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Original Research

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Association between the degree of hepatic dysfunction and complications among serologically positive and serologically negative dengue infection in children

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ABSTRACT

Objective: The objective was to analyze the degree of liver dysfunction among serologically confirmed dengue and dengue suspected cases as per the WHO criteria in children with reference to complications and mortality. **Materials and Methods:** This study was conducted on 200 children between 3 months and 15 years age group, admitted with acute febrile illness during an outbreak of dengue infection. Clinically suspected dengue based on WHO criteria and serologically confirmed dengue patients were included in the study. Liver function tests were analyzed and evaluated the degree of liver damage to assess the outcome, mortality, and prognosis of dengue infection. **Results:** Of the 200 acute febrile patients enrolled in the study, 105 (52.5%) were classified as serologically confirmed dengue, out of which 64 (61%) were dengue fever (DF) and 41 (39%) were dengue hemorrhagic fever (DHF). 95 (47.5%) were classified as suspected dengue cases, as per the WHO diagnostic criteria, out of which 54 (56.8%) were DF and 41 (43.9%) were DHF. There was severe elevation of aspartate transaminase (AST) and alanine transaminase (ALT) in both confirmed DHF (mean 452.6U/l and 210U/l) and suspected DHF (mean 694U/l and 431U/l), moderate elevation in confirmed DF (mean 286.7U/l and 162.5 U/l) and mild elevation in suspected DF (mean 80.2U/l and 48.1U/l). The AST levels were significantly elevated than the ALT levels in both confirmed and suspected cases of DF and DHF. Hepatic dysfunction was more common in confirmed dengue (66%) cases than suspected dengue (57.6%). The common degree of liver damage both in confirmed and suspected cases of DF was Grade 0 whereas in DHF Grade 1. All the patients with encephalopathy had Grade 4 liver damage. Dengue complicated by renal failure had Grades 3 and 4 liver damage. There was a significantly higher mortality rate in DHF with Grade 4 hepatic damage than DF. **Conclusion:** The degree of liver dysfunction is more significant in both serologically positive and negative DHF than DF. Severe hepatitis (Grades 3 and 4) in dengue infection has got worse outcome in terms of mortality and complications as compared to mild to moderate hepatitis (Grades 1 and 2). Therefore, severe hepatitis can be considered as a bad prognostic indicator of outcome in dengue infection.

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INTRODUCTION

Dengue viral infection is a major public health problem worldwide, estimates 50-100 million cases of dengue infection (DI) occur each year. More than 3 lakh cases of dengue hemorrhagic fever (DHF) are diagnosed each year, with the case fatality rate of DHF varying from 1% to 5% a significant number of deaths, around 24,000 cases; occur each year [1-4]. The vast majority of cases, nearly 95%, occur in children under 15 years of age and 5% of all DHF/dengue shock syndrome (DSS) cases occur in infants [5]. Hence, the dengue illness is a significant cause of pediatric morbidity and mortality. The affected children need very careful monitoring [6]. Most prevalent age group for DHF is children 5-9 years old, followed by children 10-14 years old [7]. Dengue illness caused by the dengue virus, an RNA virus, belongs to the Flavi viridae family, and consists of four serotypes (DEN1-4) [8], transmitted from the bite of *Aedes aegypti* and *Aedes albopictus* mosquitoes [9]. Infection with one serotype of dengue virus elicits lifelong homotypic immunity, but heterotypic immunity is short-lived [10].

The spectrum of clinical manifestations of DI can be asymptomatic or cause any of the following illnesses, undifferentiated fever, DF and DHF/DSS [8,11]. According to

WHO criteria, low white blood cell (WBC) count, associated with the "dengue triad" of fever, rash and headache, represent the most common diagnostic criteria for DF [1]. DHF includes the presence of acute fever, hemorrhagic tendencies, thrombocytopenia, and plasma leakage. The prominent feature of DHF is its potential to develop into fatal DSS. DSS is defined as having all the four criteria for DHF plus evidence of circulatory failure. Clinical features of DHF resemble those of DF in early febrile phase in many respects. The incubation period ranges from 5 to 8 days following by the onset of fever, headache, chill and rash. The fever usually lasts 4-7 days, and most people had a complete recovery without any complication. However, there are a number of atypical forms of dengue infection [12,13], include liver, central nervous system, cardiac and renal involvement [2]. Although the liver is not a major target organ, but acute liver failure is a severe complication of dengue infected children due to direct attack on liver cells or unregulated host immune response against the virus [10], predisposing to life-threatening hemorrhage, disseminated intravascular coagulation and encephalopathy [13]. Liver involvement in DI often demonstrated by hepatomegaly and mild-to-moderate increases in transaminase levels although jaundice and acute liver failure are generally uncommon [14]. Transaminase levels are higher in DHF/DSS than in DF and tend to return to normal 14-21 days after infection [8]. Of late, there have been reports of fulminant hepatitis with high mortality in patients with DI. The term acute hepatic failure is used to describe the development of coagulopathy, usually with international normalized ratio (INR) of >1.5. Hence, measurement of aspartate transaminase (AST) and alanine transaminase (ALT) are mandatory to see the liver involvement [3]. ALT is more liver specific enzyme, but the important characteristic of hepatic involvement with DI is a greater elevation in AST than ALT levels, ALT/AST ratio is <1. This information is useful to distinguish between liver failure caused by DI and that caused by infectious hepatitis where ALT/AST ratio is >1 [4,15].

