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Evaluation of fluid overload markers in pediatric hemodialysis patients

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Abstract

Assessment of hydration status in children undergoing hemodialysis (HD) is crucial. This study aimed to identify the techniques that can be utilized to assess fluid overload in children with end-stage renal disease (ESRD) undergoing HD. The study included 9 patients aged >5 years and < 18 years who underwent 27 HD sessions and were followed up for ≥ 1 month. The median age of the patients was 16 years (IQR: 5-17.8 years) and the female/male ratio was 1.25:1. Symptoms of volume overload were clinically observed based on 5 (18.5%) of the 27 measurements. There was a significant positive linear correlation between fluid overload by weight and pre- and post-HD bioimpedance spectroscopy (BIS) measurements (OH) ($r=0.95$ [$P=0.000$]). There was a significant difference in median IVC diameter between pre-HD and after HD ($P=0.029$). The median pre-HD IVC collapsing index was 13.8% (IRQ: 4%-46%), versus 17.1% (IRQ: 4.5%-45%) after HD; the difference was significant ($P=0.000$). BIS is the most widely used body composition monitor for estimating fluid status in children undergoing HD. The present study investigated the sensitivity of markers of volume load in children on a routine HD program. The parameters that best indicate volume load are the differences between pre-HD and post-HD BIS measurements, physical examination findings, and heart rate measurements.

Keywords: Children, hemodialysis, bioimpedance spectroscopy

Introduction

Evaluation of hydration status in children undergoing maintenance hemodialysis (HD) is vital, as fluid overload and excess fluid withdrawal are associated with high morbidity and mortality rates [1,2]. Fluid overload is associated with a high incidence of cardiovascular complications, and removal of excess fluid via ultrafiltration can lead to intradialytic hypotension, tissue ischemia, and loss of residual renal function (RRF) [3,4]. Traditionally, assessment of fluid status is based on clinical symptoms and findings, along with evaluation of such parameters as history of interdialytic symptoms, interdialytic weight gain, physical examination findings, and blood pressure [1,3,4]. Because of the challenges associated with assessing

fluid status in children, practical tools are needed to objectively evaluate fluid overload, so as to minimize morbidity. Biochemical parameters, such as ultrasonography of inferior vena cava diameter and the lungs, and bioimpedance spectroscopy (BIS) are suggested methods for assessing fluid overload and determining the dry weight in adults and children with end-stage renal disease (ESRD) [2,4]. For pediatric patients to benefit from these methods, further evidence related to the models' applicability in children is required.

The present study aimed to determine which techniques can be used to detect fluid overload in children with ESRD undergoing HD and to discuss the accuracy of these techniques based on consideration of clinical parameters. If this study can show that

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BIS is useful for detecting fluid overload in children with ESRD it will make an important contribution to the limited available data on BIS.

Material and Methods

The study included patients aged >5 years and < 18 that were enrolled in a chronic HD program and had been undergoing HD for ≥ 2 months. Patients ≤ 4 years and ≥ 18 years, those with metallic implants, and those with severe skin pathologies were excluded from this study. Patients were evaluated while enrolled in the routine HD program.

Clinical data were recorded, including weight, blood pressure (BP), median arterial pressure (MAP), pulse rate per minute, respiratory rate, and physical examination findings measured 30 min before and 30 min after each HD session. Fluid overload calculated by taking body weight (fluid overload by weight) into account was defined as the estimated excess fluid volume by body weight in predialysis based on the patient's dry weight. Dry weight was determined as the weight value in the absence of clinical signs of excess fluid, such as respiratory findings, hypertension or edema, and was evaluated as equal to the previous HD session post-HD weight (kg) in our study. Interdialytic weight gain (IDWG) (kg) was calculated using the formula, $IDWG = \text{pre-HD weight (kg)} - \text{previous HD session post-HD weight (kg)}$. The percentage of fluid overload by determined with patient's weight was calculated using the formula, $IDWG = [\text{pre-HD weight (kg)} - \text{previous HD session post-HD weight (kg)}] / \text{previous HD session post-HD weight (kg)}$. Routine HD duration and ultrafiltration (UF) volume were determined using IDWG. The fluid status in each patient was evaluated by the attending physician and was defined presence of fluid overload by physical examination was edema, wheezing on chest auscultation, low oxygen saturation, presence of 3rd or 4th heart sound or presence of hypertension. A systolic and/or diastolic BP >95th percentile for age, sex, and height was considered hypertension, and was determined based on the Z score [5]. The number of antihypertensive medications used by the patients at the of measurement was recorded.

