

Survival Analysis of Dengue Patients in Relation to Severity of Liver Dysfunction in Pakistan

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Abstract: The study aimed to analyze the survival of dengue patients in relation to liver dysfunction in Pakistan. This study was conducted by taking data from different Government as well as private tertiary care setups in Lahore from September 2010 to December 2010. A total of 60 patients were included in the study. All patients of either gender, admitted for treatment for dengue fever having age 15-69 years were taken. Patients were divided into 3 groups (Mild, moderate or severe liver dysfunction). The mean survival time for patients with mild, moderate and severe liver dysfunction was 66.000 ± 5.477 , 64.398 ± 3.890 and 38.400 ± 7.96 hours in hospital respectively with p -value < 0.01 . A significantly higher survival rate for patients with mild and moderate liver dysfunction was found in this study as compared to severe type of liver dysfunction, i.e. (Log Rank Test) = 13.464 with p -value = 0.001. Conclusively, liver dysfunction is fatal for survival of dengue patients. It is therefore suggested to include identification of liver problem in differential diagnosis of dengue fever. This in future may help in better management of dengue patients and also to cope with this recent endemic in the country.

Key words: Dengue Hemorrhagic Fever • Liver Dysfunction • Kaplan Meier Survival Curve

INTRODUCTION

Dengue is a widespread mosquito-borne infection in human beings, which in recent years has become a major public health concern. Symptomatic dengue virus infections can present with a wide range of clinical manifestations, from a mild febrile illness to a life-threatening shock syndrome. Both viral and host factors are thought to contribute to the manifestations of disease in infected persons [1]. Dengue virus infection is increasingly recognized as one of the world's emerging infectious diseases. About 50-100 million cases of dengue fever and 500,000 cases of Dengue Hemorrhagic Fever (DHF), resulting in around 24,000 deaths, are reported annually [2].

In Pakistan first reported epidemic of dengue fever was in 1994. The epidemics in Sri Lanka and India were associated with multiple dengue virus serotypes. In Asian countries where DHF is endemic, the epidemics have become progressively larger in the last 15 years. In 2005, dengue is the most important mosquito-borne viral disease affecting human [2, 3]. Dengue infection, one of the most important mosquito-transmitted diseases, is prevalent in >100 tropical and subtropical countries [2]. Despite the advancements in public health and clinical medicine, the incidence rate of dengue viral infection is increasing with an annual estimate of 50 to 100 million cases worldwide [4].

The concern of liver damage when patient is infested with dengue viral infection is a quite common and has been reported in literature since 1970 [5, 6]. Acute liver

damage is certainly a worrisome element as it poses life threatening complications like Disseminated Intravascular Coagulation (DIC), hemorrhage and encephalopathy [7]. A number of studies have established the elevation of transaminases and liver dysfunction in dengue patients worldwide [8, 9]. One retrospective review conducted in Thailand reported a percentage of 34.6% for pediatric dengue patients who had liver dysfunction [10]. Literature also shows that in 90% of dengue patients, the Aspartate Aminotransferase (AST) is observed to be higher as compared to the Alanine Aminotransferase (ALT) [11]. Many accompanying conditions as hepatotoxic drugs or attack of dengue virus directly may cause such clinical manifestations which may lead to worse outcomes for dengue patients [8].

Dengue fever has emerged as a cyclical epidemic in Pakistan and despite of mass research work done for diagnosis and management of the disease, very little is known about probability of survival of such patients and relation of liver dysfunction with this infectious disease. We considered this to be the need of hour to assess the survival time of dengue patients, with particular relation to liver dysfunction. We aim to analyze survival rate of patients with dengue having mild, moderate and severe liver dysfunction.

