

Association of Serum Protein and Bilirubin with Dengue Severity**Sandeep Kumar R Chavda¹, Bhaumik K. Saradva², Rinkal V. Ramoliya³, Nidhi S. Patel⁴**¹Senior Resident, Department of General Medicine, M.K. Shah Medical College & Research Centre, Ahmedabad²Senior Resident, Department of General Medicine, Ananta Medical College, Udaipur³M.D. Anaesthesia⁴Senior Resident, M.D. Microbiology, P.D.U. Medical College, Rajkot

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Conflict of interest: Nil

Abstract:**Background and Objectives:** This study at Geetanjali Medical College and Hospital, Udaipur, assessed Dengue severity and its association with serum Liver function parameters in 153 Dengue-positive patients.**Materials and Methods:** The study included 101 males and 52 females, with age groups 21-40 (DF), 41-60 (DHF), and 61-80 (DSS) most affected. Exclusions included malaria, liver cirrhosis, viral hepatitis, and hepatotoxic drugs. Serum Liver function parameters and haematological parameters were measured using standard biochemical tests.**Results:** In our study of 153 patients, bleeding was observed in 44 individuals (28.75%), predominantly in DHF (94.6%) and DSS (64.3%) cases, with no bleeding in the DF group. We found significantly higher mean hemoglobin levels in DSS patients compared to DF and DHF cases, Conversely, mean platelet counts were significantly lower in the DSS group compared to the DF group and DHF group. Regarding bilirubin levels, among 157 patients, mean total bilirubin was 1.56 ± 0.17 , 1.56 ± 0.16 , and 3.59 ± 0.83 mg/dl in the DF, DHF, and DSS groups, respectively. Mean direct bilirubin levels were 0.48 ± 0.06 , 0.48 ± 0.06 , and 1.83 ± 0.73 mg/dl in the DF, DHF, and DSS groups, respectively. In terms of protein levels, mean total protein was 6.24 ± 0.49 , 6.26 ± 0.57 , and 6.19 ± 0.31 gm/dl in the DF, DHF, and DSS groups, respectively, while mean serum albumin levels were 3.46 ± 0.32 , 3.44 ± 0.31 , and 3.51 ± 0.34 gm/dl in the DF, DHF, and DSS groups, respectively.**Conclusion:** As dengue severity increased, serum bilirubin levels also rose. No significant associations were found between mean serum total protein, albumin, and globulin levels and the severity of dengue in our study. Future research should focus on identifying patient-specific risk factors for hepatic impairment in dengue infection.**Keywords:** Bilirubin, Hemoglobin, Liver Diseases, Dengue, Albumin.This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

Dengue infections, caused by four distinct dengue virus serotypes, pose a substantial global health threat. Dengue fever, characterized by symptoms like fever and joint pain, has witnessed a fourfold increase in global prevalence in recent decades, putting approximately 2.5 billion people at risk [1].

These infections can vary from mild dengue fever to severe dengue, known as dengue hemorrhagic fever (DHF), which can result in capillary leakage, shock, organ dysfunction, and bleeding. Unfortunately, no specific antiviral medications or vaccines are available for dengue, and treatment primarily revolves around fluid replacement in severe cases [2]. Severe dengue is characterized by plasma leakage and impaired blood clotting, leading to symptoms such as elevated hematocrit,

decreased plasma proteins, pleural effusions, and ascites, all contributing to hypovolemic shock [3]. The World Health Organization (WHO) reclassified dengue in 2009 to emphasize severity levels, categorizing patients based on clinical and laboratory data as having dengue with or without warning signals or as having severe dengue [4].

The dengue virus can infect the liver, occasionally causing asymptomatic involvement but sometimes leading to acute fulminant hepatic failure. Hepatic impairment is a significant aspect of Dengue virus infection, affecting both hepatocytes and Kupffer cells. Elevated liver enzyme levels, especially aspartate transaminase (AST) and alanine transaminase (ALT), are common in severe dengue,

implying a connection between enzyme levels and disease severity [5-8].