The Fresenius body composition monitor (BCM) (Fresenius Medical Care, St. Wendel, Germany) is the most widely used BCM in children on HD and was used to estimate fluid status [4]. The BCM measures body composition in the entire body at 50 frequencies, ranging from 5 kHz to 1 MHz [6]. Body fluid measurement via bioimpedance was performed using bioelectrical impedance devices, following the manufacturers' instructions, as follows: 4 electrodes were placed on the same side arm and leg, 2 were placed on the anterior side of the arm (1 on the wrist and 1 on the hand 4 cm apart, and 2 were placed on the anterior leg (1 on the ankle and 1 on foot 4 cm apart) with patients in the supine position. All patient measurements were performed 30 min before and 30 min after each HD session. Data with a CI >85% were included in the study.

In this study, absolute fluid overload parameters in BIS (overhydration [OH]) and relative fluid overload (relative ECF

[OH/ECW]) were evaluated. All calculations were conducted automatically using the BCM software. The ratio of extracellular water to overhydration (OH/ECW) is a basic indicator of fluid status in BIS studies [7]. To compare individuals differing in size OH is normalized to ECW, as excess fluid first accumulates in the extracellular space [7]. A relative ECF (OH/ECW) >7% is considered to be fluid load, based on previous publications [8,9]. Severe fluid load (relative ECF >15%) is associated with mortality [8]. Normal hydration status was defined as a relative ECF of -7%-7%, as used in earlier pediatric studies, which corresponds to the 10th and 90th percentiles of the healthy population [10]. Moreover, inferior vena cava (IVC) measurements were recorded as IVC diameter and IVC-collapsing index. IVC diameter was measured at end-expiration (maximum diameter) and at end inspiration (minimum diameter) 1-2 cm below the level of the entrance of the hepatic veins, as recommended by the American Society of Echocardiography guidelines and reported by Kutty et al. [11]. IVC diameter was taken as IVC measurement in expirium (mm). Inspiratory collapse was obtained via ultrasound in M-mode. IVC collapsing index was computed using the formula, $V = (\text{IVC diameter-exp} - \text{IVC diameter-Insp}) / \text{IVC diameter-exp}$. The IVC collapsing index classification published by Stawicki et al. [12] and the maximum IVC diameter values (IVC diameter max) reported by Pellicori et al. [13] were used to interpret the data.

B lines were measured via lung ultrasonography. Ultrasound imaging was performed at bedside in B-mode. B lines are artifacts that arise from the pleural line, acting concurrently with the pleural shift and obliterating the A-lines [3]. Assessments were performed within 15 min of the start of each HD session and within 30 min after each session was completed. The protocol for this study was approved by the ethics committee (no. E-22/02-281).

Statistical Analysis

Data were analyzed using SPSS for Windows v.15.0 (SPSS Inc., Chicago, IL, USA). Data distribution was analyzed using the 1-sample Kolmogorov-Smirnov test. Descriptive statistics with normal distribution are expressed as mean $\pm$ SD, versus median (IRQ) for those with asymmetric distribution. Categorical variables are presented as percentage. Comparisons were made using Student's t-test (continuous variables) or the chi-square test (categorical variables). Cox regression analysis was performed to investigate the relationship between independent variables and dependent variables. The intersection, slope coefficient, and correlation coefficient (r^2) of the regression were computed. Pearson's correlation analysis was used to compare clinical and biomarker data between volume status changes. Logistic regression analysis was performed to identify variables that were associated with fluid overload at the 95% confidence intervals (95% CI). The level of statistical significance was set at $P < 0.05$.

