Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 04, 2023

Use of vasoactive inotropic score (VIS) as outcome predictor in fluid refractory septic shock in children in PICU of a tertiary care hospital

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ABSTRACT

Background: This study was undertaken in a teaching hospital in Kolkata to use Vasoactive Inotropic Score (VIS) as outcome predictor in fluid refractory septic shock in children admitted in PICU.

Methodology: A prospective study conducted in the Department of Paediatrics of Dr. B C Roy Post Graduate Institute of Paediatric Sciences, Kolkata, India from August 2018 to June 2020. 360 Children between the age of 12 month to 12 years were included in the study. Categorical variables were expressed as difference of mean VIS score between dead and survived which was primary outcome using Student t test and correlation between VIS score and length of stay (LOS), which was secondary outcome for the study, was studied using Pearson's correlation coefficient.

Results: Present study showed mean VIS 6 hr was 41.10 among dead patient and in survived patients it was 28.30. This difference of mean was statistically significant ($p<0.0001$). Mean VIS 24 hr was 69.56 among dead and in survived patients the mean VIS 24 hr was 45.79 and

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this was statistically significant (p<0.0001). Mean VIS 48 hr was 91.03 among expired and 45.99 among survived patients and again this was statistically significant (p<0.0001).

Conclusions: Mean VIS scores at 6 hr, 24 hr and 48 hr was higher in children who died as compared to children who survived and the difference in mean was statistically significant (p<0.001) in resource poor setting with high mortality in fluid refractory septic shock. VIS score can provide prediction of outcome in septic shock, especially in the settings with high mortality and poor resource.

Keywords: septic shock, VIS score (vasoactive inotropic score), sepsis, fluid refractory shock.

INTRODUCTION

Paediatric sepsis and septic shock remain a major cause of morbidity and mortality worldwide, despite advances in vaccines, antibiotics, and intensive care. Sepsis accounts for about 6 million neonatal and childhood deaths a year, accounting for 60-80% of annual child mortality(1). As per Lodha et al(2) that prevalence of septic shock in India is 40%. Timely management with fluids, vasopressors, and antibiotics along with good supportive care has always been the cornerstone of treatment to improve outcomes. However, over the last decade, management of septic shock has undergone a paradigm shift from protocoled guidelines-based approach like early goal-directed therapy to an individualized physiology-based approach. The focus now is also moving away from aggressive fluid and transfusion targets to a more conservative approach.

Septic shock is often a unique combination of distributive, hypovolemic and cardiogenic shock. Currently, no uniform, validated measure or scoring system exists to describe the magnitude of hemodynamic support required in paediatric sepsis.

A validated score that accurately describes cardiovascular dysfunction and correlates with other clinically relevant outcomes such as duration of mechanical ventilation and ICU stay could be used to identify high-risk patients and as an outcome in research and quality improvement.

One candidate scoring system was recently proposed by Gaies et al for use in infant cardiac surgery is VIS, expanded from the previously described Inotropic Score, quantifies the amount of cardiovascular support required by infants postoperatively and includes dopamine, dobutamine, epinephrine, milrinone, vasopressin, and norepinephrine(1). Gaies et al study

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confirms the association between VIS and clinical outcomes after paediatric cardiac surgery for the first time in a multi-institutional cohort.(3)

VIS is calculated as:

VIS= Dopamine (µg/kg/min)
+Dobutamine (µg/kg/min)
+100 × Noradrenaline (µg/kg/min)
+100 × Adrenaline (µg/kg/min)
+10× Milrinone (µg/kg/min)
+10000 ×Vasopressin (µg/kg/min) (1,3)

MATERIALS AND METHODS

A prospective study conducted in the Department of Paediatrics of Dr. B C Roy Post Graduate Institute of Paediatric Sciences, Kolkata, India from August 2018 to June 2020. 360 Children between the age of 12month to 12 years with fluid refractory septic shock admitted to PICU were included in the study.

