

## Research Article

# Role of sonography in the assessment of dengue fever with serological correlation

Basawaraj NG<sup>1\*</sup>, T. Arul Dasan<sup>2</sup>, Savitha S Patil<sup>3</sup>, Deepashri B.<sup>4</sup>

<sup>1</sup>Department of Radio-Diagnosis, BGS Global Institute of Medical Sciences & Hospital, Bangalore, Karnataka, India

<sup>2</sup>Department of Radio-Diagnosis, BMC&RI, Bangalore, Karnataka, India

<sup>3</sup>Department of Community Medicine, BGS Global Institute of Medical Sciences & Hospital, Bangalore, Karnataka, India

<sup>4</sup>Department of Radio-Diagnosis, BMC&RI, Bangalore, Karnataka, India

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### \*Correspondence:

Dr. Basawaraj NG,

E-mail: basawarajng@gmail.com

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### ABSTRACT

**Background:** Dengue, caused by a flavivirus has emerged as a major public health problem in the Indian subcontinent. This study was to assess severity of disease by ultrasound findings and to correlate ultrasound findings with blood platelet count.

**Methods:** A Cross sectional study carried out on 210 subjects who had serologically proven dengue fever were included in the study. Ultrasound of abdomen, pelvis and thorax was performed and imaging features were analysed by descriptive and analytical statistics using SPSS version 16. Chi-Square test used and P values  $\leq 0.05$  was considered to be statistically significant.

**Results:** Mean age of patients  $42 \pm 19$  years with 106(50.5%) males and 104(49.5%) females. The Gall bladder wall thickening was noted in majority (92.8%) of the study subjects followed by Right peri-renal collection in 112(53.3%), Splenomegaly in 105(50.0%) subjects and Hepatomegaly in 66(31.4%). The sonographic abnormalities including Gall bladder wall thickening, Right, Left and Bilateral perirenal collection, Splenomegaly, Hepatomegaly, Right and Left pleural effusion, were significantly higher in study subjects with decreased platelet count.

Ascites was the commonest finding in 76 study subjects with platelet count between 60000-79000 (36.2%) and in 144 study subjects (68.5%) in the 20-59 years age group. As the platelet count decreased the severity of ascites increased and was statistically significant ( $p \leq 0.05$ ).

**Conclusions:** A patient who presents with sonographically recognizable complications is more likely to have disease that requires immediate and aggressive management.

**Keywords:** Sonological abnormalities, Dengue fever, Dengue, Platelet count, Serology

### INTRODUCTION

Dengue, caused by a flavivirus has emerged as a major public health problem in the Indian subcontinent. The number of cases of dengue in India is increasing every year with outbreaks occurring in many major Indian cities.<sup>1</sup> Approximately 3 billion people worldwide live in areas at risk for transmission of the dengue flavivirus by the *Aedes aegypti* mosquito, and an estimated 100

million people worldwide are infected with the virus each year.<sup>2</sup>

Dengue has varied clinical manifestations, including dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) and is transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes. Various factors including climate change, migration and expansion of the vectors into new geographic areas has

made dengue a global concern and a significant economic burden on our country. The first reported epidemic of dengue in India was in 1963-64. Presently, dengue outbreaks are frequent and extensive, causing mayhem and testing the limits of our control measures.<sup>3,4</sup>

Four different serotypes of dengue are known, DENV 1-4, with DENV 2 and 3 being the most prevalent serotypes.<sup>4</sup> The most severe infections are caused by co-infection of two different serotypes of the dengue fever. Dengue fever (DF) presents with clinical features of sudden onset of fever with chills, rashes, headache, retro-orbital pain and severe backache. Thrombocytopenia and Hemoconcentration have been characteristics of the disease. Dengue hemorrhagic fever and dengue shock syndrome present with bleeding diathesis and shock respectively.<sup>5</sup>

Diagnosis of dengue fever is made by clinical features, blood picture and serology including immunoglobulin G, immunoglobulin M and non-structural 1(NS1) antigen, the latter being least likely to undergo antigenic variation and present in high concentration in the serum of an infected individual.<sup>6</sup>

Ultrasonography is a safe, low cost dynamic imaging modality which does not utilize ionizing radiation. Sonography is also a portable imaging method and can be done at the patient's bedside. Sonographic imaging findings in a patient correlate with capillary permeability and plasma leakage. Serial imaging with ultrasonography can help in determining the severity of the disease, early recognition of complications and prognosis in patients.<sup>6,7</sup>

For the past few years, dengue outbreaks have been occurring regularly in Bengaluru, India. The purpose of the present study is to correlate findings of sonography of thorax and abdomen with the severity of disease and serology.

