Original Article

Dengue hepatic severity score: A glimmer to the clinician

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ABSTRACT

Introduction: Recent studies from India and Thailand show that dengue infection was the most compelling cause of acute hepatic failure in children contributing to 18.5% and 34.3%, respectively, and till now, there is no proper dengue severity score based on the hepatic dysfunction, i.e. laboratory as well as clinical hepatic parameters. **Objective:** The objective of this study was to develop a new dengue hepatic severity score (DHSS) based on only hepatic dysfunction parameters. **Methods:** The present cross-sectional analytical study was conducted in the Department of Paediatrics, Burla, Sambalpur, Odisha, from November 2015 to October 2017 after getting the institutional ethical clearance. A total of 76 cases selected as per predefined inclusion and exclusion criteria, categorized into three groups after taking written informed consent of their legal hare. Relevant hepatic parameters (both clinical and laboratory) were collected, and data were finally analyzed using receiver operating characteristic curve to get a cutoff value for each group. **Results:** The cutoff value of DHSS of ≥7 between Group 1 and Group 2 evidenced by area under the curve (AUC)=99.6% with 95% confidence interval (CI) (95.6–100%), sensitivity - 100%, specificity - 94.6%, and a cutoff ≥18 between Groups 2 and 3 exhibited by AUC=100% with 95% CI (94.6–100%), sensitivity - 100%, and specificity - 94.6%. Hence, the DHSS is formulated as ≤6 (no severe hepatic dysfunction), 7–17 (severe), and ≥18 (very severe). Mean duration of hospitalization in days between three groups of hepatic dysfunction was statistically significant as evidenced by one-way ANOVA; F (2, 73)=19.83, p=0.000. **Conclusion:** DHSS system will help the primary health caregiver for triaging, early recognition, and prompt management to prevent additional deterioration.

Key words: *Dengue hepatic severity score, Hepatic dysfunction, One-way ANOVA, Receiver operating characteristic curve*

Dengue infection is a mosquito-borne viral disease which is in emerging trend and major health problem in our country as well as worldwide. The World Health Organization (WHO) estimates that about two-fifths of the world population are at risk for this dengue infection [1]. There are four serotypes of dengue virus causing dengue without warning sign, dengue with warning sign, and severe dengue according to the WHO 2009 guidelines [2]. Recovery from infection with one serotype offers lasting immunity against that individual serotype; however, future infections with different serotypes increase the danger of developing severe dengue [3,4]. In India, the annual incidence is estimated to be 7.5–32.5 million [5]. In Odisha, a state of Eastern India, the first outbreak was reported in 2010, followed by extensive outbreaks in 2011, affecting large populations. Risk of mortality in treated cases is <1% while mortality rate among untreated cases escalates to 20% [6].

Unusual manifestations involving liver and central nervous system in dengue infection have been reported [7,8]. Severity of hepatic dysfunction in youngster with dengue infection ranges from milder form of injury with rise of transaminases to severe form with jaundice and liver failure [9]. Mechanisms of liver injury in dengue may be due to direct effects of the virus or host immune response on liver cells, circulatory compromise, metabolic acidosis, and/or hypoxia caused by hypotension or localized vascular leakage inside the liver [10]. The incidence of hepatic dysfunction is more in severe dengue and dengue with warning signs [11]. Aminotransferase levels are useful in predicting the occurrence of hepatic dysfunction and spontaneous bleeding [12]. As per the studies among Indian subcontinent, the most promising cause of acute hepatic failure in children with dengue infections varies from 18.5% to 34.3% [13]. Although the liver is not the major target organ, changes such as centrilobular necrosis, fatty change, Kupffer cells hyperplasia, acidophilic bodies, and monocytic infiltration of portal tracts have been reported in patients with dengue [14,15].

In spite of an established severity score for dengue fever [16] as well as grading system for hepatic dysfunction [17], till date, there is no such dengue severity score based on the hepatic dysfunction, i.e., laboratory as well as clinical hepatic parameters. Hence, the current objective of our study is to develop a new severity score system "dengue hepatic severity score" (DHSS) basing on the above hepatic parameters to strengthen our existing healthcare system at the periphery level.

