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Association of clinical parameters and serum ferritin with dengue fever severity and in-hospital outcome in children aged 1 month to 12 years: a prospective, observational study at a tertiary care center in central India

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ABSTRACT:

— ***Objective:*** *This work aimed at studying clinical parameters observed at admission and defervescence and serum ferritin levels measured at two states and their association with dengue severity and survival.*

— ***Patients and Methods:*** *In a prospective, observational study conducted at a tertiary care center in central India, children aged 1 month-12 years of age, who were admitted in the hospital with a diagnosis of dengue fever (NS1 antigen or IgM/IgG status positive) and presenting within 84 hours of fever onset, were included. Clinical parameters and serum ferritin levels at admission and defervescences were recorded and measured.*

— ***Results:*** *Between October 2018 and October 2020, 92 dengue-positive children were enrolled. The mean age was 6.58±3.50 years, and 56.5% were female. NS1 antigen positivity was seen in 89.1% of cases. Severe disease was seen in 12% of cases, whereas in-hospital mortality rate was 3.2%. Systolic and diastolic blood pressure, pulse pressure <20 mmHg, hepatomegaly, reduced urine output and bleeding manifestations identified on admission as well as in defervescence were associated with severity and mortality in children with dengue fever. Serum ferritin levels on admission and defervescence were also associated with dengue severity (*p = *0.0001 and* p = *0.0012, respectively) and in-hospital mortality (*p = *0.0013 and* p = *0.0151, respectively).*

— ***Conclusions:*** *Clinical parameters and serum ferritin levels on admission and in defervescence are associated with severe dengue and can predict in-hospital mortality.*

— ***Keywords:*** *Dengue fever, Children, Serum ferritin, Mortality.*

INTRODUCTION

Dengue is the mosquito-borne diseases transmitted through the bite of infected mosquitoes of Aedes species. Although infection with the dengue virus (DENV) is associated with a self-limiting illness in the majority of individuals, it can cause severe clinical disease manifestations leading to shock, hemorrhage and ultimately to death. DENV may cause serious and life-threatening diseases, with increased vascular permeability and plasma leakage[1]. Antibody mediated mechanisms enhancing inflammatory reac-

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tion causing cytokine storm similar in nature to that observed in secondary Hemophagocytic lymphohistiocytosis (HLH) have been implicated in the pathophysiology of severe dengue disease[2]. Other factors implicated in disease pathogenesis include viral virulence, the age of the individual, and specific epidemiological conditions[3]. Understanding the mechanism of plasma leakage as the cause of severe symptoms was a breakthrough discovery that led to serious advances in guiding the treatment. Plasma leakage occurs around the time of defervescence, which is the time during which the transition from febrile to afebrile state occurs. During this period, there are subtle clinical and biochemical changes, exploitation of which has proved to be fruitful and promising. The causes of mortality in dengue infection are from prolonged shock, massive bleeding and fluid overload. No diagnostic/prognostic tools are available to distinguish severe dengue from non-severe dengue or other febrile illness (OFI) at early stages of illness[4,5]. As the disease progresses towards the more severe form, it goes through certain hematological and biochemical abnormalities which also reflect in the clinical condition of patient. As a part of the disease, leucopenia is observed even before the characteristic fall of platelet counts. Plasma leak leads to hemoconcentration and thereby causing rise in hematocrit levels[4]. There is derangement in liver enzymes and coagulation profile either as a result of direct damage to liver or through cytokine storm[6]. Moreover, the damaged hepatocytes also release serum ferritin, an acute phase reactant that is characteristically raised in dengue fever and thereby helps to differentiate it from other febrile illnesses[7].

