

Predictive factors of poor nutritional status in children and young adults on chronic hemodialysis: A single center experience

Facteurs prédictifs d'un mauvais état nutritionnel chez les enfants et les jeunes adultes sous hémodialyse chronique : Etude monocentrique

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ABSTRACT

Introduction-Aim: Children with kidney failure (KF) are prompt to undernutrition with subsequent growth failure. The aim of this study was to assess probable correlates of normalized protein catabolic rate (nPCR) in children on chronic hemodialysis (HD).

Methods: This prospective study included all 20-year-old or less patients undergoing chronic HD at our pediatric HD unit between 1st January 2024 and 30th April 2024. Patients included had been on HD for more than 3 months and were clinically stable. For each patient, baseline characteristics were recorded along with their echocardiogram findings. Mean nPCR was calculated and potential predictive factors were simultaneously evaluated. Our study included a univariate and a multivariate analysis. A p value less than 0.05 was considered statistically significant.

Results: A total of 40 patients were included with a mean age of 14.4 ± 3.7 years old and a sex-ratio M/F of 1.9. Twenty-two (55%) had a mean nPCR <1g/kg/day. A strong positive correlation between nPCR and the 3-months body mass index variation percentage was found with a correlation ratio of 0.82. On multivariate analysis, Patients with a single pool KT/V < 1.2 and those exhibiting left ventricular hypertrophy were more likely to have a nPCR value <1g/kg/day (OR: 7.2 and 11.1, 95% CI: 2.28 - 75.23 and 5.5-98,08, respectively). A first hour refill index > 1.7 ml/kg/h/% was also correlated with a low nPCR (Adjusted OR:5.5-95% CI: 3.2-65.2).

Conclusion: Pressure and volume control along with dialysis adequacy are promising factors in improving nutritional status and clinical outcomes in children with KF.

Key words: Children-Hemodialysis-protein catabolic rate -dialysis adequacy-refill index - Left ventricular hypertrophy.

RÉSUMÉ

Introduction-Objectif: Les enfants atteints d'insuffisance rénale terminale (IRT) sont prédisposés à la dénutrition. L'objectif de cette étude était d'évaluer les corrélations du taux catabolique protéique normalisé (nPCR) chez les enfants sous hémodialyse chronique (HDc).

Méthodes: Cette étude prospective a inclus les patients âgés de 20 ans ou moins, sous HDc entre le 1er janvier 2024 et le 30 avril 2024. Les patients inclus étaient en HD depuis plus de 3 mois et cliniquement stables. Le nPCR moyen a été calculé. L'analyse comprenait une étude univariée et multivariée. Une valeur de p < 0,05 était statistiquement significative.

Résultats: Au total, 40 patients ont été inclus, avec un âge moyen de 14,4 ± 3,7 ans. Vingt-deux patients (55 %) présentaient un nPCR moyen < 1 g/kg/jour. Une corrélation positive a été observée entre le nPCR et la variation du pourcentage de l'indice de masse corporelle (IMC), avec un coefficient de corrélation de 0,82. Les patients avec un KT/V < 1,2, ceux présentant une hypertrophie ventriculaire gauche avaient plus de probabilité d'avoir un nPCR < 1 g/kg/jour (OR: 7,2 et 11,1; IC 95 %: 2,28-75,23 et 5,5-98,08, respectivement). Un indice de remplissage à la 1ère heure > 1,7 ml/kg/h/% était corrélé à un nPCR bas (OR ajusté: 5,5; IC 95 %: 3,2-65,2).

Conclusion: Le contrôle de la pression et du volume, ainsi qu'une dialyse adéquate, apparaissent comme nécessaires pour améliorer l'état nutritionnel et les résultats cliniques chez les enfants en IRT.

Mots-clés : Enfants - Hémodialyse - Taux catabolique protéique - Adéquation de la dialyse - Indice de remplissage - Hypertrophie ventriculaire gauche

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What is known and what the article adds

The use of nPCR as gold-standard nutritional marker in children on hemodialysis, it is a key tool to ensure an adequate growth and better survival rates in these patients. To the best of our knowledge, this parameter has never been used in either children or adults undergoing hemodialysis. This study could serve as a basis for multicenter studies aimed at improving the management of patients with end-stage chronic kidney disease.

