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Original Research Article

A study on clinical profile, liver dysfunction and outcome of dengue infection in children

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ABSTRACT

Background: Dengue viral illness is a matter of serious concern in all world, specifically because of absence of specific antiviral medicine and vaccine. Severe dengue has a mortality of 2-5%, but when left untreated the mortality rate is high as 20%, and liver involvement tends to be more severe infection in children.
Methods: This is a prospective observational study conduct in our Department from July 2020 to December 2022. Total patients in our study were 90. The objective of our study was to determine the relationship between liver dysfunction, kinetics of liver function tests (LFTs) and severity of hepatitis on the outcome in pediatric dengue illness, with special attention to preserved life of patient because its life-threatening potential.
Results: Dengue confirmed cases were divided into two group; severe dengue (SD) and non-severe dengue (NSD) group. Mean age was 7.2 years ± 3.74-year Age, 38.9% were females. All cases were suffering from fever, abdominal pain was present 51.1% in cases, Liver function tests SGOT (AST), SGPT (ALT) and ALP, bilirubin and albumin were deranged in both groups of children. Outcome of study 8 (25.8%) patients out of 31 were death from severe dengue group.
Conclusions: Liver Function Tests (LFT) monitoring done during acute dengue illness was a predictor of mortality in children with Dengue illness. Higher level of derangement in Liver dysfunction in children with dengue illness associate with higher rate of mortality.

Keywords: Dengue fever, Liver function tests, Severe dengue, Viral fever, Aspartate aminotransferase

INTRODUCTION

Dengue is an arboviral infection transmitted by the bite of an insect vector, the Aedes mosquito, Dengue virus (DENV); (DENV-1 to DENV-4) belonging to the family Flaviviridae is one of most rapidly emerging infection of tropical and subtropical regions affecting rural area more than urban area, India contributed to 34% of global dengue infection worldwide.[1] Dengue fever is typically a self-limited disease with a mortality rate of less than 1% when detected early and with access to proper medical care. When treated severe dengue has a mortality of 2-5%, but when left untreated the mortality rate is as high as 20%.[2] Disease symptoms range from those of a mild febrile illness to a countless of symptoms, including frank dengue fever, dengue hemorrhagic fever (DHF) and

dengue shock syndrome (DSS).[3] Any organ system can be involved but Liver involvement is well recognized as a common complication.[4] Liver Involvement in dengue illness is common and can lead to acute liver failure

(ALF). No Single method was found effectively identify patients at high risk for dengue disease progression and poor outcome. The liver injury can range from mild asymptomatic transaminase elevation to fatal ALF, the latter being more common in children, females and certain ethnic groups Moreover, where liver involvement tends to be more severe in children with previous dengue infections.[5]

Increasing burden of dengue infection is serious concern in the world, specifically because of absence of specific antiviral drug. It also possesses a great challenge for the clinicians to recognize the severity of disease at an early phase for effective and timely management and to reduce complications and death.[6] Early recognition and prompt initiation of appropriate treatment are vital to reduce disease related morbidity.

There is enough literature found on liver involvement in dengue illness in adults. However, the pattern of liver dysfunction and changes in LFTs in children with dengue infection has not been considerably studied. No single method was effectively identifying patients at higher risk for disease progression and poor dengue outcome. We aimed to compose the relationship between liver dysfunction, kinetics of LFTs and severity of hepatitis and sequel in pediatric dengue illness.

METHODS

This is a prospective observational controlled study conduct in Department of pediatrics in our hospital SMS Medical College and J K loan hospital during period from July 2020 to December 2022. Total number of patients in our study were 90. Admitted Patients having fever of 2-12 days duration, Age of all admitted patients was between 1 and 12 years. At least one of following symptoms: rash, bleeding, or swelling in the absence of cough and cold, serologically confirmed cases of dengue. And informed written consent was taken from the parents/guardians included in this study.

Exclusion criteria were children below 1 year and more than 12 years, Patients diagnosed with fever from other causes, who had been given NSAIDs for the treatment of dengue prior to an admission, and those with pre-existing liver disease in whom a written consent was not obtained.

