CORRELATION OF ULTRASOUND MEASUREMENT OF INFERIOR VENA CAVA TO AORTA DIAMETER RATIO WITH HEMATOCRIT LEVELS AND SEVERITY OF SHOCK AMONG CHILDREN WITH DENGUE FEVER SEEN AT THE EMERGENCY ROOM OF A TERTIARY GOVERNMENT HOSPITAL

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ABSTRACT

BACKGROUND: Severe dengue is a leading cause of serious illness and death, and intensive supportive care is the most important aspect of management. Before fluid resuscitation, a baseline hematocrit is obtained, and frequent monitoring of the complete blood count is needed.

OBJECTIVE: To determine the correlation of ultrasound measurement of inferior vena cava (IVC) to aorta (Ao) diameter ratio with hematocrit levels and severity of shock among children with dengue fever.

METHODOLOGY: This is a prospective study design conducted at the Emergency Room of Philippine Children's Medical Center. Clinical data and hematocrit of the children with dengue fever aged 1 month to 17 years and 364 days old were documented. The Inferior vena cava diameter (IVC) and the Aorta (Ao) diameter ratio was determined using bedside ultrasound.

RESULTS: The IVC/Ao diameter ratio correlates with high hematocrit and dengue shock in children. There is a significantly higher proportion of subjects with a hematocrit of normal range of age among those with a ratio ≥ 1.0 . A ratio of < 0.8 is significantly associated with high hematocrit level for age. Overall, IVC/Ao diameter ratio was significantly associated with severity of Dengue illness. Sensitivity of IVC/Ao diameter ratio of < 1.00 in predicting dengue with warning signs and severe dengue was 87.7%. Specificity was higher at 97.1%. Measurement of IVC/Ao diameter ratio has high interrater and intrarater reliability.

CONCLUSION AND RECOMMENDATION: IVC/Ao diameter ratio was significantly associated with severity of dengue illness. It should be used to aid decision-making and monitor response to treatments in dengue fever.

KEYWORDS: ultrasound, inferior vena cava, Inferior Vena Cava to Aorta Diameter ratio, Hematocrit, Dengue Shock Syndrome

INTRODUCTION

The global incidence of dengue has grown dramatically in recent decades. About half of the world's population is now at risk.¹One study on the prevalence of dengue estimates that 3.9 billion people, in 128 countries, are at risk with dengue infection. Severe dengue is a leading cause of serious illness and death, most especially in Asia, particularly in the Philippines.²It is epidemic in the Philippines and considered one of its eight pervasive infectious diseases.³

The three stages of clinical presentations are classified as febrile. critical, and convalescent. The critical stage, which lasts 24-48 hours, is the most critical period, with rapid plasma leakage leading to circulatory disturbance. Patients without significant plasma leak would gradually convalesce, but those who would develop major plasma leak may deteriorate in the face of critical loss of volume.⁴Serial estimation of hematocrit is a guide to volume resuscitation during the critical phase of dengue fever, and the rise of plasma leakage.⁴ hematocrit indicates However. this needs frequent blood The turnaround time for extractions. establishing the hematocrit depends on several factors and may not be available in the initial phase of resuscitation.⁴

Many of the complications such profound shock, severe bleeding with severe disseminated intravascular coagulopathy, respiratory distress, and failure, multi-organ dysfunction of liver, kidneys and the neurological system and irreversible shock and death are preventable. Some degree of fluid overload is inevitable in patients with severe plasma leakage. The most important skill is giving patients enough intravenous fluid to maintain adequate perfusion to maintain normal vital signs, while waiting it out until plasma leakage process spontaneously reverses, at the same time avoiding excessive fluid overload.

Before fluid resuscitation, a baseline hematocrit is obtained. and frequent monitoring of the complete blood count is needed depending on the case of the patient. Aside from obtaining the hematocrit, the IVC/Aodiameter ratio can be a promising tool in objectively guiding the clinicians during the fluid resuscitation in realtime.⁵Several studies have shown the correlation of intravascular volume status with the Inferior Vena Cava (IVC) diameter in children. IVC diameter is low in children with hypovolemia.

