Original article

The Clinical Profile of Dengue Patients with Organ Involvement at Tertiary Care Hospital in Maharashtra

Dr. Nitin Sarate[1], Dr. Sarvada Tushar Katkar[2], Vidhi Bhanushali[3], Dr. Anant Arunrao Takalkar[4]

[1]Assistant Professor, [2]Senior resident, [3]Intern, Department of Medicine, Seth G. S. Medical College & KEM Hospital, Mumbai, Maharashtra

[4]Professor, Department of Community Medicine, MIMSR Medical College, Latur, Maharashtra.

Corresponding author: Dr. Anant A. Takalkar

Abstract

Introduction: Dengue is a highly endemic infectious disease of the tropical countries and is rapidly becoming a global burden. Dengue fever is a self-limiting febrile illness in majority of infections. It gets complicated with various organ involvements which increases the severity of disease both in terms of morbidity and mortality. No definite treatment has been discovered. Therefore, studies are being carried out to find out various warning signs and biochemical parameters so that treatment plans to curb them can be initiated to improve outcome and minimize duration of hospital stay. **Aims and Objectives**: To study the clinical plus laboratory profile and impact of organ involvement on outcome of dengue patients. It also aims to study the impact of pre-existing co-morbidities and other risk factors on organ involvement among dengue patients. **Materials and Methods**: An observational prospective study with 138 dengue patients with organ involvement, fulfilling inclusion and exclusion criteria was carried out. After acquiring consent, history was taken, general examination carried other and further investigations were conducted. All the data was recorded in Case Record Form and statistical analysis was carried out to obtain results. **Results**: Maximum patients were in age group 21-30 years; males more than females. Most common symptoms were fever, nausea and vomiting with abdominal pain and hemorrhagic manifestations determining severity of the disease. Hemoglobin level and platelet count was significantly less while renal function tests (BUN and Creatinine), liver enzymes (SGOT and SGPT), TLC and PT-INR value were significantly higher in the patients who died as compared to the patients who were discharged. Presence of sepsis, renal involvement and both hepatic and renal involvement were found to be associated with significant mortality. No significant association was found between preexisting co-morbidities and disease severity and outcome in Dengue patients. **Conclusion**: Monitoring for these evolution warning signs and prompt treatment to curb them is required to improve outcome and minimize duration of hospital stay.

Introduction

Dengue is one of the most prevalent and rapidly spreading arthropod borne viral disease. It is caused by any of the 4 serotypes of dengue virus (DEN1-4) and is transmitted within humans through female Aedes mosquitoes. Dengue causes a spectrum of illness ranging from inapparent or mild febrile illness to severe and fatal hemorrhagic disease. Classic dengue fever is characterized by the sudden onset of fever and a variety of non-specific signs and symptoms including frontal headache, retro orbital pain, body aches, nausea and vomiting, joint pains and rash.[1]

One of the criteria for classifying dengue cases as severe is organ involvement according to WHO's 2009 definition. [2] The pathogenesis of organ involvement is hypothesized to result

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from a combination of impaired inflammatory response and immune dysfunction, maldistribution of micro-circulatory blood or ischemic re-perfusion injury. The determinants for organ involvements were Liver involvement: high titer of alanine and/ or aspartate aminotransferase beyond 1000 IU/L or acute liver failure. Kidney involvement: acute renal failure or acute exacerbation of chronic kidney disease. Heart involvement: myocarditis, pericarditis and/ or heart failure, either acute onset or exacerbation of the underlying heart disease. Central nervous system involvement: encephalopathy, encephalitis as well as intra-cranial bleeding. [2]

This study is primarily aimed at identifying early clinical and laboratory risk factors which may be responsible for various organ involvements in dengue patients and the impact of this organ involvement on the presentation and outcome of the disease. It is also aimed at studying how pre- existing co-morbidities will affect clinical course of illness. In severe cases the case-fatality rate can be as high as 10% if untreated or 0.1% with appropriate clinical management. Therefore, the study was conducted in tertiary care hospital located in endemic region, results of which will help identify frequent risk factors leading to organ involvement giving rise to prompt management in turn decreasing mortality and morbidity due to this preventable illness.