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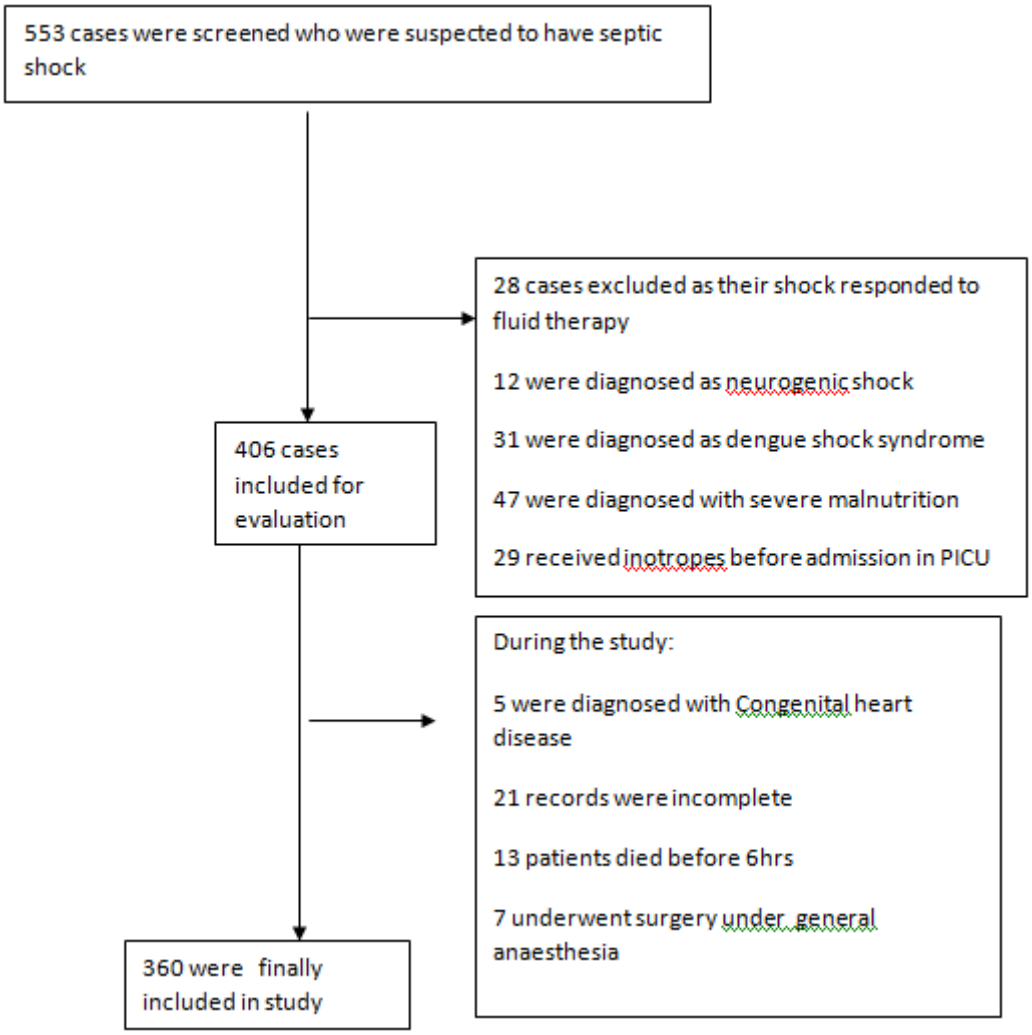

Figure 1: Recruitment of study participants

Inclusion criteria

Children from more than 12 months and less than 12 years who were be admitted to PICU of this hospital during the study period and found to have fluid refractory septic shock(4), fulfilling criteria of sepsis with shock not responding to standard fluid resuscitation, defined as per international paediatric sepsis consensus(5).

Fluid-refractory shock defined as the presence of persistent signs of shock despite at least 60 ml/kg IV fluid boluses (1). Such an aggressive stand on fluid resuscitation in septic shock has recently been questioned by the Fluid Expansion as Supportive Therapy (FEAST) trial (6), which demonstrated increased mortality in children who received fluid boluses as compared to maintenance fluids, particularly in malnourished and anaemic children. So, considering this, children who received 20-60ml/kg of bolus were also included in the study.

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Exclusion criteria

Children who had received inotropes before getting admitted to PICU, who had congenital heart disease, Down's syndrome or any other congenital malformations or syndrome, severe acute malnutrition, dengue fever and who underwent surgical intervention with general anaesthesia were excluded from the study.

