis patients (89.5%) compared to dialysis patients (66.7%; $p<0.05$). Furthermore, LVH was significantly higher in the dialysis group (55.6%) compared to the non-dialysis group (21.1%; $p<0.05$). Children requiring dialysis exhibited higher LV mass, LVMI, and fractional shortening, indicating compromised cardiac function. Ejection fraction was also significantly lower in the dialysis group (51.7 vs. 60.9 in non-dialysis; $p<0.05$).

Conclusion: These results underscore the intricate relationship between CKD, cardiovascular complications, and the impact of dialysis, emphasizing the need for tailored interventions to address the multifaceted challenges faced by children with CKD.

Keywords: Chronic kidney disease, Complications, Cardiovascular, Left ventricular hypertrophy, India.

Introduction

Chronic kidney disease (CKD) is an emerging problem worldwide.[1] With increasing awareness about kidney diseases and antenatal ultrasound screening we are detecting more children with congenital anomalies of the kidney and renal tract (CAKUT). In India, the prevalence of CKD is estimated to range from 0.79 to 1.4% in the adult population.[2, 3] The prevalence of CKD amongst Indian children is not known. Chronic kidney disease in children represents a complex and challenging clinical condition, demanding a comprehensive understanding of its diverse manifestations to optimize patient care.[4] The present study aims to provide insights into the clinical and cardiovascular profiles of children with CKD in a tertiary healthcare facility in central India. With a focus on elucidating the prevalence of cardiovascular complications, mineral and bone disorders, and the impact of dialysis on cardiac health, this investigation seeks to contribute valuable information to the evolving landscape of paediatric nephrology. Paediatric CKD poses unique challenges compared to its adult counterpart, as the developing renal system introduces distinctive aetiologies and clinical trajectories.[5] Understanding the nuances of CKD

in children is imperative, given the potential long-term implications on growth, development, and overall quality of life. Cardiovascular complications, in particular, have emerged as critical determinants of outcomes in paediatric CKD, necessitating a meticulous examination of their prevalence and associated factors.[6]

In the context of mineral and bone disorders, the intricate balance of calcium and phosphorus homeostasis is often disrupted in CKD, leading to complications such as hyperphosphatemia and hyperparathyroidism.[7] Exploring the prevalence of these disorders and their potential associations with dialysis dependency can inform targeted interventions to mitigate the risk of skeletal abnormalities and cardiovascular comorbidities. This study also endeavours to investigate proteinuria patterns, recognizing its role as a key marker of renal dysfunction and a predictor of adverse outcomes. Understanding the variations in proteinuria between children requiring and not requiring dialysis can provide crucial insights into the dynamics of renal damage in different stages of CKD.

The overarching goal of this research is to contribute to the body of knowledge guiding the tailored management of paediatric CKD. By delineating the clinical and cardiovascular intricacies specific to this population, the study aspires to inform clinicians, researchers, and healthcare providers, fostering a more nuanced approach to diagnosis, intervention, and on-going care in children grappling with the challenges of CKD.

Methods

This was a hospital based cross-sectional study with prospective enrolment of patients conducted in the Department of Paediatrics, in a tertiary healthcare facility in central India between June 2020 and December 2021. The study was approved by the Institute Human Ethics Committee (IHEC). The content of Participant Information Sheet (PIS) in local language was provided to the attenders and contents were read to them in their own language to their satisfaction.

The participants were enrolled in the study after obtaining written informed consent or assent for the attenders. The study included children, one to 18 years of age presenting to the outpatient clinic of Department of Paediatrics and/or Nephrology and/or Paediatric Nephrology with chronic kidney disease (CKD). The children were enrolled only if their glomerular filtration rates were less than 60 ml/min/1.73 m^2.

However, children with renal, other solid organ, or bone marrow transplantation; presence of cancer or human immunodeficiency virus (HIV) diagnosed in the past 12 months; with genetic syndromes; presence of any congenital/structural heart disease or myocardial disease were excluded. The present study used purposive sampling technique – convenient sampling – to enrol study participants. We defined chronic kidney disease in line with that provided by the National Kidney Foundation (2002) – presence of kidney damage for more than three months, as confirmed by kidney biopsy or markers of kidney damage, with or without a decrease in glomerular filtration rate (GFR); or GFR less than 60 mL /min/1.73 m^2 for more than three months, with or without kidney damage.

