ORIGINAL ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

Liver Transaminases as a Predictor of Dengue Hemorrhagic Fever

Udaya Ralapanawa[1]*, Malinga Gunarathne[1], Sampath Tennakoon[2], A. T. M. Alawaththegama[1]

Abstract

Objective: Elevation of serum liver transaminase is common during dengue infection. A group of dengue patients was studied to determine the relationship between the elevation of liver transaminases in dengue fever (DF) and dengue hemorrhagic fever (DHF). **Methodology:** This study was conducted to assess the predictive value of liver enzymes for DHF. During the dengue epidemic of 2017, all data pertaining to 601 dengue patients were collected in a systematic manner for purposes of conducting an analysis on the predictive value of serum levels of liver transaminase for DHF. Six hundred one patients were categorized into DF and DHF, according to the World Health Organization 2009 Dengue Management Guidelines. The data were collected retrospectively. **Results:** There were significant differences between aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels among DF and DHF patients, not only on day 5 of the critical phase but also during the acute febrile phase. The area under the ROC curve at the acute febrile phase for AST was 0.7, but in ALT, it was 0.6. However, the area under the ROC curve was 0.70, which indicates that AST at the acute febrile phase is a good indicator of the leaking tendency. According to the coordinate points of the curve, leaking can be predicted with a sensitivity of 72% and a specificity of 60% at an AST value of 59.5. **Conclusion:** The AST value of 59.5 at the acute febrile phase can be used to predict DHF. However, patients who have significantly elevated transaminase levels during the acute febrile phase have a higher tendency to develop DHF.

Keywords: Dengue fever, Dengue hemorrhagic fever, Liver transaminase

Asian Pac. J. Health Sci., (2020); DOI: 10.21276/apjhs.2020.7.4.9

Introduction

Dengue fever (DF) is a rapidly spreading disease in tropical and subtropical countries, including Sri Lanka, as it has had a huge impact on public health.[1-4] It is a mosquito-borne RNA viral disease that belongs to the genus of Flavivirus and family of Flaviviridae.[5-7] Various serotypes of the dengue virus are transmitted to humans through the bites of infected Aedes mosquitoes, principally *Aedes aegypti*; others are *Aedes albopictus* and *Aedes polynesiensis*.[5-9] According to the data from the Epidemiology Unit of the Ministry of Health, Sri Lanka, during the first 8 months of the year 2017, 125387 suspected dengue cases have been reported, compared to last year (2016) it is more than twice the amount (55, 150).[1-4]

Dengue is a clinical syndrome which has been mainly classified into symptomatic and asymptomatic disease while the symptomatic disease is classified into undifferentiated fever, DF, dengue hemorrhagic fever (DHF), and expanded dengue syndrome which is very rare.[5,10-14]

During the Dengue epidemic of 2017, our hospital had to manage a large number of dengue patients and this was a huge burden for our country because it required a lot of financial support as well as human resources. Our effort in this study is to identify the DHF patients among dengue patients in the acute febrile phase because they can be given the best care while anticipating DHF and its complications. On the other hand, this will limit the hospital admissions as almost all DF patients can be managed in a home set up like any other febrile viral disease. That will ultimately improve the outcome of DF and DHF patients and thereby reduce the burden on our country.

Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT)

AST is a mitochondrial and cytoplasmic enzyme, while ALT is a cytoplasmic enzyme. AST is found not only in the liver but also in the heart, skeletal muscle, and erythrocytes, whereas the main source of ALT is the liver. Therefore, the rising of AST could be multifactorial and could also be associated with complications of dengue such as acute liver failure, myocarditis, and myositis.[15-17] However, the liver remains the main source of AST and ALT. The involvement of the liver in DF is a commonly observable spectrum condition which varies from the mild elevation of liver transaminases to acute liver failure with or without fatal outcomes. It has been reported that 3 of 270 patients in Taiwan and 5 out of 644 patients in Vietnam had developed liver failure.[17-19] Histological patterns of autopsy specimens of the liver have described that dengue can affect the liver in many ways. Microvesicular steatosis, hepatocellular necrosis, apoptosis induced councilman bodies, inflammatory cell infiltration, Kupffer cell hyperplasia are those.[15,20,21] Dengue associated acute liver failure has a high mortality due to complications such as encephalopathy, severe bleeding, renal failure, and metabolic acidosis.[18,22,23] Patients who entered the leaking phase can go into hypovolemia and shock, causing prolonged hypoxia in hepatocytes. However, without leaking/shock, also liver can be affected by direct virus invasion and dysregulated host immune response.[20,22-36]