VIS scoring: was done at 1, 6, 24 and 48 hrs after inclusion into study as described by Gaies, et al.(3)

A study proforma was created before patient recruitment and detailed history was entered in it. General institutional PICU protocols for sepsis including an activation process for suspected sepsis was followed. With clinical indications for sepsis, treatment was done following international guidelines for recognition and treatment of paediatric septic shock(7). Primary outcome in this study was death/survival during hospitalization. Secondary outcome was LOS.

Some patients who had a cardiac arrest in the first 48 hours, subsequent VIS following the arrest event was excluded from analysis for the composite outcome but was included in the analysis for ICU LOS.

VIS Scoring was done and compared with respect to mortality rate in children with fluid refractory septic shock. There is no universal cut off value for high or low VIS Score in fluid refractory septic shock. But Haque et al used VIS score of 20 to define high and low scores in their study(8). Mean VIS scores at 1hr, 6hr, 24hr and 48 hr of patients who died was compared with patients who survived.

Statistical Analysis

For statistical analysis data were entered into a Microsoft Excel spreadsheet and then analyzed by SPSS (version 24.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Correlation was calculated by Pearson's correlation analysis. Explicit expressions that can be used to carry out various *t*-tests are given below. In each case, the formula for a test statistic that either exactly follows or closely approximates a *t*-distribution under the null hypothesis is given. Also, the appropriate degrees

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of freedom are given in each case. Each of these statistics can be used to carry out either a one-tailed test or a two-tailed test.

Once a *t* value is determined, a *p*-value can be found using a table of values from Student's t-distribution. If the calculated *p*-value is below the threshold chosen for statistical significance (usually the 0.10, the 0.05, or 0.01 level), then the null hypothesis is rejected in favour of the alternative hypothesis. The p-value ≤ 0.05 was considered statistically significant.

RESULTS

Out of 360 patients in the study population, 48% (n=141) were female and 52% (n=209) were male. Majority of children in study population were in the age group of 1 to 2 yr.184(51.1%) patients had 1 to 2 years of age, 69(19.2%) patients had 2.1 to 5 years of age and 107(29.7%) patients had > 5yr of age.

Mean fluid bolus received by patients was – 38.6 ml/kg in the 1st 24 hrs of admission in PICU

Table 1: Spectrum of diseases in the study population

Diagnosis	**Frequency**	**Percent**
Age	29	8.1%
Ards	20	5.6%
Encephalitis	8	2.2%
Measles pneumonia	17	4.7%
Meningitis	45	12.5%
Peritonitis	12	3.3%
Pneumonia	161	44.7%
Pneumonia with pneumothorax	20	5.6%
Pneumothorax	4	1.1%
Pyothorax	8	2.2%
Septicemia	28	7.8%
Uti sepsis	4	1.1%
Varicella pneumonia	4	1.1%
Total	360	100.0%

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Among dead patients, the mean VIS 1 hr (mean±S.D.) was 10.36±3.1537. In survived patients, the mean VIS 1 hr (mean±S.D.) of patients was 11.2923±1.8778. Difference of mean VIS 1hr between patients who died and who survived was statistically insignificant (p value-0.12). In dead patients, the mean VIS 6 hr (mean±S.D.) was 41.1000±24.5624. In survived patients, the mean VIS 6 hr (mean±S.D.) of patients was 28.3000±19.7357. Difference of mean VIS 6hr between patients who died and who survived was statistically significant (p<0.0001). In the dead patients, the mean VIS 24 hr (mean±S.D.) of patients was 69.5696±26.6996. In survived patients, the mean VIS 24 hr (mean±S.D.) of patients was 45.7923±31.3983. Difference of mean VIS 24 hr between patients who died and who survived was statistically significant (p<0.0001). Among dead patients, the mean VIS 48 hr (mean±S.D.) of patients was 91.0310±17.1978. In survived patients, the mean VIS 48 hr (mean±S.D.) of patients was 49.9923±41.8118. Difference of mean VIS 48 hr between patients who died and who survived was statistically significant (p<0.0001).