The children enrolled underwent a complete medical workup at presentation that incorporated a detailed history and examination including a general and systemic examination. In emergency room, resident doctors were instructed to obtain blood samples (routine LFTs), chest radiograph and ultrasonography at admission. Confirmation of dengue was done by detection of IgM antibodies specific to dengue (anti-DEN IgM capture enzyme-linked immunosorbent assay, ELISA using CDK KIT), demonstration of protein of dengue (dengue NS1) and detection of dengue genomic sequences by polymerase chain reaction in the plasma obtained at the time of admission. A repeat dengue test of IgM antibodies test was done after 1 week if the initial test was negative found. Dengue confirmed case was defined by the presence of positive DENV IgM or Dengue NS1 or detection of DENV RNA by polymerase chain reaction in plasma, provided that the clinical picture was consistent with dengue, and no alternative diagnosis was established.

Serial monitoring of liver function tests was done in confirmed dengue cases. Patients were classified into two groups, first non-severe (NSD) and second severe dengue (SD) group. Severity of hepatitis was classified as: mild, moderate and severe hepatitis. Events were noted during hospitalization. Results were analysed risk factors which led to invasive treatment was also analysed. The study was conducted in adherence to the ethical guidelines of declaration of Helsinki and its amendments. Statistical significance was taken as $P< 0.05$. The data was analysed using IBM SPSS statistics software (26 version; licensors 1989, 2019) and Microsoft Office Excel 2007.

RESULTS

In this study, dengue confirmed cases were divided into two group, according to their severity; severe (SD) and non-severe (NSD) group. Majority of cases were non-severe dengue, which was 59 (65.6%) of cases and severe dengue were 31 (34.4%) cases. The mean age was 7.2 years with a standard deviation of 3.74-year Age. In NSD was 6.89 ±3.88 year and SD was 7.81 ±3.42 year, so it was seen that majority of patients were in the age group 5 to 10 years in our study Figure 1. 61.1% of the total cases were males and 38.9% were females. Age and gender distribution were not statistically significant; In other words, the groups contain subjects with the same basic demographic characteristics.

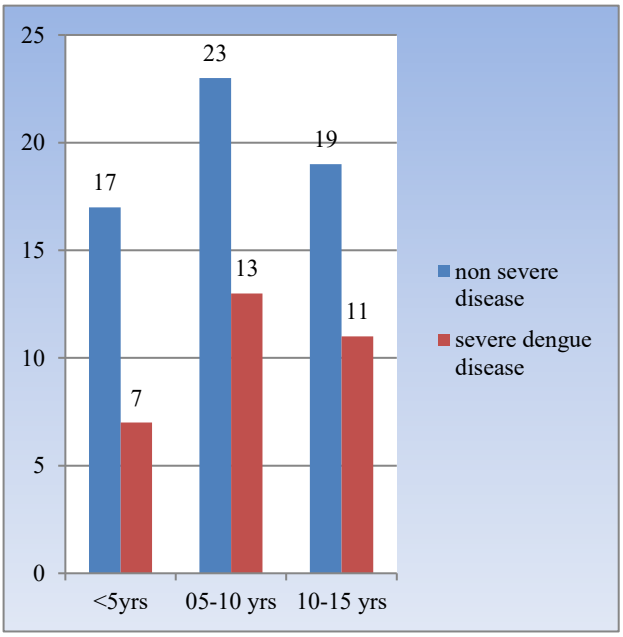

Figure 1: Disease severity in relation of age of study subject.

Out of total 90 cases, all cases were suffered from fever which was present in both severe and non-severe dengue. Abdominal pain was present in 46(51.1%) cases in which 33 were from non-severe dengue and 13 were from severe disease. Vomiting was present in 52 patients in which 32 were from non-severe and 21 were from severe disease. Rash was present in 5(5.6%) cases in which 2 were from non-severe and 3 were from severe disease. Respiratory distress was present only in 1 patient. Swelling was present in 2 cases which were from severe disease. Bleeding episode was present in 7 cases in which 4 were in severe disease group. Anuria present in one patient which was in severe disease group. Seizure and altered sensorium were present in 2 patients each from severe and non-severe group in our study Figure 2.

