SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Paediatric Nephrology

Role of IVC Indices to Determine the Volume Status in Edematous Nephrotic Syndrome Children

Dr. Tarannum Khondaker[1*], Dr. Mohammad Abu Hasnat[2], Dr. Shireen Afroz[3], Dr. Gulshan Nigar Chaudhury[1], Dr. Tahmina Ferdaus[4], Dr. Farhana Yesmin[4], Dr. Jannatul Ferdous[5], Dr. Keya Rani Saha[6]

[1]Associate Professor, Department of Paediatric Nephrology, Bangladesh Shishu Hospital & Institute
[2]Registrar, Department of Paediatric Nephrology, Bangladesh Shishu Hospital & Institute
[3]Professor & Head, Department of Paediatric Nephrology, Bangladesh Shishu Hospital & Institute
[4]Assistant Professor, Department of Paediatric Nephrology, Bangladesh Shishu Hospital & Institute
[5]Registrar, Department of Paediatric Nephrology, Bangladesh Shishu Hospital & Institute
[6]Medical Officer, DGHS

DOI: https://doi.org/10.36347/sasjm.2024.v10i11.010 | **Received:** 15.10.2024 | **Accepted:** 19.11.2024 | **Published:** 25.11.2024

***Corresponding author:** Dr. Tarannum Khondaker
Associate Professor, Department of Paediatric Nephrology, Bangladesh Shishu Hospital & Institute

Abstract **Original Research Article**

Background*:** Ultrasonography is a widely used tool for assessment of volume status of nephrotic syndrome in children. ***Objective: This study aims to assess the efficacy of sonographic assessment of inferior vena cava indices to detect this volume status. ***Methodology***: This cross-sectional study involved around 50 children of steroid-sensitive Nephrotic Syndrome relapse, attending the department of Pediatric Nephrology of Bangladesh Shishu Hospital and Institute. ***Results*:** About 64% reported non-hypovolemic status; 36% patients had hypovolemia on the basis of urinary indices. The mean value of Fe Na was 0.24 ± 0.19 Umol/L in non-hypovolemic group and 0.14 ± 0.16 Umol/L in hypovolemic group. On the basis of sonographic assessment of IVC Collapsibility index, 80% were in non-hypovolemic group and 20% were in hypovolemic group. Based on IVC Aortic ratio, 66% belonged to non-hypovolemic patient and 34% in hypovolemic group. Statistically significant relationship was not found between different volume status by urinary indices and IVC collapsibility index (p=0.463) sensitivity and specificity of IVCCI in relation to urinary indices was 27.7%; 84.3% and positive prediction value was 50%. ***Conclusion*:** The majority of patients with nephrotic syndrome followed non-hypovolemic status. IVC: Aortic ratio can be better tool for volume assessment in nephrotic syndrome children. However, large scale study should be executed to confirm the efficacy of this tool.

Keywords: Nephrotic syndrome, IVC indices, urinary indices, children, volume status.

INTRODUCTION

Idiopathic nephrotic syndrome in childhood is a common glomerulopathy characterized by heavy proteinuria, hypoalbuminemia, hypercholesterolemia and edema. Edema is the commonest presenting symptom for children with nephrotic syndrome with severity varying from mild facial puffiness to anasarca. Mild edema can relief on its own whereas moderate to severe edema is difficult to manage and requires diuretics or albumin therapy. Several studies illustrated that, children with nephrotic syndrome have a diversity of volume status which depends upon the pathophysiological process of edema formation (Ellis, D., 2016). The mechanisms of edema in nephrotic syndrome are still a matter of controversy. Massive proteinuria and sodium retention are the main contributing factors to the development of edema (Siddall, E.C. 2012).

It is compulsory to understand and differentiate between two pathological mechanisms which are: the volume expansion (overfilling) or intravascular volume depletion (underfilling) in patients with nephrotic syndrome to determine the rational treatment strategy for the management of edema (Keenswijk, W *et al.*, 2018). Assessment of the intravascular volume status, during the edematous phase of nephrotic syndrome is challenging when deciding on the use of diuretics or albumin infusion to control the edema (Gupta D, 2019).

