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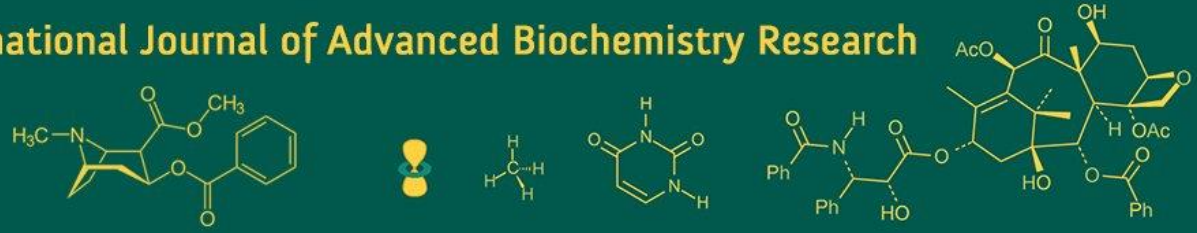

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Correlation of liver indices with thrombocytopenia in dengue infected children

Dr. Aruna Kumari Bandaru and Divya Sai Vanumu

Abstract
Objective: To evaluate and correlate the early hepatic markers with thrombocytopenia that distinguishes the acute phase of dengue from other febrile illness.
Methods: Study includes 50 controls, 54 other febrile illness and 105 dengue infected children between 3 months to 15 years age group. Liver function tests and platelet count were analyzed.
Results: There was a significant elevation of transaminases, prothrombin time, activated partial thromboplastin time, ammonia with $p<0.05$ in dengue infection than other febrile illness and controls, but significant decrease in alkaline phosphatase and platelet count. C-reactive protein was significantly raised with $P<0.05$ in other febrile illness than dengue infection and controls.
Conclusion: During an acute phase of illness, raised aspartate transaminase, activated partial thromboplastin time and platelet count <50000/mm^{3,} C-reactive protein were useful as early markers to differentiate dengue from other febrile illness.

Keywords: Activated partial thromboplastin time, alanine transaminase, aspartate transaminase, dengue infection, other febrile illness, platelet count

Introduction
Dengue infection (DI) is the most common mosquito-borne viral disease and is a major public health problem worldwide, nearly 95% occur in children [1]. During the early acute phase of DI, anti-dengue virus antibodies may not be present [2], and are often difficult to distinguish clinically from other acute febrile illnesses [3, 4]. Although the liver is not a major target organ, hepatic dysfunction is a well- recognized feature of dengue in children [5, 6]. Thrombocytopenia and coagulopathy are also prominent features of symptomatic infection. Thrombocytopenia has always been one of the criteria used by WHO guidelines as a potential indicator of clinical severity [7]. Early development of thrombocytopenia or coagulation disturbances may be predictive of subsequent complications. The significance of this study is to evaluate the early markers of acute phase of dengue.

Materials and method
We designed a prospective study of children early the course of dengue in order to identify early clinical and laboratory predictors of dengue with hepatic dysfunction before the critical stage of the disease. The eligibility criteria for entry into this study: age 3 months to 15 years, fever for 72 h, oral temperature more than 38.5 ºC. Malaria, enteric fever, hepatitis A and B, urinary tract infection, respiratory tract infection, and chronic liver diseases were excluded from the study by history, examination, and investigations.
Present study was conducted on 209 cases, out of which 50 healthy children were grouped as controls and 159 were admitted with acute febrile illness during an outbreak of dengue in Government General Hospital, Mahabubnagar, Telangana, India, from June to August 2019. Out of 159 cases, the study group includes 54 other febrile illness (OFI) and 105 DI, as per the WHO diagnostic criteria and was serologically positive IgM or NS 1 or IgG antibodies. OFI defined as patients lacking typical clinical features of dengue or no clinical evidence of bacterial infection and negative anti-dengue serology. The study was approved by the Institutional ethical committee, and informed consent was obtained from parents. A detailed history and a thorough clinical and laboratory examination were done in all the cases.
Acute-phase blood samples (3-5 ml) were obtained at the time of admission (day 2 to day 7 after the onset of fever). Samples were collected into three different blood containers. The first was a plain container into which serum was extracted for the assessment of liver