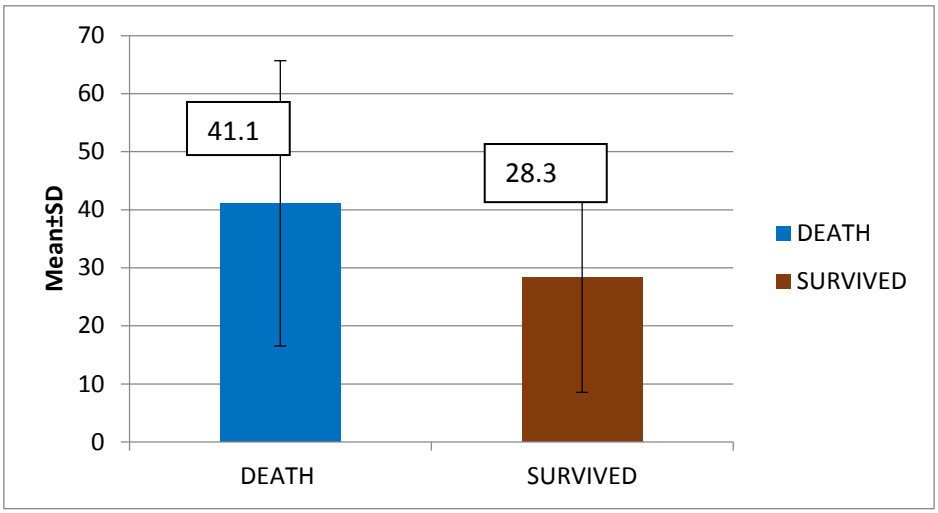

Figure 2: Mean VIS 6 Hr in dead patients Vs survived patients

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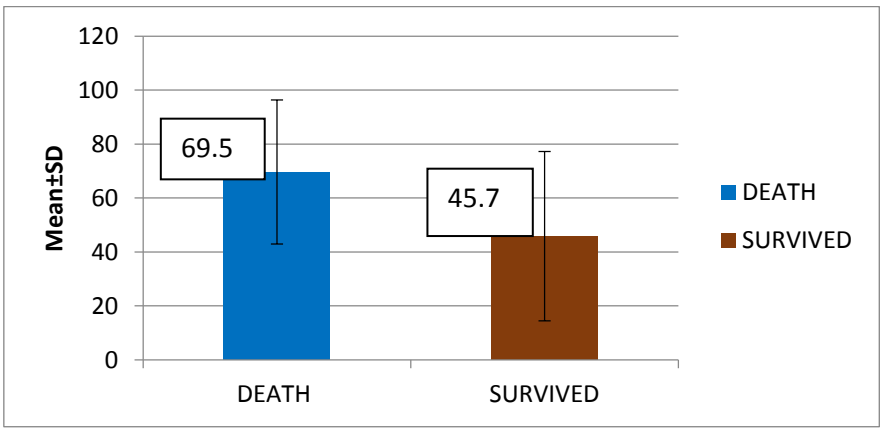

Figure 3: Mean VIS 24 Hr in dead patients Vs survived patients

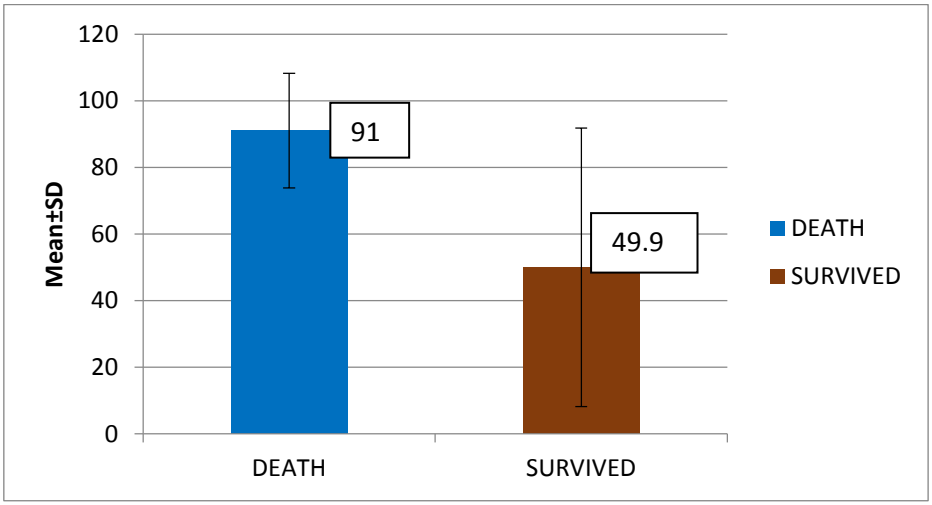

Figure 4: Mean VIS 48 Hr in dead patients Vs survived patients

Table 2: Correlation of VIS 1hr, VIS 6hr, VIS 24 HR and VIS 48 HR with length of stay (LOS)-HRS