However, there is no gold standard to assess the intravascular volume status due to the heterogenicity in clinical and biochemical characteristics in children with

nephrotic syndrome (Nalcacioglu, H., 2018). Patients with a hypovolemic state can present with nausea, vomiting, abdominal pain, dizziness, lethargy, cold periphery, tachycardia, low pulse volume, prolonged capillary refill time, low blood pressure, postural hypotension, and finally hypovolemic shock. Patients with hypervolemia may present with refractory edema, hypertension and dyspnea (Meena, J., 2020). Other parameters that can detect intravascular volume depletion are a rise in hematocrit (>8 to 10%) and high blood urea to creatinine ratio (Meena, J., 2020; Locham, J., 2019). Urinary electrolyte indices [Fractional excretion of Sodium (FENa) and Urinary Potassium Index (UKI)] have been suggested as reliable markers of intravascular volume status (Keenswijk, W., *et al.*, 2018). In a hypovolemic state, sodium excretion will be low while potassium excretion will be high due to secondary hyperaldosteronism while in primary sodium retention, low urinary sodium excretion will not be associated with increased urinary potassium excretion. In patients with nephrotic syndrome, the observed Fe Na is less than 1. But at the volume contracted state it becomes 0.2 - 0.5 which is a cut of value for hypovolemia. Similarly, a potassium index >0.6 or more than 60% indicates aldosterone activity in the distal tubule and is another indicator of hypovolemia (Meena, J., 2020; Locham, J., 2019). However, there are multiple limitations to the use of urinary indices in edema status including the use of diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and dietary salt intake (Sahay, M., 2011).

Nowadays, the assessment of Inferior vena cava indices (IVC indices) by using ultrasonography has been brought to light as a marker to detect intra vascular volume status. Point-of-care ultrasound (POCUS) is rapidly evolving with increasing its use in clinical practice for early detection of volume status and other pathologies. Due to technological advancement of newer handheld ultrasound device, POCUS has now become a reliable component of clinical examination at clinic as well as bed side in critical care unit (Sethi *et al.*, 2023).

Literature suggests that IVC indices can assist the complete estimation of the cardiac collapsibility index of patient's correlates with their intravascular function (Patil, S *et al.*, 2016; Mannarino, S., 2019; Dönmez, O,2001). Among the markers of IVC indices, IVC collapsibility index (IVCCI) and ratio of Inferior Vena Cava and Aorta (Ao) diameters (IVC/Ao ratio) were used commonly to determine the intravascular volume status in dehydrated and critically ill children (Patil, S *et al.*, 2016; El-Halaby *et al.*, 2022; M Kitakule *et al.*, 2010).

The inferior vena caval collapsibility index (IVCCI) is a dynamic parameter and an accurate determinant of right atrial pressure. It takes into account variations of IVC diameter over the various stages of the respiratory cycle. The results of different studies are variable and ended up with some limitations. The IVC size varies greatly between individuals and it does not correlate well with BMI or body surface area (BSA) and there is a lack of clear IVC diameter reference values for pediatric and adult populations (Ghaffari, S. *et al.*, 2012; Adewumi, A. A *et al.*, 2019).

A new parameter for body fluid status assessment, the IVC/Ao ratio was recently introduced. It can be a promising method of estimating body water status without the necessity of looking for reference values for each age group or calculating per BSA. Kosiak *et al.*, state that IVC/Ao is more specific in the assessment of body fluid status (Kosiak, W. 2008). Thus, measuring the IVC/Ao irrespective of the respiratory cycle has made the study simpler and patient-specific and does not necessitate looking at reference values for each age group [Sridhar, H. *et al.*, 2012; Sahay, M., 2011).

Few studies demonstrated the efficacy of IVC indices for the detection of intravascular volume status in nephrotic syndrome, but the results were variable with a small sample size (El-Halabi *et al.*, 2022; M Kitakule, 2010; Özdemir, K *et al.*, 2015). In this regard, this study was done find out the role of vena caval indices (IVCCI and IVC: aortic diameter ratio) in assessing volume status in children with nephrotic syndrome.

