



PATTERN OF LIVER FUNCTION TESTS IN DIAGNOSED CASES OF DENGUE FEVER

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ABSTRACT

Dengue fever has re-emerged in past few decades with an extensive geographic distribution of the viruses and emergence of dengue hemorrhagic fever is of great concern in new geographic regions. One of the most common abnormalities detected has been a deranged liver function tests (LFTs), especially a raised transaminase level. The aim of the study is to evaluate the LFTs in diagnosed dengue cases and correlate the derangements of test parameters with the severity of disease.

This hospital based cross sectional study carried out in 100 seropositive dengue cases was carried out in National Medical College Teaching Hospital, Birgunj. The proper consent and ethical clearance were taken and study was carried out for 6 months from October, 2022 to March, 2023. Sample from the cases were taken and LFTs were analyzed under the standard guidelines and protocol.

A total of 100 seropositive cases of dengue fever showed raised transaminases as mean ALT 203.64 ± 252.81 U/L and AST 323.72 ± 401.366 U/L. There was a significant association of transaminases with the severity of dengue fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). The mean AST, ALT levels for DSS and DHF were 1118.91 ± 114.25 U/L, 687.73 ± 94.82 U/L and 799.82 ± 152.07 , 510.53 ± 137.10 U/L, respectively. Conclusion: Alterations of liver function test parameters, especially transaminases seen in dengue cases can be applied as a marker of disease severity and can help in assessment and monitoring of dengue complication and disease outcome.

KEYWORDS: Dengue Fever, Liver Function Tests, Transaminases

INTRODUCTION

Dengue fever has re-emerged in past few decades with an wide range geographic distribution of the viruses and emergence of dengue hemorrhagic fever is of great concern.¹ In the past few years, the number of this arboviral epidemics has significantly increased.² With this pattern of increased epidemic transmission, hyper-endemicity have developed in many Asian cities and epidemic dengue hemorrhagic fever (DHF) has also emerged.³⁻⁵ The findings that are characteristics of dengue fever are thrombocytopenia, leukopenia, and elevation of hematocrit values. However, involvement of some atypical manifestations of dengue epidemic have been described, including the pattern of the hepatic tissue with elevations in aminotransferase levels and other parameters of liver function tests (LFTs).⁶

The incidence of dengue has been increasing as shown in the recent data from around the world. Over 25 billion population (405 of the population worldwide) are at the risk of developing dengue. WHO data says that about 50-100 million population may have dengue each year.⁷ Dengue fever has remarkably profound effect on multiple organ system in the body, one of the commonest being the liver. From asymptomatic elevated transaminase levels to acute liver failure (ALF), dengue reflects all the properties of a hepatic illness. The dysfunction in the liver function may be a direct viral insult on liver cells or an adverse effects of the dysregulated host immune response against the virus.⁸

The presentation of severity has a wide range in dengue fever, however, “severe” dengue (Group C) as categorized by World Health Organization (WHO) in 2009 states the dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).⁹ Before going into the liver manifestation, the case definition of dengue fever needs to be summarized. The dengue infection has been traditionally classified into dengue fever (DF), DHF and DSS (WHO 1997 Classification).^{10,11}

DF: Fever and at least two features that includes ocular pain, headache, muscle or joint pains, cutaneous rash, bleeding manifestations and reduced leukocyte count.

DHF: Fever with thrombocytopenia ($\leq 100 \times 10^9/L$), bleeding manifestations and evidence of plasma leakage.

DSS: DHF along with tachycardia or low pulse pressure (< 20 mmHg) or hypotension (systolic blood pressure < 90 mmHg).

As stated in 2009, the modified categorization of WHO, includes dengue with or without warning signs or severe dengue.⁹

Dengue: Fever with two of these presenting features: nausea, vomiting, skin rash, body ache, leukopenia, or any warning sign.

Severe dengue: There is evidence of severe plasma leakage, bleeding and organ impairment. The organ function impairment includes hepatic involvement in form of transaminases elevated beyond 1000 IU/L and also central nervous system manifestations such as alteration in sensorium or cardiac or other organ involvement.