Results

The study included 9 patients aged >5 years and <18 years.

In total, the patients underwent 27 HD sessions and 27 fluid assessments were performed. The median age of the patients was 16 years (IRQ:5-17.8 years), and the female/male ratio was 1.25:1. The median duration of HD treatment was 3.8 years (IRQ: 1.2-7.2 years). Underlying diseases included glomerulonephritis (55.5%) and congenital urinary anomalies (44.5%). The median bodyweight of the patients was 42.5 kg (IRQ:10-62 kg) (Table 1).

Table 1. Baseline characteristics of children treated with maintenance hemodialysis

Characteristic	Value
Female gender, n (%)	5 (55.5)
Patient age, years, median (range)	16 (5-17.8)
Duration of HD, years, median (range)	3.8 (1.2-7.2)
Body weight, kilograms, median (range)	42.5 (10-62)
Percentage of fluid overload by bodyweight %, median (range)	4.5 (1 to 8)
Session duration (min), median (range)	240 (180-240)
Clinical volume overload symptoms, n (%)	5 (18.5)
Requiring antihypertensive treatment, n (%)	9 (100)
Underlying diseases, n (%)	9 (100)
Glomerulonephritis	5 (55.5%)
Congenital urinary anomalies	4 (44.5%)
Serum BUN (mg/dl), median , (range)	79 (44-137)
Baseline serum creatinine (mg/dl), median, (range)	6.7 (3.4-12.8)
Baseline serum sodium (mM), mean±SD	138.6±2.76
Baseline serum potassium (mM), mean±SD	4.71±0.84

HD; hemodialysis, BUN; blood urea nitrogen

In all, 3 separate fluid assessments were performed in each patient and volume excess was evaluated clinically according to dry weight, physical examination findings, and BP. Other methods, including BIS, measurement of IVC diameter, and pulmonary ultrasonography, were also utilized to determine volume load. Symptoms of volume overload were clinically observed based on 5 (18.5%) of the 27 measurements; clinical signs of volume overload were present based on 3 of these measurements, and rales on respiratory examination and periorbital edema were noted based on 2.

Median fluid excess according to bodyweight evaluated at the time of the start of HD was 2200 mL (IRQ: 100-3000 mL), and the target UF volume was determined based on body weight. The median duration of the 27 HD sessions was 240 min (IRQ:180-

240 min). Median percentage of fluid overload by determined with patient's weight was 4.5% (IRQ:1%-8 %). In addition, patients were clinically evaluated based on peak heart rate (PHR), respiratory rate, and arterial BP, which can show signs of volume overload. When the respiratory rate and PHR at the time of HD were evaluated according to age, they were high in 66.7% and 40.7% of the patients, respectively. There was a significant difference in the respiratory rate and PHR between pre- and post-HD (P=0.02 and P=0.03, respectively). In the patients evaluated for arterial BP the median pre-HD office systolic BP standard deviation score (SBP SDS) was 2.33 (IRQ:−1.41-2.33), versus 1.48 (IRQ:−1.41-2.33) after HD. The median pre-HD office SBP SDS was significantly higher than after HD (P=0.005). The median pre-HD office diastolic BP standard deviation score (DBP SDS) was 1.64 (IRQ:−0.33-2.33), versus 1.18 (IRQ:−0.5-2.33) after HD. Moreover, the median pre-HD office DBP SDS was significantly higher than after HD (P=0.003). There was a significant difference in BP (systolic, diastolic, and MAP) at all-time points during the 27 HD sessions (P < 0.05). In all, 66.6% of the patients required multiple antihypertensive treatments.