We computed the glomerular filtration rate according to the Schwartz Formula for children less than 15 years of age. For children between 16 and 18 years of age, we used the Cockcroft-Gault formula would be used to estimate GFR. The children were divided into groups according to their glomerular filtration rates – stage 3 disease (glomerular filtration rate between 30 and 59 mL/min per 1.73 m^2); stage 4 disease (glomerular filtration rate between 15 and 29 mL/min per 1.73 m^2); stage 5 disease (glomerular filtration rate less than 15 mL/min per 1.73 m^2 or end-stage renal disease (ESRD)); and children with glomerular filtration rate less than 15 ml/min/1.73 m^2 on Dialysis.

We used a purpose predesigned, semi structured, pretested questionnaire to collect a detailed patient history that included sociodemographic characteristics, course of disease/illness, and treatment details. A complete general physical examination was done. Also, anthropometric measurements and vitals were noted.

The laboratory investigations included haemoglobin estimation, levels of sodium, potassium, serum creatinine, blood urea, calcium, phosphorus, alkaline phosphatase, bicarbonate, and parathyroid hormone levels. We also performed ambulatory blood pressure monitoring (using appropriately sized cuff attached to the non-dormant arm; readings taken every 20 minutes in the day and every hour at night) for each child over a 24-hour period using the Spacelabs Healthcare (040-1546-00) machine. Ambulatory hypertension was defined as blood pressure greater than the 95th centile for age and height. Nocturnal dipping was defined as more than 10% difference between daytime and night-time blood pressure readings. Ambulatory blood pressure index was calculated as the average BP of the child divided by the 95th centile. To determine the presence of left ventricular dysfunction echocardiogram was done.

The data obtained was manually entered into Microsoft Excel, coded, and recoded. Analysis was done using Statistical Package for the Social Sciences (SPSS) v23. Descriptive analysis was

presented using numbers and percentages for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables. Appropriate graphs were used. To test for association, Chi-square test or Fisher's exact test (two sided) was used for categorical data; independent "t" test was used for continuous data. Statistical significance was considered at $p<0.05$.

Results

The present study included a total of 75 children (1 to 18 years of age) with chronic kidney disease (CKD) having their glomerular filtration rates less than 60 ml/min/1.73 m^2. Three fourth of the children were more than or equal to 10 years of age (73.3%). Majority were males (81.3%). The causes of chronic kidney disease showed that 45.3% had uropathic cause, 36.0% had dysplastic, 14.7% had glomerular, 2.7% had cystic and 1.3% had tubular causes.

Regarding the stage of chronic kidney stage, 38.7% had stage 3, 40.0% had stage 4 and 21.3% had stage 5 and/or dialysis. Nearly three in four children (72.0%) were underweight. Of the 75 children included in the present study, 52.0% had anemia, 42.7% had proteinuria, and 46.7% had abnormal Ca x PO4 product. The mean (SD) Ca x PO4 product in the present study was 39.6 (3.5).

The results showed that 17 children (22.7%) had clinical hypertension, 68 children (90.7%) had ambulatory hypertension, 17.3% had hyperkalaemia, 60.0% had acidosis, 37.3% had hyperphosphatemia, 42.7% had hyperparathyroidism, 84.0% had proteinuria, and 29.3% children had left ventricular hypertrophy. The mean (SD) left ventricular mass among children with chronic kidney disease was 115.5 (40.9); left ventricular mass index was 52.8 (22.1); fractional shortening was 30.8 (3.8); ejection fraction was 56.3 (4.8); and E/A velocity or ratio was 1.6 (0.6). The results showed that 57 children with chronic kidney disease did not require dialysis (76.0%) whereas, 18 (24.0%) children required dialysis.

