

A Prospective, Observational Study of Correlation of Clinico-Patho-Radiological Parameters with Severity and Outcome among Children Suffering From Viral Haemorrhagic Fever

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Abstract

Original Research Article

Viral haemorrhagic fever illness is one of the most important etiological factors for paediatric intensive care unit admission. Detecting early prognostic factors for identifying the severity of viral haemorrhagic fever illness can reduce the associated paediatric mortality. Hence, the aim of our study was to compare and correlate the severity of VHF (in terms of PRISM III score) in endemic region of India with some pathological and radiological parameters in order to have equivalent judgement of prognosis and outcome. It was prospective observational study conducted in Paediatric Intensive Care Unit. Children satisfying inclusion criteria during the study period with probable viral haemorrhagic fever were evaluated for severity of illness using PRISM III Score followed by radiological investigations (chest x-ray and USG abdomen) and pathological investigations (serum aminotransferase levels) along with routine treatment protocol. Out of 94 cases, 36% had PRISM III score between 0-10, 53% between 11- 20 and 11% between 21- 30. Presence of pleural effusion on x-ray, ascites, increased gall bladder wall oedema on USG and elevated aminotransferase levels were found more in children with high PRISM III score in a statistically significant manner. High PRISM III score was associated with longer duration of stay in the PICU. The difference in duration of PICU stay is attributed to increased mortality in children with high PRISM III score. There is strong correlation of high PRISM III score with pleural effusion, ascites, gall bladder wall oedema and raised serum aminotransferase levels. Hence, these investigations can be considered to decide the severity of VHF wherever PRISM III evaluation is not possible. This will help to reduce paediatric patient's mortality in developing countries.

Keywords: PRISM III Score, Viral Haemorrhagic Fever, Dengue Fever.

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INTRODUCTION

Paediatric critical care is a dedicated speciality and delivers its services through speciality units within tertiary care centres. In the tropical countries like India, the major paediatric intensive care unit (PICU) admissions are related to infectious aetiology with high mortality. For the children who are admitted with dengue or dengue like illness, the progression of the disease is very fast. In this illness, the progressive capillary leak, bleeding manifestation, shock, acute respiratory distress syndrome (ARDS) warrants early hospitalization and specialized PICU care. Reported case fatality rates for the world are approximately 1%. But in India, the focal outbreaks have reported case-fatality rates of 3-5 % [1]. There are previous studies

which demonstrated early prognostic factors for the severity of viral haemorrhagic fever (VHF) illness. In various regions of India, studies are done to predict the PICU outcome of VHF- dengue fever but only few studies have used systemic scoring for the VHF patients. The initial assessment and judicious decision for the intensive care is very crucial in terms of saving life and also preventing guardians from unnecessary burden of PICU cost, emotional trauma [2]. In India where tertiary care centres are limited, the crucial decision for the PICU admission and the prediction of the associated morbidity/mortality is always challenging.

Scoring systems are useful for making triage decisions and assessing the performance of an intensive care unit (ICU), but they are of limited use in predicting prognosis in individual case [3]. Paediatric Risk of Mortality (PRISM) system is a revision of the Physiologic Stability Index (PSI) which assesses the severity of illness in a population of paediatric patients [4].

Hence, the aim of our study was to compare and correlate the severity of VHF (in terms of PRISM III score) in endemic region of Andhra Pradesh, India with some pathological and radiological parameters in order to have equivalent judgement of prognosis and outcome.

AIMS AND OBJECTIVES

- To correlate severity of illness (in terms of PRISM III score) with radiological (Ultrasonography-USG/X ray Chest) and pathological (aminotransferases levels) parameters.
- To correlate severity of illness (in terms of PRISM III score) with outcome of the study (in terms of mortality and length of stay in PICU).
- To discuss the formulation of early predicting factors of severity of the disease.

MATERIAL AND METHODS

It was prospective observational study conducted in Paediatric Intensive Care unit of Lotus Children's Hospital, Hyderabad. The duration of study was fourteen months. Sample size was calculated using specific formula described in previous studies. The total proportionate sample was 90 paediatric patients, and to overcome the dropouts, sample size was increased to 100. Approval of Institutional human research ethics committee was obtained and written informed consent of enrolled patient's guardian (mostly parents) were taken before conducting the study. 102 children were admitted to the Paediatric Intensive Care unit with probable viral haemorrhagic fever during the study period. All children aging between 1 month and 12 years admitted to Paediatric Intensive Care Unit and satisfying the probable case definition criteria of Viral/Dengue fever by World Health Organization (WHO) were included in the study. Children with associated sepsis and other co-morbidity or pre-existing illnesses (congenital heart disease, renal abnormalities, liver disease and haematological disorders) were excluded. Detailed history of these children regarding chief complaints, duration of illness and clinical manifestations was noted. On admission, all children admitted to PICU during the study period with probable viral haemorrhagic fever were evaluated for severity of illness using PRISM III Score followed by radiological investigations (chest x-ray and USG abdomen) and pathological investigations (serum aminotransferase