METHOD

This cross-sectional analytic study was carried out in Department of Paediatric Nephrology of Bangladesh Shishu Hospital and Institute for 12 months, from May 2022 to April 2023. The study population was children aged from 2 to 18 years, attending the Inpatient Department of Bangladesh Shishu Hospital with initial episodes and relapse of nephrotic syndrome.

All the nephrotic syndrome cases were first evaluated to determine whether they fulfilled the inclusion criteria. The parents of eligible children were explained the purpose of this study. Parents who agreed to give informed written consent were included in the study. After enrollment, history was taken from the parents regarding the age of onset and course of the disease, the onset of illness, history of vomiting, diarrhea and exposure to any drugs within one month of current illness were recorded. The eligible patients were assessed primarily and those requiring urgent resuscitation were excluded from the study. Blood pressure was measured in a comfortable posture for children in a lying position after at least 5 minutes of rest in a calm and quiet state. Blood pressure was graded in a centile chart.

After sending the sample, ultrasonography was done with SIEMENS, an Acuson NX3 Elite machine with a 2.5 -5 MHz convex transducer to detect IVC diameter and aortic diameter and IVC diameter in M mode.

Throughout the study period, 82 patients aged 2 to 18 years with initial episodes and relapse of nephrotic syndrome were screened initially. Some patients had to exit the study due to some limitations. Finally, 50 patients were included in the study.

All the information were recorded in a semi-structured questionnaire. Calculations of urinary indices parameters and sonographic parameters were done from the derived data by using the formula taken from previous literature. Patients were categorized into two groups, non-hypovolemia and hypovolemia group on the basis of urinary indices (FENa and UKI) and IVC indices (IVCCI & IVC/Ao).

Calculation of FENa & UKI by Urinary indices

Fractional excretion of sodium FENa (%):

Serum Creatinine X Urine Sodium X 100
Urine Creatinine X Serum Sodium

Urine potassium index UKI (%):

Urine Potassium X 100
(Urine sodium + Urine Potassium)

Calculation of IVCCI:

IVC Collapsibility index (IVCCI) (%):

(IVC diameter during expiration - IVC diameter during inspiration) X 100
IVC diameter during expiration

Volume status on the basis of IVCCI:

Hypovolemia: IVCCI ≥ 50% indicates hypovolemia
Non hypovolemia: IVCCI < 50% indicates non hypovolemia (either hypervolemia or euvolemia) (Gupta D *et al.,* 2019).

Calculation of IVC/Aorta index (IVC/Ao):

IVC diameter during expiration (maximum value)
Aorta diameter (maximum value)

Volume status on the basis of IVC/Ao:

Hypovolemia: <0.8 indicates hypovolemia
Non-hypovolemia: ≥0.8 or more indicates non hypovolemia (either hypervolemia or euvolemia) (Locham, 2019).

Data Processing and data Analysis:

All the data were entered into a personal computer and thoroughly checked for any possible errors. Statistical analyses were carried out by using the Statistical Package for Social Sciences (SPSS version 26.0 Chicago, Illinois). Data were expressed as numbers and percentages for categorical variables. Chi-square ($\chi 2$) test and Fisher exact test was used to see the association among qualitative variables. The sensitivity, specificity, and positive predictive value of IVCCI and IVC/aortic ratio in discrimination of volume status were calculated. ROC curve analysis was performed to investigate role of IVCCI and IVC/Aortic ratio to differentiate hypovolemic and non-hypovolemic status of Nephrotic syndrome. P value <0.05 is considered as statistically significant.

Ethics

This study utilized only medical records, it did not involve any social or legal risk to the subjects or cause any distortions of privacy. All precautions were taken so that the study did not cause any harm or delay in the treatment of the cases. All data was handled confidentially. None other than investigation regulatory authority and review committee had access to this information.

RESULT

Table 1 shows the proportion of volume status based on urinary indices among the study population. About two third of the study patients, 32 (64%) out of 50 were found to had non hypovolemia and 18 (36%) patients out of 50 had hypovolemia.

