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Research Article

Risk Factors of Severe Dengue Infection in Paediatric Patients-A Single Centre Prospective Study

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ABSTRACT

Introduction: Dengue epidemics are known to have occurred over the last three centuries in tropical, subtropical and temperate areas of the world. Dengue creates a huge burden on public health world-wide. Severe dengue can lead to more lethal condition. Hence early recognition of severe cases is important for management of paediatric dengue patients. **Objective**: To assess the risk factors of severe dengue infection in paediatric patients. **Methods**: A hospital-based prospective study was conducted at from June 2022 to November 2022 Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh. Seventy two (72) patients included in the study. In children with high degree clinical suspicion of dengue infection NS 1 antigen (who came within first 72 hours of fever) and/or dengue antibody IgM, IgG (who came after five days of fever) were performed. Positive dengue cases were taken written informed consent & interviewed on the risk factors of dengue infection. Data related to patient's demography, risk factors, clinical presentation, pattern of dengue infection and outcome were documented on the pre-structured questionnaire. **Results**: Total of 72 patients with dengue infection met the inclusion criteria, in which 29 and 43 were diagnosed as severe dengue and non-severe dengue infection, respectively. All patients were confirmed by serologic marker (NS-1 or IgM/ IgG Dengue). All subjects were carried out anamnesis, physical examination, and laboratory. Clinical and laboratory examination (complete blood count, AST, ALT, albumin, APTT, S. ferritin and d-dimer) were analysis comparing non-severe dengue and severe dengue patients. Characteristics of 72 research subjects can be seen. On bivariate analysis, there were significant differences of nutritional status, abdominal pain, vomiting, petechiae, hepatomegaly, pleural effusion, leukopenia, thrombocytopenia, hypoalbuminemia, increasing AST > 3x, elevated D- dimer, hyperferritinemia and prolonged APTT between severe and non-severe dengue group. After multivariate analysis, the prognostic factors of severe dengue were overweight/obesity (p=0.003, RR 94), vomiting (p=0.02, RR 13.3), hepatomegaly (p=0.01, RR=69.4), hyperferritinemia (p=0.01, RR=15.4) and prolonged APTT (p=0.005, RR=43.25). In overweight/obesity, vomiting, hepatomegaly, and hyperferritinemia prolonged APTT were prognostic factors in severe dengue infection in children. **Conclusion**: In conclusion, overweight/obesity, vomiting, hepatomegaly, and hyperferritinemia prolonged APTT were prognostic factors in severe dengue infection in children. Considering these factors for awareness of severe dengue in patients with dengue virus infection. Clinicians should emphasize the monitoring of these factors for early detection of serious dengue state.

Key Words: *Dengue epidemics, IgM, IgG, risk factors.*

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INTRODUCTION

Dengue epidemics are known to have occurred over the last three centuries in tropical, subtropical and temperate areas of the world [1]. The first epidemic of dengue was recorded in 1635 in the French West Indies, although a disease compatible with dengue had been reported in China as early as 1992 AD [2]. During the 18th, 19th and early 20th centuries, epidemics of dengue-like diseases were described globally in the tropics as well as in some temperate regions. The World Health Organization (WHO) estimated that approximately 2.5 billion people living in dengue-endemic countries [3]. The virus serotypes are closely related but antigenically distinct [4]. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries [5]. Annually a 100 million cases of Dengue fever and half a million cases of dengue hemorrhagic fever (DHF) occur in the world with a case fatality in Asian countries of 0.5%–3.5% [6]. In tropical countries, attack rates among susceptible populations frequently ranging from 40 to 50%, or as high as 80—90% in some cases. Of the 500 000 cases of DHF that require hospitalization every year, death rates between 2.5 and 5% are recorded, but they can be as high as 20% in very young children if the appropriate treatment is not administered rapidly [7]. Thus dengue creates a huge burden on public health world-wide. Dengue infections can result in a wide spectrum of disease severity ranging from an influenza-like illness (dengue fever; DF) to the life-threatening dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS), which, if left untreated, are associated with mortality as high as 20% [8-13]. Early diagnosis is essential and clinical suspicion is based on the frequency of symptoms in the population. The first confirmed

report of dengue infection in Bangladesh dates back to 1960s, and since then more and more new states have been reporting the disease which mostly strikes in epidemic proportions often inflicting heavy morbidity and mortality [14]. Several fatal forms of the disease i.e., DHF, DSS have been reported in Bangladesh from time to time in different parts of Farhana Ahmed et al.: Risk factors of severe dengue infection in paediatric patients-A single centre prospective study 2 Bangladesh. During all these epidemics infection occurred in active children's in the age group of 16–60 months [15,16]. The common signs and symptoms observed were fever, headache, myalgia, arthralgia and bleeding manifestations have also been observed. But severe dengue cases can lead to more critical signs and more lethal outcome. So early recognition of severe dengue cases is important for management of dengue patients.