The clinical examination features suggestive of dengue related hepatic involvement are the presence of liver enlargement and elevated transaminases.¹² The features suggesting liver involvement includes abdominal pain (18%-63%), nausea/vomiting (49%-58%) and anorexia.^{13,14} The presenting features such as abdominal pain and anorexia have been found to be significantly more common in DF than DHF. Though hepatomegaly is present in both DF and DHF but its more common in DF.¹⁵ The prevalence of hepatomegaly in the adult dengue patients ranges from 4%-52%.¹⁴⁻¹⁶ Clinically appreciable jaundice has been detected in 1.7%-17% in various series.^{13,15,16} and hyperbilirubinemia has been found to be as high as in 48% of the patients.¹⁴

One of the most common abnormalities detected has been a raised transaminase level. To be more specific regarding it, raised AST levels have been seen in 63%-97% of patients, while raised ALT levels were seen in 45%-96% of patients. In most of the studies, elevation in AST is more than ALT, more during the first week of infection, that tends to decrease to normal levels within three weeks.¹⁷ The AST that is released from damaged myocytes probably explains the higher levels of AST than those of ALT in patients with dengue fever at an earlier stage.¹⁸ Interestingly, mentioning about the De-Ritis ratio, increased AST/ALT ratio can be very much informative for differential diagnosis from acute hepatitis caused by the hepatitis A, B or C viruses where it is rarely observed.¹⁷⁻¹⁹

Thus, going through the facts regarding derangements in the liver function test parameters reflecting the severity of dengue fever with organ involvement, evaluating the function of liver in reference with the liver enzymes, ratio of AST/ALT and of course other parameters will be of great value for clinical assessment, categorization of the dengue fever in respect to severity and projecting the outcome of the dengue fever. Hence the following prospective observational study carried out in 100 dengue positive cases in this locality of Nepal will be more relevant in our setup.

RESEARCH METHODOLOGY:

This hospital based cross-sectional study was carried out in National Medical College, Birgunj, Nepal from October, 2022 to March, 2023 (6 months). A total of 100 seropositive cases (NS1, IgM, IgG, any one or in combinations) diagnosed in out-patient departments and in-patient departments of Internal Medicine and Pediatrics were enrolled in this study. The age group of patients enrolled in the study was between 10 to 60 years. Subjects with renal failure, or history previous liver failure, on anti-tubercular therapy, or psychiatric illness or with the history of chronic illness were excluded from the study. Ethical clearance (Ref. F-NMC/601/079-080) was taken from Institutional review Committee (IRC), National Medical College, Birgunj, Nepal. The proper informed consent was taken with the subjects enrolled in this study.

The samples for LFTs were obtained from the subjects and were analyzed in the Department of Laboratory Medicine under the standard guidelines and protocol. All the parameters for LFTs were analyzed in Beckman Coulter AU480, California automated biochemistry analyzer.

All the data will be entered in the Microsoft Excel 2010, converted to SPSS version 22 accordingly. Frequency and percentage will be calculated for descriptive statistics. Chi square test will be applied to compare the categorical variables. The numerical data will be expressed in the mean and standard deviation or median and interquartile ranges depending on their distribution. Receiver Operating Characteristics (ROC) curve will be plotted for the diagnostic sensitivity and specificity. P value <0.05 will be considered as statistically significant.

RESULTS

The study included 56% of the male subjects (n=56) and 44% of female subjects (n=44) who were serology positive dengue cases (NS1 or, IgM or IgG or in combination). The highest number of participants was from the 30-40 years age group (58%) followed by 40-50 years age group (25%).

Table 1: Descriptive statistics of liver function tests and blood cell counts(n=100)

Variables	N	Mean	Standard Deviation
Age	100	34.89	15.59
TLC	100	7005.60	3552.930
Polymorphs	100	64.75	15.955
Lymphocyte	100	29.34	14.986
Platelet	100	173287.00	78143.565
Total Bilirubin	100	1.9863	1.47606
Direct Bilirubin	100	1.1293	1.37784
Indirect Bilirubin	100	.8570	.31348
ALT	100	203.64	252.810
AST	100	323.72	401.366
Total Protein	100	6.4580	.58691
Albumin	100	3.5585	.40157
ALP	100	207.79	127.689

Among a total of 100 dengue infected subjects, most common presentation was of dengue fever (72%) followed by dengue hemorrhagic fever (17%) and dengue shock syndrome (11%).

