Original Research Article

The Dreadful Dengue - A Complete Clinical Chemical Complication Comparison

Dr. Venkata Tulasi Ramesh Potluri[1], Dr. Santhosh Kumar Arepalli[2], Dr. Eswar Ganti[3], Dr. Anjaneya Prasad Velivala[4], Dr. Lakshmi Spandana Potluri[5]

[1]Associate Professor of Pediatrics, [2]Assistant Professor of General Medicine, [3]Professor Emeritus of General Medicine, [4]Professor and Head of Department Of General Medicine, [5]Post Graduate Student in Department Of General Medicine,
Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation, Gannavaram, Andhra Pradesh

Corresponding Author: Dr. Lakshmi Spandana Potluri

ABSTRACT

Background: Dengue infection results from four dengue virus serotypes (DEN-1,2,3,4) of Flavivirus genus. It is the most common arboviral infection with half the world's population at risk every year. Recovery from infection by one serotype provides lifelong immunity against that serotype. In the absence of an effective antiviral agent, the treatment mainly relies on judicious fluid replacement.

Materials and methods: This is a hospital based descriptive study with 200 patients of confirmed dengue fever admitted from March 2017 to Feb 2018 and 200 from March 2018- Feb 2019. Detailed history was taken. CBP, LFT, RFT, chest X-ray, cardiac evaluation and ultrasound was done.NS1Ag, IgM and IgG dengue antibodies were estimated using Rapid strip test. The diagnosis of dengue fever, dengue hemorrhagic fever and dengue shock syndrome was based on WHO criteria.

Results: Amongst the clinical manifestations, fever was the constant symptom. There was a decrease in number of patients presenting with headache(p-0.001) and myalgias(p-0.561) while there was a significant increase in the number of patients presenting with conjunctival congestion (p-0.081), vomiting(p-0.001), rash(p-0.012), pain abdomen(p-0.041), bleeding manifestations (p<0.0001). There was an increased derangement lab parameters - hemoconcentration (p-625), leucopenia (p-0.0001), thrombocytopenia (p-0.0001), hyperbilirubinemia (p-0.06), deranged RFT(p-0.312) and liver enzymes (evaluated in categories 2-4 fold, 5-10fold, >10fold increase) SGOT(p-0.004), SGPT(p-0.002) in the present year when compared to the previous year. Evaluation of the complications showed a decrease of hypotension, while there was an increase in serositis, AKI, ARDS, DSS and hematoma formation. There were 3 cases of dengue myocarditis in 2018-19 while there were none in 2017-18. There were no fatalities in 2017-18 while there were 3 mortalities in 2018-19

Conclusion: The sudden morbid increase in the number of patients presenting with hepatopathy which could be attributed to infection with a newer serotype of Dengue virus in a previously infected patient. In the absence of an effective antiviral agent against dengue, the need for early detection management is essential to combat complications like hepatopathy and myocarditis which may prove to be fatal.

Key Words: Dengue, Hepatopathy, Myocarditis, Clinical Study, Dengue Shock Syndrome, Dengue Haemorrhagic Fever, Viral Fever

INTRODUCTION

Dengue infection in humans results from four dengue virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) of Flavivirus genus. It is the most prevalent arboviral infection in humans with almost

half of the world's population at risk every year. [1,2]

Recovery from infection by one serotype provides lifelong immunity against that particular serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections by other serotypes increase the risk of developing severe dengue. [3]

Dengue, the most extensively spread mosquito-borne disease in the world is transmitted by infected mosquitoes of Aedes species. It is the 2nd most common arthropod borne disease in India succeeding malaria. Dengue is a major international health concern that is prevalent in tropical and sub-tropical countries.

Dengue fever had a predominant urban distribution a few decades earlier, but recent researches reported an increase in prevalence from peri-urban as well as rural areas. [4,5] The expansion of dengue in India has been related to plan urbanization, changes in environmental factors, inadequate vector control, host-pathogen interactions and population immunological factors.

