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Original Research Article

Correlation of Hepatic Profile to Severity of Dengue Fever in Children: A Retrospective Cross-Sectional Study

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Abstract

Background: Dengue infection is caused by the bite of *Aedes* mosquito. All four dengue virus can cause the disease which present as a mild illness, dengue fever to severe forms like dengue hemorrhagic fever or dengue shock syndrome. Liver dysfunction in dengue varies from mild injury with elevation of AST and ALT to severe hepatic injury. The aim of our study was to assess the prevalence of hepatic dysfunction in children with dengue fever and to correlate hepatic profile to severity of dengue fever.

Aim: To correlate the hepatic profile in children with dengue fever, dengue haemorrhagic fever and dengue shock syndrome.

Materials and Methods: Retrospective Cross-Sectional Study, where data collection was done from January 2021 to December 2021 in patients with dengue antigen positive admitted in paediatric ward, ICU and reports from Biochemistry CDL, VIMS Ballari. Total 122 study population were divided into 3 groups, Group A: Dengue fever (81 Patients), Group B: Dengue haemorrhagic fever (26 patients) and Group C: Dengue shock syndrome (15 patients) constitutes 67%, 21% and 13% respectively. The various laboratory blood parameters that included in the study were Platelet count, PT, APTT, AST, ALT, TP and Albumin.

Results: There is statistical significant decrease in Platelet count, Total Protein and Albumin level as severity of dengue fever increases. There is statistical significant increase in PT, APTT, AST and ALT level as severity of dengue fever increases. In the present study, the hepatic profile (mainly transaminases) is correlated with platelet counts, there is significant negative correlation was found as severity of Dengue fever increases. But there is no significant correlation between transaminases and PT, APTT, Albumin, Total protein level as the severity of dengue fever increases.

Conclusion: We conclude that by investigating simple and low cost tests like transaminases, platelet count, PT, APTT, Total protein, albumin levels in dengue fever, helps in early intervention and management of disease which can reduce mortality due to dengue fever.

Keywords: Albumin; Dengue Haemorragic Fever; Dengue Shock Syndrome; Liver Enzymes; Platelet Counts

Introduction

Dengue infection is an arthropod - borne viral hemorrhagic fever, caused by the bite of Aedes aegypti mosquito or yellow fever mosquito. It is a major challenge to public health in South-East Asia. In most of the endemic countries, it regularly causes epidemics after a period of every 2–4 years, and India is one of such country to witness such out breaks. [1]

Estimates suggest that annually over 50 million cases of severe dengue occur in Asian countries with a case fatality rate of lesser than 5%. Out of these, at least 90% are children younger than 15 years old. [2]

The virus responsible for causing dengue, is called dengue virus (DENV). There are four dengue virus serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) which can cause the disease with following clinical presentations.

Most of the dengue infections are asymptomatic. Clinical presentations of dengue infection are of 2 types. 1. Mild or moderate form called classical 2. Severe forms, such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) in children and adults. Globally, the index of severity has increased with increasing infectivity and our country is contributing a large number of cases because of the high susceptibility and favourable climatic conditions. Most common symptom of dengue is high grade fever of 104^0 F (40^0 C) with any of the following symptoms nausea, vomiting, rash, aches and pains (retroorbital pain, muscle, joint or bone pain). Warning signs include severe stomach pain, persistent vomiting, bleeding from gums or nose, blood in urine, stools or vomit and bleeding under the skin.

Although dengue virus is a non-hepatotropic virus, hepatomegaly is commonly seen in dengue. The degree of liver dysfunction varies from mild injury with elevation of aminotransferases to even fulminant hepatic failure. [3,4]

Hepatic dysfunction in dengue infection may be attributed to direct viral effect on liver cells, leading to inflammatory process resulting in parenchymatous lesion which causes release of liver markers into the blood. Rising of aminotransferase level occurs in the acute phase of the disease and elevated liver enzymes is an early marker of dengue infection. [5]

Most common dengue related hepatic involvement is raise in transaminases levels. The raised aspartate transaminase (AST) levels are found around 63–97% of patients, whereas the elevated alanine transaminase (ALT) levels are found in 45–96% of patients. [6]

Since there is hepatocellular damage and vascular endothelial leakage by DENV infection causing low platelet count, leading to alteration in coagulation profile especially Prothrombin time and Thromboplastin time. [6]

Pathogenesis of Dengue associated with plasma leakage of proteins from vascular tissues. It is due to disturbance of the anionic glycosaminoglycan (GAG) layer on the luminal endothelial surface. This results in low plasma proteins and albumin levels. [7]

The disease has more severe presentations with the involvement of children of different age groups; therefore, if the condition is undiagnosed or untreated, the mortality of DF would be significantly increased. Thus, prompt diagnosis and management will help in reducing mortality, especially in children. [8-10]

The number of studies correlating the hepatic profile in Dengue fever, and more severe forms- Dengue haemorrhagic fever and Dengue Shock syndrome are limited in children. The aim of our study was to assess the prevalence of hepatic dysfunction in children with dengue fever and to correlate hepatic profile to severity of dengue fever.