## METHODS

The present study was a Cross sectional study. The study was approved by Institute Ethical Committee and procedures followed in this study are in accordance with the ethical standard laid down by ICMR's ethical guidelines for biomedical research on human subjects (2006). A written informed consent was obtained from all the patients who participated in the study after explaining the patient's diagnosis, the nature and purpose of the study.

A total of 210 patients with 4-87 years age group (mean of 42 yrs.) and serologically proven dengue fever were included in the study; the study was performed in tertiary care hospital from June 2014 to November 2014. All the patients underwent, immunological assay for dengue immunoglobulin G, immunoglobulin M antibodies and non-structural protein 1(NS1) antigen. The ultrasound of abdomen and chest was performed to all 210 patients by

two experienced radiologist of having 7 year's experience. The abdomen and pelvis ultrasonography was done to look for free fluid in the peritoneal cavity, gall bladder wall thickening, pericholecystic collection, liver size, liver morphology, spleen size, spleen morphology and intra-capsular Peri renal collection. The chest ultrasonography was done to look for free fluid in the pleural cavities and basal lung pathology.

## Statistical analysis

Data was entered in the SPSS, Statistical analyses were performed by statistics software; SPSS 16 (Chicago, USA). Descriptive statistics was used to provide an overview of socio-demographic profile of the study population. Chi-Square / Fisher exact test was employed to estimate the association between two variables. P values  $\leq 0.05$  was considered to be statistically significant for all tests.

## RESULTS

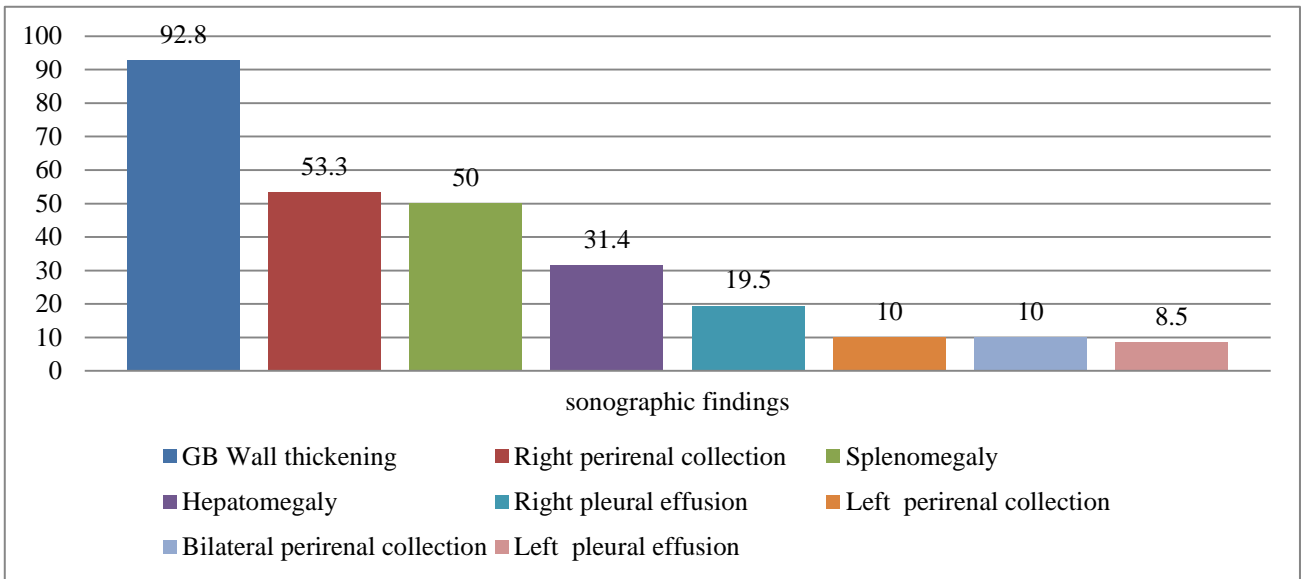
210 subjects with dengue fever were included in the study, with mean age of  $42 \pm 19$  years in the interquartile range 26, 40 and 54 years. There were 106 (50.5%) males and 104(49.5%) females. Majority of them were middle aged, between 20-59 years (68.6%), followed by 44 patients (21.0%) above 60 years and 22 patients (15.1%) below 20 years of age.

