

Original Research Article


The Impact, Clinical Relevance and Prognostic Value of Elevated Liver Aminotransferase Levels for Assessment of Dengue Severity - A Prospective Observational Study in A Tertiary Care Facility In Telangana

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Abstract

Background: In acute dengue fever, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are often elevated. The World Health Organization (WHO) established AST or ALT 1000 units/litre (U/L) as a criterion for severe dengue in its 2009 dengue guidelines. The goal of this study was to determine the clinical significance and prognostic value of AST or ALT as a marker in the diagnosis of dengue fever, dengue hemorrhagic fever (DHF) and severe dengue.

Materials and methods: This was a prospective single centre observational study conducted for a period of 12 months carried out in the Department of General Medicine, Malla Reddy Hospitals, Hyderabad. A total 150 adult patients were included and for management. The WHO grading system was used to triage the patients as group A, group B and group C according to WHO. Amongst them group A were sent home and followed up daily; group B were admitted in wards and group C were admitted to ICU in need of any emergency treatment. Study population constituted group B and C. Patients were managed and observed from time to time with review examinations to assess improvement or derangement in patient condition.

Results: Out of the serologically confirmed dengue cases, 90(60%) were male and 60(40%) were females, in which NS1 antigen positive were 133 (88.7%) and specific dengue IgM antibodies were 36 (24%). 79 (53%) had dengue fever, 63 (42%) had dengue fever with warning signs, and 8 (5.3%) suffered from severe dengue. Hepatic dysfunction was seen very commonly in all the dengue cases. Extent of ALT and AST elevation revealed good correlation with each other. Levels of ALT and AST increased significantly with increasing severity of DF, i.e., the levels of AST and ALT were significantly more in dengue with warning signs and severe dengue when compared with dengue fever without warning signs. The finding was of great clinical significance as this indicated that higher values of AST, ALT, were seen in patients with severe disease. So, we can say that grossly deranged LFT's can point towards severe form of dengue, and deranged transaminases can be used as a prognostic factor.

Conclusion: The levels of serum aminotransferase (AST and ALT) are markedly elevated in all three kinds of dengue infection, and they are strongly related to the severity of the infection. In all forms of dengue infection, serum aspartate aminotransferase (AST) levels were considerably higher than alanine aminotransferase (ALT) levels. There is a direct association when used as a prognostic marker. More is the derangement in serum transaminase level; more is the chance of the disease being severe. The number of days spent in the hospital increased as the level of transaminases became more abnormal.

Key words

Liver function, Serum Aminotransferase, Dengue, Classic Dengue, Dengue with warning signs, Dengue Hemorrhagic Fever, Dengue Shock Syndrome, AST, ALT, Alanine Amino Transferase, Aspartate Amino Transferase.

Introduction

Dengue fever is an arboviral infection, belongs to genus Flavivirus endemic to India, transmitted by mosquitos *Aedes aegypti* and *Albopictus* [1]. Dengue fever is an acute febrile illness with an incubation period of 4-7 days but may range from 3 to 14 days characterized by sudden onset of fever of 3 to 5 days duration, intense headache, myalgia, arthralgia, rash, retro-orbital pain, anorexia, and gastrointestinal disturbances.

Dengue fever can be caused by any of four genetically related but antigenically distinct

dengue virus (DENV) serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) [2]. It has wide spectrum of presentation as asymptomatic, symptomatic (mild, moderate and severe). In moderate to severe cases, it progresses in three phases: Febrile phase, Critical phase and Recovery phase.

Dengue fever is a non-hepatotropic virus, but liver damage is seen in most cases by the direct or indirect effect of the immune response as acute hepatitis, hepatomegaly, jaundice, increased aminotransferase levels [3]. In 2009, the World Health Organization (WHO) revised

its dengue guidelines and proposed severe organ impairment as one category of severe dengue in addition to severe plasma leakage and severe bleeding. Dengue fever (DF) with its severe manifestations such as DHF and DSS has emerged as a major public health problem of international concern. In most of the cases hepatic involvement prolongs the clinical course of the disease and hospital stay of the patient [4]. The hepatic involvement could be caused by the virus directly or it may be an indirect effect of hosts immune response against the virus [4]. There are not many studies related to hepatic involvement in dengue infection.

Our study concentrates mainly on the elevation of the serum transaminase levels in the dengue infections, which acts a prognostic factor for severity assessment and to determine the length of the hospital stay.