METHODS

This present observational analytical cross-sectional study was conducted at OPD/IPD of the Department of Paediatrics, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Sambalpur, a 750 bedded tertiary care hospital of western Odisha from November 2015 to October 2017 after getting approval from the Institutional Research and Ethics Committee (VIREC).

Of this 2-year study period, the first 1 year was dedicated for data collections and subsequent year for data analysis and interpretations. Based on a previous study done in 2010 [15], the prevalence of deranged liver function tests (LFTs), i.e., raised aspartate transaminases (ASTs) and alanine aminotransferase (ALT) in dengue infection was 97%. Minimum sample size calculated was 70 using n-Master v2 by single proportion absolute precision method taking proportion as 0.97, absolute precision of 4%, and confidence interval (CI) of 95%. Due to less number of cases, we have also included cases retrospectively from our hospital records from November 2013 to October 2015. Inclusion criteria were 1–14-year-old child seropositive for NS1 antigen and/or IgM antibody, whereas exclusion criteria were the presence of any severe preexisting morbidities (congenital heart disease [CHD], severe malnutrition, and developmental delay), child with coexisting malaria or enteric fever or viral hepatitis or drug-induced hepatitis. A total of 92 cases selected as per inclusion criteria, out of which 7 did not give consent and 9 excluded as per exclusion criteria. 76 cases were enrolled as study participants after giving informed consent (Fig. 1). All the children between 1 and 14 years of age seropositive for dengue NS1/IgM [18] attending to our OPD/IPD were taken by simple consecutive sampling method. All confirmed cases were categorized according to the WHO 2009 criteria [2]. As this was a hospital-based study, the study population and target population were same, i.e., the children who were satisfying the inclusion criteria.

All the routine investigations as well as LFT were done for each patient. Dengue serology (NS 1/IgM) was done using ELISA method in MERILYSER-EIA QUANT-EIA WASH. Complete blood count (CBC) was done in automated hematology analyser-HORIBA-ES60 by electrical impedance and photometry method. LFT was done in TRANSASIA by spectrophotometry technique. Serum (Sr.) electrolytes were done in by agarose gel electrophoresis and immunofixation method. Renal function tests (RFTs) were performed in TRANSULIA-CHEM-7 by kinetic method. Prothrombin time-international normalized ratio (PT-INR) was investigated in AGAPEE-CD504-08 by electromechanical clot detection technique. Sr. albumin was done by nephelometry method in TRANSULIA-CHEM-7. Bleeding time (BT) and clotting time (CT) were done by Lee and White method manually. Random blood sugar (RBS) was done in TRANSULIA-CHEM-7 by end-point technique.

We have calculated the cutoff value of each laboratory parameters for hepatic dysfunction (blood sugar, Sr. albumin, AST, ALT, alkaline phosphatase [ALP], Sr. bilirubin total and direct, PT/INR, CT, Sr. potassium [K] and sodium [Na], and Sr. urea and creatinine) by applying receiver operating characteristic (ROC) curve for each type of dengue. Among the above laboratory parameters, those have acceptable cutoff values as per ROC curve analysis were taken into account for scoring and basing on that we have given a score/number to each category (i.e., 0, 1, and 2). Then, a clinical manifestation of hepatic dysfunction was given a score of 0 (absent) and 1 (present). Laboratory parameter of hepatic dysfunction was taken as Score-A, whereas Score-B was for clinical hepatic manifestations score. Laboratory parameters of hepatic dysfunction variables (Score-A) were Sr. bilirubin total and direct, AST, ALT, ALP, CT, and PT-INR. Clinical hepatic manifestations variables (Score-B) comprises vomiting, abdominal pain and/or tenderness, hepatomegaly, ascites, loss of consciousness or seizure, bleeding manifestations (petechiae, purpura, ecchymosis, gum bleeding, epistaxis, hematemesis, GI bleed, hematochezia, and melena), respiratory distress, and shock (Table 1a). Final score, i.e., DHSS was calculated based on the score of laboratory parameters of hepatic dysfunction plus clinical hepatic manifestations scores. After getting a score for each category, we again calculated a cutoff value for each type of