Dengue virus infections cause a wide clinical spectrum of disease, from a mild febrile illness known as 'dengue fever' through to 'severe dengue', previously known as dengue haemorrhagic fever (DHF), which is characterized by capillary leakage leading to hypovolaemic shock, organ impairment and bleeding complications

Dengue fever presents with a myriad of symptoms which other than fever include but are not limited to myalgias, arthralgias, retro-orbital pain, conjunctival congestion, headache, vomiting and pain abdomen. Bleeding manifestations like melena, hematuria, bleeding gums, palatal petechiae may also be observed.

Commonest complications of dengue include hypotension followed by serositis and acute kidney injury while the less desirable complications involve the liver and cardiac parameters, manifesting as hepatopathy and myocarditis.

There are no antiviral drugs currently affective against the treatment of dengue. The treatment mainly relies on the judicious fluid replacement without overzealous management which could lead to complications like pleural effusion.

In the absence of effective antiviral treatment, a dengue vaccine has been long pursued to curb dengue transmission and reduce the increasing disease and economic burden of dengue worldwide. [6,7]

CYD-TDV is the first licensed dengue vaccine for individuals 9-45 (or 60) years of age marketed under the name of Dengvaxia®. It is a live-attenuated recombinant tetravalent vaccine administered in doses 6 months apart. Several trials have demonstrated the safe reactogenicity [8] and good immunogenicity profile of the vaccine against all serotypes. [9,10]

It was observed that over all ages (2–16 years) and among 9–16 year olds, CYD-TDV is protective against serotypes 1, 3 and 4 regardless of baseline serostatus, while efficacy against serotype 2 was significant only for dengue pre-exposed subjects. [11] Dengvaxia (R) has not yet been approved by the Ministry of Health and Family Welfare, Government of India, because more clinical trials are thought to be necessary.

Due to dengue presenting with a myriad of intersystem symptoms and complications, exact identification of clinical manifestations is important for management and limitation of the disease. The present study is a continuation of the study conducted a year earlier [12] in the same hospital in an attempt to delineate the salient clinical features and laboratory findings and compare the presentation in serologically confirmed hospitalised cases of dengue fever during the study period

MATERIALS AND METHODS
The study was undertaken as a hospital based descriptive study with

prospective and retrospective data collection. Four hundred patients with confirmed dengue fever admitted in a tertiary health care centre during a period of 2 years from March 2017 to Feb 2019 (200 patients from Feb 2017- March 2018 and 200 patients from March 2018 to Feb 2019 were selected for this study. Data from a study done previously in 2017-18 in the same centre was taken [12] and additional parameters were evaluated and compared prospectively with the data of patients admitted in the year 2018-19

NS1Ag, IgM and IgG dengue antibodies were estimated using Rapid strip test. The diagnosis of dengue fever, dengue hemorrhagic fever and dengue shock syndrome was based on the WHO criteria. [13]

Patients with classical features of dengue-fever with chills, myalgias, headache, rash, conjunctival congestion, bleeding manifestations and thrombocytopenia and had a definite positive strip test were included in the study. Patients who had malaria and enteric fever were excluded from the study.

Detailed history was taken and all the patients were clinically evaluated. A complete blood count, liver function tests, renal function tests, chest X-ray, cardiac evaluation and USG abdomen were also done.

Statistical Methods:

