To study the clinical presentation, laboratory parameters and predictors of severity in dengue fever in children in a metropolitan city in India

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Abstract

***Background*:** Dengue fever (DF) is an acute viral febrile illness commonly seen in India. If not identified and treated early, it may prove fatal.

Objectives: To assess the clinical presentation, laboratory parameters and predictors of severity in DF in children in a metropolitan city in India.

Method: This was a cross-sectional observational study of 100 cases of DF conducted at Jagjivan Ram Western Railway Hospital in Mumbai from June 2015 to May 2016. All inclusion and exclusion criteria were defined and patients were enrolled. Data were collected on the preformed questionnaire and analysed statistically on software.

Results*:* DF was commoner in males. It was equally distributed in all parts of the metropolitan city; 58% patients with DF presented without warning sign while 31% presented with warning signs. The clinical features included vomiting, abdominal pain, breathlessness, retroorbital pain, jaundice and hypotension. Fever was seen in almost 100% cases. Thrombocytopenia was the common haematological finding. Raised liver enzymes and serum bilirubin were significantly associated with DF severity. Abnormal coagulation profile was also an important finding; 16% patients had tourniquet test positive.

Conclusions: In our study, severe abdominal pain, bleeding manifestations, breathlessness, tachycardia, tachypnoea, icterus and positive tourniquet test were significantly associated with severity. Among laboratory parameters, leucopenia (<5000/ cu mm), low platelet count, hyponatraemia, increased alanine transaminase level (>1000 IU/l), icterus and positive serology for both IgM and IgG were significantly correlated with severity.

(Key words: Dengue, Fever, Thrombocytopenia, Tourniquet test, Severity markers)

Background

Dengue fever (DF) is the most common life-threatening mosquito borne febrile viral infection seen in tropical countries, manifestations ranging from asymptomatic fever to severe life threatening illness[1]. All four serotypes are capable of causing illness which may be mild to fatal[2,3,4]. The illness mainly passes through 3 different phases. The febrile phase is associated with fever, vomiting, myalgia, headache and weakness. The typical rash generally appears once fever has subsided[5,6]. Some patients may go into to a critical phase during which there may be increased capillary permeability, and haemoconcentration leading to poor organ perfusion, severe bleeding and circulatory collapse[7]. The recovery phase is characterised by the absorption of fluid, normalisation of blood pressure and laboratory parameters. Sometimes, child may have complications like dengue haemorrhagic fever (DHF), acute renal failure (ARF), infarcts, encephalitis, severe respiratory distress syndrome, myocarditis and dengue shock syndrome (DSS)[1,8].

The old World Health Organisation (WHO) classification of DHF cannot be applied to all type of dengue patients[7,10]. The mechanism behind the pathogenesis is the antibody mediated cytokine release and activation of T cells resulting in the development of a cascade leading to inflammation and increase in capillary permeability[11-13]. DF can be diagnosed by viral isolation, genome detection and by NS1 antigen and antibody detection. NS1 antigen is a highly sensitive early marker for diagnosis of DF. The antibody response can be detected around 1 week of illness leading to early and late rise of IgM and IgG antibodies respectively[14]. Tourniquet test is a good screening test for DF which indicates

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significant capillary fragility and can be found positive in 50% of the patients[15].

Dengue infection can be fatal and may lead to multi-organ dysfunction and even death, so that early identification and timely management is crucial. The clinical line of demarcation is very narrow between stages so if early severity markers are not picked up, mortality is inevitable. Studies have described various clinical features, examination findings, laboratory parameters and severity markers. The demographic strain of dengue also varies in its presentation and severity. The severity of the disease must be defined in the respective area so that proper consensus and guidelines can be framed.

Objectives

To assess the clinical presentation, laboratory parameters and predictors of severity in DF in children in a metropolitan city in India.

Method

This was a cross-sectional observational study conducted in Jagjivan Ram Western Railway Hospital, Mumbai, India on 100 dengue patients admitted in the paediatric ward from June 2015 to May 2016, a period of one year.