[1]Department of Medicine, University of Peradeniya, Sri Lanka, [2]Department of Community Medicine, University of Peradeniya, Sri Lanka

Corresponding Author: Udaya Ralapanawa, Department of Medicine, University of Peradeniya, Sri Lanka. E-mail: udayapralapanawa@yahoo.com

How to cite this article: Ralapanawa U, Gunarathne M, Tennakoon S, Alawaththegama ATM. Liver Transaminases as a Predictor of Dengue Hemorrhagic Fever. Asian Pac. J. Health Sci., 2020; 7(4):35-38

Source of support: Nil

Conflicts of interest: None

Received: 20/06/2020 **Revised:** 25/07/2020 **Accepted:** 28/08/2020

During dengue infection, the elevation of levels of liver transaminase is a common condition. Here, we studied a group of dengue patients who developed DF and DHF to find out the relationship between the degree of elevation of levels of liver transaminase and the severity of the DF to determine whether the occurrence of DHF can be predicted at the acute febrile phase.

Materials and Methods

This study was conducted to assess the predictive value of liver enzymes for DHF. During the Dengue epidemic of 2017, all data pertaining to 601 dengue patients were collected in a systematic manner for purposes of conducting an analysis on the predictive value of serum levels of liver transaminase (AST and ALT) for DHF. For the purpose of the current study, patients were selected following application of inclusion and exclusion criteria; inclusion criteria were all patients presenting with confirmed dengue infection through NS1 antigen test and IgM and IgG antibody tests and exclusion criteria were conditions that would elevate liver transaminases; history of chronic liver cell disease, long-term alcohol usage, pregnancy, and chronic renal disease; and all patients were given only paracetamol within the correct therapeutic level. Furthermore, patients who developed complications of dengue infection such as acute liver failure, myocarditis, and bleeding were also excluded from the analysis. It should be noted that patients who entered DHF were stable as none of them progressed into severe dengue stage like dengue shock syndrome. The subjects were classified into DF and DHF, according to the world health organization Dengue Management Guideline, which was published in 2009.[1] Subjects were included in the study following ethical clearance and written informed consent. Data were collected retrospectively from bed head tickets and through routine investigation reports which were carried out during hospital stay. A datasheet was used to collect data for the variables of AST and ALT.

Data were analyzed using the IDM-SPSS version 16 statistical package. Monovariate analysis was used to describe the study sample. Student's t-test was used to explore differences between mean transaminase levels within the acute phase and the critical phase. A ROC curve was fitted and sensitivity and specificity were calculated of the liver transaminases in predicting progress in to the critical stage.

Results

A total of 601 cases were included in the current analysis. All cases were in the acute febrile phase of dengue illness at the time of recruitment. Approximately 354 ALT tests were carried out and 134 did not progress to DHF, whereas the rest, 220, had progressed to DHF in that total. Mean ALT values for DF and DHF were 57.7 and 86.3, respectively, showing that significantly higher mean ALT value for DHF than DF with the P-value of 0.003. AST tests were carried out for 351 patients showed that 66.5 mean value for 134 DF and 108.9 mean value for 217 DHF patients. P-value of 0.001 showed a significant difference in their mean values as well [Table 1].

ALT and AST tests were repeated on the 5th day of DF and the critical phase of DHF patients. Among 518 ALT samples, 215 DF and 303 DHF patients were there. In that population, mean ALT values for DF and DHF were 74 and 126.3, respectively, resulting in a significant difference in the 0.048 P value. Similarly, 513 samples were collected from 214 DF to 299 DHF patients for AST. There means value for DF was 98.7 and for DHF, it was187.4. A P = 0.036 suggested that a significant difference in their means too. For emphasis, we noticed that there were significant differences between AST and ALT levels among DF and DHF patients, not only on day 5 of the critical phase but also during the acute febrile phase [Table 1].