The various parameters were tabulated and the mean and confidence interval was calculated. Chi square test and independent t test was used. The significant p value was calculated using chi square test. P value <0.05 was considered as significant. IBM spss21 version software I was used to analyse the data.
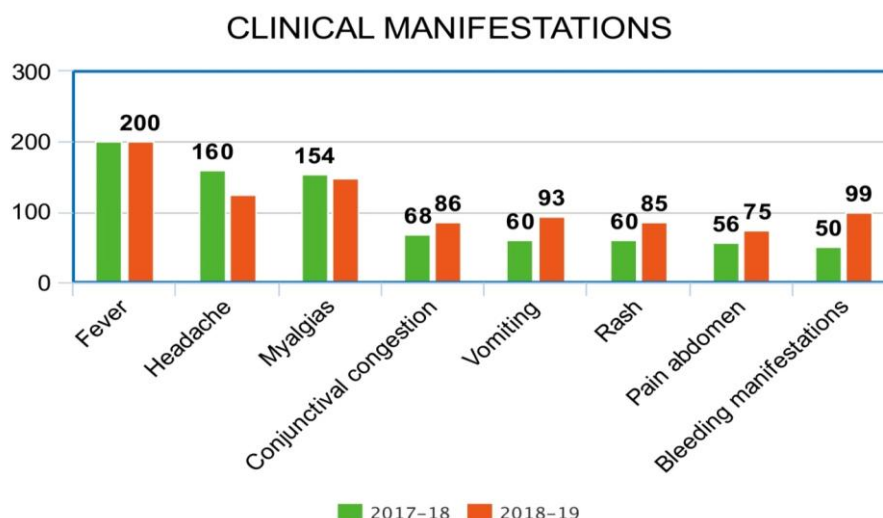
RESULTS

Data of 200 confirmed dengue patients from March 2017 to Feb 2018 was taken, statistically analysed and compared to the data of 200 patients admitted from March 2018 to Feb 2019. Most of dengue cases occurred during the month of July to October, which depicts the role of rainy season on clustering of cases.

Table 1: Number of males and females in our study

	2017-18	2018-19	
Males	60%	71%	Increased by 11%
Females	40%	29%	Decreased by 11%

In the year 2017-18 60% of the admitted patients were male while 40 percent were female. However, there was an increase in the number of male patients (71%) and a decrease in the number of female cases (29%) admitted in the year 2018-19. In both the years, maximum number of patients belonged to the age group of 20-45 with majority in the 4th decade of life.

Clinical features evaluated included- fever, headache, myalgias, conjunctival congestion, vomiting, rash, pain abdomen, bleeding manifestations and were statistically analysed.

Table 2: A comparision of the various presenting symptoms and their frequency can be seen in the table below: (significant parameters have been underlined)

| CLINICAL FEATURE	2017-18	2018-19		CHI SQUARE VALUE	P VALUE
FEVER	200	200	Constant	constant	-
HEADACHE	160	124	Decreased by 18%	0.487	0.561
MYALGIAS	154	149	Decreased by 2.5%	3.421	0.081
CONJUNCTIVAL CONGESTION	68	86	Increased by 9%	11.52	0.001
VOMITING	60	93	Increased by 16.5%	6.761	0.012
RASH	60	85	Increased by 12.5%	4.09	0.041
PAIN ABDOMEN	56	75	Increased by 9.5%	26.66	<0.0001
BLEEDING MANIFESTATIONS	50	99	Increased by 24.5%	13.267	<0.0001

Fever was the most common presentation and followed by headache and myalgias in 2017-18 while the number of patients presenting with myalgias exceeded the number presenting with headache in 2018-19. An increasing trend was seen in the number of patients presenting with associated symptoms like vomiting, blanching erythematous rash over body, pain abdomen, conjunctival congestion and bleeding manifestations while a significant decreasing trend was seen in the patients presenting with headache.

Laboratory parameters that were deranged included hemoconcentration, leukopenia, thrombocytopenia, deranged RFTs and deranged LFTs.

Table 3: A comparison of laboratory parameters (significant deviations have been underlined)

