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Original research article

A study of serum aminotransferase level changes in dengue fever and it's correlation with disease severity

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Abstract

Background and objective: To ascertain the variations in serum aminotransferase levels in severe dengue, dengue fever with warning signals, and dengue fever without warning signs and to assess the relationship between serum aminotransferase levels and dengue illness severity.

Materials and Methods: A co relational study was done on all the patients operated from 2020 to 2021 at Department of General medicine, Government General Hospital, Kurnool to investigate NS1Ag and Dengue IgM, IgG SEROLOGY, Hemogram- Hb, TLC, DLC, Platelet Counts, Hematocrit, Serum Electrolytes and Renal Function Test, Serum bilirubin, AST, ALT, ALP, USG abdomen

Results: 12 patients with increased liver enzyme levels exhibited bleeding tendencies. In our study, 13 patients exhibited hepatomegaly. A USG abdomen revealed free fluid in 30 individuals. There was no statistically significant relationship between increased liver enzymes and free fluid. Overall, 23 individuals had elevated liver enzymes. Twelve patients with bleeding tendencies, thirteen patients with hepatomegaly, and twelve patients with free fluid on USG abdomen all had elevated liver enzymes. The mean AST and ALT concentrations in our study were 186.52 IU/L and 129.91 IU/L, respectively.

Conclusion: In dengue fever, hepatic impairment is frequent. Either reactive hepatitis or direct viral damage to hepatocytes is the cause. In this study, elevated liver enzyme levels have prognostic value. Therefore, liver enzymes must be taken in order to check for problems and have predictive significance in dengue fever. Individuals with increased liver enzyme levels require more cautious monitoring than individuals with normal liver enzyme levels.

Keywords: Dengue fever, Serum aminotransferase level, hepatomegaly, bleeding tendency.

Introduction

Dengue hemorrhagic fever is an arboviral disease caused by four serotypes of the dengue virus, belonging to family-Flavivirus and transmitted by the Aedes mosquito. Dengue outbreaks are associated with considerable morbidity and mortality because of their varied spectrum of multi-organ involvement.
The spectrum of dengue fever includes:

1) Dengue fever without warning signs
2) Dengue fever with warning signs
3) Severe Dengue

Classical Dengue fever evolves through three phases:

a) Febrile phase
b) Critical phase
c) Recovery phase

Hepatic dysfunction is common in dengue fever. It is due to either the direct destruction of hepatocytes by virus or due to reactive hepatitis. It is associated with elevated aminotransferase levels in serum. Those patients with high aminotransferase levels are associated with increased bleeding, shock, ARDS, and renal failure. In addition to decreased platelet count, hepatic dysfunction is associated with an increased risk of bleeding.
Therefore, serum aminotransferase levels elevation plays an essential role in assessing the severity of dengue fever.

Aims and Objectives

1) To determine the changes in serum aminotransferase levels in dengue fever without warning signs,

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 10, 2023

dengue fever with warning signs and Severe Dengue.
2) To correlate serum aminotransferase levels with the severity of dengue fever.

Materials and Methods

Source of data

This study was conducted in Department of General medicine, GOVERNMENT GENERAL HOSPITAL, KURNOOL, over a period from 2020-21 (1 year). All Consecutive patients presenting to the medical emergency were included in the study.

Sample size

Number of patients studied: 50.

Duration of study: 1 year.

Study design: A Co-relational study.

Inclusion criteria

A) Age > 18 yrs

B) Patients with any 1 of following

1. NS1Ag positive dengue.
2. Dengue Ig M positive.
3. Dengue Ig G positive.

Exclusion criteria

a) Patients with chronic liver disease.
b) Patients positive for Malaria, Hepatitis B & C, Leptospirosis, HIV.
c) History of alcohol abuse

Method of collection of data

All Patients will undergo thorough clinical examination in the form of General Examination, Vital signs and systemic examination done. And for confirmation of Dengue fever and for assessment of severity, they will undergo the following serological and biochemical investigations.

Investigations

1. NS1Ag and Dengue IgM, IgG SEROLOGY
2. Hemogram- Hb, TLC, DLC, Platelet Counts, Hematocrit
3. Serum Electrolytes and Renal Function Tests
4. Serum bilirubin, AST, ALT, ALP
5. USG abdomen

All these investigations will be done in GOVERNMENT GENERAL HOSPITAL, KURNOOL at the time of Admission and relevant other investigations will be repeated after 24-48 hrs. Each patient will undergo above investigations and aminotransferase levels will be taken into consideration to assess for severity of dengue fever.