Another technique that we thought could show volume load in children was BIS measurement. According to BCM, the median fluid load difference (pre- and post-HD) was 2040 mL (IRQ: 300-3420 mL). The median pre-HD BIS measurement for OH was 0.6 L (IRQ:−0.3-3.2 L), versus −0.3 L (IRQ:−3.6-0.7 L) after HD. The median pre-HD BIS measurement for OH was significantly higher than after HD (P < 0.001). Furthermore, based on the OH/ECW ratio (relative fluid load), 61.5% of the patients had severe volume load and 23.1% had a mild volume load, whereas 15.4% of the patients did not have any volume load.

The median pre-HD IVC diameter was 1.01 cm (IRQ: 0.56-1.68 cm), versus 0.9 cm (IRQ: 0.49-1.54 cm) after HD; the difference was significant (P=0.029). The median pre-HD IVC collapsing index was 13.8% (IRQ: 4%-46%), versus 17.1% (IRQ: 4.5%-45%) after HD; the difference was significant (P=0.000). In 63% of the patients IVC collapsing index was <20% and was associated with an elevated CVP.

Pre-HD the median number of B-lines in lung ultrasound images was 2 (IRQ: 0-4). The presence of ≤5 B-lines was considered to be a normal variant (Table 2). The percentage of fluid overload by determined with patient's weight and the presence of

Table 2. Clinical and laboratory characteristics of patients pre- and after dialysis

	Pre-dialysis	After dialysis	p-value
Clinical overload symptoms, n (%)	5 (18.5)	1 (3.7)	0.800
Respiratory rate, median (range)	28 (16-42)	24 (18-40)	0.020
Number of peak heart rates, median (range)	96 (66-120)	90 (60-122)	0.030
Office SBP SDS, median, (range)	2.33 (-1.41-2.33)	1.48 (-1.41-2.33)	0.005
Office DBP SDS, median, (range)	1.64 (-0.33-2.33)	1.18 (-0.5-2.33)	0.003
BIS measurements for overhydration, L, median, (range)	0.6 (-0.3-3.2 L)	-0.3 L (-3.6-0.7)	<0.001
IVC diameter, cm, median, (range)	1.01 (0.56–1.68)	0.9 (0.49–1.54)	0.029
IVC-CI, %, median, (range)	13.8 (4-46%)	17.1 (4.5-45%).	<0.001

SBP; systolic blood pressure, SDS; standard deviation score, BIS; bioimpedance spectroscopy, OH; overhydration, ECW; extracellular volume, IVC; inferior vena cava, IVC-CI; inferior vena cava collapsing index

loading findings based on physical examination, the respiratory rate according to age, and the heart rate were correlated ($r=0.60$ [$P=0.001$], $r=0.51$ [$P=0.006$], and $r=0.68$ [$P<0.001$], respectively). When patients were evaluated based on the percentage of fluid overload by determined with patient's weight, a linear correlation was noted with pre-HD systolic and diastolic BP >50 th percentile ($r=0.55$ [$P=0.003$] and $r=0.48$ [$P=0.01$]). There was a significant positive linear correlation between fluid overload by weight and OH based on the difference between pre- and post-HD BIS measurement ($r=0.95$ [$P=0.000$]) (Figure 1).

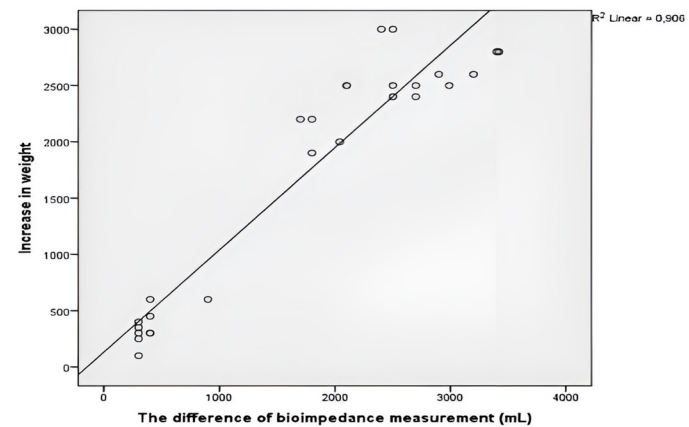


Figure 1. Correlation with fluid overload by weight

The correlation between bioimpedance onset (OH) and onset weight excess was $r=0.43$ ($P=0.02$) (Figure 2).