In summary, dengue infections have emerged as a pressing global issue, with a notable increase in cases and associated morbidity. Understanding the relationship between hematological parameters, serum liver function markers, and disease severity is pivotal for early diagnosis and the effective management of severe cases.

Materials and Methods

This observational cross-sectional study spanned 18 months, from June 2020 to November 2021, and was conducted in the General Medicine ward and ICU at Geetanjali Medical College Hospital in Udaipur. Its primary objective was to investigate the connection between liver enzyme levels and the severity of Dengue infection. The study included Dengue-positive patients, confirmed via ELISA tests for NS1 antigen and IgM/IgG antibodies, who were over 18 years old, regardless of gender.

Exclusion criteria encompassed patients with comorbidities such as malaria, liver cirrhosis, enteric fever, and viral hepatitis, as well as those on hepatotoxic medications. The study enrolled 153 consecutive patients meeting the inclusion criteria.

Laboratory testing protocols involved the use of NS1 early dengue ELISA for acute Dengue infection confirmation and capture-IgM and IgG ELISA to differentiate primary and secondary Dengue infections. Various biochemical markers, including serum albumin, platelet count, white

blood cell count, and hemoglobin levels, were measured.

Operational definitions were established as follows.

Dengue infection diagnosis: Febrile illness with dengue specific IgM capture antibody or NS1 antigen detection.

Dengue Hemorrhagic Fever (DHF): DF with hemorrhagic manifestations, low platelet count, and capillary leakage.

Dengue Shock Syndrome (DSS): Evidence of circulatory failure, pulse pressure ≤ 20 mmHg, hypotension, or shock.

DHF and DSS categorized as severe dengue infection.

Data collection was meticulously conducted using a pre-designed semi-structured study proforma, covering demographic, clinical, and laboratory data. Statistical analyses, including descriptive statistics, chi-square tests, and Student t-tests, were performed using SPSS software version 24.0.

Ethically, the study adhered to the Helsinki Declaration, obtaining prior approval from the Institutional Ethics Committee and securing written informed consent from all participants.

Results

Table 1 illustrates the relationship between age and the severity of dengue. Notably, there is a noticeable increase in dengue severity as age advances.

Table 1: Association of age with severity of dengue

Age groups, years		Dengue Severity			Total
		DF	DHF	DSS	
Less than 20	N	12	0	0	12
	%	11.80%	0.00%	0.00%	7.80%
21 to 40	N	54	5	0	59
	%	52.90%	13.50%	0.00%	38.60%
41 to 60	N	28	20	6	54
	%	27.50%	54.10%	42.90%	35.30%
61 to 80	N	8	12	8	28
	%	7.80%	32.40%	57.10%	18.30%
Total	N	102	37	14	153
	%	100.00%	100.00%	100.00%	100.00%
P Value (ANOVA)		<0.05			

Table 2 illustrates the Relationship between gender and the severity of dengue. The data suggests that dengue was not only more prevalent but also more severe in males when compared to females.

Table 2: Association of gender with severity of dengue

Age groups, years		Dengue Severity			Total
		DF	DHF	DSS	
Female	N	14	30	7	51
	%	13.70%	81.10%	50.00%	33.30%
Male	N	88	7	7	102
	%	86.30%	18.90%	50.00%	66.70%
Total	N	102	37	14	153
	%	100.00%	100.00%	100.00%	100.00%
P Value		N < 0.05			

In the DSS group, hemoglobin levels were higher, TLC was notably elevated, and platelet counts were significantly lower compared to the DF and DHF groups. As dengue severity increased, serum bilirubin levels also rose. However, our study did not identify any significant links between serum total protein, albumin, globulin levels, and dengue severity (Tables 3 and 4).