Given the variability of the clinical presentations associated with DI, laboratory confirmation is needed. Serologic tests are more commonly used to confirm the presence of antibodies to dengue virus. Primary infections are characterized by an increase in dengue-specific IgM antibodies 4-5 days after the onset of fever and by an increase in IgG antibodies only after 7-10 days. It is known that anti-dengue virus antibodies may not be present during the initial days of illness [16]. Failure to identify dengue-specific IgM or IgG antibodies during the first 5-7 days of illness does not eliminate dengue virus as the etiology of the illness. Therefore, these cases would have been interpreted as negative if they were not re-tested after 5 days. Thus, for the detection of dengue-specific antibodies, patients should be tested from day 5 of fever and onwards [4]. However, even in our seronegative patients, the presence of fever, leukopenia, and thrombocytopenia in the epidemiological setting of an outbreak makes the diagnosis fairly certain [16].

The significance of this study is (1) to evaluate the prevalence of dengue among the children and progression towards the complications. (2) to evaluate the early hepatic markers that allow the early close monitoring of children to prevent the life-threatening complications. (3) the importance of liver function tests (LFT) in both suspected dengue as well as in confirmed dengue cases during the acute phase of illness and assess the outcome, mortality and prognosis of DI according to the degree of liver damage (4) the prevalence of hepatic dysfunction both in suspected and confirmed cases of DF and DHF.

MATERIALS AND METHODS

The objective of this study was to analyze the degree of liver dysfunction among the dengue suspected cases and dengue confirmed cases in children. Nearly 95% of DI occurs in children under 15 years of age. We therefore designed a prospective study of children early the course of suspected DI in order to identify the progression and severity of hepatic dysfunction before the critical stage of disease. The eligible criteria for entry into this study: Age 3 months to 15 years, fever for 72 h, oral temperature >38.57°C. Malaria, enteric fever, hepatitis A and B, urinary tract infection, respiratory tract infection, chronic liver diseases were excluded from the study by history, examination and investigations.

Based on WHO diagnostic criteria, patients were differentiated as (1) suspected DF was defined as any patient having low WBC count, associated with the "dengue triad" of fever, rash and headache, represent the most common diagnostic criteria for DF and proved by serologically negative for dengue specific IgM or, NS 1 or IgG antibodies. (2) Confirmed DF defined as patients with clinical features suggestive of DF and proved by positive serology of dengue specific IgM or NS 1 or IgG antibodies. (3) Suspected DHF included a triad of hemorrhagic manifestations, platelet count of <1, 00,000/mm^3 and plasma leakage evidenced by rise of hematocrit (Hct) value 20% above the average and proved by serologically negative for dengue specific IgM or NS 1 or IgG antibodies (4) Confirmed DHF defined as patients with clinical features suggestive of DHF and serologically positive for dengue specific IgM or NS 1 or IgG antibodies.

Data were collected from 200 children, admitted with acute febrile illness during an outbreak of DI in tertiary hospitals of Hyderabad, India. Of 200 cases, 105 were serologically (positive) confirmed dengue cases and 95 were serologically negative (suspected) dengue cases, as per the WHO criteria. A detailed history obtained from the parents, and thorough clinical and laboratory examinations were done in all the cases. Among 105 serologically positive dengue, 62 (59%) were classified as primary infected and 43 (41%) were classified as secondary infected based on serological tests and history. All 95 serologically negative patients infected for the first time based on history. Based on serological tests, primary infections are characterized by an increase in dengue-specific IgM and NS 1 antibodies and secondary infection was characterized by the presence of high titers of IgG early in the course of the disease.

The study was approved by the Institutional Ethical Committee, and informed consent was obtained from parents. Acute-phase blood samples (3-5 ml) were obtained at the time of admission

(day 2 to day 7 after the onset of fever). Samples were collected into three different blood containers. The first was a plain container into which serum was extracted for the assessment of LFT (including bilirubin, ALT, AST, alkaline phosphatase [ALP], ammonia, creatinine), by using STAT FAX 3300 semi auto analyzer with ERBA kits supplied by Transsessia - INDIA. The second was tri-sodium citrate container from which plasma was used to detect the prothrombin time (PT) and activated partial thromboplastin time (APTT) levels within 4 h of blood collection using a semi-automated coagulometer; model Type- COA, DATA501 with TULIP kits. The third was ethylenediaminetetraacetic acid container for complete blood picture, including hemoglobin, total red blood cell, WBC, differential leukocyte count, platelet count, Hct, were analyzed within 4 hours of blood collection using sysmex XS-800i cell counter. For dengue confirmation, serological tests done using SD Bioline Dengue duo rapid test for NSI, IgM, IgG antibodies. These parameters were compared with the clinical presentations of the patients and evaluate the degree of liver damage related to the severity of the disease.