Statistical analysis

The data of all the patients will be entered into Microsoft□ Excel and analyzed using Graph pad prism version-6. Data cleaning and editing will be performed on a timely basis. The statistical significance between the groups was accessed by Chi-Square test, Fisher exact test. Data was analyzed using R studio. P <0.05 considered as significant. Percentages and proportions will be calculated wherever appropriate.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 10, 2023

Observations and Results

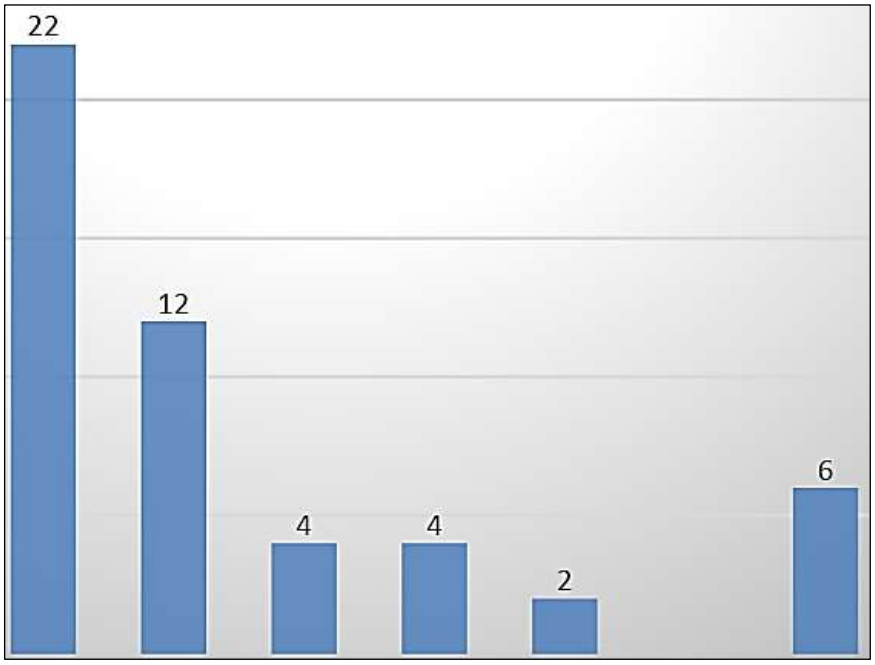


Fig 1: Age Distribution of Patients

Out of 50 patients studied, most of them were in the age group of 18-25 years (44%) and the least number in the age group of 41-45 years (4%).

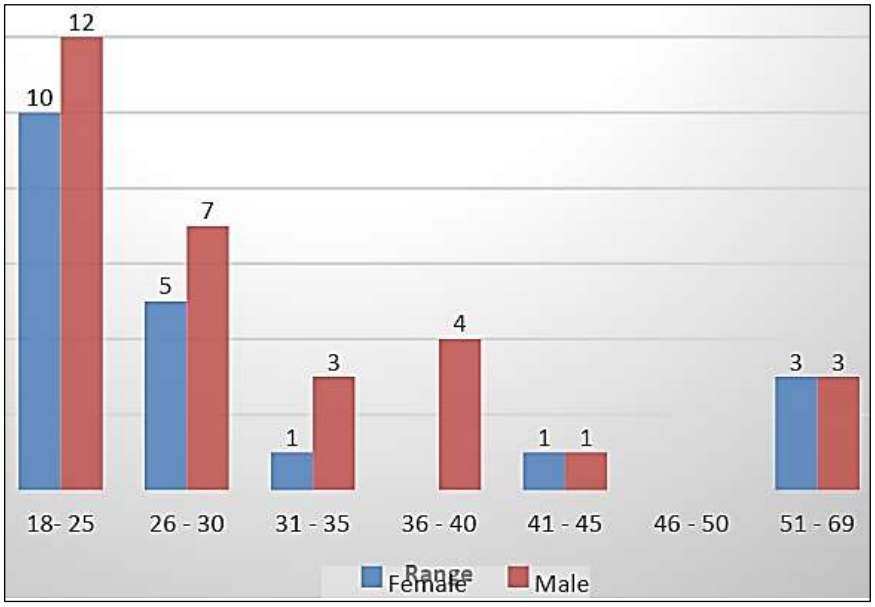


Fig 2: Sex Distribution of Patients

Out of 50 patients studied, males were 30 and females were 20. Highest number is in the age group of 18-25 years of which 12 patients were male and 10 patients were female.