Gall bladder wall thickening was noted in majority (92.8%), of the study subjects followed by right perirenal collection in 112 (53.3%), whereas left and bilateral peri-renal collection was observed in 21 (10.0%) cases only. Splenomegaly was present in 105 (50.0%) subjects and hepatomegaly in 66(31.4%). The other findings observed were right and left pleural effusion in 41 (19.5%) and 18 (8.5%) patients respectively [Table 1] and it is also depicted in (Graph).

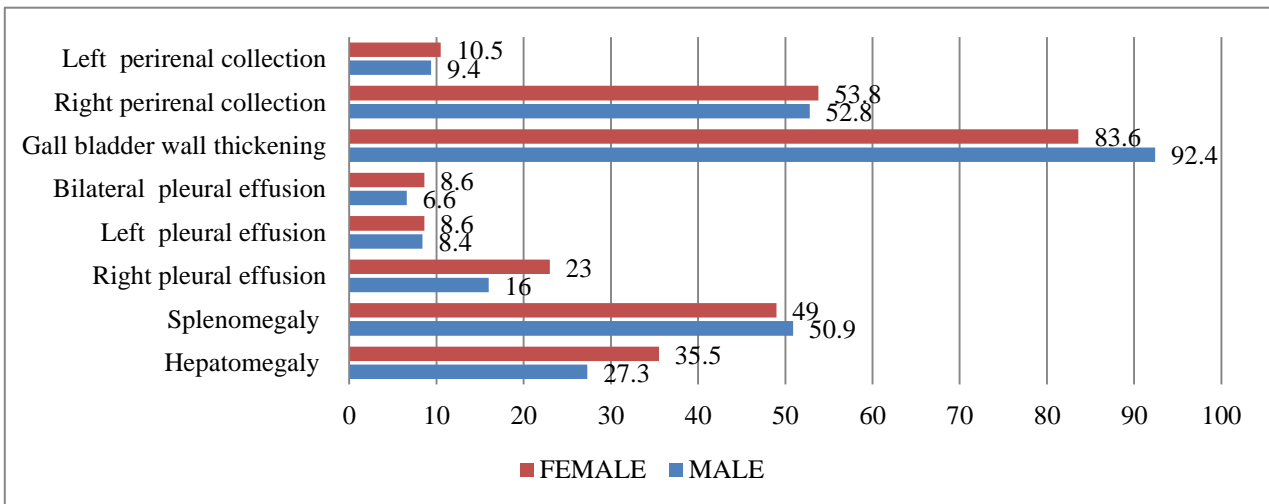
The sonographic abnormalities including gall bladder wall thickening, Right, Left and bilateral perirenal collection, splenomegaly, hepatomegaly, right and left pleural effusion, were significantly higher in patients with platelet count below 40000 [Table 1].

Hepatomegaly and splenomegaly was commonest in 0-19 years ( $\geq 50\%$ ), Right pleural effusion was commonest in 0-10 years (75%), left and bilateral pleural effusion most frequently observed in 11-19 years (38.8%), Right perirenal collection observed in all 4 patients in 0-10 years (100%) whereas left and bilateral perirenal collection most commonly found in 11-19 years (44.4%).