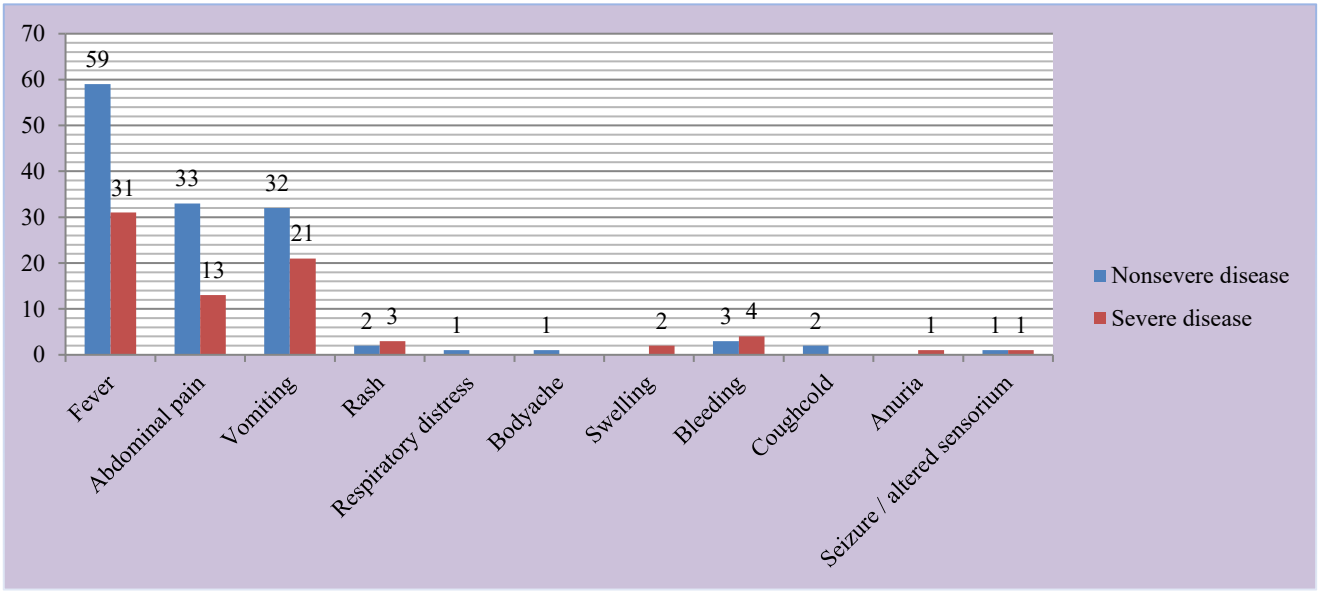

Figure 2: Frequency of clinical feature among study groups.

Out of 90 cases, 7(7.8%) patients had Capillary refill time (CRT)>2sec which were from severe disease group which suggest that severe disease group patient had shock. In our study show that 9 (10%) patients had hepatomegaly in which 6(19.4%) were in severe disease group and 3(5.1%) were in non-severe disease group. 2(2.2%) patients out of all show clinical jaundice which was found in severe dengue groups. Figure 3 shows that there was almost always deranged liver function test (LFTs). Hypo-albuminemia and hypo-proteinemia were more in severe disease group. Total 54(60%) cases had low albumin level in which 23(74.2%) were in severe disease group and 31(52.5%) cases were in non-severe disease group. Raised serum bilirubin level was found in 7 cases, all cases were in severe disease group. Out of 90 patients in present study 5(5.6%) patients found altered sensorium, and comparison of altered sensorium between severe disease and non-severe disease group which is more in severe disease group and statistically significant. Out study shows that among studied population all non-severe dengue patients were discharged. In present study 8 (25.8%) patients out of 31 were death from severe dengue disease group and considered statistically significant as $p < 0.05$ Table-1.

Table 1: Frequency of the study distribution in dengue patients with clinical outcome.

S. no.	Investigation		Non severe dengue (n=59)	Severe dengue (n=31)	P value
1	Renal function test (mg/dl)	Urea	39.97± 12.24	50.64±23.25	0.005
		Creatinine	0.45±0.19	0.66± 0.36	
2	International normalized ratio (PT-INR)		1.19± 0.16	1.39±0.31	<0.001
3	Chest x-ray findings	Ards	0	3 (9.7%)	0.049
		Pleural effusion	54 (91.5%)	25 (80.6%)	
		Normal	5 (8.5%)	3 (9.7%)	
4	SGOT(u/l) level	Day-1	125.31±104.46	600.63±885.99	<0.001
		Day-2	138.92±123.14	1693.78±3463.94	
		Day-3	142.51±126.94	1025.35±1748.19	
		Day-4	137.42±127.55	893.55±1348.7	
5		Day-1	80.28±38.7	132.03±108.91	

Continued.

