# Association of cardiac manifestations with the severity of dengue fever

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## Abstract

Background: Cardiac manifestations in dengue virus infection can range from asymptomatic bradycardia to life threatening myocarditis. The several cardiac manifestations of dengue infection include hypotension, sinus bradycardia, rhythm abnormalities, transient ventricular arrhythmias, myocarditis, transient AV block, pericardial effusion and heart failure. Amis And Objectives: To study the association of cardiac manifestations with the severity of dengue fever. Materials And Method: In the study Patients admitted in Ward/ICU hospital having Age group of  $\geq 13$  years and Confirmed dengue serology (Dengue IgG / IgM / NS1 Positive) and Fulfilling the WHO criteria for dengue were selected. Total 110 patients were enrolled in the present study by calculating the sample size with 5% allowable error with 95% confidence interval and considering positive character of 37%. Patient demographic details were noted. All the necessary investigation were performed. All the patients were evaluated using two dimensional echocardiography. The evaluation was repeated on discharge in patients having abnormal findings on first echocardiography. Results: IgM and IgG were positive in 34.55% and 19.09% of the patients respectively; while NS1 was positive in 75.45% patients. Out of 110 dengue patients; 69.1% had dengue fever, 7.3% had dengue shock syndrome and 23.6% had dengue hemorrhagic fever. In the present study based on abnormal cardiac enzymes, echocardiography and ECG 60.09% of the patients were found to have cardiac manifestations. Eight patients were found to have dengue shock syndrome of which one (0.9%) had pericardial effusion while two (1.8 %) had systolic and diastolic dysfunction each. Of the 26 patients with DHF, one (0.9%) had diastolic dysfunction. The difference was statistically significant for all echocardiography findings with respect to dengue severity (P<0.05). Out of the eight patients with DSS, six patients (75%) had positive troponin I. Out of 26 patients with DHF; seven patients (26.9%) had positive troponin I. None of the patients with DF had positivity of troponin I. This indicates the percentage of dengue patients having positive troponin I correlates with severity of dengue fever. The difference was statistically significant (P<0.001). In the present study eight patients were found to have dengue shock syndrome with 87.5% of them having raised CKMB levels compared to 42.3% and 39.5% in dengue haemorrhagic fever and dengue fever respectively. This indicates the percentage of dengue patients having abnormal CKMB correlates with severity of dengue fever. The difference was statistically significant (P<0.05). In the present study all the dengue patients recovered from illness successfully and no mortality was recorded. Conclusion: Thus we conclude that ECG, cardiac enzymes and echocardiography are the main tools to diagnose the myocardial involvement in dengue fever. DHF and DSS cases had higher degree of myocardial involvement as compared to DF cases. Key Words: cardiac manifestations, dengue, echocardiography

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## **INTRODUCTION**

The epidemiology of dengue in India was first reported in Madras (now Chennai) in 1780, and the first outbreak occurred in Calcutta (now Kolkata) in 1963; subsequent outbreaks have been reported in different parts of India.<sup>1,2</sup> The total number of dengue cases has significantly increased in India since 2001. In the early 2000s, dengue was endemic in a few southern (Maharashtra, Karnataka, Tamil Nadu and Pondicherry) and northern states (Delhi, Rajasthan, Haryana, Punjab and Chandigarh). It has recently spread to many states, including the union

