Patient Characteristics and Outcome of Multi-organ Involvement in Dengue with reference to SOFA score

ABSTRACT

Background: Mortality in severe Dengue infection is attributed to development of MODS. Clinical profile, outcome and utility of SOFA score in Dengue MODS is not well studied in Indian context. Hence, this study was conducted to describe the "patient`s" characteristics and outcome in Dengue MODS with reference to SOFA score.**Methods:**We conducted an observational cross –sectional study in medicine department, Sassoon General Hospital Pune between January 2016 to January 2020.Adult dengue patients with multiorgandysfunction based on SOFA score were included. Demographic, clinical and laboratory data were collected and analyzed. SOFA score was calculated at admission and monitor throughout admission course.**Results:** Total 69 patients were included. Male were 53.6% and mean age was 38.7±18.7 years. Most common symptoms were fever (98.6%), body ache & joint pain (69.6%), generalized weakness (62.3%), breathlessness (59.4%), headache (58%), anorexia (58%), abdominal pain & vomiting (55.1%) and bleeding manifestations(47.8%).Total 28% patients had two, 33% had three, 24.6% had four and 14.4% had ≥ 5 organs involvement. Maximum number of patients had hematological involvement (95.7%) followed by respiratory system involvement (63.8%). Mean duration of hospital stay was 9.8 days. Mortality was 43.5%. There was significant correlation of number of organs involved, pulse rate, respiratory rate, serum albumin, nervous system, respiratory system, SOFA score at admission and delta SOFA score with outcome.**Conclusion:** Dengue MODS has high mortality. Tachypnoea, tachycardia, hypoalbuminemia, respiratory failure and nervous system involvement are predictors of poor outcome. SOFA score at admission and its monitoring can serve as a useful marker to predict prognosis in dengue with multiple organ involvement.

Keywords: *Dengue, MODS, SOFA score, outcome, hypoalbuminemia*

1.INTRODUCTION

Dengue fever is vector borne disease and endemic in many states of India [1]. It is caused by the 4 serotypes belonging to arboviruses of the genus flaviviruses. The vector is mosquito Aedesaegypti [2]. Mortality in severe dengue infections is attributed to development of Multi-organ dysfunction syndrome(MODS). The manifestations of severe dengue are varied and unfortunately the exact morbidity, mortality and outcome in terms of organ dysfunction are not well studied in Indian context. Organ impairment may manifest as hepatic or renal impairment, respiratory failure, myocarditis, bleeding, encephalopathy or encephalitis [3,4].

The European Society of Intensive Care Medicine organized a consensus meeting in Paris in October 1994 to create a so-called Sepsis-related Organ Failure Assessment (SOFA) score [5], to describe quantitatively and as objectively as possible the degree of organ dysfunction over time. Six organ dysfunctions including nervous, respiratory, coagulopathy, cardiovascular, liver and renal were assessed using initial SOFA score and graded from 0 to 4. Various studies have shown the utility of SOFA score in estimating the prognosis among cases in Intensive Care Units (ICU)[6,7,8].

This study was conducted with the aim of assessing the patient's characteristics and outcome in cases of dengue with multi-organ involvement with reference to SOFA score.

2. METHODS

2.1 Study design: This was observational cross-sectional study conducted in the Department of Medicine at Sassoon General hospital, Pune between the months of January 2016 to January 2020 and approved by Ethics committee of B J Medical college and Sassoon General Hospital, Pune.

2.2 Patients: All the hospitalized patients in medicine wards and ICU diagnosed as Dengue fever as per WHO criteria [9] with two or more organ systems i.e. multiorgan involvement defined as per SOFA score [5] were included. Patients or whose relatives who refused to give consent for study and those with pre-existing chronic liver diseases, chronic kidney diseases, chronic heart failure, cerebrovascular accidents, bleeding disorders and coagulation disorders were excluded.Informed written consent was obtained.All the patients were managed as per standard treatment protocol and as per the institutes hospital`s infection policy.