The degree of liver damage was assessed according to the level of liver enzymes, PT, APTT as follows: Grade 0: Normal liver enzymes, Grade 1: Mild elevation of liver enzymes, not exceeding 3 times upper reference level (transaminases <200 U/l). Grade 2: Elevated liver enzymes levels between 3 and 10 times upper reference level (200-600 U/l). Grade 3: Acute hepatitis, with liver enzyme levels increased to 10 times upper reference level (>600 U/l). Grade 4: Evidence of hepatic failure with abnormal coagulopathy (elevated transaminases, Grades 2 and 3 liver damage with high PT, APTT, INR >1.5).

Statistical Analysis

Sofa stats were used for analysis. Results were presented as mean, standard deviation (SD) for continuous variables; frequency and percentage are given for qualitative variables. Unpaired *t*-test used for *P* values were calculated from mean, SD, number by using the Graph pad software. The significance of difference between two independent proportions was calculated using vassarstats software. A $P \leq 0.05$ was taken as statistically significant

RESULTS

Of the 200 acute febrile patients enrolled in the study, 105 (52.5%) were classified as confirmed (serologically positive) dengue and 95 (47.5%) were classified as suspected (serologically negative) dengue cases, as per the WHO diagnostic criteria. Of 105 confirmed dengue cases, 64 (61%) were DF and 41 (39%) were DHF. Of 95 suspected dengue cases, 54 (56.8%) were DF and 41 (43.9%) were DHF. The overall male to female ratio was 1.6:1 in confirmed as well as in suspected dengue cases but highest male to female ratio was observed in confirmed DF 2.2:1. Male ratio was predominant in all age groups.

There was no significant difference in total bilirubin in both confirmed and suspected cases of DF (mean 0.86 mg/ dl vs. 0.82 mg/dl, $P = 0.75$) and DHF (mean 0.94 mg/dl vs. 1.25 mg/ dl, $P = 0.197$). There was significant elevation of AST ((mean 286.7U/l vs. 80.2 U/l, $P = 0.0008$) and ALT (mean 162.5 U/l vs. 48.1U/l, $P = 0.0025$) in confirmed DF than suspected DF. There was severe elevation of AST and ALT in both confirmed DHF (mean 452.6U/l and 209.9U/l) and suspected DHF (mean 694.1U/l and 431U/l), but statistically, the elevated AST and ALT levels did not differ significantly between confirmed DHF and suspected DHF with $P = 0.324$ and 0.068. There was no significant difference in ALP among confirmed and suspected cases of DF (mean 137.8 U/L vs. 128.9 U/L, $P = 0.401$) and DHF (129 U/L vs. 140.7 U/L, $P = 0.38$), but shows mild decrease. There was significant rise of APTT (47.6 vs. 40.4 s, $P = 0.03$) between confirmed and suspected cases of DF, but there was no significant difference of PT (15.8 vs. 15.2 s, $P = 0.42$), INR (1.2 vs. 1.2, $P = 1$), ammonia (76.5 vs. 55.9 μg dl, $P = 0.3$), respectively. There was no significant difference in elevation of PT (mean 17.9 vs. 22s, $P = 0.201$), INR (mean 1.4 vs. 1.7, $P = 0.25$), APTT (48.2 vs. 51.7s, $P = 0.51$), ammonia (mean 81.3 vs. 148.8 μg/dl, $P = 0.09$) between confirmed and suspected cases of DHF [Tables 1 and 2]. There was significant rise of APTT than PT in confirmed cases of DF (50% vs. 15.6%, $P = 0.0001$) and DHF (53.7% vs. 21.9%, $P = 0.003$), but not significant in suspected cases of DF (16.7% vs. 14.8%, $P = 0.79$) and DHF (51.2% vs. 34.1%, $P = 0.12$) [Table 3].

There was a significant rise of mild to severe degree of liver damage than patients without liver damage in total serologically confirmed dengue cases (62.9% vs. 37.1%, $P = 0.0002$), as well as in serologically confirmed DF (59.8% vs. 40.6%, $P = 0.03$) and DHF (68.3% vs. 31.7%, $P = 0.0009$). Among patients with liver damage, Grade 1 liver damage (29.5%, 31 of 105) was more common. 19% (20 of 105) presented with Grade 2 liver damage, 14.3% (15 of 105) of patients had progressed to acute hepatitis (Grade 3) and 12.4% (13 of 105) had severe liver damage with fulminant hepatic failure (Grade 4). The common degree of liver damage in confirmed DF was Grade 0 (40.6%), whereas in confirmed DHF was Grade 1 (36.5%). Confirmed dengue complicated by encephalopathy was observed in 14.3% (15 of 105), all of them (100%) had significant rise of mild to severe degrees of liver damage with $P \leq 0.0001$, among these Grade 4 liver damage (86.7%, 13 of 15) was most common. Confirmed dengue complicated by renal impairment in terms of raised serum creatinine levels (>0.7 mg %) in children was observed in 14.3% (15 of 105), there was significant rise of mild to severe degree of liver damage than patients without liver damage (73.3% vs. 26.7%, $P \leq 0.01$), among these Grade 1 (33.3%) and Grade 2 (33.3%) liver damage were most common [Tables 4 and 5, Figures 1 and 2].