This study aims to determine the correlation of ultrasound measurement of inferior vena cava (IVC) to aorta (Ao) diameter ratio with hematocrit levels and severity of shock among children with dengue fever seen at the emergency room of a tertiary government hospital.

Ultrasonography may be a noninvasive and objective way to assess intravascular volume, right heart function, and confirm a diagnosis of dehydration in children. Moreno noted that the IVC is a highly compliant vessel whose size varied with central venous pressure. They studied its size and dynamics in adult patients, finding that IVC diameter correlated well with its collapsibility index.⁹A study was done in 2009 also showed that bedside ultrasonographic measurement of caval index greater than or equal to 50% is strongly associated with low central venous pressure. Hence bedside measurements of inferior vena cava using ultrasound could be a non-invasive tool to determine the central venous pressure during the initial evaluation in the emergency department.¹⁰

Recently, the use of IVC diameter and collapsibility has extended to more acutely ill patients, whether in emergency medicine or surgical patients in the intensive care unit (ICU). In a prospective observational study performed in an adult ED setting, both IVC diameter and IVC collapsibility index were correlated with volume status in adult trauma patients.¹¹Yanagawa et al. reported an IVC diameter to correlate with hypovolemia in trauma patients.¹² There was also a higher mean IVC collapsibility index in the shock group.¹³Thanakitcharu et al. showed that the inferior vena cava diameter and collapsibility index is a practical noninvasive tool to evaluate the intravascular fluid volume in critically ill patients.¹¹

This was also used in the study among diarrhea patients by Modi where they investigated the accuracy of the inferior vena cava for predicting dehydration in children with acute diarrhea in limitedresource settings. They found that point of care ultrasound of Inferior Vena Cava (IVC) to Aorta (Ao) diameter ratio was statistically status.¹⁴ associated with volume Furthermore: it increases with the administration of IV boluses. Thusthe Inferior Vena Cava (IVC) to Aorta (Ao) diameter ratio, as determined by bedside ultrasound, is an objective and non-invasive method of evaluating fluid status in children.¹⁵

There were few studies done among dengue patients. A study by Thanacharwet showed that the dynamic measures to estimate changes in hemodynamic parameters and preload should be monitored to ensure adequate fluid therapy among patients with dengue, particularly patients with dengue shock.¹⁷

Raman studied the correlation of inferior vena cava ultrasound with packed red cell volume and clinical condition in children with dengue fever. The result showed that IVC collapsibility correlates with high hematocrit and dengue shock in children. Hence they concluded that the assessment of intravascular volume status by determining the IVC collapsibility using bedside ultrasound is a non-invasive tool in children with dengue fever.¹⁸

OBJECTIVES OF THE STUDY

General objective:

To determine the correlation of ultrasound measurement of inferior vena cava (IVC) to aorta (Ao) diameter ratio with hematocrit levels and severity of shock among children with dengue fever seen at the emergency room of a tertiary government hospital.

Specific objectives:

• To determine the Inferior Vena Cava to Aorta (IVC/Ao) diameter ratio of pediatric dengue patients as measured by bedside ultrasound.

- To correlate the IVC/Ao diameter ratio with the hematocrit of children with dengue fever using bedside ultrasonography.
- To correlate the IVC/Ao diameter ratio with the severity of children with dengue fever using bedside ultrasonography.
- To determine the diagnostic accuracy of the IVC/Ao diameter ratio using bedside ultrasonography, in predicting the severity of dengue illness in terms of:
 - Specificity
 - Sensitivity
 - Positive predictive value
 - Negative predictive value
 - Positive likelihood ratio
 - Negative likelihood ratio
 - Odds ratio

METHODOLOGY

This is a prospective observational study design conducted at the Emergency Room of Philippine Children's Medical Center, Agham Road, Quezon City. This study was approved by the Institutional Review Board.