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territories.<sup>3</sup>Dengue affects people of all ages. In Southeast Asia. where dengue is hyperendemic, dengue hemorrhagic fever usually affects children younger than 15 years.<sup>4</sup> All four dengue virus serotypes (DENV-1, DENV-2 ,DENV-3 and DENV-4) can cause the disease which can present as a mild self-limiting illness, dengue fever (DF), or as the more severe forms of the disease. dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS).<sup>5</sup> In 2009, the new World Health Organization (WHO) dengue case classification dengue/severe dengue (D/SD) - was introduced, replacing the 1997 WHO dengue case classification: dengue fever/dengue hemorrhagic fever/dengue shock syndrome (DF/DHF/DSS). Although current WHO classification is recommended for continuing use because the newly suggested WHO Tropical Disease Research (TDR) classification creates about two times the workload to health care personnel.6The control of dengue infection presents challenges due to absence of specific treatment or vaccine; also difficulties in vector control. Hence the management of complications during the critical phase of dengue becomes vital. Severe dengue involves various organs like cardiovascular, central nervous system, hepatic, respiratory, renal and muscular systems. Cardiac manifestations in dengue virus infection can range from bradycardia asymptomatic to life threatening myocarditis.<sup>7,8</sup> The several cardiac manifestations of dengue infection include hypotension, sinus bradycardia, rhythm abnormalities, transient ventricular arrhythmias, myocarditis, transient AV block, pericardial effusion and heart failure. Patients with dengue do not have a formal cardiac assessment, so the frequency of subclinical dengue myocarditis and its relative contribution to the hemodynamic instability in severe dengue remains to be demonstrated.

## AMIS AND OBJECTIVES

To study the association of cardiac manifestations with the severity of dengue fever.

## MATERIALS AND METHOD

The present descriptive study was conducted in the Department of Medicine, in tertiary care hospital on patients admitted in hospital suffering with dengue from October 2016 to October 2018.

Patients with dengue fever admitted in medicine wards/ICU in the study institute were enrolled in the study. Following inclusion and exclusion criteria was used to select the study patients.

## Inclusion criteria:

• Patients admitted in Ward/ICU hospital having

Age group of  $\geq$  13 years and Confirmed dengue serology(Dengue IgG / IgM / NS1 Positive) and Fulfilling the WHO criteria for dengue were selected for the study.

#### Exclusion criteria:

- Patients on medications affecting the heart rate / rhythm.
- Patients with history of preexisting heart disease.
- Patients with electrolyte abnormalities affecting the heart rate/rhythm.
- Patients not willing to give consent for the study.
- Patients suffering from mixed infections (Malaria, leptospira).

Thus total 110 patients were enrolled in the present study by calculating the sample size with 5% allowable error with 95% confidence interval and considering positive character of 37%.9Patient details such as name and demographic details were noted on a prestructured proforma. All Patients were subjected to detailed history taking interview so as to ascertain the details of the current illness, any past illnesses similar or otherwise, ongoing medications and to rule out any cardiac disease. All patients underwent general physical and systemic examination. All patients also underwent investigations as detailed further. During general physical examination patients pulse rates and ECG were recorded only after subsidence of fever. Daily monitoring of vital signs were done and lowest recorded pulse rates, blood pressures were noted for purpose of this study. Pulse rates of patients having disproportionate tachycardia were also noted. All the necessary investigation were performed. All the patients were evaluated using two dimensional echocardiography. The evaluation was repeated on discharge in patients having abnormal findings on first echocardiography.Dengue patients positive for one of the following investigations with or without clinical features were considered as cardiac involvement. Features suggestive of rhythm disturbance, heart rate changes like sinus tachycardia or bradycardia, raised CKMB and/or troponin I and abnormal ECG and ECHO were considered for cardiac manifestations. ECG changes included sinus tachycardia, sinus bradycardia, non specific STT wave changes, inverted T waves, First degree heart block, right bundle branch block. Echocardiography changes were interpreted as; Systolic dysfunction - Refers to impaired ventricular contraction, Diastolic dysfunction – Refers to an abnormality in the filling during diastole, Ejection fraction – The fraction of the blood pumped out of a ventricle with each heartbeat (Normal value - 67 ± 12%) Pericardial effusion - An abnormal accumulation of fluid in the pericardial cavity.

## RESULTS

The present study was conducted to assess the cardiac manifestations of dengue fever. It is a two year cross-sectional descriptive study conducted in the Department of Medicine, at a tertiary care rural hospital. A total of 110 patients who presented with dengue fever from October 2016 to April 2018 were enrolled for the study.