levels) along with routine treatment protocol. The data of all PICU admitted children were collected using MS excel sheet and analysed using SPSS version 6.0 for statistical analysis. The Correlation Coefficient was calculated by Spearman Rho Correlation Coefficient Test and P value < 0.01 considered statistically significant.

RESULTS

A total of 102 cases were enrolled in the study out of which 7 cases were discharged against medical advice before 8 hours of PICU stay and 1 case died before 8 hours of PICU stay. Total 94 cases were followed and analysed during this study period. Out of 94, majority were between age of 6-12 years (38.2%), 27.5% of children were infants and 30.8% were between 1-5 years. Mean age of the study population was 4.8 years. The youngest patient was 3 months old. The sex wise distribution said that out of 94 children, 54 (57%) were males and 40 (43%) were females (sex ratio 1.35:1). Maximum children were brought to the hospital on 4th day of fever (25 i.e. 27 %). 46 % children presented during 4th – 6th day of fever. Mean day of presentation with fever was 6.5th day. Main chief complaints on admission were fever, mucosal bleeding, shock and altered sensorium.

All 94 cases admitted with probable VHF, were subjected to PRISM III scoring to prognosticate the severity of illness. Out of which, 34 (36%) had PRISM III score between 0-10, 50 (53%) children had PRISM III score between 11- 20 and 10 (11%) had PRISM III score between 21- 30. Among the radiological investigations, pleural effusion on chest x ray was found in 51 (53%) children. On USG study, ascites was seen in 66 (70%) and gallbladder wall oedema in 26(28%) children. The various laboratory abnormalities in the study population on admission were thrombocytopenia (90, i.e. 96%), metabolic acidosis (51, i.e. 54%), hypoxia (48, i.e. 50%) and altered coagulation profile (45, i.e. 48%). Abnormal Renal Function Test, i.e. elevated BUN was present in 53(56%) and serum creatinine elevated in 22(23%) children.

Among children with PRISM III score between 0 to 10, pleural effusion on x ray was found only in 5 (15%) of population, while PRISM III score between 11-20 showed effusion in 38 (76%). All cases with PRISM III score in between 21-30 i.e. 10 (100%) had pleural effusion. The correlation coefficient by Spearman's Rho for all three groups (0-10, 11-20 & 21-30) is 0.691 and the correlation between the PRISM III scores of 11-20 & 21-30 groups was statistically significant (p < 0.01) (Table-1).

Among children with PRISM III score between 0 to 10, ascites on the USG was found only in 8(24%) of population, while PRISM III score between 11-20 showed ascites in 48(96%). All cases

i.e. 10 (100%) with PRISM III score in between 21-30 had ascites. The correlation coefficient by Spearman's Rho for all these three groups is 0.727 and the correlation between the PRISM III scores of 11-20 & 21-30 groups is statistically significant ($p < 0.01$) (Table-2).

Among children with PRISM III score between 0 to 10, Gall Bladder (GB) wall oedema on the USG was found only in 6 (18%) of population, while PRISM III score between 11-20 showed GB wall oedema in 13 (26%). Seven (70%) cases with PRISM III score in between 21-30 had GB wall oedema. The correlation coefficient by Spearman's Rho for these three groups is 0.343. The correlation between the PRISM III scores of 11-20 and 21-30 groups is statistically significant ($p < 0.01$) (Table-3) even after weak positive correlation between them (correlation coefficient near 0).

Among children with PRISM III score between 0 to 10, elevated aminotransferases was found only in 9 (26%) of population, while PRISM III score between 11-20 showed elevated aminotransferases in 42 (84%). All cases (10, 100%) with PRISM III score in between 21-30 had elevated aminotransferases. The correlation coefficient by Spearman's Rho for these three groups is 0.662 and the correlation between the

PRISM III scores of 11-20 and 21-30 groups is statistically significant ($p < 0.01$) (Table-4).

