THE PREDICTORS OF THE SEVERITY OF DENGUE FEVER: A CROSS-SECTIONAL STUDY IN A TERTIARY CARE CENTER OF BANGLADESH

HOSSAIN MZ[1], SULTANA N[2], SWEETY AA[2], MAHMUD R[4], ISLAM M[5], KHAN MMH[6], SABER S[7], RAHMAN F[8], ISLAM K[9], CHOWDHURY FUH[10], ISLAM M[11], PAUL N[12], AZAD KAK[13]

Abstract:

Background: *Dengue is an endemic disease for Bangladesh with occasional outbreak. Little is known about the predictors of severe dengue.*

Methods: *This cross sectional study was conducted in the medicine department of Dhaka Medical College from April 2019 to March 2020. Total 199 consecutive patients were enrolled in this study. For the purpose of the analysis, dengue fever was classified as group I and dengue hemorrhagic fever and dengue shock syndrome was classified as group II.*

Results: *The mean (SD) age of the study population was 28.5(12.1) and 87.4% were less than 40 years of age. The male and female ratio was about 3:1. Among the total study population, 149(74.9%) patients had DF, 46 (23.1%) had DHF and only 4 (2%) had DSS on presentation. Baseline demography and clinical presentation did not significantly differ between classical dengue and severe dengue. Previous history of dengue had low association with severity (RR, 95%CI, phi, P value; 1.2, 1.04-1.40, 0.25, 0.001).Most of the laboratory parameters were similar between the groups. The number of platelet count was significantly lower in DHF and DSS [median (IQR) 43500(16500-95250], than DF [median (IQR) 65000(33000-1170000, p-value 0.01]*

Conclusion: *Previous infection with dengue virus and decreasing platelet count are the predictors of the severe dengue.*

Key word: *Dengue Fever, Predictors of severe dengue.*

DOI: *https://doi.org/10.3329/jdmc.v29i1.51175*
J Dhaka Med Coll. 2020; 29(1) : 77-82

Introduction

Dengue fever (DF) is the most common mosquito-borne viral disease in the world. Approximately 390 million people are affected worldwide every year, with around a 1% mortality rate of which 70% of the cases are predominantly in Asia[1]. On the other hand, the number of infected cases is rising exponentially over the years. Therefore, it has been a major public health threat to the world for several decades especially in the tropical and subtropical regions.

In Bangladesh, the first official dengue outbreak occurred in 2000[2]. Since then every year Bangladesh has faced a mild to severe outbreak. In 2019 dengue outbreak has been the largest with 101354 cases and 166 death[3]. Nonetheless, the more frequent and severe

1. Dr. Mohammad Zaid Hossain, Associate Professor, Department of Medicine, Dhaka Medical College Hospital, Dhaka
2. Dr. Nusrat Sultana, Assistant Professor, Department of Virology, Dhaka Medical College.
3. Dr. Afroza Akbar Sweety, Assistant Professor, Department of Virology, Dhaka Medical College.
4. Dr. Reaz Mahmud, Assistant Professor, Department of Neurology, Dhaka Medical College, Dhaka, Bangladesh.
5. Dr. Mohammed Masudul Hassan Khan, Assistant Professor, Department of Medicine, Dhaka Medical College, Dhaka
6. Dr. Muhammad Faizur Rahman, Assistant Professor, Department of Medicine, Dhaka Medical College, Dhaka
7. Dr. Sadia Saber, Assistant Professor of Medicine, Bangladesh Medical College, Dhaka
8. Dr. Farzana Rahman, Assistant Professor, Department of Medicine, Dhaka Medical College, Dhaka
9. Dr. Khairul Islam, Junior Consultant, Department of Medicine, Dhaka Medical College, Dhaka
10. Dr. Forhad Uddin Hasan Chowdhury, Registrar, Department of Medicine, Dhaka Medical College, Dhaka
11. Dr. Mazharul Islam, Honorary Medical officer, Department of medicine, Dhaka Medical College Hospital, Dhaka
12. Dr. Nandita Paul, Senior Consultant, Department of Medicine, Mugda Medical College Hospital, Dhaka
13. Prof. Khan Abul Kalam Azad, Principal & Professor of Medicine, Dhaka, Medical college Hospital.

Correspondence: Dr. Mohammad Zaid Hossain, Associate Professor, Department of Medicine, Dhaka Medical College Hospital, Phone: +8801713097627. E-mail: zhvalentino@gmail.com

Received: *22-01-2020* ***Revision:*** *29-01-2020* ***Accepted:*** *21-03-2020*

outbreak is predictable because of climate change, poor urban planning, and inadequate awareness among the population[4].