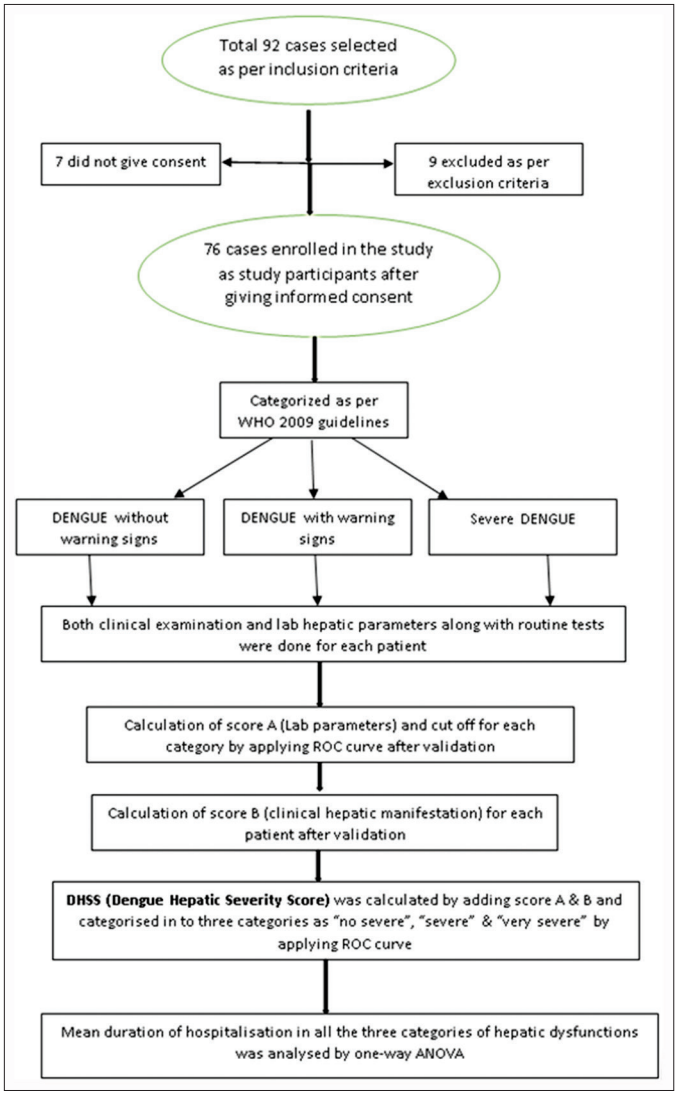

Figure 1: Study flow diagram

dengue by applying ROC curve. Then, hepatic severity score for dengue children was derived and categorized into three varieties, i.e., no severe, severe, and very severe hepatic dysfunction basing on the cutoff score.

Each patient was enrolled in the study after taking informed written consent from the parent or the legal guardian. Case report forms for each patient was filled, and data were collected in EpiData v 4.2.0 software regarding the baseline characteristics such as age, sex as confounders, and other relevant investigations such as LFT, electrolytes, CT, and RFT. Confidentiality of the data was well maintained. No part of the data was given to any open access. Data checking was done manually by both principal investigator (PI) and co-PI. Double data entries were done by PI and co-PI separately. Data validation was done by computer-assisted software EpiData v 4.2.0. Data normalcy was tested using Shapiro–Wilk and Kolmogorov–Smirnov test where p>0.05 were considered to be of normally distributed data. Non-normal data were subjected to transformation statistics (right-skewed or left-skewed data were subjected to square root and square transformation, respectively). Intergroup variabilities of continuous data were analyzed with one-way ANOVA and for categorical data with Pearson's Chi-square tests. ROC curve analysis was performed using SPSS v24 (IBM, New York, USA) and Dxt v 1.0 (BRTC, Bagayam, Vellore) software, and then, results were interpreted.