MATERIALSANDMETHODS

A hospital-based prospective study was conducted from June 2022 to November 2022 Bangladesh Shishu Hospital &Institute, Dhaka, Bangladesh. Seventy-two (72) patients included in the study. In children with high degree clinical suspicion of Dengueinfection NS 1 antigen (who came within first 72 hours of fever) and/or dengue antibody IgM, IgG (who came after fivedays of fever) were performed. Positive dengue cases were taken written informed consent & interviewed on the riskfactors of dengue infection. Data related to patient's demography, risk factors, clinical presentation, pattern of Dengueinfection and outcome were documented on the pre-structured questionnaire. Co-relation between the risk factors andmortality was also observed.All enrolled patientswere treated according tothestandard management protocol ofnational Dengue guideline (published in collaboration with WHO and Ministry of Health and Family welfare (MOHFW),Bangladesh).

Inclusion criteria:

a) Dengue patients admitted in medical and adolescent wards of Bangladesh Shishu Hospital and Institute, Dhaka, Bangladesh. Dhaka, Bangladesh.
b) Patients of all age groups, showing a temperature of >38º C for >24 hours, and clinically diagnosed as having dengue fever.

Exclusion criteria:

a) Dengue cases with definite other source of infection (e.g. respiratory or urinary tract infection, meningitis)..
b) History of bleeding tendency since birth..
c) Immuno compromised patients.

The diagnosis of severe dengue & non-severe dengue was based on the WHO (World Health Organization) 2004 criteria. WHO new classification allow more effective recognition of cases of severe dengue fever replacing DF, DHF & DSS by dengue without warning signs, dengue with warning signs and severe dengue fever. Patients were included in the study with features of dengue – fever with body ache, headache, rash, bleeding manifestations and thrombocytopenia and had a positive ELISA test. Patients who had malaria and enteric fever were excluded from the study. Detailed history and clinical examinations were done. Hematological profiles and biochemical investigations were done at the time of admission and were followed by daily (or bi-daily) investigations as required until discharge. Signs of plasma leakage were assessed by chest radiograph and abdominal ultrasonography. Specific investigations were performed in patients who presented with neurological involvement (cerebrospinal fluid analysis, neuroimaging) or hepatic failure (viral markers, typhoid fever). Statistical analysis was performed by Chi -Square test and multivariate regression analysis using the Statistical Package ―SPSS Version 20 for Social Sciences, with $p<0.05$ taken as statistically significant.

RESULTS

Total of 72 patients with dengue infection met the inclusion criteria, in which 29 and 43 were diagnosed as severe dengue and non-severe dengue infection, respectively. Characteristics of 72 research subjects can be seen in Table-1. On bivariate analysis, there were significant differences of nutritional status, abdominal pain, vomiting, petechiae, pleural effusion, leukopenia, thrombocytopenia, hypoalbuminemia, increasing AST>3x, hyperferritinemia, elevated d-dimer and APTT between severe and non-severe dengue group. After multivariate analysis, the prognostic factors of severe dengue were overweight/obesity (p=0.003, RR 94), vomiting (p=0.02, RR 13.3), hepatomegaly (p=0.01, RR=69.4), hyperferritinemia (p=0.01, RR=15.4) and prolonged APTT (p=0.005, RR=43.25). In overweight/obesity, vomiting, hepatomegaly, hyperferritinemia prolonged APTT were prognostic factors in severe dengue infection in children.