	2017-18	mean	SD	2018-19	mean	SD	Analysis	t value	p value
HEMATOCRIT > 40	120	46.37	11.4	116	45.8	10.4	Decreased by 2%	O.49	0.625
LEUKOPENIA	70	7830.5	3176.7	156	5959.9	2469.8	Increased by 43%	6.57	0.0001
THROMBOCYTOPENIA	140	89.58	57.03	161	69.46	55.2	Increased by 10.5%	3.58	0.0001
DERANGED RFT	16	-	-	23	-	-	Increased by 3.5%		0.312
HYPERBILIRUBINEMIA	42	2.09	3.36	79	2.7	3.5	Increased by 18.5%	-1.88	0.06
ELEVATED SGOT	100	151.9	175.2	195	636.7	237.9	Increased by 97.5%	-2.88	0.004
ELEVATED SGPT	44	101.5	117.4	120	518.6	189.4	Increased by 28%	-3.11	0.002
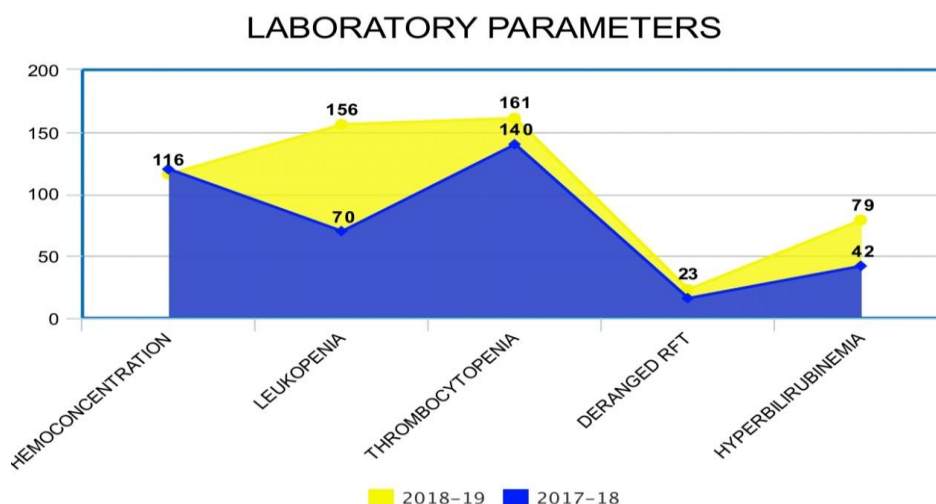
Thrombocytopenia was the most common hematological derangement seen in the patients with increase in the number of patients presenting with thrombocytopenia in 2018-19. Hemoconcentration was the next common manifestation followed by leukopenia. There was more than a 2 fold increase in the patients presenting with

leukopenia in 2018-19 when compared to 2017-18.

There was almost a 2 fold increase in the number of patients presenting with hyperbilirubinemia and also a significant increase in terms of numbers in the patients presenting with renal impairment.

Comparison of the elevation of liver enzymes SGOT and SGPT were:

Table 4: A comparison of SGOT (significant deviations have been underlined)

SGOT> 40	2017-18	2018-19	Analysis
2-4 FOLD INCREASE	40	68	Increased by 14%
5-10 FOLD INCREASE	55	95	Increased by 20%
>10 FOLD INCREASE	5	32	Increased by 13.5%

Table 5: A comparison of SGPT(significant deviations have been underlined)

SGPT >40	2017-18	2018-19	Analysis
2-4 FOLD INCREASE	6	18	Increased by 6%
5-10 FOLD INCREASE	36	78	Inceased by 21%
> 10 FOLD INCREASE	2	24	Increased by 11%

