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Elevated liver enzymes as a marker of dengue disease severity and its prognostic implications

Abhishek Mishra[1], Yogendra Man Shakya[2], Tirtha Man Shrestha[3], Arjun KC[1], Pradeep Mahat[1], Santosh Kumar Shrestha[4], Bipana KC[1], Jeevan Neupane[1]

[1]Resident, [2]Prof., [3]Asst. Prof., [4]Medical Officer, Dept. of General Practice & Emergency Medicine, Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal

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Correspondence:
Dr. Abhishek Mishra
Resident, Dept. of General Practice & Emergency Medicine, Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal
Email: abhishek.gm.mishra@gmail.com

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Abstract

Introduction: Dengue, the most important arthropod-borne disease, is transmitted to humans by mosquitos of the Aedes family. Liver dysfunction in dengue varies from mild injury with elevation of transaminases to severe hepatocyte injury. The aim of our study was to correlate the severity of the disease with the extent of hepatic dysfunction.

Method: A prospective observational study was conducted at a tertiary care center in adults presenting to the emergency department and/or OPD diagnosed with dengue fever from 24 Nov 2022 to 25 Nov 2023.

Result: Among 151 patients included in the study, males predominated - 84 (55.6%). The most common presentation was fever- in 115 (76.2%). There were 50 (33.11%) patients with Dengue without warning signs and 97 (64.23%) with warning signs. Only 4 (2.64%) were classified as severe Dengue. NS1 antigen was positive in about 141 (93.4%), Dengue IgM in 12 (7.9%), and IgG in 4 (2.6%) of the patients. Bleeding manifestations were present in about 13 (8.6%). Three required blood transfusions. There was no mortality. On multivariable OR analysis, in the severe Dengue group, both AST and ALT showed statistical significance in predicting the severity of Dengue fever.

Conclusion: Elevations in hepatic enzymes—ALT and AST—demonstrated a notable level of accuracy in determining the severity of Dengue fever and in prognosticating it. Plasma AST and ALT levels were higher in individuals who developed severe Dengue, suggesting that elevations in hepatic enzymes could be used as an early marker of the severity of dengue.

Keywords: Dengue, Liver Enzymes, Prognosis, Severity

INTRODUCTION

Dengue has been identified as one of the youngest emerging infectious diseases in Nepal. The first case of dengue was reported in 2004.[1] Most dengue infections are asymptomatic. Those with symptoms can be classified into 3 patterns, based on their severity: dengue fever (DF) without warning signs, dengue fever with warning signs, and Severe Dengue as per WHO 2009 classification.[2] In clinical practice, the diagnosis and management are based on clinical findings and abnormal initial laboratory tests.[3]

The causes of mortality in dengue infection are prolonged shock, massive bleeding, and fluid overload.[4] The main factor leading to poor prognosis or death is not being able to identify severity at presentation to the hospital.[5,6] Clinical risks and laboratory tests have been studied to forecast the severity of infection. These included gender,[6] younger age,[7] abdominal pain,[8] lethargy, cold hands and feet,[8] abnormal bleeding episodes,[9,10] secondary infection,[11] presence of ascites,[12] pleural effusion,[12] leucopenia (< 4,000/µL),[12] thrombocytopenia,[13] hemoconcentration,[13] rising serum glutamic-oxaloacetic transaminase (SGOT) and/or Serum glutamic pyruvic transaminase (SGPT), [12-15] prolonged partial thromboplastin time (PTT),[16] prolonged Prothrombin time (PT),[16] positive of the D-dimer test,[17] and gallbladder wall thickening (measured by ultrasound)[18] (Table 1)

Few studies implicate the prognostic significance of elevated liver enzymes in dengue infection severity. Our study aimed to determine whether elevation in liver enzymes can serve as a marker of severity in Dengue and be able to prognosticate it.

