Open Access

Original Article

Severity of Acute Hepatitis and Its Outcome in Patients with Dengue Fever in Tertiary Care Hospital Rawalpindi

Usama Zahid, Shazia Nisar, Salman Saleem, Abdul Rehman Azeem, Maira Aleem, Muhammad Arif Sadiq*

Department of Medicine, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan,
*Department of Hematology, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To determine the severity and outcome of acute hepatitis in dengue patients.
Study Design: Comparative cross-sectional study.
Place and Duration of Study: Pak-Emirates Military Hospital, Rawalpindi Pakistan, from Dec 2022 to Oct 2023.
Methodology: The study included 215 confirmed cases of dengue infection. Data included demographic details day of illness, clinical findings, laboratory parameters, duration of hospital stay, and mortality at the 20th day. Patients experiencing dengue complications such as bleeding and shock were monitored. We divided patients into two groups based on ALT levels: mild to moderate hepatitis with ALT levels up to 299 IU/L and severe hepatitis with ALT levels greater than 300 IU/.
Results: A total of 215 patients with dengue fever were included in this study, out of which 184(83% were male) and 31(14% were female). Out of the total sample size, 181(86%) of patients had dengue fever, 75(33%) had dengue hemorrhagic fever, and 13(6%) had dengue shock syndrome. The study showed statistically significant differences in terms of bleeding in patients with mild/moderate hepatitis (median=109.50) and severe hepatitis (median=55.92), Z=2.52, p=0.012, r=0.174.
Conclusion: This study concluded that severe hepatitis in dengue patients was associated with higher rates of dengue hemorrhagic fever and dengue shock syndrome. Severe hepatitis was also associated with decreased levels of platelets and higher rates of dengue complications like ascites and pleural effusion. It was also associated with a longer hospital stay.

Keywords: Computed tomography severity score, Dengue Fever, Dengue shock syndrome, Hepatitis.

How to Cite This Article: *Zahid U, Nisar S, Saleem S, Azeem AR, Aleem M, Sadiq MA. Severity of Acute Hepatitis and Its Outcome in Patients with Dengue Fever in Tertiary Care Hospital Rawalpindi. Pak Armed Forces Med J 2024; 74(3): 849-852. DOI: https://doi.org/10.51253/pafmj.v74i3.12007*

INTRODUCTION

Dengue fever is a mosquito-borne viral infection that is prevalent in tropical and subtropical regions of the world. It is a significant public health concern, with an estimated 390 million dengue infections occurring annually worldwide.[1] It may result in four phases of illness, which include an asymptomatic phase, acute febrile illness, also known as dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS).[2] Dengue viral infection has been recognised as one of the world's biggest emerging epidemics.[3] Most of these cases are reported from South Asian areas, which provide the most suitable environment for their nourishment and breeding. In Pakistan, many outbreaks have been reported in 2005, 2010, 2017, 2019, 2020, and 2022.[4]

Dengue is a preventable disease with timely public health and sanitary measures. The use of mosquito nets and repellants is a useful strategy .[5] Once a person has acquired dengue fever, timely recognition, treatment, and disease monitoring help with a good prognosis. But in the absence of comprehensive and timely management, dengue fever is associated with a poor prognosis .[6] Complications of dengue fever include haemorrhage, third-space fluid loss leading to shock, and multi-organ involvement, including gastrointestinal, hepatic, renal, central nervous system, and cardiac dysfunction. Liver involvement is manifested by deranged aminotransferases; CNS involvement includes encephalopathy; and cardiac manifestations include pancarditis [7]. Liver damage is caused by a variety of factors, predominantly viral proteins, hepatotoxic drugs (paracetamol), and pre-existing conditions. This leads to much more lethal outcomes in patients with DF .[8]

Liver involvement in dengue fever is a common complication, including elevated aminotransaminase levels (ALT and AST). This is due to the liver parenchymal injury secondary to ongoing inflammation and infection. Many studies around the globe have documented hepatic involvement in

Correspondence: Dr Usama Zahid, Department of Medicine, Pak Emirates Military Hospital, Rawalpindi Pakistan
Received: 03 Apr 2024, revision received: 31 Mar 2024; accepted: 30 May 2024

dengue patients. Data from epidemics in Brazil found that AST levels were higher than AST levels in dengue patients.[9] Another study from Pakistan looked into the relationship between liver injury and hospital stay and mortality, showing that hepatic injury was associated with a longer hospital stay and increased mortality.[10]. Since dengue fever has become a prominent illness in Pakistan over the past few decades, there is a lack of published data regarding the spectrum of acute hepatitis among dengue patients. Therefore, our objective is to assess the spectrum of severity, morbidity, and mortality in patients with dengue fever.