There is a remarkable increase in the elevation of SGOT in patients of dengue. 100 patients had increased levels of SGOT in 2018-19 while 195 patients had elevated SGOT levels in 2018-19.
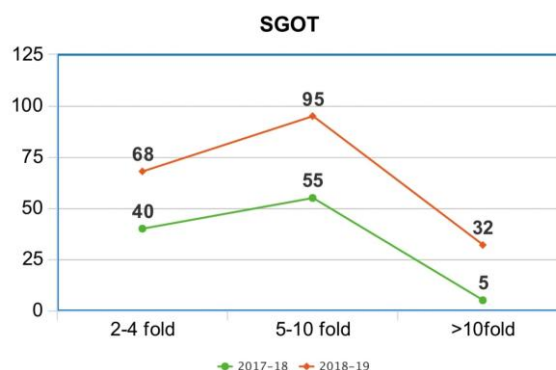
44 patients presented with an increase of SGPT levels while 120 patients had elevated SGPT levels in 2018-19. There was a 12 fold increase in the number of patients with severely deranged SGPT (SGPT>400)
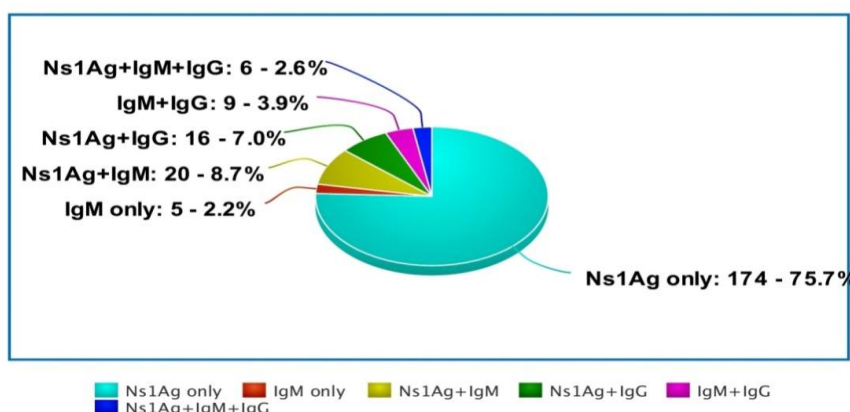
Out of the 400 patients diagnosed as having dengue fever, the diagnostic parameters were as follows:

Table 6: A comparison of serological parameters

	Ns1Ag only	IgM only	Ns1Ag + IgM	Ns1Ag+ IgG	Ig M+ IgG	Ns1Ag+ IgM+ IgG+
2017- 18	144	5	20	16	9	6
2018-19	148	9	18	11	6	8

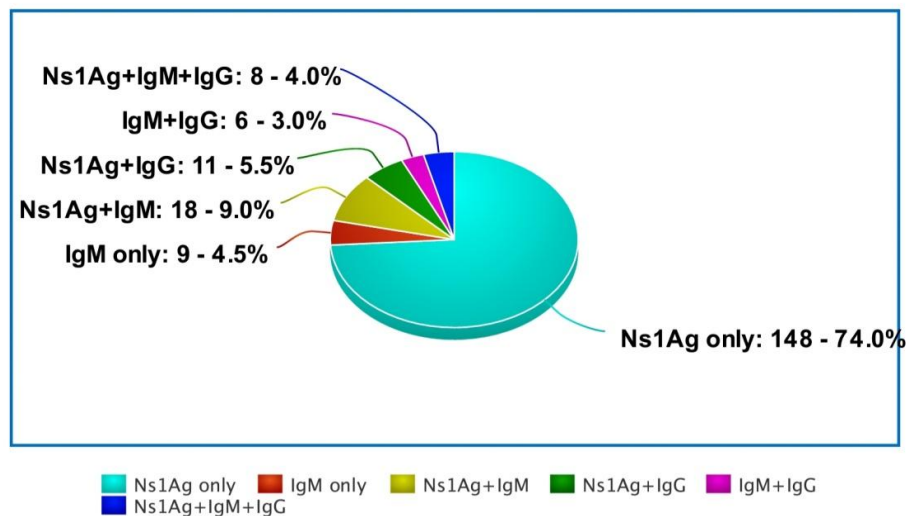Significant variation was not seen in the serological parameters.

DIAGNOSTIC PARAMETERS 2017-18

DIAGNOSTIC PARAMETERS 2018-19

Ns1Ag+IgM+IgG: 8 - 4.0%
IgM+IgG: 6 - 3.0%
Ns1Ag+IgG: 11 - 5.5%
Ns1Ag+IgM: 18 - 9.0%
IgM only: 9 - 4.5%
Ns1Ag only: 148 - 74.0%

