Clinical, haematological and radiological predictors of severe dengue in the paediatric population

***Shehraz Firoz[1], Payal Mittal[2], Ravi Teja[3], Harsh Kumar[3], Sonia Bhatt[4]**

Sri Lanka Journal of Child Health, 2023; **52(2):** 188-194
DOI: https://doi.org/10.4038/sljch.v52i2.10463

Abstract

Background: Dengue is a mosquito borne viral infection which has higher morbidity and mortality in the paediatric age group than in the adult group.

Objectives: To assess the clinical and haematological parameters for early diagnosis and better management of severe dengue (SD).

Method: A prospective observational study was conducted in the Department of Paediatrics, FH Medical College, Agra, India from September 2021 to February 2022. Confirmed dengue cases aged 1 month to 18 years were included in the study. Cases were classified into two groups, non-severe dengue (dengue fever and dengue with warning signs) and SD. All cases had complete history, clinical examination, and relevant investigations. Bivariate analysis was performed using Chi-square test and p value <0.05 was considered significant.

Results: A total of 801 confirmed cases of dengue, admitted in FH Medical College, were included in study. Of them, 564 had non-severe dengue and 237 had SD. Clinical features like gastrointestinal bleeding, lethargy, low pulse pressure, altered consciousness, ascites, bilateral pleural effusion and oliguria were significantly higher in SD as compared to non-severe dengue (p-value <0.05). Haematological parameters like severe thrombocytopenia, raised haematocrit (HCT), liver transaminase levels, deranged prothrombin time (PT) / international normalised ratio (INR), hypoalbuminaemia and radiological features like bilateral pleural effusion and ascites were significantly associated (p-value <0.05) with SD.

Conclusions: In this study, clinical features like erythema, abdominal pain, vomiting, jaundice, cough, hepato-splenomegaly, severe bleeding, lethargy, low pulse pressure, altered consciousness, ascites and bilateral pleural effusion were significantly associated with SD compared to non-severe dengue. Haematological parameters like severe thrombocytopenia, raised HCT, raised transaminase levels and deranged PT/INR and hypoalbuminaemia were also significantly associated with SD.

(Key words: Children, Severe dengue, Thrombocytopenia)

[1]*Associate Professor,* [2]*Assistant Professor,* [3]*Junior Resident,* [4]*Professor and Head*, *Department of Paediatrics, F H Medical College, Agra, India*
**Correspondence:* Dr.shehrazfiroz@gmail.com
https//orcid.org/0000-0002-4898-5529

(Received on 21 January 2023: Accepted after revision on 24 March 2023)
The authors declare that there are no conflicts of interest
Personal funding was used for the project.

Introduction

Dengue fever (DF) is a mosquito-borne arboviral infection caused by the dengue virus (DENV) which has four different serotypes. Patients infected with DENV have a wide spectrum of clinical manifestations, ranging from asymptomatic to severe dengue (SD), including dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS)[1,2]. Incidence and mortality from dengue are increasing globally with each passing year[3]. Around 1.8 million of the population which is at risk for dengue live in endemic countries of the South East Asia Region[3]. Without proper treatment, the case fatality rate in SD is more than 20% and with timely intervention, it can be reduced to less than 1%[4]. A major dengue epidemic was seen in India in 2021 during which Uttar Pradesh recorded a 10-fold increase in the number of reported cases (over 20,000)[5].

A peculiarity of DENV infection is that infection by one serotype produces serotype-specific lifelong immunity; however, instead of giving protection or remaining neutral against other serotypes, a secondary infection by a heterogeneous serotype often results in severe disease by a mechanism called antibody dependent enhancement (ADE)[6]. DSS mortality is reported to be 50 times higher than that of DF[7]. SD is a leading cause of serious illness and death among children in some Asian and Latin American countries[8]. Patients with dengue illness can sometimes develop unusual manifestations such as involvement of liver, kidneys, brain or heart with or without evidence of fluid leakage. Such unusual manifestations may be associated with co-infections and co-morbidities and are mostly a result of prolonged shock leading to organ failure. These

atypical features, if found, are defined as 'expanded dengue syndrome'[9]. Management of dengue with warning signs or SD requires hospital admission and judicious fluid management along with supportive therapy. As SD has a high mortality and morbidity and there is no specific management available, early detection of clinical and haematological parameters helps in early diagnosis and management.