function tests (LFT) by using RANDOX autoanalyzer with commercially available RANDOX kits. The second was tri-sodium citrate container from which plasma was used to detect the prothrombin time (PT) and activated partial thromboplastin time (APTT) within 4 hours of blood collection using a semi-automated coagulometer; model Type- COA, DATA501with TULIP kits. The third was an EDTA container for complete blood picture, including hemoglobin (Hb), RBC, WBC, differential leukocyte count (DLC), platelet count, hematocrit (Hct), was analyzed within 4 hours of blood collection using Sysmex XS- 800i cell counter. For dengue confirmation serological tests done by ELISA technique for NS 1, IgM, IgG antibodies.

Statistical analysis

Statistical analysis was carried out using Sofa Stats software. Results were presented as mean, standard deviation (SD) for continuous variables; the frequency and percentage were given for qualitative variables. One way ANOVA used to calculate the p-value between three different groups by Statistics calculator version 4.0. An unpaired t- test used for P values and 95% confidence intervals (CI) were calculated from the mean, SD, number by using Graph Pad software. Relative risk, the 95% confidence interval of relative risk, the significance of a difference between two independent proportions was calculated by using medcalc easy to use statistical software. A p-value of ≤ 0.05 was taken as statistically significant.

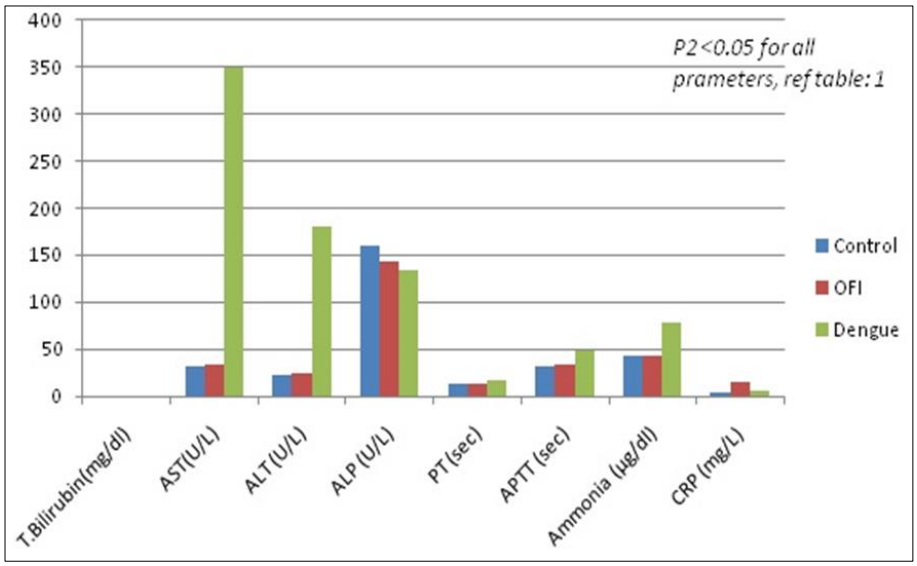
Results

There was a mild difference in LFT between controls and OFI but were within normal reference ranges. CRP was raised (15.56 mg/L vs 4.2 mg/L, *P=0.0004*, 95% CI -17.53 to -5.18) in OFI than controls. (Table 1, Fig 1). There was a significant elevation of AST (mean 349.5 U/L vs. 34.02 U/L vs. 32.68 U/L, *P=0.000*), ALT (mean 180.53U/L vs. 23.99 U/L vs22.43 U/L, *P=0.000*), PT (mean 16.8 s vs. 14.06 s vs. 13 s, *P=0.000*), international normalized ratio (INR) (mean 1.29 vs. 1.07 vs. 1.03, *P=0.003*), APTT (mean 48.3 s vs. 33.74 s vs. 32 s, *P=0.000*), and ammonia (mean 78.7 µg/dl vs. 42.87 µg/dl vs. 42 µg/dl, *P=0.027*), but significant decrease in ALP (mean 134.7 U/L vs. 143.07 U/L vs. 160.1 U/L, *P=0.006*) and platelet count (mean 64673 vs. 281083 vs. 277180/ mm^3, *P<0.0001*) in dengue than OFI and controls (Table 1, Fig 1, Fig 2).