Table-1: Baseline Characteristic (N=72)

	Characteristics	Groups		p-value
		Severe Dengue N=29(%)	NonSevereDengue N=43(%)	
Age,(year)	≤5years	5(17.2%)	8(18.6%)	0.77
	>5years	24(82.8%)	35(81.4%)	
Gender,n(%)	Male	14(42.4%)	19(57.6%)	0.76
	Female	15(38.5%)	24(61.5%)	

Referral,n(%)	Yes	19(65.5%)	18(41.9%)	0.052
	No	10(34.5%)	25(58.1%)	
Nutritional Status Non Overweight/Obesity		13(25.0%)	39(75.0%)	<0.001*
Overweight/Obesity		16(80.0%)	4(20.0%)	
DOI(dayofIllness)(day)		2-6	2-6	
LOS(lengthofStay)(day)	Duration	1-11(day)	2-8(hours)	
Outcome	Life	25(86.2%)	43(100%)	0.012*
	Death	4(13.8%)	0(0.0)	

Table-2:Prognostic Factors based on Bivariate Analysis (N=72)

Prognosticfactors	Groups		p-value	RR	95%CI
	SevereDengue N=29(%)	NonSevereDengueN= 43(%)			
Abdominalpain	25(86.2)	19(44.2)	0.002*	3.6	1.4-9.3
Nausea	26(89.7)	30(69.8)	0.13	0.788	0.62-1.0
Vomiting	19(65.5)	15(34.9)	0.022*	2.2	1.2-4.2
Epistaxis	3(10.3)	8(18.6)	0.71	0.71	0.69-2.54
Melena	4(13.8)	1(2.3)	0.16	2.16	1.25-3.7
Hematemesis	2 (6.9)	1(2.3)	0.73	1.7	0.7-4.0
Petechie	19(65.5)	15(34.9)	0.022*	2.17	1.15-4.15
Pleuraleffusion	25(86.2)	14(32.6)	<0,001*	4.95	1.9-12.7
Hepatomegaly	27(93.1)	10(23.3)	<0,001*	12.1	3.1-47.2
Hemoglobin	18(62)	22(51.2)	0.13	1.4	0.75-2.6
Leukopenia(<5000/mm3)	12(41.4)	31(72.09)	0.019*	1.7	1.09-2.9
IncreaseofHematocrit	18(62)	30(69.8)	0.74	0.83	0.46-1.5
Thrombocytopenia(≤50.000/µL)	20(69)	7(16.3)	<0,001*	3.9	2.06-7.72
Hypoalbuminemia (<3.5g/dL)	19(65.5)	5(11.6)	<0,001*	3.8	2.05-7.21
AST>3x	22(75.9)	17(39.5)	0.013*	2.46	1.2-5.03
ALT>3x	16(55.2%)	25(58.1)	0.87	0.9	0.53-1.7
IncreaseofAPTT	7(24.1)	2(4.7)	0.036*	2.27	1.4-3.7
Hyperferritinemia(>500ng/ml)	26(89.7)	13(30.2)	<0,001*	6.9	2.3-20.6
SecondaryDengueinfection	8(27.6)	15(34.9)	0.64	1.18	0.58-2.4
HighD-dimer level	10(34.5)	4(9.3)	<0,001*	3.2	2.19-4.7

Table-3: Prognostics Factors based on Multivariate Analysis

Prognosticfactors	**B**	**p**	**RR**	**95%CI**
Hepatomegaly	2.77	0.01*	69.4	2.18-287.4
IncreaseofAPTT	3.42	0.005*	43.25	2.6-699
Obesity/Overweight	4.5.3	0,003*	94	4.47-1989
Vomiting	2.59	0.02*	13.3	1.5-118.8
Leucopenia	-29.95	0.9	000	0.000
Abdominalpain	2.87	0.27	17.68	0.09-3221
Melena	-2.65	0.14	0.071	0.002-2.28
Albumin<3.5g/dL	1.26	0.22	3.5	0.47-26.54
Pleuraleffusion	-0.56	0.72	0.57	0.028-11.73
Hyperferritinemia	2.6	0.01*	15.4	2.1-8.99
AST>3x	-1.34	0.42	0.26	0.009-7.23
Petechie	2.27	0.16	9.7	0.42-226
HighD-dimer	-2.36	0.31	0.095	0.001-8.81
Thrombocytopenia(≤50.000/µL)	-7.8	0.81	0.46	0.001-291
Constant	-6.95	0.001*	0.001	------