Aims & Objectives

- To study the clinical profile and impact of organ involvement on outcome of dengue patients.
- To study laboratory profile of dengue patients with organ involvement.
- To study the impact of pre-existing co-morbidities and other risk factors on organ involvement among dengue patients.

Materials and Methods

An observational prospective study was conducted at Tertiary Care Hospital of Western India over period of 18 months after Ethics Committee approval. Sample size of 138 was considered after prevalence of dengue fever with organ involvement, was found to be 10% in a study conducted at the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University in Bangkok, Thailand. (3)

Inclusion criteria:

Patients with age above 12 years diagnosed with dengue with one or more of systemic organ involvement and were willing to give informed consent or assent. Dengue was diagnosed based on definition i.e., Dengue NS1 antigen and / or IGM ELISA in acute phase by validated immunoassay in a serum specimen (i.e., Collected <5 days of illness onset) and/or RT PCR during acute phase.

Exclusion Criteria: Patients not willing to give informed consent or presenting with mixed infection or having dengue without organ involvement.

Sample Size: As per data collected from IDSP department of institution there were 945 cases of Dengue identified in year 2016 and total 728 cases in year 2017. In a study conducted at the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University in Bangkok, Thailand (3) there were 153 cases of confirmed Dengue fever out of which 16 i.e., 10% with organ involvement. Considering above prevalence of dengue cases and organ involvement sample size for study is 138 which is calculated using following formula.

Sample Size= Z2 P(1-P)/d2

Where Z = is the number of standard deviations a given proportion is away from the mean = 1.96, P = Prevalence = 10%, q = 1-p= 90%, d = Absolute error of precision= 5%

Sample Size = $\frac{1.96^2 (0.1)(0.9)}{0.5^2} = 138$

Study Procedure: The data was recorded in a case record form which included data on following domains: (1) Patient demographic details like age, gender, etc.; (2) History and clinical examination findings; (3) Investigation such as Xray, USG, Biochemical parameters, etc. were entered in the case record form. Also, Case Record Form was used to collect information about: Clinical features at presentation; history of comorbidities; Clinical and laboratory profile and residual impairment in organ function till death/discharge and need for ICU management. This was in turn used to study the trend of the disease which led to the outcome of discharge (morbidity)/death (mortality).

Ethics: Institutional Ethics Committee approval [Ref no: EC/180/2018] was taken. The privacy of the participant and the confidentiality of the collected data was maintained and used only for the purpose of study by the people involved in the study.

Statistical analysis:
The data was compiled and tabulated using Microsoft Excel 2010 and statistical analysis was conducted with SPSS version 23 San Diego CA. Results for Qualitative Variables like gender, clinical signs, USG findings, etc. are presented as frequencies. Quantitative Variables like biochemical parameters are presented as mean (±SD). The association between dependent variables and independent factors was analyzed with the help of the Chi Square test. Mann-Whitney U test was used for non-parametric data. Level of significance is considered at 95% confidence interval ($p<0.05$).

Results:

Table 1: Age and Gender distribution

Age Group[years]	Males	Females	Total
12-20	22	05	27
21-30	26	15	41
31-40	17	10	27
41-50	09	07	16
51-60	08	02	10
61-70	12	00	12
>70years	04	01	05
Total	**98**	**40**	**138**

Out of 138 patients, there were 40 females (29 %) and 98 males (71%) belonging to different age groups as shown in Table 1. Age group containing highest frequency was 21 -30 years with total 41 patients [Males 26; Females15]. There were 27 patients both in age group 12-20 years [Males 22; Females 5] and 31-40 years [Males 17; Females 10]. The less frequent age groups included 41-50 years [Total 16 = Males 9; Females 7], 61-70 years [Total 12 Males only] and 51-60 years [Total 10 = Males 08; Females 02]. Least frequent age group was more than 70 years of age where total 5 patients were enrolled [Males 4; Female 1].