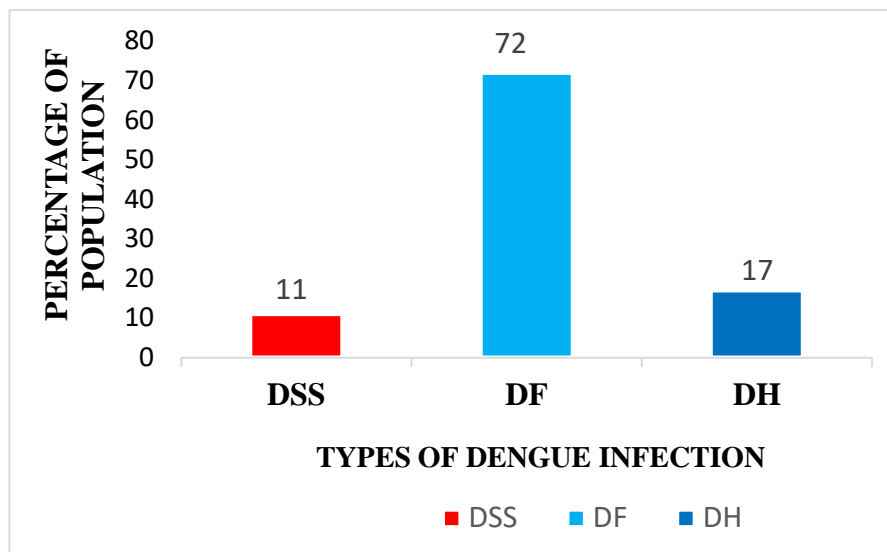


Figure 1: Distribution of the population based on types of dengue infection (n=100)

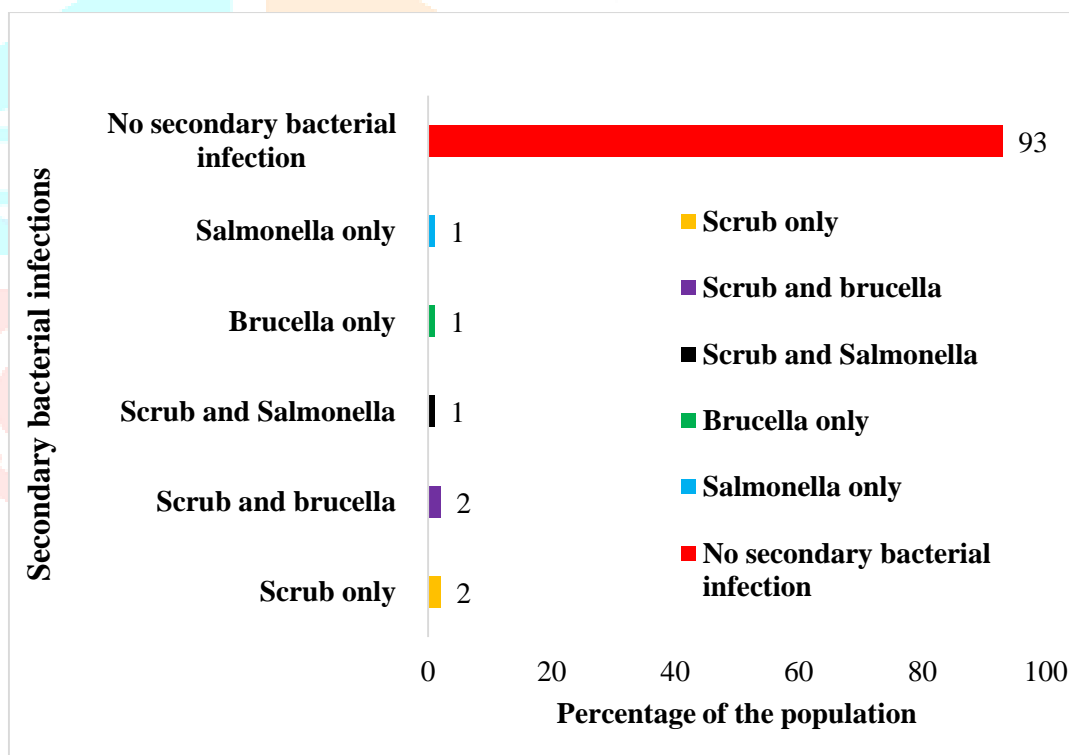


Figure 2: Clustered bar chart representing the co-infection in Dengue infected population (n=100)

The maximum cases were IgM positive (74%) followed by NS1 (47%). Both NS1 and IgM positive cases were 21% of the total.