Inclusion criteria: All suspected patients of age group 3 months to 14 years presenting with fever and typical symptoms of dengue illness, who were positive for NS1 antigen and serology were included in the study.

Exclusion criteria: The patients whose parents did not give consent for the study and children who did not fit into the age criteria were excluded from study.

All patients included in the study had a detailed history, clinical examination and laboratory parameters daily till discharge. Complete blood counts were done using an automated cell analyser with venous blood sample. All relevant investigations were done. The tourniquet test which indicates capillary fragility with increased vascular permeability is a part of WHO case definition of DF[15]. The standard method for the tourniquet test was followed. The cases in our study were defined as DF without warning signs, DF with warning sign and severe dengue as per new WHO 2011 classification[7,10].

Sample size:

n = sample size
z= 1.96 (at 95% confidence interval)
p= prevalence = 13.67%
(http://www.atmph.org/article.asp?issn=1755-6783;year=2012;volume=5;issue=1;spage=20;epage=23;aulast=Turbadkar)
q = 100-p = 86.33%
d= precision = 7% Therefore,
n = sample size for this study = 93
So sample size was taken as 100 in this study.

Ethical issues: Approval of institutional ethics committee of Jagjivan Ram Western Railway Hospital, Mumbai, India, was obtained before starting the study. Written informed consent was obtained from the parents of the children included in the study.

Statistical analysis: Data were collected on the pre-formed questionnaire. Data entry was done in Excel and analysis was done with the help of PSPP software and Sigma plot version 12. Quantitative data were presented with the help of mean, standard deviation, median and interquartile range (IQR); 'pre' and 'post' comparison among study groups were done with the help of one-way ANOVA test as per results of normality test. Qualitative data was presented with the help of frequency and percentage table; association among study group was assessed with the help of Chi-Square test and Fisher Exact test (2*2) table value less than 0.05 was taken a significant level.

Results

This study included a total of 100 patients who presented with clinical features suggesting DF. In our study mean age of children were 7.97± 3.84 years; 53 (53%) were males and 47 (47%) were females. Patients were classified according to WHO 2011 guidelines for DF. It was observed that out of the 100 patients, 58 (58%) had dengue without warning signs, 31(31%) had dengue with warning signs and 11 (11%) patients had severe dengue.

Various symptomatic presentation founds in our study are depicted in Figure 1.

Figure 1: *Presenting symptoms of dengue fever in study group*

Common findings on clinical examination were hepatomegaly with or without tenderness, tachycardia (when afebrile), hypotension, bradycardia, tachypnoea, positive tourniquet test, oedema, icterus and abnormal respiratory findings suggestive of pleural effusion. The tourniquet test (a good indicator of capillary fragility) was positive in

16% patients. The various clinical finding and their correlation with severity of dengue are depicted in Figure 2 and Table 1 respectively.

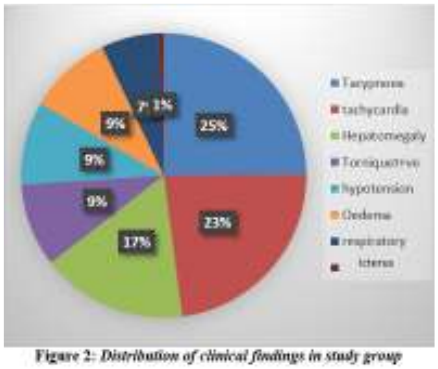

Figure 2: *Distribution of clinical findings in study group*

Table 1: ***Clinical presentations and their association to severity in various categories of dengue fever***