DISCUSSION

Dengue is a very important emerging disease of the tropical and sub-tropical regions. The identification is by clinical features but they can present with varied manifestation [17,18]. This study describes the clinical profile, laboratory features and outcome of severe dengue & non severe dengue paediatric patients. The male to female ratio in this study was 2.5:1 respectively. Fever was the most common presenting symptom (100%). Similar studies in past have also substantiated fever

as being the most common presenting symptom. On bivariate analysis, there were significant differences of thrombocytopenia, hypoalbuminemia, increasing AST>3x, nutritional status, abdominal pain, petechiae, pleural effusion, leucopenia, hyperferritinemia, high D-dimer level and APTT between severe and non-severe dengue groups. After multivariate analyzed, the prognostic factors of severe dengue were overweight/obesity (p=0.003, RR 94), vomiting (p=0.02, Farhana Ahmed et al.: Risk factors of severe dengue infection in paediatric patients-A single centre prospective study 4 RR 13.3), hepatomegaly (p=0.01, RR=69.4), hyperferritinemia (p=0.01, RR=15.4) and prolonged APTT (p=0.005, RR=43.25). The baseline characteristics of children with dengue infection and controls in this study were very similar except nutritional status and outcome. Age ≤5 years in severe dengue were 17.2% and 82.8% in subject more than 5 years old (>5 years). Non severe dengue were more common in subject > 5 years old (81.4%) than subjects with age ≤ 5 years (18.6%). Male to female proportion in severe dengue were 42.4% and 38.5%, non-severe dengue were 57.6% and 61.5% respectively. Nutritional status was statistic significantly in bivariate and multivariate analysis (RR 2.93, 95% CI 2.18-6.20) whereas the previous study by Ledika et al, excess nutrition does not appear to be a risk factor for severe dengue infection [19-20]. In addition, normal nutritional status had negative correlation with DHF and DSS [20]. However, meta analysis and systematic review recently enroled 15 studies from 2000 until 2016 reported obesity as a risk factor of severity in children with dengue infection (OR = 1.38; 95% CI:1.10, 1.73) [21]. In addition, recent study shown obese patients with dengue infection possess many clinical parameters suggestive of more severe clinical manifestations [22,23]. Severe dengue group in this study had a prolonged length of stay (1-11 days) than non- severe dengue group (2-8 days). The mortality rate in this study was 5.9% in all subjects and 50% were severe dengue patients with obesity, while other study by Patrayusha et al., [23] reported mortality rate was 6.25% and 1.03% in Mishra et al.,[24] Mortality of DHF or DSS estimated 40-50% in pitfall management. The proportion of severe dengue and non- severe dengue with vomiting were 89.7% and 69.8% respectively. Vomiting more common in DSS and expanded dengue syndrome than non-severe dengue with frequent variously range 3-5x/day. In the previous study was reported the prevalence of vomiting symptom was higher in severe dengue group than dengue infection/dengue infection with warning sign group [25]. Meta-analysis study by Zhang et al was reported nausea-vomiting, as the predictor of severe dengue in children. Vomiting was often found in dengue patients, especially in children. Vomiting could cause fluid imbalance and also difficulty in assessing the hydration state of the patient [26]. In present study, abdominal pain in severe dengue was 86.2% while in non-severe dengue groups about 44.2%. Despite statistic significantly from bivariate analysis (p= 0.002, RR 3.6) however from the regression logistic shown unsignificantly. Meta-analysis study by Zhang etal was stated abdominal pain could predict of severe dengue infection [26]. The mechanism of abdominal pain in dengue infection was unknown. Gupta et al was reported the most common specific cause of acute abdominal pain was acute hepatitis,[27] previously Shabir et al was reported proportion of abdominal pain was 32%[28] and liver involvement was the common cause of abdominal pain in dengue fever [29]. In present study, bleeding manifestation presented with epistaxis, ptechie, melena and hematemesis. Melena in severe dengue group was 13.8% and 2.3% in non-severe dengue group. Both of bivariate and multivariate analysis revealed statistic unsignificantly (p=0.16 and 0.14 respectively). Epistaxis found in 3 patients with severe dengue (10.3%) and 7 patients with non-severe dengue (18.6%) while ptechie more common in severe dengue than non-severe dengue patients (65.5% and 34.9%). Epistaxis and ptechie occurred in 3-5 days of illness. Whereas hematemesis occurred in 2 patients with severe dengue (6.9%) and 1 patient with non- severe dengue (2.3%). Statistic unsignificantly noticed in bivariate analysis (p= 0.73). Bleeding (hematemesis or melena) occurred in 5-7 day of illness. Melena range from 50cc 1000cc and leading to hemodinamic imbalance. Two patients with severe dengue required whole blood transfusion. In this study, massive bleeding and profound shock due to hematemesis and melena leading to mortality in two patients with severe dengue. Haemoglobin and haematocrit were statistic unsignificantly (p= 0.17, RR 1.4, CI 0.75-2.6 and p= 0.74, RR 0.83 CI 0.46-1.5 respectively). The proportion of thrombocytopenia, leukopenia, haemoglobin and increase of hematocrit were 69%, 41.4%, 62 % and 62% in severe dengue group. While in non-severe dengue group the proportion were 16.3%, 72.9%, 51.2% and 69.8% respectively. Otherwise, Leukopenia was common in non-severe dengue group. Hei et al was reported the most notable laboratory finding included thrombocytopenia, leukopenia, prolonged APTT and elevation of serum aminotransferase [30]. According to WHO, leukopenia is common in early phase of fever [30]. Ledika et al, in cross sectional study reported leukocyte ≥5000/mm3 in early admission associated to severe dengue in children [19]. Hepatomegaly in this study was 93.1% in severe dengue group and statistic significantly in bivariate (RR 37.18, 95% CI: 3.6-352) and multivariate analysis (RR 1.97, 95% CI = 3.1-47.2). Several study reported hepatomegaly > 2 cm in defervescence phase as prognostic factor severe dengue in children [11,12]. A significantly decreased serum albumin >0.5 gm/dl from baseline or < 3 g/dL and serious dengue disease was defined as occurrence of death, or the use amines, inotrop, colloids, mechanical ventilation, non-invasive mechanical ventilation or hemodialisis [31]. In present study, pleural effusion more common in severe dengue (86.2%) than in non-severe dengue group 32.6% with chi square revealed statistic significantly(p=0.001, RR 4.95, CI 1.9-12.7) even though unsignificantly based on multivariate analysis. This study was showed that increase of APTT in severe dengue more than non-severe dengue group with proportion are 89.7%. Increasing of APTT range from 1.5x until more than 100 seconds from the normal level. Twenty patients (72.2%) with APTT elevation acompanied with hepatomegaly. Chi-square analysis revealed statistic significantly (RR 6.9 95% CI 2.3-20.6) and also multivariate analysis carried out with logistic regression as prognostic factor of severe dengue in children (RR 43.25, 95% CI: 2.6-699). It's similar to study held by Mishra et al rise in APTT/PT also depicts severity of disease [24]. Patients with severe dengue may have coagulation abnormalities, but these are usually not sufficient to cause major bleeding. When major bleeding does occur, it is almost always associated with profound shock since this, in combination with thrombocytopaenia, hypoxia and acidosis, can lead to multiple organ failure and advanced disseminated intravascular coagulation [30]. Prolongation of APTT in acute phase