Informed consent was obtained from the parents or the guardian after the patient was selected to be part of the study. Assent was also obtained on patients >= 9 years old who were cognizant or conversant during the enrollment. If immediate stabilization was needed, the ER-resident obtained the informed consent for the study. Individual pertinent demographic, clinical data such

as age, sex, weight, height, and body mass index were collected.

Clinical assessment and observation • were performed by the investigators and were documented at the time of the arrival at the Emergency Room. In the event that dengue was highly suspected, complete blood count and blood samples for dengue serology (NS1 antigen and or Dengue IgM) were taken. A total of 5 ml of blood were extracted from the patient. Anti-dengue IgM specific antibodies can be detected 3–6 days after fever onset. If the patient is on the first to the fourth day of illness, dengue NS1 was taken. If the patient is on 5th day of illness and onwards, dengue IgM was obtained. Ultrasound of Inferior Vena Cava and aorta was done thereafter. (Figure 1)

The equipment used in this study was the Sonosite portable ultrasound machine with a cardiac probe of 5-8 MHz frequency. Measurements were taken with the subjects in the supine position. The probe was placed at the subxiphoid region, just rostral or caudal to the insertion of the left renal vein into the IVC. In this view, the liver could be used as an acoustic window. No graded compression was used to displace the intestinal gas. In addition, care was taken not to compress the abdomen to avoid compressing the vessels being measured. A transverse view of the IVC and Ao was imaged. Images were recorded over several respiratory and cardiac cycles. The maximal anterior-posterior IVC diameter and descending Ao diameter were measured, placing calipers at the anterior and posterior midpoints of each vessel (Figure 2). The

IVC to aorta ratio was calculated for each child by dividing the maximal IVC diameter in centimeters by the maximal Ao diameter in centimeters.¹⁵

Measurement also taken in was longitudinal position, and measurements on both views were recorded. The examination per patient was taken three times for the intraraterreliability. Toassess the inter-rater reliability, whenever possible, each measurement of IVC/Ao ratio was to be performed by the two investigators who were blinded to each other's measurements. In case of reading discrepancies, the measurements of IVC/Ao diameter ratio taken by the primary investigator was used in the statistical analysis. Clinical, laboratory, and ultrasonography data of each patient who are positive for NS1 antigen and or Dengue IgG and IgM was analyzed. IVC and Aorta ratio taken at the emergency room was compared with the baseline hematocrit and the severity of dengue.