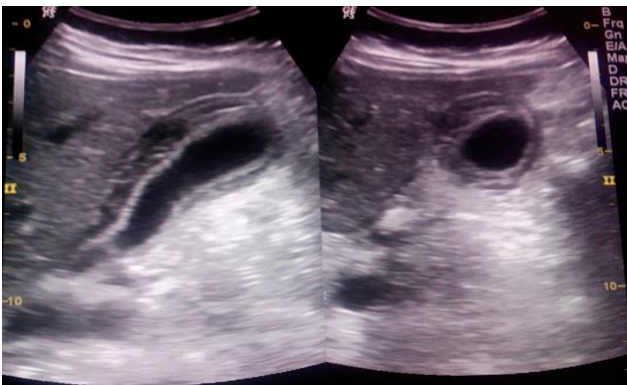
In all the patients splenomegaly, gall bladder wall thickening and right perirenal collection was commonest findings observed.



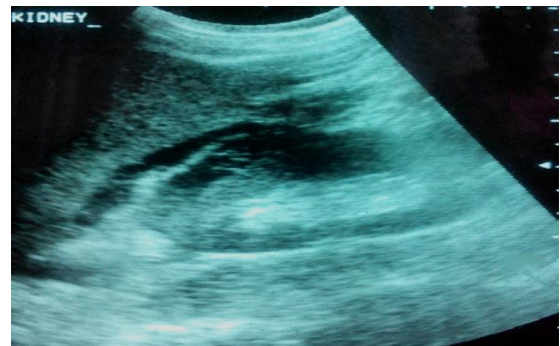
**Graph 1: Ultrasound findings in patients with Dengue fever (percentage).**



**Graph 2: Ultrasound findings in male and female (percentage).**



**Figure 1: Gall bladder wall edema and thickening denoted by white large arrows in a serologically proven 10 years old female patient of Dengue fever.**



**Figure 2: Collection in the hepatorenal fossa (white large arrows) and right intra-capsular perirenal space (5 pointed stars) in a serologically proven 37 years old male patient of Dengue fever.**

**Table 1: Sonographic findings in relation to platelet count.**

Sonographic findings	Platelet count						Total=210	X <sup>2</sup> & P Value
	5000-19000	20000-39000	40000-59000	60000-79000	80000-990000	≥ 1lakh		
Hepatomegaly	2(3.0)	18(27.3)	43(65.2)	3(4.5)	0	0	66(31.4)	1.26, 0.001
Splenomegaly	2(1.9)	18(17.1)	61(58.1)	22(21.0)	2(1.9)	0	105(50.0)	1.22, 0.001
Right pleural effusion	3(7.3)	17(41.5)	21(51.2)	0	0	0	41(19.5)	1.32, 0.001
Left pleural effusion	3(16.7)	14(77.8)	1(5.6)	0	0	0	18(8.5)	1.57, 0.001
Bilateral pleural effusion	3(18.8)	13(81.2)	0	0	0	0	16(7.6)	1.58, 0.001
Gall bladder Wall thickening	2(1.0)	18(9.2)	65(33.3)	76(39.0)	34(17.4)	0	195(92.8)	1.85, 0.001
Right perirenal collection	3(2.7)	18(16.1)	65(58.0)	25(22.3)	1(0.9)	0	112(53.3)	1.38, 0.001
Left perirenal collection	3(14.3)	18(85.7)	0	0	0	0	21(10.0)	2.10, 0.001
Bilateral perirenal collection	3(14.3)	18(85.7)	0	0	0	0	21(10.0)	2.10, 0.001