RESULTS

Among 76 serologically confirmed dengue patients (M:F=1.45:1), 49% (37) were from Group 1, 27% (21) from Group 2, and 24% (18) were from Group 3. Of 37 dengue children of Group 1, 16.2% (6) were treated on OPD basis. There is no statistically significant difference of mean age in years between Group 1 (7.66 ± 2.92), Group 2 (7.77 ± 3.18), and Group 3 (7.47 ± 2.85) as determined by F (2)=0.048, p=0.953. There is no statistically significant difference in sex distribution among three groups as defined by Pearson's Chi-square (2)=0.918, p=0.632 and Cramer's V=0.110, p=0.632. The most common symptom was fever (100%) followed by vomiting (65.8%) and least common was bleeding manifestations (22.4%). The most common sign was abdominal tenderness (50%) and hepatomegaly (50%). 37% (28) were NS1 positive and 72% (55) were IgM positive. The total percentage of dengue serology positive was more than 100% as some patients had multiple seropositive status.

All LFT parameters as well as Sr. electrolytes, RFT and RBS were taken into consideration, and cutoff value was calculated by applying ROC curve (Tables 2a and b).

The cutoff value of DHSS was ≥7 between Group 1 and Group 2 as evidenced by ROC curve having area under the curve (AUC)=99.6% with 95% CI (95.6-100%), sensitivity - 100%, specificity - 94.6%, positive likelihood ratio=18.5, and negative likelihood ratio=0 (Fig. 2). It implied the odds of DHSS increased to 18.5-fold for children with severe hepatic dysfunction as compared to no severe hepatic dysfunction and there is high probability that children with dengue will fall into severe hepatic dysfunction once they achieved the cutoff score of 7.

DHSS has a cutoff value of ≥18 among Groups 2 and 3 dengue children as exhibited by AUC=100% with 95% CI (94.6–100%), sensitivity - 100%, specificity - 94.6%, positive likelihood ratio=214,680, and negative likelihood ratio=0 (Fig. 3), which signifies that there is very less probability, i.e., 214,680 times less chance for dengue children with very severe hepatic dysfunction will fall into severe hepatic dysfunction category, whereas there is high probability that the children with dengue will fall into very severe hepatic dysfunction once they achieved the cutoff score of 18. Hence, the cutoff score for dengue hepatic severity is formulated as ≤6 (no severe hepatic dysfunction), 7–17 (severe), and ≥18 (very severe) (Table 1b).

There was statistically significant difference of mean score between three categories of hepatic dysfunction as evidenced by one-way ANOVA; F (2.73)=660.351, p=0.000. Mean score of no severe hepatic dysfunction (2.92 ± 1.92) was significantly lower as compared to very severe hepatic dysfunction (21.28 ± 1.23) and severe hepatic dysfunction (10.48 ± 1.86) as evidenced by Tukey *post hoc*, p=0.000. Mean score of very severe hepatic dysfunction (21.28 ± 1.23) was significantly higher as compared to severe hepatic dysfunction (10.48 ± 1.86) and no severe hepatic dysfunction (2.92 ± 1.92) as evidenced by

Table 1a: Score-B (clinical parameters)

Variables	Absent	Present
Vomiting	0	1
Abdominal pain/tenderness	0	1
Hepatomegaly	0	1
Ascites	0	1
Severe bleeding	0	1
Respiratory distress	0	1
Shock	0	1
Loss of consciousness/seizure	0	1

Table 1b: Final score (dengue hepatic severity score) = Score-A+Score-B (Maximum score=22)

Categories	Score
No severe hepatic dysfunction	≤6
Severe hepatic dysfunction	7–17
Very Severe hepatic dysfunction	≥18

Table 1c: Score-A (Laboratory parameters)

Variables	Cutoff values in each score		
	0	1	2
Serum bilirubin total (mg/dl)	<0.9	0.9–3.69	≥3.7
Serum bilirubin direct (mg/dl)	<0.37	0.37–1.079	≥1.08
AST (IU/L)	<85	85–140	≥141
ALT (IU/L)	<99	99–171	≥172
ALP (IU/L)	<193	193–380	≥380
Clotting time (min)	<5.0	5.0–7.9	≥8.0
PT-INR	<1.19	1.19–1.53	≥1.54

ASTs: Aspartate transaminases, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, PT-INR: Prothrombin time-international normalized ratio

