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ORIGINAL RESEARCH

Seroprevalence and Hematological Patterns of Dengue Fever with Special reference to Dengue serotyping during the period of Covid-19 pandemic in & around Ahmedabad region, Gujarat

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ABSTRACT

Background and Aim: Dengue fever is an old disease, but in the past 25 years there has been a marked global emergence and re-emergence of it, with more frequent and larger epidemics with more severe disease experienced. Dengue has been known to exist in India for more than 200 years, over the past two decades, the disease's epidemiology has undergone a significant transformation, with larger and more frequent outbreaks being documented in both urban and rural areas. The goal of the current study is to determine the seroprevalence of dengue, to know the hematological parameters in dengue positive cases and to know circulating serotypes of dengue virus in our region during the period of Covid-19 pandemic. **Material and Methods:** This study was conducted at one of the tertiary health care centers in Ahmedabad, Gujarat, India from January to December 2021. The study included the patients with dengue symptoms like fever, headache, myalgia, joint pain, bleeding etc. A total of 12247 samples from suspected dengue cases were processed. Out of 12247 samples, 7663 were analyzed by dengue NS1 antigen detection ELISA kit and 4584 by using NIV dengue IgM capture according to their duration of illness. From dengue negative samples, 445 (representative samples which were negative for dengue IgM antibody or NS1 antigen) were also tested for dengue IgG capture ELISA to know dengue IgG sero-prevalence. 108 dengue-positive samples were analyzed for dengue serotyping by molecular method. **Results:** Dengue virus seroprevalence is 9.77% in our study. Out of 1197 dengue cases, 860 (71.85%) were NS-1 positive and 337 (28.15%) were IgM positive. Cases peaked in October (30.08%). Study reveals dengue infection trends increases during and after rainfall. 38.03% of dengue positive cases having thrombocytopenia & 10.44% cases having raised hematocrit value are at risk of sever dengue fever. Most prevalent circulating serotype in our region is dengue virus type 2. Circulation of multiple serotypes and concurrent infections are also found in our region. **Conclusion:** Current pandemic of COVID-19 have no effect on dengue prevalence. Detection of hematological profile in dengue patients and dengue NS1 antigen test both are very helpful in early diagnosis of dengue infection moreover hematological profile acts as predictor in prognosis of disease and thus early treatment and effective control measures can be provided to population to prevent the catastrophic complications like DHF or DSS or death. Knowledge of circulating serotypes help us to know the current status of the serotypes in the region and can help in prediction of forthcoming outbreak.

Key Words: Dengue, Dengue NS1 antigen, Fever, Thrombocytopenia, Dengue serotypes

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INTRODUCTION

Arthropod-borne viruses (arbovirus) are a major burden on the health-care system worldwide. Dengue virus (DENV) is the most rapidly spreading arboviruses (RNA virus). Dengue virus, is a cause of great concern to public health in India. Every year, thousands of individuals are affected and contribute to the burden of health care. Dengue outbreaks have continued since the 1950s but severity of disease has increased in the last two decades.[1]

DENV is transmitted by the Aedes aegypti and Aedes albopictus mosquito and share spatiotemporal territories.[2] It belongs to the Flaviviridae family. In the early stages of infection, viruses are known to induce acute febrile illness; however, as the infection worsens, the clinical profiles change. According to a molecular clock study, these viruses are thought to have their origins in Africa 200–300 years ago. However, the Malay Peninsula is also taken into consideration as a potential source of DENV.[1] Dengue fever is an old disease, but in the past 25 years there has been a marked global emergence and re-emergence of dengue fever epidemics occur.The reasons for this global pandemic are not fully understood, but are thought to result from major demographic and societal changes that have occurred since World War II. It is estimated that between 50–100 million cases of dengue fever, 500,000 cases of DHF/DSS and more than 20,000 deaths occur each year. [3]

From 2015 to 2019, dengue cases in South East Asia (SEA) region increased by 46% (from 451,442 to 658,301). A variety of factors are responsible in SEAR for expansion and distribution of dengue mosquito vector and viruses viz. high rates of population growth, inadequate water supply and poor storage practices, sewer and waste management systems, rise in global commerce and tourism, global warming, changes in public health policy, and the development of hyper-endemicity in urban areas etc. The current situation of the high burden of dengue cases in the SEA region is coupled with the absence of effective treatment, and lack of comprehensive sustainable vector control.[4] The number of dengue cases reported to WHO increased over 8-fold, from 505,430 cases in year 2000, to over 2.4 million in year 2010, and 5.2 million in year 2019. Reported deaths between the year 2000 and 2015 increased from 960 to 4032, affecting mostly younger age group.[5]

Recently the world has experienced the most devastating pandemic of Covid-19. The goal of the current study is to determine the seroprevalence and hematological profile of dengue in patients attending tertiary care hospital in Ahmedabad and to know dengue serotypes prevalent in this region during the period of current pandemic.