METHODOLOGY

The comparative cross-sectional study was conducted at Pak Emirates Military Hospital, Rawalpindi Pakistan, from December 2022 to July 2023, after approval from Ethical and Review Board Committee (letter number A/28/EC/567/2024). The sample size was calculated using the WHO sample size calculator, with a reported prevalence of liver dysfunction in dengue patients of 35%.[11]

Inclusion Criteria: The study included patients of either gender, aged greater than 12 years, with a history of acute fever and a confirmed Dengue Nuclear Spike Protein-1 antibody positive test.

Exclusion Criteria: All patients with pyrexia of unknown aetiology or any other cause of febrile illness, unwillingness, or Dengue NS-1 negative were excluded.

A total of 670 suspected dengue patients were evaluated in the emergency and outdoor patient departments. In the study, there were 215 confirmed cases of dengue infection admitted to the dengue ward. Data was collected by conducting one-on-one interviews with the participants in accordance with a structured questionnaire. The participants were counselled in detail, and their verbal consent was sought.

Data included demographic details (age, gender, co-morbidities), day of illness, clinical findings, laboratory parameters, and duration of hospital stay. On the 20th day, mortality was also recorded. Patients experiencing dengue complications such as bleeding and shock were monitored. Laboratory parameters recorded were alanine aminotransferase, serum creatinine, and platelet counts. We divided patients into two groups based on ALT levels: mild to moderate hepatitis with ALT levels up to 299 IU/L, and severe acute hepatitis with ALT levels greater than 300 IU/L. Patients were also classified into groups of dengue fever, dengue hemorrhagic fever, and dengue shock syndrome.[12]

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 23.0. Continuous variables were computed as the mean, standard deviation, and median interquartile range. Categorical variables were represented as frequency and percentages. The normality of the data was assessed through the Kolmogorov-Smirnov test. Variables like age, duration of hospital stay, platelet levels, and ALT levels were found to not be normally distributed. Mann-Whitney A U test was conducted to compare platelet counts, bleeding rates, and ALT levels between mild, moderate, and severe hepatitis groups. Chi-square tests were applied for categorical variables, whereas Pearson correlation was used for comparison of non-normally distributed variables, with a p value of ≤0.05 taken as significant.

RESULTS

A total of 215 patients with dengue fever were included in this study, of whom 184 (83% were male) and 31(14% were female). The mean age of the patients was 37 years (IQR: 13–95 years), with 75% of the sample size less than 50 years of age. The median day of illness while reporting to the hospital was 7 days (IQR: 2–18 days). Out of the total sample size, 181(86%) of patients had dengue fever, 75(33%) had dengue hemorrhagic fever, and 13(6%) had dengue shock syndrome. Among the comorbidities, only 21(9.5%) of patients had hypertension, 23(10%) had diabetes mellitus, and 11(5%) patients had ischemic heart disease.

In terms of clinical manifestations of dengue fever, vomiting was present in 100(45% of patients), abdominal pain in 53(24% of patients), and nausea in 55(25% of patients). Table-I shows clinical features in relation to hepatitis severity. Complications of dengue fever included hepatic encephalopathy in 7(3.2%) of patients, pleural effusion in 20(9%) of patients, and ascites in 16(7.2%) of the patients. Acalculous cholecystitis was present in 20(9%) patients, and hepatomegaly was present in 49(22%). The median platelet count among patients was 66x10^9/L (IQR: 3–212x10^9/L). Similarly, median creatinine levels were 84 mmol/L (IQR: 2–345 mmol/L), while median ALT levels were 78 IU/L. (IQR: 2-615 IU/L).

Patients with mild or moderate hepatitis had a median hospital stay of 4 days (IQR: 1–12 days),

whereas those with severe hepatitis had a median hospital stay of 7.5 days (IQR: 5–15 days). This difference was statistically significant (U=225, *p*=0.07). On the contrary, patients with mild or moderate hepatitis had a median bleeding time of 2 days (IQR: 1-2 days), whereas those with severe hepatitis had a median bleeding time of 1 day (IQR: 1-2 days). This difference was also statistically significant (U=314, *p*=0.01). Patients with mild or moderate hepatitis had a median time of shock of 2 days (IQR: 1-2 days), whereas those with severe hepatitis had a median time of shock of 2 days (IQR: 1-2 days). This difference was also statistically significant (U=451, *p*=0.05). The differences in platelet counts were not statistically significant among hepatitis severity groups. Figure illustrates the prevalence of ALT levels in the sample population. Table-II shows the frequency of mild, moderate, and severe hepatitis among patients.