Table 2a: ROC curve details of Group 1 versus Group 2

Variables	AUC (%)	95% CI (%)	p value	Sensitivity (%)	Specificity (%)
Serum bilirubin total (mg/dl)	86.6	76.5–96.6	0.000	90	62
Serum bilirubin direct (mg/dl)	78.3	65–91.6	0.000	70	73
AST (IU/L)	87.3	76.7–97.9	0.000	95	99
ALT (IU/L)	93.7	87.6–99.8	0.000	95	84
ALP (IU/L)	82.4	71.7–93.1	0.000	95	84
Clotting time (min)	70.9	56.5–85.3	0.010	70	62
PT-INR	72.2	58.3–86.1	0.006	75	65
Serum albumin (gm/dl)	*11.4	0.7–22.1	0.000	25	06
RBS (mg/dl)	*40.9	25.4–56.3	0.259	55	41
Serum sodium (mmol/L)	*47.0	29.4–64.5	0.707	40	43
Serum potassium (mmol/L)	*50.0	34.6–66.1	0.967	65	43
Serum urea (mg/dl)	*41.1	24–58.1	0.270	35	46
Serum creatinine (mg/dl)	*38.6	23.3–54.0	0.016	60	25

***AUC<70% is considered as not acceptable. ASTs: Aspartate transaminases, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, PT-INR: Prothrombin time-international normalized ratio, RBS: Random blood sugar, AUC: Area under the curve, CI: Confidence interval**

Table 2b: ROC curve details of Group 2 versus Group 3

Variables	AUC (%)	95% CI (%)	p value	Sensitivity (%)	Specificity (%)
Serum bilirubin total (mg/dl)	93.4	86.5–100	0.000	83.3	81
Serum bilirubin direct (mg/dl)	89.9	80.1–99.8	0.000	88.9	85.7
AST (IU/L)	94.3	85.8–100	0.000	100	85
ALT (IU/L)	96.0	88.8–100	0.000	100	71
ALP (IU/L)	88.6	78.0–99.2	0.000	83.3	81
Clotting time (min)	100	100	0.000	100	100
PT-INR	72.2	58.3–86.1	0.006	100	100
Serum albumin (gm/dl)	*0.3	0–1	0.000	100	100
RBS (mg/dl)	*40.9	22.6–59.2	0.331	44.4	32
Serum sodium (mmol/L)	*55.8	37.2–74.4	0.535	55.6	62
Serum potassium (mmol/L)	*50.0	22.9–59.4	0.345	50	53
Serum urea (mg/dl)	*63.5	45.5–81.5	0.151	66.7	66.7
Serum creatinine (mg/dl)	*61.8	43.7–79.9	0.210	61.1	61.9

***AUC<70% is considered as not acceptable. ASTs: Aspartate transaminases, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, PT-INR: Prothrombin time-international normalized ratio, RBS: Random blood sugar, AUC: Area under the curve, CI: Confidence interval**

Tukey *post hoc* analysis, p=0.000; whereas mean score of severe hepatic dysfunction (10.48 ± 1.86) is significantly lower than very severe hepatic dysfunction (21.28 ± 1.23) but higher than no severe hepatic dysfunction (2.92 ± 1.92) as evidenced by Tukey *post hoc*, p=0.000.

There was statistically significant difference of mean duration of hospitalization in days between three groups of hepatic dysfunction as evidenced by one-way ANOVA; F=(2, 73)=19.83, p=0.000. Mean duration of hospitalization in days in no severe hepatic dysfunction (1.68 ± 1.07) was significantly lower as compared to very severe hepatic dysfunction (2.72 ± 1.96) and severe hepatic dysfunction (4.00 ± 1.20) as evidenced by Tukey *post hoc*, p=0.000. Mean duration of hospitalization in days in severe hepatic dysfunction (4.09 ± 1.22) was significantly higher as compared to no severe hepatic dysfunction (1.68 ± 1.07) and very severe hepatic dysfunction (2.72 ± 1.96) as evidenced by Tukey *post hoc* analysis, p=0.029; whereas mean duration of hospitalization in days in very severe hepatic dysfunction (2.72 ± 1.96) is significantly lower than severe hepatic dysfunction (4.00 ± 1.20) but higher than no severe hepatic dysfunction (1.68 ± 1.07) as evidenced by Tukey *post hoc*, p=0.011.