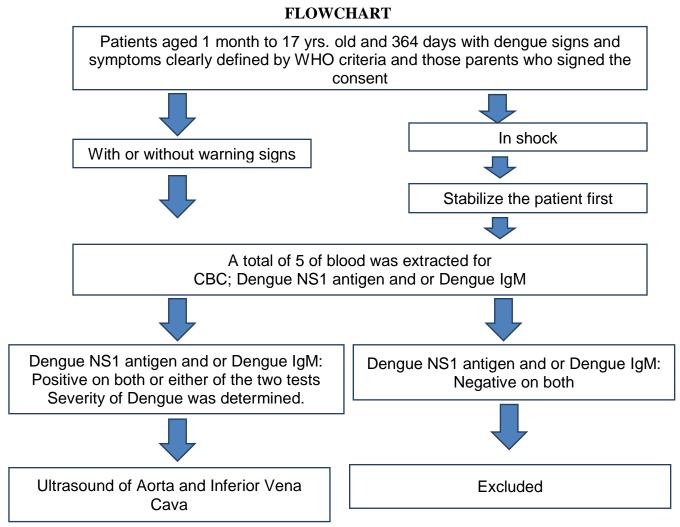


Figure 1. Selection of Participants

ULTRASOUND PROCESS

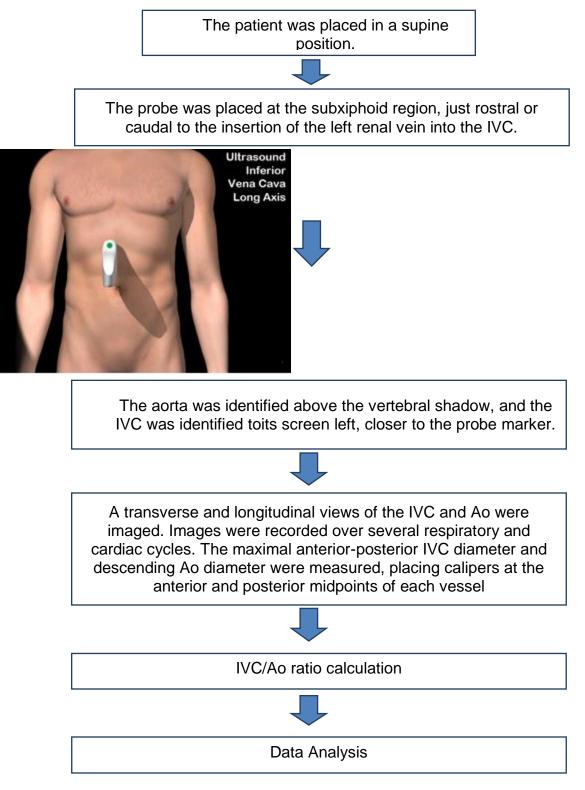


Figure 2. The Ultrasound Procedure

- The primary outcomes are the correlation coefficient of IVC to Ao diameter ratio with hematocrit and dengue severity and sensitivity, specificity, and predictive values of the ratio in predicting severe shock.
- Descriptive statistics were used to summarize the general and clinical characteristics of each participant. The clinical, laboratory and ultrasound data of children who were positive for dengue NS1 and or dengue IgG and IgM test were analyzed. Chi-square was done and Odd's ratio was computed whenever appropriate. Diagnostic accuracy parameters were determined using standard formulas. For all tests, a 95% confidence level was considered significant.Using Intraclass Correlation by2 waymixed effects model for K=2, the intrarater and interrater reliability determine calculated to the was consistency of measurements.

RESULTS

A total of 100 patients were included in the study from December 2018 to August 2019; 32 of which had Dengue Fever without warning signs, 31 with dengue fever with warning signs and 37 had dengue shock. There were more males (n=52) than females (n=48). The overall mean age of the subjects was 9.7 years. The mean age of children without warning signs, with warning signs and dengue severe are 14.7 yrs,10.3 yrs, and8.4 yrs old respectively. Of the study participants, 71 subjects presented between day 5 and day 7 after the onset of fever. Sixty-three subjects have normal BMI for age (63%). This was followed by children with severe wasting (12%) then by obese subjects (10%). (Table 1)

Table 1. Demographic and clinical
characteristics of patients $(n=100)$

Characteristics	Values
Mean age \pm SD, years.	9.74
Age range	1 month-17 yrs old
Sex	
Male	52
female	48
Anthropometrics	
BMI (kg/m ²)	
Obese	10
Overweight	7
Normal	63
Wasting	8
Severe wasting	12

IVC/Ao diameter ratio and Hematocrit levels

Table 2 shows the association of IVC/Ao diameter ratio with hematocrit levels. The ratio is significantly associated with hematocrit level. There is а significantly higher proportion of subjects with a hematocrit of normal range of age among those with anIVC/Ao diameter ratio > 1.0. Odds ratio of 108.8 means that there is 108.8 times more likely to have a hematocrit of normal range of age given anIVC/Aoratio of \geq 1.0. A level of 0.8-0.99 is not significantly associated with hematocrit level. On the other hand, anIVC/Ao diameter ratio of <0.8 is significantly associated with high hematocrit level for age (p<0.0001). It is 24.7% less likely to find a normal hematocrit for age given an IVC/Ao diameter ratio of <0.8.