■ Ns1Ag only ■ IgM only ■ Ns1Ag+IgM ■ Ns1Ag+IgG ■ IgM+IgG
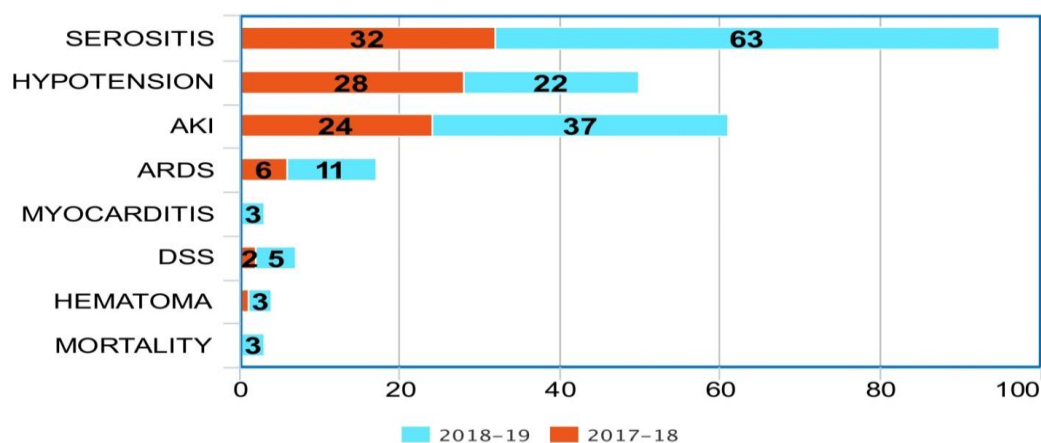■ Ns1Ag+IgM+IgG

Complications identified included serositis, hypotension, dengue shock syndrome, renal failure, myocarditis, hematoma formation, ARDS and mortality.

Table 7: A comparison of the complications studied (significant deviations have been underlined)

	2017-18	2018-19	Analysis
SEROSITIS	32	63	Increased by 15.5%
HYPOTENSION	28	22	Decreased by 3%
AKI	24	37	Increased by 6.5%
ARDS	6	8	Increased by 1%
DENGUE MYOCARDITIS	0	3	Increased by 1.5%
DSS	2	5	Increased by 1.5%
HEMATOMA FORMATION	1	3	Increased by 1%
MORTALITY	0	3	Increased by 1.5%

There was a rise in the occurance of complications in 2018-19 in comparision to the previous year except for hypotension which showed a downward trend.There was a significant increase in the number of patients presenting with serositis, with pleural effusion being the most common form followed by ascites.

COMPLICATIONS

SEROSITIS 32 63
HYPOTENSION 28 22
AKI 24 37
ARDS 6 11
MYOCARDITIS 3
DSS 2 5
HEMATOMA 3
MORTALITY 3

0 20 40 60 80 100

■ 2018–19 ■ 2017–18

Formation of a large gluteal hematoma in a patient of dengue with thrombocytopenia after an IM injection was seen in 2017. A splenic subcapsular

hematoma was detected by ultrasonography in a dengue patient who presented with fever, pain abdomen and had thrombocytopenia and >10 fold rise of liver enzymes in Aug 2018. Iatrogenic hematoma formation in the deltoid was seen in two dengue patients post IM injection in 2018.

No deaths were reported in 2017-18. There were 3 mortalities in 2018-19. One of the patients was diagnosed with IgM seropositivity and was concluded as having superadded sepsis with MODS with evidence of sepsis and rhabdomyolysis. The other patient had detectable Ns1Ag positive and presented with severe thrombocytopenia (platelets 10K) and hypotension and was diagnosed with DSS. One more patient with Ns1Ag positivity presented with heamaturia, melena, hypotension, pleural effusion, serositis and was diagnosed as having DSS and the cause of death was found to be hypovolemic shock.

DISCUSSION

Dengue is a self-limited, systemic viral infection transmitted between humans by mosquitoes. The rapidly expanding global footprint of dengue is a public health challenge with an economic burden that is currently unmet by licensed vaccines, specific therapeutic agents, or efficient vector control strategies.

