Original Article

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Transaminitis in Dengue: A Retrospective Observational Study in an Intensive Care Unit

Anaesthesia Section

KIRAN BADA REVAPPA[1], MURTHY N L NARUMILLI[2], PRADEEP RANGAPPA[3], KARTHIK RAO[4]

ABSTRACT

Introduction: Dengue fever, a frequently encountered arbo viral infection is associated with multiorgan dysfunction in its severe form. The involvement of liver characterised by transaminitis is quite prevalent in such cases admitted to Intensive Care Unit (ICU).

Aim: To evaluate the occurrence and severity of transaminitis in dengue patients admitted to the ICU. Also to find the association between transaminitis and other severity predictors of dengue (low platelet count, high packed cell volume and organ dysfunction).

Materials and Methods: This retrospective observational study was conducted at Columbia Asia Referral Hospital Yeshwanthpur, Bengaluru, Karnataka, India, from October 2019 to January 2020. Total 80 patients of either sex diagnosed with seropositive dengue were included in the study. The parameters like platelet count, packed cell volume, liver enzymes {Serum Glutamic Pyruvic Transaminase (SGPT) and Serum Glutamic Oxalacetic Transaminase (SGOT)} were recorded and followed-up during the ICU stay. Mean with standard deviation were used to represent quantitative variables whereas description of qualitative variables was done with numbers and percentages. The above variables required application of One way Analysis of Variance (ANOVA), post-hoc Turkey test, Kruskal-Wallis one way ANOVA and Chi-square tests. The differences were considered significant at p-value <0.05.

Results: Transaminitis was noted in 96.2% of the total patients. The prevalence of grade 1, 2, 3, 4 transaminitis was 21.2%, 30%, 36.2% and 8.7%, respectively. Mean platelet counts in grade 1, 2, 3 and 4 transaminitis were 19.41±13.17×10^3/µL, 16.04±11.24×10^3/µL, and 14.14±5.19×10^3/µL, and 20.57±10.47×10^3/µL, respectively. The association between mean platelet counts and grades of transaminitis was not statistically significant (p-value=0.61). Mean Packed Cell Volume (PCV) in patients with grade 1, 2, 3 and 4 transaminitis showed an increasing trend of mean PCV when compared to PCV of 35.67±1.52 in patients with normal SGOT/SGPT levels. The association between different grades of transaminitis and mean PCV values during the course of ICU stay was statistically significant (p-value=0.038).

Conclusion: Transaminitis is very common among the dengue patients in ICU and it increases in conjunction with the severity of dengue. It has an association with thrombocytopenia, organ dysfunction and a positive correlation with elevated packed cell volume.

Keywords: Acute kidney injury, Acute respiratory distress syndrome, Thrombocytopenia

INTRODUCTION

Dengue fever, transmitted by the bite of Aedes species mosquito is commonly seen in tropical and subtropical countries. The Dengue Virus (DENV) has four serotypes, so a person can possibly be infected four times. Around 100 million apparent dengue infections occur every year [1]. There is no specific antiviral treatment for dengue infection at present. Dengue in its milder forms can be associated with flu like symptoms but may progress with warning signs to severe form characterised with severe bleeding, severe plasma leakage, shock and organ dysfunction with involvement of liver, heart and brain.

According to the World Health Organisation (WHO) classification 2009, severe dengue is defined as dengue with any of these symptoms, severe bleeding, severe plasma leakage or severe organ dysfunction such as elevated transaminases ≥1,000 IU/L, impaired consciousness, cardiac and other organ involvement [2]. Acute liver failure in dengue can be complicated by severe bleeding, encephalopathy, renal failure and metabolic acidosis leading to high mortality [3,4]. Involvement of liver is the end result of oxidative stress, immune mediated injury, apoptosis and impaired liver perfusion [5-7].

Presentation with deranged Liver Function Tests (LFTs) is likely and includes hyperbilirubinaemia, elevated Aspartate Transaminase (AST) and Alanine Transaminase (ALT) and hypoalbuminaemia which can all be used as prognostic indicators [8].