Table 1: Distribution of AST and ALT values

Phase of illness	*DH/DHF*	*n*	*Mean (U/L)*	*SD*	*SEM*	*P value*
Acute phase						
ALT	DF	134	57.7	53.2	4.6	0.003
	DHF	220	86.3	81.6	5.5	
AST	DF	134	66.5	59.6	5.1	0.001
	DHF	217	108.9	102.1	6.9	
Critical/day >5						
ALT	DF	215	74	82.7	5.6	0.048
	DHF	303	126.3	268.1	15.4	
AST	DF	214	98.7	108.6	7.4	0.036
	DHF	299	187.4	439.2	25.4	

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, DF: Dengue fever, DHF: Dengue hemorrhagic fever, SD: Standard deviation, SEM: Standard error of the mean

ROC curve was drawn for AST and ALT to gain predictive values for DHF at the acute febrile phase. Area under the ROC curve for AST was 0.7, but for ALT, it was 0.6 [Figure 1]. However, the area under the ROC curve was 0.70 which indicates that AST at the acute febrile phase is a good indicator of leaking tendency. According to the coordinate points of the curve at an AST value of 59.5, leaking can be predicted with a sensitivity of 72% and a specificity of 60% [Table 2].

Discussion

Prediction of DHF patients among dengue patients during the acute febrile phase was the purpose of this study. Changes of serum levels of transaminase were used as the variables. Elevation of transaminase levels during dengue infection is due to the involvement of liver, heart, myocytes, etc. It is a common condition for both acute febrile phase and day 5 of the critical phase, but the issue is how transaminase levels are more elevated in DHF patients than DF patients even during the acute febrile phase. That means some hidden pathology is progressing in DHF patients compared to DF patients suggesting that patients who are going to have DHF are pre-decided in the acute febrile phase. Although the exact pathology behind this has not been clearly identified, the exaggeration of dysregulated host immune response and direct virus invasion in DHF patients may be the reasons for this.

During the critical phase, the reason for the elevation of ALT and AST in DHF patients than DF patients is not clearly understood. This cannot be purely due to hypoxia on target organs because all DHF patients were stable in the critical phase, as none of them developed circulatory compromisation. This means that the pathology which had taken place during the acute phase continues.

AST is more accurate than ALT in this context as in both phases, the rise of AST is more prominent than ALT. The result of 59.5 AST value in the acute febrile phase can be used as a predictor of DHF, although this is not significantly higher than its normal range (normal range of AST = 10–40). Reason behind that could be the involvement of other organs such as heart, muscles, brain, kidney, and red blood cells other than the liver.[16,17,37-38] It has been