Objectives

To assess the clinical and haematological parameters for early diagnosis and better management of SD

Method

This prospective observational study was conducted in the department of paediatrics of FH Medical College, Agra, India, from September 2021 to February 2022.

Inclusion criteria:

- Children diagnosed clinically as DF aged 1 month to 18 years.
- Cases confirmed based on the presence of NS1 antigen and/or IgM or IgG antibody by rapid immunochromatography and enzyme-linked immunosorbent assay.

Exclusion criteria:

- Children with pre-existing chronic illness or any concurrent fever causing illness such as malaria, typhoid or urinary tract infections.
- Children discharged before clinical recovery and those with co-infections.
- Parents refused to allow the children to participate in study.

Children satisfying inclusion criteria were recruited to the study. A detailed history was taken and a complete physical examination was done, including all vital parameters. Cases were classified according to the World Health Organisation (WHO) classification of dengue[1]

- Probable dengue
- Dengue with warning signs
- Severe dengue

The relevant investigations recorded were total white blood cell (WBC) count, platelet count, haematocrit (HCT), transaminases level, prothrombin time (PT)/international normalised ratio (INR), chest x-ray and ultrasonography (USG) of abdomen. Other investigations like magnetic resonance imaging (MRI) of brain and cerebrospinal fluid (CSF) analysis were done when required. Criteria used to define laboratory parameters are as follows:[10-12]

1. Haemoconcentration: More than 20% increase in HCT from baseline
2. Leucocytosis – Peripheral WBC count more than for age
3. Leucopenia – Peripheral WBC count less than 5000/μL
4. Elevated serum aspartate transaminase (AST) / alanine transaminase (ALT) - more than 40U/L
5. Deranged PT/INR – as per age
6. Hypoalbuminaemia – < 2.5 mg/dl

Patients were followed up daily for development of new symptoms, signs, or complications till discharge/death. Blood counts were repeated every 24 hours till defervescence of fever. Subsequently, patients were divided into two groups and various clinical, haematological and radiological features were compared in the two groups.

Group 1 - Non severe dengue – Included are probable dengue and dengue with warning sign
Group 2 - Severe dengue.

Ethical issues: The study was approved by the Institutional Ethics Committee, F.H. Medical College Tundla, Firozabad, India (No: FHMC/IEC/R.Cell/2022/ dated 12.09.2022). Written informed consent was obtained from the parents of the participating children and assent from the children over 12 years of age.

Statistical analysis: Descriptive data are presented as numbers or percentages. Comparison of the groups for categorical variables was done by Chi-square test. Descriptive statistics were reported as percentages and means when applicable along with standard deviation. Data were analysed using SPSS software. A two-tailed p-value smaller than 0.05 was considered statistically significant

Results

A total of 801 children were admitted with dengue over the study period. All the children were included in the study.

Table 1 shows the demographic profile of the dengue cases. Children of age group 6-10 years constituted the highest percentage (38.5%) of total cases. However, SD was more common in children between 1-5 years and they constituted 47.7% of the total SD cases.

The 801 children with dengue were categorized according to the WHO classification as shown in Table 2.

Table 1: ***Demographic profile of dengue cases***

Characteristic	Non-severe *(n=564)* *n (%)*	Severe *(n=237)* *n (%)*	Total *(n=801)* *n (%)*
Age group			
1 month to <1 year	48 (08.5)	04 (01.7)	52 (06.5)
1-5 years	166 (29.4)	113 (47.7)	279 (34.8)
6-10 years	213 (37.8)	95 (40.1)	308 (38.5)
11-18 years	137 (24.3)	25 (10.5)	162 (20.2)
Gender			
Male	351 (62.2)	135 (57.0)	486 (60.7)
Female	213 (37.8)	102 (43.0)	315 (39.3)
Residence			
Urban	300 (53.2)	134 (56.5)	434 (54.2)
Rural	264 (46.8)	103 (43.5)	367 (45.8)

Table 2: ***Children with dengue according to World Health Organisation (WHO) classification (n=801)***