DISCUSSIONS

Dengue is a major international health concern prevailing in tropical and subtropical countries. Global incidence of dengue has increased dramatically in the recent years. In our study, there is no significant difference between mean age and sex distribution between three groups of dengue children. In the present study, male children were more affected than female which was similar to that of previous study [19]. This difference might be due to more outdoor activities of males which lead to more chances of daytime mosquitoes' bite. Only serologically confirmed dengue cases are taken for study, out of which maximum are IgM positive as our study is conducted in a tertiary care center and most of the patients are referred from periphery hospital. Fever was the most

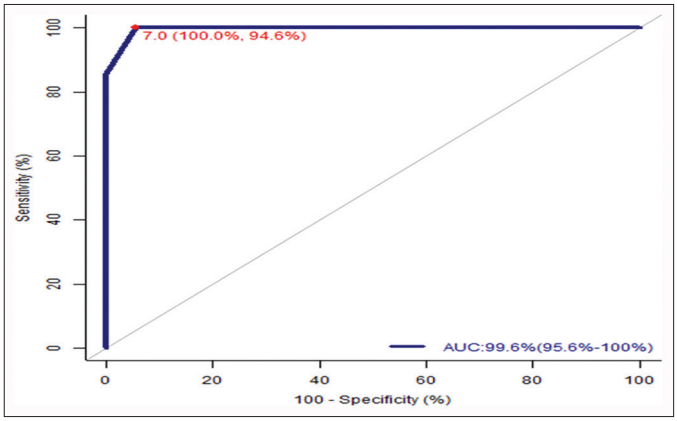

Figure 2: Dengue hepatic severity score (Group 1 vs. Group 2)

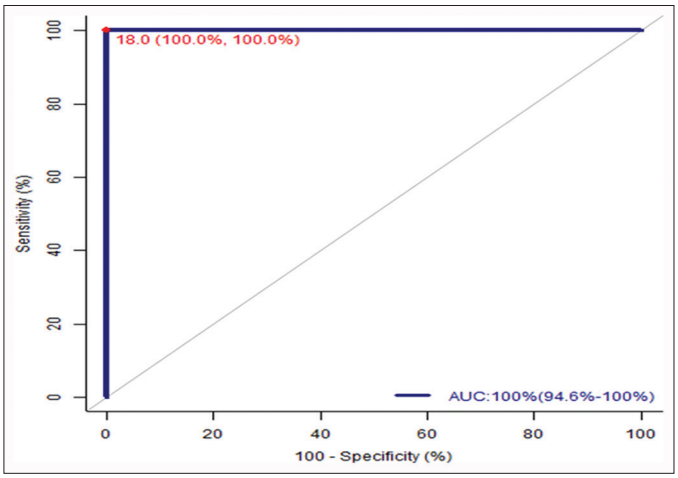

Figure 3: Dengue hepatic severity score (Group 2 vs. Group 3)

common symptom invariably present in all the three groups and this was similar to the study done in India in 2015 [19]. In our study, abdominal pain, tenderness, and hepatomegaly were found in 50% cases, which was similar to the report by other studies [9-12] with 36.4–96% of the cases. Among hepatic dysfunctions, Sr. bilirubin is raised in 34% cases similar to earlier study [19]. Liver damage with elevation of aminotransferase enzymes is a known complication of dengue infection. Hence, AST and ALT values measurements are mandatory to know the liver involvement [20]. AST levels tend to rise more than ALT levels in dengue infections [21,22]. The definite cause is not known, but it may be due to excessive release of AST from damaged myocytes during dengue [23]. In our study, ALT values were greater than AST values which were contrary to other study [24]. The AST levels return to normal more rapidly than ALT levels as AST (12.5–22 h) has a shorter half-life than ALT (32–43 h) [25]. As this is a tertiary care hospital-based study, maximum cases were referral patients from periphery hospital which in turn may account for the greater ALT values than AST in our study. Similarly, ALP levels were raised more in Groups 2 and 3 which were similar to previous study [25]. PT-INR and CT values were increased in Group 3 cases.