MATERIAL AND METHODS

Present cross- sectional descriptive study was conducted at Microbiology department of one of the tertiary care centers in Ahmedabad, Gujarat, India from January to December 2021. All the patients having clinical signs & symptoms of the dengue such as fever, headache, myalgia, joint pain and bleeding manifestations etc., were included in the study. Ethical approval to conduct this study has been is taken from the Institutional Ethical Committee.

All the relevant details from the patient were elicited using preformed proforma. Intravenous samples approximately 3 to 5 ml were taken in plain vacutainers for serological tests and in EDTA vacutainers for hematological tests. Samples in plain vacutainers were centrifuged at 3000 rpm for 5 minutes for separation of serum. Patient information from the lab request form was loaded into the laboratory information system, and sample ID was generated in accordance with the test request. Serum samples were preserved at 4° C till testing.

A total of 12247 samples were processed from patient having signs and symptoms of the dengue infection. Out of 12247 samples, 7663 samples were tested with dengue NS1 antigen detection ELISA kit (Microlisa kit), in which history of duration of illness was less than or equal to 5 days and 4584 samples were tested with NIV dengue IgM capture ELISA (MAC ELISA), in which history of duration of illness was more than 5 days. Among dengue positive samples, 108 samples were also tested for real time Reverse Transcripted Polymerase Chain Reaction (rRT PCR) and for multiplex real time RTPCR kit to detect dengue serotypes. A total of 987 Dengue patients' EDTA samples were processed for hematological examination by Horiba Pentra XLR cell counter.

Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2019) and then exported to data editor page of SPSS version 19 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were described as means and standard deviations or median and interquartile range based on their distribution. Qualitative variables were presented as count and percentages. For all tests, confidence level and level of significance were set at 95% and 5% respectively.

RESULTS

A total of 12247 samples from the patients having signs and symptoms of dengue infection were enrolled in this study. Out of the total samples, 7663 samples were tested with dengue NS1 antigen detection ELISA kit (Microlisa kit), and 4584 samples were tested with NIV dengue IgM capture ELISA kit (MAC ELISA) according to their duration of illness, among which, 1197 (09.77%) patients were found positive for dengue, which is shown in table 1.

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Table 1: NS1 antigen and IgM antibody serological test distribution among dengue cases

Test Name	Total samples tested from suspected cases	Positive cases from suspected cases	Percentage of positive cases from total positive cases (n=1197)
Dengue NS1 Antigen ELISA	7663 (62.57%)	860 (11.22%)	71.85%
Dengue IgM Capture MAC ELISA	4584 (37.43%)	337 (7.35%)	28.15%
Total	12247 (100%)	1197 (9.77%)	100%

Out of 1197 positive samples maximum number of dengue positive cases were found in age group 21 to 30 years (366, 30.58%), followed by 11 to 20 years (303, 25.31%) and 0 to 10 years (213, 17.79%) (table 2).