Aim and objectives

- The Aim of this study was to study the prognostic value of serum transaminases (AST/ALT) in patients with Dengue infection presenting to a tertiary-care hospital.
- The raised value of serum transaminases (AST/ALT) as a prognostic factor in assessing the severity of the disease and prolonged hospital stay.

Materials and methods

This was a prospective single centre observational study conducted for a period of 12 months carried out in the Department of General Medicine, Malla Reddy Hospitals, Hyderabad. A total 150 adult patients were included and for management. The WHO grading system was used to triage the patients as group A, group B and group C according to WHO. Amongst them group A was sent home and followed up daily; group B was admitted in wards and group C was admitted to ICU in need of any emergency treatment. Study population constituted group B

and C. Patients were managed and observed from time to time with review examinations to assess improvement or derangement in patient condition.

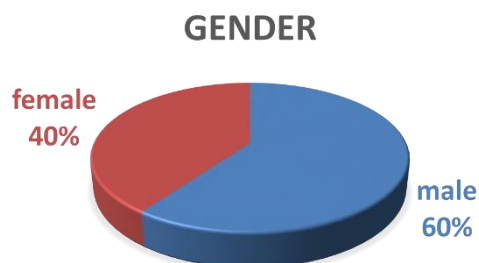
Results

After meeting the inclusion and exclusion criteria, 150 Dengue IgM or NS1 positive individuals were enrolled in the study. NS1 antibodies were found in 133 (88.7%) patients, while dengue specific IgM antibodies were found in 36 (24%) patients (**Graph - 1**). According to WHO categorization, 79 patients (52.7%) had dengue fever, 63 (42%) had dengue fever with warning signs, and 8 (5.3%) had severe dengue fever (**Graph - 2 and 3**).

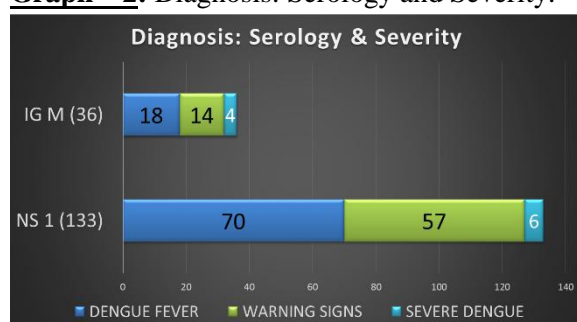
Mean age of dengue infection patients was 31.55 \pm 12.48 years and a male to female ratio of roughly 3:2. Dengue presented with a variety of symptoms, fever symptom was present in all the 150 patients (100%), Headache present in 98 patients (65%), Retro-Orbital Pain in 51 patients (34%), Arthralgia in 73 patients (48.7%), Myalgia in 101 patients (67.3%), Vomiting in 70 patients (46.7%), Pain abdomen in 63 patients (42%). Hepatic dysfunction was seen very commonly in all the dengue cases. Hyperbilirubinemia was seen in 14 patients (9.3%) (total), direct hyperbilirubinemia was seen in 17 patients (11.3%). Hypoalbuminemia was seen in even larger subgroup of patients i.e., 104(69.3%). Raised serum alkaline phosphatase (ALP) found in 43 (28.7%) patients. In all the dengue cases, hepatic impairment was prevalent. Serum transaminase levels were increased in large group of patients, AST in 128 patients (85.33%) and ALT in 126 patients (84%). Mean AST levels were significantly higher than ALT levels. Mean AST level being 167.30 \pm 244.1 and mean ALT level being 122.91 \pm 227.69. The extent of ALT and AST rise showed a strong association. Deranged hepatic parameters (Hyperbilirubinemia, elevated transaminases, hypoproteinaemia, and hypoalbuminaemia) were seen in higher number and more severe in

Dengue with warning signs and Severe Dengue as compared to classical Dengue fever.

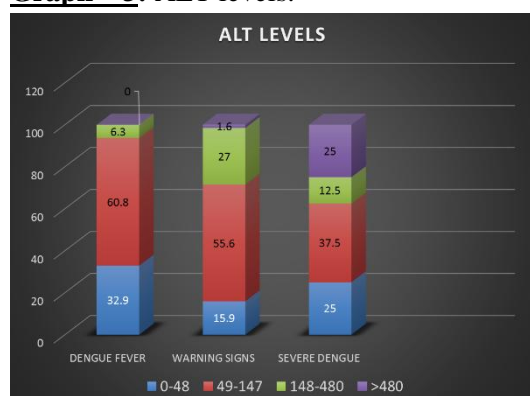
Graph – 1: Gender distribution.