Table 2 showed the proportion of volume status among study patients on the basis of sonographic assessment of IVC Collapsibility index. Most of the patients, 40 (80%) out of 50 was in non-hypovolemic group and 10 (20%) out of 50 patient was in hypovolemic group. The mean value of non-hypovolemia in IVCCI was 33 ± 7.1 and the mean value of hypovolemia was 61 ± 5.9.

Table 3 showed the proportion of different volume status by IVC-Aortic ratio. Here, about two third of the patient 33 (66%) out of 50 patients were in non - hypovolemic patient and 17 (34%) were in hypovolemic group. The mean value of IVC aortic ratio was 0.91 ± 0.56 in non-hypovolemic status, whereas the mean value of hypovolemia was 0.66 ± 0.097.

Table 4 showed relationship between volume status by urinary indices and volume status IVC Collapsibility Index. Statistically significant relationship was not found between urinary indices and IVC Collapsibility index.

Table 5 demonstrates comparison of volume status between urinary indices and IVC/Aorta ratio. Statistically significant relationship was found between the different volume status of Urinary indices and IVC/Aorta ratio (p=0.0001).

The ROC analysis yielded an area under the curve (AUC) value of 0.569 (95% CI: 0.402-0.735), indicating that the predictive ability of the IVC collapsibility index for hypovolemia is limited. The sensitivity and specificity at the determined cut-off value of 36.0 were 50% and 62.5%, respectively. The p-value associated with the AUC suggests that the results are not statistically significant (p = 0.425).

Table 1: Proportion of different volume status by urinary indices (N=50)

Volume status on the basis of urinary indices	Number of patients (n)	Percentage (%)
Non hypovolemia UKI < 0.6 FENa <1	32	64.0
Hypovolemia UKI ≥ 0.6 FENa< 1	18	36.0

Table 2: Proportion and mean value of different volume status by IVCCI (N=50)

(IVCCI)	Number of patients n (%)	Values Mean ±SD	Max value	Min Value
Non hypovolemia IVCCI= <50	40 (80)	33 ± 7.1	49.5	22.0
Hypovolemia IVCCI = ≥50	10 (20)	61 ± 5.9	68.0	51.0

*IVCCI: Inferior Vena Caval Collapsibility Index

Table 3: Proportion and mean value of different volume status by IVC/Ao (N=50)

Volume status by Inferior vena caval aortic ratio (IVC: Ao)	No. of patients n (%)	Value Mean ± SD	Max Value	Min value
Non-hypovolemia IVC: Ao ≥0.8	33 (66)	0.91 ± 0.56	1.1	0.81
Hypovolemia <0.8	17 (34)	0.66 ± 0.097	0.74	0.4

Data were expressed as mean ± SD.

Table 4: Association of volume status between sonographic assessment of IVCCI and urinary indices (N=50)

IVC collapsibility index	Urinary indices			p value
	Hypovolemia	Non hypovolemia	Total	
Hypovolemia	5 (27.7%)	5 (15.6%)	10	p=0.463**
Non-Hypovolemia	13 (72.2%)	27 (84.3%)	40	
Total	18	32	50	

Chi square test=** was done to analyze the data.

Table 5: Association of volume status between sonographic assessment of IVC: Aortic index and urinary indices (n=50)

IVC/Aorta ratio	Urine Indices			p value
	Hypovolemia	Non hypovolemia	Total	
Hypovolemia	12 (66.7%)	5 (15.6%)	17	p=0.0001**
Non hypovolemia	6 (33.3%)	27 (84.3%.)	33	
Total	18	32	50	

Chi square test= **were done to analyze the data.