INTRODUCTION

Children with kidney failure (KF) are prompt to undernutrition due to the renal disease related inflammation-induced wasting process (1). Nutritional status has been reported as a predictive factor of mortality in patients with KF (2). Comparing to adults, malnutrition in children is believed to have heavier consequences as it also interferes with growth and cognitive development (3). Ensuring an adequate nutritional status is therefore a major target in hemodialysis (HD) children. Consequently, a proper assessment of nutritional status, and a better understanding of possible predictive factors of undernutrition would ensure better clinical outcomes for these patients. Nutritional assessment is however complicated as anthropometric parameters, commonly used in the general pediatric population, are hampered in HD patients due to several limitations (4). Normalized protein catabolic rate (nPCR) is a quantified measure described almost 20 years ago that estimates dietary protein intake in HD patients, and is considered to be an alternative nutritional status assessment method for dialysis patients (5,6). The aim of this study was to assess probable correlates of normalized protein catabolic rate (nPCR) in children on chronic hemodialysis (HD).

METHODS

Definitions

nPCR: The nPCR is a formula commonly used to assess dietary protein intake in dialysis patients, as a means towards determining nutritional adequacy, a major problem in many KF patients particularly those undergoing dialysis. nPCR is calculated based on the urea nitrogen appearance rate, which reflects the amount of protein broken down by the body. y simulating dialysis cycles with the urea kinetic model (UKM), in 1996 Depner and Daugirdas succeeded in deriving accurate equations to estimate PCRn from pre-dialysis blood urea nitrogen (BUN) values and the dialysis dose (Kt/V). They validated the formulas in a group of patients undergoing 2 or 3 hemodialysis (HD) sessions a week, which were the most frequent treatment schedules at the time (3-5). More recently, there has been growing interest in more frequent dialysis rhythms, especially in the setting of home HD (HHD), for which nPCR formulas are lacking.

BMI: The BMI is a calculated measure of a person's body

weight (in kilograms) divided by the square of their height (in meters). BMI categories for children and teens are based on sex-specific BMI-for-age percentiles (or BMI percentiles):

- Underweight: Less than the 5th percentile
- Healthy Weight: 5th percentile to less than the 85th percentile
- Overweight: 85th percentile to less than the 95th percentile
- Obesity: 95th percentile or greater
- Severe Obesity: 120% of the 95^{th} percentile or greater, or 35 kg/m^2 or greater

Study population

We conducted a single-center prospective study including all 20-year-old or less patients undergoing chronic HD at our pediatric HD unit between 1st January 2024 and 30th April 2024.

Patients included were on HD for more than 3 months and were clinically stable. During their follow-up, all patients exhibiting acute illness were excluded.

A baseline data recording was performed for all patients and included:

- Patient's age, gender, primary kidney disease, HD access, residual urinary output (RUO) and history of hypertension.
- During the study, all patients had an echocardiography.
- For patients with hypertension, the following parameters were also recorded:
 - History of acute complications related to hypertension including posterior reversible encephalopathy syndrome (PRES) and congestive heart failure.
 - Number of antihypertensive drugs.

For each patient, three determinations of nPCR were made at a minimum interval of one month each and their mean value was calculated.

nPCR value, expressed in g/kg/day, was calculated using the modified version of Borah's equation:

$$nPCR = 5.43 \times \frac{UGR}{TBW_{PD} \times 10} + 0.17$$
 , where:

-TBW_PD: post dialysis total body water, expressed in deciliters (dL) and calculated using the formula:

 TBW_{pD} =5.8 × PDW , PDW being the post dialysis weight, expressed in kilograms (Kg)

-UGR (mg/min) = Urea generation rate, calculated as followed: $UGR = \frac{BUN_{PreD} \times TBW_{PreD} - BUN_{PD} \times TBW_{PD}}{T}$

where $PreD_{BUN}$ and PD_{BUN} refer to blood urea nitrogen's (BUN) pre-dialysis' and post dialysis' measurements, respectively.

TBW_{PreD} refers to pre-dialysis total body water expressed in deciliters (dL) and calculated as followed:

- -TBW $_{\rm PreD}$ =5.8 × PreDW, where PreDW refers to pre-dialysis weight, expressed in kg.
- -T is the time, expressed in minutes, from the end of one dialysis treatment to the beginning of the next. We used pre- and post-dialysis BUN from the same session to calculate nPCR, as suggested by some studies (7-8).