2.3 Data collection: Demographic data, relevant clinical and medical history was noted. Physical examination and Tourniquet test were performed in all patients.Blood investigations done included Dengue serology (Dengue NS1, IgM), serial hemograms, renal function tests, liver function tests (LFT) and Prothrombin time (PT). Arterial blood gas analysis, urine routine microscopy, Cerebrospinal fluid analysis, Electrocardiogram, Chest X-ray, Ultrasound abdomen, CT brain and Fundus examination were performed in indicated patients. Coinfections with Malaria, Leptospira, typhoid, scrub typhus and otherhepatotropic viruses were excluded by doing relevant investigations. Number of organs involved were noted. SOFA score was noted at admission and monitor throughout the course of admission. Patient outcome was assessed in terms of discharge or death.

2.4 Statistical analysis: Data analysis was done using statistical software SPSS (Statistical Package for Social Sciences)version21.0. Demographic and clinical data were analysed using descriptive statistics and reportedasmeanwithstandarddeviation (SD) and median with range for

continuousvariablesandasfrequenciesandpercentageforcategoricalvariables.Forcontinuous variables, t-test was used for normally distributed variables and Mann WhitneyU test for in-homogenously distributed variables. Categorical variables were comparedusing chi square test. P value less than or equal to 0.05was considered statisticallysignificant.

3. RESULTS

3.1 Demography and Medical History

Out of 610 patients serologically confirmed Dengue patientsadmitted during this period, 78 (12.8%) had multi-organ involvement. Total 69 patients were included in study and 9 patients were excluded due to pre-existing chronic liver and renal diseases in them. Males were37 (53.6%)and females were 32 (46.4%). Mean age was38.7 (± 18.73) years and the age-range was 13 to 80 years. Most common age group was 21 to 30 years.Residents of rural area were 29 (42%) and urban area 40 (58%). Total 12 (17.4%) patients had comorbidities. Hypertension was most common comorbidity followed by hypothyroidism, Diabetes Mellitus and coronary artery disease. Past history of dengue infection was present in 4 (5.8%), Chikungunya in 2 (2.8%) and malaria in 1 (1.4%) patients.

3.2 Clinical manifestations

Various clinical and bleeding manifestations inDengue MODS are shown in Table 1 and 2 respectively.

On clinical examination at admission, 35 (50.7%) were febrile (temperature ≥ 99°F) and 28 (40.6%) patients had tachypnoea(respiratory rate >20/ minute). Tachycardia (pulse>100/min) was present in 43 (62.3%) and bradycardia (pulse<60/min) in 3 (4.4%) patients. Hypotension was seen in 23 (33.3%) patients.

Clinical manifestations	Number of patients N=69	Percentage (%)
Fever	68	98.6
Chills/ Rigors	62	89.9
Generalised weakness and fatigue	43	62.3
Breathlessness	41	59.4
Anorexia	40	58

Jaundice	18	26.1
Blurring of vision	14	20.3
Decrease urine output	8	11.6
Diarrhoea	15	21.7
Headache	40	58.0
Rash	11	15.9
Body ache and joint pain	48	69.6
Vomiting and Pain in abdomen	38	55.1
Seizure	11	15.9
Loss of consciousness	9	13.0
Altered sensorium	23	33.3
Bleeding	33	47.8
Positive Tourniquet test	15	21.7
Serositis (Ascites / Pleural Effusion / Joint Effusion)	24	34.8

Table 1: Various clinical manifestations in Dengue MODS

Bleeding manifestations	**Number of patients N=69**	**Percentage (%)**
Hematemesis	8	11.6
Malena	22	31.9
Haemoptysis	3	4.4
PR bleed	3	4.4
Haematuria	4	5.8
PV bleeding	3	4.4
Epistaxis	2	2.9
Gum/Oral Bleed	4	5.8

