

# Relationship Between Serum Lactate Dehydrogenase Levels and Dengue Severity

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## Abstract

**Background:** To determine relationship between the levels of serum Lactate Dehydrogenase (LDH) on admission and prognosis of dengue fever.

**Methods:** Patients (n=62) admitted with the diagnosis of dengue fever were included. On admission, serum LDH levels were measured in all patients and to find relationship we monitored all patients upto discharge. Monitoring was done for vitals, different blood parameters and duration of hospitalization.

**Results:** Forty one (66.1%) were males and 33.9% (n=21) were females with mean age 31.73±13years. During hospital stay, 61.3% patients had Dengue fever (DF) while 39.7% patients developed dengue hemorrhagic fever (DHF). LDH levels were higher in patients with DHF (mean 618.38U/L±219) as compared to the patients with dengue fever (mean 316.45U/L±104). Mann Whitney U test showed the difference was statistically significant (p<0.001).

**Conclusion:** Patients with early increase in serum LDH showed more complications as compared to low serum LDH level. High LDH can be used to predict outcome in dengue patients.

**Keywords:** Lactate dehydrogenase, Dengue fever (DF), Dengue hemorrhagic fever (DHF), Dengue shock syndrome (DSS)

## Introduction

Dengue is a vector borne disease epidemic with high morbidity and mortality. This disease is caused by dengue virus having 4 serotypes DENV-1 to 4.<sup>1</sup> It is mainly transmitted to humans by bite of female *Aedes aegypti* and *Aedes albopictus* mosquito but it can also be transmitted through blood transfusion, trans placental route, organ transplantation and needle stick or sharps injuries.<sup>2-6</sup> It is the most prevalent epidemic nowadays, across the world and especially in the Asia. It affects about 50-100 million people per year as per WHO statistics.<sup>7</sup> In Pakistan, first dengue epidemic was reported in 1994.<sup>8</sup> During 2011 dengue outbreak

in Pakistan there were more than 20,000 cases and 300 deaths reported.<sup>9</sup>

Dengue has varied clinical manifestations ranging from mild flu like symptoms, fever, arthralgia, myalgia, mild GI symptoms to potentially fatal complications of vascular leakage. It can be detected in asymptomatic case or may present as undifferentiated fever, Dengue fever (DF), Dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS) and Expanded dengue syndrome (EDS).<sup>10</sup> While DF is a mild, self-limiting disease DHF and DSS may be fatal if not diagnosed and treated timely and appropriately. Dengue passes through three clinical stages; Febrile phase which may last for 2 to 10 days after which patient may enter Recovery phase characterized by resolution of fever and other associated symptoms, or patient may progress into Critical phase marked by resolution of fever and appearance of fluid leakage (10). Most of the complications of dengue occur around the period of defervescence.<sup>11</sup>

Dengue causes micro vascular inflammation throughout the body, as evidenced by the increased markers of inflammation e.g. cytokines, chemokines, VEGF and other angiogenic factors.<sup>12-18</sup> Injury to vascular endothelial cells results from a complex interaction between the circulating proteins of dengue virus and host immune response. Activation of cellular and humoral immune response increases vascular permeability, which may be manifested by ascites, pleural effusion or shock.<sup>19</sup>

Lactate dehydrogenase (LDH) is an intracellular enzyme abundantly found in body tissues e.g. muscles, liver, placenta, RBCs, reticuloendothelial system. Its serum levels increase after cell injury. It has been evaluated as prognostic marker of various inflammatory states e.g. sepsis, infections, MI, malignancies and cardio-pulmonary compromise. It is thought to be a marker of vascular permeability in immune mediated lung injury.<sup>20-24</sup> Serum LDH levels are increased in DF. Various studies show that LDH levels are higher in DHF and DSS patients.<sup>25-28</sup> An early increase in LDH (three times the normal value)

was an independent predictor of DHF. Dengue has very high rate of admission in tertiary care hospitals. Severe dengue requires aggressive monitoring, thus posing a burden on health system. So, the search for the prognostic factors, may help to reduce the rate of hospitalizations, as well as disease mortality and morbidity. This study evaluated the relation of admission serum LDH levels with severity of DF.

### Patients and Methods

This cross sectional comparative study was carried out from 5th September 2016 to 27th November 2016 in the Dengue Inpatient Department of Benazir Bhutto Hospital (BBH), Rawalpindi. We included the patients aged 18 to 80 years, admitted consecutively with probable DF and having positive NS1 antigen and/or dengue IgM. Patients with negative dengue serology, taking anti-platelet medications, having platelet disorder, hemolytic anemia or co morbidities (like IHD, hepatitis due to non-dengue cause, pancreatitis, chronic renal or liver disease) and infections other than dengue were excluded. Patients were managed as per standard guidelines of Dengue expert advisory group (DEAG) and were categorized as DF and DHF(30) as described below. DF was defined as fever of 2-7 days with at least two of the following- headache, retro-orbital pain, arthralgia/bone pain, myalgia, Rash, leucopenia (TLC of less than  $5 \times 10^9$ ), thrombocytopenia (platelets less than 150,000/uL) without any evidence of plasma leakage. DHF was defined as fever with bleeding, thrombocytopenia (platelets less than 100,000/uL) and plasma leakage as indicated by one of the following >20% increase in haematocrit from baseline, >20% decrease in haematocrit after IV fluids or imaging evidence of plasma leakage e.g. ascites, pleural effusion, GB wall thickness or pericholecystic fluid. Serum LDH levels of less than 200 units/ liters were considered normal. Patients were divided into two groups depending upon their disease outcome. Group 1 included the patients who had DF. Whereas, Group 2 consisted of the patients who progressed to DHF. A structured Proforma was developed and used for data collection. Data was analyzed using SPSS 24 version. LDH levels were compared between the two groups by Mann Whitney U test, and chi square test was applied wherever appropriate.