WHO classification	Number (%)
Dengue fever	165 (20.6)
Dengue fever with warning signs	399 (49.8)
Severe dengue	237 (29.6)
Dengue haemorrhagic fever (DHF)	110 (13.6)
Dengue shock syndrome (DSS)	127 (15.9)

Table 3 shows the clinical manifestations of the cases. Clinical features such as erythema, abdominal pain, anorexia, vomiting, hepatomegaly, respiratory distress, splenomegaly, oedema, altered sensorium, jaundice, oliguria, ascites, lethargy, low pulse pressure and gastrointestinal bleeding were significantly associated with SD compared to non-severe dengue.

Table 3: ***Clinical manifestations of the dengue cases***

Clinical feature	Non severe *(n=564)* *n (%)*	Severe *(n=237)* *n (%)*	Total *(n=801)* *n (%)*	p-value
Fever	547 (96.9)	232 (97.9)	779 (97.2)	0.4747
Erythema	80 (14.1)	120 (50.6)	200 (24.9)	**<0.0001**
Nasal bleeding	68 (12.0)	28 (11.8)	96 (12.0)	0.9232
Body pain	171 (30.3)	63 (26.5)	234 (29.2)	0.2884
Abdominal pain	238 (42.2)	199 (83.9)	437 (54.5)	**<0.0001**
Anorexia	345 (61.1)	14 (05.9)	359 (44.8)	**<0.0001**
Loose stools	50 (09.1)	12 (05.0)	62 (07.7)	0.0661
Vomiting	251 (44.5)	177 (74.6)	428 (53.4)	**<0.0001**
Hepatomegaly	218 (39.9)	186 (78.4)	545 (68.0)	**<0.0001**
Seizure	39 (07.1)	15 (06.3)	54 (06.7)	0.7628
Respiratory distress	44 (07.8)	56 (23.6)	100 (12.4)	**<0.0001**
Splenomegaly	30 (05.3)	184 (77.6)	214 (26.7)	**<0.0001**
Oedema	92 (16.3)	129 (54.4)	221 (27.6)	**<0.0001**
Altered sensorium	12 (02.1)	135 (57.0)	147 (18.4)	**<0.0001**
Flushing	44 (07.8)	12 (05.0)	56 (06.9)	0.1654
Petechiae	241 (42.7)	84 (35.4)	325 (40.5)	0.0552
Jaundice	10 (01.7)	113 (47.7)	123 (15.4)	**<0.0001**
Sore throat	54 (09.5)	21 (08.8)	75 (09.4)	0.7516
Itching	292 (51.7)	118 (49.7)	410 (51.1)	0.6081
Rhinorrhea	29 (05.1)	19 (08.0)	48 (05.9)	0.7516
Lymphadenopathy	32 (05.6)	11 (04.6)	43 (05.3)	0.5540
Oliguria	0	59 (24.8)	59 (07.3)	**<0.0001**
Ascites	25 (04.4)	135 (41.6)	160 (19.9)	**<0.0001**
Lethargy	59 (10.4)	93 (39.2)	152 (18.9)	**<0.0001**
Low pulse pressure	94 (16.6)	223 (94.0)	317 (39.5)	**<0.0001**
Gastrointestinal bleeding	0	120 (50.6)	120 (15.0)	**<0.0001**

Haematological parameters like severe thrombocytopenia (<50,000/cu mm) raised HCT (≥20%), elevated AST and ALT, deranged PT/INR and hypoalbuminaemia were significantly associated with disease severity. Radiological features suggesting bilateral pleural effusion and ascites were significantly associated with disease severity (Table 4).