Among the children within the study ($n = 94$), 85 (90%) children were discharged, 9 (10 %) have expired. Out of total number of deaths ($n = 9$) in the children, 7(78%) children expired with PRISM III score more than 20 as compared to 2 (22%) children with PRISM III score less than 20. The p value is statistically significant (< 0.01). The correlation coefficient is very significant for the high PRISM III score (Table-5).

The children with PRISM III score with 0-10 on arrival to PICU had majority (24 Out of 34, 71%) of 1 day stay in PICU. 2-3 days of stay was found maximum (29 out of 50, 58%) in 11-20 PRISM III score. In children with PRISM III score between 20-30 score, 90% (9 out of 10) had more than 4 days of PICU stay. The duration of stay in PICU was more in children with high PRISM III score on arrival. High PRISM III score was associated with more duration of the stay in the PICU as difference in duration of PICU stay is attributed to increased mortality in children with high PRISM III score. The Correlation Coefficient is 0.889 by Spearman Rho Correlation Coefficient Test and P value is < 0.01 which is statistically significant (Table-6).

Table-1: Correlation of PRISM III score with pleural effusion on the x- ray

PRISM III SCORE	X ray EFFUSION		TOTAL
	PRESENT	NORMAL	
0---10	5(15%)	29(85%)	34
11---20	38(76%)	12(24%)	50
21---30	10(100%)	00	10

Table-2: Correlation of PRISM III score with Ascites on the USG

PRISM III SCORE	USG ASCITES		TOTAL
	PRESENT	NIL	
0---10	8(24%)	26(76%)	34
11---20	48(96%)	2(4%)	50
21---30	10(100%)	0	10

Table-3: Correlation of PRISM III score with Gall Bladder wall oedema on the USG

PRISM III SCORE	GALL BLADDER WALL EDEMA		TOTAL
	PRESENT	ABSENT	
0---10	6(18%)	28(82%)	34
11---20	13(26%)	37(74%)	50
21---30	7(70%)	3(30%)	10

Table-4: Correlation of PRISM III score with elevated aminotransferases

PRISM III SCORE	AMINOTRANSFERASES LEVELS		TOTAL
	ELEVATED	NORMAL	
0---10	9(26%)	25(74%)	34
11---20	42(84%)	8(16%)	50
21---30	10(100%)	0	10

Table-5: Correlation of PRISM III score with mortality

PRISM III SCORE	MORTALITY N=9
0---10	0
11---20	2(22%)

21---30	7(78%)
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Table-6: Correlation of PRISM III score and length of stay in PICU

PRISM III SCORE	Number of days stay in PICU			TOTAL
	1 day	2--3 days	>4 days	
0---10	24	10	0	34
11---20	1	29	20	50
21---30	0	1	9	10

DISCUSSION

The term Viral Haemorrhagic Fever is used to describe a severe multisystem syndrome. Characteristically, the overall vascular system is damaged and the body's ability to regulate itself is impaired. These symptoms are often accompanied by haemorrhage (bleeding). However, this bleeding is rarely life-threatening. Dengue fever is a flaviviral infection of humans spread by *Aedes aegypti* mosquito which breeds more commonly in stored clean waters, is commonest among viral haemorrhagic fever.

For the prediction of the severity and likely outcome in PICU settings the widely accepted scoring system is PRISM III score, PRELOD score [5-7]. Many previous studies have showed that PRISM III score has good predictive value in assessing the probability of mortality in PICU.

In this study of children with probable VHF, the correlation of severity of illness (in terms of PRISM III score) with radiological (USG/X ray Chest) and pathological (aminotransferases levels) parameters and with outcome of the study (mortality and length of stay in PICU) was evaluated and analysed. During the study period, 94 children were evaluated and subjected to PRISM III scoring.

In VHF like dengue fever, involvement of younger age group is an indicator of higher incidence of infection [8]. In our study, the proportion of infants affected was 27.5 suggesting high endemicity of dengue. However there have been studies reporting increasing endemicity of dengue in urban and peri-urban region of South-east Asia [9-11]. As seen in previous studies [10-15], fever, bleeding tendencies, rash and shock were common complaints on presentation. We have observed that, majority of the children had thrombocytopenia, metabolic acidosis, hypoxia and altered coagulation profile. We also observed unusual complaints of Central nervous system manifestations like altered sensorium (low Glasgow Coma Scale) and abnormal papillary reaction.