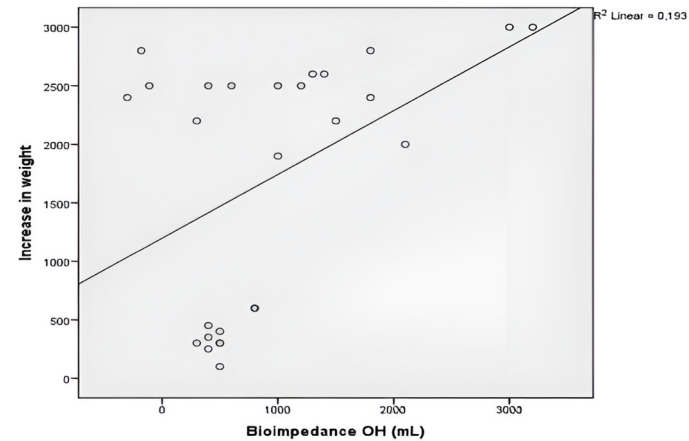


Figure 2. Correlation with fluid overload by weight

There wasn't a linear correlation between the percentage of fluid overload by determined with patient's weight and BIS measurement (OH/ECW) ($r=-0.37$ [$P=0.05$]). A linear correlation was observed between IVC diameter ($r=0.5$ [$P=0.007$]) and the percentage of fluid overload by determined with patient's weight, but there wasn't a significant negative linear relationship between IVC collapsing index ($r=0.3$ [$P=0.11$]) (Figure 3). In addition, the number of B-lines in lung ultrasound images did not have a linear correlation with the percentage of fluid overload by determined with patient's weight ($r=-0.06$ [$P=0.7$]) (Table 3).

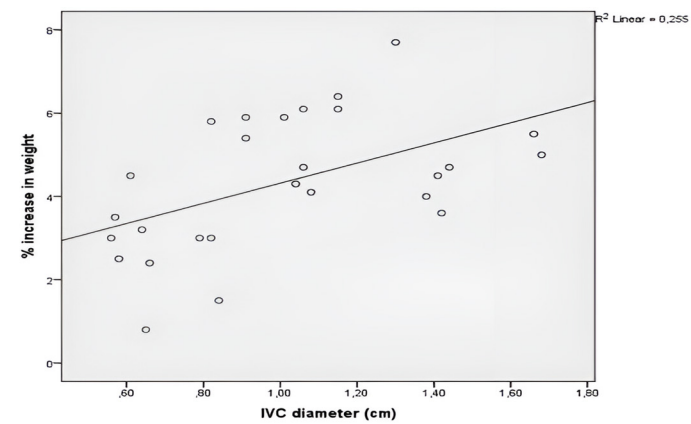


Figure 3. Correlation with fluid overload by propositional by weight

Table 3. Correlation of fluid load determined by excess weight with clinical parameters

	r value	p-value
Presence of hypervolemia findings on physical examination	0.60	0.001
Respiratory rate (by age)	0.51	0.006
Number of peak heart rates (by age)	0.68	<0.001
BIS measurement difference pre- and post-dialysis OH	0.95	<0.001
Pre – dialysis OH	0.43	0.020
Pre – dialysis OH/ECW	-0.37	0.050
Systolic blood pressure above 50p	0.55	0.003
Diastolic blood pressure above 50p	0.48	0.010
IVC diameter	0.50	0.007
IVC collapsibility index	0.30	0.110
B-lines on lung ultrasound	-0.06	0.700

SBP; systolic blood pressure, SDS; standard deviation score, BIS; bioimpedance spectroscopy, OH; overhydration, ECW; extracellular volume, IVC; inferior vena cava, IVC-CI; inferior vena cava collapsing index

The percentage of fluid overload by determined with patient's weight and BIS measurement were significant parameters for predicting fluid overload based on logistic regression analysis ($P=0.03$ and $P=0.04$, respectively) (Table 4).

