Inferior Vena Cava Collapsibility Index: A Precise Non-invasive Tool for Evaluation of Edema in Children with Nephrotic Syndrome.

Hanan El-Halaby

Mansoura University Faculty of Medicine

Ashraf Bakr

Mansoura University Faculty of Medicine

Mohamed El-Assmy

Mansoura University Faculty of Medicine

Hussein Abdelaziz Abdalla

Mansoura University Faculty of Medicine

Marwa Salem

Mansoura University Faculty of Medicine

Riham Eid (✉ rihameid@mans.edu.eg)

Mansoura University Faculty of Medicine <https://orcid.org/0000-0003-2193-9028>

Research Article

Keywords: Children, Nephrotic syndrome, Intravascular volume, inferior vena cava, Atrial natriuretic peptide, Body composition monitor

Posted Date: April 16th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-397289/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Evaluating the volume status in children with Idiopathic nephrotic syndrome (INS) is mandatory to guide treatment and avoid unnecessary possibly hazardous albumin use. This study aimed to evaluate and compare the available tools used for volume status assessment and differentiating type of edema in children with INS. Sixty children with active INS were included and subdivided into hypovolemic and non-hypovolemic groups based on fractional excretion of sodium (FeNa%) and clinical assessment. All patients were studied for Inferior vena cava collapsibility index (IVCCI), plasma atrial natriuretic peptide (ANP) concentration and Body composition monitor (BCM). Forty-four patients (77.3%) had non-hypovolemic and 16 (26.7%) had hypovolemic states. Plasma ANP levels didn't differ between hypovolemic and non-hypovolemic subgroups. IVCCI was higher in hypovolemic group ($p < 0.001$) with sensitivity 87.5% and specificity 81.8% for hypovolemia detection while BCM-over hydration (BCM-OH) values were higher in non-hypovolemic group ($p = 0.04$) with sensitivity = 68.2% and specificity = 75% for detection of hypervolemia. FeNa% showed negative significant correlation with IVCCI ($r = -0.578$, $p < 0.001$) and positive significant correlation with BCM-OH ($r = 0.33$, $p = 0.018$), while FeNa% showed non-significant correlation to plasma ANP concentration ($p = 0.25$).

Conclusion: Non-hypovolemic edema is more frequent in edematous INS children than hypovolemic states. IVCCI is a reliable non-invasive bedside tool for evaluating volume status in INS children and is superior to BCM while plasma ANP levels can't discriminate type of edema in INS.

Summary:

What is known:

- It is critical to differentiate types of edema of NS to design a therapeutic plan for each patient.
- There is no bedside gold standard diagnostic modality to differentiate types of edema.

What is new:

- IVCCI is a reliable non-invasive bedside tool for evaluating volume status in INS and is superior to BCM.
- Plasma ANP levels can't discriminate type of edema in INS.

Introduction:

Edema in Idiopathic nephrotic syndrome (INS); may be either hypovolemic or non-hypovolemic [1, 2]. There was a trend to treat edematous INS children with albumin and furosemide, which is appropriate for hypovolemic patients; however, in non-hypovolemic patients, this can precipitate fluid overload. So, it is critical to differentiate both types of edema to design an individualized therapeutic plan for each patient [3]. A significant issue in the consideration of assessing the volume burden in children with INS is the lack of a rapid bedside gold standard diagnostic modality. Some literatures relied on the presence or absence

of hypovolemic symptoms and signs [4] or radioactive labeling techniques [5]. Later researches explored the roles of inferior vena cava collapsibility index (IVCCI) and left atrial diameter (LAD) assessed by echocardiography (ECHO) [6, 7] and over hydration (OH) value assessed by bioimpedance spectroscopy (BIS) technique such as body composition monitor (BCM) [8] for volume burden assessment. IVCCI has strong correlation to central venous pressure so it decreases with increased intra vascular volume and have been widely used for volume status assessment in hemodialysis and critically ill patients and less frequently in INS [9–12]. BIS technique is a non-invasive, rapid, easy to use and relatively inexpensive modality that estimates body fluid distribution in intracellular and extracellular spaces in addition to nutritional status[13]. It has been extensively used to estimate the volume load in dialysis patients [14, 15] however, its value INS is little mentioned. [8, 16]

The contributory role of plasma atrial natriuretic peptide (ANP) concentration, as a volume regulatory hormone, in edema formation in children with NS was widely studied previously [4, 17, 18]. However, conflicting results of ANP levels and its capability in differentiating type of edema in different children with INS were reported [18, 19, 20]. This study was carried out to evaluate the volume status in children with INS differentiated into hypovolemic and non-hypovolemic states by FeNa% and clinical assessment. We also evaluated the use of IVCCI, BCM and plasma ANP levels to differentiate type of edema in INS children.