In total suspected dengue (seronegative), there was no significant difference in patients with liver damage and without liver damage (49.5% vs. 50.5%, $P = 0.89$). Among patients with liver damage, 24.8% presented with mild degree of liver damage (Grade 1), 8.4% presented with Grade 2 liver damage, 13.7% of the patients had progressed to acute hepatitis (Grade 3) and 9.5% had severe liver damage with fulminant hepatic failure (Grade 4). There was a significant rise of suspected DF without liver damage compared to suspected DF with liver

Table 1: Comparison of LFT in confirmed (serologically positive) DF and suspected (serologically negative) DF

	T. bilirubin mg/dl	D. Bilirubin mg/dl	AST (U/l)	ALT (U/l)	ALP (U/l)	PT (s)	INR	APTT (s)	Ammonia μg/dl
Confirmed DF mean±SD	0.86±0.68	0.32±0.46	286.7±426.3	162.5±264.3	137.8±46.4	15.8±4.6	1.2±0.4	47.6±20.4	76.5±138.7
Suspected DF mean±SD	0.82±0.7	0.3±0.6	80.2±118.3	48.1±71.5	128.9±67.7	15.2±3.3	1.2±0.3	40.4±15.5	40.4±15.5
P value	0.75	0.84	0.0008	0.0025	0.401	0.425	1	0.035	0.3

SD: Standard deviation, LFT: Liver function tests, DF: Dengue fever, PT: Prothrombin time, APTT: Activated partial thromboplastin time, INR: International normalized ratio, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase

Table 2: Comparison of LFT in confirmed DHF and suspected DHF

	T. bilirubin mg/dl	D. Bilirubin mg/dl	AST (U/l)	ALT (U/l)	ALP (U/l)	PT (s)	INR	APTT (s)	Ammonia μg/dl
Confirmed DF mean±SD	0.94±0.8	0.37±0.6	452.6±1126.3	209.9±437.8	129±53	17.9±10.9	1.4±0.9	48.2±21.4	81.3±134.4
Suspected DF mean±SD	1.25±1.3	0.53±0.9	694.1±1075.4	431±628.9	140.7±65.7	22±17.9	1.7±1.4	51.7±25.8	148.8±211.5
P value	0.197	0.346	0.324	0.068	0.378	0.201	0.252	0.505	0.088

SD: Standard deviation, LFT: Liver function tests, DF: Dengue fever, PT: Prothrombin time, APTT: Activated partial thromboplastin time, INR: International normalized ratio, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, DHF: Dengue hemorrhagic fever

Table 3: Comparison of prevalence of raised APTT and PT in confirmed and suspected dengue cases

	n (%)		*P* value
	APTT	PT	
Confirmed DF (64)	32 (50)	10 (15.6)	0.0001
Suspected DF (54)	9 (16.7)	8 (14.8)	0.79
Confirmed DHF (41)	22 (53.7)	9 (21.9)	0.003
Suspected DHF (41)	21 (51.2	14 (34.1)	0.12

DF: Dengue fever, PT: Prothrombin time, APTT: Activated partial thromboplastin time, DHF: Dengue hemorrhagic fever

Table 4: Comparison of confirmed dengue cases with liver damage and without liver damage

	n (%)		*P* value
	With liver damage	Without liver damage	
DF	38 (59.4)	26 (40.6)	0.033
DHF	28 (68.3)	13 (31.7)	0.0009
Encephalopathy	15 (100)	0 (0)	<0.0001
Renal impairment	11 (73.3)	4 (26.7)	0.01
Total dengue (105)	66 (62.9)	39 (37.1)	0.0002

DF: Dengue fever, DHF: Dengue hemorrhagic fever

damage (72.2% vs. 27.7%, $P < 0.0002$). In suspected DHF, the common degree of liver damage was Grade 1 (36.6%), there was significant rise of patients with liver damage than without liver damage (78% vs. 22%, $P < 0.0002$). Suspected dengue complicated by encephalopathy was observed in 17.9% (17 of 95), there was significant rise of patients with liver damage than without liver damage (88.2% vs. 11.8%, $P < 0.0001$), most common degree of liver damage was Grade 3 (64.7%, 11 of 17). Suspected dengue complicated by renal impairment was observed in 13.7% (13 of 95), there was significant rise of patients with liver damage than without liver damage (76.9% vs. 23%, $P = 0.006$), most common degree of liver damage was Grade 3 (46.2%) and Grade 4 (46.2%) [Tables 6 and 7, Figures 3 and 4].

Serologically confirmed DF was more prevalent in <1 year age group (35.9%, mean 0.6 year), among these patients the common degree of liver damage was Grade 1 (34.8%) while in remaining age groups Grade 0 liver damage was most commonly observed. Confirmed DF complicated by encephalopathy was more common in <1 year age group (21.7%) with Grade 4 liver damage. Confirmed DF complicated by renal impairment was more common in 11-15 years age group (37.8%). The highest prevalence of confirmed DHF (41.5%, mean 7.6 year) was observed in 6-10 years age group, among these patients the common degree of liver damage was Grade 1 (47%). The degree of liver damage was severe (Grades 2-4, 40%) in <1 year age group even though the prevalence of DHF was less. Confirmed DHF complicated by encephalopathy was more common in <1 year (40%) age group with Grade 4 liver damage. Confirmed DHF complicated by renal impairment was more common in 6-10 years age group (17.6%) [Table 8].

