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STUDY TO CORRELATE CLINICAL, HEMATOLOGICAL & SEROLOGICAL FINDINGS WITH DISEASE SEVERITY & CLINICAL OUTCOME IN CONFIRMED DENGUE CASES AT A TERTIARY HOSPITAL

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ABSTRACT

Background: Dengue is the most important arthropod borne viral infection of humans. The increasing number of cases and deaths in these patients due to clinical and hematological complications are rising, thus present study was aimed to study correlation of clinical, hematological & serological findings with disease severity & clinical outcome in confirmed dengue cases at a tertiary hospital. **Material and Methods:** Present study was single-center, prospective, observational study, conducted in patients diagnosed as positive for Dengue NS1 antigen or Dengue Ig-M antibodies/ IgG antibodies. **Results:** The maximum numbers of cases were in the age group of 11-20 years (36.80%), followed by in 21-30 years (21.80%). It was observed that the clinical data diagnosis of DF (77.20%) cases, DHF (18.64%) followed by DSS (4.20%). Among the cases the clinical symptoms like Myalgia, Arthralgia, Vomiting, Pain abdomen, Rashes, Shock and tourniquet test was statistically significant.(P<0.05) Out of 500 cases (19.69%) showed positivity for NS1 antigen. The observation for individual markers IgG antibody were statistically significant with p-value of 0.001 and significant for IgM antibody with p-value of 0.03. The observations were statistically significant for combined NS1+IgM and NS1+IgM+IgG with a *p*- value of < 0.01. The correlation of the clinical spectrum of dengue with thrombocytopenia was highly significant with *p*- value was <0.01. The maximum numbers of cases were recovered (93.6%), followed by discharged against medical

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advice or referred (4.6%). The patients expired were 9 (1.8%). The correlation of the clinical spectrum of dengue with died patients was significant with *p*- value was <0.05. The correlation of the thrombocytopenia with died patients was significant with *p*- value was <0.05. **Conclusion:** Pronounced hematological changes are associated with the disease severity and play an important role in recognizing the illness in the early stage.

Keywords: dengue, NS1 antigen, Dengue hemorrhagic fever, dengue shock syndrome.

INTRODUCTION

Dengue is the most important arthropod borne viral infection of humans.[1] WHO estimates 50-100 million cases of Dengue occur each year and more than three hundred thousand cases of Dengue hemorrhagic fever (DHF) are diagnosed each year resulting in 24000 deaths per year. [2] Dengue is an acute viral disease caused by a virus belonging to the broad group of Arboviruses, family Flaviviridae, subfamily Flaviviridae and genus Flavivirus.[3]

This viral infection may be asymptomatic or may cause undifferentiated febrile illness (viral Syndrome), dengue fever (DF), or dengue hemorrhagic fever (DHF), including dengue shock syndrome (DSS). [4] Early diagnosis can be done based on clinical features, hematological parameters and by rapid diagnostic kits for anti-dengue antibodies which are the most readily available tool utilized in all public sector hospitals and private labs.[5]

Among the laboratory methods available for diagnosis of dengue, the serological tests which detect the NS1 antigen and IgM antibodies by MAC ELISA, virus isolation, viral nucleic acid detection tests are considered as the most specific tests. However facilities that can support viral culture are expensive and time consuming and are not always available.[6] The increasing number of cases and deaths in these patients due to clinical and hematological complications are rising, thus present study was aimed to study correlation of clinical, hematological & serological findings with disease severity & clinical outcome in confirmed dengue cases at a tertiary hospital

MATERIAL AND METHODS

Present study was single-center, prospective, observational study, conducted in department of Pathology, at Al-Ameen Medical College and Hospital, Vijayapur and District Hospital Vijayapur. India. Study duration was from December 2016 to July 2018.. Study approval was obtained from institutional ethical committee.