Table 2: Clinical features of the patients included in the study

Clinical symptoms	Frequency
Fever	135
Vomiting	110

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Abdominal pain	59
Breathlessness	15
Retro orbital pain	0
Hemorrhagic manifestations	40
Oliguria	27
YDU/YDS	22
Altered sensorium	5

Fever was the most common symptom seen in 135 patients followed by vomiting and abdominal pain seen in 110 and 59 patients respectively. 27 patients were presented with oliguria, 22 patients with yellowish discoloration of urine, 15 patients with breathlessness and 5 patients with altered sensorium. [Table 2]

Table 3: Biochemical parameters upon admission, peak, and towards the end in the patient subgroups as per the outcome (discharge / death)

Biochemical Parameter		Patient outcome		p-value
		Discharged	Death	
Haemoglobin	Admission	12.38 ± 1.95	11.30 ± 2.26	0.1100
	Peak	12.22 ± 2.04	9.80 ± 2.59	
	End	12.08 ± 1.72	9.47 ± 2.47	
TLC	Admission	6662.09 ±11491.02	9522.22 ±4777.49	0.0100
	Peak	6555.12 ±11657.31	12522.22 ±9239.42	
	End	7642.64 ±10992.73	12911.11 ±9414.67	
Platelet Count	Admission	108348.84 ±77919.90	95555.56 ± 60023.14	0.0001
	Peak	102224.81 ± 80095.28	75555.56 ± 60023.14	
	End	204310.08 ± 54081.22	82222.22 ± 57831.17	
BUN	Admission	24.81 ± 36.47	74.06 ± 79.12	0.0001
	Peak	24.61 ± 37.34	100.56 ± 78.98	
	End	10.81 ± 4.96	107.98 ± 103.46	
Creatinine	Admission	2.031 ± 2.78	9.433 ± 14.04	0.0001
	Peak	1.984 ± 2.75	6.00 ±5.92	
	End	1.72 ± 8.82	5.52 ± 5.31	
SGOT	Admission	238.34 ±549.91	309.67 ±521.04	0.028
	Peak	332.65 ±1021.21	423.22 ± 597.73	
	End	100.58 ± 499.28	262.44 ± 290.32	
SGPT	Admission	159.56 ±244.22	273.56 ±482.92	0.040
	Peak	171.22 ±277.00	350.56 ± 494.94	
	End	58.26 ± 152.37	213.56 ± 226.06	

PT-INR	Admission	0.93 ± 0.25	1.31 ± 0.98	0.0001
	Peak	1.06 ± 1.11	1.93 ± 2.14	
	End	0.95 ± 0.26	2.04 ± 2.07	

Clinical signs: Icterus was encountered in 9 patients followed by pallor in 7. Lymphadenopathy, cyanosis and clubbing were not seen in any of the patients.

Biochemical profile: Hemoglobin level and platelet counts were reduced in death outcome group. BUN and Creatinine, SGOT and SGPT, TLC and PT-INR values were seen to be increasing in patients who died compared to those who were discharged. [Table 3]

In 107 patients rapid diagnostic test [NS1 antigen] were used and 47 patients were diagnosed based on ELISA testing. None of our patients was diagnosed with PCR testing.

Radiological investigations: 125 Chest x-rays did not show any abnormality, 9 were suggestive of pleural effusion and 3 were suggestive of pulmonary oedema. On USG, acute kidney injury was the most common finding encountered in 32 patients followed by ascites in 28 and hepatomegaly and/or altered liver echo texture in 22 patients. In 11 patients, USGs were suggestive of pleural effusion and 6 patients showed splenomegaly. There were 5 pregnant patients carrying SLIUG reflected in USG findings. Computed tomography were conducted for 12 patients out of which most common was HRCT Chest [6 patients], followed by CT brain in 4 patients. MRI Brain was done for one patient showing hemorrhagic encephalitic findings.

