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Comparative Analysis of Inferior Vena Cava Index and Collapsibility Index as Indicators of Body Fluid Volume Status in Children with Nephrotic Syndrome

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ABSTRACT

Nephrotic syndrome is the most common renal disease in children, characterized by edema due to fluid accumulation in the interstitial fluid compartment. Edema in nephrotic syndrome can be explained by the underfill and overfill hypotheses. The underfill hypothesis suggests that hypoalbuminemia leads to fluid sequestration in the interstitial compartment, while the overfill hypothesis attributes edema to a primary renal defect in sodium excretion. Accurate assessment of intravascular volume status is crucial for effective treatment. This study compares the Inferior Vena Cava Index (IVCI) and Inferior Vena Cava Collapsibility Index (IVCCI) as measures of body fluid volume in children with nephrotic syndrome. This cross-sectional observational study was conducted in the Department of Pediatrics at Pt B D Sharma PGIMS, Rohtak. A total of 60 children aged 1-14 years were included, with 30 children diagnosed with nephrotic syndrome (cases) and 30 healthy children (controls). IVCI and IVCCI were measured using ultrasound and the body surface area was calculated. Statistical analysis was performed using SPSS version 21.0, with significance set at $p<0.05$. The mean age of cases was 5.57±3.02 years and controls were 5.73±3.10 years. The mean IVC diameter at inspiration and expiration was significantly higher in cases (0.70±0.24 cm and 0.92±0.29 cm, respectively) compared to controls (0.51±0.12 cm and 0.68±0.10 cm, respectively) (p=0.001). The mean IVCI was significantly higher in cases (1.07±0.39) compared to controls (0.44±0.19) (p=0.001). There was no significant difference in mean IVCCI between cases (24.65±10.16) and controls (25.41±11.62) (p=0.787). Based on IVCI, 20% of cases were hypovolemic, 46.7% were euvolemic and 33.3% were hypervolemic. All cases were hypervolemic according to IVCCI, while 3.3% of controls were hypovolemic or euvolemic and 96.7% were hypervolemic. IVCI underestimated body fluid volume status in both control and nephrotic syndrome children, while IVCCI overestimated intravascular volume status. The study supports the overfill hypothesis, with 33.3% of edematous patients showing IVCI >1.15 and IVCCI <50%. Further studies are needed to define accurate cut-offs for IVCI and IVCCI in Indian children.

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Key Words

Nephritic syndrome, edema, inferior vena cava index (IVCI), inferior vena cava collapsibility index (IVCCI), body fluid volume, pediatric nephrology

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INTRODUCTION

Nephrotic syndrome is the most common renal disease in children, with an annual incidence of approximately 2-7 per 100,000 children in Western countries and an even higher incidence in Southern Asia[1]. Edema is the most common symptom in nephrotic syndrome[2]. There are two primary theories explaining the development of edema in nephrotic syndrome: the underfill hypothesis and the overfill hypothesis[3,4].

Edema in nephrotic syndrome is characterized by swelling due to fluid accumulation in the interstitial fluid compartment. This massive generalized edema (anasarca) is the main reason for hospital admission, particularly in children with primary minimal change disease (MCD). Hypoalbuminemia, caused by the selective loss of large amounts of albumin in the urine, leads to lower plasma oncotic pressure and favors fluid sequestration in the interstitial compartment. Additionally, renal sodium and fluid retention maintain intravascular volume and blood pressure, preventing an underfill state[3,4].

The overfill hypothesis suggests that edema results from a primary renal defect in sodium excretion, independent of low oncotic pressure, leading to primary extracellular volume expansion and secondary fluid leakage into the interstitial space. This results in massive urinary protein loss and hypoalbuminemia, which causes fluid movement from the vascular space to the interstitium[5-7].

There is evidence of both intravascular volume expansion (overfilling) and intravascular volume depletion (under filling) in patients with nephrotic syndrome[8]. Accurate understanding of intravascular volume status is crucial for effective treatment in nephrotic syndrome. Diuretics are well tolerated in patients with vessel overfilling due to sodium retention, but they worsen the condition in patients with vessel under filling. Thus, body fluid assessment is critical for appropriate treatment[9,10].