Presentation	Dengue without warning signs	Dengue with warning signs	Severe Dengue	Total cases	Significance
Final diagnosis - n (%)	58 (58.0)	31 (31.0)	11 (11.0)	100 (100.0)	-
Vomiting					
Yes - *n (%)*	19 (32.8)	13 (41.9)	06 (54.5)	38 (38.0)	X^2 – 2.158
No - *n (%)*	39 (67.2)	18 (58.1)	05 (45.5)	62 (62.0)	P= 0.340
Abdominal pain					
Yes - *n (%)*	15 (25.9)	18 (58.1)	09 (81.8)	42 (42.0)	X^2 – 16.644
No - *n (%)*	43 (74.1)	13 (41.9)	02 (18.2)	58 (58.0)	p <0.01*
Bleeding					
Yes - *n (%)*	01 (01.7)	11 (35.5)	09 (81.8)	21 (21.0)	X^2 – 41.435
No - *n (%)*	57 (98.3)	20 (64.5)	02 (18.2)	79 (79.0)	p <0.01*
Breathlessness					
Yes - *n (%)*	01 (01.7)	03 (09.7)	03 (27.3)	07 (07.0)	X^2 – 9,766
No - *n (%)*	57 (98.3)	28 (90.3)	08 (72.7)	93 (93.0)	P= 0.008*
Retro-orbital pain					
Yes - *n (%)*	07 (12.1)	08 (25.8)	02 (18.2)	17 (17.0)	X^2 – 0.388
No - *n (%)*	51 (87.9)	23 (74.2)	09 (81.8)	83 (83.0)	P= 0.824
Pulse					
Normal	41 (70.7)	18 (58.1)	0 (0.0)	59 (59.0)	X^2 – 20.850;
Bradycardia	01 (01.7)	0 (0.0)	01 (09.1)	02 (02.0)	P= 0.001*
Tachycardia	16 (27.6)	13 (41.9)	10 (90.9)	39 (39.0)	
Tachypnoea					
Yes - *n (%)*	23 (39.7)	14 (45.2)	11 (100.0)	48 (48.0)	X^2 – 13.630
No - *n (%)*	35 (60.3)	17 (54.8)	0 (0.0)	52 (52.0)	P= 0.001*
Hypotension					
Yes - *n (%)*	0 (0.0)	06 (19.4)	10 (90.9)	16 (16.0)	X^2 – 57.230
No - *n (%)*	58 (100.0)	25 (80.6)	01 (09.1)	84 (84.0)	p < 0.001*
Icterus					
Yes - *n (%)*	0 (0.0)	0 (0.0)	01 (09.1)	01 (09.1)	X^2 – 8.173
No - *n (%)*	58 (100.0)	31 (100.0)	10 (90.9)	99 (90.9)	P= 0.017*
Tourniquet test					X^2 – 9.188
Positive - *n (%)*	04 (06.9)	08 (25.8)	04 (36.4)	16 (16.0)	P= 0.010*
Negative - *n (%)*	54 (93.1)	23 (74.2)	07 (63.6)	84 (84.0)	

**Significant*

Among laboratory abnormalities leucopenia was a common finding. Raised haematocrit or fall of haematocrit after giving intravenous fluid fluids by 20% was statistically non-significant. In our study thrombocytopenia was a common haematological finding. It was further graded as 5% patients with platelet counts <20,000/cu mm, 80% of whom had bleeding,12% patients with platelet counts between 20,001-50,000/cu mm, amongst whom 58.3% had bleeding and 38% patients with platelet counts between 50,001-100,000/cu mm, 21% of whom had bleeding. Only 4.4% of the 45% patient with platelets >100,000/cu mm had bleeding.

We found that 72.4% patients had raised serum aspartate transaminase (AST), 64.3% had raised serum alanine transaminase (ALT) and 4.1% patients had bilirubin >2 g/dl. We found AST was deranged in a greater number of patients. Abnormal coagulation profile was also an important finding and we got the highest mean values of both prothrombin time (PT) (19.78±4.06 seconds) and activated partial thromboplastin time (aPTT) (81.44±22.32 seconds) in severe dengue. Out of 100 seropositive cases, performed by rapid strip test, 72 had NS-1 positive, 31 had IgM positive and 14 had IgG positive. Various laboratory parameters and their association with different class and severity are shown in Table 2.

