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ORIGINAL ARTICLE

ELEVATED LIVER ENZYMES IN DENGUE FEVER: IMPLICATIONS FOR DISEASE SEVERITY

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ABSTRACT

Background: The spectrum of liver dysfunction in dengue fever varies widely. It is important to gain a comprehensive understanding of liver involvement in dengue fever, focusing on the temporal progression of hepatic function abnormalities. The objectives of this study were to analyze the pattern of liver enzyme abnormalities in patients with dengue fever and its association with the severity of the disease.

Materials and Methods: This descriptive study was conducted at Hayatabad Medical Complex, Peshawar. A total of 180 patients diagnosed with dengue fever were included. Liver enzymes were measured. R-value was calculated using the equation R = ALT/ULN) ÷ (ALP/ULN). The severity of the disease, as measured by a decline in the Glasgow Coma Scale (GCS) or spontaneous bleeding, was correlated with the R factor. IBM SPSS version 24 was used for the statistical analysis.

Results: The mean age of the patients was 37.23±10.433 years. The number of male participants were 134 (74.4%). Mean ±S.D (Standard deviation) for bilirubin and ALT (alanine transaminase) was 1.21 ±0.582mg/dl, 126.98 ±67.88IU/L respectively. The mean R value was 4.01 ±1.43. Severe disease was observed in 79 patients (43.9%). The odds ratio for R-factor (value >4.3) and the likelihood of severe disease was 11.0 (95% CI 5.5-22.3).

Conclusion: Transaminitis and hypoalbuminemia are biochemical markers of severe dengue disease that may be used to detect and monitor hepatic failure. An R-factor value of more than 4.3 increases the likelihood of severe disease.

KEY WORDS: Dengue Fever; Disease Severity; Liver Injury; Transaminitis; Hypoalbuminemia.

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INTRODUCTION

The prevalence of dengue virus infection poses a significant public health issue in regions characterized by tropical and subtropical temperatures worldwide. Dengue fever has a high prevalence in almost all states in India, serving as the predominant factor leading to hospitalization.[1] Historically, the condition's prevalence was mostly seen in urban areas; however, contemporary evidence suggests its emergence in peri-urban and rural settings as well.[2] According to a study published by the World Health Organization (WHO), 26,000 cases of dengue fever were documented during the first three quarters of the previous year, resulting in 56 fatalities. The anticipated figures of the reports are projected to be higher due to the under-reporting prevalent in remote rural regions. Consequently, the extent of the dengue sickness burden in Pakistan may be significantly underestimated.[3]

The occurrence of liver parenchymal damage leading to subsequent disruptions and abnormalities in liver enzyme levels and functions has been extensively documented in the literature.[4] The spectrum of liver dysfunction may vary from mild impairment characterized by increased levels of transaminases to severe hepatocyte destruction resulting in the manifestation of jaundice. The prevalence of liver dysfunction reported in patients with dengue fever is 67%.[5] Hepatic damage arises from a combination of direct hepatotoxicity and an aberrant host immune response to the viral infection. While instances of fulminant hepatic failure have occurred sporadically,

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transaminase derangements are often reversible and may indicate the severity of the illness.[6] Gaining a comprehensive understanding of the processes behind liver involvement in dengue fever, specifically focusing on the temporal progression of hepatic function abnormalities, is of utmost importance. This research aimed to examine alterations in hepatic enzymes during the illness and evaluate the extent of disease severity in relation to the liver damage pattern. An endeavor was made to address this information gap by executing a research study within our community.

MATERIALS AND METHODS

Study design and settings: This descriptive study was conducted at the departments of Gastroenterology and Medicine at Hayatabad Medical Complex, Peshawar, between June 2021 and September 2022.

Sampling: Male and female patients with dengue fever aging more than 18 years were enrolled. Dengue fever was diagnosed based on clinical symptoms comprising of fever, aches/pains, and gastrointestinal upsets and confirmed by the positive dengue serology or dengue virus antigen detection (NS1). Patients with chronic liver disease, malarial parasite positive, blood dyscrasias, and patients with a previous history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis were excluded from the study. The study was carried out after receiving permission from the institution's ethical committee and in compliance with the established guidelines.

Sample size and Technique: The number of participants registered were 180. The sample size was calculated using the WHO sample size formula, taking the prevalence of liver dysfunction as 67% with 7% margin of error and confidence level of 95%. The participants were recruited using a non-probability consecutive sampling technique.