At each nPCR determination, the following parameters were also collected:

- Anthropometric data: dry body weight and body mass index (BMI).
- Biochemical data: serum creatinine, hemoglobin, albumin, protein, total calcium, serum phosphate, parathyroid hormone (PTH) levels and standard C-reactive protein.
- The first hour refill index (RI), expressed in ml/kg/h/%, was calculated using the formula:

R1=UF $_{\rm R}$ /BVR, where UF $_{\rm R}$ refers to the ultrafiltration rate, expressed in ml/kg/h and BVR is the percent blood volume reduction in the first hour of dialysis. BVR was calculated using the formula:

-
$$BVR = \left(\frac{Ht_0}{Ht_1} - 1\right) \times 100$$
 where Ht_0 and Ht_1 refer

to the Ht level in pre dialysis and at one hour of dialysis session, respectively.

-Single-pool Kt/V (spKt/V), calculated using the Daugirdas formula:

-
$$\ln\left(\frac{BUN_{PD}}{BUN_{preD}} - 0.008 \times t\right) + \left(4 - 3.5 \times \frac{BUN_{PD}}{BUN_{preD}}\right) \times UF/PDW$$

Where t, expressed in hours refers to HD session duration, UF is the ultrafiltration volume expressed in L and PDW refers to post dialysis weight expressed in Kg.

At the last nPCR determination, patient's dry body weight (DBW) was compared to its baseline value. The 3-months DBW and BMI variations were expressed in grams and percentages.

Mean value of nPCR was used as a nutritional assessment tool with a cut-off value of 1g/kg/day as suggested by some studies (8-9).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 26.0 software. Graphs were generated using ggplot and Rstudio. A p value less than 0.05 was considered statistically significant.

Patients with a mean nPCR < 1 g/kg/day were compared with those characterized by a mean nPCR \geq 1 g/kg/day for all the parameters under study.

The baseline characteristics of the study cohort were expressed as numbers and proportions, mean plus or minus standard deviation (SD), or median and interquartile range (IQR) depending on the variable's normality test.

Correlations between nPCR and the 3-months BMI variations percentage were assessed using the Pearson correlation method.

The assessment of nPCR's potential predictive factors was made initially by a univariate analysis using:

- Chi-square test or Fisher's exact test for categorical variables
- T student test or Mann U Whitney's test for continuous variables depending on the variables' distribution.

Multivariate analysis was performed using binary logistic regression. Covariables included in multivariate analysis were variables with a p value less than 0.2 in univariate

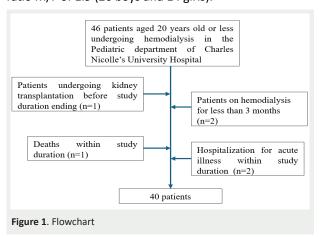
analysis. Dependent variables collinearity was checked using a correlation matrix. Results of multivariate analysis were all expressed in adjusted odds ratio (AOR) with a confidence interval (CI) of 95%.

Patient consent

For all patients included in this study, consent was obtained from the legal guardian (father or mother) after explaining the purpose of the study and the samples that would be collected.

RESULTS

A total of 40 patients were included in our study (Figure 1). Their mean age was 14.4 ± 3.7 years old with a sexratio M/F of 1.9 (26 boys and 14 girls).



Baseline nutritional assessment revealed a mean BMI of 15.5± 2.7 kg/m². When classified by age and gender, 35% (n=14) of these patients were underweight. Baseline characteristics of our study population are summarized in table 1.

Twenty-two (55%) patients had a mean nPCR value less than 1g/kg/day. Correlation analysis of nPCR and the 3-months BMI variations percentage revealed a positive and approximately linear association between these two features, with a correlation coefficient of 0.82. On the other hand, positive 3-months BMI variations percentage was significantly associated with a mean nPCR value greater than 1 g/kg/day (Figure 2).