Table 2: ***Common laboratory findings in various categories of dengue fever***

Laboratory finding	Dengue without warning signs (n=58)	Dengue with warning signs (n=31)	Severe dengue (n=11)	Total cases (n=100)	Significance
WBC on admission					
Low - *n (%)*	27 (46.6)	22 (71.0)	05 (45.5)	54 (54.0)	X^2 – 11.869
Normal - *n (%)*	25 (43.1)	06 (19.4)	02 (18.2)	33 (33.0)	P= 0.018*
High - *n (%)*	06 (10.3)	03 (09.7)	04 (36.4)	13 (13.0)	
Change in haematocrit					
Yes - *n (%)*	25 (43.1)	19 (61.3)	08 (72.7)	52 (52.0)	X^2 – 4.805
No - *n (%)*	33 (56.9)	12 (38.7)	03 (27.3)	48 (48.0)	P= 0.091
Platelet count per cu mm					
<20,000 - *n (%)*	0 (0.0)	05 (16.1)	0 (0.0)	05 (05.0)	
20,000-50,000 - *n (%)*	01 (01.7)	04 (12.9)	07 (63.6)	12 (12.0)	X^2 – 53.350
50,000-100,000 - *n (%)*	20 (34.5)	14 (45.2)	04 (36.4)	38 (38.0)	P= 0.000*
> 100,000 - *n (%)*	37 (63.8)	08 (25.8)	0 (0.0)	45 (45.0)	
Serum sodium	**(n=10)**	**(n=15)**	**(n=11)**	**(n=36)**	
Low - *n (%)*	07 (70.0)	09 (60.0)	10 (90.9)	26 (72.2)	X^2 – 37.31
Normal - *n (%)*	03 (30.0)	06 (40.0)	01 (09.1)	10 (27.7)	P= 0.000*
Aspartate transaminase	**(n=56)**	**(n=31)**	**(n=11)**	**(n=98)**	
High - *n (%)*	38 (67.8)	23 (74.2)	10 (90.9)	71 (72.4)	X^2 – 20.247
Normal - *n (%)*	18 (32.2)	8 (25.8)	01 (09.1)	27 (27.5)	p <0.001*
Alanine transaminase	**(n=56)**	**(n=31)**	**(n=11)**	**(n=98)**	
High - *n (%)*	31 (55.3)	21 (67.7)	11 (100.0)	63 (64.3)	X^2 – 9.794;
Normal - *n (%)*	25 (44.6)	10 (32.3)	0 (0.0)	35 (35.7)	p < 0.044
Serum bilirubin	**(n=55)**	**(n=31)**	**(n=11)**	**(n=97)**	
High - *n (%)*	0 (0.0)	02 (06.5)	02 (18.2)	04 (04.1)	X^2 – 10.659
Normal - *n (%)*	55 (32.2)	29 (93.5)	09 (81.8)	93 (95.9)	P= 0.031
IgM + IgG	**(n=58)**	**(n=31)**	**(n=11)**	**(n=100)**	
Positive - *n (%)*	01 (01.7)	03 (09.7)	06 (54.5)	10 (10.0)	X^2 – 28.67
Negative - *n (%)*	57 (98.3)	28 (90.3)	05 (45.5)	90 (90.0)	P=0.00

**Significant*

Discussion

Dengue was found to be more prevalent in males; the reason might be that male child is more exposed to outer open environment as he is engaged in more outdoor activities. Pai Jakribettu R, *et al*[16] in a study on 69 dengue patients found similar results. In our study 58% patients were in group of dengue without warning signs. A study by Jain A, *et al*[17] found that out of 58 patients 43 (76%) were simple dengue fever, 11 (20%) were dengue with warning signs, and 2 (3%) were severe dengue.