Table2.IVC/AodiameterratioandHematocrit

		Hematocrit (normal range for age)	Hematocrit (high for age)	Total	p-value
USG FINDING	≥1.0	40(81%)	2 (3.9%)	42	<0.0001 Odd's ratio 108.8 (22.24-552.9)
IVC/Ao ratio	0.80- 0.99	6	12	18	0.141
	<0.8	3	37	40	<0.0001 Odd's ratio 0.0247 (0.006)
TOTAL		49	51	100	

IVC/Ao diameter ratio and Severity of Dengue Illness

Overall, IVC/Ao diameter ratio was significantly associated with severity of Dengue illness. 97% of those without warning signs had IVC/Ao diameter ratio of \geq 1.00. For those with warning signs, 63.4% had anIVC/Ao diameter ratio of from 0.8-0.99, and 93% with severe dengue had anIVC/Ao diameter ratio of <0.80. (Table 3)

Table 3. IVC/Ao diameter ratio and Severityof Dengue Illness

		Dengue fever without warning signs	Dengue with Warning Signs	Severe Dengue	Total	p-value
USG	≥1.0	34	8	0	42	<0.0001
FINDING IVC/Ao	0.80-0.99	1	14	3	18	<0.0001
ratio	<0.8	0	0	40	40	<0.0001
TOTAL	,	35	22	43	100	

overall: p < 0.0001

Diagnostic Accuracy Of US Measurement Of Aorta To IVC Diameter Ratio In Predicting Severe Dengue

Sensitivity or the probability of identifying those with true disease, of IVC/Ao diameter ratio of <1.00 in predicting dengue with warning signs and severe dengue (grouped) was 87.7%. Specificity or the probability of identifying those without the disease (without warning signs) was higher at 97.1%. Positive predictive value or diagnostic yield, or the probability of those with IVC/Ao diameter ratio of <1.00 having dengue with warning signs or severe dengue was 98.3% while negative predictive value was 80.9%

The Positive Likelihood Ratio (LR+) in our study was 30. 69, a strong evidence that those with a value of <1.00 very likely to have warning signs or severe dengue, and that we can rule in the disease. LR- was 0.127, strong evidence (near zero value) for those with ratio values of \geq 1.00 not to have warning signs or severe dengue. (Table 4) Table4.DiagnosticaccuracyofUSmeasurement of IVC diameter to Aoratio inpredictingseveredengue(Withwarningsigns + SevereDengue)

	Sensitivity	Specificity	Positive predictive value	Negative Predictive Value	Likelihood Ratio +	Likelihood Ratio (-)
Value (%)	87.7	97.1	98.3	80.9	30.69	0.127
95% confidence Interval	76.6-94.2	83.4-99.8	89.5-99.9	65.4-90.8	4.44- 212.3	0.066- 0.243

With an IVC/Ao diameter ratio value of <1.00 predicting severe dengue only, sensitivity was higher at 100%, specificity lower at 73.7%. PPV lower at 74.1% and NPV higher at 100%. LR+ was lower than when the disease classification included dengue with warning signs. This means that with a narrower disease classification, we can identify all those with severe dengue, with a bigger false positive though, and with a value of \geq 1.00, we can identify all those without severe dengue. (Table 5)

Table 5. Diagnostic accuracy of USmeasurement of IVC to Aodiameter ratio inpredicting severe dengue (Severe Dengue)

	Sensitivity	Specificity	Positive predictive value	Negative Predictive Value	Likelihood Ratio +	Likelihood Ratio (-)
Value (%)	100	73.7	74.1	100	3.8	NA
95% confidence Interval	89.7-100	60.1-84.1	60.7-84.3	89.6-100	2.46-5.86	NA

Reliability

Sixty paired measurements of IVC/Ao diameter ratios were made to measure the interrater reliability. Intra-class correlation (ICC) using 2 way mixed effects model for K=2was done. The results show a consistency rating of 0.8804. This means that there is high interrater reliability. For the intrarater reliability in 100 subjects, the Intra-class correlation (ICC) consistency rating was 0.9137 which also being interpreted as high.

DISCUSSION

As measured by bedside ultrasound, the IVC/Ao ratio is lower in children with dengue fever with warning signs and severe dengue. Futhermore, IVC/Ao ratio (<1.0) is also low in patients with high hematocrit value. Thus, the IVC/Ao ratio as determined by bedside US, is an objective and noninvasive method of evaluating severity of dengue.