Area Under the Curve							
Test Result Variable(s): IVC collapsibility index							
AUC	**Std. Error**	**Cut off value**	**Sensitivity**	**Specificity**	**p-value**	**95% CI**	
						Lower	**Upper**
0.569	0.085	36.0	50%	62.5%	0.425	0.402	0.735

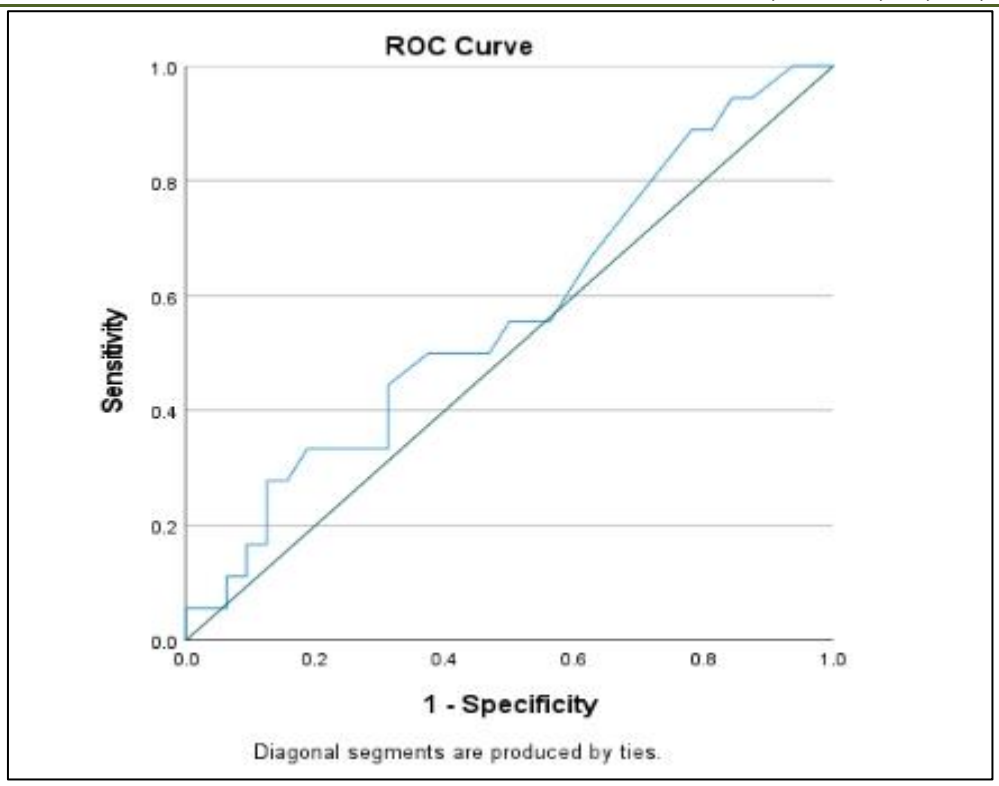

Figure 1: ROC analysis was performed to predict the best cut off value of IVC collapsibility index of hypovolemia

DISCUSSION

Volume status assessment is a challenging step in children with nephrotic syndrome. Hence, up-to-date research is seeking a new non-invasive tool that can be easily available, cheap, and effective to detect volume status in these children. However, study related to volume status assessment in nephrotic children was scarce and showed inconclusive result in various study (Naglcacliogu, 2018). Gupta D *et al.,* revealed that sonographic assessment of the inferior vena caval collapsibility index is a marker to detect volume status in nephrotic syndrome children (Gupta, 2019). Another study done by Locham showed that IVC: aortic indices are a reliable marker of volume status in nephrotic children than IVCCI. (Locham, 2019). Therefore, this study was conducted to assess the volume status in nephrotic syndrome children to determine the efficacy of sonographic assessment.

Patients were categorized into two groups; hypovolemia and non-hypovolemia based on their FENa and urine potassium index according to documented value in previously published study (Keenswijk, 2018; Locham,2019).

FENa values showed variability in many literatures which makes this a less useful indicator of volume status noted by Kerniski *et al.,* (Keenswijk, 2018). The reason for the variability of FENa result may be due to the status of early and late relapse, differential edema state and variable sodium exposure. Hence in this study, primarily UKI along with FENa was used to differentiate volume status. According to the IVCCI and IVC aortic ratio which was determined by sonography, patients were categorize again into two groups; hypovolemia and non-hypovolemic based on previous literature. (Gupta D *et al.,* 2015; Locham, 2019).