Subjects And Methods:

Patients: This study was carried out at the pediatric nephrology unit at Mansoura University Children's Hospital over a period of 3 years. During this period 86 children with INS were admitted, 60 were enrolled in the study and were further classified into hypovolemic and non-hypovolemic groups based on FeNa% and clinical findings. Nephrotic syndrome was defined as per the “International Study for Kidney Diseases in Children” criteria [21]. Active NS, defined as the presence of nephrotic range proteinuria [urine protein/creatinine (UPC) ratio > 2]. Steroid resistant nephrotic syndrome (SRNS), Steroid responsive NS included: Steroid-dependent nephrotic syndrome (SDNS), Frequent relapsing nephrotic syndrome (FRNS) and infrequent relapsing NS (IFRNS) were defined as per “Kidney Disease Improving Global Outcomes” Guidelines [22]. Exclusion criteria included: children with congenital or infantile NS, secondary NS, patients with impaired kidney function or active infection at time of admission and those who refused to participate in the study. The patient's body weight, blood pressure, pulse rate, and degree of edema were assessed on admission day. Hypertension was defined as an average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) that is greater than or equal to the 95th percentile for sex, age, and height on three or more occasions [23]. Blood samples were drawn to measure serum albumin, creatinine, blood urea nitrogen (BUN), serum Sodium, hemoglobin and hematocrit. Urine samples were collected for urinary protein, creatinine and sodium. The patients' volume states were evaluated by: 1) fractional excretion of sodium (FeNa%) that was calculated by following the standard formula: $(\text{Urinary Na} \times \text{Plasma Cr}) \times 100 / (\text{Urinary Cr} \times \text{Plasma Na})$. Patients were considered as hypovolemic when FeNa% is less than 0.2% [3, 24] 2) Clinical assessment. All hypovolemic patients received intravenous (IV) albumin (20 %) at a dose of 0.5 g/kg twice daily over 2–3 hours followed by IV furosemide at 1 mg/kg per dose

near the end of albumin infusion. The non-hypovolemic group received IV furosemide at 1 mg/kg per dose (maximum 40 mg) twice daily, and oral amiloride hydrochloride tablets at a dose of 0.5 mg/kg/day once daily, maximum of 20 mg/day).

Inferior Vena Cava Collapsibility Index (IVCCI) measurement: Ultrasonographic examinations were carried out by a single investigator, pediatrician who had 7 -year-experience in ultrasonography using a portable doppler ultrasonography (Micromax, Sonosite; USA, 2008) with a 5 to 1 MHz curvilinear transducer array. Inferior vena cava (IVC) diameter was measured in supine position during expiration and inspiration. The inspiratory and expiratory diameters of the IVC were measured at real time; 2 cm from its entrance into the atrium. The measurements were repeated for 3 times and the average was calculated. The IVC collapsibility index (IVCCI) was calculated by the following formula: $[(\text{maximal diameter of IVC on expiration} - \text{minimal diameter on inspiration}) / (\text{maximal diameter on expiration})] \times 100$ [6]. This assessment was done on admission day.

Body composition monitoring-overhydration (BCM-OH): On admission; total body bioelectrical impedance measurements were carried out by a single investigator via body composition monitoring (BCM) device (BCM, Fresenius Medical Care D GmbH, Germany). Two electrodes were placed one to the patient's hand and the other to the foot on the same side [13]. The electrodes were then connected to the device using a cable.

Plasma Atrial Natriuretic Peptide (ANP) concentration: Plasma ANP concentration was measured by the use of Enzyme-Linked Immunosorbent Assay (ELISA) technique via sandwich immunometric assays kits (Sunred biological Technology Co., Shanghai) for in vitro quantitative measurement of ANP concentrations in plasma. The assessment was done at the same time of IVCCI and BCM measurements.

Statistical analysis

The patients' data are presented as numbers (percentage), means and standard deviation or medians with interquartile range. The patients' groups were compared using Student's t, Mann-Whitney, chi-square, and Fisher's exact tests. The patients were divided according to FeNa% and compared using Student's t, Mann-Whitney, chi-square, and Fisher's exact tests. Correlations between tools used were evaluated by Spearman's correlation for non-parametric data and Pearson correlation for parametric data. A cut-off value with receiver operator characteristic (ROC) curves, sensitivity and specificity were done to evaluate the tools used in edema assessment. A p-value of less than 0.05 was considered significant. The statistical analysis was done by IBM® SPSS® Statistics SPSS (statistical package for social sciences) version 25.