Early recognition of these obvious clinical and laboratory parameters has been aimed at predicting the disease severity and intervening timely to obtain the desired results. Early diagnosis of severe dengue illness not only has the potential to reduce morbidity and mortality, but could also reduce the economic impact of dengue illness by decreasing the duration of hospitalization and the number of patients who will develop shock[7]. However, for many endemic countries this is not a feasible option, and simple and inexpensive strategies that rely on clinical and/or readily available laboratory parameters to provide a reliable early diagnosis are needed. Currently, there is no anti-viral against dengue, and the treatment for patients with suspected dengue is supportive care consisting of rehydration and anti-pyretics[8]. The occurrence of hyperferritinemia in dengue virus infected patients is indicative of highly active disease resulting in immune activation and coagulation disturbances. Therefore, it is recommended that patients with hyperferritinemia are monitored carefully[8].

The pattern of biochemical changes in the early stages of the illness and their usefulness as predictors of different phases of the illness are not well known in Indian setting. This study aims at targeting the initial as well as defervescence period, the last coinciding with the critical period to predict the advancement towards severe disease by utilizing simple clinical and laboratory parameters and thereby can help taking the early interventions timely. The present study also aims at using serum ferritin, an acute phase reactant, to predict severe diseases. The primary aim of the current study is to identify clinical and laboratory parameters predictive of severity of dengue fever and the secondary aim is to study the correlation between serum ferritin levels and severity of dengue.

PATIENTS AND METHODS

Study Design and Setting

This was a prospective, observational study. The study was conducted in the Department of Pediatrics at a tertiary care center in central India for two years from October 2018 to October 2020. The Centre provides high-resource tertiary care with intensive care facility in central India. Study protocol was approved by the Institutional Ethics Committee of the Center. A written informed valid consent was taken from either or both parents and/or caretaker guardian of the child in specially designed consent form.

Study Population

In this study, pediatric patients aged 1 month to 12 years of age, admitted to tertiary care hospital WARD with complain of fever for 84 hours or more and whose blood sample was positive for NS1 or IgM against dengue were included. Patients with hemoglobinopathies, multiple transfused patients, patients suffering from chronic diseases and those not willing to participate were excluded from the study.

Study Procedure

Data were collected using structured data collection sheets, which included demographic information including age, sex, and duration of admission. Data from physiological status, like heart rate, respiratory rate, temperature, capillary refill time, blood pressure and urine output, liver size, sign of dehydration like sunken eyeballs, conjunctival congestion, were also recorded. Severe dengue was considered in presence of any of the following: severe plasma leakage that leads to shock (dengue shock) and/or fluid accumulation with respiratory distress; severe bleeding; severe organ impairment[9]. Blood pressure (BP) was measured in supine position in the right arm with the patient in comfortable position. Appropriate-sized cuff was used; systolic blood pressure was recorded at first Korotkoff sound and diastolic pressure at fifth Korotkoff sound by experienced on duty doctors. Pulse pressure was taken as the difference between the systolic and diastolic BP. Urine

output was collected and measured by using Foleys; for infants, diaper weight method was used. A cut off value lower than 0.9 ml/kg/hr was considered as low urine output[10]. Urine output at admission was measured after 24 hrs in the ward/ICU. It was then again taken into consideration at defervescence period to correlate with severity. Liver span was measured using ultrasonographic evaluation of liver size by experienced sonologist. Evidence of third spacing was considered on chest X-ray as well as ultrasonography (USG). Right lateral decubitus X-ray of chest was performed, then interpretated by a senior physician. USG abdomen and chest were done to look for signs of fluid collection as evidence of third spacing. Coagulation profile was analyzed by filling 2 ml of blood in colored citrate bulb and placing it in Sysmex CA-1500 (Siemens, Mumbai, India) using multidilutional analysis (MDA). Rapid test (NS1/IgM/IgG) was performed by rapid test kits, which work on the principle of precipitation reaction. Reported sensitivity was 66% and specificity was 90%. Serum ferritin assessments were obtained by immunoturbidimetry method using machine XL 640 (Transasia Bio-Medicals, India). Hyperferritinemia is defined as a serum ferritin level higher than 500 ug/L for all practical as well as clinical purposes, as per the HLH 2004 criteria[8]. All the parameters were also assessed during the defervescence period. We defined defervescence as two consecutive temperatures lower than 38 degrees centigrade taken 24 hrs apart[5].