Clinical methods for assessing body fluid volume, such as blood pressure, pulse, heart rate, 24-hour urine output and changes in body weight, are not accurate. Central venous pressure measurement is invasive, while biochemical parameters like fractional excretion of sodium and vasoactive hormone measurements such as atrial natriuretic peptide, vasopressin, plasma renin activity, aldosterone, and angiotensin-II are expensive and not readily available. Although echocardiography is non-invasive and common in determining dry weight, it is expensive and not always accessible[9,10]. Ultrasound, however, is a cheap, non-invasive and readily available method to estimate body fluid volume. In the pediatric intensive care unit (ICU), treatment depends on hemodynamic monitoring. Establishing intravascular volume with fluids and vasoactive Medications to develop normal systemic perfusion are crucial for reducing the risk of organ failure and death[1,2]. Clinical parameters are imprecise and CVP measurement is invasive. Biochemical parameters are expensive and difficult to interpret. Inferior vena cava index (IVCI) and inferior vena cava collapsibility index (IVCCI) measurements using echocardiography and ultrasonography are frequently used in adults because they can non-invasively determine intravascular volume burden[2].

Ultrasound usage has rapidly increased in emergency care due to its risk-free, non-invasive and quick diagnostic capabilities. It is essential for fluid management, which is foundational in emergency medicine evaluation and treatment protocols like BLUE, RUSH and FALLS. The inferior vena cava collapsibility index has emerged as a critical predictor of fluid status, studied extensively in various populations such as dialysis patients, trauma patients, and sepsis patients[11-13].

Non-invasive methods like IVCI and IVCCI measurements could provide a reliable, quick assessment of fluid status in children with nephrotic syndrome. This study aims to assess the effectiveness of these indices in predicting body fluid volume and determining which index provides better clinical utility.

MATERIALS AND METHODS

Study Setting and Design: This cross-sectional observational study titled Comparison of the Inferior Vena Cava Index and Inferior Vena Cava Collapsibility Index as a measure of body fluid volume status in children with Nephrotic Syndrome was conducted in the Department of Pediatrics at Pt B D Sharma PGIMS, Rohtak. The study was approved by the Postgraduate Board of Studies and the Ethics Committee at Pt. B. D. Sharma University of Health Sciences, Rohtak.

Study Period: The study was conducted over a period of one year from the date of commencement.

Study Population: The study included children aged 1-14 years diagnosed with nephrotic syndrome (cases) and age-and sex-matched healthy children without chronic disease (controls).

Sample Size: Using G-power software with 80% power and a 5% significance level, the sample size was determined to be 60 participants, comprising 30 cases and 30 controls.

Inclusion Criteria:

- Children with nephrotic syndrome (first episode or relapse) aged 1-14 years.
- Diagnosis confirmed by urine examination (3+or 4+ proteinuria, spot urine protein/creatinine ratio >2.0, or urine protein excretion >1g/m²/24 hr), serum cholesterol (>200 mg/dl), increased triglyceride levels and serum albumin <2.5 g/dl.

Exclusion Criteria:

- Children with nephritic-nephrotic combination pathologies.
- Hemodynamically unstable children.
- Children with severe respiratory distress or on respiratory support.
- Lack of parental/caregiver consent.

Study Methodology: After obtaining IEC approval, patients were enrolled based on the inclusion and exclusion criteria. Detailed history, physical examination and appropriate investigations were conducted. Thirty children with nephrotic syndrome were recruited as cases and thirty healthy, age-and sex-matched children without chronic disease were recruited as controls. Written informed consent was obtained from the caregivers of all participants.

Measurement of IVCI and IVCCI: Inferior Vena Cava Index (IVCI) and Inferior Vena Cava Collapsibility Index (IVCCI) were calculated using ultrasound:

- **IVCI:** Expiration max. Diameter (cm)+Inspiration min. diameter (cm) 2×BSA \ frac {\text{Expiration max. diameter (cm)+Inspiration min. diameter (cm)}} {2} \times \text {BSA} 2 Expiration max. diameter (cm)+Inspiration min. diameter (cm)×BSA
- **IVCCI:** Expiration max. Diameter (cm) - Inspiration min. diameter (cm) Expiration max. Diameter (cm) ×100\frac {\text {Expiration max. diameter (cm)-Inspiration min. diameter (cm)}} {\text {Expiration max. diameter (cm)}} \times 100 Expiration max. Diameter (cm) Expiration max. diameter (cm)-Inspiration min. diameter (cm)×100

Body Surface Area Calculation: Body surface area (BSA) was calculated using the formula: BSA=4×weight in kg+790 + weight in kg \ text {BSA} = \frac {4 \times \text {weight in kg}+7} {90+\text {weight in kg}} BSA = 90+weight in kg 4×weigh in kg+7.