Results:

Based on FeNa%, the patients were divided into non-hypovolemic group (44 patients) (FeNa% >0.2) while 16 patients were classified as hypovolemic (FeNa% < 0.2). The detailed clinical, laboratory and volume status assessment variables for both groups are presented and compared in Table 1. Plasma ANP levels

did not show any significant differences between hypovolemic and non-hypovolemic groups ($p > 0.05$ for all). At day 30 of admission, out of the 60 patients with edema involved in the study, 4 patients did not respond to treatment and required combined albumin infusion + furosemide infusion combined with oral diuretics with no response in 2 of them who required daily ultrafiltration.

Table 1

Clinical and laboratory data of Hypovolemic vs non-hypovolemic patients with active INS at time of initial enrolment in the study and after resolution of edema:

	Hypovolemic patients (n = 16)	Non-hypovolemic patients (n = 44)	<i>P</i>
Age at diagnosis (years)	3.08 ± 1.3	3.8 ± 2.01	0.2
Age at enrolment (years)	6.2 ± 2.5	6.5 ± 2.9	0.76
Duration of illness (month)	39.3 ± 27.4	33.25 ± 28.4	0.46
Sex male/female	8/8	38/6	0.003
Type of NS:			
First attack	2	30	< 0.001
SDNS	0	4	
FRNS	2	2	
SRNS	12	8	
Outcome of edema: resolved	13	43	0.024
Non-resolved	3	1	
Percentage of weight reduction at end of treatment (%)	16.9 ± 11.3	11.1 ± 7.04	0.02
SBP (mmHg): (at time of enrollment)	105.3 ± 10.5	111.4 ± 12.2	0.04
DBP (mmHg): (at time of enrollment)	71.6 ± 14.2	71.05 ± 12.2	0.88
Heart rate (/m): (at time of enrollment)	94.2 ± 10.5	89.8 ± 9.7	0.13

NS: nephrotic syndrome, SD: standard deviation, GFR: glomerular filtration rate, U pr/cr: urinary protein to creatinine ration, FRNS: frequent relapsing nephrotic syndrome, SDNS: steroid dependent nephrotic syndrome, IFRNS: infrequent relapsing nephrotic syndrome, SRNS: steroid resistant nephrotic syndrome, FeNa%: fractional excretion of sodium, IVCCI: inferior vena cava collapsibility index, ANP: atrial natriuretic peptide, BCM: body composition monitor, OH: over hydration, SBP: systolic blood pressure, BBP: diastolic blood pressure. * presented as median and interquartile range.

	Hypovolemic patients (n = 16)	Non-hypovolemic patients (n = 44)	<i>P</i>
Serum albumin (g/dl)	1.95 ± 0.48	1.7 ± 0.26	0.04
Serum creatinine (mg/dl)	0.46 ± 0.14	0.58 ± 0.2	0.024
Serum Na (mEq/L)	131.4 ± 5.6	137.3 ± 5.4	0.001
BUN (mg/dl)	19.4 ± 3.3	16.2 ± 4.1	0.007
FeNa(%)	0.16 ± 0.12	1.59 ± 0.67	< 0.001
ANP (ng/ml)	132.97 ± 59.2	127.9 ± 51.7	0.7
Hemoglobin (g/dl)	13.1 ± 1.3	11.1 ± 1.2	<
Hematocrit (%)	43.8 ± 3.3	37.8 ± 7.9	0.001
IVCCI: on admission	48.97 ± 10.2	30.37 ± 10.98	< 0.001
BCM-OH:	1.5(1.95)*	2.2(1.9)*	0.01
NS: nephrotic syndrome, SD: standard deviation, GFR: glomerular filtration rate, U pr/cr: urinary protein to creatinine ration, FRNS: frequent relapsing nephrotic syndrome, SDNS: steroid dependent nephrotic syndrome, IFRNS: infrequent relapsing nephrotic syndrome, SRNS: steroid resistant nephrotic syndrome, FeNa%: fractional excretion of sodium, IVCCI: inferior vena cava collapsibility index, ANP: atrial natriuretic peptide, BCM: body composition monitor, OH: over hydration, SBP: systolic blood pressure, BBP: diastolic blood pressure. * presented as median and interquartile range.			

To evaluate the use of IVCCI, ANP levels and BCM-OH values as tools for evaluating volume status and differentiating edema type versus FeNa%, FeNa% showed negative significant correlation with IVCCI ($r = -0.578$, $p < 0.001$) (Fig. 1A) and positive significant correlation with BCM-OH ($r = 0.33$, $p = 0.018$) (Fig. 1B), while FeNa% showed non-significant correlation to plasma ANP level ($p = 0.25$). Also, IVCCI and BCM-OH showed negative significant correlation (Fig. 1C) suggesting the consistency of the 2 proposed tools for volume status evaluation. To assess the cutoff value of IVCCI, BCM-OH and plasma ANP concentration that discriminate the volume states in children with active NS, ROC curves for IVCCI, BCM-OH and serum ANP was plotted against volume state (Fig. 2) and showed a cutoff point of 37.5, sensitivity = 87.5% & Specificity = 81.8% for hypovolemia detection with an area under the curve (AUC) of 0.878 for IVCCI and for BCM-OH, a cutoff point of 1.55 for detection of hypervolemia (sensitivity = 68.2% and specificity = 75%) and AUC of 0.719. While area under the curve for hypovolemia detection for both BCM-OH and ANP were non-discriminative (AUC = 0.28 and 0.51 respectively).