Table 1: Distribution of dengue patients according to demographic characteristics

Parameter		Number (n=110)	Percentage
	14-24	29	26.4%
	25-34	30	27.3%
Ago Croups (voors)	35-44	23	20.9%
Age Groups (years)	45-54	17	15.4%
	55-64	10	9.1%
	65-74	1	0.9%
Gender	Male	68	61.8%
	Female	42	38.2%
Total		110	100.0%

Most number of patients were from younger ages like 30 patients (27.3%) and 29(26.4%) patients in the 25-34 years age group and 14-24 years age group respectively. There were 23 patients (20.9%) in the 35-44 years age group, 17 (15.4%) patients in the 45-54 years age group, 10 patients (9.1%) in the 55-64 years age group and 1 patient (0.9%) in 65-74 years age group showing least dengue patients in older age group. In the present study 62% of the patients were males and 38% were females. The male to female ratio was 1.62:1.

Table 2: Distribution of	dengue patient	ts according to sy	mptoms and Dengu	le Serological Test

	Deremeter	Total number of subjects (n=110	
	Parameter		Percentage
	Fever	104	94.54
	Rash	48	43.64
	Headache	81	73.64
Symptom	Vomiting	18	16.36
	Abdominal Pain	28	25.45
	Breathlessness	2	1.82
	Bone and muscle pain	91	82.73
	IgM	38	34.55
Test	lgG	21	19.09
NS1		83	75 45

In the present study fever was the commonest clinical presentation noted in 94.54% of the patients followed by bone and muscle pain in 82.73% patients. The other presentations observed were headache (73.64%), rash (43.64%), vomiting (16.36%), abdominal pain (25.45%) and breathlessness (1.82%). No cardiac symptoms like chest pain, palpitation or swelling of feet were noted in the dengue patients in this study. In the present study IgM and IgG were positive in 34.55% and 19.09% of the patients respectively; while NS1 was positive in 75.45% patients.

Table 3: Distribution of patients according to severity of dengue					
Soverity of Depays Fover	Total number of subjects (n=110)				
Severity of Deligue rever	Number	Percentage			
Dengue Fever (DF)	76	69.1			
Dengue Shock Syndrome (DSS)	8	7.3			
Dengue Hemorrhagic Fever (DHF)	26	23.6			
Total	110	100			

In this study out of 110 dengue patients; 69.1% had dengue fever, 7.3% had dengue shock syndrome and 23.6% had dengue hemorrhagic fever.

Table 4: Cardiac manifestations in dengue patients					
Cardian Manifectations	Total number of subjects (n=110)				
	Number	Percentage			
Present	67	60.09			
Absent	43	39.91			
Total	110	100			

In the present study based on abnormal cardiac enzymes, echocardiography and ECG 60.09% of the patients were found to have cardiac manifestations.

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Table 5: Comparison of Echocardiography findings with dengue severity						
		Dengue Severity			Total	P Value
		DF	DHF	DSS		
Pericardial effusion	Absent	76 (69.1%)	26 (23.6%)	7 (6.4%)	109 (99.1%)	0.002
	Present	0 (0%)	0 (0%)	1 (0.9%)	1 (0.9%)	0.002
Systolic Dysfunction	Absent	76 (69.1%)	26 (23.6%)	6 (5.5%)	108 (98.2%)	0.000
	Present	0 (0%)	0 (0%)	2 (1.8%)	2 (1.8%)	0.000
Diastolic Dysfunction	Absent	76 (69.1%)	25 (22.7%)	6 (5.5%)	107 (97.3%)	0.000
	Present	0 (0%)	1 (0.9%)	2 (1.8%)	3 (2.7%)	0.000
Total		76 (69.1%)	26 (23.6%)	8 (7.3%)	110 (100	%)

In this study of the eight patients were found to have dengue shock syndrome of which one (0.9%) had pericardial effusion while two (1.8%) had systolic and diastolic dysfunction each. Of the 26 patients with DHF, one (0.9%) had diastolic dysfunction. The difference was statistically significant for all echocardiography findings with respect to dengue severity (P<0.05).