The highest prevalence of suspected DF was observed in 6-10 years age group (40.7%). The degree of liver damage was Grade 0 in all the age groups except <1 year age group where the degree of liver damage was Grade 1. Suspected DF complicated by encephalopathy (60%) and renal impairment (20%) was more common in <1 year age group. In suspected DHF highest prevalence was observed in 1-5 years age group (34.1%). The degree of liver damage was Grade 4 (50%) in <1 year age group, and Grade 1 was observed in all other age groups. Suspected DHF complicated by encephalopathy was more common in <1 years age group (50%), all of them associated with Grade 4 liver damage. Suspected DHF complicated by renal impairment more common in 1-5 years age group (21.4%) [Table 9]. Hence, DI patients of <1 year age group is a risk factor for a severe degree of liver damage and complications.

The mortality rate of DI was 5% in our study. 10 of 200 DI patients died, among these nine of 10 had DHF. Five were confirmed DHF and four were suspected DHF with Grade 4 liver damage, 1 of 10 had DF with Grade 3 liver damage. All 10 deaths associated with encephalopathy. 2 of 10 patients had renal failure.

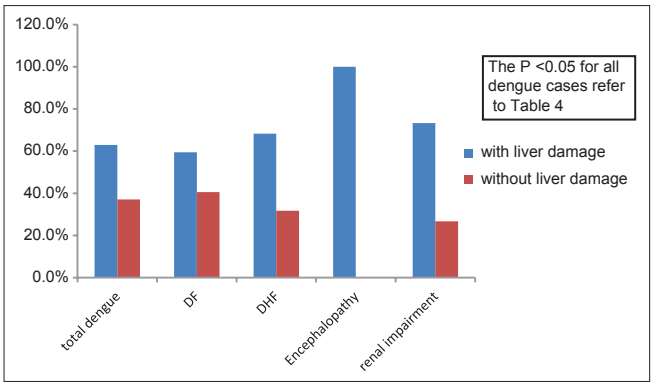

Figure 1: Comparison of confirmed dengue cases with liver damage and without liver damage

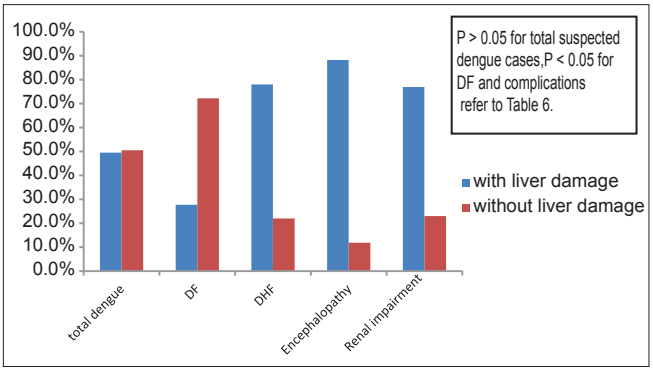

Figure 3: Comparison of suspected dengue cases with liver damage and without liver damage

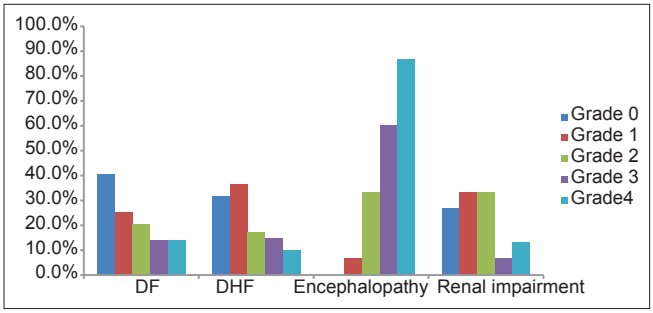

Figure 2: Prevalence of degree of liver damage in serologically confirmed dengue with complications

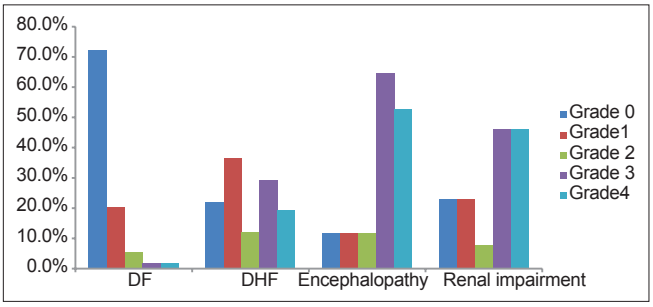

Figure 4: Prevalence of degree of liver damage in suspected dengue (serologically negative) with complications