Table 4: Treatment received considering patients' severity and symptoms

Treatment	**Frequency**
Hydration	132
Ceftriaxone	137
Piperacillin+Tazobactam	50
Artesunate	133
Methylprednisolone	10
Paracetamol	138
Pantoprazole	137
Ondansetron	117
Blood&Bloodproducts	22
Oxygen support	16
Dialysis	13
Vitamin K	2
Inotropes	2

Treatment in these Dengue patients was primarily symptomatic and supportive. All patients were given antipyretics paracetamol [138] as fever was the most common presentation (135 patients). To prevent dehydration and subsequent complications, prompt and meticulous fluid therapy i.e. hydration [132] was the mainstay of treatment. Proton pump inhibitors like pantoprazole [137] and ondansetron [117] were also administered commonly in view of significant patients presenting with nausea and vomiting. Artesunate combination therapy [133] administered as India is malaria endemic region. Blood and blood products were used

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in case of severe thrombocytopenia and bleeding manifestations. 16 patients required oxygen therapy and 13 patients were given hemodialysis for renal failure. [Table 4]

Table 5: Relationship of Organ involvement and the patient outcome

Organ Involvement	Present	Patient Outcome			p-value	Correlation coefficient of organ involvement with death
		Discharged	Death	Total		
Leukopenia	No	73	8	81	0.057	0.213
	Yes	56	1	57		
Sepsis	No	124	4	128	0.0001	0.492
	Yes	5	5	10		
Thrombocytopenia	No	39	3	42	0.845	0.219
	Yes	90	6	96		
Serositis	No	100	8	108	0.424	0.327
	Yes	29	1	30		
Hepatic involvement	No	28	4	32	0.118	0.240
	Yes	101	5	106		
Renal involvement	No	99	3	102	0.004	0.230
	Yes	30	6	36		
Pulmonary involvement	No	110	7	117	0.545	0.423
	Yes	19	2	21		
Hepatic and Renal involvement	No	114	5	119	0.006	0.235
	Yes	15	4	19		

Relationship of organ involvement and the patient outcome – Sepsis, Renal involvement and both combined Hepatic and renal involvement is associated with higher death outcomes. Involvement of Leukopenia, Thrombocytopenia, Serositis, Hepatic and Pulmonary involvement is not associated with increased severity in disease course. [Table 5]

Table 6: Relation between pre-existing co-morbidities and patient outcome and correlation coefficient between it and duration of hospital stay.

Co-morbidities	Patient Outcome			p-value	Correlation coefficient with duration of hospital stay
	Discharged	Death	Total		
Present	34	5	39	9	0.076
Absent	95	4	99		

39 patients presented with different co-morbidities out of which 5 died and 34 were discharged. The Chi-square test has a p value of 0.060. The Pearson correlation between the presence of comorbidities and duration of hospital stay has a p value of 0.076. [Table 6]

Discussion:

In the study there were 138 patients having dengue with organ involvement with percentage of males

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(71%) being more than females (29%). Previous studies from Cambodia, Malaysia, Sri Lanka, Singapore, the Philippines and India found that males are more prone to DF than females, suggesting that the more common outdoor work habits of males gave them more chances than females to be bitten by mosquitoes.[4,5] Highest frequency was seen in age group 21-30 years (41 patients) followed by age groups 12-20 years and 31-40 years containing 27 patients. This is similar to a study conducted by Kumar A et al which showed that the majority of dengue patients were from 15-44 years age group. [6]

Fever was the most common symptom seen in135 patients similar to other Indian and around the world studies. [6,7,8,9,10,11] According to studies, [12,13] abdominal pain is considered as one of the significant risk factors for identifying severity of disease and also mortality. Abdominal pain was the third most common symptom presenting in 59 out of 138 patients in our study. 40 patients were presented with different types of hemorrhagic manifestations in the form of skin manifestations - purpura and rash, hematuria, melena, menorrhagia, etc. Comprehensive guidelines for prevention and control of dengue and dengue hemorrhagic fever[14] mention hemorrhagic manifestations as a risk factor for deaths in dengue. Our findings show that abdominal pain and hemorrhagic manifestation hints at underlying organ involvement which increases the severity of disease in terms of morbidity and mortality and hence is in accordance with the studies mentioned above. Therefore, one should look out for these early warning symptoms in dengue patients so that the underlying cause can be treated early giving rise to better outcomes.