correlates with the severity of infection and can be made as early indicator DSS/DHF [32,33]. Plasma leakage in dengue patients also directly related to APTT level. Previously, Budastra et al found that there was significant relationship between prolonged APTT during early stages of DHF with bleeding manifestation at the later stage of disease [32]. Another hypothesis of coagulopathy is NS-1 protein excreted during early stage infection will bind to prothrombin may inhibit its activation. Chuang et al was suggested that molecular mimicry between DENV and coagulation factors can induce the production of auto antibodies with biological effects similar to those of anti thrombinantibody/ATAs found in dengue patients. These coagulation- factor cross- reactive anti-DENV antibodies can interfere with the balance of coagulation and fibrinolysis [33]. In this study, elevation AST>3x in severe dengue groups and non-severe dengue group were 75.9% and 39.5% respectively. Both of elevation of ALT >3x found insevere and non-severe dengue groups (55.2% and 58.1%). However Lee et al reported liver Farhana Ahmed et al.: Risk factors of severe dengue infection in paediatric patients-A single centre prospective study 5 function tests done at earlier dates might not reflect the extent of liver involvement in acute dengue infection. The highest AST level was seen on day6 of illness and both AST level were significantly higher in severe dengue patients [34]. In this study AST and ALT were performed in 48 hours in early admission suggest the result were statistic unsignificantly. In this study, S. Ferrittin level is found higher in severe dengue patients. In a study conducted in south India by soundravally R et al, concluded that raised serum ferritin level could predict the severity of dengue with sensitivity and specificly of 76.9% and 83.3% respectively [35]. Another study carried out in one hundred and seventy seventhai children evaluating ferritin level during the clinical course showed similar finding [36]. Naganna J. et al found high D-dimer has positive correlation bleeding group with high PT APTT & INR. But in this study, on multivariate analysis, no was found significant relationship [37].