The most common biochemical abnormality has been raised transaminases levels. The elevated AST levels are seen in 63-97% of cases, whereas the elevated ALT levels are documented in 45-96% of cases [9]. The median aspartate AST and ALT are found to be significantly higher in severe dengue than in uncomplicated dengue cases [9]. This hinted at a possible association between transaminitis and worsening disease severity.

With this background of transaminases levels in dengue, this study was designed with the aim to estimate the occurrence of transaminitis and its association with the severity predictors of dengue like low platelet count, high packed cell volume and organ dysfunction. {Acute Kidney Injury (AKI) and Acute Respiratory Distress Syndrome (ARDS)} in the patients admitted to Intensive Care Unit (ICU).

MATERIALS AND METHODS

This retrospective observational study was conducted at Columbia Asia Referral Hospital Yeshwanthpur, Bengaluru, Karnataka, India, from October 2019 to January 2020. It was a retrospective observational study where patients history, clinical and laboratory parameters were included. The privacy and personal details of the patients was not compromised. The tenets of the Declaration of Helsinki were followed.

Sample size calculation: Based on the assumption of 80% prevalence of transaminitis in dengue [9], α error of 5% (Zα=1.96), β error of 20% (Z_β=0.842) and a power of 80%, the calculated sample size was 80 according to the following formula:

$$n=(Z_\alpha^2 \times p \times q)/d^2$$

Where Z_α=Standardised normal deviate (Z value) for α =0.05=1.96

p=Prevalence of transaminitis in dengue=80%

q=100-80=20%

d=Absolute precision=9%

n=(1.96^2×80×20)/9^2=76, rounded up to 80.

Inclusion criteria: All patients who were diagnosed positive for NS1 antigen of dengue and required Intensive Care Unit (ICU) admission during May to September of 2019 were included in the study.

Exclusion criteria: Patients who are discharged against medical advice were excluded from the study.

Study Procedure

The patient clinical details and the investigation reports were recorded from the hospital based computer software after taking consent from the hospital authorities. The details were entered in the preformat designed for the study. Baseline investigations included complete haemogram, liver and renal function tests, coagulation parameters, venous/arterial blood gas analysis, chest radiograph and ultrasound abdomen and pelvis. If the investigations were found to be repeated, then the most abnormal value of Packed Cell Volume (PCV), platelet count, transaminases and coagulation parameters were considered for analysis. The severity of the transaminitis was graded according to the European Association for the Study of the Liver-Drug Induced Liver Injury (EASL-DILI) grading of transaminitis [Table/Fig-1] [10].

Severity grading of transaminitis	Cut-off value SGOT (AST)	Cut-off value SGPT (ALT)
Grade 0 (normal)	15-41 IU/L	17-63 IU/L
Grade 1 (<3 times)	42-122 IU/L	64-188 IU/L
Grade 2 (3-5 times)	123-205 IU/L	189-315 IU/L
Grade 3 (>5-20 times)	206-820 IU/L	316-1260 IU/L
Grade 4 (>20 times)	>820 IU/L	>1260 IU/L

[Table/Fig-1]: Grading of severity of transaminitis.
*A patient was included in the corresponding grade if one of either SGOT or SGPT value was elevated above the cut-off value

STATISTICAL ANALYSIS

The Mean±SD were used to represent quantitative variables whereas description of qualitative variables was done with numbers and percentages. One way Analysis of Variance (ANOVA), post-hoc Turkey test, Kruskal-Wallis one way ANOVA, and Chi-square tests were applied. A 5% level of significance was considered statistically significant (p-value <0.05). The Statistical Package for the Social Science (SPSS) version 16.0 was used for data analysis.

RESULTS

A total of 80 patients diagnosed with dengue were admitted to the ICU during the study period. The mean age was 35±13.88 years [Table/Fig-2].

Age (years)	Gender		Total n (%)
	Female n (%)	Male n (%)	
≤20	2 (6.1%)	5 (10.6%)	7 (8.8%)
21-30	11 (33.3%)	19 (40.4%)	30 (37.5%)
31-40	10 (30.3%)	13 (27.7%)	23 (28.8%)
41-50	3 (9.1%)	5 (10.6%)	8 (10%)
51-60	5 (15.2%)	2 (4.3%)	7 (8.8%)
>60	2 (6.1%)	3 (6.4%)	5 (6.2%)
Total	33 (100%)	47 (100%)	80 (100%)

[Table/Fig-2]: Demographic details of patients.