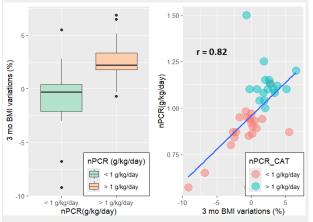


Figure 2. nPCR and the 3 months body mass index variation percentage: correlation and association plots

Patient's characteris	Total study population (n=40 26 (65%) / 14 (35%) 14.4 ± 3.7		
Gender (Male/Female) Age (years, mean ± SD)			
			Primary
kidney disease	CKDu	4 (10%)	
	focal and segmental glomerulosclerosis	3 (7.5%)	
	Nephronophthisis	3 (7.5%)	
	Primary hyperoxaluria	2 (5%)	
	Hemolytic uremic syndrome	1 (2.5%)	
	Cystinosis	1 (2.5%)	
	Renal Sarcoidosis	1 (2.5%)	
	Familial hypomagnesemia with hypercalciuria	1 (2.5%)	
	Joubert syndrome	1 (2.5%)	
	Alport syndrome	1 (2.5%)	
	Cacchi-Ricci disease	1 (2.5%)	
Anuric patients		29 (72.5%)	
Hemodialysis vintage (months, medium [IQR])		27 [9.3 – 47]	
Vascular access (AVF/CVC)		38 (95%) / 2(5%)	
History of hypertension		27 (67.5%)	
Acute hypertension	PRES	2 (5%)	
related	Acute heart failure	12 (30%)	
complications	Total	14 (35%)	
Echocardiography	Pulmonary hypertension	4 (10%)	
findings	Restrictive cardiomyopathy	2 (5%)	
	Left ventricular hypertrophy24 (60%)		
	Left ventricular dysfunction	2 (5%)	
	Normal echocardiography	13 (32.5%)	
Number of antihypertensive	0/1/2	14 (35%) / 4 (109 / 11 (27.5%)	
drugs	3/4	4 (10%) / 7 (17,5%)	
Dry body weight (Kg, mean ± SD)		32 ± 12	
BMI (kg/m², mean ±	SD)	15.5± 2.7	

CAKUT= Congenital anomalies of the kidneys and urinary tracts. AVF=arteriovenous fistula. CVC=central venous catheter. PRES=Posterior reversible encephalopathy syndrome. BMI=Body mass index. CKDu = chronic kidney disease of unknown origin

On univariate analysis, when compared to patients with a mean nPCR \geq 1 g/kg/day, those with a mean nPCR<1g/kg/day had a higher first hour refill index (p=0.002) and a lower spKT/V (p=0.008). Univariate analysis' findings are summarized in table 2.

On multivariate analysis when testing for dependent variables collinearity, left ventricular hypertrophy was strongly correlated to hyperphosphatemia and hypertension (r=0.8 and 0.7, respectively) (Figure 3).

Our final regression model identified R1, SpKT/V and left ventricular hypertrophy as independent predictive factors of a nPCR value less than 1g/kg/day (table 3)

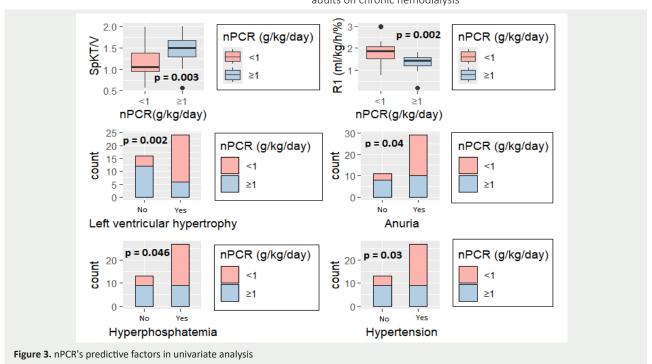
Table 2. Assessment of n-PCR's probable predictive factors in univariate analysis (1).