Table 2: Various bleeding manifestations

3.3 Laboratory Data

Low hemoglobin (<10 g/dl) was seen in 24.6%. Leukopenia (<4000/mm^3) and leucocytosis (>11000/mm^3) were present in 11.6% each. Thrombocytopenia (< 150000/mm^3) was present in 95.7% patients. At admission, patients with ≤30,000/mm^3 platelet count were 19 (27.5%), 30001-50000 were 18 (26.1%), 50001-75000 were 10 (14.5%) ,75001-10000 were 7 (10.1%) and >100000 were 15 (21.7%). Maximum patients had platelet count below 30000 with lowest platelet count of 7,000 on admission. On Day 5, out of 51 who survived, platelet count ≤30000 were present in 6 (11.8%), 30001-50000 in 7 (13.7%), 50001-75000 in 6 (11.8%), 75001-100000 in 10 (19.6%) and >100000 in 22 (43.1%) patients. Maximum patients had platelet count >100000 on Day 5. On Discharge or death, out of 69 patients, 5 (7.2%) had platelet count ≤30000, 9 (13%) had 30001-50000, 4 (5.8%) had 50001-75000, 5 (7.2%) had 75001-100000 and 46 (66.7%) had >100000. Liver function tests (LFT) was done in 67 patients. Total number of patients with total Bilirubin < 2 mg/dl were 46 (68.7%), in range of 2-5 were 10 (14.9%) and > 5 mg/dl were 11 (16.4%). Abnormal Aspartate transaminase (AST) (>38 IU/L) and Alanine transaminase (ALT) (>41 IU/L) were present in 59 (88.1%) and 46 (68.7%) patients respectively. AST was more than ALT in 85.1% patients. Alkaline Phosphatase (ALP) was raised (>140 IU/L) in 30 (44.8%) patients. Low serum Albumin (<3.5 g/dl) was present in 43 (64.2%) and elevated Prothrombin time (>15.4 seconds) in 11 (16.4%) patients.

3.4 Imaging

Chest X-ray was done in 66 patients. Abnormal Chest X-ray was present in 34 (51.5%). Pleural effusion was seen in 14 (21.2%), infiltrates in 15 (22.7%) and consolidation in 13 (19.7%) patients. Ultrasound abdomen was performed in 34 patients. Pseudo Gall bladder oedema was present in 19 (55.9%), acalculouscholecystitis in 4 (11.76%), hepatomegaly in 6 (17.7%) patients and splenomegaly in 4 (11.8%) patients. Freefluid was present in 20 (58.8%) which was minimal in most cases and pleural effusion mostly right sided in 14 (41.2%) patients.

3.5 Organ involvement

In our study, based on SOFA Score, patients with two organs involvement were 19 (28%), three were 23 (33%), four were 17 (24.6%), five were 7 (10.1%) and six were 3 (4.3%). Cardiovascular system involved in 22 (31.9%), coagulation system in 66 (95.7%), liver in 27 (39.1%), Nervous system in 31 (44.9%), renal system in 39 (56.5%) and respiratory system in 44 (63.8%).

3.6 Morbidity

Mean duration of stay in hospital which includes both outside and our hospital staywas 9.8 days. Patients with two, three, four, five and sixorgans involvement had mean stay of 8.8± 3.5 days,11.4 ± 9.5 days, 10.1 ± 7 days, 8.4 ± 4.2 days and 6 ± 4.6 days respectively.

3.7 Outcome

In our study, total 30 (43.5%) patients died. Out of 37 males, 18 (48.6%) died and out of 32 females, 12 (37.5%) died. Total 16 (61.5%) out of 29 patients residing in rural area died and 14 (35%) out of 40 patients residing in urban died. Maximum deaths were in age group 21-30 years. Above 60 years of age, 8 out of 12 patients died. Mortality rate below 20 years was 41.7%, between 21-30 years was 36.8%, between 31-40 years was 44.4%, between 41-60 years was 35.3% and above 60 years was 66.7%. There was no significant correlation of age, gender or residing area with outcome as $p > 0.05$.

Out of 33 patients with bleeding, 15 (45.5%) died. Total 14 (40%) patients died out of 35 who were febrile at admission and 8 (34.8%) died out of 23 who presented with hypotension. There was no significant correlation of bleeding, temperature or blood pressure with outcome as p value > 0.05. Out of 23 patients with tachycardia at presentation, 15 (65.2%) died and 15 (32.6%) died out of 46 patients with pulse ≤100. Total 20 (71.4%) died out of 28 patients with tachypnoea and10 (24.4%) died out 43 patients with normal respiratory rate. Therefore, there was significant correlation of pulse and respiratory rate with outcome as $p < 0.05$.

Table 3,4 and 5 outline the outcome with respect to LFT, number and each type of organ involvement respectively.