DF occurs due to the acute infection caused by four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) of the dengue virus[5]. The features of dengue patients may include symptoms like fever, typically lasting for 5 to 7 days, with saddleback or biphasic curve manifested by a second phase fever lasting for one or two days. Headache, retro-orbital pain, muscular pain/ myalgia, joint pain/arthralgia, marked fatigue lasting for days to weeks are common. Other symptoms, such as rash, gastrointestinal symptoms including nausea or vomiting respiratory tract symptoms including cough, sore throat, and nasal congestion may appear depending on the pattern and severity of the disease[1].

Peripheral blood parameters are characterized by leucopenia (White Blood Cells (WBC) < 5000 cells/mm3), thrombocytopenia (< 150,000 cells/ mm3), rising hematocrit (5–10%). In Dengue Hemorrhagic Fever (DHF) plasma leakage occurs which is usually evidenced by ascites or pleural effusion. Additional laboratory findings include an elevated level of serum aspartate transaminase (AST), ALT. Decrease of Serum Albumin and S calcium levels are frequent in both adults and children with dengue fever[3].

The severity of the dengue fever varies from asymptomatic febrile illness to life-threatening Dengue hemorrhagic fever (DHF) or Dengue shock syndrome (DSS)[5]. The fatality of the dengue fever occurs largely in DHF and DSS. It has been observed that management in appropriate time can reduce the case fatality[6]. If the risk factors for the progression of the dengue fever are known, close monitoring of the susceptible patients will be possible. It will be helpful in reducing the case fatality in a cost-effective way for the resource limited country like Bangladesh.

Very little is known about the risk factors for the prediction of the severity of the Dengue fever.

In this cross-sectional study we observed the clinical feature and the laboratory parameters of the Dengue fever. To determine the risk factors for the severity we compare the clinical features and different laboratory parameters among the different severity of dengue patient.

Methodology

This cross sectional study was carried out at the department of Medicine, of Dhaka medical college hospital from March 2019 to March 2020. The recruitment was limited to patients more than 18 years of age, both sexes with positive NS1 antigen or positive IgM antibody for dengue. Pregnant women and critical dengue patient were excluded from the study. Written informed consent was obtained from all the patients or from a legal representative where necessary. Ethical approval was taken from the ethical review committee of the respective institute. No priori sample size calculation and statistical power was determined. Total 199 patients were recruited according to mentioned inclusion and exclusion criteria.

Procedure:

A case record form was constructed to collect base line information, like demography, clinical features, and associated co-morbidities. Details physical examination was done. Clinical investigations which included complete blood count, blood sugar, serum creatinine, alanine aminotransferase(ALT), aspartate amino-transferase(AST), serum calcium, serum albumin was done in every patient during the admission or with in 24 hour of admission to know the baseline parameter. Repeated investigation was done according to patient need and as per physician's decision.

All the hematological investigations were done in the laboratory of DMCH using Beckman Coulter analyzer model AU480, USA.

Dengue viral infection was classified according to National Guideline of Bangladesh[3]. Like dengue fever as typical signs symptoms of the dengue with NS-I antigen or IgM positivity without evidence of plasma leakage with or without hemorrhage. Dengue hemorrhagic fever as typical features mentioned above with evidence of plasma leakage (as evident by positive tourniquet test, 20% increase in hematocrit, presence of ascites or pleural effusion). Dengue shock syndrome as typical feature mentioned above and evidence of shock (narrow pulse pressure, less than 20 mm Hg and or hypotension)

Statistical analysis:

Statistical analysis was done by SPSS 23 version. Qualitative variables were expressed in n(%), normally distribute quantitative

variables as mean (SD) and non-normal quantitative variables as Median (IQR).For the purpose of the analysis dengue fever was classified as group I and dengue hemorrhagic fever and dengue shock syndrome was classified as group II. For the comparison of qualitative variable chi square test was done. To measure the strength of association phi coefficient and relative risk (RR) with 95% CI was determined. For the comparison of normally distributed quantitative variables independent sample t test was done. Strength of association was determined with partial eta square. Non normal quantitative variables was compared with maan-whitney U test. P value less than 0.05 was considered as significant in two tail test.

Results

Of 288 patient screened for eligibility, total of 199 dengue patients were included in the study from March 2019 to March 2020. The mean (SD) age of the study population was 28.5(12.1) and 87.4% were less than 40 years of age. The male and female ratio was about 3:1. Among the total study population 149(74.9%) patients had DF, 46 (23.1%) had DHF and only 4 (2%) had DSS on presentation. No death was reported during the study from recruited patients. Most of the patients were 42.2 % were student (42. 2%) followed by businessman (19.1 %) and service holder (17.4%). About 9% patient had previous dengue.