Table 4: ***Haematological and radiological parameters of children with dengue***:

Parameter	Non-severe *(n=564)* *n (%)*	Severe *(n=237)* *n (%)*	Total *(n=801)* *n (%)*	p-value
Leucocytosis	234 (41.4)	82 (34.5)	316 (39.4)	0.0686
Leucopenia	120 (21.2)	57 (24.0)	177 (22.0)	0.3878
Thrombocytopenia				
<100,000/cu mm	381 (67.5)	32 (13.5)	413 (51.5)	**<0.0001**
<50,000/cu mm	183 (32.4)	205 (86.4)	388 (48.4)	**<0.0001**
Haematocrit (≥20%)	95 (16.8)	221 (93.2)	316 (39.4)	**<0.0001**
Aspartate transaminase (raised)	179 (31.7)	180 (75.9)	359 (44.8)	**<0.0001**
Alanine transaminase (raised)	77 (31.3)	184 (77.6)	363 (45.3)	**<0.0001**
Prothrombin time/INR (deranged)	78 (13.8)	89 (37.5)	167 (20.8)	**<0.0001**
Hypoalbuminaemia	94 (16.6)	127 (53.5)	221 (27.5)	**<0.0001**
NSI antigen	536 (95.0)	90 (37.9)	626 (78.1)	**<0.0001**
NSI+ IgM/ IgG	54 (09.5)	121 (51.0)	175 (21.8)	**<0.0001**
Chest x-ray				
Unilateral pleural effusion	18 (03.1)	22 (09.2)	40 (04.9)	**<0.001**
Bilateral pleural effusion	06 (01.0)	21 (08.8)	27 (03.3)	**<0.0001**
Ultrasonography of abdomen				
Gallbladder wall thickening	141 (25.0)	60 (25.3)	257 (32.0)	0.9249
Ascites	25 (04.4)	135 (56.9)	160 (19.9)	**<0.0001**
Acalculous cholecystitis	359 (63.6)	151 (63.7)	510 (63.6)	0.9870

Discussion

In the present study, the most commonly affected age group was 6-10 years, while the incidence of SD was more in the 1-5-year age group. In contrast, studies by Reddy A, *et al*[13] and Jain H[14] found the 5-10-year age group to be significantly associated with SD. Children aged 1-5 years presenting with SD could be due to an immaturely developed immune system. SD was more common in males as compared to females in this study which was similar to studies by Reddy A, *et al*[13] and Afroze S, *et al*[15]. This gender difference can be due to the relatively more exposed body surface area. Children from urban areas were affected more than children from rural areas probably because urban lifestyle is more commonly associated with breeding of mosquitoes, which was similar to studies by Suresh A, *et al*[16] and Shah PS, *et al*[17]. In our study, 29.7% children had SD which was comparable to a study by Afroze S, *et al*[15] who reported 32% cases of SD. However, the study by Jain H[14] found 12.3% of SD cases, which might be due to a relatively small sample size.

Erythema was significantly associated with SD, similar to a study by Reddy A, *et al*[13]. Another important observation in the study was the statistically significant association of lethargy with SD. Meta-analysis conducted by Tsheten T, *et al*[18] also showed that lethargy was significantly associated with the severity of dengue. In our study, vomiting, abdominal pain and jaundice were associated with SD which was similar to studies by Tsheten T, *et al*[18] and Arora SK, *et al*[19]. However, in the study by Arora SK, *et al*[19], jaundice was not significantly associated with SD. In the present study, hepatomegaly and splenomegaly were significantly associated with SD. There were similar findings in studies by Malleshappa K, *et al*[20], Arora SK, *et al*[19] and Reddy A, *et al*[13]. Respiratory distress was significantly associated with SD which was similar to studies by Reddy A, *et al*[13], Naaraayan SA, *et al*[21] and Reddy GC, *et al*[22]. It might be due to plural effusion or pulmonary oedema.

In our study, bleeding manifestations like epistaxis were not associated with SD, whereas gastrointestinal bleeding was significantly associated with SD which was similar to the study by Tsheten T, *et al*[18]. Central nervous system (CNS) manifestations like altered sensorium were significantly associated with SD. There were similar findings in studies by Afroze S, *et al*[15] and Khan MAS, *et al*[23]. The altered sensorium is either secondary to multi-systemic derangements like shock, hepatitis or coagulopathy leading to dengue encephalopathy or direct neuronal infiltration of CNS by the dengue virus. In the present study, clinical features of plasma leakage in form of ascites, pleural effusion and oedema were significantly seen in SD cases. There were similar findings in studies by Yuan K, *et al*[24] and Arora SK, *et al*[19]. Low pulse pressure and oliguria were significantly associated with SD cases, which was similar to the study by Reddy A, *et al*[13].