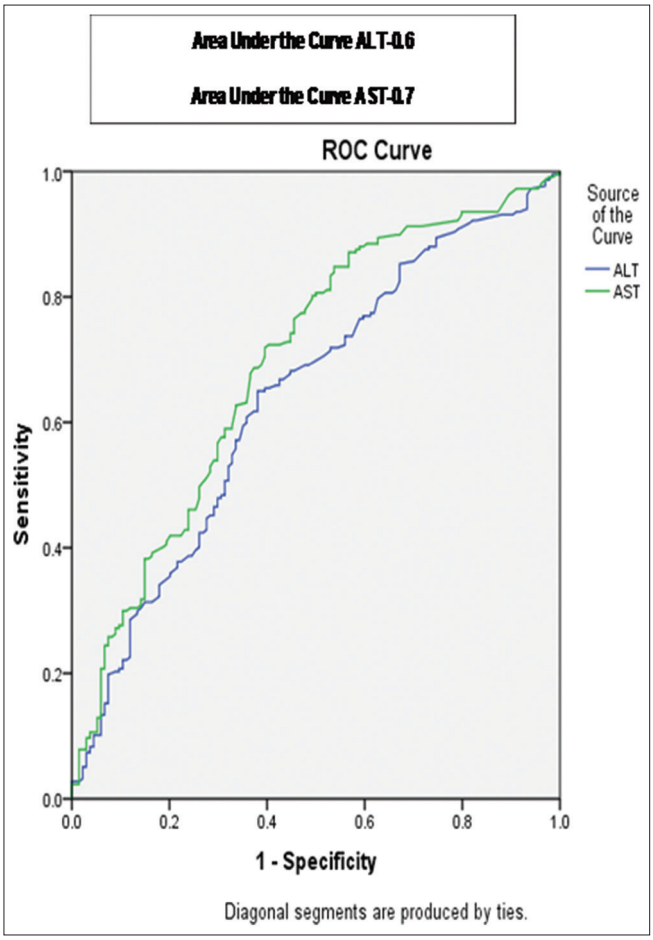

Figure 1: Discriminatory performance of aspartate aminotransferase and alanine aminotransferase

Table 2: Coordinates of the curve

Test result variable	*Positive if greater than or equal to*	*Sensitivity*	*Specificity*
AST	59.5	0.72	0.6

AST: Aspartate aminotransferase

reported that transaminase started to rise during the acute febrile phase and AST peaked on the 6th day of the illness while ALT peaked on the 7th day of the illness. It may also be a reason for AST to elevate more than ALT in our study since AST was more toward its peak than ALT at the time we collected blood samples for AST and ALT (blood samples for AST and ALT during the acute febrile phase and day 5 of critical phase and most patients progressed to the critical phase around day 5 were collected). Similarly, in a study which was carried out in Singapore, it was also observed that elevated liver transaminase levels were associated with DHF, but threshold values were unable to be received to differentiate DF from DHF.[17] Going beyond this study done in Taiwan, it was found that both ALT and AST were independent predictors of DHF.[16,38]

Conclusion

AST remains more sensitive and specific than ALT, reflecting that AST value of 59.5 at the acute febrile phase can be used to predict DHF. However, patients who have significantly elevated transaminase levels at the acute febrile phase have a higher tendency to develop DHF and they need more medical attention than others to overcome the DHF and its complications.

Limitations

Several short comes have been identified in this study. We could not assess the AST and ALT levels at regular intervals in our patients rather than waiting for clinical evidence. We assume that elevated AST and ALT were only from the liver and other causes which could elevate the AST and ALT were excluded only through history. The current study was restricted to only hospitalized patients and conducted in a single hospital. Identification of dengue virus serotype and correlation of liver involvement was not carried out in this study. A strong generalization of the findings may be limited without a multi-center study or a meta-analysis of similar data obtained from two or more regions.

Ethics Approval and Consent to Participate

Ethics approval and consent to participate – ethical approval for the research work has been obtained from the Institutional Ethical Review Committee of the Faculty of Medicine, University of Peradeniya, Sri Lanka.

Consent for Publication

Consent for publication was taken from all the participants before data collection and from all the authors of the study.

Availability of Data and Material

The data of the study are available with the authors of the study and are secured with password protection for which only the authors have access to. The raw datasets supporting this article can be made available by emailing the corresponding author.

Authors' Contributions

UR conceived the research idea and guided it. Data collection and literature review were done by UR, MG, and ATMA. Analysis and interpretation of data were done by ST, UR, and MG. Drafting of the manuscript was done by MG and UR. UR guided the other authors in data analysis, interpretation, and corrected the final manuscript. All authors were involved in the study and read and approved the final manuscript.

Acknowledgments

We all express our gratitude to all participants who consented to take part in this study.

Authors' Information

UR (MBBS, MD, MRCP [UK], FRCP [London], FRCP [Edin]) is Professor in Medicine and Consultant Physician, Department of Medicine, University of Peradeniya, Sri Lanka. MG (MBBS) and ATMA (MBBS) are Temporary Lecturers and Research Assistants, Department of Medicine, University of Peradeniya, Sri Lanka. ST is Professor in Community Medicine, Department of Community Medicine, University of Peradeniya.