S. no.	Investigation		Non severe dengue (n=59)	Severe dengue (n=31)	P value
	Serum ALP level (u/l)	Day-2	98.46± 59.52	161.68±147.71	0.001
		Day-3	105.42±64.96	189.84±166.65	
		Day-4	106.02±83.17	148.19±99.75	
6	Serum total protein (g/dl)	Day-1	5.19±0.97	4.84± 0.84	0.091
		Day-2	5.27±0.95	4.8±0.9	0.024
		Day-3	5.27±0.87	4.8±0.93	0.019
		Day-4	5.34±0.79	5.06± 0.91	0.139
7	Serum total bilirubin (mg/dl)	Day-1	0.51±0.18	1.39± 2.77	0.017
		Day-2	0.47±0.17	1.14± 2.62	0.052
		Day-3	0.41±0.13	1.15± 2.74	0.042
		Day-4	0.42±0.16	1.16± 2.97	0.056

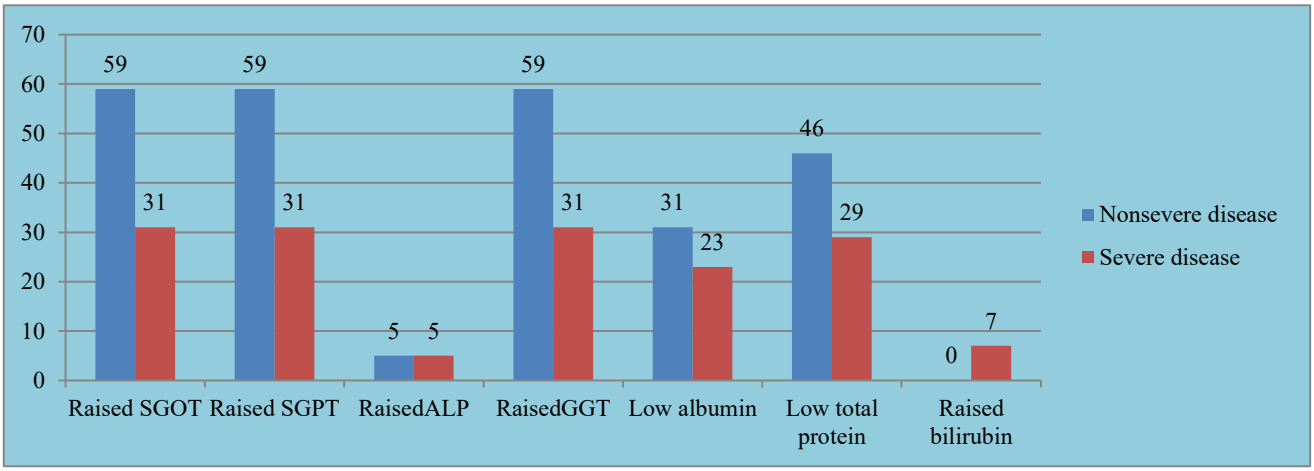

Figure 3: Abnormal liver function test in relation to disease severity among study subjects.