Ultrasound Equipment and Positioning: The ultrasound was performed using a SIMON'S ACUSON-X-300 machine with both convex and linear probes, depending on the patient's habitus. The convex probe frequency was 2-5 MHz and the linear probe frequency was 5-10 MHz. The measurements were taken with the patient in a supine position, 2 cm distal to the right atrium along the subcostal long axis. Maximum IVC diameter was measured during inspiration and minimum IVC diameter during expiration.

Statistical Analysis: The data were analyzed using SPSS version 21.0. Quantitative variables were expressed as mean and standard deviation, while qualitative variables were expressed as frequency and Percentage. The student t-test was used to compare mean values between groups and the chi-square test was used to analyze frequency differences. A $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSIONS

Demographic Characteristics: A total of 60 patients were enrolled in the study, comprising 30 children with nephrotic syndrome (cases) and 30 healthy age- and sex-matched children (controls). The mean age among the case group was 5.57±3.02 years, and in the control group, it was 5.73±3.10 years, with no statistically significant difference (p=0.834). The distribution of males and females in the case group was 46.7% males and 53.3% females, while in the control group, it was 50% males and 50% females, with no significant difference (p=0.796).

Table 1: Age Distribution

Group	Mean Age (years)	SD	p-value
Cases	5.57	3.02	0.834
Controls	5.73	3.10	

Table 2: Gender Distribution

Group	Male (%)	Female (%)	p-value
Cases	46.7	53.3	0.796
Controls	50.0	50.0	

Table 3: Body Surface Area

Group	Mean BSA (m²)	SD	p-value
Cases	0.80	0.20	0.119
Controls	0.72	0.20	

Table 4: Blood Pressure

Group	Systolic BP Mean (mm Hg)	Systolic BP SD	Diastolic BP Mean (mm Hg)	Diastolic BP SD	p-value Systolic	p-value Diastolic
Cases	99.93	8.49	59.87	9.81	0.020	0.010
Controls	95.27	6.42	54.20	6.16		

Table 5: Urine Protein

Group	Nil (%)	1+ (%)	2+ (%)	3+ (%)	4+ (%)	p-value
Cases	0.0	0.0	23.3	70.0	6.7	0.001
Controls	80.0	20.0	0.0	0.0	0.0	

Table 6: Serum Albumin and Cholesterol

Group	Mean Albumin (g/dl)	Albumin SD	Mean Cholesterol (mg/dl)	Cholesterol SD	p-value Albumin	p-value Cholesterol
Cases	2.98	0.24	382.40	93.80	0.001	0.001
Controls	4.22	0.67	110.90	11.42		

Table 7: IVC Diameter

Group	Inspiration Mean (cm)	Inspiration SD	Expiration Mean (cm)	Expiration SD	p-value Inspiration	p-value Expiration
Cases	0.70	0.24	0.92	0.29	0.001	0.001
Controls	0.51	0.12	0.68	0.10		

Table 8: IVC Index

Group	Mean IVCI	IVCI SD	p-value
Cases	1.07	0.39	0.001
Controls	0.44	0.19	

Table 9: IVC Volume Status

Volume Status	Cases (%)	Controls (%)	p-value
Hypovolemic	20	93.3	0.509
Euvolemic	46.7	6.7	
Hypervolemic	33.3	0.0	

Table 10: IVC Collapsibility Index

Group	Mean IVCCI	IVCCI SD	p-value
Cases	24.65	10.16	0.787
Controls	25.41	11.62	

Table 11: IVC Collapsibility Volume Status

Volume Status	Cases (%)	Controls (%)	p-value
Hypovolemic or Euvolemic	0	3.3	0.001
Hypervolemic	100	96.7	

Body Surface Area: The mean body surface area (BSA) in the case group was 0.80±0.20 m² and in the control group, it was 0.72±0.20 m², with no significant difference between the groups (p=0.119).

Blood Pressure: The mean systolic blood pressure was significantly higher in the case group (99.93±8.49 mm Hg) compared to the control group (95.27±6.42 mm Hg) (p=0.020). Similarly, the mean diastolic blood pressure was significantly higher in the case group (59.87±9.81 mm Hg) compared to the control group (54.20±6.16 mm Hg) (p=0.010).

Urine Protein: All patients in the case group had 2+ or more proteinuria, with 23.3% having 2+, 70% having 3+ and 6.7% having 4 + proteinuria. In the control group, 80% had no proteinuria and 20% had 1+proteinuria, with a significant difference between the groups (p=0.001).