Among 80, 59 (73.8%) patients had dengue with warning signs and 12 (15%) patients manifested severe dengue, according to the latest WHO classification 2009. The distribution of patients as per WHO classification and EASL-DILI grading of transaminitis is presented in [Table/Fig-3].

Transaminitis grading	WHO classification			Total
	Dengue fever	Dengue with warning signs	Severe	
0	-	2 (2.5%)	1 (1.2%)	3 (3.8%)
1	3 (3.8%)	14 (17.5%)	-	17 (21.2%)
2	2 (2.5%)	21 (26.2%)	1 (1.2%)	24 (30%)
3	4 (5%)	21 (26.2%)	4 (5%)	29 (36.2%)
4	-	1 (1.2%)	6 (7.5%)	7 (8.8%)
Total	9 (11.2%)	59 (73.8%)	12 (15%)	80 (100%)

[Table/Fig-3]: Distribution of grading of transaminitis and WHO classification of dengue.

Only 3 (3.8%) patients had jaundice at presentation. Pain abdomen was noted in 22 (27.5%) patients. Only two patients had abnormal coagulation parameters and both had severe transaminitis. A 12 (15%) patients had bleeding manifestations among which seven patients had grade 3 and two patients had grade 4 transaminitis [Table/Fig-4]. Transaminitis was seen in 72 (80%) patients at time of admission to ICU, however, it was present in total of 77 (96.2%) patients during the course of ICU stay. Out of seven patients with grade 4 transaminitis, six patients had severe dengue [Table/Fig-4].

Transaminitis	Jaundice n (%)	Pain in abdomen n (%)	Bleeding n (%)
Grade 0 (n=3)	0	0	0
Grade 1 (n=17)	1 (5.9%)	4 (23.5%)	0
Grade 2 (n=24)	0	7 (29.2%)	3 (12.5%)
Grade 3 (n=29)	1 (3.4%)	9 (31%)	7 (24.1%)
Grade 4 (n=7)	1 (14.3%)	2 (28.6%)	2 (28.6%)
Total (n=80)	3 (3.8%)	22 (27.5%)	12 (15%)

[Table/Fig-4]: Transaminitis and dengue manifestations.

Thrombocytopaenia with platelet count less than 150×10^3/µL was seen in 77 (96.2%) patients admitted to the ICU and its severity worsened with increasing grade of transaminitis. The mean platelet count was 17.81±13.61×10^3/µL. The patients who did not have transaminitis had a higher mean platelet count at 52.00±41.57×10^3/µL. However, there was no statistically significant association between platelet count and different grades of transaminitis (p-value=0.61) during the course of ICU stay [Table/Fig-5].

Transaminitis grading	n	Packed cell volume (%) (Mean±SD)	Platelet count (×10^3/µL)	
			Mean±SD	Mean rank
0	3	35.67±1.53	52.00±41.57	53.33
1	17	46.24±7.3	19.41±13.17	43.74
2	24	45.33±6.0	16.04±11.25	37.06
3	29	45.52±5.8	14.14±5.19	38.40
4	7	40.86±6.9	20.57±10.47	47.64
Total	80	44.84±6.5	17.81±13.61	
F/χ^2-value		2.66	2.68	
p-value		0.039	0.61	

[Table/Fig-5]: Severity of transaminitis and its association with Packed Cell Volume (PCV), platelet count.

Mean PCV of all patients in the study was 44.84±6.51%. Patients with transaminitis had elevated levels of PCV compared to patients with normal SGOT/SGPT levels. Mean PCV in patients with grade 0, 1, 2, 3 and 4 transaminitis were 35.67±1.53%, 46.28±7.09%, 45.26±6.16%, 45.52±5.80%, 40.86±6.96% respectively. The association between the different grades of transaminitis and PCV was found to be statistically significant (p-value=0.038) [Table/Fig-5]. However, no statistically significant difference was found on comparing two different grades of transaminitis individually [Table/Fig-6].