Factors associated with children with CKD requiring or not requiring dialysis: The results showed that the mean (SD) Ca x PO4 product was 37.2 (2.3) among children with CKD not requiring dialysis – significantly lower than that reported among children with dialysis (Mean 41.5, SD 4.7; $p<0.001$). Among children requiring dialysis it was found that 66.7% had hyperphosphatemia, in comparison with 28.1% among children not requiring dialysis; a statistically significant difference ($p<0.05$). Similarly, among children requiring dialysis, it was found that 66.7% had hyperparathyroidism, in comparison with 35.1% children not requiring dialysis; a statistically significant difference ($p<0.05$). The results showed that 89.5% children not requiring dialysis had proteinuria, whereas a significantly lower proportion of children (66.7%) requiring dialysis had proteinuria ($p<0.05$).

More than half the children (55.6%) requiring dialysis had left ventricular hypertrophy, in comparison with 21.1% children not requiring dialysis – a statistically significant difference ($p<0.05$). The mean (SD) left ventricular mass (Mean 143.1, SD 42.7) and left ventricular mass index (Mean 63.6, SD 22.7) were significantly higher among children requiring dialysis, in comparison with children not requiring dialysis ($p<0.05$). We found that the mean (SD) fractional shortening among children not requiring dialysis was 33.2 (2.4), in comparison with children requiring dialysis (Mean 28.4, SD 5.2) – a statistically significant difference ($p<0.05$). The mean (SD) ejection fraction in children not requiring dialysis was significantly higher than in children requiring dialysis (60.9 (4.2) vs 51.7 (5.3)) ($p<0.05$).

However, the results did not show any statistically significant difference between children requiring or not requiring dialysis in terms of body mass index, anemia, hyperkalaemia, acidosis, and E/A velocity.

Table 1: Baseline characteristics of children with chronic kidney disease

		Number	Percentage
		N = 75	%
Age (in years)	Less than or equal to 9	20	26.7
	10 and above	55	73.3
Gender	Male	61	81.3
	Female	14	18.7
Cause	Cystic	2	2.7
	Glomerular	11	14.7
	Tubular	1	1.3
	Dysplastic	27	36.0
	Uropathic	34	45.3
CKD stage	CKD stage 3	29	38.7
	CKD stage 4	30	40.0

	CKD stage 5 and dialysis	16	21.3
Body mass index	Underweight	54	72.0
	Normal	21	28.0
Anemia	Present	39	52.0
	Absent	36	48.0
Proteinuria	Present	32	42.7
	Absent	43	57.3
Abnormal Ca x PO4 product	Present	35	46.7
	Absent	40	53.3