Discussion:

Generalized edema is the main cause of hospitalization of children with INS and if not treated wisely may lead to death. In this study, we investigated different tools used for discrimination of the type of edema; we studied IVCCI, BCM and plasma ANP concentration. The 60 INS patients were divided into two groups as hypovolemic and non-hypovolemic according to the above-mentioned clinical and laboratory criteria. Kapur et al. [3] defined the hypovolemic patients who had FeNa% of $< 1\%$. However, in phase 2 of their study, the FeNa% criterion for the volume status was modified and patients with FeNa% of $< 0.2\%$ were identified with volume contraction which we have applied in addition to clinical assessment to differentiate edema types. In the current work, 73.3% of the studied patients were non-hypovolemic; the same observation was noted by Buyukavci and colleagues [7] who reported that 75% of their patients were non-hypovolemic and another study also in 2015, by Ozdemir et al; with 65% of the studied patients reported to be non-hypovolemic [8]. There are multiple limitations of the use of urinary indices in edema status evaluation in INS including: use of diuretics or angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and dietary salt intake [24]. This is why the search is continuous for other simple accurate tools for evaluation of volume status, directing and monitoring the treatment of edema in INS patients.

Based on clinical assessment along with the FeNa%, non-hypovolemic patients were treated with diuretics only and hypovolemic patients received albumin and furosemide. Applying this treatment strategy yielded 93.3% (56 patients) success rate while edema did not resolve in only 4 patients. Similar results have been reported by Kapur and colleagues who reported the safety of the use of diuretics only in treating NS children with non-hypovolemic states [3] avoiding unnecessary possible hazardous use of albumin.

Bioimpedance has been long applied to evaluate body composition and hydration status in both hemodialysis and peritoneal dialysis patients. Studies demonstrated that strict BCM guided fluid management led to better blood pressure control, a decrease in arterial stiffness, a reduction of intradialytic symptoms and a better survival [14, 15] however, its value in evaluation of edema in INS was evaluated only in limited studies [8, 16]. Brantlov and colleagues reported the valuable use of BCM to distinguish children with active NS from well-treated and healthy children [25] and also Ozdemir et al; [8] reported significant differences in volume load assessment by BCM between INS children with localized versus those with generalized edema. Other researchers also reported the total body water assessed by BIS to be much higher in edematous versus non-edematous INS children [26, 27]. However, BCM showed moderate sensitivity and specificity for detecting hypervolemia, and was non-discriminative for hypovolemia. Ozdemir and colleagues compared bioimpedance results between the controls and the NS patients and concluded that this method has a sensitivity of 65% and a specificity of 90% but when comparing patients with generalized and localized edema that bioimpedance had a sensitivity of 83% and a specificity of 80% regarding the presence and severity of volume overload [8]. So, BCM can detect presence and severity of volume load but can't determine site of extra fluids is placed interstitial or intravascular and consequently can be used to monitor response to edema treatment however, its role in differentiating edema type is limited.

In the present study, it was observed that IVCCI was significantly higher in hypovolemic children with active NS than in non-hypovolemic subgroup. Previous studies had searched for the usefulness of IVCCI in volume burden detection in INS and conflicting results were observed. In accordance with our results; Tabel and colleagues studied 18 children diagnosed as MCD and followed up the non-hypovolemic children for 5–7 days till edema resolved, he observed IVCCI values were significantly increased with diuretic therapy, patients changed from hypervolemia to euvolemic state [28]. Donmez et al; [6] studied the value of IVCCI, to determine the volume load in children with minimal lesion nephrotic syndrome and noted that IVCCI in nephrotic edematous patients was less than nephrotic non-edematous group and healthy control group, indicating hypovolemic state in edematous patients. On the other hand, In 2015, Buyukavci and his coworkers [7] studied SSNS children versus healthy control; IVCCI didn't differ among both groups. Furthermore, IVCCI was not significantly different between hypovolemic and non-hypovolemic subgroups within the active NS group. Another study by Gurgoze et al., [9] studied NS subgroups (relapse-edematous, relapse-edema free and remission), were compared. They found non-significant difference between groups as regard to IVCCI. To assess the discriminative value of IVCCI as indicator of volume status in active NS, ROC curve was plotted and showed a cutoff point 37.5, with an AUC of 0.88 i.e. very good discriminator and more than this point refers to hypovolemic state and less indicates non-hypovolemia, with sensitivity = 75% & Specificity = 86%. However, Ozdemir et al; [8] concluded that using the IVCCI to determine volume load, the sensitivity was 95% and the specificity was 10% using a 50% level as discriminating between hypovolemic and non-hypovolemic states and that BIS may be superior to IVCCI in determining volume load in children with INS which is also against our results.