The symptomatic presentation in our study supports the observations made by Ahmed S, *et al*[18] that frequent clinical features were fever, abdominal pain and vomiting which were seen in 97%, 68% and 68% patients respectively. Similar types of clinical presentation were observed in studies by Shah GS, *et al*[19] and Mittal H *et al*[20]. In our study almost 100% of the children with dengue presented with fever, 71% with abdominal pain and 63% with headache. Prathyusha CV, *et al*[21] in a study among 80 patients with DF showed that fever was seen almost in 100% of the cases followed by abdominal pain and vomiting. In our study, pain in abdomen, respiratory complaints and bleeding manifestations were significantly correlated with severity of dengue with a p value <0.05; hence patients with these symptoms should be monitored closely for possibility of severe dengue. The various bleeding manifestations in our study were petechiae, bleeding gums, melaena and prolonged bleeding at puncture sites but no patient had menorrhagia.

Though persistent vomiting is considered to be one of the warning signs for severe dengue, in our study vomiting was not a common finding in severe dengue. The probable explanation for this is the early diagnosis and early use of anti-emetics. A similar cross-sectional study by Ledika MA, *et al*[22] showed that continuous and persistent vomiting was a feature of severe dengue infection. Tachycardia and low blood pressure were found to be seen more with severe dengue infections. Among hepatic manifestations, hepatomegaly, icterus, bleeding manifestations and raised enzyme levels were common. Hence patients with these features should be monitored closely for possibility of severe disease. Roy A, *et al*[23] studied the spectrum of hepatic involvement and concluded that when a patient presents with undifferentiated fever, jaundice, liver enlargement and abnormal liver function tests, then dengue should be considered in an endemic area. Prathyusha CV, *et al*[21] found hepatomegaly in 33.7%, tourniquet test in 38.7% and bradycardia during convalescence in 13% of the patients. Our study supports the same findings too.

Among laboratory parameters, leucopenia was found in 54% patients with severe dengue infection. Similarly, Prathyusha CV, *et al*[21] found leucopenia in 66.2% patients. Leucopenia can be a good marker in treatment and monitoring of dengue patient. It may persist in first week but once recovery starts, leucopenia will be replaced by increase in counts. As per study done by Arshad I, *et al*[24], 49% patients had

leucopenia less than 4000 /cu mm but Ledika MA, *et al*[22] found leucocyte counts >5000/cu mm in 78.3% patients. Other common haematological findings were raised haematocrit or fall of haematocrit after giving intravenous fluids by 20% found in 52% patients which was not statistically significant (p=0.091). A study by Dhooria G, *et al*[25] on laboratory parameters found that only 27% patients showed significant haematocrit changes, so we cannot rely on haemodilution and haemoconcentration to assess the severity of DF. Ahmed S, *et al*[18] also observed poor correlation between raised haematocrit and dengue severity particularly in area where anaemia is prevalent. Though the rise of haemoglobin and rise or fall of haematocrit can be evidence of fluid leakage, as the baseline haematocrit reports are not available at the time of admission, it cannot be a reliable marker at the time of admission, but it can be monitored regularly guiding us for fluid management therapy.

In our study thrombocytopenia was a common haematological finding. It was found that with increasing severity of thrombocytopenia, risk of bleeding increased (p<0.001). It was found to be more common in patient with severe dengue infection. Arshad I, *et al*[24], found that low platelets count below 50,000/cu mm was associated with poor outcome of the disease. Similarly, studies conducted by Prathyusha CV, *et al*[21] and Dhooria G, *et al*[25] also found poor correlation between thrombocytopenia and bleeding diathesis. In our study hyponatraemia was found in 26 patients and 90.9% patients with severe dengue had hyponatraemia. Joshi R, *et al*[26] also found similar findings concluding that along with other parameters hyponatremia can be used as a good predictor of severity of dengue.

Among liver parameters, raised ALT and serum bilirubin were found to be more in patients with severe type of infection as compared to AST. No patient had levels more than 1000 IU/L, severe hepatitis or acute liver failure. We found that AST was deranged in a greater number of patients as compared to ALT. The results of correlation of serum bilirubin were different in a study conducted by Pai Jakribettu R, *et al*[16]. A study on Sri Lankan children by Jayarajah U, *et al*[27] showed that liver enzymes are not significantly deranged in different sub group of dengue and it all depends upon the onset of critical phase which varies. Same results were also seen by Lee LK, *et al*[28] explaining that although high transaminase level increased with dengue severity, they cannot differentiate between DF and severe dengue.