Table 5: Degree of liver damage in confirmed dengue cases with complications

Clinical presentation	*N* (%)	Male	Female	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
DF	64	44 (68.8)	20 (31.2)	26 (40.6)	16 (25)	13 (20.3)	9 (14)	9 (14)
DHF	41	21 (51.2)	20 (48.8)	13 (31.7)	15 (36.5)	7 (17.1)	6 (14.6)	4 (9.7)
Encephalopathy	15	12 (80)	3 (20)	0 (0)	1 (6.7)	5 (33.3)	9 (60)	13 (86.7)
Renal impairment	15	12 (80)	3 (20)	4 (26.7)	5 (33.3)	5 (33.3)	1 (6.7)	2 (13.3)
Total dengue	105	64 (60.9)	40 (38.1)	39 (37.1)	31 (29.5)	20 (19)	15 (14.3)	13 (12.4)

DF: Dengue fever, DHF: Dengue hemorrhagic fever

Table 6: Comparison of suspected dengue cases with liver damage and without liver damage

	n (%)		*P* value
	With liver damage	Without liver damage	
DF (54)	15 (27.7)	39 (72.2)	<0.0002
DHF (41)	32 (78)	9 (22)	<0.0002
Encephalopathy	15 (88.2)	2 (11.8)	<0.0001
Renal impairment	10 (76.9)	3 (23)	0.006
Total dengue (95)	47 (49.5)	48 (50.5)	0.89

DF: Dengue fever, DHF: Dengue hemorrhagic fever

DISCUSSION

Many dengue infections are often difficult to distinguish clinically from other acute febrile illnesses. Early recognition of clinical signs, symptoms, and risk factors for dengue are helpful. In our study, both serologically positive (confirmed) and serologically negative (suspected) cases of dengue were analyzed for changes in the degree of liver damage. There was a significant elevation of transaminases (AST and ALT) in confirmed DF than suspected DF, but not significant between confirmed DHF and suspected DHF. There was no significant difference in ALP levels among confirmed and suspected cases of DF and DHF but shows mild decrease, which disagrees with the Jagadishkumar et al and Wahid et al study in which ALP levels were raised [3,17]. Our study is consistent with the results from Wong (2008) and Kuo et al (1992) studies reported that AST levels were significantly higher than ALT levels [18,19]. Thus, during early febrile illness before confirming serologically the elevated transaminase levels are the early predictors of DI, especially AST.

In our study, there was a significant rise of APTT between confirmed and suspected cases of DF. APTT is a predictor of bleeding manifestation in DHF, significant relationship between prolonged APTT and early stages of DHF [7,20]. In our study, APTT being affected more than PT in confirmed cases of dengue. Thus, elevated APTT is the early predictor of dengue complications. Early diagnosis should be helpful for optimal management to achieve a favorable outcome.

Table 7: Degree of liver damage in suspected dengue cases with complications

Clinical presentation	*N* (%)	male	Female	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
DF	54 (56.8)	31 (57.4)	23 (42.6)	39 (72.2)	11 (20.4)	3 (5.5)	1 (1.9)	1 (1.9)
DHF	41 (43.2)	28 (68.3)	13 (31.7)	9 (22)	15 (36.6)	5 (12.2)	12 (29.3)	8 (19.5)
Encephalopathy	17 (17.9)	12 (70.6)	5 (29.4)	2 (11.8)	2 (11.8)	2 (11.8)	11 (64.7)	9 (52.9)
Renal impairment	13 (13.7)	12 (92.3)	1 (7.7)	3 (23)	3 (23)	1 (7.7)	6 (46.2)	6 (46.2)
Total dengue	95	59 (62.1)	36 (37.9)	48 (50.5)	26 (24.8)	8 (8.4)	13 (13.7)	9 (9.5)

DF: Dengue fever, DHF: Dengue hemorrhagic fever

Table 8: Degree of hepatic dysfunction and renal failure in different age groups of confirmed dengue

Age (years)	*N* (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Encephalopathy	Renal failure
DF (64)								
<1	23 (35.9)	5 (21.7)	8 (34.8)	4 (17.4)	6 (26)	5 (21.7)	5 (21.7)	0 (0)
1-5	17 (26.5)	6 (35.3)	4 (23.5)	5 (29.4)	2 (11.8)	4 (23.5)	3 (17.6)	2 (11.8)
6-10	16 (25)	10 (62.5)	4 (25)	2 (12.5)	0 (0)	0 (0)	0 (0)	4 (25)
11-15	8 (12.5)	5 (62.5)	1 (12.5)	1 (12.5)	0 (0)	0 (0)	1 (12.5)	3 (37.8)
DHF (41)								
<1	5 (12.2)	1 (20)	0 (0)	2 (40)	2 (40)	2 (40)	2 (40)	0 (0)
1-5	13 (31.7)	6 (46.2)	2 (15.4)	2 (15.4)	3 (23)	3 (23)	3 (23)	2 (15.4)
6-10	17 (41.5)	6 (35.3)	8 (47)	2 (11.8)	1 (5.9)	1 (5.9)	2 (11.8)	3 (17.6)
11-15	6 (14.6)	2 (33.3)	3 (50)	2 (16.7)	0 (0)	1 (16.7)	0 (0)	1 (16.7)

DF: Dengue fever, DHF: Dengue hemorrhagic fever

Table 9: Degree of hepatic dysfunction and renal failure in different age groups of suspected dengue