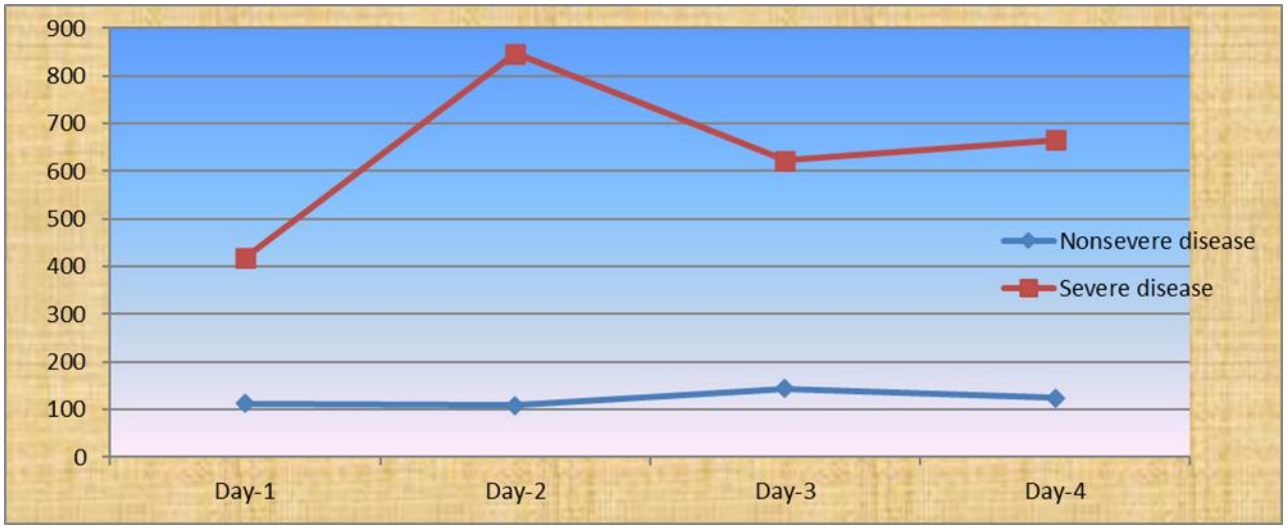

Figure 4: Time trend of serum SGPT level in relation to disease severity.

Our study shows comparison of RFT between severe and non-severe disease group. Serum urea and creatinine both are deranged in severe disease group and statistically significant since p < 0.05. Present study shows comparison of PT/INR between severe and non-severe group which was more deranged in severe disease group and found statistically significant. In this study shows comparison of CXR findings between severe and non-severe disease group. Pleural effusion had been common in both group but ARDS present in severe disease group more frequently. The relationship of chest X-ray finding with the outcome was statistically significant. The relationship of serum SGOT level, serum SGPT level and

serum ALP level increase in all dengue cases, in which maximum increase found on day 2 of observation in SGOT Level, SGPT level and which maximum increase found on day 3 of observation in ALP Level in this study. Increase in serum SGOT level, serum SGPT level and serum ALP level present in both severe and non-severe disease group Figure 4. This indicates that there is a true difference among the present study groups and the difference is statistically significant. This study shows serum GGT level deranged both in severe and non-severe disease but more in severe disease group. Value of serum GGT level considered statistically significant as $p < 0.05$ at day-3.

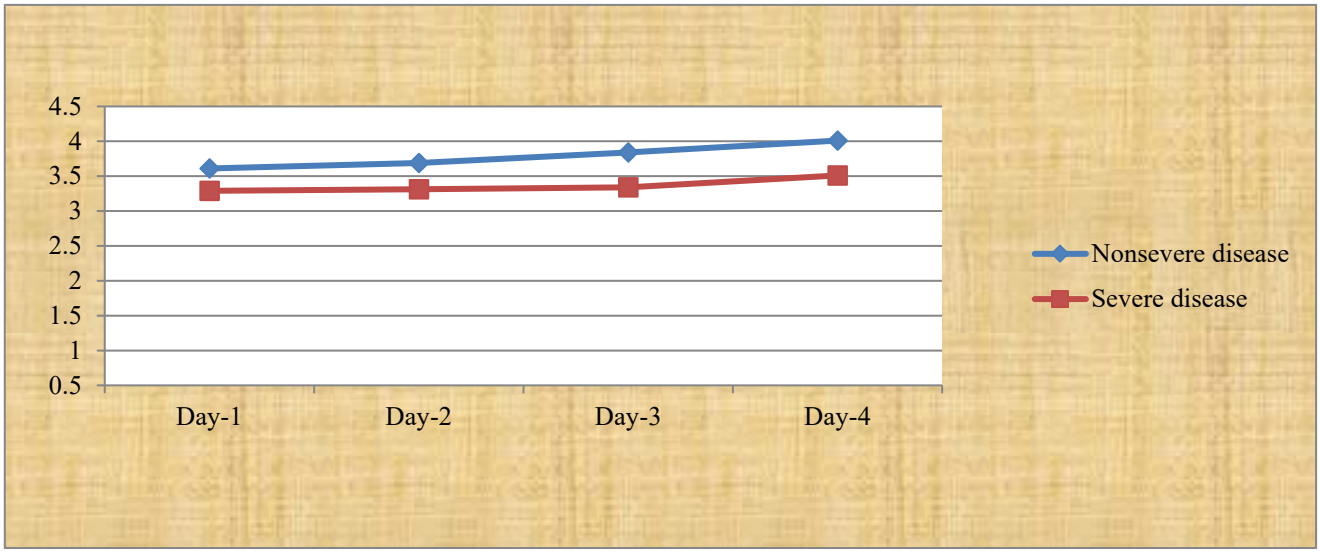

Figure 5: Time trend of serum albumin in relation to disease severity.