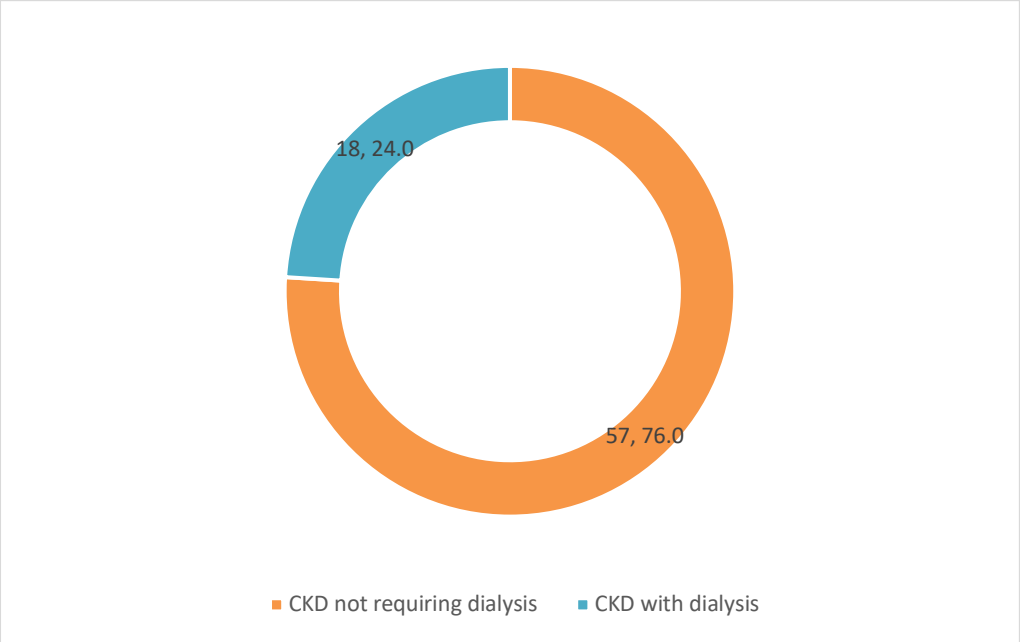

Figure 1: Distribution of children with CKD, by requirement of dialysis

Table 2: Factors associated with children with CKD requiring or not requiring dialysis

		CKD not requiring dialysis N = 57	CKD with dialysis N = 18	Total N = 75	P value
		n (%) or Mean (SD)	n (%) or Mean (SD)	n (%) or Mean (SD)	
BMI category	-1 to +1	17 (29.8)	4 (22.2)	21 (28.0)	0.533
	Others/Underweight	40 (70.2)	14 (77.8)	54 (72.0)	
Ca x PO4 product		37.2 (2.3)	41.5 (4.7)	39.6 (3.5)	<0.001*
Anemia	Present	27 (47.4)	12 (66.7)	39 (52.0)	0.158
	Absent	30 (52.6)	6 (33.3)	36 (48.0)	
Hyperkalaemia	Present	10 (17.5)	3 (16.7)	13 (17.3)	0.932
	Absent	47 (82.5)	15 (83.3)	62 (82.7)	
Acidosis	Present	35 (61.4)	10 (55.6)	45 (60.0)	0.659
	Absent	22 (38.6)	8 (44.4)	30 (40.0)	
Hyperphosphatemia	Present	16 (28.1)	12 (66.7)	28 (37.3)	0.005*
	Absent	41 (71.9)	6 (33.3)	47 (62.7)	
Hyperparathyroidism	Present	20 (35.1)	12 (66.7)	32 (42.7)	0.022*
	Absent	37 (64.9)	6 (33.3)	43 (57.3)	
Proteinuria	Present	51 (89.5)	12 (66.7)	63 (84.0)	0.029*
	Absent	6 (10.5)	6 (33.3)	12 (16.0)	
LVH	Present	12 (21.1)	10 (55.6)	22 (29.3)	0.007*
	Absent	45 (78.9)	8 (44.4)	53 (70.7)	
LV mass		87.9 (39.2)	143.1 (42.7)	115.5 (40.9)	<0.001*
LVMI		41.9 (21.4)	63.6 (22.7)	52.8 (22.1)	0.031*
Fractional shortening		33.2 (2.4)	28.4 (5.2)	30.8 (3.8)	0.023*

Ejection fraction	60.9 (4.2)	51.7 (5.3)	56.3 (4.8)	0.003*
E/A velocity	1.6 (0.2)	1.5 (0.9)	1.6 (0.6)	0.721
*Statistically significant at p<0.05				

Discussion

The results of the present study provide valuable insights into the characteristics and clinical profile of children with chronic kidney disease (CKD) in a tertiary healthcare facility in central India. The study population consisted of 75 children with CKD, with a notable predominance of males (81.3%). The majority of the children were aged 10 years and above (73.3%). This age distribution is consistent with previous studies highlighting a higher prevalence of CKD in older children, possibly reflecting the cumulative impact of various etiological factors over time.[8]

Uropathic causes emerged as the leading etiological factor, accounting for 45.3% of cases, followed by dysplastic (36.0%), glomerular (14.7%), cystic (2.7%), and tubular causes (1.3%). This distribution aligns with global trends, with urological anomalies being a common cause of paediatric CKD.[9] However, the higher prevalence of dysplastic causes in this cohort warrants further investigation and may have implications for preventive strategies and early detection. The distribution of CKD stages in the study population revealed that 38.7% were at stage 3, 40.0% at stage 4, and 21.3% at stage 5 and/or requiring dialysis. This distribution indicates a substantial proportion of children presenting at advanced stages of CKD, emphasizing the need for early detection and intervention to slow disease progression.[10] A concerning finding is the high prevalence of underweight children in the study cohort, with 72.0% classified as such. Malnutrition is a common complication in paediatric CKD and is associated with poorer outcomes, including delayed growth and increased morbidity and mortality.[11] The study identified several complications associated with CKD in the paediatric population. More than half of the children had anemia (52.0%), a well-documented consequence of impaired renal function.[12] Additionally, proteinuria was observed in 42.7% of cases, emphasizing the impact of CKD on renal function. Abnormal calcium-phosphorus product was present in 46.7% of children, highlighting the mineral metabolism disturbances often seen in CKD.[13]