Table 6: Comparison of Troponin I with dengue severity						
Donguo Sovority	Trope	onin I	Total	P Value		
Deligue Severity	Negative	Positive				
Dengue Fever	76 (69.1%)	0 (0%)	76 (69.1%)			
Dengue haemorrhagic fever	19 (17.3%)	7 (6.4%)	26 (23.6%)	0.000		
Dengue shock syndrome	2 (1.8%)	6 (5.5%)	8 (7.3%)	0.000		
Total	97 (88.2%)	13 (11.8%)	110 (100%)			

In this study out of the eight patients with DSS, six patients (75%) had positive troponin I. Out of 26 patients with DHF; seven patients (26.9%) had positive troponin I. None of the patients with DF had positivity of troponin I. This indicates the percentage of dengue patients having positive troponin I correlates with severity of dengue fever. The difference was statistically significant (P<0.001).

Table 7: Comparison of CKMB with dengue severity:						
Dengue Severity	СКМВ		Total	P Value		
	25 or less	>25				
Dengue Fever	46 (41.8%)	30 (27.3%)	76 (69.1%)			
Dengue haemorrhagic fever	15 (13.6%)	11 (10%)	26 (23.6%)	0.03		
Dengue shock syndrome	1 (0.9%)	7 (6.4%)	8 (7.3%)			
Total	62 (56.4%)	48 (43.6%)	110 (100%)			

In the present study eight patients were found to have dengue shock syndrome with 87.5% of them having raised CKMB levels compared to 42.3% and 39.5% in dengue haemorrhagic fever and dengue fever respectively. This indicates the percentage of dengue patients having abnormal CKMB correlates with severity of dengue fever. The difference was statistically significant (P<0.05). In the present study all the dengue patients recovered from illness successfully and no mortality was recorded.

## DISCUSSION

Many infectious diseases cause relative bradycardia, such as typhoid fever, Chlamydia pneumoniae, and legionnaire's disease. Various viral infections cause myocardial damage, either by invasion or an autoimmune reaction resulting in myocardial inflammation. The cardiac abnormalities in dengue are invariably benign, transient, and self-limited and are attributed to subclinical viral myocarditis. Cardiac manifestation in dengue fever ranges from asymptomatic bradycardia to severe myocarditis.<sup>10</sup> Cardiac abnormalities including various ECG abnormality (sinus bradycardia, and prolongation of PR interval, transient AV block, transient ventricular arrhythmias), myocarditis, systolic and diastolic dysfunction and pericardial effusion have been observed during acute phase of viral dengue infection.<sup>8,11</sup> Rhythm disturbance such as sinus bradycardia and ventricular ectopics, have also been reported during convalescence period of dengue fever.<sup>12</sup>Even though numerous studies are present detailing the various manifestations of dengue fever only a few highlight the cardiac manifestations in it. Studies regarding the same in Indian centres are handful. There are a few studies done in Southeast Asian countries to help compare inferences from those studies to the inferences in this study. A few recent studies in centres all over India also highlight the cardiac manifestations of Dengue fever. This study was conducted over a period of 2 years in a tertiary health care institute in patients presenting with dengue after confirmed serology testing. A total of 110 patients were enrolled for this study after explaining them nature of this study and what it entails. In our study the mean age of the study population was