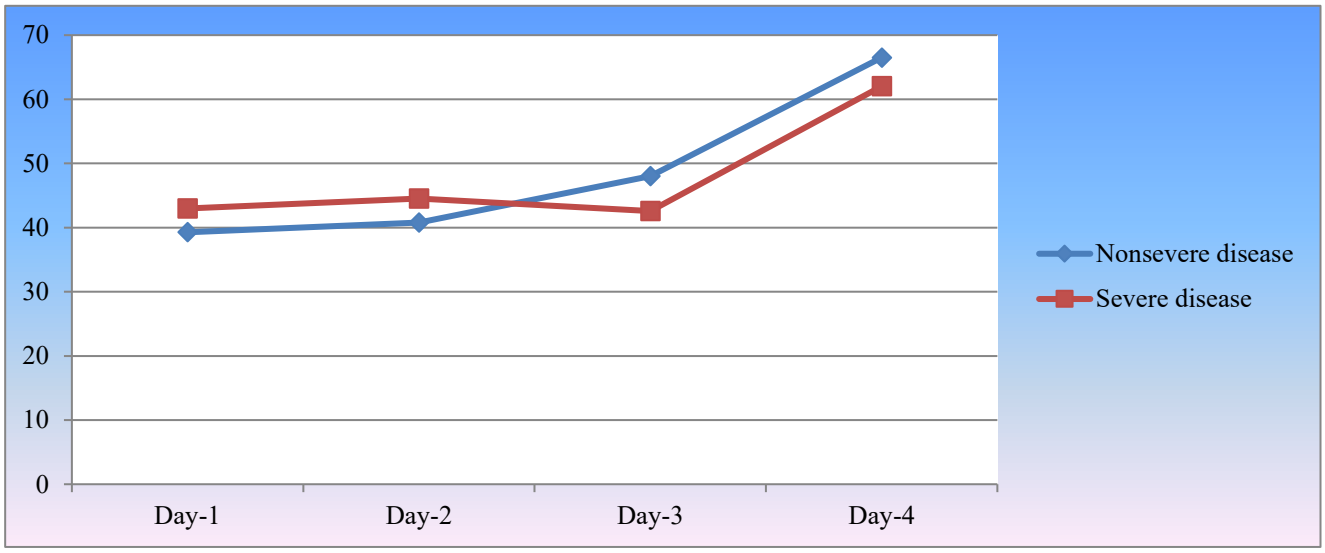

Figure 6: Time trend of thrombocytopenia in relation to disease severity.

Table 2: Observation of the blood parameter and investigation in dengue patient.

S. no.	Distribution		Non severe dengue (NSD)	Severe dengue (SD)	P value
1	Age group (years)	<5	17 (28.8%)	7 (22.6%)	0.406
		5-10	23 (39%)	13 (41.9%)	
		>10	19(32.2%)	11 (35.5%)	
2	Gender	Male	24 (40.7%)	11 (35.5%)	0.064
		Female	35 (59.3%)	20 (64.5%)	
3	Capillary refill time	< 2 second	59 (100%)	24 (77.4%)	<0.001

Continued.

S. no.	Distribution		Non severe dengue (NSD)	Severe dengue (SD)	P value
		> 2 second	0	7 (22.6%)	
4	Hepatomegaly	Yes	3 (5.1%)	6 (19.4%)	0.059
		No	56 (94.9%)	25 (80.6%)	
5	Clinical jaundice	Present	0	2 (6.5%)	0.116
		Absent	59 (100%)	29 (93.5%)	
6	Altered sensorium	Present	1 (1.7%)	4 (12.9%)	0.046
		Absent	58 (98.3%)	27 (87.1%)	
7	Outcome of dengue disease	Discharge	59 (100%)	23 (74.2%)	<0.001
		Death	0	8 (25.8%)	

In present study shows hypoalbuminemia present in both severe and non-severe disease group. Blood albumin values at presentation shows significant correlation with the disease severity Figure 5. And blood parameter also shows hypo proteinemia present in both severe and non-severe disease group more in day 3 of observation. The relationship of serum protein value with the dengue severity reached statistical significance at day 2 and 3 of observation. Table-2 shows serum bilirubin comparison between severe and non- severe group which was more increased in severe group and statistically significant at day 1and 3 of observation. This study also shows that thrombocytopenia present in both severe and non- severe group but more in severe disease group and more on day 3rd of observation Figure 6.