To assess the role of possible role of plasma ANP concentration in differentiating edema type, despite being higher in both groups before edema resolution, this elevation did not reach significant difference between hypovolemic and non-hypovolemic groups. This indicates that ANP plays a role in edema formation in active NS but not in the specific type of edema and there is some sort of renal resistance to ANP diuretic and natriuretic actions. In NS, resistance to serum ANP is an observation in experimental animals and humans [29, 30], these studies showed that ANP levels were frequently elevated in INS children than in healthy or remission children. Moreover, Cataliotti et al., observed increased plasma ANP concentration that frequently correlated with the edema severity [31]. Increased plasma ANP concentration may be a compensatory mechanism to induce diuresis and natriuresis. The ANP-dependent natriuresis is blunted, reflecting a dampening of ANP-dependent signaling mechanism, and resulting in failure of ANP to correct extracellular volume burden in nephrotic patients [32].

Nalcacioglu et al; reported that serum N-terminal pro-brain natriuretic peptide (NT-proBNP) values were statistically higher in active NS compared to remission and control [33] but they also reported no correlation between BIS and NT-proBNP in patients group that was explained as variation of the relation between NT-proBNP and hydration status which may be explained by down regulation of natriuretic peptide receptors leading to renal unresponsiveness and that no hypovolemia reported in their studied group supported by the high extracellular water without any change in intracellular water. A summary of the characteristics and results of the previous studies exploring methods of evaluation of edema in INS

children are presented in Table 2. Concerning plasma ANP, it was noted that ANP concentrations were higher in hypovolemic group than in non-hypovolemic; however, this difference did not reach statistical significance. When discussing the role of ANP in fluid distribution in intravascular or the interstitial space, we rely on the direct effect of ANP on systemic vascular system rather than the renal receptor mechanism. ANP affect the endothelial cells of systemic capillaries directly to modulate transcapillary fluid shift out of the blood vessels into the interstitial space and hence induce hypovolemia [34, 35].

Table 2

Summary of Characteristics and main findings of current study and previous studies assessing volume status in children with INS

First author /[reference]	Year	country	Number of patients	Assessment tools	Outcome
El-Halaby et al; [current]	2021	Egypt	60 active NS 40 NS in remission	FeNa% IVCCI BCM-OH ANP	Non-hypovolemic state is more common in active NS children. IVCCI is simple, sensitive and specific tool to differentiate active NS from NS in remission and also to detect edema type in NS.
Brantlov et al; [25]	2019	Denmark	8 active NS 5 NS in remission 38 healthy control	BIS measurement	BIS can distinguish children with active NS from well-treated and healthy children
Nalcacioglu et al; [33]	2018	Turkey	19 Active NS 25 healthy control	NT-proBNP BIA FeNa% Renin, aldosterone IVCI, LAD	Renin, aldosterone, ECHO finding did not differ between both groups while NT-proBNP showed significant difference.
Buyukavci et al; [7]	2015	Turkey	32 SSNS 30 healthy control	FeNa% IVCCI, LAD, AD, LVMI.	Most of children with SSNS are non-hypovolemic and ECHO is reliable for evaluation of volume status.
Ozdemir et al; [8]	2015	Turkey	34 active NS 20 healthy control	IVCI IVCCI BCM	BIS may be superior to echocardiography in determining volume load in children with NS

INS: idiopathic nephrotic syndrome, BIS: bioimpedance spectroscopy, ANP: atrial natriuretic peptide, FeNa: fractional excretion of sodium, IVCI: inferior vena cava index, LAD: left atrial diameter, BCM-OH: body composition monitor-over hydration, MCD: minimal lesion nephrotic syndrome, ADH: antidiuretic hormone, AD: aortic diameter NT-proBNP: n-terminal pro brain natriuretic peptide, ECHO: Echocardiogram, SSNS: steroid sensitive nephrotic syndrome.