Table 1: Comparison of mean of LFT in DI with OFI and controls.

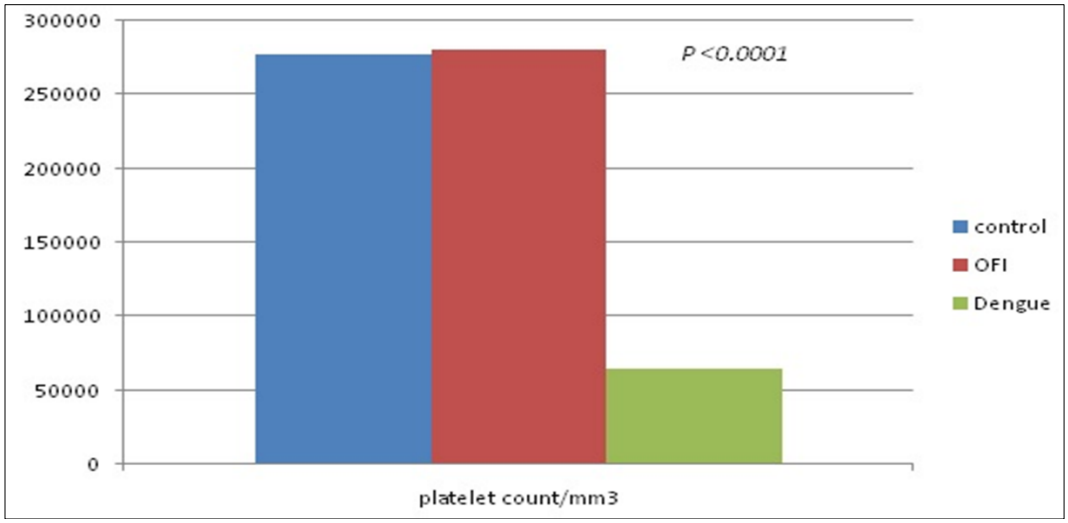
Parameters	Control	OFI	*P 1*	DI	*P 2*
	Mean ± SD	**Mean ± SD**		**Mean ± SD**	
T.Bilirubin (mg/dl)	0.56± 0.22	0.76 ± 0.53	0.014*	0.9 ± 0.7	0.003*
AST (U/L)	32.68 ± 10	34.02 ± 18.6	0.65	349.5 ± 769.7	0.000*
ALT (U/L)	22.48 ± 16.7	23.99 ± 16.1	0.64	180.53± 338.7	0.000*
ALP (U/L)	160.1 ± 40.1	143.07 ± 45.48	0.04*	134.7 ± 48.7	0.006*
PT (sec)	13.72 ± 1.22	14.06 ± 2.3	0.23	16.8 ± 7.9	0.000*
INR	1.03 ± 0	1.07 ± 0.2	0.16	1.29 ± 0.7	0.003*
APTT (sec)	32 ± 0	33.74 ± 7.0	0.08	48.3 ± 21.2	0.000*
Ammonia(µg/dl)	43.4 ± 4.07	42.87 ± 0.9	0.35	78.7 ± 135.8	0.027*
Platelet Count/mm^3	277180 ± 124923	281083 ± 142390	0.88	64673 ± 57537	<0.0001*
CRP (mg/L)	4.2 ± 0.24	15.56 ± 22	0.0004*	6.83 ± 10.5	0.000*

DI: Dengue infection; OFI: Other Febrile Illness; SD: standard deviation; AST: Aspartate Transaminase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; PT: Prothrombin Time; INR: international normalized ratio; APTT: Activated Partial Thromboplastin Time; CRP: C - reactive protein; P1: Significance between OFI and controls; P2: Significance between DI, OFI and controls; *significant



AST: Aspartate transaminase; ALT: Alanine Transaminase; ALP: Alkaline phosohatase; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; CRP: C - reactive protein; P2: significance between dengue, OFI and control.