DISCUSSION

Dengue viral infection is highly emerging infections of the tropical and subtropical regions, affecting more rural and urban areas due to several factors including climate change. Disease symptoms range from those of mild febrile viral syndrome to a myriad of symptoms, including frank dengue fever, DHF and DSS. While any organ system can be involved; liver involvement is well recognized as a common complication. There are a range of hematologic and biochemical parameters were changes which occur during the course of the dengue illness. Recently, most literature has suggested that raised hepatic transaminases or aminotransferases aspartate transaminase (AST), alanine transaminase (ALT) levels in dengue viral infection, demonstrate that the liver is one of the main targets for the dengue virus. The liver injury can range from mild asymptomatic transaminase elevation to fatal ALF, the latter being more common in children, females and certain ethnic groups. It has been established in earlier studies that when hepatic dysfunction is associated with encephalopathy, the mortality is extremely high. Moreover, liver dysfunction can aggravate the bleeding manifestation and disseminated intravascular coagulation, which are associated with poor outcome. Hence, monitoring of LFTs is critical to assess the severity of liver involvement and promptly initiate appropriate supportive treatment to decrease the morbidity and mortality. In our study there were total 90 patients, out of them 24 (26.7%) were less <5 years, 36 (40%) were between 5-10 years and 30 (33.3%) were more than 10 years. Mean age of the patients was 7.21±3.74 years. Similarly, mean age of patients in studies conducted by Shubhankar Mishra et al[7] 8.7 year The maximum number of cases, 33 (34.02%), was seen in the group above 11 years of age. Out of total 90 patients in our study there were 55 (61.1%) males and 35 (38.9%) females showing male preponderance with M: F ratio of 1.5:1. Similar studies conducted by Debarati Guha-Sapir et al in Lucknow showed a M:F ratio of 1.9:1.[8] According to study conducted by Ricardo Tristão-SáI et al, there were total 90 patients in the study, in which females accounted for 52.2% (47/90) and males comprised 47% (43/90).[9] Dhrubajyoti Bandy opadhyay et al conducted study on 110 cases and found that 55.5% were males and 45.5% were females.[10] Out of total 90 cases in the study, severe dengue in our study was present in 31(34.4%) and non-severe dengue was present in 59(65.6%) of patients. A similar study was conducted by Shubhankar Mishra et al7 total of 97 cases were classified into 84 (86.59%) non-severe and 13 (13.40%) severe dengue cases.

In our study fever is almost always present among 90 study subject fever present in all (100%) of patients in both severe and non-severe disease. Abdominal pain 46 (51.1%) study subject in which 33 (55.9%) from non-severe disease and 13 (41.9%) were from severe disease group, vomiting was present in total 52 (57.8%) study subjects 32 (54.2%) were from non- severe disease group and 21 (67.7%) were in severe disease group. Rash was present only in 5 study subjects 2 (3.4%) in non-severe disease group and 3 (9.7%) were in severe disease group. Respiratory distress was present only in 1 study subject which was in severe disease group, swelling all over body was present in 2 (2.2%) of study population, both were from severe disease group. Bleeding was present in 7 (7.8%) of study subject in which 4 (12.9%) were from severe disease group and 3 (5.1%) belonged to non-severe disease group, anuria was presenting complain of only 1 (1.1%) study subject which was from severe disease group (3.2%). Seizure was a presenting complain in 2 (2.2%) study subject in which 1 (1.7%) belongs to non-severe disease group and 1 (3.2%) belongs to severe disease group.