First author /[reference]	Year	country	Number of patients	Assessment tools	Outcome
Kapur et al; [3]	2009	USA	16 severe oedema	FeNa% Renin, aldosterone, ADH	FeNa% is useful in distinguishing hypovolemic versus non-hypovolemic NS children with severe edema. The use of diuretics alone in non-hypovolemic patients is safe and effective.
Dönmez et al; [6]	2001	Turkey	12 MCD	FeNa%, ANP, renin, aldosterone, IVCI, IVCCI, LAD	IVCI, IVCCI, and LAD and reliable methods for assessing the intravascular volume in patients with MCD.
INS: idiopathic nephrotic syndrome, BIS: bioimpedance spectroscopy, ANP: atrial natriuretic peptide, FeNa: fractional excretion of sodium, IVCI: inferior vena cava index, LAD: left atrial diameter, BCM-OH: body composition monitor-over hydration, MCD: minimal lesion nephrotic syndrome, ADH: antidiuretic hormone, AD: aortic diameter NT-proBNP: n-terminal pro brain natriuretic peptide, ECHO: Echocardiogram, SSNS: steroid sensitive nephrotic syndrome.					

Limitations of the current work lie in the facts that it is a single center study, did not assess plasma renin activity and aldosterone levels and the need for larger patient numbers with serial application of the studied tools during the course of edema to confirm these preliminary findings.

Conclusion:

Assessment of hydration status in INS children is critical for management of edema. IVCCI is a sensitive and specific tool for discriminating types of edema in NS superior to BCM while serum ANP levels don't seem to be differentiating for the type of edema in INS. Further studies with larger number of subjects are required to confirm these findings.

Abbreviations:

ACEIs: Angiotensin-converting enzyme inhibitors

AD: Aortic diameter.

ADH: Antidiuretic hormone.

ANP: atrial natriuretic peptide

ARBs: angiotensin receptor blockers

AUC: Area under the curve.

BCM: Body composition monitor.

BIS: bioimpedance spectroscopy

BUN: Blood urea nitrogen

Cr: creatinine.

DBP: Diastolic blood pressure.

ECHO: Echocardiography

ELISA: Enzyme-Linked Immunosorbent Assay

FENa%: fractional excretion of sodium.

FRNS: frequent relapsing nephrotic syndrome.

IFRNS: infrequent relapsing NS

INS: Idiopathic nephrotic syndrome.

IVC: Inferior vena cava

IVCCI: inferior vena cava collapsibility index

LAD: left atrial diameter.

MCD: Minimal change disease.

OH: Over hydration.

ROC: Receiver operator characteristic

SBP: Systolic blood pressure

SDNS: Steroid dependent nephrotic syndrome

SPSS: Statistical package for social sciences

SRNS: Steroid resistant nephrotic syndrome

UPC: Urinary protein/ creatinine.

Declarations:

Funding:

no funding received

Conflict of interest/Competing interests:

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and material:

data and material are available upon request.

Code availability:

Non applicable.

Authors' contributions:

Dr. Hanan El-Halaby: Share in research hypothesis and research protocol, IVCCI and BCM measurements for all patients, did the statistical analysis of the data, write the first draft of the manuscript and revised and approved the final manuscript.

Dr. Ashraf Bakr: Research hypothesis and plan, supervised the provided medical care to all patients and revised and approved the final manuscript.

Dr. Mohamed El-Assmy: Share in research hypothesis and research protocol, supervised the provided medical care to all patients and revised and approved the final manuscript.

Dr. Hussein Abdelaziz Abdalla: Share in research hypothesis and research protocol, performed all biochemical tests for all patients and revised and approved the final manuscript.

Dr. Marwa Salem: Share in research protocol, collected patients' blood samples and clinical data and revised and approved the final manuscript.

Dr. Riham Eid: Research protocol and plan, provided medical care to some patients, shared in statistical analysis, shared in writing the draft of the manuscript and revised and approved the final manuscript.

Ethical Approval:

This study was reviewed and approved by Mansoura Faculty of Medicine Institutional Research Board (R.21.02.1189)

Consent to participate:

An informed consent was obtained from all patients' guardians before enrolment in the study.

Consent for publication:

References:

1. Siddall EC, Radhakrishnan J (2012) The pathophysiology of edema formation in the nephrotic syndrome. *Kidney Int* 82:635-642. DOI: 10.1038/ki.2012.180.
2. Bockenhauer D (2013) Over- or underfill: not all nephrotic states are created equal. *Pediatr Nephrol* 28:1153-1156. DOI:[1007/s00467-013-2435-6](https://doi.org/10.1007/s00467-013-2435-6)
3. Kapur G, Valentini RP, Imam AA, Mattoo TK (2009) Treatment of severe edema in children with nephrotic syndrome with diuretics alone—a prospective study. *Clin J Am Soc Nephrol* 4:907-913. DOI:10.2215/CJN.04390808
4. Vande Walle JG, Donckerwolcke RA, Koomans HA (1999) Pathophysiology of edema formation in children with nephrotic syndrome not due to minimal change disease. *J Am Soc Nephrol* 10:323-331. PMID: 10215332.
5. Vande Walle J, Donckerwolcke R, Boer P, van Isselt HW, Koomans HA, Joles JA (1996) Blood volume, colloid osmotic pressure and F-cell ratio in children with the nephrotic syndrome. *Kidney Int* 49:1471-1477. DOI:[1038/ki.1996.207](https://doi.org/10.1038/ki.1996.207)
6. Donmez O, Mir S, Ozyurek R, Cura A, Kabasakal C (2001) Inferior vena cava indices determine volume load in minimal lesion nephrotic syndrome. *Pediatr Nephrol* 16:251-255. DOI:[1007/s004670000536](https://doi.org/10.1007/s004670000536)
7. Buyukavci MA, Civilibal M, Elevli M, Selcuk Duru HN (2015) Hypo- and hypervolemic edema in children with steroid sensitive nephrotic syndrome. *Turk J Med Sci* 45:178-183. PMID: 25790549
8. Ozdemir K, Mir MS, Dincel N, Bozabali S, Kaplan Bulut I, Yilmaz E, Sozeri B (2015) Bioimpedance for assessing volume status in children with nephrotic syndrome. *Turk J Med Sci* 45:339-344. PMID: 26084125
9. Gurgoze MK, Gunduz Z, Poyrazoglu MH, Dursun I, Uzum K, Dusunsel R (2011) Role of sodium during formation of edema in children with nephrotic syndrome. *Pediatrics International* 53:50-56. DOI:[1111/j.1442-200X.2010.03192.x](https://doi.org/10.1111/j.1442-200X.2010.03192.x)
10. Cheriex EC, Leunissen KM, Janssen JH, Mooy JM, van Hooff JP (1989) Echography of the inferior vena cava is a simple and reliable tool for estimation of 'dry weight' in hemodialysis patients. *Nephrol Dial Transplant*. 4:563-568. PMID: 2507979.
11. Ilyas A, Ishtiaq W, Assad S, Ghazanfar H, Mansoor S, Haris M, Qadeer A, Akhtar A (2017) Correlation of IVC Diameter and Collapsibility Index with Central Venous Pressure in the Assessment of Intravascular Volume in Critically Ill Patients. *Cureus* 9: e1025. DOI: [7759/cureus.1025](https://doi.org/10.7759/cureus.1025)
12. Karacabey S, Sanri E, Guneyssel O (2016) A Non-invasive Method for Assessment of Intravascular Fluid Status: Inferior Vena Cava Diameters and Collapsibility Index. *Pak J Med Sci* 32:836-840. DOI: 10.12669/pjms.324.10290.

13. Mialich MS, Sicchieri JMF, Junior AAJ (2014) Analysis of Body Composition: A Critical Review of the Use of Bioelectrical Impedance Analysis. *International Journal of Clinical Nutrition* 2:1-10.
14. Onofriescu M, Hogas S, Voroneanu L, Apetrii M, Nistor I, Kanbay M, Covic AC (2014) Bioimpedance-guided fluid management in maintenance hemodialysis: a pilot randomized controlled trial. *Am J Kidney Dis.* 64:111–118. DOI: 10.1053/j.ajkd.2014.01.420
15. Patel HV, Annigeri RA, Kowdle PC, Rao BS, Seshadri R, Balasubramanian S, Vadamalai V (2019) Bioimpedance Spectroscopy-Guided Ultrafiltration Normalizes Hydration and Reduces Intradialytic Adverse Events in Hemodialysis Patients. *Indian J Nephrol* 29:1-7. DOI: 10.4103/ijn.IJN_150_18. PMID: 30814786.
16. Jiang F, Bo Y, Cui T, Zhou Y, Li Z, Ma L, Bi Z (2010) Estimating the hydration status in nephrotic patients by leg electrical resistivity measuring method. *Nephrology (Carlton)* 15:476-479. DOI: [1111/j.1440-1797.2010.01267.x](https://doi.org/10.1111/j.1440-1797.2010.01267.x)
17. Rodriguez-Iturbe B, Colic D, Parra G, Gutkowska J (1990) Atrial natriuretic factor in the acute nephritic and nephrotic syndromes. *Kidney Int* 38:512-517. DOI: [1038/ki.1990.233](https://doi.org/10.1038/ki.1990.233)
18. Vande Walle JG, Donckerwolcke RA, van Isselt JW, Derkx FH, Joles JA, Koomans HA (1995) Volume regulation in children with early relapse of minimal-change nephrosis with or without hypovolaemic symptoms. *Lancet* 346:148-152. DOI: [1016/S0140-6736\(95\)91210-X](https://doi.org/10.1016/S0140-6736(95)91210-X)
19. Peterson C, Madsen B, Perlman A, Chan AY, Myers BD (1988) Atrial natriuretic peptide and the renal response to hypervolemia in nephrotic humans. *Kidney Int* 34:825-831. DOI: [1038/ki.1988.256](https://doi.org/10.1038/ki.1988.256).
20. Garin EH, Paul RV (1990) Atrial natriuretic factor in idiopathic minimal-lesion nephrotic syndrome. *Child Nephrol Urol* 10:65-67. PMID: 2147579
21. The primary nephrotic syndrome in children. (1981). Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. *Journal of Pediatrics*, 98, 561–564. DOI: [1016/s0022-3476\(81\)80760-3](https://doi.org/10.1016/s0022-3476(81)80760-3)
22. <https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2012-GNGuideline-English.pdf>
23. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 114:555-576. PMID: 15286277.
24. Sahay M (2011) Urinary indices in nephrotic syndrome. *Indian J Nephro* 21:152-153. DOI:10.4103/0971-4065.83027
25. Brantlov S, Jødal L, Frydensbjerg Andersen R, Lange A, Rittig S, Ward LC (2019) Bioimpedance Resistance Indices and Cell Membrane Capacitance Used to Assess Disease Status and Cell Membrane Integrity in Children with Nephrotic Syndrome. *Scientific World Journal*. 9;2019:4274856. DOI: 10.1155/2019/4274856.
26. Drozd D, Sancewicz-Pach K, Wierchowska-Słowiacek E (2000) Value of bioelectrical impedance analysis in the assessment of body water in children with nephrotic syndrome: initial results. *Polski merkuriusz lekarski: organ Polskiego Towarzystwa Lekarskiego* 8:224-225. PMID: 10897621.