MATERIALS AND METHODS

In this study, longitudinal study design was used to collect the data from different Government as well as private tertiary care setups in Lahore from September 2010 to December 2010. A total of 60 patients were included in the study. All patients admitted for treatment having age 15-69 years of both genders were taken. The diagnosis was made on the basis of Dengue fever scoring system, if a patient had a score of ≥ 6 patient was diagnosed as dengue fever. Patients of known chronic liver disease due to any cause were excluded from the study. Patients with positive HBsAg, IgM to HAV or HEV were also excluded. All patients who had taken any Alternative medication or were on any other known hepatotoxic drug for the last 6 months were also not included. Other diagnostic possibilities were investigated on an individual case to case basis. Informed consent was taken and data was collected. Patients were divided into 3 groups and categorized to have mild, moderate or severe liver dysfunction. Group I included patients who had two folds or lesser increase in liver enzymes (Mild liver dysfunction), in Group II patients LFT were between 2 to 4 fold greater than normal (Moderate liver dysfunction),

Group III patients had LFT's greater than 4 fold or normal (Severe liver dysfunction). The normal range was taken as follows.

Table A. Criteria for severity of liver dysfunction

	<i>Normal</i>	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>
AST	5-40	41-80	81-150	≥ 151
ALT	7-32	33-66	67-132	≥ 133

All data was entered and analyzed by using SPSS version 20. Mean \pm S.E.M (Standard error of mean) was used for all quantitative data like age (Years), duration of fever and LFTs. Frequency (%) was used for qualitative data, like gender, severity of disease and final outcome (Discharged or dead). Survival analysis (Kaplan Meier survival curve with Log Rank Mental Cox was used to see the effects of severity of liver dysfunctions. P-value $\leq 5\%$ was taken as significant.

RESULTS

Out of total 60 recruited patients, 23 (38.3%) patients had mild liver dysfunction among whom 22 (96%) were discharged and 1 (4%) died, 32 (53.3%) presented with moderate liver dysfunction in which 26 (81%) were discharged and 6 (19%) died and remaining 5 (8%) patients were presented with severe type of liver dysfunction and all of them (100%) died during hospital stay. The death rate increased significantly in patients who presented with moderate to severe type of liver dysfunction, p-value = 0.000 (< 0.001). The mean survival time for patients with mild, moderate and sever liver dysfunction was 66.000 ± 5.477 , 64.398 ± 3.890 and 38.400 ± 7.96 respectively, p-value < 0.01 . The median survival time among patients of dengue was reduced significantly with increase of severity of liver dysfunction.

A significantly higher survival rate for patients with mild and moderate liver dysfunction was found in this study as compared to severe type of liver dysfunction, i.e. (Log Rank Mental Cox)= 13.464 with p-value = 0.001.

The Kaplan-Meier survival analysis curve contains total survival time in hours in the period admission to discharge / death of patients during treatment of dengue patients with different grades of liver dysfunction (Mild, moderate and sever). Here in this study our event under consideration was death of patients during hospitalization and censored was considered as patients discharge. Patients with mild liver dysfunction have longer survival time and with severe liver dysfunction has higher mortality in this study i.e. Log rank test (P < 0.001).