Table 2: Distribution of population based on Seropositivity (n=100)

Seropositivity	Positive	Negative
NS1	47	53
IgM	74	20
IgG	1	99
NS1 and IgM positive	21	79
NS1, IgM & IgG positive	1	99

The table below shows the mean values of different hematological parameters and LFTs in respect to male and females.

Table 3: Comparison of variables between male and female patients (n=100)

Parameters	Gender	N	Mean	Standard Deviation	P value*
TLC	Female	44	7703.64	4149.170	0.82
	Male	56	6457.14	2926.842	
Neutrophils	Female	44	67.36	16.618	0.14
	Male	56	62.70	15.249	
Lymphocyte	Female	44	27.20	15.586	0.20
	Male	56	31.02	14.415	
Platelets	Female	44	174136.36	75881.668	0.92
	Male	56	172619.64	80553.019	
Total Bilirubin	Female	44	1.9227	1.35620	0.70
	Male	56	2.0363	1.57416	
Direct Bilirubin	Female	44	1.0195	1.22699	0.48
	Male	56	1.2155	1.49097	
Indirect Bilirubin	Female	44	.9032	.31720	0.19
	Male	56	.8207	.30850	
ALT	Female	44	194.50	236.540	0.75
	Male	56	210.82	266.796	
AST	Female	44	303.55	374.726	0.65
	Male	56	339.57	423.800	
Total; Protein	Female	44	6.4145	.61291	0.51
	Male	56	6.4921	.56889	
Albumin	Female	44	3.5666	.44625	0.85
	Male	56	3.5521	.36672	
ALP	Female	44	208.84	128.799	0.94
	Male	56	206.96	127.972	

There was a significant association of transaminases with the severity of Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). The mean AST, ALT levels for DSS and DHF were 1118.91 ± 114.25 U/L, 687.73 ± 94.82 U/L and 799.82 ± 152.07 , 510.53 ± 137.10 U/L, respectively. The level of albumin was also significantly low in the cases of DSS (3.17 ± 0.12 g/dL) and DHF (3.11 ± 0.31 g/dL) as compared to normal level of albumin in DF (3.72 ± 0.71 g/dL). Similarly, the bilirubin levels were significantly deranged in DSS and DHF (4.12 ± 0.83 mg/dL and 3.77 ± 1.50 mg/dL) as compared to that in DF (1.23 ± 0.63 mg/dL).

Table 4: Comparison of liver function test parameters among three groups (n=100)

S. No.	Variables	DSS	DF	DHF	P value (DSS vs DF)	P value (DSS vs DHF)	P value (DF vs DHF)
1	Total bilirubin	4.12 ± 0.83	1.23 ± 0.63	3.77 ± 1.50	0.00	0.54	0.00
2	Direct bilirubin	3.27 ± 0.91	0.42 ± 0.53	2.70 ± 1.39	0.00	0.15	0.00
3	Indirect bilirubin	0.84 ± 0.35	0.81 ± 0.26	1.06 ± 0.40	0.92	0.16	0.00
4	ALT	687.73 ± 94.82	57.22 ± 54.93	510.53 ± 137.10	0.00	0.00	0.00
5	AST	1118.91 ± 114.25	89.82 ± 99.27	799.82 ± 152.07	0.00	0.00	0.00
6	ALP	371.55 ± 101.85	142.11 ± 47.54	380.00 ± 122.52	0.00	0.95	0.00
7	Total protein	5.78 ± 0.21	6.74 ± 0.36	5.69 ± 0.46	0.00	0.99	0.00
8	Albumin	3.17 ± 0.12	3.72 ± 0.71	3.11 ± 0.31	0.00	0.85	0.00

Table 5: Correlation of liver function test parameters with the severity of dengue infection

S. No.	Variables	r value	P value
1	Total bilirubin	0.89	0.37
2	Direct bilirubin	0.5	0.65
3	Indirect bilirubin	0.21	0.02
4	ALT	-0.08	0.93
5	AST	-0.03	0.75
6	ALP	0.16	0.09
7	Total protein	-0.18	0.06
8	Albumin	-0.16	0.10