Data collection procedure: The participants were grouped into dengue fever with or without severe disease. The severity of the disease was based on derangement of the GCS level and spontaneous bleeding. GCS below 13 and bleeding from any site of the body, including rectal bleeding, epistaxis, hematuria, or spontaneous bruises over the body, were considered clinically significant for labeling severe dengue fever. The patient's demographic information (age, gender, BMI), the severity of dengue, presenting symptoms, clinical signs, and laboratory parameters such as complete blood count, bilirubin, and liver enzymes, including ALT and ALP levels, were recorded. Liver injury was determined by calculating the R-value using the equation: R = [patient ALT/ULN ALT ÷ patient ALP/ULN ALP].

Data analysis procedure: Data was recorded on an Excel spreadsheet and analyzed using IBM SPSS version 24. Continuous data was presented as mean ± SD, while categorical data was presented as frequencies and percentages. The means of continuous data were compared using the student T-test. Categorical variables were compared using the chi-square test. The cut-off for the R-factor was determined using ROC curve analysis. The sensitivity and specificity of the R-factor were determined for predicting the severity of the disease. The severity of the disease was correlated with the R-factor using the Pearson chi-square test of significance, and the p-value was determined. The odds ratio and Cramer v values were determined to assess the association's strength. The cut-off for statistical significance was set at ≤0.05.

RESULTS

Total number of participant were 180, 134 were male and 46 were female. As illustrated in table 1, the mean value for age was 37.23 years, with a standard deviation (SD) of 10.43. The mean ±SD value for BMI and bilirubin was 24.99±1.82 kg/m^2 and 1.21±0.582 mg/dl respectively while the mean ±SD value for R-factor was 4.01±1.43 with minimum and maximum values of 1.19 and 6.73 respectively.

The number of male patients was 134 (74.4%). Fever with aches and pains were the most commonly reported complaints, recorded in 73 participants (40.6%), followed by gastrointestinal upsets (31, 17.2%), and a combination of these complaints was found in 76 patients (42.2%). Severe disease was recorded in 43.9% of patients (n = 79), while the remaining 101 participants (56.1%) had dengue fever of non-severe nature.

Table 1. Baseline demographics and laboratory parameters (n = 180)

Variable	Minimum	Maximum	Mean±Sd	Skewness
Age (years)	19	62	37.23±10.433	0.315
BMI (kg/m2)	20.0	31.1	24.99±1.82	0.562
Platelet count (x103)	29	137	84.06±31.66	-0.037
Bilirubin (mg/dl)	0.5	2.8	1.21±0.582	0.101
ALT (IU/L)	29	321	126.98±67.88	0.586
ALP (IU/L)	62	167	105.38±62.32	0.284
Albumin (gm/dl)	2.70	4.30	3.53±0.39	-0.217
R factor	1.19	6.73	4.01±1.43	-0.352

Figure 1. Frequency and percentage of patients according to disease severity (n = 180)

Table 2 compares the baseline and laboratory characteristics of patients with and without shock. The mean ±SD ALT for non-severe versus severe disease was 80.910 ±33.403 IU/L versus 185.898 ± 53.664 IU/L. Similarly, the mean ±SD for ALP in non-severe disease was 84.485 ±11.852 IU/L as compared to 132.101 ±15.644 IU/L.

To test the probability of R-value for predicting the severity of disease, ROC (Receiver Operating Characteristic Curve) was generated, as displayed in Figure 2. The curve was entirely above the reference diagonal; hence, the test was interpretable. The value for the area under the curve was 0.815. Taking the cut-off for the R-value as 4.33, the values for sensitivity and 1-specificity in the coordinates of the curve were 0.785 and 0.198, respectively, which led to sensitivity and specificity of 78.5% and 80.2%, respectively.

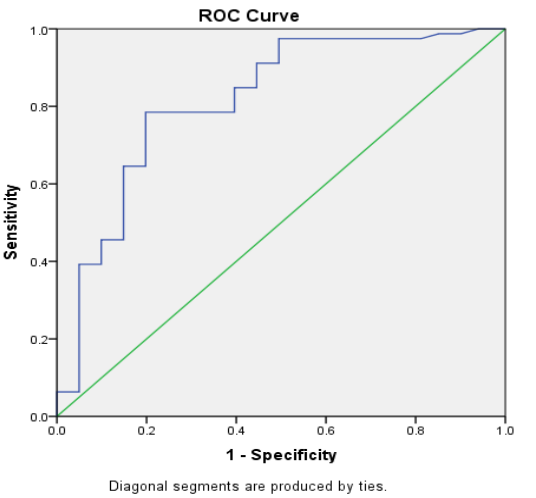

Figure 2. ROC curve for R-value

Table 2. Comparison of demographics and laboratory parameters of patients based on disease severity (n = 180)