A study done by Locham *et al.,* also showed that out of 20 patients, 14 patients (70%) were in hypervolemic group based on urinary indices and only 2 patients (10%) were in hypovolemic group indicating secondary sodium retention. (Locham, 2019). Another study done in Turkey by Büyükavcı *et al.,* showed out of 32 children, 24 cases (75%) were hypervolemic. (Büyükavcı *et al.,* 2015). A recent study by Kallyani Pillai revealed most of the patients 56.1% based on FE Na and 68.3% based on UKI were in the hypervolemic group (Pillai, 2022). All these findings were consistent with our study.

Previous study done by Gupta *et al.,* revealed that about 70% of the nephrotic syndrome child were in the hypervolemic group and the mean value of IVCCI was 35. 6 ± 13 % which was similar to the IVCCI mean value of the non-hypovolemic group in current study (Gupta, 2019).

In addition, Ozdemir *et al.,* concluded that the sensitivity of IVCCI to detect volume load was 95% and the specificity was 10% (Özdemir K, *et al.,* 2015). The different result of IVCCI index in various study for detection of volume status could be due to the variation in age, body surface area, non-specific paediatric cut-off

value and variation in IVCCI throughout the respiratory cycle.

Relevant study conducted by Harshita *et al.*, focused the effectiveness of inferior vena cava and aorta (IVC/Aorta) index. Results showed the mean IVC/Aorta index in patients who had normal CVP range was 1.2 ± 0.12 SD, while in patients with low CVP, the mean index was 0.7 ± 0.09 SD; patients with high CVP, the mean index was 1.6 ± 0.05 SD (Sridhar, H *et al.*, 2012). The mean values were relatively similar to current study.

Furthermore, other study by Locham *et al.*, showed among 16 patient of nephrotic syndrome, 3 patients had IVC/Ao index in hypovolemic range. Two of the three children also had urinary indices suggestive of hypovolemia suggesting better performance of IVC/Ao (Locham J, 2019).

Meanwhile, a study done by AA Adewumi *et al.*, revealed the IVC aortic ratio in Nigerian children had a cut-off point of 0.86 with sensitivity of 96.67% and specificity of 96.67%, to predict dehydrated children (Adewumi, A.A. *et al.*, 2019).

CONCLUSION

Majority of children with nephrotic syndrome in this series were in non-hypovolemic status based on urinary indices and inferior vena caval indices. A significant association was found between urinary indices and inferior vena caval aortic ratio for volume assessment in nephrotic syndrome. Inferior vena caval aortic ratio is a better tool with 72.2% sensitivity and 84.4% specificity at its best cut-off value.