Table-I: Comparison of Clinical Features in Patients with Mild to Moderate and Severe Hepatitis (n=215)

Clinical Manifestations		Mild to Moderate Hepatitis n(%)	Severe Hepatitis n(%)
Abdominal Pain	Yes	50(24)	3(50)
	No	150(71)	3(50)
Vomiting	Yes	97(46)	3(50)
	No	112(53)	3(50)
Fever	Yes	186(89)	5(83)
	No	23(11)	1(16)
Pleural Effusion	Yes	18(8)	2(33)
	No	191(91)	4(66)
Cholecystitis	Yes	20(9)	0(0)
	No	189(90)	6(100)
Ascites	Yes	14(6)	2(33)
	No	195(93)	4(66)

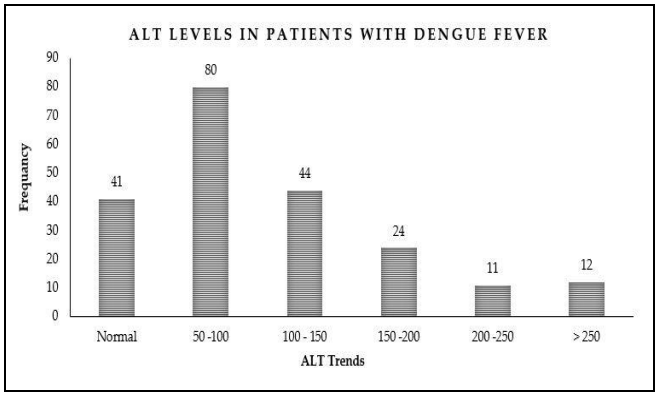

Figure: ALT Levels in Dengue Patients (n=215)

Table-II: Overview of Patients Among Mild-Moderate and Severe Hepatitis Groups (n=215)

Hepatitis severity	ALT Levels (IU/ L)	Number of Patients n(%)
Mild to Moderate	<299	209(94.6%)
Severe disease	>300	6(2.7%)

DISCUSSION

In recent years, dengue virus infection has occurred more frequently in the form of outbreaks, with increased mortality and morbidity. Dengue has impacted not only Pakistan, but is also reported worldwide, with a higher prevalence in South Asian and African countries. The first case of dengue fever illness was reported in 1994 in Pakistan.[12]. Since then, there have been numerous outbreaks reported in Pakistan. This study revealed that a higher number of males than females were affected, a finding that could be attributed to a variety of factors such as dressing and cultural differences, or whether males are more likely to seek medical attention.[13].

This study revealed that 88% of the patients reported chills and rigors as their primary symptom, in line with studies conducted by Khan *et al*. [14]. Our study showed that 84% of patients had chills and rigors. Another study reported these symptoms in 85% of cases (15). In our study, 24% of patients had abdominal pain; this was reported to be the same trend in most of the studies.[16] Body aches, myalgias, and headaches were reported in 70% of the patients.

Bleeding disorder in our study was reported at 34%. Our study showed 8% of dengue patients had pleural effusion, while other studies showed 13.2% and 13.6% of patients had reported pleural effusion.[17,18] One study reported ascites in 12% of cases, while our study showed ascites in 7% of the patients.[19] In our study, DSS and sepsis were reported in 5% and 3% of the patients, respectively. The literature reports mortality rates ranging from 0.15% to 7%.[20]

This study reflects the impact of dengue fever on liver parenchyma, as well as its adverse effects on its functionality, complications, and disability. Many studies have been conducted on liver involvement in dengue fever, which supports our data and outcomes.[21] We came up with results showing derangement in liver functions and increased aminotransferases as a result of dengue illness, which sometimes may lead to DHF and DSS-like complications. Almost 80% of patients in our study showed raised aminotransferases (ALT).

The severity of liver damage is postulated by different immunity responses by the host to the infection, which include innate and acquired immunity, as well as the virulence of the dengue virus, which results in parenchymal injury.[22] Despite this, the host's response to this illness remains unknown.

Researchers have found dengue virus replication in the postmortems of patients who have died from dengue illness, indicating that the host immunity response plays an unregulated role, leading to parenchymal injury and an elevation of transaminases.

CONCLUSION

This study concluded that severe hepatitis in dengue patients was associated with higher rates of dengue hemorrhagic fever and dengue shock syndrome. Severe hepatitis was also associated with decreased levels of platelets and higher rates of dengue complications like ascites and pleural effusion. It was also associated with a longer hospital stay.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

UZ, SN: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

SS, ARA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MA, MAS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

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.