Statistical Analysis

With reference to a published study[11] considering 80% power of study and 10% margin of error, we calculated a sample size of 92 people. Data analysis accomplished using tables and charts were prepared using Microsoft Word and Excel spread sheet. Continuous variables were presented as Mean±SD. Categorical variables were expressed in frequency and percentages. Continuous variables were compared between two groups by performing independent *t*-test for normalized data and Mann-Whitney test for non-normalized data. Categorical variables were compared by performing the Chi-square test. For counts <5, Fisher exact test was used wherever applicable. *p*-value < 0.05 was considered as statistically significant. Statistical software STATA (StataCorp LLC, College Station, TX, USA) version 14.0 was used for the statistical analysis.

RESULTS

In total, 92 cases of dengue were enrolled in the study. Table 1 describes the baseline characteristics of the patients. The mean age was 6.58±3.50 years, and the majority was between 6-12 years (56.5%). By gender, 56.5% were females and 43.5% were males with an M:F ratio of 0.7. By method of diagnosis, 89.1% were diagnosed as NS1 antigen positive, whereas 10.9% were diagnosed on IgM antibody positivity. In the clinical parameters, SBP below 5th centile and DBP below 5th centile were observed in 62% and 59.8% of cases, respectively, while pulse pressure <20 mmHg was seen in 42.4% of cases. Among other clinical parameters, liver span >50th centile for age was seen in 48.9% of cases, 3rd spacing on ultrasound or X-ray in 63.0% of cases, and reduced urine output in 34.8%. 50% of the cases had bleeding manifestations.

Table 1. Demographic and baseline characteristics in study participants.

Parameters	n (%)
Age in years (Mean±SD)	6.58±3.50
1 month - 1 year	11 (12.0)
1 year - 6 years	29 (31.5)
6 year - 12 years	52 (56.5)
Gender	
Male	40 (43.5)
Female	52 (56.5)
Dengue diagnosis	
NS1 Positive	82 (89.1)
IgM Positive	10 (10.9)
Clinical parameters	
SBP (mm of Hg) < 5th centile	57 (62.0)
DBP (mm of Hg) < 5th centile	55 (59.8)
Pulse Pressure < 20 mmHg	39 (42.4)
Liver span >50th centile for age	45 (48.9)
3rd spacing on Ultrasonography or X-ray	58 (63.0)
Reduced urine output (< 0.9 ml/kg/hr)	32 (34.8)
Bleeding manifestation	46 (50.0)

NS1: Nonstructural protein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

Table 2 shows the clinical parameters on admission and at defervescence with severity of dengue. All the clinical parameters on admission and in defervescence were found in a significantly higher proportion of cases with severe dengue than in non-severe dengue, except for DBP <5th centile in the defervescence period for which no significant difference was observed.

In the survivors and non-survivors (Table 3), all clinical parameters assessed at admission showed significant association with mortality, as indicated by significantly higher proportion of the clinical parameters in non-survivors compared to survivors. At defervescence, only pulse pressure <20 mmHg (p = 0.040) and decreased urine output (p = 0.016) were associated with significant difference in proportion of survivors and non-survivors. There was no significant difference the proportion of patients in the survivors and non-survivors with respect to SBP <5th centile (p = 0.225), DBP <5th centile (p = 0.342), liver span >50th centile (p = 0.643), 3rd spacing on USG or X-ray (p = 0.178) and bleeding manifestations (p = 0.078; Figure 1).

Table 2. Comparison of different parameters on admission and at defervescence in sever and non-severe dengue.