In our study hepatomegaly was found in 9 (10%) of study population more in severe disease group 6 (19.4%) as

compared to non-severe disease group 3 (5.1%). Deranged liver function tests were found in all study population in present study. AST levels were found to more derange than serum bilirubin level. And AST level was more deranged than ALT levels and in 1st week of disease illness. Serum bilirubin was raised in 7 (7.8%) of study population all were in severe disease group which were 7 (22.6%) population of severe disease group. Jayanta Samanta et al conducted a similar study. Among clinical features of hepatic involvement, patients have abdominal pain (18%-63%), nausea/vomiting (49%-58%) and anorexia.[11] Symptoms such as abdominal pain and anorexia had been found to be significantly more common in DF than DHF. Hepatomegaly was present in both DF and DHF but more common in DF. The frequency of hepatomegaly in the adult dengue patients ranges from 4%-52%. Clinical jaundice had been detected in 1.7%-17% in various series and hyperbilirubinemia had been found to be as high as 48%.

Similar study conducted by Samitha Fernando et al shows that AST, ALT and gamma glutamyl transferase (GGT) levels were elevated in patients with dengue infection throughout the illness.[12] The highest AST levels were found on day 6 of dengue illness and both AST and GGT levels were significantly higher in patients with SD, as compared to those with NSD, on day 5 and 6 of dengue illness. Three patients with SD had AST and ALT values of >1000/IU in the absence of any fluid leakage or a rise in the hematocrit level (≥20%). We also found that peak of the AST levels and the lowest serum albumin levels were seen 24 hours before the maximum fluid leakage and 24 hours after the peak in viraemia.

Out of 90 cases, hypoproteinaemia was present in total 54 (60%) of subject in our study in which 23 (74.2%) were from SD group and 31 (52.5%) from NSD group. Suhendro Suwarto et al conducted study in Private hospital in Jakarta in 2015 and found that out of total 120 patients, hypoalbuminemia was seen in 87 (67.5%) of patient.[13] Thrombocytopenia was present in all cases, more in SD group and maximum on day 3rd of observation. Similar results were observed in a study conducted in Bangalore in 2015, by Selvan et al among 300 children.[16] It was seen that thrombocytopenia was seen in 92% of patients. Among these thrombocytopenic children, mild thrombocytopenia was seen in 32%, moderate thrombocytopenia was seen in 55.7% and severe thrombocytopenia in 11.5% of the case. According to study conducted by Raj et al among 196 children admitted in pediatric ward in B. J. Medical college Ahmedabad, it was seen that 176 (89.7%) had platelets count <1lac and 52 (26.5%) had severe thrombocytopenia, i.e., platelet count <20000/µl.[17] Kunal Tewari et al conducted study on 57 children and found that thrombocytopenia (platelet count<1lac) was seen in 67% of patients.[16]

In our study, X Ray abnormality was detected in 91.1% (82) cases in which 79 (87.8%) cases had pleural effusion and 3 (3.3%) had ARDS like picture which all were from SD group. Wang et al conduct a similar study 363 DHF patients from June to December 2002 in southern Taiwan, and a total of 468CXRs were obtained and reviewed.[17] More than 50% of these found abnormalities after the 3rd day, with infiltration only and small pleural effusion were as the major findings. Progressive changes seen during the first week and improvements found were second week observed in these abnormal Chest X-rays.

In our study out of 90 cases 82 (91.1%) were discharged successfully in which 59 (100%) were belongs to NSD group and 23 (74.2%) cases belongs to SD group. Death occurs in 8 (25.8%) cases which all were belongs to SD group. Sachdev et al conduct a study during the study period of 42 months, 172 patients with dengue fever were admitted to PICU.[18] A total of 78(45.3%) patients with SD fever were included and analyzed. There were 20 (25.6%) deaths.

Limitations

Present study is Single hospital and institution based, limiting generalizability, there are limited number of patients so low data of morbidities and mortality which may be changed when study is conducted on large number of population and there was no long-term follow-up to assess outcomes beyond the disease period.

CONCLUSION

LFT monitoring done during acute illness was observed that a predictor of mortality in children with Dengue illness. Higher level of derangement in liver function tests like bilirubin, PT/INR in children with dengue disease associate with higher rate of mortality and poor outcome. The application of LFT monitoring is quite simple because it utilizes laboratory parameters which are routinely used in clinical practice and available at all levels of patient care Centre and therefore can be used by clinicians to identify which patients are at high risk for developing severe disease and thus can be used in prognostication. Therefore, this help in reducing morbidity and mortality associated with bleeding or liver failure.

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Ethical approval: The study was approved by institutional ethical committee of S.M.S. medical college Jaipur Rajasthan

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