All the patients presented with fever. Among the other clinical features the commonest was headache (81.4%) closely followed by vomiting (62. 3%), and myalgia (62.3%). Fatigue, retro-orbital pain, and arthralgia were present in 56.3%, 46.2%, and 41.2% cases respectively. (Table-1)

Table I

Clinical and laboratory features of the dengue fever (n=199)

Variable	Result
Age Mean(SD)	28.5(12.1)
Age group n (%)	
<40	174(87.4)
40-60	17(8.5)
>60	8(4)
Occupation n (%)	
House wife	31(15.6)
Student	84(42.2)
Business man	38(19.1)
Service holder	35(17.6)

Table I (Cont'd)

Variable	Result
Others	11(5.5)
Presenting complaints n (%)	
Fever	191(100)
Headache	162(81.4)
Retro-orbital pain	92(46.2)
Myalgia	124(62.3)
Arthralgia	82(41.2)
FatigueRash	112(56.3)52(26.1)
Nausea or vomiting	124(62.3)
Cough	45(22.6)
Diarrhea	71(35.7)
Abdominal Pain	74(37.2)
Previous history of Dengue	19((9.5%)
Examination	
Pulse Median(IQR)	76(70-84)
Systolic pressure, Median(IQR)	120(11-130)
Diastolic pressure, Median(IQR)	70(70-75)
Lymphadenopathy n (%)	4(2)
Sub-conjunctival hemorrhage n (%)	8(4)
Hepatomegaly n (%)	18(9)
Investigations [Median(IQR)]	
Hb%	14(12-14)
ESR	15(8-29)
Total WBC count	5140(400-7770)
Neutrophil %	58(43-72)
Lymphocyte%	32(21-45)
Platelet count	57000(30000-110000)
HCT%	41(36-44)
MCV femtoliters per cell	84(81-87)
MCH picograms	28(27-29)
MCHC g/dl	33(32-34)
Calcium mg/dl	7.6(7.1-8.2)
SGPT unit	72(41-125)
SGOT unit	90(49-162)
Diagnosis	
Dengue Fever [a]	149(74.9)
DHF[b]	46(23.1)
DSS[c]	4(2)

[a] DF- typical signs symptoms of the dengue with NS-I antigen or IgM positivity without evidence of plasma leakage with or without hemorrhage

[b] DHF- Dengue hemorrhagic fever as typical features mentioned above with evidence of plasma leakage (as evident by positive tourniquet test, 20% increase in hematocrit, presence of ascites or pleural effusion)

[c]DSS- Dengue shock syndrome as typical feature mentioned above and evidence of shock (narrow pulse pressure, less than 20 mm Hg and or hypotension)

The presenting age, gender and clinical presentation did not vary between group I (DF) and group II (DHF, DSS) (Table2). Previous history of dengue had low association with severity (RR, 95%CI, phi, P value; 1.2, 1.04-1.40, 0.25, 0.001). On hematological parameters, 83.9% of patients showed thrombocytopenia (table 1) whereas the median platelet count was 57000 /mm^3 (IQR 30000-110000). However, the number of platelet count was significantly lower in DHF and DSS [median (IQR) 43500(16500-95250], than DF [median (IQR) 65000(33000-1170000, p-value 0.01]. ALT and AST also increased in more severe dengue patients (median 71 vs. 90 and 85 vs. 108respectively) though not significant (p=0.68 and 0.37 respectively). Table II

Table-II

Comparison of the risk factors between classical Dengue Fever (group I) and severe Dengue (DHF, DSS)

Variable	Group-1[d] N=149	Group-2[e] N=50	P value	Phi/partial eta squared	RR 95%CI
Age Mean(SD)	29.36(12.3)	26.16(11.38)	0.11	0.16[b]	1.8
Gender Male	110(73.8)	43(86)	0.08	0.12	(0.94-3.9)
Presenting complaints n (%)					
Fever	149(100)	50(100)			
Headache	119(79.9)	43(86)	0.41	0.07	1.4(0.67-3.07)
Retro-orbital pain	71(47.7)	21(42)	0.51	-0.49	0.90(0.68-1.19)
Myalgia	96(64.4)	28(56)	0.31	-0.75	0.81(0.55-1.18)
Arthralgia	62(41.6)	20(40)	0.87	-0.01	0.97(0.75-1.27)
Fatigue	86(57.7)	26(52)	0.51	-0.05	0.88(0.62-1.24)
Rash	38(25.5)	14(28)	0.71	0.025	1.03(0.85-1.26)
Nausea or vomiting	95(63.8)	29(58)	0.50	-0.05	0.86(0.59-1.27)
Cough	34(22.8)	19(22)	1.0	0.01	0.99(0.84-1.17)
Diarrhea	54(36.2)	17(34)	0.87	-0.02	0.97(0.77-1.22)
Abdominal Pain	57(38.3)	17(34)	0.62	-0.04	0.94(0.74-1.18)
Previous history of dengue	8(5.4)	11(22)	0.001	0.25	1.2(1.04-1.40)
Examination					
Pulse Median(IQR)	77.2(9.6)	79.1(11.7)	0.25[c]	0.56[b]	
Systolic pressure	119(20.2)	116(21.3)	0.39[c]	0.32[b]	
Diastolic pressure	70.3(8.5)	70.2(7.5)	0.97[c]	0.23[b]	
Investigations Median(IQR)					
Total count	5050 (3990-7560)	5550 (3957-8556)	0.80[a]		
Neutrophil	58(43-72)	59(43-69)	0.88[a]		
Lymphocyte	33(21-45)	31(20-48)	0.79[a]		
Platelet count	65000 (33000-117000)	43500 (16500-95250)	0.01[a]		
HCT	41(35-44)	41(38-45)	0.33[a]		
Calcium	7.6(7.2-8.2)	7.6(7.1-8.2)	0.85[a]		
SGPT	71(39-119)	90(43-133)	0.68[a]		
SGOT	85(49-159)	108(48-184)	0.37[a]		