Age (years)	*N* (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Encephalopathy	Renal failure
DF (54)								
<1	5 (9.2)	1 (20)	3 (60)	1 (20)	0 (0)	2 (40)	3 (60)	1 (20)
1-5	21 (38.9)	13 (61.9)	6 (28.6)	2 (9.5)	0 (0)	1 (4.7)	0 (0)	0 (0)
6-10	22 (40.7)	19 (86.4)	2 (9)	0 (0)	1 (4.5)	0 (0)	2 (9)	2 (9)
11-15	6 (11.1)	6 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)
DHF (41)								
<1	6 (14.6)	1 (16.7)	2 (33.3)	0 (0)	2 (33.3)	3 (50)	3 (50)	0 (0)
1-5	14 (34.1)	4 (28.6)	4 (28.6)	3 (21.4)	3 (21.4)	3 (21.4)	5 (35.7)	3 (21.4)
6-10	9 (21.9)	1 (11.1)	3 (33.3)	1 (11.1)	3 (33.3)	2 (22.2)	4 (44.4)	1 (11.1)
11-15	12 (29.3)	2 (16.7)	6 (50)	2 (16.7)	2 (16.7)	1 (8.3)	1 (8.3)	2 (16.6)

In this study, we noticed a high relation between the degree of liver damage and the presence of complications. The common degree of liver damage both in confirmed and suspected cases of DF was Grade 0 whereas in DHF Grade 1 liver damage was observed. Our study is consistent with the results from Nguyen et al (1997) reported that DHF may cause mild to moderate liver dysfunction in most cases; only some patients may suffer from acute liver failure leading to encephalopathy and death [21]. Ageep and Elgasim (2012) reported that DHF cause severe degree (Grades 2 and 3) of liver damage which disagrees with our study [22]. In our study we found that clinical complications like bleeding, renal failure, and encephalopathy were higher in those who had severe hepatitis, suggesting that the degree of liver injury may be related to the severity of dengue infection. Similar data have been suggested by Seneviratne et al [8]. We can postulate that deranged liver functions may have a significant role in bleeding in addition to thrombocytopenia. Increased PT in hepatocellular disease implies Grade 4 liver damage. PT is the most important predictor of prognosis identify patient at high risk of death mandates close monitoring for encephalopathy [23]. Because of the great functional reserve, liver failure of homeostasis usually does not occur except in severe or long-standing liver disease. Thus, testing for coagulation defect is not a screening procedure but rather a means of following the progress of the disease or of assessing the risk of bleeding before the invasive procedure [15]. The severity of coagulation abnormality appears to be directly proportional to the extent of hepatocellular damage. Grade 4 hepatic dysfunction was significantly associated with encephalopathy in our study.

There are case reports of acute renal failure in DF in the literature, but none of them have been studied along with liver involvement. Lee et al (2009) reported that acute renal failure occurs in 3.3% of patients with DHF [24], but in our study the incidence was 14.3% in confirmed dengue and 13.7% in suspected dengue cases. Thus, the involvement of the kidneys was also related to the severity of liver damage; again this may be a part from the hepato-renal syndrome or direct virulence. Our study is consistent with the results from Ageep and Elgasim (2012) reported that dengue with encephalopathy patients associated with Grade 4 liver damage and dengue with renal involvement patients associated with Grades 3 and 4 liver damage [22]. One case suffered from a severe degree of renal failure (creatinine 3.9 mg %) in DHF and none in DF. All patients from renal failure recovered fully by conservative treatment.

In our study, the prevalent age group was 1-5 years in all DI as per the WHO criteria. The mean age of children with DHF was significantly higher than that of DF (7.6 year vs. 0.6 year). Dengue with <1 year age group is vulnerable for a severe degree of liver damage and complications. The common degree of liver damage observed in <1 year age group was Grade 1 in DF, Grade 2-4 in DHF, Grade 4 in dengue complicated by encephalopathy. Hence, the risk factor for progression towards the severe degree of liver damage and complications in dengue are male gender, children with <1 year age group, elevated transaminase levels (particularly AST), PT, INR >1.5, APTT, and hyperammonemia.

The mortality rate of DI was 5% in our study, higher than other studies [2,5], in which the mortality rate is 3.7% and 2.7%. The cause of death in these patients was severe dengue with multi-organ dysfunction with acute liver failure with hepatic encephalopathy. Hence, we can postulate that severe hepatitis with Grade 4 may be a significant contributing factor to mortality in patients with DI. Thus, our study highlights the mortality with a degree of hepatic dysfunction in dengue patients. There was a significantly higher mortality rate in both confirmed and suspected DHF with Grade 4 hepatic damage than DF. Hence, we cannot eliminate serologically negative DHF; they should be monitor and treated as serologically positive DHF. LFT are useful in detecting, diagnosing, evaluating severity, monitoring therapy, and assessing the degree followed by the prognosis of the liver disease and dysfunction. They are also useful in directing further diagnostic workup [15].