		Length of stay (LOS)-hours	Remarks
VIS 1hr	Pearson Correlation Coefficient (r)	0.341	Positive Correlation
	p-value	<0.001	Significant
	Number	360	
VIS 6hr	Pearson Correlation Coefficient (r)	-0.43	Negative Correlation
	p-value	0.412	Not Significant
	Number	360	

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VIS 24 HR	Pearson Correlation Coefficient (r)	-0.330	Negative Correlation
	p-value	0.362	Not Significant
	Number	360	
VIS 48 HR	Pearson Correlation Coefficient (r)	-0.480	Negative Correlation
	p-value	0.539	Not Significant
	Number	356	

Table 3: Spectrum of various inotropes used among the study population

DOPAMINE	100%	360
DOBUTAMINE	21.7%	79
NORADRENALINE	43.7%	157
ADRENALINE	34.1%	123
MILRINONE	8.9%	32

Table 4: Distribution of mean VIS_1hr OUTCOME: Group

		Number	**Mean**	**SD**	**Minimum**	**Maximum**	**Median**	**p-value**
MEANS VIS_1hr OUTCOME	DEATH	230	10.3652	3.1537	10.0000	14.0000	10.0000	0.12
	SURVIVED	130	11.2923	1.8778	10.0000	14.0000	10.0000	

Table 5: Distribution of mean of VIS 6 hr : outcome group

		Number	**Mean**	**SD**	**Minimum**	**Maximum**	**Median**	**p-value**
VIS 6hr	DEATH	230	41.1000	24.5624	10.0000	95.0000	44.0000	<0.0001
	SURVIVED	130	28.3000	19.7357	10.0000	65.0000	14.0000	

Table 6: Distribution of mean of VIS 24 HR: outcome group

		Number	**Mean**	**SD**	**Minimum**	**Maximum**	**Median**	**p-value**
VIS 24HR	DEATH	230	69.5696	26.6996	34.0000	110.0000	74.0000	<0.0001
	SURVIVED	130	45.7923	31.3983	5.0000	95.0000	55.0000	

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Table 7: Distribution of mean of VIS 48Hr: outcome group

		Number	Mean	SD	Minimum	Maximum	Median	p-value
VIS 48 HR	DEATH	226	91.0310	17.1978	10.0000	114.0000	95.0000	<0.0001
	SURVIVED	130	49.9923	41.8118	0.0000	104.0000	32.0000	

DISCUSSION

In paediatric sepsis, there is a need for validated surrogate outcome measures. VIS was validated for such purposes of prediction of outcome in paediatric septic shock by McIntosh et al(9). Although VIS has been validated in paediatric cardiac surgery(3), and has been used in previous studies of paediatric patients with severe sepsis to describe the severity of illness and as a measure of hemodynamic support (10), only two prior study by Haque et al (8) and McIntosh et al (9) has shown an association between maximal VIS and outcomes in paediatric sepsis. This study complements the study by Haque et al(8) done in a resource-poor setting with high mortality and McIntosh et al (9) done in a resource-rich setting with a medically complex, low mortality cohort of children with septic shock.

The results obtained in this study has been discussed below-

VIS 1hr and outcome: In this study mean VIS at 1 hr among patient who died was 10.36, while mean VIS at 1 hr among patient who survived was 11.29. Finding of this study shows that VIS at 1 hr is associated with lower mortality which was statistically insignificant(p-value0.32). This finding is was in corroboration with observation by Haque et al(8) in a study at Karachi, Pakistan and McIntosh et al (9) in the study at Colorado .

VIS 6hr and outcome: In this study mean VIS at 6 hr among patient who died was 41.1000±24.5624, while mean VIS at 6 hr among patient who survived was 28.3000±19.7357. Finding of this study shows that higher VIS at 6 hr is associated with mortality which was statistically significant ($p<0.001$). This finding is was similar to as observed by Haque et al(8) and by McIntosh et al (9).