METHOD

A prospective observational study was conducted after obtaining ethical approval from the Institutional Review Committee of the Institute of Medicine, Maharajgunj Medical Campus [Reference number: {345 (6-11) E2 079/80}]. Data was collected from 24 November 2022 to 25 November 2023. The study population included all adult patients who presented to the Emergency Department and/or Outpatient department of the General Practice of the Institute of Medicine, TUTH, who were clinically/serologically diagnosed with Dengue Fever. Informed consent was diligently obtained from all participants. Pregnancy, trauma patients, and immunocompromised patients were excluded from the study. The nonprobability sampling-convenience Sampling method was used. The sample size was calculated by using the following formula:

Sample size (N) = $[\{(Z\ (1-\alpha)\}^2 \times p\ (1-p)\}]/\ d^2$
Where,
Z (1-α) = standard normal variate {at 5% type I error ($p<0.05$, it is 1.96)}
P = expected proportion of dengue based on previous studies 0.11[20]
d = precision of estimate or absolute error, taken as 5%.
Applying the above values to the formula, the sample size is 151.

The data obtained were organized in MS Excel 2018, followed by the use of IBM® SPSS® version 22 (IBM Corp., Armonk, USA) for analysis and visualization. The demographic parameters were expressed in frequency, percentage, mean, and standard deviation where appropriate. Significant parameters—dengue without warning signs, Dengue with warning signs, and severe Dengue—were analyzed by multivariable polytomous logistic regression to identify significant characteristics associated with severity.

RESULT

Among 151 patients, males 84 (55.6%) outnumbered females 67 (44.4%). The age group was between 15 and 72, with a mean age of 33.09 years and a standard deviation of 13.49. About 77 (51%) of the patients presented to the Emergency Department, and 74 (49%) to the outpatient department.

The most common presentation of the patient was fever 115 (76.2%) of the cases followed by retro orbital pain in 96 (63.6%) of cases. The least common symptom was cough, seen in only 2 (1.3%) (Table 3). The most common warning signs were vomiting- seen in about 80 (53%) of the cases followed by nausea and abdominal pain- 73 (48.3%) and 48

Table 1. WHO 2009 Dengue fever classification[19]

Dengue without warning signs	Dengue with warning signs	Severe Dengue
The person lived or travelled in an area of dengue transmission in the last 14 days, has a sudden high fever typically of 2 to 7 days duration, and presents TWO or more of the following manifestations: • Nausea, vomiting • Exanthema/rash • Myalgia/arthralgia • Headache, retro-orbital pain • Petechiae or tourniquet test positive • Leukopenia	Dengue (as defined to the left) with any of the following: • Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation (e.g. ascites, pleural effusion) • Mucosal bleeding • Lethargy, restlessness • Liver enlargement > 2 cm • Laboratory: increase in hematocrit, concurrent with rapid decrease in platelet count.	Dengue with at least 1 of the following: • Severe plasma leakage leading to shock (dengue shock syndrome) or fluid accumulation with respiratory distress • Severe bleeding (as evaluated by a clinician) • Severe organ involvement (i.e., AST or ALT 1000 or greater, impaired consciousness, organ failure).

(31.8%) respectively. Bleeding manifestations were present in about 13 (8.6%) of the cases. The various laboratory biomarkers are tabulated in table 3. The lowest hematocrit was 14.7% and the lowest platelet count was 7500. Similarly, the highest AST level was 773 U/L and ALT was 827 U/L. The lowest TLC was 1500 cells/µL. NS1 antigen was positive in about 141 (93.4%), Dengue IgM in 12 (7.9%) and Dengue IgG in 4 (2.6%) of the patients. (Table 4). Around 50 (33.11%) of the patients were classified as Dengue without warning signs, 97 (64.23%) as Dengue fever with warning signs and about 4 (2.64%) as severe Dengue. (Table 5).

Table 2. Clinical features of patients at presentation, N=151

Parameters	Present N(%)	Absent N(%)
Fever	115(76.2%)	36(23.8%)
Retro orbital pain	96(63.6%)	55(36.4%)
Headache	80(53%)	71(47%)
Vomiting	80(53%)	71(47%)
Nausea	73(48.3%)	78(51.7%)
Abdominal Pain	48(31.8%)	103(68.2%)
Myalgia	41(27.2%)	110(72.8%)
Rashes	36(23.8%)	115(76.2%)
Anorexia	34(22.5%)	117(77.5%)
Chills /Rigor	20(13.2%)	131(86.8%)
Bleeding manifestations	13(8.6%)	138(91.4%)
Cough	2(1.3%)	149(98.7%)