Table 2: Age distribution of dengue positive cases

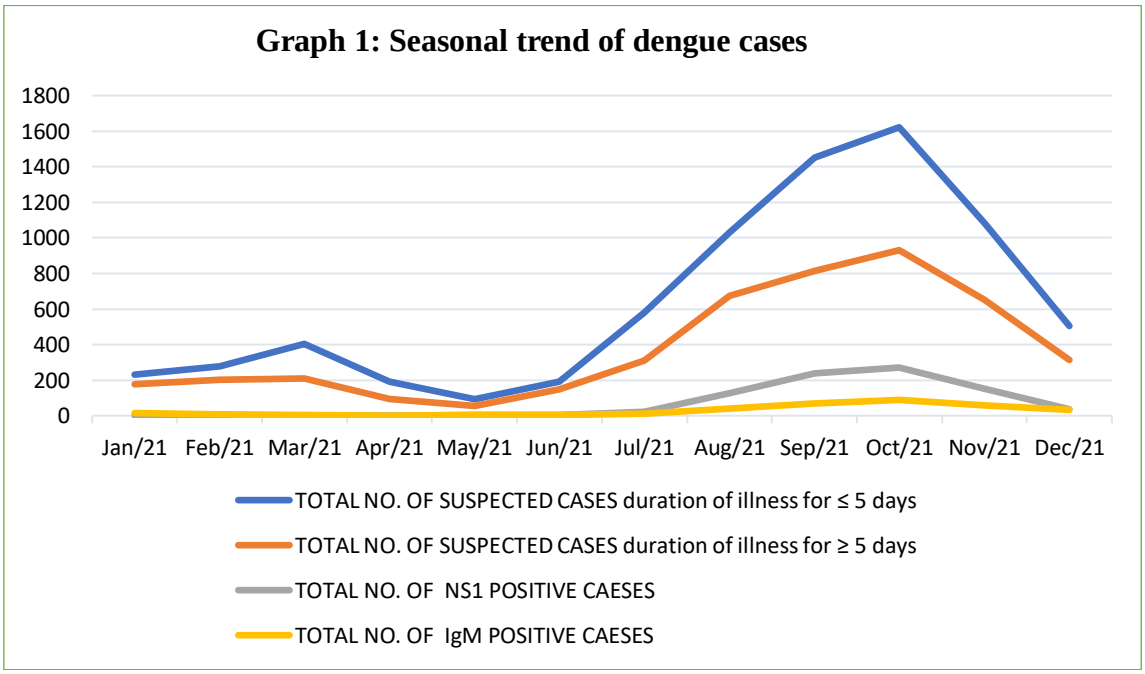
Age	Total Suspected Dengue Cases	Total(NS1 + IgM) Positive Dengue Cases
0 to 10	1457	213 (17.79%)
11 to 20	2352	303 (25.31%)
21 to 30	3597	366 (30.58%)
31 to 40	1822	150 (12.53%)
41 to 50	1331	90 (7.52%)
51 to 60	934	45 (3.76%)
Above 60	754	30 (2.51%)
Total	12247	1197 (100%)

Table 3 shows gender distribution among dengue positive cases. It shows that males (63%)were affected higher than females (37%) and male to female ratio is 1.7:1

Table 3: Gender distribution of dengue cases

Gender	Total suspected cases	Total(NS1 +IgM) Positive cases
Male	6612 (53.99%)	754 (63%)
Female	5635 (46.01%)	443 (37%)
Total	12247	1197 (100%)

Monthly distribution of positive cases shows that maximum number of dengue positive cases were found in October 360(30.08%) followed by September 308(25.73%) and November 211(17.63%). Gradual increase in dengue cases were reported from July. (Graph 1)



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A total of 986 dengue positive cases were evaluated for Hematological parameters like platelet count, WBC count and hematocrit value. As shown in table 4, among total 986 cases, 38.03 % of the cases had less than one lakh platelet count and 61.97% of cases had more than one lakh platelet count. Total 236 (23.94%) dengue cases had below 4 thousand WBC count (leucopenia) and 750 (76.06%)denguecaseshadabove4thousandWBCcount. 103 (10.44%) dengue cases had raised hematocrit from baseline, 357 (36.21%) dengue cases had low hematocrit and 526 (53.35%) dengue positive cases had baseline normal hematocrit.

Table 4: Hematological parameters in dengue

Haematological Parameters		Number of positive cases (n =986)	Percentage
Platelet count	< 1 lakh/cumm	375	38.03%
	>1 lakh/cumm	611	61.97%
WBC count	<4000/cumm	236	23.94%
	4000-10000/cumm	632	64.10%
	≥11000/cumm	118	11.96%
Haematocrit value	< 35 %	357	36.21%
	35 % to 45 %	526	53.35%
	> 45 %	103	10.44%

It is evident from table 5, that Dengue serotype 2 (74.07%) was more prevalent in our region than other serotypes.

Table 5: Prevalence of dengue serotype (n=108)

Serotype	Positive	Percentage
DENV1	14	12.96%
DENV2	80	74.07%
DENV3	11	10.19%
DENV4	0	0%
DENV1&2	3	2.78%
Total	108	100%

DISCUSSION

Dengue virus (DENV) disease may present with a range of acute clinical manifestations from undifferentiated symptoms, such as fever, myalgia, and headache, to the severe disease including plasma leakage, hemorrhage, and eventually death. India contributed to 6% of total dengue cases of SEAR during 2009, which has increased to 33.5% in 2018.[6] Dengue infection can be identified by, a number of laboratory techniques including detection of NS1 antigen, IgM antibody and IgG antibody ELISA, viral isolation, RNA detection, and rapid diagnostic test.[2]