35.15±13.2. The youngest patient was 16 years old and the oldest patient was aged 68 years. The male to female ratio (M:F) was 1.62:1 suggesting male preponderance (Table 1and2). These findings were comparable to a study by Miranda et  $al^{13}$ , Malavige et  $al^{14}$  and Adriana O et  $al^{15}$ . In the present study fever was the commonest clinical presentation noted in 94.54% of patients followed by bone and muscle pain in 82.73% patients. The other presentations observed were headache (73.64%), rash (43.64%), vomiting (16.36%), abdominal pain (25.45%) and breathlessness (1.82%). In another study by M Arora et al<sup>9</sup>, majority of the patients presented with myalgia (97.5%) followed by fever (92.5%). Other presentations like headache, rash, vomiting, abdominal pain and breathlessness were noted among 79.17%, 33.33%, 30.83%, 12.5% and 0.83% respectively. Rachel Daniel et  $al^7$ , had patients with presenting symptoms were: fever (96.8%), headache (77.2%), abdominal pain (62.4%), diarrhoea (15.2%), bleeding (15.2%), skin rash (13.2%), pruritus (10.4%), sore throat (5.2%), and seizures (0.8%). Recently, Kumar A. et al<sup>16</sup>, in his record-based study conducted in a coastal district of Karnataka to assess the clinical manifestations, trend and outcome of all confirmed dengue cases admitted in a tertiary care hospital assessed the laboratory confirmed cases from 2002 to 2008 from Medical Records Department (MRD). Of the 466 patients, the most common presentation was fever 462 (99.1%), followed by myalgia 301 (64.6%), vomiting 222 (47.6%), headache 222 (47.6%) and abdominal pain 175 (37.6%). Malavige et al14, in their study had fever (100%) as the most common presenting symptom followed by myalgia (76%), headache (66%), vomiting (63%) and abdominal pain (16%). In the present study while checking for dengue serology testing, IgM and IgG were positive in 34.55% and 19.09% of the patients respectively; while NS1 was positive in 75.45% patients. In a study conducted by MU Rabbani *et al*<sup>17</sup>, 92.2% patients had NS1Ag positive, IgM antibody was raised in 19.3% patients and 15.8% patients had raised IgG antibody level. In a study done by S Sheetal *et al*<sup>12</sup>, 79% patients were Dengue NS1 positive and 21% patients were Dengue IgM positive. The serology shows close to comparable results in these studies. In this study out of 110 dengue patients; 69.1% had DF, 7.3% had DSS and 23.6% had DHF. In a study conducted by Adriana O Guilarde et al<sup>15</sup>, 23.2% were classified as DHF and 50.3% were classified as DF showing almost similar finding compared to our study. Another study by M Arora et al<sup>9</sup>, showed 16.7% patients with DF, 70.8% patients with DHF and 12.5% patients with DSS thus having some variations compared to our study and with the other study as compared to previously.In the present study echocardiography showed pericardial effusion in 0.91%

patients, systolic dysfunction in 1.82% patients; while dysfunction. 2.73% patients had diastolic Echocardiography repeated for these patients on discharge showed normal findings. In a study done by Prasanth B et al<sup>18</sup>, 16% patients had myocardial involvement based on echocardiography. In a study conducted by VK Gupta *et al*<sup>19</sup>, mild diastolic dysfunction was seen in 14.2 % patients and no other abnormal echocardiography findings were observed. In this study of the eight patients were found to have dengue shock syndrome of which one (0.9%) had pericardial effusion while two (1.8 %) had systolic and diastolic dysfunction each. Of the 26 patients with DHF, one (0.9%) had diastolic dysfunction. The difference was statistically significant for all echocardiography findings with respect to dengue severity (P<0.05). In this study out of the eight patients with DSS, six patients (75%) had positive troponin I. Out of 26 patients with DHF; seven patients (26.9%) had positive troponin I. None of the patients with DF had positivity of troponin I. This indicates the percentage of dengue patients having positive troponin I correlates with severity of dengue fever. The difference was statistically significant (P<0.001). In the present study eight patients were found to have dengue shock syndrome with 87.5% of them having raised CKMB levels compared to 42.3% and 39.5% in dengue haemorrhagic fever and dengue fever respectively. This indicates the percentage of dengue patients having abnormal CKMB correlates with severity of dengue fever. The difference was statistically significant (P<0.05).In the present study based on abnormal cardiac enzymes, echocardiography and ECG 60.09% of the patients were found to have cardiac manifestations. In a study by M Arora *et al*<sup>9</sup>, the incidence of cardiac manifestations was found to be higher in patients with dengue shock syndrome with eight (53.33%) out of 15 patients having cardiac enzymes elevation compared to 30 (35.29%) out of 55 and six (30%) out of 20 patients with dengue hemorrhagic fever and dengue fever respectively. Although the difference was not statistically significant (p=0.325). In our study the correlation based on echocardiography, cardiac enzymes compared with dengue severity showed statistical significance (p<0.05) which entails higher cardiac involvement as dengue severity increases like in DHF and DSS. Cases of DSS had highest cardiac involvement as seen with cardiac enzymes, ECG and echocardiography.

### CONCLUSION

Thus we conclude that ECG, cardiac enzymes and echocardiography are the main tools to diagnose the myocardial involvement in dengue fever. DHF and DSS cases had higher degree of myocardial involvement as compared to DF cases.

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