Grading (I)	Grading (J)	Mean difference (I-J)	Stand ard error	p-value
0	1	-10.569	3.912	0.063
	2	-9.667	3.826	0.096
	3	-9.851	3.789	0.081
	4	-5.190	4.311	0.749
1	2	0.902	1.980	0.991
	3	0.718	1.908	0.996
	4	5.378	2.806	0.317
2	3	-0.184	1.724	1.000
	4	4.476	2.684	0.460
3	4	4.660	2.631	0.398

[Table/Fig-6]: Post-hoc Turkey test for high Packed Cell Volume (PCV) (multiple comparisons).

A total of four patients had Acute Kidney Injury (AKI) during the course of ICU stay and all four had transaminitis. One patient each from grade 3 and grade 4 transaminitis required renal replacement therapy. Only one patient developed ARDS who had normal transaminases. A total of six patients with grade 3 and grade 4 transaminitis required vasopressors for the treatment of shock. Two patients succumbed during the course of ICU stay [Table/Fig-7].

Transaminitis grading	Number of patients	Acute kidney injury (n)	Renal replacement therapy (n)	ARDS (n)	Shock (n)	Death (n)
0	3	0	0	1	0	0
1	17	1	0	0	0	0
2	24	0	0	0	0	0
3	29	1	1	0	4	1
4	7	2	1	0	2	1
Total	80	4	2	1	6	2

[Table/Fig-7]: Severity of transaminitis and organ dysfunction.
*ARDS: Acute respiratory distress syndrome

DISCUSSION

The WHO categorisation of dengue modified in 2009 includes [2]:

- Dengue: fever, nausea, vomiting, body ache, skin rash, leukopaenia, or any warning sign.
- Warning signs include abdominal pain or tenderness, vomiting, clinically evident effusion or ascites, bleeding, hepatomegaly, or rise in haematocrit (≥20%) with rapid reduction in platelet count (<50000/mm^3).
- Severe dengue: severe bleeding, severe plasma leakage, or severe organ impairment includes elevated transaminases beyond 1000 IU/L and central nervous system manifestations or cardiac or other organ involvement.

In this study, the prevalence of dengue without warning signs (11.2%) was lower compared to dengue with warning signs (73.8%) and severe dengue (15%). The inclusion of only ICU patients in the study could be the reason for higher prevalence of more severe cases.

The mean age of the present study patients was 35±13.88 years which is similar to the reported mean age of 34.30±15.0 years in a study conducted in coastal Karnataka by Gandhi K and Shetty M [11]. Among 80 patients in the present study, 47 were males and 33 patients were females (M:F ratio was 1.4: 1) in the present study. This is similar to that reported by Agarwal R et al., and Ray G et al., where the M:F ratio was found to be 1.9:1 and 1:0.57, respectively [12,13].

Transaminitis has been the most common abnormality in dengue related hepatic involvement. Raised AST levels was seen in 63-97% of patients, while raised ALT levels in 45-96% of patients, as per Samanta J and Sharma V [9]. The average AST values ranged from 93.3-174 U/L, while ALT from 86-88.5 U/L in some studies [14,15]. In a Brazilian study, by Souza LJ et al., more than a 10-fold rise was observed in 3.8% cases whereas in other studies such values were encountered between 1.8% and 11.1% of total cases [14,16,17]. The median AST and ALT values have been reported to be higher in severe dengue than for uncomplicated dengue cases [14,18,19]. This indicates a possible association between worsening transaminitis and severe forms of dengue.

Median AST values for dengue without warning signs, dengue with warning signs, and severe dengue were 83.5 U/L, 92 U/L, and 124 U/L, respectively (p-value=0.001); median ALT values were 49 U/L, 53 U/L, and 73.5 U/L (p-value=0.002) in a study by Lee LK et al., [8]. In the present study aminotransferase levels even though had an association could not adequately differentiate between dengue severity.

In the present study, 96.2% of the total patients were noted to have transaminitis. According to EASL-DILI grading of transaminitis the prevalence of grade 1, 2, 3, 4 transaminitis was 21.2%, 30%, 36.2%, 8.7%, respectively [Table/Fig-4]. Six out of seven patients with grade 4 transaminitis had severe dengue and out of twenty nine patients with grade 3 transaminitis, four patients had severe dengue and twenty one patients were noted to have dengue with warning signs.