Table 3. Laboratory biomarkers of patients at presentation

Parameters, unit	Range	Mean ± SD
Systolic BP, mmHg	70-160	123.64±18.70
Diastolic BP, mmHg	60-120	79.47±13.06
TLC, cells/µL	1500-18000	4620.13±2852.44
Neutrophil count, %	22.80-92	58.41±15.14
Hb, gm%	4.9-18.2	13.66±2.36
PCV, %	14.7-54.60	40.399±7.10
Platelets, cells/µL	7500-363000	119015.89±74879.19
SGPT (ALT), U/L	13-827	73.90±114.11
SGOT (AST), U/L	15-773	93.70±144.47

Table 4. Serology of patients

Serology	Positive N(%)	Negative N(%)
Dengue NS1 Antigen	141(93.4%)	8(5.3%)
Dengue IgM	12(7.9%)	139(92.1%)
Dengue IgG	4(2.6%)	147(97.4%)

Only about 4 (2.64%) of the patients had severe dengue. All of them were shifted to the intensive care unit. Three of them required blood transfusion. There was no mortality. On multivariable OR analysis, in the severe Dengue group, both AST and ALT showed statistical significance in predicting the severity of Dengue fever, as evidenced by the odds ratio (>1) and P value (< 0.05).

DISCUSSION

In a retrospective observational cross-sectional study done by Swamy AM et al. involving 120 patients, AST was elevated in 66.7%, 78.6%, and 91.7% of patients with dengue without warning signs, warning signs, and severe dengue, respectively. ALT was elevated in 42.4%, 52.4%, and 91.7% of patients with dengue without warning signs, warning signs, and severe dengue, respectively. Patients with elevated AST (93.8%) and ALT (81.2%) had a higher incidence of bleeding manifestations.[21] This is also consistent with our study findings, in which in the severe Dengue group, both AST and ALT showed statistical significance in predicting the severity of Dengue fever.

In a similar study done by Kalayanarooj S et al., a prospective observational study conducted to identify early indicators of acute dengue virus infection, which included 172 patients, concluded that Plasma AST levels were higher in those who developed Dengue fever with warning signs than in those without warning signs. This is also consistent with our study findings, in which, in the severe Dengue group, AST showed statistical significance in predicting the severity of Dengue fever.[22]

The main limitation of our study was that it was done in a single center; hence, the results may not be generalized. Other limitations include a small sample size and selection bias.

Table 5. Multivariable OR (Odd's Ratio) and 95% CI (Confidence Interval) of dengue fever

Parameters	Dengue without warning signs N(%)			Dengue with warning signs N(%)			Severe Dengue N(%)		
	50 (33.11%)			97 (64.23%)			4 (2.64%)		
	Odd's Ratio	95% CI	P value	Odd's Ratio	95% CI	P value	Odd's Ratio	95% CI	P value
AST	0.98	0.9409 to 1.0207	0.3301	0.9963	0.9912 to 1.0014	0.1573	1.0764	0.0000000432 to 2.683500000	<0.0001
ALT	0.66	0.5544 to 0.7932	<0.0001	1.0098	0.9997 to 1.0199	0.0561	1.0822	4.4356E-178 to 2.640100000	0.0003
Platelets	1	1.0000 to 1.0000	0.2434	1	1.0000 to 1.0000	0.2013	1.0002	0.6362 to 1.5725	0.0002
TLC	1	0.9998 to 1.0002	0.7473	1	0.9999 to 1.0002	0.6164	1.0013	0.0000 to 27773.7243	0.0012
PCV, %	1.03	0.9411 to 1.1338	0.4953	1.0086	0.9592 to 1.0607	0.7373	0.0923	0.9852 to 1.0357	0.0004

CONCLUSION

In our study, elevations in hepatic enzymes—ALT and AST—demonstrated a notable level of accuracy in determining the severity of Dengue fever and in prognosticating it. Plasma AST and ALT levels were higher in individuals who developed severe Dengue as compared to those with no warning signs, suggesting that elevations in hepatic enzymes could be used as an early marker of the severity of Dengue.

DECLARATIONS

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Conflict of Interest
None

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None

Ethical Clearance
It was obtained from IRC of IOM, TUTH [Reference number: {345 (6-11) E2 079/80}]

Consent for Publication
All authors have approved the final version of the manuscript.

Consent of study
Informed consent has been taken from the patients.

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