CONCLUSION

Dengue is one amongst the key causes of undifferentiated fever. It presents as an extremely broad wellness and is hardly recognized as a clinical entity by primary health care physicians. This study support additional studies on applying intervention measures to boost the diagnostic accuracy and exactness at the first tending level in dandy fever endemic regions. In conclusion, overweight/obesity, vomiting, hepatomegaly, hyperferritinemia and high d-dimer level and prolonged APTT were prognostic factors in severe dengue infection in children. Considering these factors for awareness of severe dengue in patients with dengue virus infection. Clinicians should emphasize the monitoring of these factors for early detection of serious dengue state.

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REFERENCES

1. Tuiskunen Bäck, A., &Lundkvist, Å(2013). Dengue viruses–an overview. Infection ecology & epidemiology; 3(1):19839.
2. Welsch, S., Miller, S., Romero-Brey, I., Merz, A., Bleck, C. K., Walther, P., &Bartenschlager, R(2009). Composition andthree-dimensional architecture of the dengue virus replication and assembly sites. Cell host &microbe; 5(4):365-375.
3. WHO(2019). Dengue and severe dengue. Available: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue/
4. Shah MY, Naqash MM, Goel RK, Galhan D, Kumar S, Chhabra V, et al(2016). Clinical profile of dengue fever infection in patients admitted in tertiary care centre Agroha, Hisar, Haryana, India. Int J of Res M ScI; 4(6):2146-149.
5. Srinivasa K, Ajay J, Manjunath GA(2017). Clinical profile and outcome of dengue among hospitalized children - a single centre prospective study. J Pediatr Res; 4(02):145-50.
6. Rao M, Aparna A, Jyothi RC(2016). Clinical profile and outcome of dengue infections in children. IOSR; 15 (2): 07-13.
7. Halstead,S.B.(2000).Global Perspectives on Dengue Research.
8. Alam ABM, Sadat S, Swapan Z, Ahmed A(2009). Clinical profile of dengue fever inchildren.BJCH;33(2):55-58.
9. WHO (2009) Dengue Guidelines for Diagnosis, Treatment, Prevention and Control WHO. http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf.
10. Dengue in Kerala: Acriticalreview.ICMRBulletin.2006;36:13–22.
11. Konar NR, Mandal AK, Saha AK(1966). Hemorrhagic fever in Kolkata. J Assoc PhysiciansIndia; 14:331–40.
12. Abdul Kader MS, Kandaswamy P, Appavoo NC, Anuradha(1997). Outbreak and control of dengue in a village of Dharmapuri, Tamil Nadu. J CommunDis; 29:69–72.
13. Narayanan M, Aravind MA, Thilothammal N, Prema R, Sargunam CS, Ramamurty N(2002). Dengue fever epidemicin Chennai-a study of clinical profile and outcome. Indian Pediatr; 39:1027–33.
14. Aggarwal A, Chandra J, Aneja S, PatwariAK, Dutta AK(1998). An epidemic of dengue hemorrhagic fever and dengue shock syndrome in children in Delhi. Indian Pediatr; 35:727–32.
15. Balaya S, Paul SD,D' Lima LV, Pavri KM(1969). Investigations on an outbreak of dengue in Delhi in 1967. Indian J

Med Res; 5:767–74.