From present study Liver function tests can be utilised as a routine initial part of the investigative studies in a patient with suspected dengue fever. And also serial monitoring of liver function tests should be done to identify high-risk cases.

Study was proceeded with following objectives

1. To evaluate alterations in the hepatic profile in children with dengue fever, dengue haemorrhagic fever and dengue shock syndrome.
2. To correlate the hepatic profile in children with dengue fever, dengue haemorrhagic fever and dengue shock syndrome.

Materials and Methods

This was a Retrospective Cross-Sectional Study, where data collection was done for 1year from January 2021 to December 2021. Data was collected from patients with dengue antigen positive /Ig G positive admitted in paediatric ward and ICU, Department of paediatrics and also from Central diagnostic laboratory, department of Biochemistry, Vijayanagara Institute of Medical Sciences Ballari. This study was approved by institutional ethical committee. Ref No: VIMS: 66/2022 Dated: 10/10/2022. It has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

The sample size was calculated to be a minimum of 122, assuming the anticipated prevalence of hepatic dysfunction in dengue to be around 50%, assuming α error 5% ($Z_\alpha = 1.96$) and β error 20% ($Z_\beta = 0.842$) and a power of 80%, with a precision of 5%, according to the following formula:

$$n = \frac{[(Z_\alpha + Z_\beta)^2 + pq]}{d^2}$$

Where p = prevalence; q= (1- p); and d = precision.

The details of all children with dengue fever admitted during the study period will be collected from the admission registers in the department of paediatrics and their case sheets & discharge summaries will be collected from MRD and reviewed in detail.

The patients will be designated as dengue fever (Group A), dengue haemorrhagic fever (Group B) and dengue shock syndrome (Group C) based on the following criteria. [9]

Dengue fever (Group A)	Fever <15days, plus 2 or more of the following manifestations: Headache, myalgia, arthralgia, retro-orbital pain,nausea/vomiting, skin rash and supportive serology	Dengue antigen positive/ IgG, IgM Positive.
Dengue haemorrhagic fever (DHF) (Group B)	Fever of 2-7 days with bleeding manifestations indicated by positive tourniquet test/petechiae, ecchymoses, purpura/bleeding mucosa/hematemesis, melena.	Platelet count <100,000/mm3 Plasma leakage as evidenced by rise in PCV>20%, fall in PCV by 20% after IV fluids, pleural effusion, ascites, hypoalbuminemia
Dengue shock syndrome (Group C)	DHF + weak pulse, hypotension, narrow pulse pressure and cold dry skin	Platelet count< 100000/cmm,

Inclusion Criteria

- The children age group of 6 months to 14yrs admitted to medical college hospital with dengue antigen positive /Ig G positivity.
- Children with clinically diagnosed dengue fever, dengue haemorrhagic fever and dengue shock syndrome

Exclusion Criteria

- Children with the age group of below 6 months and above 14 years
- Children with preexisting liver disease and infections causing hepatitis like Malaria, Hepatitis B, Enteric fever and Leptospirosis.
- Children with preexisting bleeding disorders

Total 122 study population were divided into 3 groups, Group A: Dengue fever (81 Patients), Group B: Dengue haemorrhagic fever (DHF) (26 patients) and Group C: Dengue shock syndrome (DSS) (15 patients) constitutes 67%, 21% and 13% respectively.

The various laboratory blood parameters that included in the study were Platelet count, PT (Prothrombin time), APTT (Activated Partial Thromboplastin time), AST (Aspartate Transaminase), ALT (Alanine Transaminase), TP (Total protein) and Albumin.

Statistics

All results obtained was statistically analysed by Statistical Package for the Social Science (SPSS) version 20 software. Descriptive statistics were analyzed by chi-square test. Comparison of multiple means across disease severity will be done using One Way-ANOVA. Pearson´s correlation coefficient test will be used to calculate the correlation between variables (transaminases and platelet count). A two tailed probability value of <0.05 (95% CI) will be accepted as the level of statistical significance.

Results

The details of all 122 children, age group of 6 months to 14yrs with dengue antigen positive /Ig G positivity, attended OPD and admitted during the study period will be collected. Study group were selected from the admission registers in the department of paediatrics and their case sheets & discharge summaries will be collected from MRD and reviewed in detail.