For coagulation profile we got highest mean values of both PT (19.78 ± 4.06 seconds) and aPTT (81.44±22.32) in severe type of infection. A study done by Ayyub M, *et al*[29] found significant elevation of aPTT in 25.6% of cases. Our study supports that aPTT was found to be deranged more as compared to PT which is found to be more closely related with severe infection and poor outcome. Tourniquet test was performed in all patients and was positive in 16%. Mittal H *et al*[20] found that 33.3% patients had tourniquet test positive which was associated with severe dengue. In contrast to our study, Prathyusha CV, *et al*[21] concluded that specificity and sensitivity of this test was 88% and 56% respectively and that it was not a good screening test to predict haemorrhagic manifestation in dengue. Out of 100 seropositive cases, 10 patients had both positive IgG and IgM which was more commonly seen with severe type of dengue infection. In our present study the common complications found were plasma leakage (11%), shock (10%), myocarditis (10%) and encephalopathy (3%); except for plasma leakage, all other complications were associated with severe dengue only. The various neurological complications like encephalopathy, hypokalaemic paralysis, viral myositis and encephalomyelitis were found by Verma R, *et al*[30].

In our study, clinical predictors of severity were severe abdominal pain, bleeding manifestations, breathlessness, tachycardia, tachypnoea, icterus and positive tourniquet test which were associated with significant p value. Among laboratory parameters, leucopenia less than 5000 cu mm, low platelet count, hyponatremia, increased level of ALT >1000 IU/l, icterus and positive serology for both IgM and IgG were significantly correlated with severity while changes in haematocrit and AST values were found to be not significant. Various predictors of severity associated with severe dengue infection have also been defined by Tsheten T, *et al*[31].

We provided symptomatic treatment to all patients like antipyretics for fever, antiemetics for vomiting, encouraging oral fluids, analgesics for body ache and headache, antibiotics when DF was associated with some other bacterial infections. Intravenous fluid of choice was isotonic fluids. We used only 0.9% normal saline. Intravenous fluid was required in all patients with severe dengue. Three patients required ionotropic support and ventilator support. In our study all patients recovered completely. Improved outcome was because of many factors like good awareness, early referral to higher centre, early appropriate intervention and diagnosis, quick pick up of severity markers, good quality care and well equipped paediatric intensive care facility being a metropolitan city.

Conclusions

In our study, clinical predictors of severity were severe abdominal pain, bleeding manifestations, breathlessness, tachycardia, tachypnoea, icterus and positive tourniquet test which were all associated

with significant p values. Among laboratory parameters leucopenia less than 5000 per cu mm, low platelet count, hyponatraemia, increased level of ALT >1000 IU/l, icterus and positive serology for both IgM and IgG were significantly correlated with severity.

References

1. Khetarpal N, Khanna I. Dengue fever: Causes, complications, and vaccine strategies. *Journal of Immunology Research* 2016; **2016**: 6803098. https://doi.org/10.1155/2016/6803098 PMid: 27525287 PMCid: PMC4971387

2. Yboa BC, Labrague LJ. Dengue knowledge and preventive practices among rural residents in Samar province, Philippines. *American Journal of Public Health Research* 2013; **1**(2): 47-52. https://doi.org/10.12691/ajphr-1-2-2

3. Gubler DJ. Dengue and dengue haemorrhagic fever. *Clinical Microbiology Reviews* 1998; **11**(3): 480-96. https://doi.org/10.1128/CMR.11.3.480 PMid: 9665979 PMCid: PMC88892

4. Gubler DJ. 1988. Dengue, p. 223–260. In T. P. Monath (ed.), Epidemiology of arthropod-borne viral diseases. CRC Press, Inc., Boca Raton, Fla.p223-260. https://doi.org/10.1201/9780429280245-10