		nPCR ≥ 1 g/ kg/day 18 (45%)	nPCR < 1 g/ kg/day 22 (55%)	р
Gender	Female	7 (50%)	7 (50%)	ns
	Male	11 (42.3%)	15 (57.7%)	
Age (Mean ± SD)		15.5 ± 3.4	14.06 ± 3.7	ns
HD vintage (months; r [IIQ])	medium	25 [6 – 48]	27 [18.5 – 43]	ns
Anuria	No	8 (72.7%)	3 (27.3%)	0.04
	Yes	10 (34.5%)	19 (65.5%)	
History of	No	9 (69.2%)	4 (30.8%)	0.03
hypertension	Yes	9 (33.3%)	18 (66.7%)	
Number of	0	9 (64.3%)	5 (35.7%)	ns
antihypertensive	1	1 (25.0%)	3 (75.0%)	
drugs	2	3 (27.3%)	8 (72.7%)	
	3	3 (75.0%)	1 (25.0%)	
	4	2 (28.6%)	5 (71.4%)	
History of acute	No	18 (45.0%)	22 (55.0%)	ns
hypertension related complications	Yes	7 (50.0%)	7 (50.0%)	
Left ventricular hypertrophy	No	12 (75.0%)	4 (25.0%)	0.00
	Yes	6 (25.0%)	18 (75.0%)	
Hyperphosphatemia	No	9 (69.2%)	4 (30.8%)	0.04
	Yes	9 (33.3%)	18 (66.7%)	
Serum phosphate (mr	nol/l)	1.8 ± 0.4	2.07 ± 0.7	ns
PTH (ng/ml)		806 [433-1280]	1140 [416-1910]	ns
Total serum calcium (mmol/l, mean± SD)		2.2 ± 0.1	2.3±0.3	ns
Serum hemoglobin (g/L, mean± SD)		90 ± 21	90±18	ns
Serum creatinine (μmol/L,		968.5 [669.2 –		ns
medium [IIQ])		1133.8]	1259]	
C-reactive protein (mg medium [IIQ])		3.7 [1.3 – 12.3]		ns
Serum albumin (g/l, me			39±4	ns
Serum total protein le mean± SD)	vels (g/l,		85 ±7	ns
SpKT/V <1.2	No		8 (36.4%)	0.00
	Yes	3 (16.7%)	14 (63.6%)	
SpKT/V (mean±SD)		1.4 ± 0.3	1.1±0.4	0.00
R1 (ml/kg/h/%, mean		1.3 ± 0.5	1.8±2.1	0.00
R1 range (ml/kg/h/%)		14 (77.8%)	8 (36,4%)	0.01
	≥1.7	4 (22.2%)	14 (63.6%)	
Pre dialysis systolic and/or diastolic	No	14 (77.8%)	16 (72.7%)	ns
hypertension (mmHg, mean± SD)	Yes	4 (22.2%)	6 (27.3%)	

SD: Standard Deviation. IIQ: interquartile range. HD: Hemodialysis. PTH: Parathyroid Hormone

Table 3. nPCR's associated factors on multivariate analysis

	p value	Adjusted OR	95% CI
A first hour refill index ≥1.7 ml/kg/h/%,	0.02	5.5	3.2 - 65.2
Single pool KT/V < 1.2	0.01	7.2	2.28 -75.23
Left ventricular hypertrophy	0.007	11.1	5.5 - 98.08



Discussion

Children with KF are prompt to undernutrition and protein energy wasting (PEW) due to the renal disease related nutritional disturbances and inflammation-induced wasting process (1). Comparing to adults, malnutrition in children is considered to have heavier consequences as it interferes with growth and neuro-cognitive development (3).

In our study, higher nPCR values were positively correlated with weight gain. This correlation was established years ago. In fact, nPCR was initially proposed as a measure of dietary protein intake in children on chronic HD in the 1980s (8). In the study conducted by Juarez-Congelosi et al, the odds of developing weight loss in adolescents on chronic HD were four times greater for patients with a nPCR value less than 1 g/kg/day compared to others (8). Apart from that, a low nPCR has also been linked to an increased mortality in patients with KF (2). Based on these findings, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/DOQI) guidelines included nPCR among the recommended nutritional markers for children on HD (6).

Our study did not find a significant association between serum albumin and nPCR. This can be explained by the fact that serum albumin may be a poor predictor of nutritional status in children with KF, as many other factors cause hypoalbuminemia, such as infection, inflammation, proteinuria and volume overload (8). This was also the case for the study conducted by Juarez-Congelosi et al where persistent weight loss rates did not vary with serum albumin for the entire study cohort (9). AspKT/V value less than 1.2 was an independent predictive factor of a nPCR lower than 1g/kg/day in our pediatric HD patients, which is in line with the studies conducted by Paglialonga et al and Soetikno et al (8,10). Whether this correlation is simply due to the use of the same data for

calculating both parameters, or a true association, is a matter of debate. A study conducted by Teixeira Nunes et al evaluated the relationship between dialysis adequacy and nutritional status in HD patients (11). There was a correlation of Kt/V with anthropometric parameters such as body mass index, arm circumference, and midarm muscle circumference. Another study focused on the evaluation of the relationship between protein daily consumption and dialysis adequacy (12). In this study, the delivered dose of HD therapy was directly correlated with the amount of consumed protein per kilogram body weight, but this correlation was only significant for patients who consume 1.2 g/kg body weight or less (12). Based on these findings, dialysis adequacy's correlation with nutritional status in HD patients tends to go beyond a simple mathematical artefact.