### Results

Sixty-two patients were included in the study. Male were predominant (Table 1). Male to female ratio was 1.94:1 in study population, 1.5:1 in group 1 and 3:1 in group 2. Mean LDH level of the study population was  $433.32 \pm 216$  U/L. LDH levels were quantitatively

higher in group 2 as compared to group (Table 2). Patients were further stratified according to their LDH levels into three categories and compared between the two groups (Table 3).

**Table 1- Demographic profile of the patients.**

	Total n=62	Group 1 61.3%(n=38)	Group 2 38.7%(n=24)	p- value
Mean Age (Years)	31.7 $\pm 13.40$	32.47 $\pm 14.67$	30.54 $\pm 11.30$	0.822
Male No (%)	41(66.1)	23(60.53)	18(75)	0.041
Duration of fever* (Mean $\pm$ SD)	5.21 $\pm 1.92$	5.21 $\pm 1.92$	5.21 $\pm 1.97$	0.997
Duration of hospital stay* (Mean $\pm$ SD)	3.53 $\pm 1.43$	3.6 $\pm 1.41$	3.3 $\pm 1.46$	0.390

\*In days.

**Table 2- Comparison of mean serum LDH levels between the two groups**

Disease Group	LDH levels on admission ( U / L )	p value
Group 1 (Mean $\pm$ SD)	316.45 $\pm$ 104	<0.001
Group 2 (Mean $\pm$ SD)	618.38 $\pm$ 219	

**Table 3: Group wise comparison of LDH categories.**

LDH levels U/L	Disease Group		P value
	Group 1	Group 2	
Less than 200	15.8%(n=6)	0 %	<0.001
200 to 600	73.8%(n=31)	26.2%(n=11)	
More than 600	7.1%(n=1)	92.9%(n=13)	

### Discussion

Many studies show that serum LDH levels are raised in DF but there are very limited studies evaluating it as a prognostic marker in this disease. No study has been found in Pakistan regarding the prognostic role of LDH in dengue. In this study, it was noted that LDH levels are elevated to more than 200 U/L in all of the DHF patients and majority of DF patients. LDH levels at admission were significantly higher in patients who progress to DHF ( $618.38 \pm 219$ U/L) as compared to those with simple DF ( $316.45 \pm 104$ U/L),  $p < 0.001$ . These results are similar to those reported by Sirikutt et al and Villar-Centeno et al although mean levels in this study are lower in each group than reported in above mentioned studies, While Liao B et al reported slightly lower levels in both DF and DHF, 213.68 U/L

and 448.17 U/L respectively.<sup>25,26,29,30</sup> Patients in Group 2 had 3-fold increase in LDH levels. It was noted that although some patient with simple DF had normal values of serum LDH, whereas, none of the patients in group 2 was found to have normal LDH levels. In majority of group 2 patients (92%) LDH levels were more than 600 units/liter, as reported by Ravishankar et al.<sup>31</sup>

In our study, majority of the patients were males (65.3% in group 1 and 75% in group 2), matching those reported in WHO surveillance data and study done by Agarwal et al, the reason for this gender difference is not clearly understood but may be due to the greater exposure of males to mosquitoes due to their outdoor occupational activities.<sup>32-34</sup> We found that males are more likely to develop severe form of the disease as reflected by the differences in gender ratios between the two groups, literature has controversial results about this relation, results of Vicente CR et al(35) favor our finding.<sup>35</sup> Whereas, Villar-Centeno and Rasul CH et al found no gender differences between those developing DHF as compared to those who did not.<sup>29,36</sup>

Mean age of our patients was 31.7 ±13.4 years which was slightly higher than that mentioned by Villar-Centeno(29). Patients in DHF group were relatively younger than DF group but the difference was not statistically significant(p-value 0.82) whereas, previous study reported higher age in patients with severe dengue.<sup>35</sup>

In our study mean duration of illness at the time of presentation was 5.21 days, while duration of hospitalization was 3.53 days, there was no difference between the two groups regarding these parameters with p values of 0.997 and 0.390 respectively. Similar results are reported in previous studies.<sup>29</sup> But this was a small study with a relatively small sample size, carried out on relatively healthy adults without any major co morbidities. Single sample for LDH levels was on average sought on 5th day of fever. Critical Phase in dengue usually extends from 3 to 7 days, seeking LDH levels at this time may have maximum impact. Moreover, this study only included patients admitted in a tertiary care hospital, which mostly represent most severe form of disease. So, further larger prospective studies including the populations missing in this study at earlier stages of disease, are required to test this association.

## Conclusion

1. Serum LDH levels were found elevated in DHF patients. This correlation may be used as a predictor for severity in DF. Elevated levels of LDH on day 5 in dengue fever

point towards the diagnosis of DHF. A cut off value of more than 600 U/L was seen in majority of these patients.

2. Biomarker, like LDH, can lead to the establishment of predictors of dengue severity that is very important to control disease and reduction in morbidity and mortality caused by this disease.

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