Table 1: Co-Relation of AST Levels with Severity of Dengue Fever

	Dengue fever without Warning Signs	Dengue fever with Warning Signs	Severe Dengue
AST High	1	20	2

AST levels were high in 1 patient with dengue fever without warning signs and 20 patients with dengue fever with warning signs and both the patients with severe dengue. This shows that AST levels co-relate with severity of dengue fever.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 10, 2023

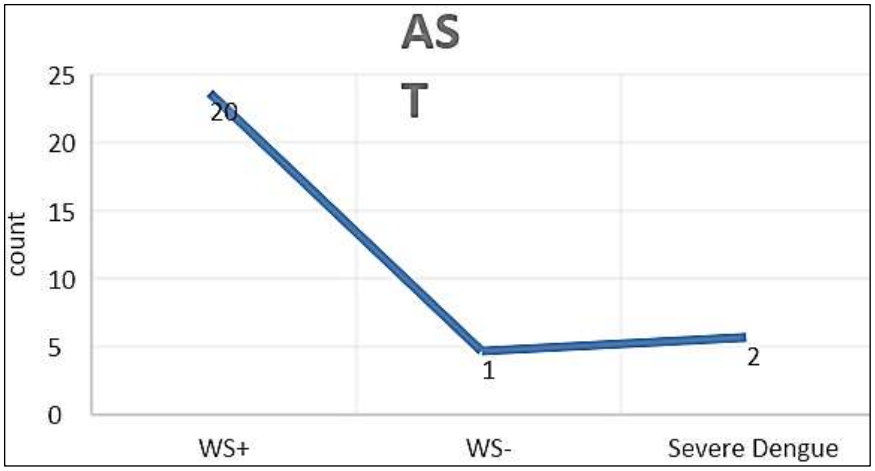


Fig 3: Co-Relation of AST Levels with Severity of Dengue Fever

Table 2: Significance between AST Levels and Bleeding Tendencies

		Bleeding		Total
		Absent	Present	
AST	High	11	12	23
	Low	20	7	27
Total		31	19	50

Chi square test was applied to test the significance between the AST levels and bleeding tendencies. There was a significant difference (p = 0.04) found between the variations in the AST levels and the bleeding tendencies. This implies that bleeding tendency depends upon the levels of AST.

Table 3: Significance between AST Levels and Thrombocytopenia

		Thrombocytopenia		Total
		Absent	Present	
AST	High	0	23	23
	Low	3	24	27
Total		3	47	50

Fisher exact test was applied to test the significance between the AST levels and thrombocytopenia. There was a significant difference (p = 0.02) found between the variations in the AST levels and thrombocytopenia. This implies that thrombocytopenia depends upon the levels of AST.

Table 4: Significance between AST Levels and free Fluid in Abdomen

		Free fluid		Total
		Absent	Present	
AST	High	10	13	23
	Low	10	17	27
Total		20	30	50

Chi square test was applied to test the significance between the AST levels and free fluid in abdomen. There was a no significant difference (p = 0.64) found between the variations in the AST levels and free fluid in abdomen. This implies that free fluid in abdomen does not depend upon the levels of AST.

Table 5: Significance between ALT Levels and Free Fluid in Abdomen

Variable		Free fluid		Total
		Absent	Present	
ALT	High	10	12	22
	Low	10	18	28
Total		20	30	50

Chi square test was applied to test the significance between the ALT levels and free fluid in abdomen. There was a no significant difference (p = 0.48) found between the variations in the ALT levels and free fluid in abdomen. This implies that free fluid in abdomen does not depend upon the levels of ALT.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 10, 2023

Table 6: Significance between AST Levels and Hepatomegaly

Variable		Hepatomegaly		Total
		Absent	Present	
AST	High	10	13	23
	Low	27	0	27
Total		37	13	50

Fisher exact test was applied to test the significance between the AST levels and hepatomegaly. There was a significant difference (p=0.01) found between the variations in the AST levels and hepatomegaly. This implies that hepatomegaly depends upon the levels of AST.