Parameter	Admission			Defervescence		
	Severe (n=11)	Non-severe (n=81)	*p*-value	Severe (n=11)	Non-severe (n=81)	*p*-value
SBP (mm of Hg) < 5th centile	11 (100.0)	29 (35.80)	0.0001	10 (90.91)	47 (58.0)	0.035
DBP (mm of Hg) < 5th centile	9 (81.82)	29 (35.80)	0.004	6 (54.55)	49 (60.5)	0.706
Pulse Pressure < 20 mmHg	4 (36.36)	0	<0.0001	11 (100.0)	28 (34.57)	<0.0001
Liver span >50th centile for age	7 (63.64)	8 (9.88)	<0.0001	9 (81.82)	36 (44.44)	0.020
3rd spacing on USG or X-ray	4 (36.36)	0	<0.0001	11 (100.0)	47 (58.02)	0.007
Decreased urine output (<0.9 ml/kg/h)	6 (54.55)	13 (16.05)	0.003	9 (81.82)	23 (28.40)	<0.0001
Bleeding manifestation	4 (36.36)	0	<0.0001	4 (36.36)	35 (43.21)	<0.0001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, USG: Ultrasonography.

Table 3. Comparison of clinical parameters on admission and at defervescence in survivors and non-survivors.

Parameter	Admission			Defervescence		
	Non-survivor (n=11)	Survivor (n=81)	*p*-value	Non-survivor (n=11)	Survivor (n=81)	*p*-value
SBP (mm of hg) < 5th centile	3 (100.00)	37 (41.47)	0.045	3 (100.0)	54 (60.7)	0.225
DBP (mm of hg) < 5th centile	2 (66.67)	36 (40.45)	0.0364	1 (33.3)	54 (60.7)	0.342
Pulse Pressure < 20 mm Hg	3 (100.0)	1 (1.12)	<0.0001	3 (100.0)	36 (40.4)	0.040
Liver span more than 50th centile for age	3 (100.0)	12 (13.48)	<0.0001	2 (66.7)	43 (48.3)	0.643
3rd spacing on USG or X-ray	3 (100.0)	1 (1.12)	<0.0001	3 (100.0)	55 (61.8)	0.178
Decreased urine output (<0.9 ml/kg/h)	2 (66.7)	17 (19.10)	0.045	3 (100.0)	29 (32.6)	0.016
Bleeding manifestation	2 (66.7)	2 (2.25)	<0.0001	3 (100.0)	43 (48.3)	0.078

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, USG: Ultrasonography.

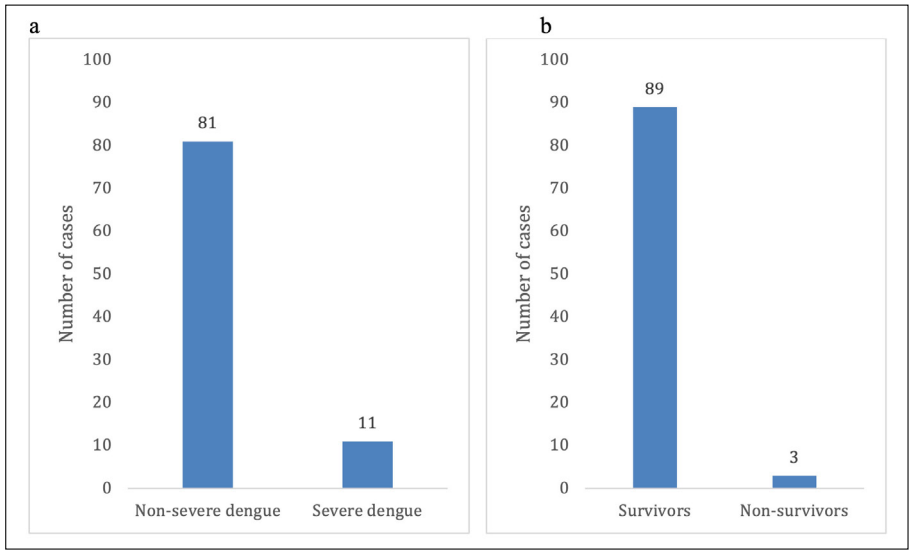

Figure 1. Prevalence rate of COVID-19 infection and receiving between students and staff.