CONCLUSION

The useful early hepatic markers in DI are AST and APTT; AST distinguishes the acute phase of dengue from other febrile illness while APTT predicts disease severity in DI during early acute phase before confirming serologically. Severe hepatitis (Grades 3 and 4) can be considered as a bad prognostic indicator of outcome in terms of mortality and complications as compared to mild to moderate hepatitis (Grades 1 and 2). Thus, evaluation of LFT during the acute phase of DI is important for clinicians working in endemic as well as in non-endemic areas to assess the outcome, mortality, and prognosis according to the degree of liver damage.

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REFERENCES

1. Gubler DJ. Dengue and dengue hemorrhagic fever. Clin Microbiol Rev 1998;11:480-96.
2. Parkash O, Almas A, Jafri SM, Hamid S, Akhtar J, Alishah H. Severity of acute hepatitis and its outcome in patients with dengue fever in a tertiary care hospital Karachi, Pakistan (South Asia). BMC Gastroenterol 2010;10:43.
3. Wahid SF, Sanusi S, Zawawi MM, Ali RA. A comparison of the pattern of liver involvement in dengue hemorrhagic fever with classic dengue fever. Southeast Asian J Trop Med Public Health 2000;31:259-63.
4. Chongsrisawat V, Hutagalung Y, Poovorawan Y. Liver function test results and outcomes in children with acute liver failure due to dengue infection. Southeast Asian J Trop Med Public Health 2009;40:47-53.
5. Nguyen TH, Lei HY, Nguyen TL, Lin YS, Huang KJ, Le BL, et al Dengue hemorrhagic fever in infants: A study of clinical and cytokine profiles. J Infect Dis 2004;189:221-32.
6. Singhi S, Kissoon N, Bansal A. Dengue and dengue hemorrhagic fever: Management issues in an intensive care unit. J Pediatr (Rio J) 2007;83:S22-35.
7. Chuansumrit A, Puripokai C, Butthep P, Wongtiraporn W, Sasanakul W, Tangnararatchakit K, et al Laboratory predictors of dengue shock syndrome during the febrile stage. Southeast Asian J Trop Med Public Health 2010;41:326-32.
8. Seneviratne SL, Malavige GN, de Silva HJ. Pathogenesis of liver involvement during dengue viral infections. Trans R Soc Trop Med Hyg 2006;100:608-14.
9. Guzmán MG, Kourí G. Dengue: An update. Lancet Infect Dis 2002;2:33-42.
10. Kalayanarooj S, Vaughn DW, Nimmannitya S, Green S, Suntayakorn S, Kunentrasai N, et al Early clinical and laboratory indicators of acute dengue illness. J Infect Dis 1997;176:313-21.
11. Priyadarshini D, Gadia RR, Tripathy A, Gurukumar KR, Bhagat A, Patwardhan S, *et al* Clinical findings and pro-inflammatory cytokines in dengue patients in Western India: A facility-based study. PLoS One 2010;5:e8709.
12. Wiwanitkit V. Liver dysfunction in Dengue infection: An analysis of the previously published Thai cases. J Ayub Med Coll Abbottabad 2007;19:10-2.
13. Gulati S, Maheshwari A. Atypical manifestations of dengue. Trop Med Int Health 2007;12:1087-95.
14. Trung DT, Thao le TT, Hien TT, Hung NT, Vinh NN, Hien PT, *et al* Liver involvement associated with dengue infection in adults in Vietnam. Am J Trop Med Hyg 2010;83:774-80.
15. Tolman KG, Rej R. Liver function. In: Burtis CA, Ashwood ER. Teitz Text Book of Clinical Biochemistry. 3rd ed. Saunders: Elsevier Health Sciences Publishers; 1999. p. 652-3.
16. Itha S, Kashyap R, Krishnani N, Saraswat VA, Choudhuri G, Aggarwal R. Profile of liver involvement in dengue virus infection. Natl Med J India 2005;18:127-30.
17. Jagadishkumar K, Jain P, Manjunath VG, Umesh L. Hepatic involvement in dengue Fever in children. Iran J Pediatr 2012;22:231-6.
18. Wong M, Shen E. The utility of liver function tests in dengue. Ann Acad Med Singapore 2008;37:82-3.
19. Kuo CH, Tai DI, Chang-Chien CS, Lan CK, Chiou SS, Liaw YF. Liver biochemical tests and dengue fever. Am J Trop Med Hyg 1992;47:265-70.
20. Huang YH, Liu CC, Wang ST, Lei HY, Liu HL, Lin YS, *et al* Activation of coagulation and fibrinolysis during dengue virus infection. J Med Virol 2001;63:247-51.
21. Nguyen TL, Nguyen TH, Tieu NT. The impact of dengue haemorrhagic fever on liver function. Res Virol 1997;148:273-7.
22. Ageep AK, Abu Elgasim S. A correlation study between clinical manifestations of dengue fever and the degree of liver injury. J Microbiol Antimicrob 2012;4:45-8.
23. Tygstrup N, Ranek L. Assessment of prognosis in fulminant hepatic failure. Semin Liver Dis 1986;6:129-37.
24. Lee IK, Liu JW, Yang KD. Clinical characteristics, risk factors, and outcomes in adults experiencing dengue hemorrhagic fever complicated with acute renal failure. Am J Trop Med Hyg 2009;80:651-5.

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