The study identified a significant burden of hypertension among the paediatric CKD population, with 22.7% presenting with clinical hypertension. However, a striking 90.7% had ambulatory hypertension, indicating that continuous blood pressure monitoring captured a larger proportion of hypertensive cases. The high prevalence of hypertension in children with CKD is consistent with existing literature, emphasizing the importance of regular blood pressure monitoring in this population to facilitate early detection and management.[14] Metabolic abnormalities were prevalent in the study cohort. Hyperkalaemia was observed in 17.3% of children, highlighting the impact of impaired renal function on electrolyte balance. Acidosis, affecting 60.0% of the children, and hyperphosphatemia (37.3%) underscore the complex metabolic derangements associated with CKD. These findings emphasize the multifaceted nature of CKD and the need for comprehensive metabolic management.[10] The study identified a high prevalence of hyperparathyroidism (42.7%) and hyperphosphatemia (37.3%), indicative of disrupted mineral and bone metabolism in children with CKD. These findings underscore the importance of close monitoring and interventions to address these complications and mitigate the risk of renal osteodystrophy and associated morbidities.[15] The study evaluated cardiovascular complications, revealing that 29.3% of children with CKD had left ventricular hypertrophy (LVH). This finding is consistent with previous research establishing the link between CKD and cardiovascular complications in the paediatric population.[16] The mean values for left ventricular mass, left ventricular mass index, fractional shortening, ejection fraction, and E/A velocity provide a comprehensive assessment of cardiac structure and function. The alterations in these parameters underscore the impact of CKD on cardiac health, necessitating regular cardiac evaluations in the management of paediatric CKD.[17] A substantial proportion of children (84.0%) in the study presented with proteinuria, a well-established marker of renal dysfunction. Persistent proteinuria is associated with an increased risk of progression to end-stage renal disease and cardiovascular complications.[18]

The findings of this study, indicating that a substantial majority (76.0%) of children with chronic kidney disease (CKD) did not require dialysis, while 24.0% required dialysis, prompt a comprehensive discussion on the implications, factors influencing the need for dialysis, and the broader context of paediatric CKD management. The observation that a significant proportion of children with CKD did not require dialysis aligns with the concept of conservative or non-dialytic management in paediatric nephrology. Non-dialytic approaches often focus on optimizing medical management, nutritional support, and addressing underlying aetiologies to slow the progression of CKD.[19] Early detection and intervention, coupled with advancements in medical therapies, may contribute to the delay or avoidance of dialysis

in some cases.[20] Several factors may contribute to the decision to initiate dialysis in paediatric CKD patients. The severity of renal dysfunction, as reflected in the glomerular filtration rate (GFR), often guides clinical decisions.[21] The etiology of CKD, presence of complications such as uncontrolled hypertension, electrolyte imbalances, and uremic symptoms, as well as the overall clinical status of the child, are critical considerations.[10, 11] Clinical guidelines, such as those provided by the Kidney Disease: Improving Global Outcomes (KDIGO) initiative, emphasize the importance of individualized care in paediatric CKD management. Regular assessment of GFR, monitoring of complications, and timely intervention are crucial components of care to optimize outcomes and delay the need for renal replacement therapy.[22, 23]