5. Platt KB, Linthicum KJ, Myint KS, Innis BL, Lerdthusnee K, Vaughn DW. Impact of dengue virus infection on feeding behaviour of Aedes aegypti. *American Journal of Tropical Medicine and Hygiene* 1997; **57**(2): 119-25. https://doi.org/10.4269/ajtmh.1997.57.119 PMid: 9288801

6. Ramabhatta S, Palaniappan S, Hanumantharayappa N, Begum SV. The clinical and serological profile of paediatric dengue. *Indian Journal of Pediatrics* 2017; **84**(12): 897-901. https://doi.org/10.1007/s12098-017-2423-0 PMid: 28887788

7. Hadinegoro SR. The revised WHO dengue case classification: Does the system need to be modified? *Paediatrics and International Child Health* 2012; 32(Suppl. 1): 33-8. https://doi.org/10.1179/2046904712Z.00000000052 PMid: 22668448 PMCid: PMC3381438

8. Pothapregada S, Kamalakannan B, Thulasingam M. Clinical profile of atypical manifestations of dengue fever. *Indian Journal of Pediatrics* 2016; **83**(6): 493-9. https://doi.org/10.1007/s12098-015-1942-9 PMid: 26725457 PMCid: PMC7102293

9. Harris E, Videa E, Pérez L, Sandoval E, Téllez Y, Perez ML, *et al.* Clinical, epidemiologic, and virologic features of dengue in the 1998 epidemic in Nicaragua. *American Journal of Tropical Medicine and Hygiene* 2000; **63**(1): 5-11. https://doi.org/10.4269/ajtmh.2000.63.5 PMid: 11357995

10. Setiati TE, Mairuhu AT, Koraka P, Supriatna M, Mac Gillavry MR, Brandjes DP, et al. Dengue disease severity in Indonesian children: an evaluation of the World Health Organization classification system. *BMC Infectious Diseases* 2007; **7**(1): 1. https://doi.org/10.1186/1471-2334-7-22 PMid: 17386105 PMCid: PMC1847434

11. Lei HY, Yeh TM, Liu HS, Lin YS, Chen SH, Liu CC. Immunopathogenesis of dengue virus infection. *Journal of Biomedical Science* 2001; **8**(5): 377–88. https://doi.org/10.1007/BF02255946 PMid: 11549879

12. Halstead SB. Pathogenesis of dengue: Challenges to molecular biology. *Science* 1988; **239**(4839): 476-81. https://doi.org/10.1126/science.3277268 PMid: 3277268

13. Liu CC, Huang KJ, Lin YS, Yeh TM, Liu HS, Lei HY. Transient CD4/CD8 ratio inversion and aberrant immune activation during dengue virus infection. *Journal of Medical Virology* 2002; **68**(2): 241-52. https://doi.org/10.1002/jmv.10198 PMid: 12210415

14. Muller DA, Depelsenaire AC, Young PR. Clinical and laboratory diagnosis of dengue virus infection. *Journal of Infectious Diseases* 2017; **215**(suppl_2): S89-S95.

https://doi.org/10.1093/infdis/jiw649
PMid: 28403441

15. Phuong CXT, Nhan NT, Wills B, Kneen R, Ha NTT, Mai TTT, *et al.* Evaluation of the World Health Organization standard tourniquet test and a modified tourniquet test in the diagnosis of dengue infection in Vietnam. *Tropical Medicine and International Health* 2002; **7**(2):125-32. https://doi.org/10.1046/j.13653156.2002.00841.x
PMid: 11841702

16. Pai Jakribettu R, Boloor R, Thaliath A, George SY, George T, Ponadka Rai M, et al. Correlation of clinico-haematological parameters in paediatric dengue: A retrospective Study. *Journal of Tropical Medicine* 2015; **2015**: 647162. https://doi.org/10.1155/2015/647162
PMid: 26819620 PMCid: PMC4706955

17. Jain A, Shah AN, Patel P, Desai M, Somani S, Parikh P, *et al.* A clinico-haematological profile of dengue outbreak among healthcare professionals in a tertiary care hospital of Ahmedabad with analysis on economic impact. *National Journal of Community Medicine* 2013; **4**: 286-90.