Severity	Parameters	Minimum	Maximum	Mean	SD
Without shock/non-severe (n = 101)	Age (years)	19	62	37.53	11.286
	BMI (kg/m^2)	20.00	31.00	25.1614	2.05251
	Platelet (x10^3)	80	137	106.86	18.129
	Bilirubin (mg/dl)	0.5	1.1	0.808	0.1626
	ALT (IU/L)	29.00	132.00	80.9109	33.40302
	ALP (IU/L)	62.00	102.00	84.4851	11.85210
	Albumin (gm/dl)	3.10	4.30	3.7970	.24185
	R value	1.19	6.48	3.3681	1.38025
Shock/ severe (n = 79)	Age (years)	21	59	36.84	9.285
	BMI (kg/m^2)	23.00	28.00	24.7810	1.45664
	Platelet (x10^3)	29	123	54.91	18.588
	Bilirubin (mg/dl)	0.5	2.8	1.737	0.5087
	ALT (IU/L)	29.00	321.00	185.8987	53.66434
	ALP (IU/L)	76.00	167.00	132.1013	15.64477
	Albumin (gm/dl)	2.70	4.00	3.1867	.25162
	R value	1.24	6.73	4.8399	1.02780

Table 3. Contingency table analysis and odds ratio for association between R factor and disease severity (n = 180)

		Severity		Total	Chi square p value	Cramer V value	Odds ratio (95%ci ub-lb)
		Without shock/ non-severe	Shock/ severe				
R factor	4.3 or below	76	17	93	<0.001	0.534	11.0 (5.5-22.3)
		81.7%	18.3%	100.0%			
	More than 4.3	25	62	87			
		28.7%	71.3%	100.0%			
Total		101	79	180			
		56.1%	43.9%	100.0%			

Contingency table analysis was used to assess the association between the R-factor and severity using chi-square test which yielded p-value of <0.001, which is less than 0.05. Hence, the assumption that there is a significant association between severity and R-factor is satisfied. The strength of association was positive and moderately with an odds ratio of 11.0 as shown in table 3.

DISCUSSION

The mean age of patients in our study was 37.23 years. Our study participants' mean age was slightly higher than the South Indian study by Gandhi and colleagues, who reported that the mean age was 34.30 years.[7] The slight variation in the findings may be attributed to the small sample size of 27 patients in the later study. Additionally, the number of male participants in our study was 134 (74.4%) with male to female ratio of 2.9: 1. Male participants were in higher proportion in our study as compared to the results of Swamy et al.[8] Agarwal and colleagues and Ray et al. also reported lower proportion of male participants compared to our study.[9, 10] This difference may be attributed to socio-cultural reasons where female patients tend to seek medical care at local health facilities than travelling to distant tertiary care centers.

The percentages of patients in our study with severe and without severe disease were (43.9%) (n = 79) and 56.1% (n=101), respectively. In our study, severe disease was observed in a higher percentage of patients (43.9 %) compared to the Swamy et al. study where severe disease was observed in 35.0%.[8] The authors classified the patients with warning signs into a separate category, which could have led to a lower proportion of patients with severe disease as opposed to our study, where all patients with alarming clinical or laboratory features were placed in the group of patients with severe disease.

The postulated mechanism for liver damage in dengue infection involves the mediation of cytokines. It has been shown that elevated levels of inflammatory markers are associated with increased liver transaminase levels in children affected by dengue.[10,11] Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are recognized as biomarkers of hepatocellular injury.[12] In our study, patients with more severe diseases were more likely to have elevated transaminases than other enzymes, such as alkaline phosphatase. In our study, patients with severe dengue had lower serum albumin levels. Additionally, severe dengue patients had significantly lower levels of albumin. Bandyopadhyay D et al. have arrived at comparable findings.[13] The studies conducted by Tinambunan et al. and Soni et al. have shown that patients with severe dengue fever have significantly higher levels of liver enzymes and usually have prolonged hospitalization duration.[14, 15] Therefore, the transaminase increase indicates a more advanced stage of the illness.

In our study, an evaluation was conducted to examine the alterations in alakaline phosphatase (ALP), serum bilirubin, and serum albumin concentrations. Notably, a subset of patients had elevated levels of ALP or serum bilirubin but without beyond a certain threshold. This observation implies the presence of mild cholestasis.[11] The occurrence of oxidative stress has been shown in cases of dengue infections, which has been found to be associated with the severity of the disease and alteration in liver enzymes.[12]

CONCLUSION

Liver injury is one of the common complications observed in patients with dengue fever, evident by increased levels of transaminases. The levels of transaminases exhibit an upward trend in conjunction with the severity of dengue infection. This is evidenced by a rise in R- factor, as these transaminase levels are directly correlated with disease severity. The levels of transaminases were found to be higher than those of alkaline phosphatases in individuals with severe dengue fever as compared to non-severe dengue fever. These biochemical indicators, elevated transaminase levels, and hypoalbuminemia, should be used to detect and monitor hepatic dysfunction in patients with dengue.