[a] maan-whitney u test
[b] partial eta square
[c] unpaired t test
[d] group-1 DF
[e] Group 2-DHF, DSS

Discussion

In this cross sectional study of 199 patients revealed that dengue is most prevalent among the younger age group, male patient and urban population. Most of the patient presented with fever, headache, myalgia, fatigue, retro-orbital pain and vomiting or nausea. Only decreased platelet count and previous dengue infection are associated with more severe illness.

Therefore, demographic character, clinical features does not predict the severity. None of the laboratory features excepting platelet count as well does not predict the severity of the dengue.

Previously Dhaka was the epicenter of the dengue outbreak in Bangladesh[7]. This study also reflect the same findings as more than 75% of the patient in this study were from the urban area of Dhaka.

In this study, prevalence of dengue is three times higher in male gender. The finding is similar to findings to other study in home and abroad[5,8]. However, a recent publication from western Nepal by N. college et al found that females infected more than males[8]. Sociocultural background of that region might have play a role for this dissimilar findings. In Bangladesh male predominance can be due to increasing outdoor activities and higher mobility. Most of the study population was young, similar to study done by E. Khan and M. Kisat et al where they noted the mean age was 24 years in 2007[9]. However, a population of all ages can be infected by the Dengue virus depending on the exposure.

The current study reveals 100% of cases presented with fever which is predictable since the study was conducted on hospital admitted patients. It also corresponds with other study done in Srilanka and India[10,11]. Headache (81.4%), myalgia (62.3%), Nausea, and vomiting (62.3%) are the most frequent clinical symptoms that appear in this study. These trio symptoms have been reported as the commonest besides fever by both national and international authors[5,11]. Around half of the patient presented with fatigue a joint pain and about one third of the patient presented with abdominal pain and diarrhea.

On the other hand, prevalence of retro orbital pain was much lower than other studies (46% vs. 78%)[12]. Previous history of dengue is found to be the predictor of severity. This was probably due to cross immunity to other serotype might enhance the immune reaction.

Leukopenia is the established biochemical feature of DF which occurs due to the direct suppression of bone marrow due to the infection[13]. In This study about half of the patient had finds 48.2% of patients had leukopenia which is similar to other study[14].

Thrombocytopenia is the most common characteristic laboratory findings of DF. This study also replicate this statement. Other study also had the similar findings[11,12]. This study also showed that decreasing platelet count is associated with the severe dengue. A combination of decreased platelet count and raised hematocrit is a marker of progression to plasma leakage. In this study, the median HCT was 41 for both DF and more severe DHF and DSS with no statistical significance. This might be due to small size of the sample. In most of the case blood sample was taken after resuscitation, as immediate lab facility was not available. Furthermore it is the referral Centre, so patient also received resuscitation treatment prior to hospitalization in DMCH from other institute.

Damages to the liver with elevated AST and ALT are common in both adults and children DF and DHF[3]. In this study Median ALT and AST is higher. But they are not a severity indicator, as no statistical significance was found between the DF and severe dengue (DHF, DSS).

This study was done on patients more than 18 years. We cannot generalize the findings to child population. Only 4 patient with DSS was included in this study, so we cannot comment about the predictors of the DSS from this study.

This was a single centered study done on a limited number of population. As blood sample cannot be drawn before the resuscitation, true base line laboratory parameter was not obtained.

Conclusion:

Fever, Headache, myalgia, nausea, and vomiting are the most common clinical features followed by pain in the back of the eyes, joint pain, abdominal pain, diarrhea, rashes, and bleeding manifestation. Thrombocytopenia, hepatic dysfunction, and leukopenia are the hallmarks of dengue infection. Previous infection with dengue virus and decreasing platelet count are the predictors of the sever dengue.

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