Study population were divided into 3 groups, Group A: Dengue fever (81 Patients), Group B: Dengue haemorrhagic fever (DHF) (26 patients) and Group C: Dengue shock syndrome (DSS) (15 patients) constitutes 67%, 21% and 13% respectively. Patients with preexisting liver and bleeding disorders were excluded. All data was collected from recordings of ward, ICU and Central diagnostic Laboratory.

The various laboratory blood parameters that included in the study were Platelet count, PT (Prothrombin time), APTT (Activated Partial Thromboplastin time), AST (Aspartate Transaminase), ALT (Alanine Transaminase), TP (Total protein) and Albumin.

Table /Fig- 1

Variables	Dengue fever	N	Mean	Std. Dev	F value	p value*
Age (yrs)	DF	81	8.10	3.813	.382	.684
	DHF	26	7.38	3.383		
	DSS	15	7.67	4.254		
	Total	122	7.89	3.763		

*ANOVA

[Table /Fig- 1]: Mean age among study group is 7.89 ± 3.8 years. There is no sinificant age difference among the study subjects who had Dengue fever (DF), Dengue haemorrhagic fever (DHF) and Dengue shock syndrome (DSS) (F – 0.382, p – 0.684)

Table /Fig- 2

Variables	Dengue fever	N	Mean	Std. Dev	F value	p value*
Platelet count (lakhs)	DF	81	.83	.519	31.268	.000
	DHF	26	.15	.368		
	DSS	15	.07	.258		
	Total	122	.59	.571		
PT (Sec)	DF	81	12.35	1.002	247.351	.000
	DHF	26	18.04	3.736		
	DSS	15	24.00	2.035		
	Total	122	14.99	4.557		
APTT(Sec)	DF	81	24.54	3.127	360.273	.000
	DHF	26	52.04	3.944		
	DSS	15	47.93	11.628		
	Total	122	33.28	13.366		
TP(g/dl)	DF	81	6.358	.6765	20.706	.000
	DHF	26	5.846	.3679		
	DSS	15	5.367	.4806		
	Total	122	6.127	.6940		
Albumin(g/dl)	DF	81	3.70	.660	22.989	.000
	DHF	26	3.00	0.000		
	DSS	15	3.00	0.000		
	Total	122	3.47	.632		
AST (IU/L)	DF	81	73.20	30.31	69.500	.000
	DHF	26	141.91	25.80		
	DSS	15	145.69	37.49		
	Total	122	97.10	45.97		
ALT (IU/L)	DF	81	62.07	27.85	63.775	.000
	DHF	26	109.19	21.02		
	DSS	15	124.12	24.52		
	Total	122	81.09	37.76		

*ANOVA

[Table /Fig- 2]: Platelet count: Mean value of platelets in DF is 0.83 lakhs, in DHF is 0.15 lakhs and DSS is 0.07 lakhs. There is significant decrease in platelet counts as severity of dengue fever increases.

Prothrombin time (PT): Mean value of protrombin time in DF is 12.35 sec, in DHF is 18.04 sec and in DSS is 24 sec. There is significant increase in Prothrombin time as severity of dengue fever increases.

Activated partial thromboplastin time (APTT): Mean value of APTT in DF is 24.54 sec, in DHF is 52.04 sec and in DSS is 47.93 sec. There is significant increase in Activated partial thromboplastin time.

Total Protein (g/dl): Mean value of Total protein in DF is 6.358 g/dl, in DHF is 5.846 g/dl and in DSS is 5.367 g/dl. There is significant decrease in Total protein level as severity of dengue fever increases.

Albumin (g/dl): Mean value of Albumin in DF is 3.7 g/dl, in DHF is 3 g/dl and in DSS is 3 g/dl. There is significant decrease in Total protein level.

AST (IU/L): Mean value of AST in DF is 73.20 IU/L, in DHF is 141.91 IU/L and in DSS is 145.69 IU/L. There is significant increase in AST level as severity of dengue fever increases.

ALT (IU/L): Mean value of ALT in DF is 62.07 IU/L, in DHF is 109.19 IU/L and in DSS is 124.12 IU/L. There is significant increase in ALT level as severity of dengue fever increases.