On serology, 78.1% cases were NS1 positive, and majority were non-severe dengue whereas 21.8% cases were NS1 and IgM or IgG positive. Children with positive NS1 along with IgG were significantly associated with SD. It signifies re-infection of dengue associated with SD. Similar findings were seen in the study by Afroze S, *et al*[15]. On chest x-ray, bilateral pleural effusion was associated with SD, which was similar to the study by Reddy GC, *et al*[22], On USG of abdomen, ascites was the common finding associated with SD. There was a similar finding in the study by Pothepragada S, *et al*[25] on univariate analysis. Unlike the present study, a study by Malleshappa K, *et al*[20] suggested ascites and pleural effusion were not significantly associated with SD. They found perinephric oedema was significantly associated with dengue severity.

In haematological parameters, a predominant feature of dengue was thrombocytopenia. Suggested mechanisms that contribute to thrombocytopenia in dengue include reduced thrombopoiesis through bone marrow suppression and increased platelet clearance in peripheral blood. Regarding reduced thrombopoiesis, hematopoietic suppression is a well-known phenomenon during DENV infection. A marked bone marrow hypocellularity is described at onset of the febrile phase with pancytopenia, including megakaryocytes[26]. Severe thrombocytopenia (<50,000 platelets/cu mm) was significantly associated with SD. A study by Sreenivasan P, *et al*[27] showed thrombocytopenia between 40,000 to <100,000 platelets/cu mm was significantly associated with SD. There were similar findings in a study by Nandwani S, *et al*[28] where the initial platelet count (<20,000/cu mm) was significantly associated with mortality. In our study, about 48.4% of the total population had severe thrombocytopenia whereas bleeding manifestation such as epistaxis and gastrointestinal bleeding were 12% and 15% of total cases respectively and there was no correlation between severe thrombocytopenia and bleeding manifestations. Similar findings were seen in studies by Avasthi S, *et al*[29] and Laul A, *et al*[30]. Temporary alteration of endothelial glycocalyx and functional capillary leak cause haemoconcentration and raised HCT. Raised HCT was also significantly associated with SD cases in our study, which was comparable to a study by Yuan K, *et al*[24]. PT/INR values and hypoalbuminaemia were significantly (p-value <0.0001) seen in SD cases. Similar findings were seen in studies by Reddy A, *et al*[13] and Balakrishnan VS, *et al*[31]. Raised AST/ALT was significantly associated with SD. Similar findings were seen in studies by Yuan K, *et al*[24] and Balakrishnan VS, *et al*[31]. Neither leucocytosis nor leucopenia was significantly associated with dengue severity in this study, which was similar to a study conducted by Arora SK, *et al*[19].

The strength of the study was a good sample size to represent the population. One limitation of the study was that it was confined to a single tertiary care centre; hence there could be a selection bias and observational bias. Another limitation is that some patient samples were taken after fluid resuscitation was done in cases of emergencies which can result in error of HCT values. Larger prospective studies are needed to validate the findings observed in this study. Virus serotyping also was not done.

Conclusions

In this study, clinical features like erythema, abdominal pain, vomiting, jaundice, cough, hepato-splenomegaly, severe bleeding, lethargy, low pulse pressure, altered consciousness, ascites and bilateral pleural effusion were significantly associated with severe dengue compared to non-severe dengue. Haematological parameters like severe thrombocytopenia, raised HCT, raised transaminase levels and deranged PT/INR and hypoalbuminemia were also significantly associated with severe dengue.