Fig 1: Comparison of mean of LFT in DI with OFI and controls.



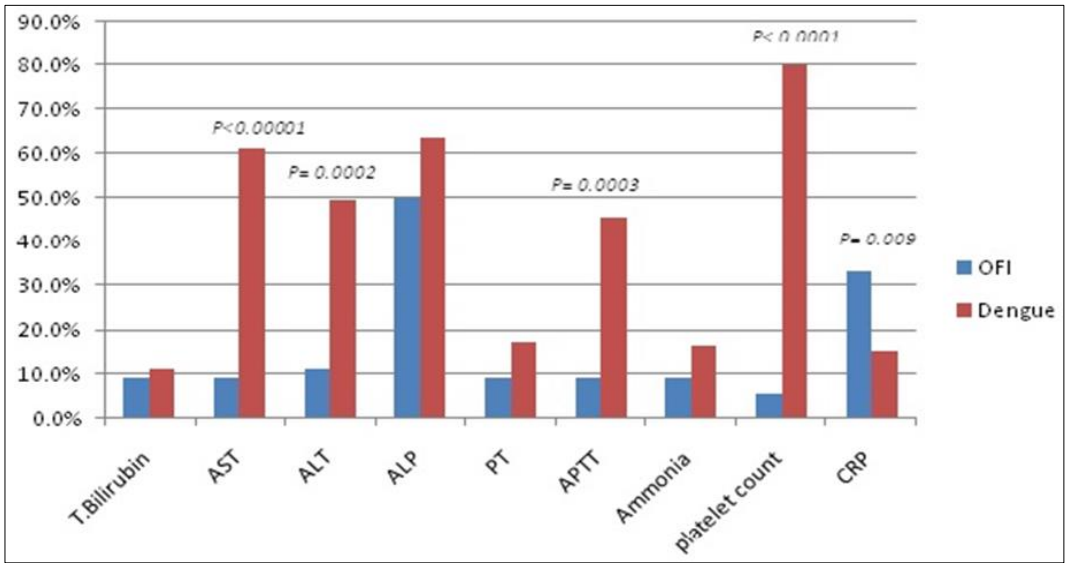
The prevalence of raised AST (61 % vs. 9.3 %, *P<0.0001,* RR 6.6, 95% CI 2.82- 15.38), ALT (49.5% vs. 11.1%, *P=0.0002,* RR 4.6, 95% CI 2.05 – 9.71), APTT (45.7% vs. 9.3%, *P=0.0003,* RR 4.94, 95% CI 2.09 – 11.67) were significantly higher in DI than OFI. The prevalence of raised CRP was significantly more in OFI (33.3% vs. 15.2%, *P=0.009,* RR 0.46, 95% CI 0.25 – 0.82) than DI. The prevalence of raised levels of total bilirubin, ALP, PT, INR, ammonia was not significant between OFI and DI with *P >0.05.* The prevalence of decreased platelet count was significantly more in DI than OFI (80% vs. 5.5%, *P<0.0001,* RR 14.4, 95% CI 4.8 – 43.4) (Table 2, Fig 3).