Conflict of Interest: None

REFERENCES

- Adewumi, A. A., Braimoh, K. T., Adesiyun, O. A. M., Ololu-Zubair, H. T., & Idowu, B. M. (2019). Correlation of sonographic inferior vena cava and aorta diameter ratio with dehydration in Nigerian children. *Nigerian Journal of Clinical Practice*, *22*(7), 950-956.
- Büyükavci, M. A., Çivilibal, M., Elevli, M., & Selçuk Duru, H. N. (2015). Hypo- and hypervolemic edema in children with steroid sensitive nephrotic syndrome. *Turk J Med Sci*, *45*, 178-83.
- Dönmez, O., Mir, S., Özyürek, R., Cura, A., & Kabasakal, C. (2001). Inferior vena cava indices determine volume load in minimal lesion nephrotic syndrome. *Pediatric nephrology*, *16*, 251-255.
- El-Halaby, H., Bakr, A., El-Assmy, M., Abdalla, H. A., Salem, M., & Eid, R. (2022). Inferior Vena Cava Collapsibility Index: A Precise, Noninvasive Tool for Evaluation of Edema in Children with Nephrotic Syndrome. *Indian Journal of Pediatrics*, *89*(11), 1113-1116.
- Ghaffari, S., Malaki, M., Ghaffari, M. R., & Asiaie, K. (2012). Inferior vena cava index in edematous patients. *Journal of cardiovascular and thoracic research*, *4*(3), 69.
- Gupta, D., Devpura, K., & Agrawal, K. K. (2019). Comparison of the inferior vena cava index and inferior vena cava collapsibility index obtained by ultrasound as a measure of body fluid volume status in children with nephrotic syndrome. *International Journal of Contemporary Pediatrics*, *6*(3), 129.
- Keenswijk, W., Ilias, M. I., Raes, A., Donckerwolcke, R., & Walle, J. V. (2018). Urinary potassium to urinary potassium plus sodium ratio can accurately identify hypovolemia in nephrotic syndrome: a provisional study. *European Journal of Pediatrics*, *177*, 79-84.
- Kosiak, W., Swieton, D., & Piskunowicz, M. (2008). Sonographic inferior vena cava/aorta diameter index, a new approach to the body fluid status assessment in children and young adults in emergency ultrasound—preliminary study. *The American journal of emergency medicine*, *26*(3), 320-325.
- Locham, J., Dalal, S. S., & Arora, H. S. (2019). Sodium retention and intravascular volume status in childhood nephrotic syndrome. *Int J Adv Nephrol Res*, *2*, 1-7.
- Kitakule, M., & Mayo, P. (2010). Use of ultrasound to assess fluid responsiveness in the intensive care unit. *The Open Critical Care Medicine Journal*, *3*(1).
- Mannarino, S., Bulzomì, P., Codazzi, A.C., Rispoli, G.A., Tinelli, C., De Silvestri, A., Manzoni, F., & Chiapedi, S. (2019). Inferior vena cava, abdominal aorta, and IVC-to-aorta ratio in healthy Caucasian children: Ultrasound Z-scores according to BSA and age. *Journal of Cardiology*, *74*(4), 388-393.
- Nalcacioglu, H., Ozkaya, O., Baysal, K., Kafali, H. C., 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*(1), 48-56.6
- Özdemir, K., Mir, M. S., Dincel, N., Bozabali, S., Bulut, İ. K., Yilmaz, E., & Sözeri, B. (2015). Bioimpedance for assessing volume status in children with nephrotic syndrome. *Turkish Journal of Medical Sciences*, *45*(2), 339-344.
- Patil, S., Jadhav, S., Shetty, N., Kharge, J., Puttegowda, B., Ramalingam, R., & Cholenahally, M. N. (2016). Assessment of inferior vena cava diameter by echocardiography in normal Indian population: A prospective observational study. *Indian heart journal*, *68*, S26-S30.
- Pillai, K., Jalaludeen, J., & Parvathy, V. K. (2023). Non-invasive assessment of volume status of children with edema due to steroid sensitive nephrotic syndrome using urinary indices and

inferior venacava ultrasonography. *Asian Journal of Medical Sciences*, *14*(1), 217-221.

- Sahay, M. (2011). Urinary indices in nephrotic syndrome. *Indian Journal of Nephrology*, *21*(3), 152.
- Sethi, S. K., Raina, R., Korotala, A., Rad, A. H., Vadhera, A., & Badeli, H. (2023). Point of care ultrasound in paediatric nephrology. *pediatr Nephrol*, *38*(6), 1733-1751.
- Siddall, E. C., & Radhakrishnan, J. (2012). The pathophysiology of edema formation in the nephrotic syndrome. *Kidney international*, *82*(6), 635-642.
- Sridhar, H., Mangalore, P., Chandrasekaran, V. P., & Manikam, R. (2012). Caval aorta index and central venous pressure correlation in assessing fluid status! "Ultrasound Bridging the Gap". *International Scholarly Research Notices*, *2012*.
- Tamura, H., (2021). Trends in pediatric nephrotic syndrome. *World Journal of Nephrology*, *10*(5), 88.
- Topaloĝlu, R., Saatçi, Ü., Arikan, M., Canpinar, H., Bakkaloĝlu, A., & Kansu, E. (1994). T-cell subsets, interleukin-2 receptor expression and production of interleukin-2 in minimal change nephrotic syndrome. *Pediatric nephrology*, *8*, 649-652.