Different laboratory parameters were recorded on admission, peak and outcome. Trends were studied according to final outcome subgroups i.e., discharge and death. The mean hemoglobin trend was found to be low for patients with death outcome group [Admission 11.3; Peak 9.8; End 9.46 g %] when compared to discharged patients' group [Admission 12.38; Peak12.21; End 12.07]. A similar conclusion was reached by a study conducted by Chua MN and el [1993] [15]where hemoglobin value of less than 9 mg/dl was associated with a 4-fold higher risk of mortality and/or severity.

A further novel finding is that there is significant leukocytosis (p value 0.010) in the death outcome group (Admission - 9522.2; Peak -12522.22; End -12911.11/mm3) compared to discharged patients (Admission - 6662.2; Peak - 6555.12; End - 7642.64/mm3). Some study concluded that white cell count > 5,000/µL is a prognostic factor for dengue severity [16] while others found leucopenia due to bone marrow suppression. [17,18,19] Stress accompanied with shock may somehow cause leukocytosis is formulated by one study. [20]

Platelet count for discharged patient (Admission 1.08; Peak 1.02; End 2.04 lac/mm3) and for death subgroup (Admission 0.95; Peak 0.75; End 0.82lac/mm3) with p value < 0.0001 which is highly significant. So, thrombocytopenia is significantly associated with severity of disease and mortality. A similar conclusion was reached in study by Chua MN et al in 1993. [15]

Mean BUN (100.5 vs 24.6) & Creatine level (6 vs 1.9) was high in death outcome group as compared to discharged patient group which is very statistically significant with p value of 0.0001. This implies that blood urea nitrogen and serum creatinine levels have a direct impact on mortality of dengue patients. Similar findings were found by Kuoetal., (2008) and Mallhietal. (2016) [21,22]

Liver enzymes- SGOT levels in Discharged patients: Admission 238.3; Peak 332.6; End 100.5 and in Death outcome subgroup patients: Admission 309.6; Peak 423.2; End 262.4. SGPT levels in Discharged patients Admission 159.5; Peak 171.2; End 58.2 IU and in Death outcome subgroup patients Admission 124 273.6; Peak 350.5; End 213.5 IU. The p value for SGOT and SGPT were 0.040 and 0.028 respectively which is significant. Hence, both SGOT and SGPT were significantly higher in the patients who died as compared to discharged group. In various studies, the median aspartate transaminase (SGOT) and alanine transaminase (SGPT) values have been found to be higher for sever forms of dengue than for uncomplicated dengue fever therefore in accordance with result obtained. [23,24,25]

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PT-INR levels in discharged patients were Admission 0.9; Peak 10.6; End 0.9 and in death outcome subgroup were Admission 1.3; Peak 1.92; End 2. There is a significantly elevated PT- INR value in death subgroup (p value = 0.0001). This is consistent with what has been found in study by Chua MN et al in 1993[15] depicting that prolongation of prothrombin time is associated with higher fatality. Other studies also found that prolonged PTT and prolonged PT are prognostic factors for DHF and DSS. [26,27]

In this study there were 39 patients with different morbidities like diabetes mellitus, hypertension, retroviral disease, chronic kidney disease, liver disorders, heart disease, aplastic anemia etc. Out of these 39 patients, 34 were discharged and 5 were having death prognosis. The Chi-square test has a p value of 0.060 which is not significant. Contrary to findings of previous studies[12,28] which show significant correlations between presence of comorbidities and disease severity and mortality, our results show that presence of comorbidities does not significantly affect the patient outcomes. Also, the Pearson correlation between presence of comorbidities and hospital stay duration has a p value of 0.076 which is not significant.