Fig 2: Comparison of platelet count among DI, OFI and Control

Table 2: Comparison of Prevalence of abnormal LFT in OFI and DI

Parameters	OFI No (%)	DI No (%)	*P* value	Relative Risk	95% confidence Intervals(CI)
T.Bilirubin (>2mg/dl)	5 (9.3)	6(11.1)	0.41	0.62	0.19 – 1.93
AST (>60 U/l)	5(9.3)	64 (61)	<0.0001*	6.6	2.82 – 15.38
ALT (>45 U/l)	6(11.1)	52 (49.5)	0.0002*	4.6	2.05 – 9.71
ALP (<135 U/l)	27(50)	67 (63.8)	0.11	1.28	0.94 – 1.73
PT (>18sec)	5(9.3)	18 (17.1)	0.2	1.85	0.73 – 4.72
INR (>1.5)	5(9.3)	13(12.4)	0.56	1.34	0.5 – 3.55
APTT (>44sec)	5(9.3)	48 (45.7)	0.0003*	4.94	2.09 – 11.67
Ammonia (>68 µg/dl)	5(9.3)	17 (16.2)	0.245	1.75	0.68 – 4.48
Platelet count (<1 lakh/mm^3)	3(5.5)	84 (80)	<0.0001*	14.4	4.8 – 43.4
CRP (>4.1 mg/L)	18(33.3)	16 (15.2)	0.009*	0.46	0.25 – 0.82

DI: Dengue infection; OFI: Other Febrile Illness AST: Aspartate Transaminase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase, PT: Prothrombin time INR: international normalized ratio; APTT: Activated Partial Thromboplastin Time; CRP: C - reactive protein; *significant.



AST: Aspartate transaminase; ALT: Alanine Transaminase; ALP: Alkaline phosphatase; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; CRP: C-Reactive protein.

Fig 3: Comparison of Prevalence of abnormal LFT in OFI and DI

The prevalence of raised AST was significantly higher than ALT in DI (61% vs. 49.5%, *P=0.04*), whereas not significant in OFI (9.3% vs. 11.1%, *P=0.38*) and controls (12% vs. 12%, *P=0.5*). APTT being affected more than PT in DI. There was a significant rise of APTT than PT in DI (45.7% vs. 17.1%, *P=0.0001*), but not significant in OFI (9.3% vs. 9.3%, *P=0.5*) and controls (10% vs. 10%, *P=0.5*) (Table 3).

Table 3: Comparison of prevalence between AST, ALT and APTT, PT among study cases.

Study Cases	AST No (%)	ALT No (%)	*P 1* value	APTT No (%)	PT No (%)	*P2* value
Dengue (105)	64(61)	52(49.5)	0.04*	48 (45.7)	18 (17.1)	0.0001*
OFI (54)	5(9.3)	6 (11.1)	0.38	5 (9.3)	5 (9.3)	0.5
Controls (50)	6 (12)	6 (12)	0.5	5 (10)	5 (10)	0.5

DI: Dengue infection; OFI: Other febrile illness; AST: Aspartate Transaminase; ALT: Alanine Transaminase; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; P1: significance between AST and ALT; P2: significance between APTT and PT; *significant.

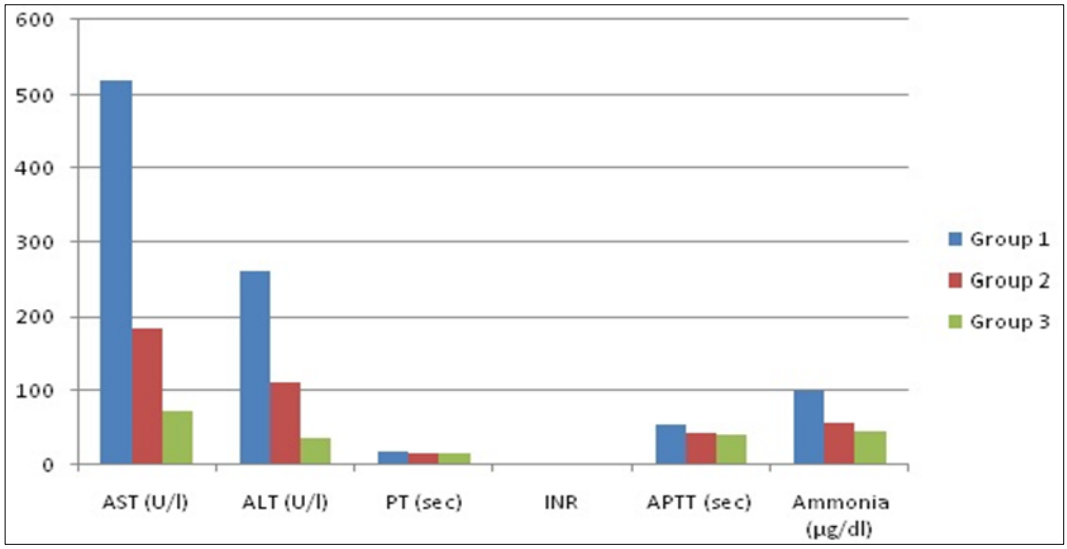
Based on the levels of platelet count the dengue-infected children were grouped as follows: Group 1: Dengue with platelet count <50000/mm^3,
Group 2: Dengue with the platelet count between 50000 – 100000 mm^3,
Group 3: Dengue with Platelet count >100000/mm^3.