This study confirms some earlier pilot data showing that the inferior vena cava collapsibility estimated by qualitative method is significant in children with dengue shock and a high hematocrit value.¹⁶ Furthermore, this is the first study to demonstrate the use of IVC/Ao ratio in establishing the severity of dengue shock as well as its correlation in hematocrit. In our study, results show that children with diagnosis of dengue with no warning signs have normal hemodynamic status and IVC/Ao ratio of ≥ 1.0 while children with severe dengue have IVC/Ao ratio of <0.8 and high hematocrit for age.

The low IVC/Ao ratio in patients with dengue is due to severe plama leakage and gastrointestinal losses such as vomiting, diarrhea and poor intake. Furthemore, bleeding could also contribute in some cases. Plasma leakage in dengue is associated with increased hematocrit and decrease in intravascular volume, leading to shock in children.⁴Hematocrit is a vital tool that guides fluid resuscitation in addition to clinical assessment of dengue fever in pediatric emergency setting. The turnaround time for estimating the hematocrit depends on a number of factors and may not be available in the initial phase of resuscitation. This study shows that IVC/Ao ratio of <0.8cm is correlated with hemoconcentration, indicating intravascular volume depletion. Bedside US has been recommended for monitoring and assessment of plasma leakage and to predict disease severity in children with severe dengue illness.²⁰

The pathogenesis of plama leakage in dengue has been extensively studied. Both innate immunity (NK cells and complement system) and adaptive immunity (humoral and cell-mediated immunity) play a role in the pathogenesis of DHF/DSS. Cytokines are implicated in the pathogenesis of vascular compromise and hemorrhage in dengue virus infection. Dengue viral infection causes the release of both inflammatory and inhibitory cytokines, and the net outcome will depend on the balance of cytokine actions. The levels of T-cell activation markers (soluble IL-2 receptor, soluble CD4 and CD8, IL-2, IFN- γ), IFNmonokines (TNF α. β), and granulocyte-macrophage colony-stimulating factor (GM-CSF) are increased with even

higher levels present in patients who develop DHF/DSS. Elevated IL-6 levels are associated with a higher incidence of both shock and ascites. Similarly, high levels of IL-8 can be recovered from the serum and pleural fluid of patients with DSS activation .Complement mediated by nonstructural viral protein NS1 leads to local and systemic generation of anaphylatoxins and terminal complement complex (SC5b-9), which may contribute to the pathogenesis of the vascular leakage that occurs in patients with DHF/DSS (16).Endothelial cells also undergo apoptosis, which causes disruption of the endothelial cell barrier and the syndrome of generalized vascular leakage.²¹

Assessment of the size of the inferior vena cava (IVC) and its change in diameter in response to respiration have been investigated as a tool to screen for severe hypovolaemia, predict fluid responsiveness (FR) and assess potential intolerance to fluid loading. IVC size, collapsibility (IVCc) and distensibility (IVCd) have gained acceptance by emergency and intensive care unit (ICU) clinicians as fluid responsiveness predictors in patients with shock. The ease acquisition. reproducibility of of measurements and increasing availability of ultrasound devices have supported the expansion of its use.²²

This study however was designed around a novel parameter: the ratio between the IVC and Ao diameters. The premise stems from the fact that the IVC and Ao diameter will be different in each child, possibly correlating with factors such as age, gender, weight, height and body surface area.²³ However, the Ao diameter was predicted to be fairly stable within each child despite hydration because it is a vessel with low compliance, especially when compared to IVC. To address the question if Ao diameter could be affected by intravascular depletion and resultant activation of tachycardia and the sympathetic system, Sonneson et al found that the sympathetic stimulation did not alter the mechanical properties of the abdominal aorta.²⁴ Furthermore, Yanagawa et al reported a study of adults in hypovolemic shock in which the diameter of the abdominal aorta remained constant despite large volumes of blood loss.¹² Hence Ao diameter should not change much with the changes in the intravascular volume. In our study, the Ao diameter was found to remain stable in each subject. Thus, Ao diameter serves as an internal control for each child. The aorta is a no collapsible structure and maintains a relatively constant diameter irrespective of the fluid status. The aortic diameter correlates with BSA, age, and sex of the patient. Kosiak et al. research study states that IVC/Ao is more specific in the assessment of body fluid status. 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.²⁵