Inclusion criteria

- Patients diagnosed as positive for Dengue NS1 antigen or Dengue Ig-M antibodies/ IgG antibodies, willing to participate in present study

Exclusion criteria

- Patients aged less than 05 years and above and 70 years
- Serological positive cases of dengue which are also positive for other co existent infections like malaria, typhoid etc

Study was explained to patients in local language & written consent was taken for participation & study. Data such as socio-demographic details such as age, sex, occupation,

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marital status, complaints, findings of the clinical examination, hematological findings and serological findings with outcome was collected.

For serology a venous blood sample was collected from patients and transported to the laboratory immediately. SD Bioline Dengue NS1+ Antibody Combo Card Test Kits was used to detect NS1 antigen, IgM and IgG antibodies and the test results were express as positives/negatives for antigen and both antibodies.

On admission, 5 ml of blood was drawn from antecubital vein. Hematological parameters were done by collecting 2 ml of venous blood sample in EDTA prefilled tubes/bulbs and transported to the laboratory immediately. The analysis was done by the automated Hematology analyzer ABX Pentra 60: 5 part Analyzer. The samples were coded according to standard operating procedure to eliminate the bias in the study. The cases were classified as Anemia, Leukopenia, and Thrombocytopenia following the WHO Classification (1997). All data analysis had been done by using SPSS (version 22) for windows. The initial measures of each group were compared with the final measures of the study

RESULTS

The maximum numbers of cases were in the age group of 11-20 years (36.80%), followed by in 21-30 years (21.80%). The patients ranged from 05 to 70 years and mean age among the distribution of cases was 24.16 ±10.12 years. Out of 500 cases females (283 cases; 56.6%) were the most affected with Dengue infection when compared to males (217 cases; 43.4%) and male to female ratio was 1:1.31. Among children males (98 cases; 19.60%) outnumbered females (92 cases; 18.40%) and male to female ratio was 1:0.93; while in adults females (157 cases; 31.40%) outnumbered males (153 cases; 30.60%) and male to female ratio was 1:1.03. It was observed that the clinical data diagnosis of DF (77.20%) cases, DHF (18.64%) followed by DSS (4.20%).

Table 1: General characteristics

Age groups (in years)	**No. of patients**	**Percentage**
5-10	83	16.60
11-20	184	36.80
21-30	109	21.80
31-40	36	07.20
41-50	41	08.20
51-60	33	06.60
61-70	14	02.80
Mean age (mean ± SD)		
Gender		
Male	217	43.40
Female	283	56.60
Final diagnosis		
DF	386	77.20
DHF	93	18.60
DSS	21	04.20

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The mode of presentation in the present study was fever (100%), followed by headache (70.2%), myalgia (63%), arthralgia (48.2%), retro-orbital pain (46%), pain abdomen (21.2%), hepatomegaly (21.6%), rashes (17.4%), petechiae (13.8%), Splenomegaly (13.4%) and CNS manifestations (1.4%). Among the cases the clinical symptoms like Myalgia, Arthralgia, Vomiting, Pain abdomen, Rashes, Shock and tourniquet test was statistically significant.(P<0.05)

Table 2: Relation of clinical presentation of dengue cases among final diagnosis:

Clinical Presentation	DF		DHF		DSS		*p*-value
	No	%	No	%	No	%	
Fever	386	100.00	93	100.0	21	100	0.31 (NS)
Headache	251	65.03	79	84.95	21	100	0.43 (NS)
Myalgia	243	62.95	65	69.89	07	33.33	0.03 (S)
Arthralgia	219	56.74	16	17.20	06	28.57	0.03 (S)
Retro-orbital pain	172	44.56	47	50.54	11	52.38	0.001 (S)
Vomiting	61	15.80	46	49.46	08	38.10	0.01 (S)
Pain abdomen	53	13.73	41	44.09	12	57.14	0.003 (S)
Rash	41	10.62	39	41.94	07	33.33	0.011 (S)
Tourniquet test	76	19.69	23	24.73	21	100.00	0.04 (S)
Petechiae	16	4.15	34	36.56	19	90.48	0.73 (NS)
Hepatomegaly	57	14.77	33	35.48	18	85.71	0.06 (NS)
Splenomegaly	19	4.92	31	33.33	17	80.95	0.81 (NS)
Shock	00	0.00	08	8.60	21	100	0.001 (S)
Pleural effusion	00	0.00	15	16.13	08	38.10	0.06 (NS)
Ascites	00	0.00	17	18.28	07	33.33	0.08 (NS)
CNS manifestation	00	0.00	03	3.23	04	19.05	0.12 (NS)