Table 3: Comparison of hematological parameters between patients with DF, DHF and DSS

Hematological investigations	DF		DHF		DSS		p value
	Mean	SD	Mean	SD	Mean	SD	
Hematocrit (%)	43.67	2.03	44.14	1.31	47.21	2.63	< 0.05
Hemoglobin (gm%)	11.65	2.08	12.46	2.28	14.79	2.61	< 0.01
Platelet (per ml)	87775.2	14374.3	75785	26761.8	48358.8	27786.7	< 0.01
Total Leucocyte Count (per cu mm)	10460.8	2324.17	12098.8	3705.43	15270.1	3316.65	< 0.05
Prothrombin time (seconds)	12.49	2.5	12.51	4.51	12.43	3.51	0.86

Table 4. Comparison of Liver function parameters between patients with DF, DHF and DSS

Parameter	DF		DHF		DSS		p value
	Mean	SD	Mean	SD	Mean	SD	
Total bilirubin (mg/dl)	1.56	0.17	1.56	0.16	3.59	0.83	< 0.05
Direct bilirubin (mg/dl)	0.48	0.06	0.48	0.06	1.83	0.73	< 0.05
Total protein (gm/dl)	6.24	0.49	6.26	0.57	6.19	0.31	0.88
Albumin (gm/dl)	3.46	0.32	3.44	0.31	3.51	0.34	0.75
Globulin (gm/dl)	2.77	0.6	2.82	0.62	2.67	0.44	0.71

Discussion

In our study, we observed that the average hemoglobin levels in the DSS group were notably higher than those in the DF and DHF groups, while the total leukocyte count (TLC) was substantially greater in the DSS group compared to the DF and DHF groups. Conversely, the platelet count in the DSS group was significantly lower than in the DF and DHF groups. These findings are consistent with those reported by Rajoo Singh et al. [10].

An elevated hematocrit suggests the occurrence of plasma leakage due to widespread capillary leakage, hypotension, rhabdomyolysis, hemolysis, and severe DIC, leading to ischemia, hypoxia, and multiorgan failure. Proper fluid management is crucial in such cases [11]. In dengue, vasculopathy and thrombocytopenia may also contribute to bleeding. The reabsorption of plasma leakage occurs during the convalescent period. Therefore, monitoring hematocrit levels is essential for the appropriate management of dengue patients [12].

In our study, involving a total of 157 patients, the mean total bilirubin levels were 1.56 ± 0.17 mg/dl in the DF group, 1.56 ± 0.16 mg/dl in the DHF group, and 3.59 ± 0.83 mg/dl in the DSS group. This observed difference was statistically significant with a p-value of < 0.05. Similarly, the mean direct bilirubin levels were 0.48 ± 0.06 mg/dl in the DF group, 0.48 ± 0.06 mg/dl in the DHF group, and 1.83 ± 0.73 mg/dl in the DSS group, and this difference was statistically significant with a p-value of 0.05. In a study conducted by Bandyopadhyay et al. [13] involving 110 patients, none of the patients exhibited hyperbilirubinemia. The mean total bilirubin levels in their study were

1.2 ± 0.29 mg/dl in the DF group, 1.54 ± 0.6 mg/dl in the DHF group, and 2.80 ± 0.87 mg/dl in the DSS group. Amit Soni [14] and colleagues found that out of 281 patients, 10 individuals (3.6 percent) had bilirubin levels exceeding 3 mg/dl. Among the patients, male individuals had a mean total bilirubin level of 1.44 ± 0.66 , while female individuals had a mean total bilirubin level of 1.32 ± 0.83 . Furthermore, Itha et al. [15] reported that hyperbilirubinemia (>2 mg/dl) was observed in 12 out of 40 patients (30%), and the serum bilirubin level was higher in DSS patients compared to DF or DHF patients. Our findings align with these studies, indicating elevated serum bilirubin levels in dengue fever patients.

Conclusion

Mean total and direct bilirubin levels increase with severity of Dengue. No significant associations were found between serum total protein, albumin, and globulin levels and the severity of dengue in our study. Future research should focus on identifying patient-specific risk factors for hepatic impairment in dengue infection. Furthermore, larger multi-center studies are warranted to validate and strengthen our findings. Increased sample sizes would provide more robust evidence and a broader understanding of the relationship between liver function markers and dengue severity.

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