Total 57 patients were having leucopenia (56 were discharged and one died). Presence of leucopenia (p=0.057) does not significantly affect the patient outcomes. Out of 10 patients having sepsis, 5 were discharged and 5 died. Presence of sepsis (p=0.0001) in dengue patients is highly significantly associated with deaths. The correlation coefficient value of 0.492 indicates very strong positive association between sepsis and death. Rapid diagnostic tests for dengue may need to be routinely used in adult patients presenting with sepsis and septic shock in tropical countries. As A number of adult patients who died of dengue are misdiagnosed as severe sepsis and septic shock. [29]

Out of 96 patients with thrombocytopenia, 90 were discharged and 6 died. Presence of thrombocytopenia (p=0.845 and correlation coefficient = 0.219) does not significantly affect the patient outcomes. Out of 30 patients with serositis, 29 were discharged and one died. Presence of serositis (p= 0.424 and correlation coefficient = 0.327) does not significantly affect the patient outcomes.
Liver damage is one of the common complications of dengue and transaminitis, hypoalbuminemia and reversal of A: G ratio should be used as biochemical markers in dengue patients to detect and monitor hepatic dysfunction (24).Liver was found to be the most frequent organ affected in this study. There are remarkable metabolic alterations in the hepatocytes of three DENV cases (1, 2 and 3), with the presence of single or multiple small lipid vesicles (microsteatosis) and/or large vesicles (macrosteatosis). There were 106 patients with hepatic involvement, and 101 were discharged and 5 died. Hepatic involvement (p=0.118 and r=0.24) does not significantly affect the patient outcomes.
36 patients were having renal involvement out of which 30 discharged and 6 died. Renal involvement (p=0.004) in patients of dengue is significantly associated with death. The correlation coefficient value of 0.244 indicates strong positive association between renal involvement and death. Similar findings were found by Kuoetal.,(2008) and Mallhietal.(2016). [21,22] It may be due to a) direct injury like in other infectious disease b) indirect mechanism through immune system or c) hypotension DSS leading to decreased renal blood supply and renal failure. (30) Early identification of renal insufficiency should be a priority in patients with dengue to allow for timely intervention.

There were 19 patients with combined renal and hepatic involvement; 15 discharged and 4 died. Presence of combined Hepatic and Renal involvement (p=0.006) in patients of dengue is significantly associated with deaths. The correlation coefficient has a value of 0.235 which indicates strong positive association between hepatic and renal involvement together with death. Similar results were noted in previous studies viz Samitha Fernando et al. [31]

Out of 21 patients with pulmonary involvement, 19 were discharged and 2 died. Pulmonary involvement (p=0.545) does not significantly affect the patient outcomes. Study conducted by Po´voa TF et al in 2014[32] described that Dengue virus appears to potentially infect macrophages and

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lung endothelial and epithelial cells. Pulmonary complications can present as pleural effusion, pneumonitis, no cardiogenic pulmonary edema [acute respiratory distress syndrome (ARDS)], and hemorrhage/hemoptysis. These complications coincide with capillary leak syndrome and thrombocytopenia.

Conclusion

We have studied 138 dengue patients with various organ involvements. Maximum patients were in age group 21-30 years, males more than females. The most common symptoms were fever, nausea and vomiting. Abdominal pain and hemorrhagic manifestations were encountered as next most common symptoms and were determinants of severity of the disease.

Hemoglobin level and platelet count was significantly less in the people who died as compared to the discharged patients. Renal function tests - Blood Urea Nitrogen and Serum Creatinine levels were significantly more in the people who died as compared to the discharged patients. Also, both SGOT and SGPT were significantly higher in the patients who died as compared to the patients who were discharged. Significant leukocytosis and elevated PT-INR value were seen in death subgroup.

Liver was most common organ involved in Dengue patients in the study group. Presence of sepsis in dengue patients (128) is significantly associated with deaths. There was also strong positive association between renal involvement and death. Patients with hepatic and renal involvement together were found to be associated with significant mortality. There was no significant association between preexisting co-morbidities and disease severity and outcome in Dengue patients.

Vector preventive measures, along with early diagnosis of dengue viral infection, monitoring for evolution warning signs, and initiation of appropriate treatment accordingly are important measures to be taken to reduce the severity of dengue in terms of both morbidity and mortality and also for decreasing mean duration for hospital admission stay and for more effective utilization of health care facilities.

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