Table 4. Comparison of different parameters on admission and at defervescence in sever and non-severe dengue.

	Admission			Defervescence		
	Severe (n=11)	**Non-severe (n=81)**	***p*-value**	**Severe (n=11)**	**Non-severe (n=81)**	***p*-value**
Parameter	851.3±565.1	444.3±252.5	0.0001	872 (569-4,051)	408 (49-2,102)	0.0012
	Admission			**Defervescence**		
	Non-survivor (n=11)	**Survivor (n=81)**	***p*-value**	**Non-survivor (n=11)**	**Survivor (n=81)**	***p*-value**
Serum ferritin (µg/L)	1,082.0±6,758.0	473.1±316.4	0.0013	3,365 (963-4,051)	413 (49-2,102)	0.0151

The association of serum ferritin levels with severity and survival outcome is shown in Table 4. The mean serum ferritin levels were significantly higher in the sever dengue cases on admission (851.3±565.1 µg/L *vs.* 444.3±252.5 µg/L, $p = 0.0001$). Similarly, at defervescence also, the median levels of ferritin were significantly higher in severe dengue cases (872 µg/L *vs.* 408 µg/L, $p = 0.0012$). Also, serum ferritin levels at admission ($p = 0.0013$) and at defervescence ($p = 0.0151$) were significantly higher in non-survivors compared to survivors.

DISCUSSION

Globally, dengue fever in children has a significant impact on morbidity and mortality. In children with fever lasting > 3 days, annual incidence of dengue fever has been reported to be 49.5 per 1,000 children per year[12]. If not identified early in the course, dengue fever can lead to severe illness and may pose risk of adverse outcomes. We observed severe dengue disease developed in nearly 12% of cases whereas in-hospital mortality occurred in 3.2%. In a similar study from Odisha, Mishra et al[13] reported severe dengue in 13.4% cases and mortality rate of 1.03%. The mortality increases with severity of dengue. In a study of 78 severe dengue cases, Sachdev et al[14] reported a mortality rate of 25.6%. Multiple factors are predictors of severe dengue and mortality. Hypotension is an important factor. Pongpan et al[4] found that falls in mean systolic BP predicted the severity. However, diastolic BP did not show significant correlation, as it remained the same during the disease course. In their study, Gonçalves et al[15] reported the similar trend of hypotension leading to severe disease attributing it to the inherently permeable vascular structure in children. Alikunju et al[16] also found the similar trends with 21.9% of patients presenting in hypotension. We observed that hypotension during defervescence was correlated with disease severity (p-value = 0.035) and hypotension on admission was significantly correlated with mortality (p-value = 0.045). Similar to these findings, our study presented all cases of severe disease and death had below 5th centile BP. There was serial fall in BP, which ultimately predicted severe disease both at presentation (p-value = 0.0001) as during defervescence (p-value = 0.035) and correlated with disease mortality (p-value = 0.045). However, the diastolic BP below 5th centile during defervescence period did not predict severe disease (p-value = 0.706), neither mortality (p-value = 0.342). Pongpan et al[4] found the mean pulse pressure in non-severe cases to fall from 33.1 to 24.8 mm of hg in severe cases, thereby correlating to disease severity. Similarly, our findings reported a pulse pressure <20 mm hg which was seen in although a much smaller number of cases, showing significant correlation with severity (p-value = 0.0001), as well as mortality (p-value = 0.0001). Additionally, 11 patients with severe disease (p-value = 0.0001), as well as all 3 patients who died of disease, had narrow pulse pressure reported at defervescence. However, Sreenivasan et al[17] conducted a study in which they used narrow pulse pressure as a surrogate to study fluid leak and development of severe disease, and no significant correlation was found in their study. Alikunju et al[15] found that 43.5% of subjects had hepatomegaly at presentation, and a significant number of them landed in severe disease. Similar results were reported by Mohan et al[18]. Our finding revealed hepatomegaly in 75% of population who died. However, it failed to correlate with mortality (p-value = 0.643). Similarly, in their study, Pongpan et al[4] found that only 2.1% of cases in mild category had hepatomegaly. However, it rose to 61.1% in severe disease and showed significant correlation; however, they failed to correlate hepatomegaly with mortality in defervescence period[4]. Rao[19] stated that 63% of patients with pleural effusion developed severe diseases. The present study came up with the evidence that third spacing indicated on X-rays, as well as USG at presentation, were significant for predicting severe diseases (p-value = 0.0001), as well as deaths (p-value = 0.0001). The same finding reflected in defervescence period wherein 81% of severe cases showing third spacing, but the correlation with mortality (p-value = 0.178) could not be established. However, Pongpan et al[4] reported that none of the patients had pleural effusion in mild category; however, 37.8% of patients in the severe category had pleural effu-