Table 4. Logistic regression analysis of parameters for fluid overload

Parameter	Multivariate Analysis		
	Odds Ratio	95% confidence intervals	p value
Percent fluid load by weight	1.002	1-1.003	0.03
BIS measurement	0.998	0.996-1.001	0.04
IVC diameter	0.969	0.927-1.034	0.20
IVC-CI index	1.028	0.932-1.133	0.58
B-lines on lung ultrasound	0.729	0.412-1.287	0.27

BIS; bioimpedance spectroscopy, IVC; inferior vena cava, IVC-CI; inferior vena cava collapsing index

Discussion

Fluid overload in patients with ESRD undergoing maintenance HD is the primary cause of cardiovascular-related mortality [14]; therefore, accurate diagnosis and treatment of volume load are

of considerable importance in such patients. The present study investigated the sensitivity of markers of volume load in children enrolled in a routine HD program. The parameters that best showed volume load were the differences between pre- and post-HD bioimpedance (OH) and physical examination findings, and heart rate measurements. Furthermore, relative OH (OH/ECW ratio), IVC collapsing index, and lung B lines did not have any value for predicting fluid overload. Based on the present study's BIS data, we think that BIS can be considered an effective method for the assessment of volume load in children.

BIS is highly sensitive to the volume and distribution of fluid, and facilitates objective assessment of fluid status by measuring OH [4,15,16]. BIS measurement is non-invasive, well-tolerated, inexpensive, and easy to perform [15]. Various studies have investigated the use of bioimpedance methods in patients undergoing HD [6,9,17,18]. Earlier studies on children reported inconsistent findings regarding the applicability of BIS, resulting in the lack of consensus [3,15,19]. In the present study bioimpedance data evaluation by weight-for-weight excess showed that there is a very strong positive linear correlation between fluid overload by weight, and the difference between pre- and post-HD BIS measurement of OH, which is consistent with Yang et al. [7]. A similar study showed that the mean difference in weight reduction was correlated with the mean difference in BIS-OH [20]. Moreover, it was previously reported that intradialytic weight loss in children undergoing HD correlated well with changes in fluid status measured via BIS [21].

In the present study there was a moderate correlation between bioimpedance OH and excess volume by onset weight. Yang et al. [7], on the other hand, did not observe a significant correlation between OH and volume load by weight. Additionally, the relationship between relative ECW and volume load by excess weight remains to be clarified [22,19]. Similarly, in the present study an otherwise linear correlation was not noted between the percentage of fluid overload by determined with patient's weight and BIS measurement of OH/ECW.

Given the consistent findings of the 2 BCM measurements made at the start and end of HD, and the volume of UF administered, we think bioimpedance may be considered a predictor of volume load in pediatric patients undergoing HD. Moreover, the excellent performance of the planned UF volume for HD provided a method for estimating the accuracy of the device. Likewise, Davies [15] and Davenport [18] reported that bioimpedance can assist clinical decision-making of volume assessment in patients undergoing HD. Zaloszyk et al. [20] supported the utility of clinical evaluation of OH in pediatric HD patients, and suggested that bioimpedance and measurement of hydration status should be utilized.