References

1. World Health Organization. Dengue guidelines for diagnosis, treatment, prevention and control: new edition. [Internet] Geneva (2009). (Accessed on 10/10/22) Available at: https://apps.who.int/iris/handle/10665/44188

2. World Health Organization. Dengue haemorrhagic fever: diagnosis, treatment, prevention and control, 2nd edition [Internet](1997). Accessed on 10/10/22. Available at: https://apps.who.int/iris/handle/10665/41988

3. World Health Organization. Country Office for India. 2015. National guidelines for clinical management of dengue fever. Accessed on 11/1022. Available at: https://apps.who.int/iris/handle/10665/208893

4. World Health Organization. Regional Office for South-East Asia. (2011). Comprehensive Guideline for Prevention and Control of Dengue and Dengue Haemorrhagic Fever. Revised and expanded edition. WHO Regional Office for South-East Asia. Cited Date:29 March 2020. Accessed on 10/10/22. Available at: https://apps.who.int/iris/handle/10665/204894

5. National Centre for Vector Borne Diseases Control. India. Directorate General of Health Services, Ministry of Health and Family welfare. 2022 Dengue/DHF Situation in India: Dengue cases and Deaths in the Country since 2015. [Updated: September 13, 2022; cited 9 December 2021] Available from: <htttps://nvbdcp.gov.in/index4.php?lang=1& level = 0 & linked = 431 & lid=3715>

6. Uno N, Ross TM. Dengue virus and the host innate immune response. *Emerging Microbes and Infections* 2018; **7**(1): 167. https://doi.org/10.1038/s41426-018-0168-0
PMid: 30301880 PMCid: PMC6177401

7. Anders KL, Nguyet NM, Chau NV, Hung NT, Thuy TT, Lien le B, *et al.* Epidemiological factors associated with dengue shock syndrome and mortality in hospitalized dengue patients in Ho Chi Minh City, Vietnam. *American Journal of Tropical Medicine and Hygiene* 2011; **84**(1): 127-34. https://doi.org/10.4269/ajtmh.2011.100476
PMid: 21212214 PMCid: PMC3005500

8. WHO. Geneva. Dengue and severe dengue [Internet]. 2019. Accessed on:11/10/22. Available at: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue/

9. National Malaria Elimination & Aedes Transmitted Disease Control Program. Disease Control Unit. Directorate General of Health Services. 2018. National Guidelines for Clinical Management of Dengue Syndrome – 4th Edition, Bangladesh [revised: May 2020, Accessed on: 11/10/22]. Available from: https://drive.google.com/file/d/1Xzz6XsnBzAd8nyskk2EWX0kv7BwQ6ymL/view.

10. Padmaprakash KV, Jha VK, Bhushan S, Deepkamal, Sowmya KC. Demographic and clinical profile of dengue fever in a tertiary care hospital of South India. *Journal of the Association of Physicians India* 2020; **68**(11): 24-7.

11. Lo SF. Reference interval for laboratory test and procedures; Kliegman, Robert. Nelson Textbook of Pediatrics First South Asia Ed. New Delhi, PA: Elsevier, 2016p.3464-3466

12. Hughes HK, Kahl LK. The Harriet Lane Handbook. 1st South Asian edition. New Delhi (India). Elsevier, Inc.2017. pg.317, 377.

13. Reddy A, Reddy D, Musali SR. A study on predictors of severe dengue in paediatric patients in a tertiary care hospital in Telangana. *Indian Journal of Child Health* 2021; **8**(4): 162–5. https://doi.org/10.32677/IJCH.2021.v08.i04.006

14. Jain H. Clinical profile and outcome of dengue fever in hospitalized children of South Rajasthan, India. *International Journal of Contemporary Pediatrics* 2016: **3**: 546-9. https://doi.org/10.18203/23493291.ijcp20161035

15. Afroze S, Shakur S, Wahab A, Shakur S. Clinical profile of dengue and predictors of its severity among children. *American Journal of Pediatrics* 2019; **5**(4): 219-23. https://doi.org/10.11648/j.ajp.20190504.19

16. Suresh A, Sreedhar KV, Mathew J, Vijaykumar.KN, Ajithlal PM, Saini P *et al.* Seroprevalence of dengue in urban and rural settings in Kerala, India. *Current Science* 2021: **121**: 233-8. https://doi.org/10.18520/cs/v121/i2/233-238

17. Shah PS, Deoshatwar A, Karad S, Mhaske S, Singh A, Bachal RV *et al.* Seroprevalence of dengue in a rural and an urbanized village: A pilot study from rural western India. *Journal of Vector Borne Diseases* 2017; **54**(2): 172-6.