Laboratory parameters were taken as Score-A (Table 1c). However, not all the laboratory parameters were taken into consideration for score. We have also done CBC, but we have not included those parameters, as our point of interest was only hepatic dysfunction parameters. We have taken RBS, Sr. sodium, Sr. potassium, Sr. urea, Sr. creatinine, Sr. bilirubin total and direct, AST, ALT, ALP, Sr. albumin, PT-INR, and CT as these laboratory parameters affect or alter the liver functions. RBS is monitored as there may be hypoglycemia in hepatic pathology [26]. Low Sr. sodium (hyponatremia) is a known complication in liver disease which leads to altered sensorium or seizure [27]. Low Sr. potassium (hypokalemia) is noted in liver dysfunctions which in turn affect other systems of the body [27]. Sr. urea and creatinine is taken due to the chance of hepatorenal syndrome resulting in uremia, azotemia [28]. Sr. bilirubin total and direct, AST, ALT, ALP, and Sr. albumin levels were measured as these parameters altered most in liver dysfunctions [19-22]. CT and PT-INR were evaluated due to their alteration in severe hepatic dysfunction, whereas BT was not included as its derangement reflects platelet disorder, and further, we have included bleeding manifestations in clinical hepatic parameters [19-22,29]. Of these, only those parameters were considered for score whose cutoff values were acceptable as evidenced by AUC ≥70% in ROC curve.

In ROC curve analysis, although p value is statistically significant, the test is said to be acceptable only when AUC ≥70%. In our study, RBS, Sr. sodium, Sr. potassium, Sr. urea, Sr. creatinine, and Sr. albumin were excluded from scoring system due to the fact that their cutoff values were not acceptable as exhibited by AUC <70%. Hence, these parameters were not included in Score-A.

We have also given points to various clinical hepatic manifestations based on its presence (1) or absence (0) and named it as Score-B (Table 1a). The variables included for score were vomiting, pain abdomen and/or tenderness, hepatomegaly, ascites, bleeding manifestations, respiratory distress, loss of consciousness or seizure, and shock. These specific clinical features were considered for score due to the fact that all these parameters were there in dengue classification, the WHO 2009. We have included vomiting as it is one of the common symptoms in liver disease as well as in dengue. Pain abdomen and/or tenderness occur due to stretching of the liver capsules, a cardinal feature of liver involvement [30], so included in score. Hepatomegaly is an important sign found in liver diseases due to infections or inflammation [30], hence, considered for score. Ascites is also commonly seen in dengue with warning signs and other liver diseases [31]. We have taken only clinical ascites not the sonographically proved one as our score system is meant for primary health caregivers in periphery hospital as well where ultrasound facility is rare. Bleeding manifestations, respiratory distress, loss of consciousness or seizure, and shock are included because these are the main clinical signs and symptoms seen in severe dengue as well as other severe liver diseases [29-31]. We have not included fever in our score as it is present invariably in all three groups of dengue. Jaundice also not included, though it is a main symptom in liver diseases as sometimes it is difficult to appreciate in anicteric phase, so we have taken Sr. bilirubin

instead which is more confirmatory [20]. We have not done tourniquet test also as low proportion of positive tourniquet test seen in Indian studies may be due to the darker skin color in Indian children [22].

Like other studies, the current study is also not devoid of limitations. Since this is a cross-sectional study, level of evidence is low. As it is a hospital-based study in a tertiary care center with limited resources, its result could not be generalized. It is a single-center study with small sample size, so the results were not devoid of confounder, interactions despite our relentless efforts. This study was also not devoid of selection bias due to sampling technique and data collection method from existing records. In view of the above-mentioned limitations, long-term follow-up was required for validity of the study and test of reliability was needed, and therefore, in future, a larger multicenter cohort study is awaited to do time trend analysis to assess the prediction of progression from one category to other. We have planned to test the reliability of this score system at community level and this is under process.

CONCLUSION

The results of the present study conclude that DHSS could be a useful tool to predict and treat severity of dengue infections in future so that a primary health caregiver can receive the maximum benefit for triaging, early recognition, and prompt management which in turn will reduce the morbidities, mortalities, financial burden of the parents, and the government as well.

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