In this study, children with high PRISM III score were found to have more incidence of pleural effusion on chest x ray. As found by Betty Chacko and Gayathri Subramanian *et al.*, [16], this may be due to increase in capillary permeability with leakage of fluid, electrolytes and sometimes RBC. Presence of effusion and ascites on X-ray/USG was predictive of Dengue

Shock Syndrome (DSS). In their study, a total of 73 cases were enrolled. Mean age of the study population was 7.87 years with 16 (21.92%) infants. The children with effusion on USG/X-ray were also associated with severity. Higher PRISM III score correlated well with presence of pleural effusion on chest x-ray.

In this study, with PRISM III score between 0 to 10, ascites on the USG was found only in 8(24%) of population, while PRISM III score between 11-20 showed ascites in 48(96%). All cases with PRISM III score in between 21-30 had ascites 10(100%). While PRISM III score between 0 to 10, GB wall edema on the USG was found only in 6(18%) of population, while PRISM III score between 11-20 showed GB wall edema in 13(26%). 7(70%) cases with PRISM III score in between 21-30 had GB wall edema.

The Correlation Coefficient by Spearman's Rho for ascites and GB wall edema are 0.727 and 0.343 respectively. Though the correlation is more positive for ascites compared to the GB wall edema, the correlation with the PRISM III score with individual two parameters are statistically significant ($p < 0.01$). Higher PRISM III score is associated with ascites and correlation between these two is very high. Compared to the GB wall edema, gall bladder wall thickening cannot be taken as a sole definitive sign of severe dengue fever, in the paediatric age group.

In the study done by Srikiatkachorn, Anon *et al.*, [17]; serial ultrasound examination was done to delineate the locations and the timing of plasma leakage and to evaluate the usefulness of ultrasound in detecting plasma leakage in DHF. The ultrasound examinations of the abdomen and right thorax were performed in 158 suspected dengue cases to detect ascites, thickened gall bladder wall and pleural effusions. Ultrasonographic evidence of plasma leakage was detected in DHF cases starting from 2 days before defervescence and in some cases within 3 days after fever onset. Pleural effusion was the most common ultrasonographic sign of plasma leakage (62% of DHF cases). Thickening of the gallbladder wall and ascites were detected less frequently (43% and 52% of DHF cases respectively) and resolved more rapidly than pleural effusions. The size of pleural effusions, ascites and gall bladder wall thickness in DHF grade I and II were smaller than those in grade III patients. The study concluded that Ultrasound examination is a useful tool for detecting plasma leakage in dengue infection.

In another study by James A. Colbert, BA, Aubree Gordon *et al.*, [18], Gallbladder wall thickening (GBWT) measured by ultrasound was significantly associated with severe dengue, as well as with hallmark features i.e. thrombocytopenia and elevated haematocrit. 73 children with clinical symptoms consistent with DF were studied. Ultrasound-measured GBWT was found to be significantly different between all 3(DF/DHF/DSS) subgroups of patients when adjusted for age and sex ($P < 0.01$). In conclusion, ultrasound appears to be useful for diagnosing paediatric DHF/DSS and as a prognostic indication for patients with increased risk of developing severe disease. Ascites, pleural effusion and GB wall thickening on USG suggested that presence of capillary leak phase called Critical phase [19] was significantly associated with severe dengue fever. Thus, ascites and GB wall thickening on USG are correlating with the high PRISM III score.

In our study, it was found that the elevated aminotransferases levels were significantly correlated with the high PRISM III score ($p < 0.01$).

In the multicentre analysis by Souza LJ, Alves JG *et al.*, [20], 44.5% presented alterations in the aminotransferase levels (grade B), 16.9% presented grade C liver involvement and 3.8% of the patients had progressed to acute hepatitis (grade D). The average values for the rise in aspartate aminotransferase and alanine aminotransferase were 93.3 U/L and 86.0 U/L respectively. The maximum alterations were observed among females ($p < 0.001$), cases of dengue hemorrhagic fever ($p < 0.001$), and cases with sequential infections ($p = 0.001$) concluding Liver damage with elevation of aminotransferases as a common complication of dengue virus infection in these patients. The study did not comment on the severity or the outcome in the patients. In a retrospective study by Dr. Chongsrisawat V *et al.*, [21], 53 patients less than 15 years old with a diagnosis of Acute Liver Failure (ALF) in DHF were studied. The diagnosis of ALF was based on prothrombin time prolongation to greater than 2 times the normal value and the presence of encephalopathy without pre-existing liver disease. The patients were divided into 2 groups: group I ($n = 16$) had DHF with ALF and group II ($n = 37$) had ALF due to other causes. DHF patients had AST levels significantly higher than ALT levels. The mortality rate in group I (50%) was lower than in group II (72.9%), although the difference was not statistically significant. A study of Betty Chacko and Gayathri Subramanian *et al.*, [16] showed that serum glutamic pyruvic transaminase (SGPT) ≥ 40 IU was predictive of DSS. Therefore, the study concluded that elevated serum aminotransferase was significantly correlated with the high PRISM III score and predictive of severity of probable viral haemorrhagic fever.