Serum Albumin and Cholesterol: The mean serum albumin was significantly lower in the case group (2.98±0.24 g/dl) compared to the control group (4.22±0.67 g/dl) (p=0.001). The mean serum cholesterol level was significantly higher in the case group (382.40±93.80 mg/dl) compared to the control group (110.90±11.42 mg/dl) (p=0.001).

Inferior Vena Cava Measurements:

IVC Diameter: The mean IVC diameter at inspiration was significantly higher in the case group (0.70±0.24 cm) compared to the control group (0.51±0.12 cm) (p=0.001). Similarly, the mean IVC diameter at expiration was significantly higher in the case group (0.92±0.29 cm) compared to the control group (0.68±0.10 cm) (p=0.001).

IVC Index (IVCI): The mean IVCI was significantly higher in the case group (1.07±0.39) compared to the control group (0.44±0.19) (p=0.001). According to the IVCI, 20% of the children in the case group were hypovolemic, 46.7% were euvolemic and 33.3% were hypervolemic. In the control group, 93.3% were hypovolemic and 6.7% were euvolemic (p=0.509).

IVC Collapsibility Index (IVCCI): The mean IVCCI was 24.65±10.16 in the case group and 25.41±11.62 in the control group, with no significant difference between the groups (p=0.787). According to the IVCCI, all children in the case group (100%) were hypervolemic, while in the control group, 96.7% were hypervolemic and 3.3% were hypovolemic or euvolemic (p=0.001). (Table 1-11)

Assessment of intravascular fluid status in children with nephrotic syndrome is of utmost importance to decide on diuretic therapy in cases with significant edema. Various methods have been utilized to predict fluid change in the venous system, such as monitoring the inferior vena cava collapsibility index (IVCCI) or the diameter of the inferior vena cava (dIVC) as dynamic parameters, which are considered more practical than central venous pressure (CVP) in children and adults[1,2]. Previous studies have established the validity of IVC diameter and collapsibility index as reliable measures of intravascular volume. Horoz *et al.* (2022) conducted a study to determine the reference values for IVC and aorta diameters and the mean IVCCI in healthy, normovolemic children. The study involved 1,938 children and the collapsibility index was found to be 37.2% (SD 11.8), with significant positive correlation with age-related changes in IVC and aorta diameters. However, obtaining accurate readings in children can be challenging, particularly in those with cardiac insufficiency or heart disease, due to inter-observer variability in measurement techniques (4-7).

In our study, we found that the mean age among cases (5.57±3.02 years) and controls (5.73±3.10 years) was comparable (P=0.834), similar to findings by Akyildiz B and Ozsoylu S, who reported an average age of 58.5±28.5 months .Babaie et al. also reported a median age of 36.8 (1.5-144) months, which aligns with our findings.

Our results showed that using the IVCCI with a cut-off of 50% overestimated fluid status, as almost all children, even in the control group, were found to be hypervolemic. In contrast, the IVC index (IVCI) with a cut-off value of <0.8 indicated hypovolemia in 93.3% of children in the control group . Gupta *et al.* observed that the mean maximal IVC diameter during expiration was comparable between cases and controls, whereas the mean minimum diameter during inspiration was significantly higher in cases. This study highlights that the IVCCI, which accounts for respiratory cycle fluctuations, is a more dynamic measure compared to static IVC measurements.

Our findings differ from those of Ozdemir *et al.,* who reported no significant difference in IVCI between children with nephrotic syndrome and controls, but found significantly lower IVCCI values in nephrotic syndrome patients compared to controls. Similarly, Donmez *et al.* evaluated inferior vena cava indices in children with minimal change nephrotic syndrome (MCNS) and found no significant difference in IVCI between edematous nephrotic patients and healthy controls, although IVCCI was significantly different[9-13]. Additionally, Nalcacioglu *et al.* utilized bioelectrical impedance analysis, NT-Pro BNP and IVCI to measure body fluid volume in children with nephrotic syndrome, suggesting that these methods could complement traditional ultrasonographic measurements to provide a more comprehensive assessment of fluid status.

CONCLUSION

In conclusion, while the IVCCI appears to be a useful dynamic parameter for assessing fluid status in children with nephrotic syndrome, its overestimation of fluid Status in our study suggests a need for further refinement of its cut-off values. The IVCI, with a cut-off of <0.8, may offer a more accurate indication of hypovolemia. Future studies should aim to standardize measurement techniques and establish more precise cut-off values to enhance the reliability of these non-invasive methods in clinical practice.

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