DISCUSSION

A total of 100 dengue positive cases (56 males and 44 females) were enrolled in our study and the liver function tests with some other investigations like hemogram were done in the samples obtained from them. Among a total of 100 dengue infected subjects, most common presentation was of dengue fever (72%) followed by dengue hemorrhagic fever (17%) and dengue shock syndrome (11%). The study showed the majority of the participants had deranged liver function with higher levels of the transaminases (Mean AST: 323.72 ± 401.366 U/L and ALT: 203.64 ± 252.81 U/L). The AST levels as mentioned above was higher as compared to ALT levels. There was a significant association of transaminases with the severity of Dengue

Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). The mean AST, ALT levels for DSS and DHF were 1118.91 ± 114.25 U/L, 687.73 ± 94.82 U/L and 799.82 ± 152.07 , 510.53 ± 137.10 U/L, respectively.

The results showed the significant association of the parameters of the liver function test in the DSS and DHF. However, majority of the participants (cases of DF) in the study had the mild liver involvement with slightly elevated AST (89.82 ± 99.27 IU/L), ALT (57.22 ± 54.93 IU/L). The level of albumin was also significantly low in the cases of DSS (3.17 ± 0.12 g/dL) and DHF (3.11 ± 0.31 g/dL) as compared to normal level of albumin in DF (3.72 ± 0.71 g/dL). Similarly, the bilirubin levels were significantly deranged in DSS and DHF (4.12 ± 0.83 mg/dL and 3.77 ± 1.50 mg/dL) as compared to that in DF (1.23 ± 0.63 mg/dL). The results showed a strong relation of the disease severity with the derangements in liver function tests. The participants with DSS had the most deranged levels of liver function parameters followed by the DHF. The participants of DF only had a minimal derangement in liver function tests.

A study done in 2012 by Lee et al. showed that elevated AST and ALT occurred in 86% and 46%, respectively with certain participants had AST or ALT ≥ 1000 U/L. The median AST and ALT values were significantly higher with increasing dengue severity by both WHO 1997 and 2009 criteria. The result also mentions that there was significant overlap in AST and ALT values among patients with dengue with or without warning signs and severe dengue, and between those with DF and DHF. The result of this study agrees with the findings of our study.¹¹

Another study done in West Bengal during dengue outbreak in 2012 by Saha et al. in 1226 dengue cases showed that patients with DF were 170 and DHF was 1,056, among which those with ALT ≥ 75 U/L were 43 and 570, respectively. Patients with ALT $> 151-300$, $> 300-450$, and > 450 U/L were 186, 77, and 34, respectively. Affected DF (n=43) and DHF (n=570) patients presented with symptoms and signs similar to viral hepatitis, but ascites, pleural effusion, raised INR, bleeding, and hypoalbuminemia were present only in DHF patients. In dengue fever, there was a wide range of hepatic dysfunction mimicking acute viral hepatitis. The results were also with accordance with our findings.¹⁵

A study by Ghandi et al. reported 89% of the cases had alterations in the aminotransferase levels, with 37% categorized into Grade B, 30% into Grade C, and 22% as Grade D or acute hepatitis ($P < 0.001$). Aspartate aminotransferase (AST) levels were higher compared to the levels of alanine aminotransferase (ALT) (mean: 390.7 U/L and 296.9 U/L, respectively). The results of this study also support and are similar to the findings of our study.²⁰

However, our study has certain limitations such as the smaller sample size. May be due this the exact association of the transaminases with different grades of dengue fever could not have been ascertained. So, a large study with wide analysis of other different variables is necessary to truly establish the associations. But still the study gives a better picture of the liver functions test parameters in relation with the different grades of dengue infection.

CONCLUSION

Dengue fever as an endemic in our surrounding have alterations of liver function test parameters, especially transaminases almost in all the participants. The findings of the liver functions tests can be applied as a marker of disease severity and can help in assessment and monitoring of dengue complication and disease outcome.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

ACKNOWLEDGEMENT

This research was supported by all the faculties and staffs of Department of Biochemistry and Internal Medicine, National Medical College Teaching Hospital, Birgunj, Nepal. We share a heartfelt thanks for all the involved individuals in this study.

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