Out of 500 cases (19.69%) showed positivity for NS1 antigen. The observation for individual markers IgG antibody were statistically significant with p-value of 0.001 and significant for IgM antibody with p-value of 0.03. The observations were statistically significant for combined NS1+IgM and NS1+IgM+IgG with a *p*- value of < 0.01.

Table 3: Distribution of dengue cases according to serology

Test	DF	%	DHF	%	DSS	%	*p*-value
NS1	76	19.69	11	11.83	00	0.00	0.12 (NS)
IgM	84	21.76	34	36.56	00	0.00	0.03 (S)
IgG	40	11.92	12	12.90	00	0.00	0.001 (S)
NS1+IgM	63	15.80	17	18.28	07	33.33	0.004 (S)
IgM+IgG	53	13.73	21	22.58	11	52.38	0.21 (NS)
NS1+IgM+IgG	00	0.00	00	0.00	03	14.29	0.0001 (S)

The majority of the patients had Anemia (47.4%) followed by normal hemoglobin (36.4%) and increased hemoglobin percentage (16.2%). Among the distribution of cases based on hemoglobin levels, Anemia was statistically significant with a *p*-value of <0.05.

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Hematocrit levels ranged from 13.9% to 58.5% with mean being 32.2%. Hematocrit levels were raised in (34.6%) cases and found to be decreased in (29.2%) and normal in (36.2%) of the cases. The significant number of cases were showing hemo-concentration among DHF and DSS the raised Hematocrit levels were statistically highly significant with a *p*-value of <0.001.

Leukopenia was observed in (43.6%), Leukocytosis (7.20%) and the WBC counts were normal in (49.2%). The observations for Leukopenia and leukocytosis were statistically significant with *p*-value of 0.01.

Neutropenia were observed in (25.6%) of cases, Neutrophilia were seen in (9.8%) and normal Absolute Neutrophil Counts (64.6%). Neutropenia were observed in DHF (56 cases), DSS (11 cases) and DF (61 cases) cases. The observation for Neutropenia were statistically significant with a *p*-value of <0.01.

Among cases absolute lymphocyte count were normal in (12.60%) cases, lymphopenia in (33.4%) cases and showed lymphocytosis in (54%) cases. The values observed for lymphocytosis and lymphopenia were statistically significant with a *p*-value of 0.05.

The platelet count ranged from 17,000 to 5,63,000 /cumm with the mean of 1,20,046 /cumm. Out of 500 cases (62.6%) cases showed thrombocytopenia (platelet < 100,000 cells/cumm and 187 (37.4%) cases showed platelet count above or equal to 1, 00,000/cumm. The correlation of the clinical spectrum of dengue with thrombocytopenia was highly significant with *p*- value was <0.01.