Table 7: Significance between Alt Levels and Hepatomegaly

		Hepatomegaly		Total
		Absent	Present	
ALT	High	9	13	22
	Low	28	0	28
Total		37	13	50

Fisher exact test was applied to test the significance between the ALT levels and hepatomegaly. There was a significant difference (p=0.01) found between the variations in the ALT levels and hepatomegaly. This implies that hepatomegaly depends upon the levels of ALT.

Table 8: Correlation between AST Levels and Platelets

		AST	Platelets
AST	Pearson Correlation	1	-.342*
	Sig. (2-tailed)		.015
	N	50	50
Platelets	Pearson Correlation	-.342*	1
	Sig. (2-tailed)	.015	
	N	50	50

There was a significant negative correlation between AST levels and platelet count. This implies that increase in AST levels is associated with decrease in platelets.

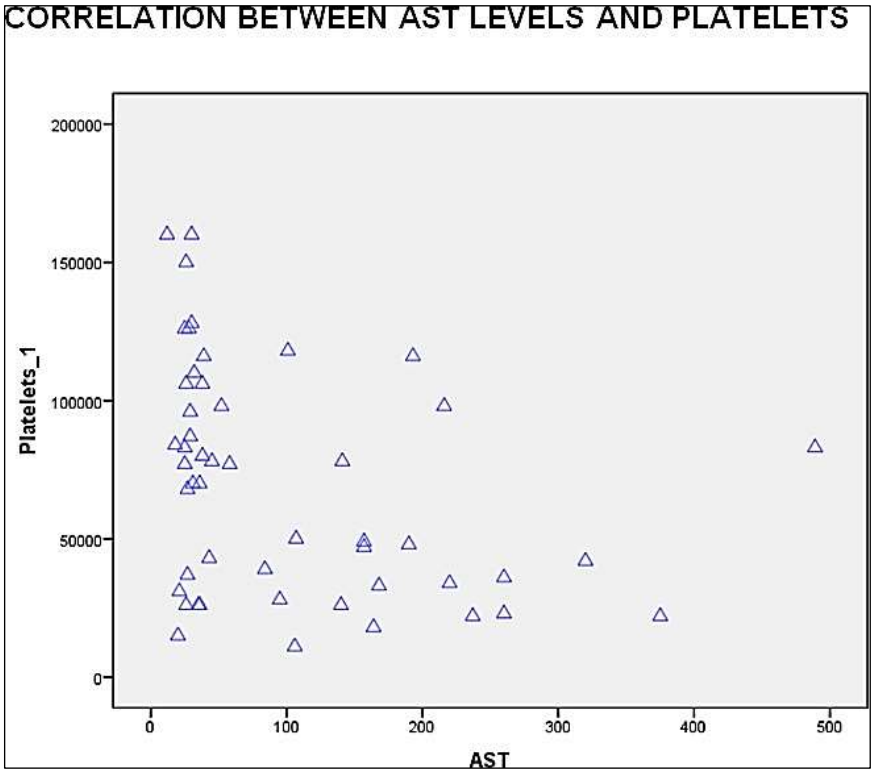
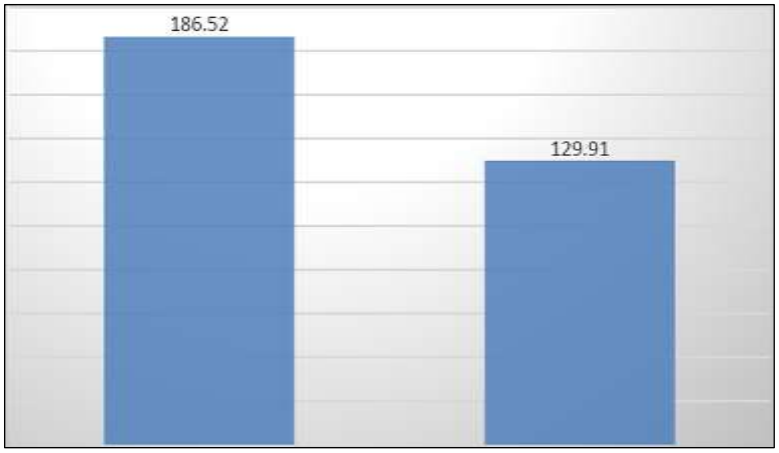


Fig 4: Mean Value of Serum Aminotransferases in Liver Enzymes Elevated Patients

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 10, 2023

In our study, of those patients with elevated liver enzymes, AST levels were found to be higher than ALT levels.