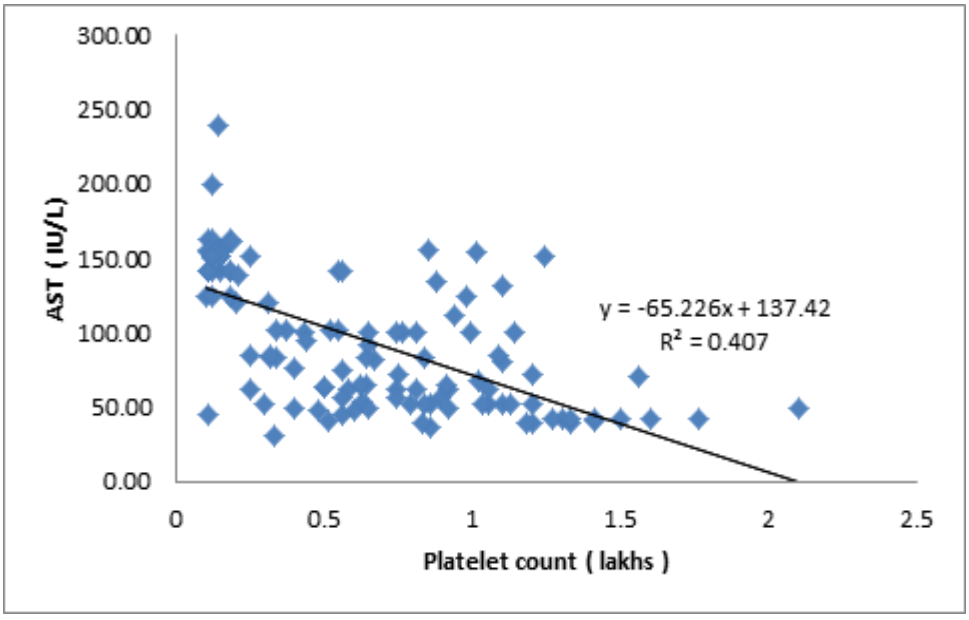
Table /Fig- 3

Pearson's correlation with AST (IU/L)							
Classification of dengue		ALT (IU/L)	Platelet count (lakhs)	PT (Sec)	APTT (Sec)	TP (g/dl)	Albumin (g/dl)
Dengue fever (n - 81)	r value	.760**	-.265*	-.064	-.272*	-.051	-.178
	p value	.000	.017	.570	.014	.651	.112
Dengue Hemorrhagic fever (n - 26)	r value	.904**	-.260	-.098	.089	.220	-.344
	p value	.000	.199	.633	.665	.281	.086
Dengue Shock Syndrome (n - 15)	r value	.876**	-.921**	.205	.089	-.560*	-.656**
	p value	.000	.000	.464	.752	.030	.008

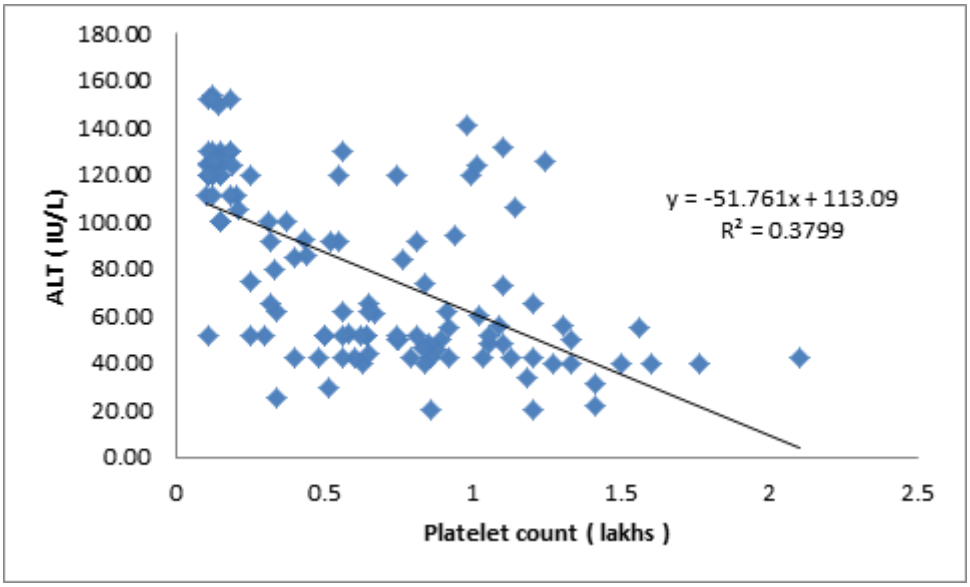
Table /Fig- 4

Pearson's correlation with ALT (IU/L)						
Classification of dengue		Platelet count (lakhs)	PT (Sec)	APTT(Sec)	TP(g/dl)	Albumin(g/dl)
Dengue fever (n - 81)	r value	-.280*	-.065	.072	-.037	-.140
	p value	.011	.567	.524	.746	.211
Dengue Hemorrhagic fever (n - 26)	r value	-.286	.048	.143	.308	-.380
	p value	.157	.816	.484	.126	.056
Dengue Shock Syndrome (n - 15)	r value	-.884**	.248	-.106	-.323	-.377
	p value	.000	.373	.708	.241	.166

[Table /Fig- 4]: Above tables 3 & 4 shows, correlation of hepatic profile (Transaminases) with severity of Dengue fever. There is a negative correlation among transaminases and platelet counts. As the severity of dengue fever increases the transaminases level increases and platelet count decreases. But there is no significant correlation between transaminases and PT, APTT, Albumin and Total protein level as the severity of dengue fever increases.