sion, which was statistically significant and predicted mortality. Potts et al[5] studied pediatric population in CART algorithm and found clinical bleeding to be a significant predictor in both early and late phases of the diseases with severity. Additionally, Alikunju et al[16] reported bleeding manifestations at presentation in 25.4% patients, which correlated significantly to severe disease. In contrast with these abovementioned studies, we found that bleeding manifestation at admission, as well as in defervescence period, had a significant correlation in predicting the development of the severe disease (p-value = 0.0001), as well as mortality (p-value = 0.0001). Additionally, Pongpan et al[4] also reported petechiae in 6.9% cases in mild disease which rose to 15% in severe disease and mortality, but they failed to establish correlation with mortality. Manoharan et al[20] found that low urine output (lower than 0.9 ml/kg/hour), which was present only in 5% of patients at presentation in mild cases, increased reaching 50% patient in severe disease category. In the present study, decreased urine output lower than 0.9 ml/kg/hour at presentation was found to be significantly associated with disease severity (p-value = 0.003), with 54% cases of severe disease and 75% cases who died (p-value = 0.045), showing this finding. It also significantly correlated with severity (p-value = 0.0001) (81% patients) and death (p-value = 0.016) during defervescence period. Alikunju et al[16] studied the severity of dengue disease in which they found 91% of patients as NS1 positive with only 2% being IgG positive; that was similar to our study but without any significant correlation. However, Valero et al[7] correlated disease severity with NS1 positivity, with no evidence of significant correlation noted.

Raised serum ferritin levels can be used to discriminate dengue and other febrile illnesses. Hyperferritinemia indicates a highly active disease resulting in immune activation and coagulation disturbances[8]. van de Weg et al[8] found that hyperferritinemia in dengue was strongly associated with thrombocytopenia and increased levels of liver enzymes and both activation of the coagulation and the fibrinolytic systems. Our study reported that mean levels of serum ferritin were significantly associated with prediction of severity (p-value = 0.0001), as well as mortality (p-value = 0.0013) at presentation and during the defervescence period. The mean value at presentation in severe disease was 851.27 ug/L and 1,082 ug/l in those who died. At defervescence it was 872 ug/l for severe disease and 3,365 ug/L in those who died. Similarly, Valero et al[7] found that increased levels of ferritin (p < 0.0001) were observed in dengue patients.

CONCLUSIONS

We observed that various clinical parameters, such as reduced BP, reduced pulse pressure, hepatomegaly, reduced urine output on admission and during the defervescence period can predict the severe dengue and mortality in admitted children with dengue fever. Serum ferritin levels on admission, as well as in defervescence, were also elevated in sever dengue patients and in those who died in hospital. It can therefore be considered for differentiation of patients who can progress to severe dengue during hospitalization. Further studies are necessary to determine the discriminative power of serum ferritin as marker to predict sever dengue in children.

Funding
None.

Conflict of Interest
None.

Ethics Approval
Study protocol was approved by the GMCH Institutional Ethics Committee.

Informed Consent:
A written informed valid consent was taken from either or both and/or caretaker of the patient in a specific designed consent form.

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