The second week of dengue illness, a critical phase of effervescences is dominated by plasma leakage manifesting with raised haematocrit levels [20]. Swamy AM et al., reported significantly elevated mean haematocrit levels in cases with raised liver enzymes when compared to patients with normal transaminases haematocrit (42.5±6.4 vs 39.7±7.4%; p-value=0.04) [21].

In the present study, patients with transaminitis had elevated levels of PCV compared to patients without transaminitis. Mean PCV in patients with grade 1, 2, 3 and 4 transaminitis are 46.28±7.09%, 45.26±6.16%, 45.52±5.80%, 40.86±6.96% respectively. The association between transaminitis and highest PCV during the course of ICU stay was statistically significant. However, no statistically significant difference was found on comparing two different grades of transaminitis individually.

Swami AM et al., reported significantly low mean platelet count in patients with transaminitis as compared to patients with normal transaminases {platelet count (81033.7±59256.8) vs (147967.7±44726.9) cumm; p-value ≤0.0001 respectively}. They also found that patients with elevated AST (93.8%) and ALT (81.2%) had a higher occurrence of bleeding. The AST and ALT levels increase with worsening severity of dengue as indicated by a reduction in platelet count since they have a negative correlation with each other (p-value ≤0.0001) [21].

In this study, thrombocytopenia with platelet count less than 150×10^3/μL was seen in 77 (96.25%) patients and its severity worsened with increasing grade of transaminitis. The patients without transaminitis had a higher mean platelet count. However, no statistically significant association could be found between platelet count and different grades of transaminitis during the course of ICU stay.

Coagulopathy {International Normalised Ratio (INR) >1.5} has been documented by Saha AK et al., in 11% of dengue patients [18], while prolonged Prothrombin Time (PT), partial thromboplastic time were noted in 34-42.5% of the cases in other studies [16,17]. Increasing episodes of bleeding are found to be associated with worsening transaminitis [15,22]. In the present study, only two patients had abnormal coagulation parameters and both had severe transaminitis. A 12 (15%) had bleeding manifestations among which nine patients had higher grade of transaminitis.

The onset of Jaundice carries poor prognosis in dengue. Itha S et al., reported jaundice in 15% of their study population while Karoli R et al., Kio CH et al., Trung DT et al., have noted hyperbilirubinaemia among 1.7-17% of dengue patients [4,16,22,23].

In present study jaundice was noted in 3 (3.8%) patients, with one each in grade 1, grade 3 and grade 4 transaminitis.

In the present study, four patients had AKI and all had transaminitis. One patient each from grade 3 and grade 4 transaminitis required renal replacement therapy. One patient who developed ARDS had grade 0 transaminitis. Two patients succumbed during the course of ICU stay; one was a 44-year-old pregnant lady with severe dengue and multiple organ dysfunction syndrome (shock, AKI,) who succumbed within 24 hours of ICU admission. The second patient was a 61-year-old male with multiple co-morbidities who presented with severe dengue and shock, requiring vasopressors, mechanical ventilation and renal replacement therapy during the course of ICU care. These two patients had grade 3 and grade 4 transaminitis, respectively.

Limitation(s)

It was a retrospective study. Only the patients presenting to the ICU were included, possibly leading to congregation of more severe cases. The less severe patients treated in outpatient clinics and wards were missed out. So, the results may not accurately represent the entire population.

CONCLUSION(S)

Transaminitis is very common among the dengue patients in ICU. The grading of transaminitis increases in conjunction with severity of dengue and is associated with thrombocytopenia and organ dysfunction. It has a positive correlation with elevated packed cell volume.

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PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Anaesthesiology and Critical Care, SS Institute of Medical Sciences and Research Centre, Davangere, Karnataka, India.
2. Consultant, Department of Critical Care, AIG Hospitals, Gachibowli, Hyderabad, Telangana, India.
3. Senior Consultant, Department of Critical Care, Manipal Hospital Yeshwanthpur, Bengaluru, Karnataka, India.
4. Senior Consultant, Department of Critical Care, Manipal Hospital Yeshwanthpur, Bengaluru, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Kiran Bada Revappa,
2035/32, 13th Cross, Anjaneya Layout, Davangere, Karnataka, India.
E-mail: drkiranbr@gmail.com

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