

# Evaluation of Cardiac Biomarkers in Dengue Myocarditis in a Tertiary Care Hospital in Eastern India

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## ABSTRACT

**Introduction:** Dengue, a vector borne viral infection transmitted by *Aedes mosquito* has recently become a major public health concern in the tropical regions of the world. In addition to the two major life threatening complications- Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS), a variety of cardiac complications have been recognised, the most common being myocarditis.

**Aim:** To study and compare the quantity of different cardiac biomarkers in patients of Dengue Fever with and without myocarditis.

**Materials and Methods:** This was a hospital-based retrospective observational study done in a Tertiary Care Hospital, Kolkata, West Bengal, India from June 2019 to November 2019. Dengue patients with diagnosed myocarditis on day 7 of fever based on electro and echocardiogram changes of left ventricular ejection fraction less than 50% were considered as cases (n=41). Age and sex matched dengue patients with normal electro and

echocardiogram changes were considered as control (n=43). After obtaining Institutional Ethics Committee Clearance, laboratory data were collected from samples coded and assayed for markers of acute cardiac myocyte damage such as total Creatine Kinase (CK), CK-Muscle Brain (CK-MB), Troponin T (Trop T) and cardiac failure biomarker N-Terminal pro Brain Natriuretic Peptide (NT-proBNP). Statistical analysis of the data was performed using Statistical Package for Social Sciences (SPSS 20).

**Results:** Cardiac biomarkers CK, CK-MB, Trop T and NT-proBNP levels in cases were higher compared to controls (p-value <0.05). Trop T and NT-proBNP were positively correlated to each other (r-value: 0.44). Trop T changes could also predict significantly the rise in NT-proBNP in circulation (p<0.05).

**Conclusion:** It reconfirmed the need of routine monitoring of cardiac biomarkers in conjunction with other cardiac function tests in early diagnosis and or management of myocarditis, a severe complication of Dengue Viral Infection (DENV).

**Keywords:** Creatine kinase, Creatine kinase-muscle brain, Dengue, N-terminal pro brain natriuretic peptide, Troponin T

## INTRODUCTION

Dengue, a vector borne viral infection of Flaviviridae family is transmitted by *Aedes mosquito* has recently become a major public health concern in the tropical regions of the world. Modelling estimate indicates 390 million dengue virus infections per year, of which 96 million manifest clinically with any severe symptoms related to the disease [1]. Prevalence studies estimated that 3.9 billion people are at risk of infection with dengue viruses. Despite a risk of infection exists across 129 countries, 70% of the actual burden is in Asia [1,2]. All the serotypes of the virus can cause dengue fever, a self limiting febrile illness [3]. The sequential or secondary infection by different serotypes of dengue virus induces the two major life threatening complications- Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) which is due to cross-reactive non-neutralising antibodies from previous dengue virus infection [4]. This is also characterised by cytokine mediated increased vascular permeability by T cells which destroy dengue-infected cells [5], and this syndrome in its most severe form can threaten the patient's life [6].

Presence of viral proteins C and Non-Structural Protein 1 (NS1) in confocal microscopic examination of cultured human skeletal muscle myotubes have revealed that heart and skeletal muscles are target organs for DENV [7]. Viruses induced increase in intracellular calcium ions and interference with calcium homeostasis is responsible for altered myocardial contractility and evolution of arrhythmias. Increased calcium produces mitochondrial pore opening, cytochrome c release, caspase activation, and nuclear apoptosis in cells exposed to infection [8]. It is known fact that dengue virus has preference to infect peripheral blood and vasculature more than vital organs, particularly myocardium [9,10]. Still, a range of

cardiac complications have been documented, the most common being myocarditis, although conduction defects and arrhythmias have also been reported [11,12]. Myocardial damage in dengue is hypothesised to be orchestrated by a combination of both direct virus and subsequent immune mediated mechanism [13].

To date, various studies had addressed the correlation of cardiac involvement in dengue with various biochemical and haematological parameters with diverse results [14,15]. With this background, this study was designed to evaluate and compare the biochemical changes of cardiac biomarkers like total CK, CK-MB, Trop T and cardiac failure biomarker NT-proBNP between patients of Dengue Fever with Myocarditis (DFM) as cases and age and sex matched patients of Dengue Fever without Myocarditis (DFWM) as controls.