References

1. Ministry of Health Sri Lanka. Dengue Update; 2017. Available from: http://www.epid.gov.lk/web/index.php?option=com_content&view=article&id=171%3Adengue-update&catid=51%3Amessage-for-public&Itemid=487&lang=en. [Last accessed on 2017 Nov 09].
2. WHO. Dengue Fever-Sri Lanka; 2017. Available from: http://www.who.int/csr/don/19-july-2017-dengue-sri-lanka/en/%0A%0A. [Last accessed on 2017 Oct 10].
3. Ministry of Health Sri Lanka. DENGUE; 2017. Available from: http://www.dengue.lk. [Last accessed on 2017 Oct 10].
4. Ministry of Health Sri Lanka. National Dengue Control Unit; 2017. Available from: http://www.dengue.health.gov.lk. [Last accessed on 2017 Oct 10].
5. World Health Organization, Regional Office for South-East Asia. Dengue: Guidelines for Diagnosis, Treatment, Prevention, and Control. Geneva: World Health Organization; 2009. p. 147.
6. CDC. Dengue. Available from: https://www.cdc.gov/dengue/index.html. [Last accessed on 2017 Oct 10].
7. Wiwanitkit V. Dengue fever: Diagnosis and treatment. Expert Rev Anti Infect Ther 2010;8:841-5.
8. Jayalath T, Ralapanawa U, Karunaratne S, Dassanayake UK, Pathirage M, Singheprathapa R, *et al*. Knowledge and attitude regarding dengue fever among the outdoor patients of the teaching hospital Peradeniya, Sri Lanka. Int J Med Res Health Sci 2018;7:77-84.
9. Ralapanawa DM, Jayawickreme KP, Ekanayake EM, Jayalath T, Herath D. Fatal massive pulmonary hemorrhage in dengue infection. Epidemiology (Sunnyvale) 2016;6:2161-5.
10. Ministry of Health of Sri Lanka and Ceylon College of Physicians. Guidelines on Management of Dengue Fever and Dengue Haemorrhagic Fever in Adults; 2012. Available from: http://www.epid.gov.lk/web/images/pdf/Publication/guidelines_for_the_management_of_df_and_dhf_in_adults.pdf. [Last accessed on 2017 Feb 23].
11. Kularatne SA, Weerakoon KG, Munasinghe R, Ralapanawa UK, Pathirage M. Trends of fluid requirement in dengue fever and dengue haemorrhagic fever: A single centre experience in Sri Lanka. BMC Res Notes 2015;8:130.
12. Dandeniya CL, Ralapanawa DM, Jayalath WA, Kularatne SA. Atypical manifestations of dengue infection due to co-infection with either hepatitis A or leptospirosis: Two case reports, Sri Lankan. J Infect Dis 2015;5:36-40.
13. Ralapanawa DM, Kularatne SA, Jayalath WA. Guillain-barre syndrome following dengue fever and literature review. BMC Res Notes 2015;8:729.
14. Ralapanawa DM, Kularatne SA. Current management of dengue in adults: A review. IMJM 2015;14:29-42.
15. Ahmed F. Dengue and the liver. SM J Hepat Res Treat 2015;1:1-5.
16. Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. Gastroenterology 2002;123:1367-84.
17. Lee LK, Gan VC, Lee VJ, Tan AS, Leo YS, Lye DC. Clinical relevance and discriminatory value of elevated liver aminotransferase levels for dengue severity. PLoS Negl Trop Dis 2012;6:1-8.
18. Trung DT, Thao LT, Hien TT, Hung NT, Vinh NN, Hien PT, *et al*. Liver involvement associated with dengue infection in adults in Vietnam. Am J Trop Med Hyg 2010;83:774-80.
19. Ageep A. Degree of liver injury in dengue virus infection. J Gen Mol Virol 2012;4:1-5.
20. Samanta J. Dengue and its effects on liver. World J Clin Cases 2015;3:125.
21. Wali JP, Biswas A, Handa R, Aggarwal P, Wig N, Dwivedi SN. Dengue haemorrhagic fever in adults: A prospective study of 110 cases. Trop Doct 1999;29:27-30.