27. Bozzetto S, Piccoli A, Montini G (2010) Bioelectrical impedance vector analysis to evaluate relative hydration status. *Pediatr Nephrol* 25:329. DOI: [1007/s00467-009-1326-3](https://doi.org/10.1007/s00467-009-1326-3)
28. Tabel Y, Mungan I, Karakurt C, Kocak G, Gungor S (2008) Is edema in minimal change disease of childhood really hypovolemic? *Int Urol Nephrol* 40:757-761. DOI: [1007/s11255-008-9344-9](https://doi.org/10.1007/s11255-008-9344-9)
29. Bae EH, Lee J, Ma SK, Kim SW (2009) Changes of atrial natriuretic Peptide system in rats with puromycin aminonucleoside-induced nephrotic syndrome. *Korean J Physiol Pharmacol* 13:1-7. DOI:[4196/kjpp.2009.13.1.1](https://doi.org/10.4196/kjpp.2009.13.1.1)
30. Plum J, Mirzaian Y, Grabensee B (1996) Atrial natriuretic peptide, sodium retention, and proteinuria in nephrotic syndrome. *Nephrol Dial Transpl* 11:1034-1042. PMID: 8671965
31. Cataliotti A, Malatino LS, Jougasaki M, Zoccali C, Castellino P, Giacone G, et al. (2001) Circulating natriuretic peptide concentrations in patients with end-stage renal disease: role of brain natriuretic peptide as a biomarker for ventricular remodeling. *Mayo Clin Proc.* 76:1111-1119. DOI: 10.4065/76.11.1111.
32. Ray EC, Rondon-Berrios H, Boyd CR, Kleyman TR (2015) Sodium retention and volume expansion in nephrotic syndrome: implications for hypertension. *Adv chronic kidney Dis* 22:179-184. DOI: [1053/j.ackd.2014.11.006](https://doi.org/10.53/j.ackd.2014.11.006).
33. Nalcacioglu H, Ozkaya O, Baysal K, Kafali HC, Avci B, Tekcan D, Genc G (2018) The role of bioelectrical impedance analysis, NT-ProBNP and inferior vena cava sonography in the assessment of body fluid volume in children with nephrotic syndrome. *Nefrologia.* 38:48-56. DOI: 10.1016/j.nefro.2017.04.003.
34. Huxley VH, Tucker VL, Verburg KM, Freeman RH (1987) Increased capillary hydraulic conductivity induced by atrial natriuretic peptide. *Circ Res* 60:304-307. DOI: [1161/01.res.60.2.304](https://doi.org/10.1161/01.res.60.2.304)
35. Hisanaga S, Yamamoto Y, Kida O, Kato J, Fujimoto S, Tanaka K (1989) Plasma concentration and renal effect of human atrial natriuretic peptide in nephrotic syndrome. *Nihon Jinzo Gakkai Shi* 31:661-669. PMID: 2529385.

Figures

Figure 1

Correlation of A) FeNa% and IVCC, B) FeNa% and BCM-OH and C) IVCCI and BCM-OH.

Figure 2

Receiver operating characteristic (ROC) curve to: A) inferior vena cava collapsibility index (IVCCI), B) BCM-OH, C) ANP to discriminate volume states in children with active INS.