Table 4: Correlation of Clinical spectrum and hematological profile

	No. of Cases (%)	**DF**	**DHF**	**DSS**	***p*-value**
Hemoglobin (gm/dl)					
Anemia (<12)	237 (47.40 %)	207	24	06	0.012 (S)
Normal (12-15)	182 (36.40 %)	109	58	15	0.08 (S)
Increased (>15)	81 (16.20 %)	70	11	00	0.03 (S)
Hematocrit					
Decreased (<35%)	146 (29.20 %)	146	00	00	0.001 (S)
Normal (35-40%)	181 (36.20 %)	181	00	00	0.0002 (S)
Increased (>40%)	173 (34.60 %)	59	93	21	<0.001 (S)
TOTAL WBC COUNT (c/cumm)					
Leukopenia (<5000)	218 (43.60 %)	155	50	13	0.03 (S)
Normal (5000-11,000)	246 (49.20 %)	197	41	08	0.21 (S)
Leukocytosis (>11,000)	36 (07.20 %)	34	02	00	0.01 (S)
Absolute Neutrophil count (c/cumm)					
Neutropenia (<1600)	128 (25.60 %)	61	56	11	0.001 (S)
Normal (1600-9000)	323 (64.60 %)	289	24	10	0.002 (S)
Neutrophilia (>9000)	49 (09.80 %)	38	11	00	0.001 (S)

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Absolute Lymphocyte count (c/cumm)					
Lymphopenia (<800)	167 (33.40 %)	115	47	05	0.01 (S)
Normal (800-5500)	63 (12.60 %)	43	04	16	0.08 (NS)
Lymphocytosis (>5500)	270 (54.00 %)	228	42	00	0.03 (S)
Platelets (c/cumm)					
<1,00,000	313 (62.60 %)	232	90	21	0.021 (S)
≥1,00,000	187 (37.40 %)	154	03	00	0.001 (S)

The maximum numbers of cases were recovered (93.6%), followed by discharged against medical advice or referred (4.6%). The patients expired were 9 (1.8%). The correlation of the clinical spectrum of dengue with died patients was significant with *p*- value was <0.05.

Table 5: Correlation of Clinical spectrum and Outcome:

Outcome	**No. of Cases (%)**	**DF**	**DHF**	**DSS**	***p*-value**
Expired	468 (93.60 %)	382	74	12	0.09 (NS)
Discharged/Referred	09 (01.80 %)	00	00	09	0.03 (S)
Recovered	23 (04.60 %)	04	19	00	0.21 (NS)

The correlation of the thrombocytopenia with died patients was significant with *p*- value was <0.05.

Table 6: Correlation of thrombocytopenia and outcome:

Outcome	**No. of Cases (%)**	**DF**	**DHF**	**DSS**	***p*-value**
Expired	468 (93.60 %)	228	74	12	0.41 (NS)
Discharged/Referred	09 (01.80 %)	00	00	09	0.04 (S)
Recovered	23 (04.60 %)	04	16	00	0.39 (NS)

DISCUSSION

Dengue fever continues to be one of the important public health problems in India. Dengue virus infection may be asymptomatic or may cause undifferentiated febrile illness (viral Syndrome), dengue fever (DF), or dengue hemorrhagic fever (DHF) including dengue shock syndrome (DSS).

In the present study, the maximum numbers of cases were in the age group of 11-20 years (36.80%), followed by in 21-30 years (21.80%). The patients ranged from 05 to 70 years and mean age among the distribution of cases was 24.16 ±10.12 years. This may be due to young adults are being more active outside from the home. The findings of the present study were similar to the observations by conducted by studies by Shaista Choudhary et al.,[7] and Prathyusha et al.[8] The mean age of distribution was 23.13 years.

In the present study, out of 500 cases females (283 cases; 56.6%) were the most affected with Dengue infection when compared to males (217 cases; 43.4%) and male to female ratio was 1:1.31. The findings were similar to the studies conducted by Fransisca RF

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et al.,[9] females (53.25%) and males (46.5 %). In present and other study showed that the incidence of dengue is more common in males than females this is because males are more frequently exposed to the risk of acquiring dengue than females because of their outdoor life which they lead.