**Table 2: Association of Sonographic findings in relation to different age groups.**

USG Findings	Age in year's n (%)				Total, n=210	X <sup>2</sup> & P value
	0-10, n=4	11-19, n=18	20-59, n=144	≥60, n=44		
Hepatomegaly	2(50.0)	9(50.0)	48(33.3)	7(15.9)	66(31.4)	8.68, 0.03
Splenomegaly	4(100)	12(66.6)	72(50.0)	17(38.6)	105(50.0)	8.27, 0.04
Right pleural effusion	3(75.0)	8(44.4)	28(19.4)	2(4.5)	41(19.5)	21.23, 0.001
Left pleural effusion	0	7(38.8)	11(7.6)	0	18(8.5)	25.77, 0.001
Bilateral pleural effusion	0	7(38.8)	9(6.2)	0	16(7.6)	29.34, 0.001
Gall bladder wall thickening	4(100)	17(94.4)	136(94.4)	38(86.3)	195(92.8)	3.72, 0.29
Right perirenal collection	4(100)	13(72.2)	82(56.9)	13(29.5)	112(53.3)	16.83, 0.001
Left perirenal collection	1(25.0)	8(44.4)	12(8.3)	0	21(10.0)	30.0, 0.001
Bilateral perirenal collection	1(25.0)	8(44.4)	12(8.3)	0	21(10.0)	30.0, 0.001

**Table 3: Association of ascites with various factors.**

Variables	Ascites n (%)					Total	X <sup>2</sup> & P value
	No ascites	Minimal ascites	Mild ascites	Moderate ascites	Gross ascites		
<b>Platelet count</b>							
5000-19000	0	0	0	0	3(100)	3(1.4)	4.71, 0.001
20000-39000	0	0	1(5.6)	11(61.1)	6(33.3)	18(8.6)	
40000-59000	0	0	56(86.2)	8(12.3)	1(1.5)	65(31.0)	
60000-79000	0	9(11.8)	67(88.2)	0	0	76(36.2)	
80000-990000	1(2.8)	26(74.3)	8(22.9)	0	0	35(16.7)	
≥ 1lakh	13(100)	0	0	0	0	13(6.2)	
Total	14(6.7)	35(16.7)	132(62.9)	19(9.0)	10(4.8)	210(100)	
<b>Gender</b>							
Male	6(5.7)	14(13.2)	72(67.9)	10(9.4)	4(3.8)	106(50.5)	3.21, 0.52
Female	8(7.7)	21(20.2)	60(57.7)	9(8.7)	6(5.8)	104(49.5)	
Total	14(6.7)	35(16.7)	132(62.9)	19(9.0)	10(4.8)	210(100)	
<b>Age category[In Years]</b>							
0-10	0	0	2(50.0)	2(50.0)	0	4(1.9)	44.79, 0.001
11-19	0	1(5.6)	10(55.6)	2(11.1)	5(27.8)	18(8.6)	
20-59	9(6.2)	21(14.6)	94(65.3)	15(10.4)	5(3.5)	144(68.5)	
>60	5(11.4)	13(29.5)	26(59.1)	0	0	44(21.0)	
Total	14(6.7)	35(16.7)	132(62.9)	19(9.0)	10(4.8)	210	

All the sonological abnormalities detected were significantly higher in lower age group that is less than 20 years as compared to  $\geq 20$  years of age groups ( $p \leq 0.05$ ). However gall bladder wall thickening finding was similar in all age groups. (Table 2) There was no significant difference in the sonological abnormalities between males and females ( $p \geq 0.05$ ) (Graph 2).

Ascites was noted in 196 (93.3%) subjects, out of whom 35 (16.7%) had minimal ascites 132 (62.9%) had mild ascites and gross ascites was observed in 19 (9.0%) subjects. Ascites was most common finding in patients with platelet count between 60000-79000 [76 (36.2%)] and in patients in 20-59 years of age group 144 (68.5%). Gross ascites observed in patients with platelet count 5000-19000, moderate ascites with platelet count between 20000-39000, mild and minimal ascites observed in patients with platelet count  $> 40000$ . It is noted that as the platelet count decreases the quantity of ascites increases and which was statistically significant ( $p \leq 0.05$ ). In patient aged 10-19 years gross ascites was commonest with 27.8%, moderate ascites in 0-10 years of age group and mild ascites in 20-59 years of age group and this difference in a ascites grading within different age group was statistically significant. However there was no significant difference in males and females with ascites level [Table 3].