The mean calcium-phosphorus (Ca x PO4) product serves as a valuable indicator of mineral metabolism in CKD. In this study, children not requiring dialysis exhibited a significantly lower mean Ca x PO4 product (37.2) compared to those requiring dialysis (41.5, $p<0.001$). This difference suggests a more favourable mineral balance in the non-dialysis group, possibly attributed to preserved renal function and the ability to maintain phosphorus homeostasis.[24] Among children requiring dialysis, a significantly higher proportion had hyperphosphatemia (66.7%) and hyperparathyroidism (66.7%) compared to those not requiring dialysis (28.1% and 35.1% respectively; $p<0.05$ for both). These findings underscore the challenges in managing mineral and bone disorders in the dialysis-dependent population. Elevated phosphorus levels and secondary hyperparathyroidism are common complications in advanced CKD and are associated with an increased risk of cardiovascular morbidity and mortality.[25] Proteinuria is a well-established marker of renal dysfunction and is associated with adverse outcomes in CKD. Interestingly, a higher proportion of children not requiring dialysis (89.5%) had proteinuria compared to those requiring dialysis (66.7%, $p<0.05$). This counterintuitive finding may be attributed to the heterogeneous nature of proteinuria in CKD, where factors such as glomerular filtration rate, tubular dysfunction, and the underlying etiology contribute to the variability in proteinuria patterns.[26] The observed differences in mineral metabolism and proteinuria between children with CKD requiring and not requiring dialysis have several clinical implications. The identification of higher rates of hyperphosphatemia and hyperparathyroidism in the dialysis group emphasizes the importance of vigilant monitoring and targeted interventions to optimize mineral balance in this population. The unexpectedly lower proteinuria in the dialysis group warrants further exploration to understand the complex interplay of factors influencing protein excretion in the context of renal replacement therapy.

The study reveals a significantly higher prevalence of LVH among children requiring dialysis (55.6%) compared to those not requiring dialysis (21.1%, $p<0.05$). LVH is a well-established consequence of CKD, especially in its advanced stages, and is associated with increased cardiovascular morbidity and mortality.[10] The elevated risk of LVH in the dialysis group emphasizes the importance of meticulous cardiovascular surveillance in these children. The mean left ventricular mass and left ventricular mass index were both significantly higher among children requiring dialysis compared to those not requiring dialysis ($p<0.05$). These parameters provide insights into the structural changes in the heart associated with CKD. Increased left ventricular mass is often indicative of cardiac remodelling in response to chronic hemodynamic stress, such as hypertension and volume overload, both common in CKD.[27] Children not requiring dialysis exhibited a significantly higher mean fractional shortening (33.2 vs. 28.4, $p<0.05$) and ejection fraction (60.9 vs. 51.7, $p<0.05$) compared to those requiring dialysis. These indices reflect the systolic function of the heart, and the lower values in the dialysis group suggest impaired cardiac contractility. The compromised cardiac function in children requiring dialysis highlights the need for targeted interventions to mitigate the cardiovascular impact of renal dysfunction.[28]

The study's cross-sectional nature limits the ability to establish causation or determine the temporal sequence of events. Longitudinal studies are crucial for understanding the trajectory of cardiovascular changes in paediatric CKD. Additionally, the study's single-centre design may impact the generalizability of findings to broader populations.

Conclusion

In conclusion, the findings shed light on the prevalence of cardiovascular complications, mineral and bone disorders, and the impact of dialysis on cardiac health in this vulnerable paediatric population. The study reveals a substantial burden of cardiovascular complications among children with CKD, with LVH being more prevalent in those requiring dialysis.

The significantly higher LV mass and altered systolic function observed in the dialysis group emphasizes the need for careful cardiovascular monitoring and early intervention in the management of paediatric CKD. Mineral and bone disorders, particularly hyperphosphatemia and hyperparathyroidism, were more pronounced in children requiring dialysis, highlighting the challenges in maintaining mineral balance in

advanced stages of CKD. The observed differences in proteinuria patterns between the dialysis and non-dialysis groups further contribute to our understanding of the complex renal and cardiovascular interplay in this population. These findings underscore the importance of a multidisciplinary approach to the care of children with CKD, involving nephrologists, cardiologists, and other specialists. Early detection, comprehensive management of mineral and bone disorders, and targeted interventions to optimize cardiovascular health are crucial in improving outcomes and enhancing the overall quality of life for children with CKD.

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