Group 1 cases had a significant rise of AST (mean 518.1 vs. 183.7 vs. 73.1 IU/l, *P=0.034*), ALT (mean 261.4 vs. 56.3 vs. 43.7 IU/l, *P=0.015*), PT (mean 18.6 vs. 14.8 vs. 14.1sec, *P=0.028*), INR (mean 1.4 vs.1.1 vs. 1.1, *P=0.049*), and APTT (mean 53.9 vs. 42.2 vs. 40 sec, *P=0.008*), respectively than Group 2 and 3 cases (Table 4, Fig 4).

Table 4: Correlation of LFT with platelet count in DI

Platelet count/mm^3	AST (U/l)	ALT (U/l)	PT (sec)	INR	APTT (sec)	Ammonia (µg/dl)
Group 1 <50000 Mean ± SD No (%)	518.1 ±976.5 44 (74.6)	261.4 ± 410.4 41 (69.5)	18.6 ± 10.1 16 (27.1)	1.4 ± 0.8 12 (20.3)	53.9 ± 24.1 34 (57.6)	100.6 ± 175.7 12 (20.3)
Group 2 50000-1 lakh Mean ± SD No (%)	183.7 ± 295.7 15 (60)	111.4 ± 222.3 12 (48)	14.8 ± 2.1 1 (4)	1.1 ± 0.2 1 (4)	42.2 ± 16.9 7 (28)	56.3 ± 50.4 2 (8)
Group 3 >1 lakh Mean ± SD No (%)	73.1 ± 109.3 5 (23.8)	35.5 ± 37.5 2 (9.5)	14.1 ± 1.9 1 (4.8)	1.1 ± 0.1 0 (0)	40 ± 9.6 6 (28.6)	43.7 ± 3.3 1 (4.8)
P1 value	0.034*	0.015*	0.028*	0.049*	0.008*	0.345
P2 value	0.18	0.06	0.017*	0.06	0.013*	0.17
P3 value	0.014*	0.005*	0.89	0.36	0.96	0.665
P4 value	<0.0001*	<0.0001*	0.033*	0.023*	0.023*	0.1