## MATERIALS AND METHODS

This retrospective hospital based observational study was done in the Microbiology Department of IDBG Hospital Kolkata and Department of Biochemistry of IPGMER, Kolkata. After obtaining clearance from Institutional Ethics Committee (IDBGH/Ethics/2447) all procedures followed were in accordance with the Helsinki Declaration of 1975 that was revised in 2000. Symptomatic patients admitted in a Tertiary Care Center and fulfilling the inclusion criteria following serological testing were included in this study conducted for a period of 6 months from June 2019 to November 2019. Collection of laboratory data of all cases and controls were undertaken with history and clinical data of each patient that was recorded formally, evaluated retrospectively in present study.

Patients admitted in the IDBG, Hospital with Dengue with coronary manifestation within 18-65 years of age are taken as cases and controls are selected as ethnicity, age and sex matched having

all the exclusion criteria and no obvious coronary manifestation. Being an observational study, formal sample size calculation is not done here. Keeping time and logistic constraints in mind 41 cases (DFM) and 43 controls (DFWM) have been included in this study.

**Inclusion criteria:** Serologically diagnosed Dengue patients with clinical features suggestive of cardiac involvement with abnormal electro and echocardiogram findings within 7 days of fever were considered for the study. ECHO findings of Left Ventricular Ejection Fraction (LVEF) of <50% was considered abnormal [16]. These patients had typical manifestations of acute viral infection such as fever, myalgia. Gradually, there was development of progressive dyspnoea one or two weeks after start of acute symptoms suggestive of possible cardiac involvement as sequelae of dengue infection [17].

**Exclusion criteria:** It included patients having conditions which might cause falsely elevated Trop T, CK-MB or total CK levels, such as sepsis, kidney failure or chronic kidney disease, cancer chemotherapy, pulmonary embolism, cocaine and similar drug use, injury to heart or skeletal muscle, surgery, chest trauma, asthma, malignancies, pre-existing myopathies, endocrine disorder. Moreover, cases with previous history of heart disease like arrhythmias or heart failure due to cardiac conditions other than viral myocarditis were excluded from the study [18].

**Sample analysis:** At the time of admission, data regarding age, sex, risk factors, onset and grade of symptoms were collected in detail according to standard hospital protocol. Study population consisted of people residing within 4 km radius from the place of study in areas of dengue epidemicity. All investigation details were documented. During stay in hospital, as part of routine clinical workout, venous blood samples were collected from each case and control after 12 hours of fasting. Blood sample was collected randomly by standard venipuncture technique into clotted vials using aseptic precautions from those of cases and controls. Complete clot formation was ensured prior to centrifugation. Serum was separated after centrifuging for 15 minutes, and was analysed for all the parameters on the same day. Dengue NS1 antigen was detected by Enzyme Linked Immunosorbant Assay (ELISA; InBios, USA). A 3<sup>rd</sup> generation IgM capture ELISA (Panbio, Abbott, India) was then performed according to manufacturer's instructions for confirmation of presence of anti-Dengue antibodies. All patients

underwent Electrocardiography (ECG) of all leads along with 2-dimensional Echocardiography (ECHO). All samples were coded and assayed for markers of acute cardiac myocyte damage such as total CK, CK-MB, Trop T and cardiac failure biomarker NT-proBNP in a blind fashion by an investigator who was unaware of the subjects' clinical status. Cardiac enzymes were estimated biochemically by automated analyser (Transasia, India) [19]. Trop T was measured using an enzyme-linked fluorescent assay (VIDAS Trop T. Ultra, bioMérieux, France) [20]. NT-proBNP levels were measured by an ELISA (VIDAS NT-proBNP, bioMérieux, France) [21]. All these data were analysed retrospectively.