Lab Parameters		**Outcome**		**Total**	**p-value**
		Discharge	Death		
Bilirubin	Normal	28	18	46	0.157
	Abnormal	9	12	21	
SGOT	Normal	5	3	8	0.999
	Abnormal	34	25	59	

SGPT	Normal	14	7	21	0.428
	Abnormal	25	21	46	
ALP	Normal	22	14	36	0.619
	Abnormal	16	14	30	
Albumin	Normal	19	4	23	0.008*
	Abnormal	20	23	43	
	Abnormal	4	7	11	

Table 3: Liver function test versus outcome

Number of organs involved	**Outcome**		**Total**	**p-value**
	Discharge	Death		
2	19	0	19	< 0.001
3	11	12	23	
4	9	8	17	
5	0	7	7	
6	0	3	3	
Total	39	30	69	

Table 4: Number of organs involved versus outcome

Organ Involved	**Outcome**		**Total**	**p-value**
	Discharge	**Death**		
Cardiovascular	9	13	22	0.117
Coagulation	38	28	66	0.576
Liver	14	13	27	0.621
Nervous system	11	20	31	0.002*
Renal system	20	19	39	0.340
Respiratory system	15	29	44	< 0.001*

Table 5: Outcome with respect to each type of organ involvement

3.8 SOFA score and outcome

Mean SOFA score at admission in patients who survived was 4.67±1.77 and in patients who died was 6.10±2.99. Mean of maximum SOFA score in patients who survived was 4.82±1.68 and patients who died was 9.57±2.30. There was significant correlation of SOFA score at admission and maximum SOFA score with outcome. Out of 36 patients whose SOFA score was more on Day 1 of admission as compared to subsequent days, 34 (94.5%) survived and 2 (5.5%) died. Total 28 (84.8%) patients out of 33 died whose SOFA score was more on subsequent days than on Day 1. There was significant correlation of change in SOFA score i.e. Delta SOFA score with outcome. Increased mortality was noted with increased SOFA score on subsequent days during course of admission.

4. DISCUSSION

Very few studies have been done on multiorgan involvement in Dengue and its outcome with reference to SOFA score worldwide [9]. In this study, around 13% patients admitted with Dengue infection had multiorgan involvement. Majority of patients belong to younger age group probably due to higher cytokine storm leading to MODS in them. Male and female ratio was 1.16 and male predominance is attributed to greater vulnerability for mosquito bite due to outdoor work involved in occupation and clothing habits. Patients belonging to rural areas were 42% and there is trend of dengue incidence shifting from urban to rural areas due to large scale development activities, industrialization, urbanisation, rapid transportation, changing lifestyles and lack of adequate water supply[10].

Fever was most common presentation in our study associated with chills, body ache, joint pain, fatigue, headache and retro orbital pain in majority patients. Fever varied from 99-104 ^{0}F. Rash as presenting complaint was present in 15.9% patients as compared to 21% reported by Rajender et al [11] and 20% by Kashinkunti et al [12] and erythematous blanching rash was most type followed by maculopapular and morbilliform type.Anorexia, abdominal pain and vomiting were most common gastrointestinal symptoms. Various causes of abdominal pain in our study were acute hepatitis, acute pancreatitis, acalculouscholecystitis, diffuse peritonitis and acute inflammatory colitis. Most common respiratory symptom was breathlessness followed by cough and pleuritic chest pain. Among Central Nervous system (CNS) symptoms, headache was most common symptom followed by altered sensorium and seizure.

At admission, hypotension was present in 33.3% in our study attributed to Dengue shock syndrome, haemorrhagic shock secondary to bleeding, myocarditis, pulmonary embolism and septicaemia. Rajendra et al [10] reported hypotension in 20% patients. Tachycardia and tachypnoeawere present in 33.3% and 40.6% patients respectivelyas compared to 33.3% and 12.7% respectively as seen in study by Salagre et al [13].

Anaemia was seen in 24.6% patients attributed to high bleeding manifestation as seen in our study cohort, septicaemia and low baseline haemoglobin in Indian females. Transient bone marrow suppression seen in Dengue resulted in leukopenia as seen in 11.6% patients. Systemic Inflammatory response syndrome (SIRS) and septicaemia leading to MODS attributed to leucocytosis present in 11.6% in our study.