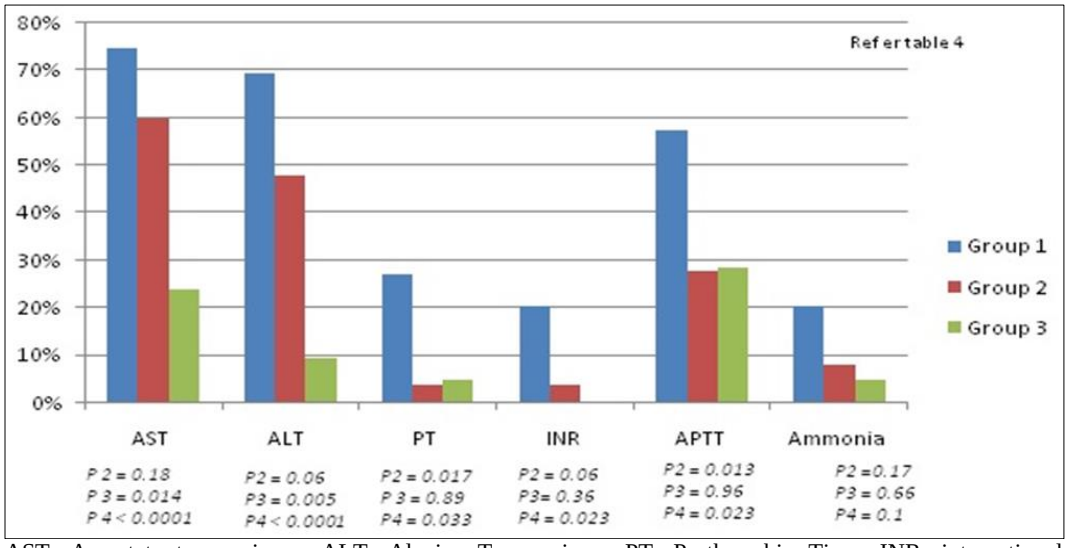
AST: Aspartate transaminase, ALT: Alanine Transaminase PT: Prothrombin Time; INR: international normalized ratio APTT: Activated Partial Thromboplastin Time; P1: significance of the mean between three groups;
P2: significance of prevalence between group 1 and 2, P3: significance of prevalence between group 2 and 3;
P4: significance of prevalence between group 1 and 3; *significant



AST: Aspartate transaminase, ALT: Alanine Transaminase PT: Prothrombin Time; INR: international normalized ratio; APTT: Activated Partial Thromboplastin Time; Group 1: Platelet count <50000/mm^3; Group 2: Platelet count 50000 to 1 lakh /mm^3; Group 3: Platelet count > 1 lakh / mm^3.

Fig 4: Correlation of means of LFT with platelet count in DI

The prevalence of PT and APTT (27.1% vs. 4%, *P=0.017* and 57.6% vs. 28%, *P=0.013*) were significantly more in Group 1 than in Group 2, but not significant in AST, ALT, INR and ammonia levels with *P*>0.05. The prevalence of AST and ALT (60% vs. 23.8%, *P=0.014* and 48% vs.9.5%, *P=0.*005) were significantly more in Group 2 than in Group 3, but not significant in PT, INR, APTT and ammonia with *P*>0.05. The prevalence of AST (74.6% vs. 23.8%, *P<0.0001*), ALT (69.5% vs. 9.55%, *p<0.0001*), PT (27.1% vs. 4.8%, *p=0.033*), INR (20.3%vs. 0%, *p=0.026*), and APTT (57.6% vs. 28.6%, *p=0.023*) were significantly more in Group 1 than in Group 3, but not significant in ammonia levels with *P*>0.05 (Table 4, Fig 5). The mortality rate of DI was 4.76%. Five of 105 DI children died.



AST: Aspartate transaminase, ALT: Alanine Transaminase PT: Prothrombin Time; INR: international normalized ratio APTT: Activated Partial Thromboplastin Time; Group 1: Platelet count <50000/mm^3, Group 2: Platelet count 50000 to 1 lakh /mm^3; Group 3: Platelet count > 1 lakh / mm^3. P1: significance of the mean between three groups; P2: significance of prevalence between group 1 and 2, P3: significance of prevalence between group 2 and 3; P4: significance of prevalence between group 1 and 3; *significant.

Fig 5: Correlation of prevalence of LFT with platelet count in DI

Discussion

Many DI is often difficult to distinguish clinically from OFI during the early acute phase of illness. Liver involvement is common in DI with mild elevation of serum transaminases. The characteristic features of DHF/DSS include capillary leakage, thrombocytopenia, and coagulopathy.

In our study DI and OFI were analyzed for changes in LFT and showed that all liver parameters were significantly raised particularly; transaminases, PT, APTT, ammonia in DI compared to OFI and controls, but ALP and platelet count were significantly decreased. There was no significant difference in LFT and platelet counts in OFI and controls. Decreased ALP in our study disagrees with the Kalenahalli Jagadish kumar *et al*. and Wahid *et al*. study in which ALP levels were raised [8, 6]. CRP was markedly elevated in OFI when compared with DI and controls. CRP is an acute phase reactant, is a marker of inflammation in the body.