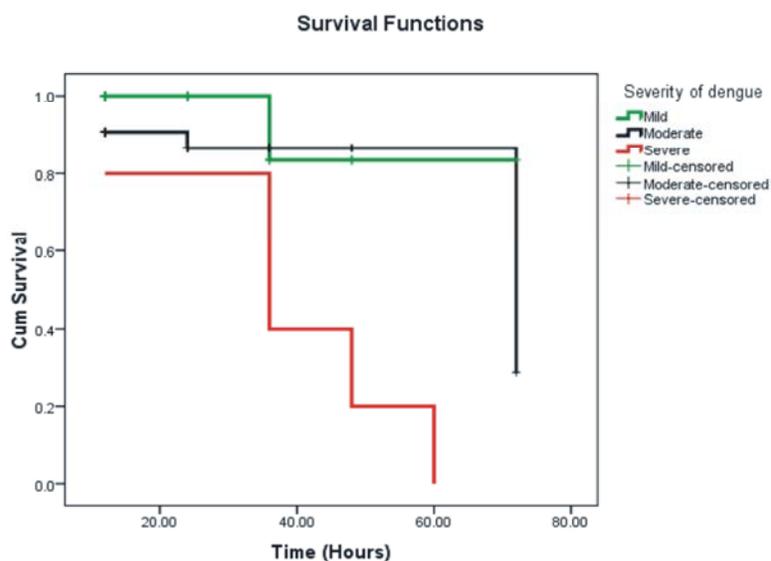


Fig. 1: (Log Rank Mental Cox)= 13.464 with p-value = 0.001

Table 1: Comparison of final outcome and severity of dengue

		Final Outcome		Total	p-value
		Discharged	Dead		
Severity of dengue	Mild	22 (95.7%)	1(4.3%)	23 (100.0%)	0.000
	Moderate	26 (81.2%)	6 (18.8%)	32 (100.0%)	
	Severe	0 (.0%)	5 (100.0%)	5 (100.0%)	
Total	48 (80.0%)	12 (20.0%)	60 (100.0%)		

Table 2: Comparison of survival time with severity of dengue

Means and Medians for Survival Time									
		Mean ^a				Median			
		95% Confidence Interval							
		95% Confidence Interval			95% Confidence Interval				
Severity of dengue	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound	
Mild	66.000	5.477	55.265	76.735	
Moderate	64.398	3.890	56.774	72.021	72.000	19.675	33.437	110.563	
Severe	38.400	7.960	22.799	54.001	36.000	13.145	10.235	61.765	
Overall	59.248	3.634	52.127	66.370	72.000	6.772	58.727	85.273	

a. Estimation is limited to the largest survival time if it is censored.

Table 3: Overall comparison

Overall Comparisons			
	Chi-Square	Df	Sig.
Log Rank (Mantel-Cox)	13.464	2	.001

Test of equality of survival distributions for the different levels of Severity of dengue.

DISCUSSION

Dengue Hemorrhagic fever has been declared as an endemic in South Asia by the World Health Organization (WHO). WHO currently estimates the

annual dengue infection in about 50 million people globally. In 2007 alone, there were more than 890,000 reported cases of dengue in the Americas, of which 26 000 cases were Dengue Hemorrhagic Fever (DHF). [9, 10].

Hence our study aimed to recognize the fact if the severity of liver damage effected the survival of dengue patients. Understanding of this may help to manage and support liver functioning and improve health outcomes among dengue infected patients.

Among total 60 dengue patients included in our study, 38.3% had mild grade of liver dysfunction, whereas 53.3% had moderate level of liver dysfunction and 8% had severe liver dysfunction. Among the dengue patients with mild liver dysfunction, the mortality rate was 4%, in moderate liver dysfunction it was 19% while in severe liver dysfunction the mortality was 100%. The overall mortality rate of dengue patients was 20% in our study. These results were highly compatible with another study conducted in Karachi showing 66.7% mortality in severe hepatitis group compared to 33.3% in mild to moderate hepatitis [7].

In this steed additionally, the mean survival time for patients with mild, moderate and sever liver dysfunction was 66.000 ± 5.477 , 64.398 ± 3.890 and 38.400 ± 7.96 hours respectively, p -value < 0.01 . The median survival time among patients of dengue was reduced significantly with increase of severity of liver dysfunction. Another study in Karachi Pakistan showed the mean time of hospital stay of dengue patients was 87.12 hours with mild/moderate hepatitis and 103.2 hours with severe hepatitis. Contrarily to our study, here the mean time of hospital stay increased with severity of liver problem; however mortality was significantly high in severe liver problem group [7].

The Kaplan-Meier survival analysis curve showed that patients in our study having with mild liver dysfunction have longer survival and with severe liver dysfunction has higher mortality in this study i.e. Log rank test ($P < 0.001$). This too, was supported by another study conducted in Pakistan that showed 60% patients with DHF and having hepatology problem compared to only 40% with DF. They concluded that liver problem aggravates the severity of dengue fever [11].

CONCLUSION

Conclusively, liver disease is an important neglected entity which may be a fatal for dengue patients. It is therefore suggested to include identification of liver problem in differential diagnosis of dengue fever. One attribute of which can evidently be elevated AST compared to ALT. This in future may help in better management of dengue patients and also to cope with this recent endemic in our country.

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