REFERENCES

1. Kalluru PKR, Mamilla M, Valisekka SS, Mandyam S, Calderon Martinez E, Posani S, et al. Aminotransferases in Relation to the Severity of Dengue: A Systematic Review. Cureus 2023;15(5):e39436. https://doi.org/10.7759/cureus.39436
2. Senaratne T, Carr J, Noordeen F. Elevation in liver enzymes is associated with increased IL-2 and predicts severe outcomes in clinically apparent dengue virus infection. Cytokine 2016; 83:182-8. https://doi.org/10.1016/j.cyto.2016.04.010
3. Khan U, Azeem S. The rising toll of dengue cases in Pakistan every year: An incipient crisis. Ann Med Surg 2022;76:103549. https://doi.org/10.1016/j.amsu.2022.103549
4. Suleman M, Faryal R, Alam MM, Zaidi SSZ. Demographic characteristics of dengue virus outbreaks in Khyber Pakhtunkhwa province, Pakistan during 2003-2015. J Formosan Med Assoc 2017;116(9):727-9. https://doi.org/10.1016/j.jfma.2017.02.004
5. Mohamud MA, Qazi U, Latif A, Khan IU, Anwar S. Dengue Outbreak Response and Control in Khyber Pakhtunkhwa, Pakistan: A Mixed Methods Study. J Epidemiol Glob Health 2020;10(1):74-81. https://doi.org/10.2991/jegh.k.191125.001
6. Khan J, Adil M, Wang G, Tsheten T, Zhang D, Pan W, et al. A cross-sectional study to assess the epidemiological situation and associated risk factors of dengue fever; knowledge, attitudes, and practices about dengue prevention in Khyber Pakhtunkhwa Province, Pakistan. Front Public Health 2022;10:923277. https://doi.org/10.3389/fpubh.2022.923277
7. Gandhi K, Shetty M. Profile of liver function test in patients with dengue infection in South India. Med J DY Patil Univ 2013;6:370-2. https://doi.org/10.4103/0975-2870.118269
8. Swamy AM, Mahesh PY, Rajashekar ST. Liver function in dengue and its correlation with disease severity: a retrospective cross-sectional observational study in a tertiary care center in Coastal India. Pan Afr Med J 2021;40:261. https://doi.org/10.11604/pamj.2021.40.261.29795
9. Agarwal R, Kapoor S, Nagar R, Misra A, Tandon R, Mathur A, et al. A clinical study of the patients with dengue hemorrhagic fever during the epidemic of 1996 at Lucknow, India. Southeast Asian J Trop Med Public Health 1999;30(4):735-40.
10. Ray G, Kumar V, Kapoor AK, Dutta AK, Batra S. Status of antioxidants and other biochemical abnormalities in children with dengue fever. J Trop Pediatr 1999;45(1):4-7. https://doi.org/10.1093/tropej/45.1.4
11. Shah PS, Alagarasu K, Karad S, Deoshatwar A, Jadhav SM, Raut T, et al. Seroprevalence and incidence of primary dengue infections among children in a rural region of Maharashtra, Western India. BMC Infect Dis 2019;19(1):296. https://doi.org/10.1186/s12879-019-3937-z
12. Samanta J, Sharma V. Dengue and its effects on liver. World J Clin Cases 2015;3(2):125-31. https://doi.org/10.12998/wjcc.v3.i2.125
13. Bandyopadhyay D, Chattaraj S, Hajra A, Mukhopadhyay S, Ganesan V. A Study on Spectrum of Hepatobiliary Dysfunctions and Pattern of Liver Involvement in Dengue Infection. J Clin Diagn Res 2016;10(5):Oc21-6. https://doi.org/10.7860/JCDR/2016/16946.7784
14. Tinambunan E, Katu S, Halim R, Mubin A, editors. Correlation between hematologic profile and transaminase enzymes with hospitalization duration dengue. IOP Conference Series: Earth Environ Sci 2018;125(1):012068. https://doi.org/10.1088/1755-1315/125/1/012068
15. Soni A, Patel P, Malhi N, Avasthi G. Spectrum of liver dysfunction in patients with dengue infection and the markers of severe disease: study from a tertiary care centre in Punjab. J Liver Res Disord Ther 2017;3(4):95-8. https://doi.org/10.15406/jlrdt.2017.03.00063

CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	WA, MY
Acquisition, Analysis or Interpretation of Data:	WA, MY, MK, MS, MA, SR
Manuscript Writing & Approval:	WA, MY, MK, MS, MA, SR

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.