22. Malavige G, Ranatunga P, Jayaratne S, Wijesiriwardana B, Seneviratne S, Karunatilaka D. Dengue viral infections as a cause of encephalopathy YR-2007/4/1. Indian J Med Microbiol 2007;25:143-5.
23. Fernando S, Wijewickrama A, Gomes L, Punchihewa CT, Madusanka SD, Dissanayake H, *et al*. Patterns and causes of liver involvement in acute dengue infection. BMC Infect Dis 2016;16:319.
24. Marianneau P, Steffan AM, Royer C, Drouet MT, Jaeck D, Kirn A, *et al*. Infection of primary cultures of human Kupffer cells by dengue virus: No viral progeny synthesis, but cytokine production is evident. J Virol 1999;73:5201-6.
25. Thongtan T, Panyim S, Smith DR. Apoptosis in dengue virus infected liver cell lines HepG2 and Hep3B. J Med Virol 2004;72:436-44.
26. Póvoa TF, Oliveira ER, Basílio-de-Oliveira CA, Nuovo GJ, Chagas VL, Salomão NG, *et al*. Peripheral organs of dengue fatal cases present strong pro-inflammatory response with participation of IFN-gamma-, TNF-alphaand RANTES-producing cells. PLoS One 2016;11:e0168973.
27. Couvelard A, Marianneau P, Bedel C, Drouet MT, Vachon F, Henin D, *et al*. Report of a fatal case of dengue infection with hepatitis: Demonstration of dengue antigens in hepatocytes and liver apoptosis. Hum Pathol 1999;30:1106-10.
28. Smith DR, Khakpoor A. Involvement of the liver in dengue infections. Dengue Bull 2009;33:75-86.
29. Balsitis SJ, Coloma J, Castro G, Alava A, Flores D, McKerrow JH, *et al*. Tropism of dengue virus in mice and humans defined by viral nonstructural protein 3-specific immunostaining. Am J Trop Med Hyg 2009;80:416-24.
30. Basilio-de-Oliveira CA, Aguiar GR, Baldanza MS, Barth OM, Eyer-Silva WA, Paes M V. Pathologic study of a fatal case of dengue-3 virus infection in Rio de Janeiro, Brazil. Braz J Infect Dis 2005;9:341-7.
31. Huerre MR, Lan NT, Marianneau P, Hue NB, Khun H, Hung NT, *et al*. Liver histopathology and biological correlates in five cases of fatal dengue fever in Vietnamese children. Virchows Arch 2001;438:107-15.
32. Suksanpaisan L, Susantad T, Smith DR. Characterization of dengue virus entry into HepG2 cells. J Biomed Sci 2009;16:17.
33. El-Bacha T, Midlej V, da Silva AP, da Costa LS, Benchimol M, Galina A, *et al*. Mitochondrial and bioenergetic dysfunction in human hepatic cells infected with dengue 2 virus. Biochim Biophys Acta 2007;1772:1158-66.
34. de Oliveira França RF, Zucoloto S, da Fonseca BA. A BALB/c mouse model shows that liver involvement in dengue disease is immune-mediated. Exp Mol Pathol 2010;89:321-6.
35. Chaturvedi UC, Elbishbishi EA, Agarwal R, Raghupathy R, Nagar R, Tandon R, *et al*. Sequential production of cytokines by dengue virus-infected human peripheral blood leukocyte cultures. J Med Virol 1999;59:335-40.
36. Guabiraba R, Besnard AG, Marques RE, Maillet I, Fagundes CT, Conceicao TM, *et al*. IL-22 modulates IL-17A production and controls inflammation and tissue damage in experimental dengue infection. Eur J Immunol 2013;43:1529-44.
37. De Souza LJ, Alves JG, Nogueira RM, Neto CG, Bastos DA, Siqueira EW, *et al*. Aminotransferase changes and acute hepatitis in patients with dengue fever: Analysis of 1,585 cases. Braz J Infect Dis 2004;8:156-63.
38. Lee MS, Hwang KP, Chen TC, Lu PL, Chen TP. Clinical characteristics of dengue and dengue hemorrhagic fever in a medical center of southern Taiwan during the 2002 epidemic. J Microbiol Immunol Infect 2006;39:121-9.