This study includes cases, presented with clinical signs and symptoms suggestive of dengue, at tertiary care hospital, Ahmedabad from January 2021 to December 2021, during ongoing COVID-19 pandemic. A total of 12247 blood samples were tested for dengue. Of the total samples tested, 1197 were found positive for dengue infection. So seroprevalence of acute dengue infection in our study is 9.77% (1197/12247) which is well correlated with study carried out by Patel P et al[7] (9.68%) and Patel Bhavikakumari C et al[8] (11.52%). Study done by Kumar M et al[9] showed only 3.55% dengue positivity, which was very low compare to this study & reason behind it may be due to study duration, which was from July 2014 to June 2015, which was done quite few years ago in comparison to current study. COVID-19 pandemic has very little impact in the cases of dengue fever in year 2021.

Majority of the patient attended the hospital in their acute phase of the disease i.e., in first 5 days of the fever and illness so, they were tested by dengue NS1 antigen ELISA (n=7663, 62.57%) from which 860 (11.22%) were found positive. NS1 antigen is a highly conserved glycoprotein for all the dengue serotypes and it stimulates a strong humoral response. It is detectable in blood from the first day after the onset of fever, and is also detectable in the presence of IgM antibodies and even when viral RNA is negative by RT-PCR.[10] So, detection of this antigen is very useful in early diagnosis of dengue infection. Among the total patients, 4584 patients visited hospital after 5 days of the fever, so they were tested by dengue IgM Capture MAC ELISA (n=4584, 37.43%) from which 337 (7.35%) were found positive. Out of the total 1197 dengue (NS1+ IgM) positive cases, 860 (71.85%) were NS-1 antigen positive, 337 (28.15%) were dengue IgM antibody positive. Our data shows accordance with the study done by Patel S D et al[11] which shows 78.71% dengue NS1 antigen positive cases and 21.28% dengue IgM antibody positive cases.

In this study, dengue positivity was highest (n=366, 30.58%) in the adult age group of 21 to 30 years followed by the younger age group of 11 to 20 years (n=303, 25.31%), children of 0 to 10 years (n=213, 17.79%), 31 to 40 years (n=150, 12.53%), 41 to 50 years (n=90, 7.52%), 51 to 60 years (n=45, 3.76%) and above 60 years (n=30, 2.51%). This finding is

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well correlated with study done by Tadavi J et al[12] and Patel S D et al[11] in which 21-30 years age group showed highest prevalence of 29.60% & 36.30% respectively.

From the total 1197 dengue positive cases, 63% (754/1197) were males and 37% (443/1197) females, which is correlated with other studies done by Kumar M et al[9], Patel P et al[7], Tadavi J et al[12] and Chhotala YH et al.[13] This may be due to males are more exposed during day time by bite of aedes mosquitoes as they travel frequently and may be due to negligent health behavior among the Indian female.

Seasonal trend of the dengue cases showed that gradual increase in the cases reported in July, pick appeared on October & then the cases started to decline. Sporadic cases also appeared during the summer season. The high number of cases during monsoon and post monsoon season are due to increasing number of aedes vector due to high breeding and longer survival during rainy season.

A total of 986 dengue positive individuals, were followed up for their hematological profiles like platelet count, WBC count and hematocrit level. Study shows that 375 (38.03%) dengue cases had less than 1 lakh/cu mm platelet count which indicate thrombocytopenia and 611 cases (61.97%) had more than 1 lakh/cu mm platelet count. Ferede G et al[14] found 59.8% cases of thrombocytopenia and Patel Bhavikakumari C et al[8] found 27.97% cases of thrombocytopenia in dengue cases. Laboratory findings such as thrombocytopenia and a rising hematocrit in DHF cases are usually observed by day 3 or 4 of the illness.[15] The complex mechanism of thrombocytopenia remains unclear. Possible mechanisms of thrombocytopenia could be, direct bone marrow suppression by the virus; anti dengue antibody-mediated platelet destruction, peripheral consumption of platelets and isolated viral replication in the platelet. It can be due to increased peripheral destruction, inadequate production or abnormal pooling. [15]

Out of 986 dengue positive cases, 236 (23.94%) cases had WBC count below 4000/cu mm (leucopenia), 632 (64.10%) dengue positive cases had WBC count between 4000-10000/cu mm and 118 cases (11.96%) had more than 11000/cu mm WBC count. This data correlates with the study done by Patel Bhavikakumari C et al[8] in which they observed 22.87% cases of leucopenia. Ferede G et al[14] found 26.5% cases of leucopenia and Joshi A A et al[16] observed 36% cases of leucopenia in their study. Leukopenia is well established feature of dengue fever which is due to the direct marrow suppression by the virus.[8] It is evident from table 5 that, 103 (10.44%) dengue cases had raised hematocrit from baseline which is well correlated with study carried out by Ferede G et al[14] (9.8% cases).