18. Tsheten T, Clements ACA, Gray DJ, Adhikary RK, Furuya-Kanamori L, Wangdi K. Clinical predictors of severe dengue: a systematic review and meta-analysis. *Infectious Diseases of Poverty* 2021; **10**: 123. https://doi.org/10.1186/s40249-02100908-2
PMid: 34627388 PMCid: PMC8501593

19. Arora SK, Nandan D, Sharma A, Benerjee P, Singh DP. Predictors of severe dengue amongst children as per the revised WHO classification. *Journal of Vector Borne Diseases* 2021; **58**(4): 329-34.

https://doi.org/10.4103/0972-9062.318312
PMid: 35381822

20. Malleshappa K, Srinivasa K. Role of ultrasound in early prediction of severity of dengue infection. *Indian Journal of Child Health* 2017; **4**(2): 155-8. https://doi.org/10.32677/IJCH.2017.v04.i02.011

21. Naaraayan SA, Sundar KC. Risk factors of severe dengue in children: A nested case-control study. *Journal of Pediatric Critical Care* 2021; **8**: 224-8. https://doi.org/10.4103/jpcc.jpcc_59_21

22. Reddy GC, Nagendra K. Clinical and diagnostic features of dengue haemorrhagic fever in children. *International Journal of Contemporary Pediatrics* 2018; **5**: 791. https://doi.org/10.18203/23493291.ijcp20181387

23. Khan MAS, Al-Mosabbir A, Raheem E, Ahmed A, Rouf RR, Hasan M, *et al.* Clinical spectrum and predictors of severity of dengue among children in 2019 outbreak: A Multicenter Hospital-Based Study in Bangladesh. *BMC Pediatrics* 2021; **21**(1): 478. https://doi.org/10.1186/s12887-02102947-y PMid: 34715835 PMCid: PMC8555185

24. Yuan K, Chen Y, Zhong M, Lin Y, Liu L. Risk and predictive factors for severe dengue infection: A systematic review and meta-analysis. *PloS One* 2022; **17**(4): e0267186. https://doi.org/10.1371/journal.pone.0267186 PMid: 35427400 PMCid: PMC9012395

25. Pothapregada S, Kullu P, Kamalakannan B, Thulasingam M. Is ultrasound a useful tool to predict severe dengue infection? *Indian Journal of Pediatrics* 2016; **83**(6): 500-4. https://doi.org/10.1007/s12098-015-2013-y PMid:26846603

26. Quirino-Teixeira AC, Andrade FB, Mendonça-Pinheiro MB, Rozini SV, Hottz ED. Platelets in dengue infection: more than a numbers game. *Platelets* 2021; **33**: 176-83. https://doi.org/10.1080/09537104.2021.1921722 PMid: 34027810

27. Sreenivasan P, Geetha S, Sasikala K. Development of a prognostic prediction model to determine severe dengue in children. *Indian Journal of Pediatrics* 2018; **85**(6): 433–9. https://doi.org/10.1007/s12098-017-2591-y PMid: 29344875

28. Nandwani S, Bhakhri BK, Singh N, Rai R, Singh DK. (). Early hematological parameters as predictors for outcomes in children with dengue in northern India: A retrospective analysis. *Revista da Sociedade Brasileira de Medicina Tropical* 2021; **54**: e05192020. https://doi.org/10.1590/0037-8682-0519-2020 PMid: 33533817 PMCid: PMC7849329

29. Avasthi S, Singh VK, Kumar S, Kumar A, Dutta S. The changing spectrum of dengue fever in the 2009 epidemic in North India: A tertiary teaching hospital-based study. *Journal of Clinical Diagnosis and Research* 2012; **6**: 999-1002.

30. Laul A, Paul P, Merugumala V, Pathak R, Miglani U, Saxena P. Clinical profiles of dengue infection during an outbreak in northern India. *Journal of Tropical Medicine* 2016: **2016**: 5917934. https://doi.org/10.1155/2016/5917934 PMid: 28025597 PMCid: PMC5153462

31. Balakrishnan VS, SimnaL L, Kailas L. The coagulation profile of children admitted with dengue fever and correlation with clinical severity. *International Journal of Contemporary Pediatrics* 2017; **4**: 2109. https://doi.org/10.18203/23493291.ijcp20174741