VIS 24hr and outcome: In this study mean VIS at 24 hr among patient who died was 69.5696±26.6996., while mean VIS 24 hr among patient who survived was 45.7923±31.3983. Finding of this study shows that higher VIS at 24 hr is associated with mortality which was statistically significant ($p<0.001$).This finding is was similar to as observed by Haque et al(8) in a study at Karachi, Pakistan and McIntosh et al (9) in a study at Colorado.

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VIS 48 hr and outcome: In this study mean VIS at 48 hr among patient who died was 91.0310±17.1978, while mean VIS 48 hr among patient, who survived was 49.9923±41.8118. Finding of this study shows that higher VIS at 48 hr is associated with mortality which was statistically significant ($p<0.001$). This finding is was similar to as observed by Haque et al(8) at Karachi and McIntosh et al (9) at Colorado.

Correlation between VIS 1hr and LOS (length of stay): A Positive Pearson's correlation coefficient (r value +0.34), with $p<0.001$ found between VIS 1 hr vs. length of stay (LOS) and it was statistically significant ($p<0.0001$). Thus, patients with higher VIS 1 hr had longer LOS as compared to those patients with lower VIS score. This finding is was similar to as observed McIntosh et al (9) and by Haque et al(8).

Correlation between VIS 6 hr and LOS (length of stay): A Negative Pearson's correlation coefficient (r value -0.43), with p value 0.421 found between VIS 6 hr vs. length of stay (LOS) and it was statistically not significant (p 0.421) in this sample population. Thus, no correlation could be established between VIS 6 Hr and LOS.

Correlation between VIS 24hr and LOS (length of stay): A Negative Pearson's correlation coefficient (r value -0.33), p value 0.362 found between VIS 6 hr vs. length of stay (LOS) and it was statistically not significant (p 0.362) in this sample population. Thus, no correlation could be established between VIS 24 Hr and LOS in this study population.

VIS 48 hr and LOS (length of stay): A Negative Pearson's correlation coefficient (r value -0.48), p value 0.539 found between VIS 6 hr vs. length of stay (LOS) and it was statistically not significant (p 0.362) in this sample population. Therefore, no correlation could be established between VIS 48 Hr and LOS in this study population. Thus, in this study our objective of comparison of VIS score and outcome, showed that those patients who died had higher VIS score at 6hr,24hr and 48hr as compared to those who survived.

But correlation between VIS score and LOS could not be established in the study population, as Pearson's correlation coefficients(r) value showed negative correlation between VIS score and LOS which was not statistically significant (p value >0.05). This may be due to unusually high mortality in this season due to pneumonia in our institute and across many centers in Kolkata. This finding is not in concordance with McIntosh et al (9) in her study at Colorado

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,which showed prolonged duration of stay in patient with higher VIS at 48 hr. It may also be due the study was done in setting with low mortality in septic shock and there is variation in severity of sepsis in different cohorts.

Limitations noted were –firstly, it was a single-centre study from a tertiary children's hospital and may not be generalized to all institutions that care for pediatric sepsis patients. Secondly, data were collected retrospectively from case sheets. Thirdly, as is true in all observational studies, treatments were not dictated by the study, so individual clinician and institutional practices such as threshold for initiation of cardiovascular support may have affected the VIS. Fourthly, although patients diagnosed with dilated cardiomyopathy/myocarditis were excluded from the study as they had cardiogenic shock, all patients did not have an objective measure of cardiac function so we were unable to draw conclusions between groups of patients with and without myocardial dysfunction. Finally, due to the lack of long-term follow-up, we were unable to assess the association of VIS with longer term mortality after hospitalization or functional outcomes. There are only two previous studies on association between VIS score and outcome in septic shock.

CONCLUSION

Higher VIS scores at 6hr, 24hr and 48 hr were observed in patients who died as compared to who survived of fluid refractory septic shock. The result of this study shows that high VIS scores is associated with poorer outcome in resource poor settings in fluid refractory septic shock, which is in synchrony with the literature available.

VIS score can provide prediction of outcome in septic shock, especially in the settings with high mortality and poor resource. It can be helpful in early and appropriate mobilisation of manpower and equipments for management of patients with septic shock.

Ethical approval: The study was approved by the Institutional Ethics Committee and Institutional scientific committee.

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