Only the patients who were seropositive for Ns1Ag or IgM were considered for the study. When results for the two years were studied, there wasn't much differentiation in the serological parameters. Non structural protein1 (NS1) dengue virus antigen begins to appear in blood from day one of infection while IgM antibodies from seventh day onwards. Dengue specific IgG antibody appear after 14 days and persist for life in case of primary infection and rise within 1-2 days after onset of symptoms in secondary infection. [15]

In the present study maximum numbers of patients were admitted in the rainy season (August to October). Stagnation of water on roadside ditches and in various other areas is related to favourable conditions for growth of vector Aedes aegypti. In this comparative study, the admissions were maximum in the month of August to September. Majority of cases were reported during monsoon & post monsoon seasons, in accordance with the reported patterns of dengue transmission. [14] The correlation between occurrence of dengue and monsoon is clearly evident in this study and previous studies conducted. [16][17]

In 2017-18 most of the patients admitted belonged to the age group of 15-40 years. The same trend occurred in 2018--19 as well. This was also reported in other studies. [17] In both the years, maximum number of patients admitted belonged to the 4th decade of life. Results from a study done by Surendrakumar et al showed a maximum number of cases in the 3 rd decade of life [18] However, when dengue fever presented in individuals greater than 50 years of age, there was an increase in the rate and severity of complications, which could be attributated to reinfection with a differet serotype. This increase in severity is substantiated by the facts published in WHO guidelines. [3]

Males and females presented in a ratio of 1:1.39 (60% and 40%) respectively in 2017-18. There was an increasing male preponderance (71%) in 2018-19 with male to female ratio being 2.45:1. The male to female ratio is found to1.7:1, in a study conducted by Ashwini Kumar et al, [14] whereas another study by Rajesh et al [17] showed slightly higher ratio of 2.67:1 which is close to our statistics of 2018-19.

An analysis of the clinical manifestations of dengue shows that fever was the most common presenting symptom. History of recordable fever or clinically recorded fever was present in all the 400 patients included in our study.

In 2017-18, headache was the next most common symptom seen in about 80% of the patients while in 2018-19, there was a decrease in the occurrence of headache, with 61% of the patients presenting with

headache. Myalgia was the next common presentation which also presented in a decreasing trend. 2017-18 had more patients manifesting with headache while compared to myalgias while the study in 201-19 shows more patients presenting with myalgias compared to headache. This result correlated with the study done by Anuradha et al, whose study population most commonly presented with myalgias followed by headache. [19]

There was a significant increase in the number of patients presenting with abdominal pain and vomiting in 2018-19 when compared to 2017-18. There was also a 10% increase in the number of patients presenting with conjunctival congestion.

Bleeding manifestations were increased two fold in 2018-19 compared to the previous year. However this remarkable increase in the number of patients presenting with bleeding manifestations was not associated with a similarly significant increase in the number of cases presenting with thrombocytopenia. There was a 50% increase in the number of cases had bleeding manifestations while there was only a 10% increase in the patients presenting with thrombocytopenia. Bleeding manifestations reported in other studies include, Ashwini Kumar [14] et al, reported in 26.6% and Tejushree A. et al, reported in 3.84% of patients. [20]

When the various hematological parameters were analysed, there was a slight reduction in the number of cases presenting with hemoconcentration, while there was a significant >2 fold rise in the number of patients presenting with leukopenia. Increased hematocrit was seen in about 30% on the patients in the study conducted by Mavilla et al, while our study had an increase of 60-58%. Prafulla Datta et al [21] reported 30% of the patients presented with leukopenia while our study had 30% of patients presenting with leukopenia in 2017-18 and 78% patients presenting with leukopenia in 2018-19.