In the present study, the mode of presentation in the present study was fever (100%), followed by headache (70.2%), myalgia (63%), arthralgia (48.2%), retro-orbital pain (46%), pain abdomen (21.2%), hepatomegaly (21.6%), rashes (17.4%), petechiae (13.8%), Splenomegaly (13.4%) and CNS manifestations (1.4%). Similar findings were noted by Low et al.,[10] Kalayanarooj et al.,[11] Neeraja et al.,[12] & Singh et al.,[13]

The dengue cases were classified as per criteria by WHO (1997), into DF, DHF and DSS. The present study showed DF (77.2%) cases which was almost correlating with the studies conducted by Sri Rezeki et al.,[14] (67.1%). The present study had (18.6%) DHF and (4.2%) DSS. The occurrence of DSS when compared with the study of Kumar et al.,[15] (7.3%) had a good correlation.

In the present study of 500 cases (19.69%) showed positivity for NS-1 antigen, (21.76%) were positive for Ig-M antibodies and (11.92%) were positive for Ig-G antibodies alone. The NS-1 positivity was comparable to the studies of Datta et al.,[16] (23.3%). The serological pattern for the Ig-M and Ig-G was almost comparable to the studies conducted by Kularatne et al.,[17] with Ig-M (18%) and Ig-G (12%). In the present study the cases positive for combined NS-1 + IgM; was correlating with the study of Kulkarni et al.,[18] (11%). In the studies of Kularatne[43] et al they had not considered NS-1 in the panel. It can be stated that the diagnosis of dengue would have been missed in many of their cases.

The dengue cases positive for any solitary marker in the present study (65.4%) was close to observations of Ho et al.,[19] (64.7%), Neeti M et al.,[20] (53.5%) and Jaitley et al.,[22] (52.2%). The findings in present study in general, substantiate the findings as reported in earlier studies and reaffirm the use of NS-1 antigen and Ig-M/Ig-G as complimentary diagnostic tests in suspected cases of dengue infections.

In the present study, the maximum numbers of cases were recovered (93.6%), followed by discharged against medical advice or referred (4.6%). The patients expired were 9 (1.8%). Similar findings were seen in study by Rajesh Deshwal et al.,[22] (1.8%) mortality and Vibha Gajera et al.,[23] (0.77%).

Significant morbidity and mortality can result if early recognition and monitoring of severe forms are not done. If left untreated, the mortality of DHF or DSS patients may be as high as 40-50%. Early recognition of illness, careful monitoring and appropriate fluid therapy alone have decreased mortality to 1%. If shock is identified when pulse pressure starts to drop and intravenous fluids are administered, the outcome will be excellent. Recovery is fast and most patients recover in 24-48 hours without any sequelae. The outcome may not be so good if the patient develops cold extremities.

Most deaths from DHF/DSS are caused by prolonged shock, massive bleeding, fluid overload and acute liver failure with encephalopathy. Severe refractory shock, DIC, ARDS, liver failure and neurological manifestations singly or in combination were the commonest causes of death in a recent series.

Dengue infection is increasing proportional to increased urbanization and compromised sanitation measures. Fever associated with headache, retroorbital pain,

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erythematous morbilliform rash, conjunctival suffusion and itching in palms and soles along with thrombocytopenia, leucopenia, should prompt a clinician on the possibility of dengue infection. Platelet transfusions have little role in management of dengue patients. Early diagnosis, careful monitoring and proper fluid management goes a long way in reducing the mortality due to dengue hemorrhagic fever and shock syndrome.

CONCLUSION

Detection of NS1 antigen and IgM & IgG antibodies were positive in all the cases of dengue when done with rapid card tests. A single NS-1 / Ig-M marker was elevated in DF cases and more than one parameter was seen elevated in DHF and DSS cases. Among the hematological parameters the severity of anemia was more in DF cases whereas leukopenia, thrombocytopenia and raised hematocrit was more predominant in DHF and DSS cases.

Pronounced hematological changes are associated with the disease severity and play an important role in recognizing the illness in the early stage and these would be the appropriate steps taken to modify the outcome of the disease. This study concludes that parameter like platelet count, haematocrit, leukocyte count & serological studies aid greatly in clinical monitoring of patients.

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