In our study, abnormal ALT and AST were observed in 68.6% and 88.1% patients respectively compared to 80% and 90% as reported in Kuo et al [14]. AST was more than ALT in 85.1% patients and similar finding was observed in study by Shukla et al [15]. AST has various sources including heart, striated muscle, erythrocytes and liver, whilst ALT has primarily hepatic origin [16]. Dengue virus causes acute insult to these non-hepatic tissues resulting in higher AST levels compared to ALT. Impaired albumin production by damaged hepatocytes due to dengue virus and septicaemia resulted in hypoalbuminemia as observed in 65.2% patients.

Maximum patients had 3 organ involvements with coagulation as most common organ involved which was also seenin study bySalagre et al [13]. Mean duration of hospital stay was 9.8 days in our study as compared to7.4 days seen in Gopal Krishna et al study [17]. Mean duration of hospital stay was more in patients with 3 and 4 organs involvement as patients with 2 organ involvement improved early and with 5 and 6 organs died early in disease course.

In our study, mortality was 43.5%. Jog et al [9] and Chen et al [18] reported 26.6% and 23.1% mortality respectively. Higher mortality was attributed to higher organ involvement (39% had ≥ 4 organ involvement) in our study and patient reaching tertiary centre late in the course of disease due delay in referral by primary care physician and negligence by patients. Mortality was 75% in patients above 60 years of age due to higher comorbidities in them. Mortality was higher in males than females because most of them presented at late stage of disease due to negligence and higher prevalence of alcohol and smoking addictions among them which acted as confounding factor in disease

progression. Tachycardia and tachypnoea at admission were predictors of poor outcome. Both are components of SIRS that lead to MODS.Salagre et al [13] observed tachypnoea but not tachycardia had significant correlation with outcome. Hypoalbuminemia was significantly associated with higher mortality and similar finding was noted in study by Jog et al [9].

In our study, involvement of Respiratory (decreased PiO2/FiO2) and Nervous system (decreased GCS) were significantly associated with poor outcome.Similar findings were noted by Chen et al [18]. Pneumonia, pleural effusion, Acute Respiratory Distress syndrome (ARDS), sepsis and aspiration were responsible for respiratory involvement. Dengue encephalitis, aseptic meningitis, pyogenic meningitis due to secondary infection, intracranial bleed, cortical venous sinus thrombosis and metabolic & septic encephalopathy were several causes leading to nervous system involvement.

Higher SOFA score at admission was associated with poor outcome in our study. Higher mortality was seen in patients with progressive increase in SOFA score during the course of admission. Patients with improvement in SOFA score were discharged early. These results were comparable to study by Jog et al [9]. Thus, calculating SOFA score at admission and its monitoring in Dengue MODS patients can be useful in predicting prognosis.

There are several limitations in our study. First is referral bias and many patients were referred at terminal stage to our government tertiary centre resulting in higher mortality. Second is smaller number of patients.

5. CONCLUSION

Multiorgan involvement in Dengue has high mortality. Tachypnoea, tachycardia and hypoalbuminemia are early predictors of poor outcome. Respiratory failure and nervous system involvement are associated with high mortality. This study suggests early intervention and referral to tertiary centre by physician before multiorgan involvement sets in to reduce mortality. SOFA score is good predictor of prognosis in Dengue MODS and should be calculated at admission and monitor during course of admission.

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COMPETING INTERESTS

“Authors have declared that no competing interests exist”

AUTHORS` CONTRIBUTION

Sonali Salvi designed the study, wrote the protocol, managed the literature search and edited the manuscript. Arun Vaidya designed the study, wrote the first draft of manuscript, managed the analyses and literature searches of the study. All authors read and approved the final manuscript.

CONSENT

All authors declare that that `written informed consent’ was obtained from all the patients for this study.

ETHICS APPROVAL

This study was approved by Ethics committee of B J Government Medical college and Sassoon General Hospital, Pune.

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ABBREVIATIONS

MODS: Multi-organ dysfunction syndrome

SOFA: Sepsis-related Organ Failure Assessment

LFT: Liver function tests

PT: Prothrombin time

ALT:Alanine transaminase

AST:Aspartate transaminase

ALP:Alkaline Phosphatase

SIRS: Systemic Inflammatory response syndrome

ARDS:Acute Respiratory Distress syndrome