## DISCUSSION

Dengue is emerging as one of the most important mosquito borne diseases in India. *Aedes aegypti* mosquitoes that transmit the disease breed in man-made containers such as tanks, pitchers, discarded containers etc. in which water has stagnated for over a week. Thus, the success of control measures have become a reflection of sanitation and hygienic practices achieved. The cases of dengue peak in the monsoon season in most parts of the country but have become perennial in the southern states and Gujarat.<sup>8,9</sup>

An annual average ( $\pm$  standard deviation [SD]) of 20,474 ( $\pm 13,760$ ) dengue cases and 132 ( $\pm 57$ ) deaths caused by dengue were reported between 2006 and 2012 by the National Vector Borne Diseases Control Program. The number of cases peaked in the year 2013, when 75808 cases were reported with 193 deaths, declining to 33320 cases in 2014 (up to 30th November).<sup>3,8</sup>

However, case fatality rate has steadily declined from 3.3 % in 1996 to 0.3 % in 2013. The situation continues to be grave and a matter of national and global concern.<sup>8</sup>

Dengue has myriad clinical manifestations with unpredictable evolution and outcome. The disease typically begins with an acute febrile phase lasting 2-7 days and is accompanied by flushing, generalized body ache, myalgia, arthralgia and headache. Increased

capillary permeability reflected by progressive increase in hematocrit heralds the beginning of critical phase at around 3-7 days of illness. Severe hemorrhagic manifestations and shock secondary to plasma leakage may occur at this stage. Leukopenia and declining platelet counts are also seen preceding this stage.<sup>6</sup>

Serological diagnosis is confirmatory of dengue and includes direct methods such as virus isolation and NS1 antigen detection and indirect methods such as IgM and IgG antibody detection.<sup>10</sup> It is in the recognition of the complications occurring in the critical phase that sonography has an increasingly important role. Sonography is a readily available, cost-effective method for the recognition of above complications and directly impacts the management of patients with dengue. The commonly recognized sonological abnormalities in the abdomen and thorax of patients in the present study include from thickening of gall bladder wall, ascites, perirenal collection, pleural effusion, hepatomegaly and splenomegaly. Thickening and edema of gall bladder wall was found to be the most frequent finding in our study.

Most of the patients who presented to us were aged between 20-59 years with sonographic findings being more severe in younger than in older patients. All the above imaging features have statistically significant association with the severity of disease as reflected by the patient's platelet count with the most complications occurring at lower platelet counts.

Studies conducted by Balasubramian et al and Srikiatkachorn et al have shown that Ultrasonographic findings of plasma leakage are seen before significant changes in the Hematocrit. Hence, ultrasonography has a high negative predictive value in the diagnosis of dengue hemorrhagic fever.<sup>11,12</sup> A study by Venkata Sai and Krishnan R13 concluded that during an epidemic of dengue, presence of thickened gall bladder wall, pleural effusion and ascites strongly favour the diagnosis of dengue fever.<sup>13</sup>

In another study conducted by Joshi, et al during the epidemic in 1997, right sided pleural effusion was the commonest finding, whereas gall bladder wall thickening was the most frequent finding in ours.<sup>5</sup> Our findings correlated with a similar study conducted by Santhosh et al with gall bladder wall thickening being the most frequent finding in both studies. Pleural effusion was seen in 29.5% of patients while it was seen in 60% of the patients in the study conducted by Santhosh et al.<sup>9</sup> The study by Pramuljo and Harun SR states that pleural effusion can be found on the right and in bilateral pleural spaces but no isolated left pleural effusion, our study agrees with Pramuljo and Harun SR et al.<sup>14</sup> Setiawan et al states that increased gall bladder thickening associated with increased severity of disease, our study agrees with Setiawan et al.<sup>15</sup>



## CONCLUSION

Sonographic features of thickened GB wall, Splenomegaly, Pleural effusion (both or either side), Ascites, Hepatomegaly, Perirenal collection (both or on either side) observed in the present study strongly indicates the diagnosis of dengue fever in patients presenting with fever with other relevant history. The degree of thrombocytopenia showed a significant association to abnormal ultrasound features in our study. All the Sonological abnormalities detected were significantly higher in lower age group < 20 years of age. A patient who presents with sonographically recognizable complications is more likely to have disease which may help in immediate and aggressive management.

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