Based on the clinical and laboratory parameters, dengue infection is divided in dengue fever and severe dengue hemorrhagic manifestation. Platelet count less than 1 lakh and hemoconcentration more than 20% quantifies for the diagnosis of DHF. Hemoconcentration is an abnormality observed in this disease which is measured by increased hematocrit. Higher hematocrit is related to increased severity and is explained by the increased plasma permeability which is the basic pathophysiological alteration in dengue.[8] Progressive increase in hematocrit level and rapid decrease in platelet count are the warning signs of critical phase (leakage phage) of moderate dengue fever that is an early objective indicator of plasma leakage. The disease may progress towards sever DF and these cases are the candidates for immediate intravenous fluid replacement.[17] In our study 38.03% cases had platelet count less than 1lakh/cu mm and 10.44% cases had hematocrit value more than 45%. So, according to the above criteria these cases may progress towards sever dengue infection or DHF and need to be monitored carefully.

It is observed that out of 108 serotyping cases, 80 (74.07%) cases were identified as dengue serotype 2 (DENV-2), followed by 14 (12.96%) cases as dengue serotype 1 (DENV 1), 11 (10.19%) cases as dengue serotype 3 (DENV 3) and 3 (2.78%) cases had found with dual infection of DENV 1 and DENV 2. It is evident that dengue serotype 2 is more prevalent than other serotypes in our region. Gupta A et al[18] and Alagarasu K et al[19] also observed that DENV-2 was the most prevalent serotype in their studies.

A multi-centre study carried out by Viral Research & Diagnostic Laboratory Network (VRDLN) in India in 2018, showed circulation of all four serotypes in Gujarat.[19] Our study shows co-circulation of DENV 2, DENV 3 & DENV 1in our region in 2021 (during COVID-19 pandemic duration) in Gujarat. Thus, circulation of multiple serotypes in our region suggest that Gujarat is becoming hyperendemic state & this is known to increase the probability of secondary infection, leading to a higher risk of severe dengue disease.[20]

Concurrent infections with multiple serotypes (DENV 2 & DENV 1) in the same patient are observed in 2.78% of cases in our study. This is due to co-circulation of several serotypes of dengue viruses in our region.[21] This may influence the clinical expression of the disease & is considered as a major factor for the emergence of DHF.[22] Among all the serotypes combinations, Antibody dependent enhancement (ADE) is remarkably observed when serotype 1 infection is followed by serotype 2, which also claims to be the most severe form of dengue infection.[2] According to the present study, serotype 1 prevalence was 13%, so these patients are to be tressed and monitored carefully for reinfection to prevent grave complications happening in future.

CONCLUSION

The continued annual occurrence of DENV fever in India leads to unprecedented conditions, which cause severe complications, an increase in the burden on the

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healthcare system, and other specialized services. In spite of ongoing COVID-19 pandemic, prevalence of dengue in our study remains comparably same as that of previous years. Dengue is more prevalent in the adult age group and it has more preference towards the male gender. Population who are at risk for daytime biting of mosquitoes should be counselled for use of mosquito control measures e.g., repellents, creams, liquids and wearing full sleeve shirts and full pants with socks.

Dengue NS1 antigen detection is very helpful in early diagnosis of acute dengue infection. Thrombocytopenia, increased hematocrit and leucopenia are initial evidence of dengue infection and constitute value as indicators for provisional and early diagnosis of dengue as well as predictor for sever dengue infection, individually or in combination. So, by assessing the hematological parameters, early effective treatment and control measures can be provided to population and the catastrophic complications e.g., DHF or DSS or death can be prevented.

As multiple serotypes are circulating in our geographical area, Gujarat is hyperendemic region for dengue infection. Circulation of dengue virus serotype 2 (DENV-2) is more prevalent in our region and it has a higher propensity to cause DHF/DSS. Concurrent infection with DENV 2 and DENV 1 is also found in our study. Therefore, monitoring of serotype distribution is necessary to prevent grave complications happening in the future.

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