16. Yacoub S, Wills B(2014). Predicting outcome from dengue. BMC Medicine;12:147-57.
17. Pichainarong N, Mongkalangoon N, Kalayanarooj S, Chaveepojnkamjorn W(2006). Relationship between body size andseverity of dengue hemorrhagic fever among children aged 0- 14 years. Southeast Asian J Trop Med Public Health; 37(2):283-88.
18. Wang CC, Lee IK, Su MC, Lin HI, Huang YC, Liu SF, et al(2009). Differences in clinical and laboratory characteristics and disease severity between children and adults with dengue virus infection in Taiwan, 2002. Trans R Soc TropMedHyg;103(9):871-77.
19. Ledika MA, Setiabudi D, Dhamayanti M(2015). Association between clinical profiles and severe dengue Infection in children in developing country. American Journal Epidemiology and Infectious Disease; 3(3):45-9.
20. Trang NTHT, Long NP, Hue TTM, Hung LP, Trung TD , Dinh DN, et al(2016). Association between nutritional status and dengue infection: a systematic review and meta-analysis. BMC Infec Dis. Apr 20;16:172.
21. Zulkipli MS, Dahlui M, Jamil N, Wai HVC, Bulgiba A, Rampai S, et al(2018). The association between obesity and dengueseverityamongpediatricpatients:A systematic review and meta analysis. Plos Negl Trop Dis. Feb7;12(2):1-22.
22. Tan VPK, Ngim CF, Lee EZ, Ramadas A, Pong LY, Hassan SY, et al(2018). The association between obesity and denguevirus(DENV)infectioninhospitalised patients. PlosOne; 13(7):e0200698.W
23. Prathyusha CV, Rao MS, Sudarsini P, Rao KUM(2013). Clinico-haematological profile and outcome of dengue fever in children. Int J Curr Microbiol AppSci; 2(10):338-46.
24. MishraS, Ramanathan R, Agarwalla S(2016). Clinical Profile of Dengue Fever in Children: A Study from Southern Odisha, India. Scientifica:1-6.
25. Vuong NL, Manh DH, Mai NT, Phuc LH, Luong VT, Quan V Detal(2016). Criteria of‑persistent vomiting‖ in the WHO 2009 warning signs for dengue case classification; 44:14
26. Zhang H, Zou YP, Peng HJ, Zhang XH, Zhou FY, Liu ZH, Chen GX(2014). Predictive symptoms and signs of severe dengue disease for patients with dengue fever: ameta-analysis. Biomed ResearchInt. July1;1-10.
27. Gupta BK, Nehera HR, Parmar S, Meena SL, Gajraj S et al(2017). Acute abdomen presentation in dengue fever during recent outbreak. Jacute Disease; 6(5):198-204.
28. SabbirB, QadirH, ShafiF, Mahboob F(2012). Acute abdominal pain in Dengue Fever. PJMHS; 6:155-8.
29. Jagadish kumar K; Jain P, Manjunath VG, Umesh L(2011). Hepatic involvement in dengue fever in children. Iran J Pediatr; 22(2):231-6.
30. Lei HY, Huang KJ, Lin YS, Liu HS, Liu CC(2008). Immuno pathogenesis of dengue hemorrhagic fever. Am J Infect Dis; 4:1-9.
31. Suwarto S, Nainggolan L, Sinto R, Effendi B, Ibrahim E, Suryamin M, R. Sasmono T(2016). Dengue score: a proposed diagnostic predictor for pleural effusion and/or ascites in adults with dengue infection. BMC Infectious Diseases; 16:322.
32. Budastra IN, Arhana BNP, Mudita IB(2009). Plasma prothrombin time and activated partial thrombo plast in time aspredictorsofbleeding manifestationduringdenguehemorrhagic fever.PaediatrIndones.2009;49(2):69-74.
33. Chuang YC, Lin YS, Liu HS, Yeh TM. Molecular Mimicry between Dengue Virus and Coagulation Factors InducesAntibodiesTo InhibitThrombinActivityand Enhance Fibrinolysis.J Virol.2014;88(23):13759–68.
34. Lee LK, Gan VC, Lee VJ, Tan AS, Leo YS, Lye DC et al. Clinical relevance and discriminatory value of elevatedliver aminotransferase levels for dengue severity.PlosOne.20126(6):1676.
35. SoundravallyR,AgieshkumarB,DaisyM,SherinJ,CleetusCC,2015. Ferritinlevels predict severedengue. *Infection*43:13–19
36. Chaiyaratana W, Chuansumrit A,Atamasirikul K, Tangnararatchakit K. Serum ferritin levels in children withdengueinfection. SoutheastAsianJTropMedPublic Health. 2008;399(5):832-868.
37. Naganna J, GoudGs, Sneha D, Suram VK, Correlation of D-dimer level with severity of dengue fever. Eur. J. Mol.Clin. Med. 2022;9(3), 10239-47.