In our study, a first hour refill index (R1) value greater than 1.7% was also and independent predictive factor of a nPCR value less than 1g/kg/day, which is in line with the study conducted by Paglialonga et al (7). A high first hour refill index (i.e., UF rate to BVR ratio), in the absence of intradialytic hypotension, actually means that the patient can tolerate a more aggressive UF rate with low blood volume change, probably due to volume overload (7).

Kang et al recently demonstrated that overhydration was associated with a decrease in muscle mass indices and the development of sarcopenia in patients on peritoneal dialysis (13). An international study involving 8883 prevalent HD patients demonstrated that fluid overload was associated with both malnutrition and inflammation (14). A recent study reported that fluid overload contributes to inducing hypercatabolism and stimulates oxidation phosphorylation mechanisms in muscle cells (15). In addition, salt tissue accumulation associated with fluid overload contributes to the hypercatabolic state through locally inflammatory mechanisms (16).

LVH is in fact an adaptive response to increased cardiac work, typically caused by combined pressure and volume

overload, resulting in cardiomyocyte hypertrophy and increased intercellular matrix (17). In patients with uncontrolled hypertension, increased afterload induces cardiac hypertrophy through chronic hemodynamic stress on the myocardium (18). High phosphate levels on the other hand induce vascular calcification decreasing therefore vascular compliance and leading to an increased afterload. On the other hand, LVH related to hyperphosphatemia is also due to the paracrine effect of FGF23 on cardiomyocytes (19).

Some reports suggested that LVH is associated with an ongoing low-inflammatory state. A Study conducted by Rosello-Lleti al evaluated the relationship between inflammatory activation and left ventricular mass in patients with essential hypertension (20). Inflammatory markers included in this study were plasma soluble tumor necrosis factor (TNF) receptors, interleukin-6, and interleukin-1 receptor antagonist. Hypertensive patients with LVH had higher inflammatory cytokine levels than the group without hypertrophy (p < 0.001) (20). Another population-based cohort demonstrated the existence of a strong correlation between high-sensitivity C-reactive protein and LVH. Authors of this study considered LVH as low-level inflammatory state in patients with hypertension (21). Inflammation plays a key role in disease-related malnutrition, leading to anorexia, muscle catabolism, and insulin resistance, which are stimulating a catabolic state (22).

The main strength of our study is related to its prospective nature enabling a more thorough patient selection and monitoring allowing a proper identification of predictive factors of poor nutritional status in children and young adults on chronic hemodialysis. The results of our study should however be interpreted in the context of some limitations, the most important being the small study population. Also, some parameters were not included in our study as they were unavailable in our center such as impedencemetry for clinical assessment and FGF-23 levels for a more thorough biochemical assessment.

Our results reinforce the need for a more generalized use for nPCR in nutritional assessment of pediatric HD patients. Focusing on dialysis adequacy, a proper pressure and volume control in these patients would improve their clinical outcomes. Our study also highlights a potential role of hyperphospatemia and chronic kidney disease mineral and bone disorders (CKD-MBD) in poor nutritional outcomes. We emphasize on the need for larger population-based studies to further confirm our findings.

Conclusion

The use of nPCR as gold-standard nutritional marker in children on HD allows a proper nutritional assessment and is therefore a key tool to ensure an adequate growth and better survival rates in these patients. Our study highlights the burden of cardiovascular disease on nutritional status in HD patients. Pressure and volume control along with dialysis adequacy and early management of CKD-MBD are promising factors in improving nutritional status and

clinical outcomes in children with KF.

LIST OF ABBREVIATIONS:

KF: Kidney failure

nPCR: normalized protein catabolic rate

HD: Hemodialysis

M: Male F: Female

PRES: Posterior reversible encephalopathy syndrome

RUO: residual urinary output

TBW_PD: Post dialysis total body water

UGR: Urea generation rate

pre-BUN: Blood urea nitrogen's pre-dialysis **PD-BUN**: Blood urea nitrogen's post dialysis

BMI: Body mass index **PTH**: Parathyroid hormone

RI: Refill Index

BVR: Blood volume reduction

UF: Ultrafiltration SD: Standard deviation AOR: adjusted odds ratio CI: Confidence interval

CAKUT: Congenital abnormalities of the kidneys and urinary tracts

LVH: Left ventricular hypertrophy

CKD-MBD: Chronic kidney disease mineral and bone disorders

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