AST levels were significantly higher than ALT levels in DI, which agrees with Wong (2008) and Kuo *et al*. (1992) studies [9, 10], but not significant in OFI, and controls. Hyperbilirubinemia was observed in 11.1% of DI associated with elevated transaminase levels, hyperammonemia, and abnormal coagulopathy indicates the severity of DI. The incidence of raised AST, ALT, APTT and thrombocytopenia were significantly higher in DI than in OFI. The relative risk of raised AST, ALT, APTT and thrombocytopenia were 6.6, 4.6, 4.94, and 14.4 times more in DI than in OFI. Significant thrombocytopenia was universal in the dengue-infected children, and a strong association with the subsequent severity of vascular leakage was apparent from a very early stage [11]. Hemconcentration and marked thrombocytopenia are two major characteristic features of DHF/DSS. The pathogenesis of thrombocytopenia is poorly understood. It was suggested that dengue virus-induced bone marrow suppression, depressed platelet synthesis resulted in thrombocytopenia [12]. Wills B *et al*. 2001 study [11], reported mild thrombocytopenia in the OFI, but in our study, the platelet counts were within normal reference intervals. The incidence of raised CRP was significantly more in OFI than DI.

During acute DI, coagulation parameters such as platelet counts, APTT are altered. APTT and PT are indicators of intrinsic and extrinsic pathways of coagulation, respectively. In our study APTT being affected more than PT in DI, suggesting that a defect occurs in the intrinsic pathway of coagulation, which agrees with previous studies [9, 10, 13, 14], but not significant in OFI, and controls. APTT prolongation in the acute stage of DI correlate with disease severity and can be used as early indicators of DHF/DSS. Since the liver is known to be the site for synthesis of most coagulation factors, reduced levels of coagulation factors are either the results of increased consumption or impaired synthesis, results in prolongation of APTT.

It has long been established that there is abnormal hemostasis in patients with DI with platelet dysfunction, coagulopathy, vasculopathy, and immune- or virus-related destruction of platelets. In our study DI with platelet count <50000/mm^3 had a significant rise of transaminases and coagulation factors, particularly APTT. As the platelet count decreases, the prevalence of raised transaminase levels gradually increase, whereas the prevalence of raised PT and APTT were significantly increased only when the platelet count reaches <50000/mm^3 indicating that elevated serum

transaminase levels correlate with that of hemorrhage in DI, which agrees with Kalayanarooj *et al*. study 1997 [15]. The decreased platelet count correlated with the increased transaminase levels and coagulation factors, particularly APTT, but there was no correlation with hyperammonemia. Thus, there was a significant association between bleeding tendencies and platelet count <50000/mm^3, prolonged APTT, high transaminase levels, particularly AST, which is inconsistent with other studies [16, 17], but disagree with other studies [18, 19] reported that there was no correlation between bleeding tendencies and platelet counts in DI. Other studies reported that in children, there is less correlation between platelet count and disease severity [20, 21].

The mortality rate of the DI was 4.76% in our study, slightly higher when compared with other studies [1, 5], in which the mortality rate is 3.7% and 2.7%. Five of 105 dengue infected patients died. All these patients had transaminase levels more than 600U/l, elevated PT (>18sec), INR (>2), APTT (>100), hyperammonemia and platelet count <50000/mm^3. Hence, there was a significantly higher mortality rate in DI with severe hepatitis with abnormal coagulopathy and platelet count <50000/mm^3.

Conclusion

Abnormal LFT, abnormal coagulopathy, and thrombocytopenia are typical and consistent findings during the acute phase of DI, may differentiate from OFI, especially elevated AST, APTT and platelet count <50000/mm^3 are useful as early markers and strongly associate with the severity of vascular leakage. CRP can be used as a marker in conjunction with LFT to distinguish DI from OFI.

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