Another method by which volume load can be evaluated in HD patients is IVC collapsing index. Adult studies show that echocardiography can be used to determine dry weight, and some pediatric studies support this [23-27]. In addition, Dietel et

al. [28] published reference curves for maximum IVC diameter based on ultrasonographic measurements in 206 pediatric patients. The limited number of studies that evaluated this technique in pediatric HD patients observed a decrease in IVC diameter and an increased in IVC collapsing index after HD [22,25,26,29]. In the present study the median IVC diameter before HD was significantly higher than after HD. Additionally, a linear correlation was observed between IVC diameter and the percentage of fluid overload by determined with patient's weight, but there wasn't a strong negative linear relationship between IVC collapsing index and the percentage of fluid overload by determined with patient's weight. The inconsistency in the present findings regarding IVC measurements might have been due to the limitations of the study, such as its small patient population. Moreover, IVC measurements can be affected by comorbid conditions, such as systemic hypertension, pulmonary hypertension, and diastolic dysfunction [3,22]. Consistent with earlier studies, the present findings indicate that measuring IVC diameter to assess OH in children can be helpful when assessing hydration status.

Thanks to its practicality and low cost, lung ultrasound imaging has become an increasingly popular method used for detecting fluid overload in HD patients. The method is proven to be reliable in adult HD patients [30,31] and some studies report the significance of its use in detecting fluid overload in children [3]. A single-center pediatric study that evaluated lung ultrasound showed that it was a practical and sensitive method for measuring fluid overload in children with HD-dependent ESCD [4]. In the present study, however, lung ultrasound findings were not predictive of fluid overload. Moreover, there wasn't a significant linear correlation between lung ultrasound B-line measurements and the percentage of fluid overload by determined with patient's weight. Respiratory findings due to pulmonary load were detected in 3 of the present study's patients; however, there was no positive B line on ultrasound. Many studies have used numerical data on B lines, but have not specified a clear limit for abnormal values. Some data indicate that the accepted cutoff value for abnormal B lines is 2. In the present study the pathological value for B lines was determined to be >5, which might be why a significant result for lung B lines wasn't observed in the 3 patients with findings of respiratory system overload.

Physical examination, combined with pre-HD blood pressure and assessment of interdialytic weight gain (IDWG), currently constitute the main elements of fluid assessment in pediatric patients undergoing HD [4]; however, some studies have shown that hydration status is misleading in determining fluid status due to the difficulty of clinical evaluation [20,32]. The present findings show there is a moderate correlation between the presence of volume overload findings on physical examination and FO by weight.

Traditionally, the presence of hypertension and weight gain in patients undergoing HD is considered to be a guide when evaluating volume [7]. Extracellular volume overload is involved

in the etiology of hypertension in children with ESRD; however, it is well-documented that this condition is multifactorial, as it is affected by such physiological changes as impaired heart function, exercise, and stress [4,33]. A study on European peritoneal dialysis patients reported that there is a significant correlation between OH and BP [6]. The median office SBP SDS and DBP SDS at the start of HD and after HD were significantly different in the present study's patients that were evaluated for BP, whereas there was a moderate linear correlation between onset systolic and diastolic BP >50th percentile when the patients were evaluated according to the percentage of fluid overload by determined with patient's weight. It is possible that the present study did not observe a strong correlation between SBP and volume overload because all the patients were receiving antihypertensive treatment. Although systolic and diastolic BP alone are not sufficient for predicting fluid overload, use with other clinical parameters could increase their sensitivity.

The most important limitation of the present study is that there isn't a gold standard for volume load assessment to be used for comparison. Another limitation is that the patient population was small and only a few of the patients had clinical findings, such as loading in the respiratory system or edema and, therefore, statistically evaluation may be difficult. Despite these limitations, findings on the practicality and usefulness of fluid assessment techniques have been presented, and the findings make an important contribution to those from the small number of earlier studies on markers of volume load in pediatric HD patients.

Conclusion

In conclusion, the present findings indicate that use of BIS measurement could help determine volume load in pediatric HD patients; however, we emphasize the need for larger scale long-term studies to more clearly discern its contribution to long-term patient outcomes. Moreover, physical examination findings and PHR measurements are among the parameters that best show volume load, in addition to the difference between pre- and post-HD BIS measurements. All of these methods can be used easily in routine practice.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

The protocol for this study was approved by the ethics committee (no. E-22/02-281).

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