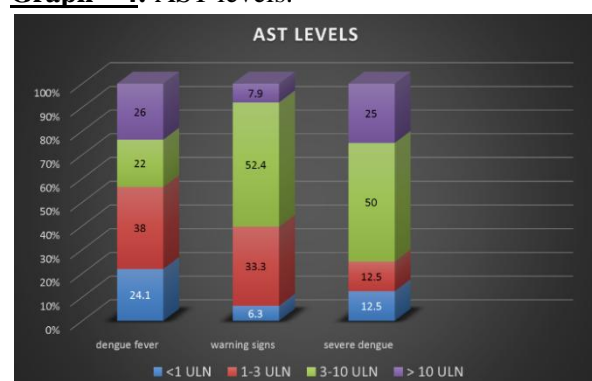
Graph – 2: Diagnosis: Serology and Severity.



Graph – 3: ALT levels.



Graph – 4: AST levels.



Discussion

The purpose of this single-centre prospective study was to study the association between dengue infections, and its severity with the lab levels of serum transaminases. A total of 150 dengue cases were studied, all of whom were either Dengue IgM or Dengue NS1 positive.

According to the revised WHO classification, 79 patients (52.7 percent) had dengue fever, 63 (42 percent) had dengue fever with warning signs, and 8 (5.3 percent) had severe dengue fever. Because this classification hasn't been utilized in earlier studies, the results can't be compared. Even if the occurrences of severe and non-severe dengue are equal, the incidences of severe dengue are higher.

The mean age of the patients in our study was 31.55 ± 12.48 years, with a 3:2 male to female ratio, can be compared with Amit Soni, et al. [5] a recent study in which the mean age was 43.13 ± 15.50 years and the male to female ratio was 2:1. Also in Rajoo, et al. [6] who found that the average age was 31.6 years, with a male-to-female ratio of 3.3:1, which is similar to our findings. Different hypotheses have been proposed to explain the discrepancies in gender distribution, as studies conducted in hospitals only depict the patient population who seek treatment and is not a true representation of the actual affected population. Kaplan, et al. explained that disease transmission indoors during the day impacted more females than males, whereas Goh, et al. [7] and Ooi, et al. [8] reasoned that because the disease's vector, Aedes, is widely disseminated in the outside environment, females have a lower incidence. The most common presenting symptom was fever, followed by myalgia and headache.

Bleeding manifestations were seen very less commonly in our study as compared to old studies i.e., only in 20 out of 150 cases. Most common of which was Malena, found in 12 patients (8%), followed by hematuria found in 4

patients (2.7%), hematochezia found in 2 patients (1.3%), whereas bleeding gums and hematemesis were found in 1 patient each (i.e. 0.7%).

When it comes to hepatic dysfunction, the extent of ALT and AST increase showed a strong association. The levels of ALT and AST increased dramatically as the severity of DF worsened. Although severe dengue patients exhibited significantly higher median AST and ALT values than non-severe dengue patients, only a handful had AST or ALT levels greater than 1000 U/L.

When compared to DF patients, hyperbilirubinemia was substantially more common and severe in patients with Dengue with warning signs and severe dengue. In our study, the mean bilirubin level in dengue fever patients was 0.63 ± 0.31 , 0.797 ± 0.75 in dengue with warning signs, and 2.598 ± 3.053 in severe dengue. Hyperbilirubinemia was also shown to be much more common in patients with severe dengue fever, with mean values of 0.78 in dengue fever, 2.01 in dengue hemorrhagic fever, and 2.69 in dengue shock syndrome, according to Amit Soni, et al. [5]. The findings of Rajoo, et al. study [6] were likewise. As a result, evidence suggests that a high bilirubin level may be a poor prognostic indicator in dengue patients [6].

AST and ALT levels were abnormal in 128 (85.33%) and 126 (84.0%) of the patients in our study, respectively. Even if the results are smaller than those of Rajoo, et al. [6], they are comparable [6]. A higher level of ALP and serum bilirubin were noted in a smaller proportion of patients, i.e., 43 (28.7%) and 14 (9%), respectively similar to that of studies conducted by Itha, et al. [9] and Rajoo, et al. [6].

Aspartate aminotransferase (AST) levels are higher than alanine aminotransferase (ALT) levels in dengue infection. Our findings support this trend in dengue fever, as well as the findings and values found in old studies conducted [9-11].