Among the variables studied, though all are significant as ($p < 0.01$) GB wall oedema has poor

correlation coefficient and maximum for Ascites in USG examination.

Out of total number of deaths ($n = 9$) in the children, 7(78%) children expired with PRISM score more than 20 as compared to 2 (22%) children with PRISM score less than 20. The p value is statistically significant. (< 0.01). The correlation coefficient is very significant for the high PRISM score. In a study by Henny R. Iskandar [6], evaluated performance of the Paediatric Logistic Organ Dysfunction (PELOD) score compared with the Paediatric Risk of Mortality III (PRISM III) for predicting Dengue mortality in the PICU. A total of 42 patients (48% boys, 52% girls) admitted to the PICU were studied. PELOD and PRISM scores were evaluated on the first day. Median age of the children was 7 years. Death occurred in 11.9% of the patients with DSS. Analysis showed that the mean PELOD score was 7.2 (Mann-Whitney U test between survivors and nonsurvivors was significant at $P = 0.001$) compared with the PRISM III (mean score was significant also at $P = 0.008$). Concluding PELOD and PRISM III scores showed a good discrimination for predicting mortality in patients with DSS in the PICU. A study by Singhal, N.Kumar *et al.*, [5], has showed that PRISM score has good predictive value in assessing the probability of mortality in PICU. In this study 100 sick children who have been admitted in PICU were taken and their PRISM scores were calculated. Out of 100 children, 18 expired and 82 survived. 49 children had PRISM score < 10 out of them 4 expired, 45 children had PRISM score between 10-19 out of them 11 expired, 3 children had PRISM score 20-29 out of them 1 expired and 3 children had PRISM score above 30 out of them 1 expired. The children with high PRISM Score at arrival to Tertiary care PICU has got poor outcome. A study by Robert K Kanter *et al.*, [22], has concluded that PRISM score has a measure of illness severity provides an estimate of hospital mortality probability. The study was performed on patients admitted to PICU at four centres and mortality was quantitatively estimated as a function of PRISM scores obtained at referring hospitals. Mortality probability exceeds 10% at score of 13 and exceeds 50% at a score of 24. The higher the PRISM III score on arrival to the PICU, poorer is the outcome.

In our study, the duration of stay in PICU was more in children with high PRISM score on arrival. Lower the PRISM score, lesser is the duration of PICU stay. A study by Erik Michel *et al.*, [23], studied 2000 cases to determine the impact of PRISM score on length of PICU stay. They concluded that therapeutic intervention modulates the natural course of the disease thus counteracting both disease severity as initially scored by PRISM, and length of stay. This being true, the inverse correlation between PRISM and Length of stay might be a candidate indicator of quality of care. This difference in duration of PICU stay is attributed to increased mortality in children with high PRISM score.

Thus, the extent of plasma loss in viral haemorrhagic fever is highly variable and is the key feature that determines the clinical severity in the critical phase. Some patients with a less severe form of dengue do not develop plasma leak and steadily improve after defervescence. The signs and symptoms, laboratory and radiological investigation detecting plasma leak phase early are of immense important in the management, predicting severity of the VHF like dengue fever and are also good indicators of the early referral to the tertiary units.

In developing countries where even a primary health care is not promising and well established, it is very difficult for the patients to reach tertiary care centres for thorough investigations, proper diagnosis and treatment. Considering VHF paediatric patients, it was not possible for each parent/guardian to seek out for PICU setups and well equipped laboratories due to low socioeconomic status. Hence, we can advise investigations like chest x-ray, USG abdomen and serum aminotransferase levels for the predicting the severity of the illness. Based on this, physicians practicing in peripheral region where PICU setups are limited can easily take decisions of referral to tertiary care centres or stepping up the monitoring and care of seriously ill patients. This will definitely help in reducing the mortality and morbidity associated with the VHF.

CONCLUSION

To conclude, it was found that there is strong correlation of high PRISM III score with pleural effusion, ascites, gall bladder wall oedema and raised serum aminotransferase levels. Hence, these investigations can be considered to decide the severity of VHF wherever PRISM III evaluation is not possible. This will help to reduce paediatric patient's mortality in developing countries.

Conflict of Interest: None

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