Results

1. Out of 50 patients, 30 were male and 20 were female in our study.
2. Most of the patients were in the age group of 18-25 and none of them were below 18 years.
3. Statistically, there was no significance between liver enzymes and age and gender groups.
4. In our study, AST levels were significantly higher than ALT levels.
5. Thrombocytopenia was noted in 47 patients of which 19 had bleeding and 28 had no bleeding.
6. There was a negative correlation between levels of liver enzymes and platelet count.
7. Bleeding tendencies were seen in 12 patients with elevated liver enzymes. Statistically, there was significance between elevated liver enzymes and bleeding tendencies.
8. 13 patients had hepatomegaly in our study. Elevated AST levels were seen in all patients with hepatomegaly. Statistically, there was significance between elevated liver enzymes and hepatomegaly.
9. 30 patients had free fluid in USG abdomen. Statistically, there was no significance between elevated liver enzymes and free fluid.
10. Elevated liver enzymes were found in 23 patients overall. Elevated liver enzymes were found in 12 patients with bleeding tendencies, 13 patients with hepatomegaly and 12 patients with free fluid in USG abdomen.
11. Mean levels of AST in our study was 186.52 IU/L, and mean levels of ALT in our study was 129.91 IU/L.

Discussion

The clinical manifestation of Dengue stands upon the shoulders of two modes of pathogenesis; Vasculopathy and Coagulopathy.

Pathogenesis of liver injury in dengue

- Hepatic injury is a crucial feature seen in Dengue virus infection.
- Hepatocytes and Kupffer cells are principal targets for DENV infection.
- For infecting cells, the major rate-limiting step is the viral attachment to the receptors present on a host cell's surface. The E protein has a role in the attachment of the virus.
- It has been postulated that the binding of DENVs onto hepatocytes is facilitatory; one binding promotes successive particles' binding. After binding of the virus, internalization is by either direct fusion or endocytosis.

Hepatic dysfunction in Dengue is common. It is due to either

a) The direct effect of the virus on hepatocytes.
b) Due to immune-mediated hepatitis.

Varying degrees of liver involvement is seen during acute dengue infection and are thought to result from hepatocyte apoptosis directly by the virus, hypoxic damage due to impaired liver perfusion resulting from fluid leakage, oxidative stress, or immune-mediated injury. Hepatic involvement in dengue fever is in the form of elevated serum aminotransferase. Those patients with elevated liver enzymes are more likely to have an increased risk of bleeding tendencies, shock, ARDS, renal failure and acalculous cholecystitis. In addition to decreased platelet count, hepatic dysfunction plays a significant role in bleeding. Hence, it is mandatory to evaluate serum aminotransferases in all patients with dengue fever.
Gagnon *et al*. (1999) have reported that CD4+ cytotoxic T cells are responsible for liver destruction in

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 10, 2023

dengue fever involving a mechanism which involves bystander lyses". 'CD4+ mediated cytotoxicity' occurs via two pathways.

1. Activated CD4+ cytotoxic T cells release perforin and granzymes.
2. 'Fas on the target cell interacts with Fas ligand on the T cells.'

Histological changes in the liver secondary to dengue infection include:

1. Hepatocellular necrosis.
2. Councilman bodies.
3. Kupffer cell hyperplasia and destruction.
4. Micro vesicular steatosis.
5. Cellular infiltrates at the portal tract.

In our study, out of 50 patients studied, most of them were in the age group of 18-25 years (44%), males were 30 and females were 20 and 23(46%) patients had elevated liver enzymes.