A study done by Sridhar et al shows that the mean IVC/Ao in euvolemic patients is 1.2 ± 0.12 SD, hypovolemic is $0.7 \pm$ 0.09 SD, and volume overloaded is $1.6 \pm$ 0.05 SD, respectively.²⁶ The utility of IVC/Ao in trauma patients by Son et al., quoted that non trauma patients had a mean IVC/Aorta index of 1.26 ± 0.17 SD and trauma patients had a mean index of 0.80 ± 0.33 SD.²⁷ Sonographic IVC/Ao for fluid status in young individuals from the American Journal of Emergency Medicine concluded that for the healthy young population, the IVC/Ao reference value is 1.2 ± 0.17 SD. The IVC/Aoratio seems to play a very important role in diagnosing fluid status in emergency patients.

In our study, it was observed that the IVC/Ao ratio \geq 1.0 is observed in dengue without warning signs and those with normal hematoctritvalues for age while those with severe dengue and significant hemoconcentration had IVC/Ao diameter ratios of <0.8.

Our study showed that the IVC/Ao diameter ratio of <1.00 in predicting dengue with warning signs and severe dengue (grouped) was 87.7%. While the specificity or the probability of identifying those without the disease (without warning signs) was higher at 97.1%. Positive predictive value or diagnostic yield, or the probability of those with IVC/Ao diameter ratio of <1.00 having dengue with warning signs or severe dengue was 98.3% while negative predictive value was 80.9%. With a ratio value of <1.00 predicting severe dengue only, sensitivity was higher at 100%, specificity lower at 73.7%, PPV lower at 74.1% and NPV higher at 100%.

Intraobserver and interobserver reliabilities were measured. This study showed a high interrater and intrarater agreement. Previous researches demonstrated good interobserver agreement

in the measurement of IVC as performed by emergency physicians.²⁸ pediatric Measurements of IVC/Ao diameter taken by emergency physicians has good the interrater reliability.²⁹ Furthermore, bedside US and the measurement of IVC/Ao ratio can be ascertained in the first few minutes as assessment and initial steps of resuscitation are performed and can provide valuable supportive data regarding the need for fluids. The simplicity of the examination technique with quite constant measurement eliminate points can the examiner dependence. The IVC/Ao index seems to be more adequate and correlates more precisely with the clinical course^{.25}

CONCLUSION

The IVC/Ao ratio correlates with the severity of dengue fever and with the hematocrit in the emergency setting. Overall, the IVC/Ao diameter ratio was significantly associated with the severity of dengue illness. Those without warning signs had IVC/Ao diameter ratio of ≥ 1.00 . For those with warning signs, 63.4% had an IVC/Ao diameter ratio from 0.8-0.99, and 93% with severe dengue had an IVC/Ao diameter ratio of <0.80.Thus, the IVC/Aodiameter ratio is a helpful noninvasive bedside tool which supplements the clinical assessment of intravascular volume children with status in dengue shock.Knowing the IVC/Ao ratio would prompt the clinicians to be more aggressive in the management of severe dengue at the ER level.

RECOMMENDATIONS

Based on this study, the following are the recommendations:

- 1. The Emergency department should dedicated ultrasound systems have for Bedside bedside use. ultrasonography should be incorporated in the skills of consultants, residents and fellows. It should used be to aid decision-making monitor and The response to treatments. physician can utilize their history and physical examination findings and integrate these with their ultrasound findings into the patient's assessment.
- 2. Despite the increasing incorporation of handheld ultrasound and bedside ultrasonoraphy in multiple areas of medicine, formal evaluation in methods to generalize this technique is warranted.
- 3. Ultrasound of IVC and aorta should be done in suspected dengue cases. If the IVC/Ao ratio is <0.8 cm, a referral to critical care division should be done.
- 4. More data are needed to establish normal values in children with euvolemia and no normograms yet exist for the IVC/Ao ratio in either children or adults.

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