This is in contrast to the pattern seen in viral hepatitis, in which ALT levels are higher than AST levels. The specific cause is unknown, but it has been postulated that excessive AST release from injured monocytes during dengue infection may be to blame [12].

In our study, the mean AST level was 167.3 ± 244.1 and the mean ALT level was 122.91 ± 227.69 . AST values in dengue subgroups are 104.49 ± 79.88 in DF, 199.58 ± 139.70 in dengue with warning signs, and 566.00 ± 888.29 in severe dengue infection; and ALT levels are 78.58 ± 52.88 in Dengue fever, 129.35 ± 94.99 in Dengue with Warning signs, and 509.875 ± 893.73 in severe dengue infection. That is, it rises in proportion to the severity of the sickness, implying that the extent of liver damage is linked to the severity of the dengue infection similar and comparable to Souza et al. [13]. All patients with dengue infection had an increase in serum aminotransferase, directly correlating with severity of infection. The finding is of great clinical significance as this indicates that higher values of AST, ALT, Bilirubin, ALP and INR are seen in patients with severe disease.

From the above, one can conclude that severely deranged LFTs (serum ALT and AST) indicate a severe form of dengue. The presence of a liver injury has been proposed as a good positive prognostic factor for the development of severe dengue fever [14].

The findings of Chhina, et al. [15] were remarkably comparable to ours. They found that the DHF group (significantly higher values of AST and ALT) and the DSS group (significantly higher values of all biochemical liver tests) had more hepatic injury than the DF group, suggesting that the severity of dengue infection may be related to the degree of liver injury.

Another study, Kuo, et al. [16] found that higher levels of aminotransferases were linked to increasing illness severity.

Albumin levels are normally affected in chronic liver disease, but because dengue is an acute illness, albumin levels should remain stable, although hypoalbuminemia to some extent was observed in our study in severe dengue cases.

Jaundice can arise for a variety of reasons in cases of Dengue Fever, Dengue with Warning Signs, or Severe Dengue. It can be caused by dengue virus-induced liver damage, as well as hypoxia and tissue ischemia in cases of dengue shock [17].

There was no evidence of hepatic encephalopathy in any of the patients in our study. In a few earlier studies, this was seen in a few severe dengue cases. Metabolic acidosis, severe disseminated intravascular coagulation, extensive bleeding or oedema in the brain, or hyponatremia due to excessive fluid delivery are all possible causes of neurological symptoms in dengue infection [18]. The comparison of results of our study with few old studies is as per **Table - 1**.

As it is a hospital-based study so it is not true representation of all dengue infection. Majority of dengue infections are treated on outpatient basis and only few who are very symptomatic or have grossly deranged laboratory parameters are treated in hospital.

Conclusion

Dengue is associated with a moderate increase in aminotransferases and, less frequently, acute hepatitis. The levels of serum aminotransferase (AST and ALT) are significantly higher in all three types of dengue infection studied in this study, and they are directly associated to the severity of the infection. In all forms of dengue infection, serum aspartate aminotransferase (AST) levels were considerably higher than alanine aminotransferase (ALT) levels and there is a direct association when considered as a prognostic marker. More is the derangement in serum transaminase level; more is the chance of the disease being severe. And also, more deranged the level of transaminases more was the number of days of hospitalization.

Table – 1: The comparison of results of our study with few old studies.

Variables	Our study	Soni, et al. [4]	Sharma S., et al. [9]	Chhina, et al. [14]
No. of Pts.	150	281	98	214
Age in yrs	31.55 ± 12.48	43.13 ± 15.50	26.3 ± 10	31.6
M: F ratio	3:2	2:1	3:1	3.3:1
DF	79(52.7%)	248 (88.3%)	-	174 (81.3%)
D with WS	63(42%)	-	-	-
Severe Dengue	8(5.3%)	33(11.8%)	98(100%)	40(18.7%)
Hemorrhagic manifestation	13.30%	-	56.1%	40.6%
Platelet count	61032 ± 49011	55400±36300(Males) 98100±371000 (Females)	30000±25000	48500±2600
AST (U/L)	167.3 ± 244.1	687.28 ± 3037.94	274 ± 634	353.7 ± 49.6
ALT (U/L)	122.91 ± 227.69	293.65 ± 1041.89	143 ± 242	218.6 ± 27.2
ALP (U/L)	91.19 ± 54.59	112.14 ± 82.17	196 ± 155	135.2 ± 6.5
T. Bilirubin	0.803 ± 0.954	0.95 ± 0.72	0.9 ± 0.6	0.93 ± 0.09

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