Graph 1



Graph 2

The above Graphs 1 & 2 shows that, as the Transaminases (AST & ALT) levels increases the severity of dengue fever increases which is characterised by decrease in platelet count.

Discussion

In 75% of dengue patients liver involvement in the form of elevated transaminases was commonly found. Serum transaminases (SGOT & SGPT) levels increases with increase in severity of dengue which is indicated by fall in platelet count as they are negatively correlated with each other. Liver damage is one of the common complications of dengue and of elevated transaminases, hypoalbuminemia and reversal of A: G ratio used as biochemical markers in dengue patients to detect and monitor hepatic dysfunction in early stage to avoid complications.

In the present study, mean value of platelets in DF is 0.83 lakhs, in DHF is 0.15 lakhs and DSS is 0.07 lakhs. There is significant decrease in platelet counts as severity of dengue fever increases. Mean value of protrombin time in DF is 12.35 sec, in DHF is 18.04 sec and in DSS is 24 sec. There is significant increase in Prothrombin time as severity of dengue fever increases. Mean value of APTT in DF is 24.54 sec, in DHF is 52.04 sec and in DSS is 47.93 sec. There is significant increase in Activated partial thromboplastin time. Mean value of Total protein in DF is 6.358 g/dl, in DHF is 5.846 g/dl and in DSS is 5.367 g/dl. There is significant decrease in Total protein level as severity of dengue fever increases. Mean value of Albumin in DF is 3.7 g/dl, in DHF is 3 g/dl and in DSS is 3 g/dl. There is significant decrease in Total protein level. Mean value of AST in DF is 73.20 IU/L, in DHF is 141.91 IU/L and in DSS is 145.69 IU/L. There is significant increase in AST level as severity of dengue fever increases. Mean value of ALT in DF is 62.07 IU/L, in DHF is 109.19 IU/L and in DSS is 124.12 IU/L. There is significant increase in ALT level as severity of dengue fever increases.

As observed in the present study there was significant negative correlation between transaminases and platelet counts. Which suggest that as the severity of dengue fever increases the transaminases level increases and platelet count decreases. By analysing these markers we can detect liver damage early in dengue fever and prevent further complications.

Samanta J, Sharma V observed increased transaminase levels with increasing disease severity. There is increase in PT and APTT levels as the disease progress, this finding was similar to present study. [11]

Gandhi K, Shetty M observed significant fall in platelet counts, significant elevation of transaminases and significant fall in a serum albumin levels as dengue fever progress to dengue haemorrhagic fever. Similar results were observed in present study. [12]

Reduction in albumin levels were highly predictor of disease entering into critical phase of dengue hemorrhagic fever. According to Eresha Jasinge et al both transaminase rise initially in both dengue fever and dengue hemorrhagic fever. Both albumin and cholesterol decreased significantly at the time of entering into the critical phase. Which was similar to our results there is significant elevation of transaminases and sinificant fall in albumin levels as disease progresses. [13]

According to Adane T and Getawa S in dengue fever there is Liver involvement as disease progress, which is characterised by prolongation of APTT and PT due to decreased coagulation factors synthesis. [14] In present study similar significant elevation of APTT and PT is observed.

Balakrishnan V et al showed similar elevation of PT and APTT levels in dengue fever which was significant and positively correlated with clinical severity. This findings were similar to present study. [15]

Conclusion

In the present study the authors found significant elevation of serum transaminases, PT and APTT and significant reduction in platelet count and albumin levels. These pattern of change in serum parameters in children with dengue infection would help to anticipate the progression to different clinical stages thus enabling effective management and prevention of complications which can help in reducing the mortality of dengue fever.

Limitations

a) Dengue infection is not only common in children but also in adults it is common. Further study in adults is necessary to generalise disease complications in population.
b) Sample size is less so we cannot generalise the result on whole population

Scope

Further study can be done in patients with negative immunology test but the symptoms suggestive of dengue fever helps in identifying disese variants and complications in dengue fever.

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