18. Ahmed S, Arif F, Yahya Y, Rehman A, Abbas K, Ashraf S, *et al.* Dengue fever outbreak in Karachi 2006--a study of profile and outcome of children under 15 years of age. *Journal of the Pakistan Medical Association* 2008; **58**(1): 4.

19. Shah GS, Islam S, Das BK. Clinical and laboratory profile of dengue infection in children. *Kathmandu University Medical Journal* 2005; **4**(1): 40-3.

20. Mittal H, Faridi MM, Arora SK, Patil R. Clinico-haematological profile and platelet trends in children with dengue during 2010 epidemic in north India. *Indian Journal of Pediatrics* 2012; **79**(4): 467-71. https://doi.org/10.1007/s12098-011-0586-7
PMid: 22037856

21. Prathyusha CV, Rao MS, Sudarsini P, Rao KM. Clinico-haematological profile and outcome of dengue fever in children. *International Journal of Current Microbiology and Applied Sciences* 2013; **2**(10): 338-46.

22. Ledika MA, Setiabudi D, Dhamayanti M. Association between clinical profiles and severe dengue infection in children in developing country. *American Journal of Epidemiology and Infectious Disease* 2015; **3**(3): 45-9.

23. Roy A, Sarkar D, Chakraborty S, Chaudhuri J, Ghosh P, Chakraborty S. Profile of hepatic involvement by dengue virus in dengue infected children. *North American Journal of Medical Sciences* 2013; **5**(8): 480. https://doi.org/10.4103/1947-2714.117313
PMid: 24083224 PMCid: PMC3784926

24. Arshad I, Malik FA, Hussain A, Shah SA. Dengue fever; Clinico-pathological correlations and their associations with poor outcome. *Professional Medical Journal* 2011; **18**: 57-63. https://doi.org/10.29309/TPMJ/2011.18.01.1859

25. Dhooria G, Bhat D, Bains H. Clinical profile and outcome in children of dengue haemorrhagic fever in North India. *Iranian Journal of Pediatrics* 2008; **18**(3): 222-8.

26. Joshi R, Bai V. Profile of dengue patients admitted to a tertiary care hospital in Mumbai. *Turkish Journal of Pediatrics* 2011; **53**(6): 626.

27. Jayarajah U, Madarasinghe M, Hapugoda D, Dissanayake U, Perera L, Kannangara V*, et al*. Clinical and biochemical characteristics of dengue infections in children from Sri Lanka. *Global Pediatric Health* 2020; **7**: 2333794X20974207. https://doi.org/10.1177/2333794X20974207
PMid: 33283028 PMCid: PMC7686613

28. Lee LK, Gan VC, Lee VJ, Tan AS, Leo YS, Lye DC. Clinical relevance and discriminatory value of elevated liver aminotransferase levels for dengue severity. *PLoS Neglected Tropical Diseases* 2012; **6**(6): e1676. https://doi.org/10.1371/journal.pntd.0001676
PMid: 22679523 PMCid: PMC3367991

29. Ayyub M, Khazindar AM, Lubbad EH, Barlas S, Alfi AY, Al-Ukayli S. Characteristics of dengue fever in a large public hospital, Jeddah, Saudi Arabia.

Journal of Ayub Medical College Abbottabad 2006; **18**(2): 9-13.

30. Verma R, Sharma P, Garg RK, Atam V, Singh MK, Mehrotra HS. Neurological complications of dengue fever: Experience from a tertiary centre of north India. *Annals of Indian Academy of Neurology* 2011; **14**(4): 272-8. https://doi.org/10.4103/0972-2327.91946 PMid: 22346016 PMCid: PMC3271466

31. Tsheten T, Clements ACA, Gray DJ, Adhikary RK, Kanamon LF, Wanodi K. Clinical predictors of severe dengue: a systematic review and meta-analysis. *Infectious Diseases of Poverty* 2021; **10**: 123. https://doi.org/10.1186/s40249-021-00908-2 PMid: 34627388 PMCid: PMC8501593