Table 9: Comparative Studies on Liver Dysfunction in Dengue Fever

Ref.	Patients	Raised AST	Raised ALT	AST > ALT	Hyper-bilirubinemia	> 10 fold rise (AST, ALT)
Kuo *et al*[57]	270	93.30%	82.20%	+	7.20%	11.1%, 7.4%
Souza *et al*[58]	1585	63.40%	45%	+	-	3.4%, 1.8%
Itha *et al*[59]	45	96%	96%	Equal	30%	-
Wong *et al*[60]	127	90.60%	71.70%	+ in 75.6%	13.4%	10.2%, 9.5%
Parkash *et al*[61]	699	95%	86%	+	-	15%
Trung *et al*[62]	644	97%	97%	+	1.7%	-
Lee *et al*[63]	690	86%	46%	-	-	1%
Karoli *et al*[64]	138	92%		+	48%	-
Saha *et al*[65]	1226				16.9%	

Chen HC *et al*. in 2004 found out that three-tenth of patients with Dengue had hepatic involvement. Hepatic involvement is significantly higher in Asian populations from 31.92%. They also found out that the rate of hepatic dysfunction in shock patients was higher than that of non-shock patients.

Chen HC *et al*. in 2004 reported that there was a "significant correlation between T lymphocyte activation and liver dysfunction in immunocompetent mice".

Souza *et al*. found that liver enzymes were significantly elevated in 63% of dengue fever patients.

Parkash *et al*. showed that liver dysfunction was seen in 95% of patients.

Kuo *et al*. found that liver enzymes were significantly elevated in 93% of dengue fever patients.

Lee *et al*. showed that liver dysfunction was seen in 86% of patients.

In one study, about three-tenths of all patients are presented with liver dysfunction. Liver dysfunction is considerably higher in Asian populations ranging from 30-90%. The rate of liver dysfunction in patients with shock is higher than the patient without shock.

Trung *et al*. showed that liver dysfunction was seen in 97% of patients.

Karoli *et al*. found that liver enzymes were significantly elevated in 92% of dengue fever patients.

Itha *et al*. found that liver enzymes were significantly elevated in 96% of dengue fever patients.

Tancharoen *et al*. found that AST and ALT's mean values were significantly increased in patients with Dengue fever with warning signs.

Kho CH *et al*. reported that increased AST and ALT levels are associated with severe bleeding manifestations in dengue patients.

The mean Aspartate transaminase (AST) and Alanine transaminase (ALT) values have been higher for severe Dengue forms than for dengue fever without warning signs. This hints at an association between increased transaminase levels with increasing disease severity. The mean values of liver enzymes were higher in the febrile and the severe phases of Dengue.

AST has several sources, including the heart, striated muscle, erythrocytes, and liver, while ALT is primarily hepatic in origin. Acute insult to these non-hepatic tissues by the DENV can result in higher AST elevations compared to ALT rise. Therefore, a rise in AST might not be a true reflection of hepatic involvement.

Liver damage is more common among females in a large study from Brazil (74.6% of females than 52.2% of males), with 4.2% having acute hepatitis. In our study, no statistically significant difference was found between males and females as far as transaminase elevation level was concerned.

In our study, AST and ALT values were significantly elevated in individuals with the following features:

1. Patients with dengue fever with warning signs or severe Dengue.
2. Thrombocytopenia or an increased hematocrit.
3. Nausea/Vomiting.
4. Hepatomegaly.
5. Bleeding tendencies.

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Dengue pathogenesis is not fully understood and multifactorial, ranging from direct viral injury, the dysregulated immune response to hypoxic/ischemic injury, and even secondary to drugs such as PCM used commonly for the treatment of this illness.
Mortality data are comparable with other causes of ALF, although adults have been reported to have a slightly better prognosis as compared to children, in whom it is 50%-66%.

Limitation of study

1. Small sample size (50).
2. We did not check for dengue virus subtypes.
3. Almost all the patients with dengue fever had thrombocytopenia.
4. The duration of study is one year only.
5. Antibody titers were not quantitated.

Conclusion

Hepatic dysfunction is common in dengue fever. It is due to either the direct destruction of hepatocytes by virus or due to reactive hepatitis. It is characterized by elevated liver enzymes, AST more than ALT levels. Those patients with elevated aminotransferase levels are associated with increased bleeding, shock, ARDS, and renal failure. In addition to decreased platelet count, hepatic dysfunction is associated with an increased risk of bleeding.
In addition to thrombocytopenia, hepatic involvement plays a significant role in bleeding. Elevated liver enzymes have got prognostic value in this study. Hence, liver enzymes are mandatory in dengue fever to look for complications, and it is of prognostic value. Those patients with elevated liver enzymes should be monitored carefully than those with normal liver enzymes.

Conflict of Interest: None.

Funding Support: Nil.

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