REFERENCES

1. Shakoor MT, Ayub S, Ayub Z. Dengue fever: Pakistan's worst nightmare. WHO South East Asia J Public Health 2012; 1(3): 229–231. https://doi.org/10.4103/2224-3151.207018
2. Parkash O, Almas A, Wasim Jafri S, Hamid S, Akhtar J, Alishah H. Severity of acute hepatitis and its outcome in patients with dengue fever in a tertiary care hospital Karachi, Pakistan (South Asia). BMC Gastroenterology. 2010; 10: 43. https://doi.org/10.1186/1471-230x-10-43
3. Boillat-Blanco N, Klaassen B, Mbarack Z, Samaka J, Mlaganile T, Masimba J, et al. Dengue fever in Dar es Salaam, Tanzania: clinical features and outcome in populations of black and non-black racial category. BMC Infect Dis 2018; 18(1): 3549. https://doi.org/10.1186%2Fs12879-018-3549-z
4. Akinsolu FT, de Paiva VN, Souza SS, Varga O.Patent landscape of neglected tropical diseases: an analysis of worldwide patent families. Global Health 2017; 13(1): 82. https://doi.org/10.1186/s12992-017-0306-9
5. Butt MU, Mohammad S, Iqbal A. Dengue fever outbreak 2010: Clinical experience in a teaching hospital of Lahore Pakistan. Pak J Med Health Sci 2011; 5: 265-269.
6. Kaur G, Kumar V, Puri S, Tyagi R, Singh A, Kaur H. Predictors of dengue-related mortality in young adults in a tertiary care centre in North India. J Family Med Prim Care. 2020; 9(2): 694. https://doi.org/10.4103%2Fjfmpc.jfmpc_605_19
7. Khan MY, Venkateshwarlu C, Sandeep N, Krishna AH. A Study of Clinical and Laboratory Profile of Dengue Fever in a Tertiary Care Hospital, Nizamabad, Telangana State, India. Int J Contemp Med Res 2016; 3(8)2454-7379.
8. Morrison AC. Twenty-Seven Years of Field Studies on Dengue and Aedes aegypti in Latin America. InHistory of Arbovirology: Memories from the Field: Volume I: Personal Reflections 2023. Cham: Springer International Publishing. https://doi.org/10.1155%2F2017%2F8045435
9. Prajapati R, Mehta R, Kabrawala M, Nandwani S, Patel N, Sethia M, et al. Dengue hepatitis: Incidence, spectrum and outcome. Indian J Gastroenterol 2023 ;42(3): 355-360. https://doi.org/10.1007/s12664-023-01405-0
10. Man O, Kraay A, Thomas R, Trostle J, Lee GO, Robbins C, et al. Characterizing dengue transmission in rural areas: A systematic review. PLoS Neglected Trop Dis 2023; 17(6): e0011333. https://doi.org/10.1371/journal.pntd.0011333
11. 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
12. Khan TA, Nisar S, Qureshi MM, Israr M, Samiullah M. Dengue fever outbreak in twin cities; a tertiary care center experience. Pak Armed Forces Med J 2021; 71(5): 1524–1528. https://doi.org/10.51253/pafmj.v71i5.4165
13. Shukla S, Jadhav SM, Gurav YK, Parashar D, Alagarasu K. Serum ferritin level as a prognostic biomarker for predicting dengue disease severity: A systematic review and meta-analysis. Rev Med Virol 2023: e2468. https://doi.org/10.1002/rmv.2468
14. Khan J, Khan I, Ghaffar A, Khalid B. Epidemiological trends and risk factors associated with dengue disease in Pakistan (1980-2014): A systematic literature search and analysis. BMC Public Health 2018 ;18(1): 1–13. https://doi.org/10.1186%2Fs12889-018-5676-2
15. Karki B, Salah NH, Srivastava G, Muduli A, Yadav RB. A simulation study for dengue virus detection using surface plasmon resonance sensor heterostructure of silver, barium titanate, and cerium oxide. Plasmonics 2023: 01907-9 http://doi.org/10.1007/s11468-023-01907-9
16. Nguyen TL, Nguyen TH, Tieu NT. The impact of dengue haemorrhagic fever on liver function. Res Virol 1997; 148(4): 273-277. https://doi.org/10.1016/s0923-2516(97)88364-1
17. Qureshi JA, Notta NJ, Salahuddin N, Zaman V, Khan JA. An epidemic of Dengue fever in Karachi--associated clinical manifestations. J Pak Med Assoc 1997; 47(7): 178-181.
18. Burke DS, Nisalak A, Johnson DE, Scott RM. A prospective study of dengue infections in Bangkok. Am J Trop Med Hygiene 1988 ;38(1): 172-180. https://doi.org/10.4269/ajtmh.1988.38.172
19. Fujimoto DE, Koifman S. Clinical and laboratory characteristics of patients with dengue hemorrhagic fever manifestations and their transfusion profile. Rev Bras Hematol Hemoter 2014; 36(2): 115–120. https://doi.org/10.5581%2F1516-8484.20140027
20. Deshwal R, Qureshi MI, Singh R. Clinical and Laboratory Profile of Dengue Fever. J Assoc Physicians India 2015; 63(12): 30-32.https://doi.org/10.37268/mjphm/vol.20/no.2/art.422
21. Wasay M, Channa R, Jumani M, Zafar A. Changing patterns and outcome of Dengue infection; report from a tertiary care hospital in Pakistan. J Pak Med Assoc 2008; 58(9): 488-489.