Hyperbilirubinemia was seen in 42 patients in 2018-19 while 79 patients presented with hyperbilirubinemia in 2018-19. This considerable increase could be attributed to an increasing presentation of hepatopathy in cases of dengue. Results of hyperbilirubinemia in our study were not in accordance with the results in a study conducted by Narasimhan et al, who only had 5% of patients presenting with hyperbilirubinemia. [20]

When the elevation of liver enzymes was evaluated, it was noticed that there was a morbid rise in the elevation of SGOT and SGPT levels in 2018-19 when compared to 2017-18.The number of patients with mild and moderate increase of SGOT levels doubled while there was a 6 fold rise in the number of patients who had a >10% rise in SGOT levels. The percentage rise of SGOT levels in previous studies were as follows:

SGOT	Narasimhan et al [22]	Amit Soni et al [23]	Surendra et al [18]	Dr. pisms 2017-18	Dr.psims 2018-19
2-4 FOLD	26%	45%	16%	20%	34%
4-10 FOLD	25%	36%	8%	27.5%	57.5%
>10 FOLD	15%	16%	12%	2.5%	18%

SGPT levels were also found to be significantly elevated in 2018-19 when compared to the previous year. The number of patients with a mild rise in SGPT levels increased 3 fold, while the number with moderate rise increased 2 fold and a dramatic increase was seen in the number of patients with >10 fold rise of SGPT levels which increased by 12 fold. When compared to other studies the results were as follows

SGPT	Narasimhan et al [22]	Amit soni et al [23]	Surendra et al [18]	Dr. Psims 2017-18	Dr. Psims 2018-19
2-4 FOLD	18%	27.8%	10%	3%	9%
4-10 FOLD	20%	59%	8%	18%	39%
>10 FOLD	11%	8.9%	12%	1%	12%

Comparision of all these studies also showed that there was a significantly higher rise in the SGOT levels compared to the SGPT levels.

Serositis was found th be the most common complication in both the years. The incidence of AKI was found to increase in 2018-19 when compared to 2017-18. Hypotension presented with a decreasing trend in 2018-19 when compared to 2017-18, however there were two deaths in 2018-19 due to hypotension precipitating hypovolemic shock. Other studies also reported deaths due to hypotension in seropositive dengue patients. [24][25] ARDS was found in 3% of the cases in our study. A study by Ashwini et al shows ARDS to be the significant complication occurring in 33% of the patients. [12]

Dengue myocarditis was not reported in 2017-18 while our study in 2018-19 reported the incidence of 3 cases of dengue myocarditis. This was confirmed by echocardiogram and troponin levels. The presence of tachycardia and development of shock early in the disease were seen in patients with dengue myocarditis. Hepatopathy and myocarditis were also reported in other studies as the complications of dengue which needed strict observation and intervention failing which there was recorded fatality secondary to these complications. [25]

Gluteal hematoma formation was reported in one case in 2017-18 secondary to an IM injection. Iatrogenic deltoid hematoma formation secondary to IM injections taken outside our hospital was seen in two patients in 2018-19. A spontaneous splenic subcapsular hematoma formation was also seen in one patient who presented with acute abdominal pain and deranged LFTs in addition to fever and thrombocytopenia. The formation of spontaneous muscle hematomas was also previously reported in other studies. [26]

After analysis of the above parameters, it has been observed that there is an increase in the occurrence of complications which could be attributed to delayed presentation or infection with a different serotypes in the patients admitted into our hospital.

CONCLUSION

Comparative analysis of patients with dengue fever in 2 different years shows that there is a significant increase in the number of patients presenting with complications. There was a sudden morbid increase in the number of patients presenting with hepatopathy which could be attributed to infection with a newer serotype of Dengue virus in a previously infected patient and since most of our patients belonged to their 4th decade of life; living in an endemic area, were more likely to have had a previous dengue infection.

Previous studies prove that the dengue virus can affect any tissue in the human body including the skin, intestines and muscles unlike other viral fevers. Hence proper identification of clinical symptoms and serology tests for patients presenting with fever is necessary for early detection of Dengue fever and to initiate prompt management. Once there is multisystem involvement, there is only supportive management that can be administered in the patient and hope for the best in the absence of an effective antiviral agent affective against the dengue virus.

In the absence of effective antiviral medication and the likely emergence of new strains, there is an increased need for the development of an effective dengue vaccine, for the future generations, especially in the tropical and subtropical countries. Through our study we stress that, detection of hepatopathy in any dengue patient is important from the onset of illness and should be tailored to prevent further complications which when left unmanaged may lead into fatalities.

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