## STATISTICAL ANALYSIS

Statistical analysis of the data was performed using SPSS 20 and inferences were drawn. Comparison of continuous variables between cases and control groups were evaluated using Student's t-test. Categorical variables were compared using Pearson's chi-square test ( $\chi^2$ ) test. Probability value  $p < 0.05$  was considered to be statistically significant at a confidence limit of 95%. Pearson's correlation test was performed to establish the strength of association between continuous variables ( $r$  value). As a predictive analysis, the multiple linear regressions were used to explain the relationship between one continuous dependent variable and multiple independent variables.

## RESULTS

Post screening the final eligible study population comprised of 41 cases (DFM) and 43 controls (DFWM) that were age and sex matched as far as possible by Independent t-test and chi-square tests, respectively. Baseline characteristics of the entire study population and results of comparison of various cardiac biochemical parameters values between cases and controls are highlighted in [Table/Fig-1]. Presence or absence of independent risk factors such as Diabetes Mellitus, hypertension, smoking, documented viral fever within last three months prior to dengue infection was found to have no statistical bearing on development of myocarditis. Serological screening and confirmation of Dengue was completed for the entire study population within first 5 days of fever. ECHO and ECG were then performed in cases with symptoms of cardiac involvement. Progressive dyspnoea was observed in 8 cases with myocarditis within first week of Dengue

Parameter (Mean±SD)		Dengue Fever with Myocarditis (DFM) (Cases, n=41)	Dengue Fever without Myocarditis (DFWM) (Controls, n=43)	p-value
Age (In years)		48±10	43±12	0.41*
Sex distribution	Male	26	24	0.47**
	Female	15	19	
Independent Risk Factors (Diabetes Mellitus, Hypertension, Smoking, Documented viral fever within last 3 months)		20 (48%)	25 (58%)	0.38**
		21 (52%)	18 (42%)	
Days of onset of dyspnoea	<7	8	NIL	
	7-14	19	NIL	
	>14	14	NIL	
Grade of dyspnoea (NYHA classification)	Class I	6 (14%)	NIL	
	Class II	10 (25%)	NIL	
	Class III	23 (56%)	NIL	
	Class IV	2 (5%)	NIL	
Palpitation		6	2	
Total CK (U/L)		201±57	158±49	0.0102*
CK-MB (U/L)		27±6.8	22±5.6	0.0107*
Trop T (ng/ml)		0.61±0.04	0.07±0.01	0.0001*
NT-proBNP (125 µg/L)		1210±25	192±76	<.001*

**[Table/Fig-1]:** Baseline characteristics and comparison of serum levels of cardiac biomarkers in cases and controls on Day 7 of fever.

p-value <0.05: Significant

\*Independent t-test, \*\*Chi-square test ( $\chi^2$ )

NYHA: New York heart association

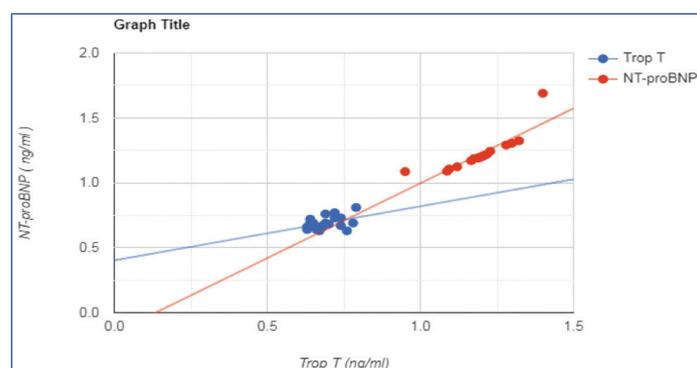
fever. It had developed gradually in rest during 2<sup>nd</sup> and 3<sup>rd</sup> week of infection (n=19 and 14, respectively). Majority of patients with myocarditis had developed Grade III dyspnoea. Palpitation was complained by few cases and controls. However, only 3 cases had ECG findings of true ventricular tachycardia while the rest were non-specific. Cases had elevated levels for all the cardiac enzymes and proteins compared to controls. The differences were statistically significant. Pearson's correlation analysis was performed to observe the change in NT-proBNP levels with respect to rise in cardiac markers. In cases, only Trop T showed positive correlation with NT-proBNP levels (r-value: 0.44) [Table/Fig-2-3]. A multiple regression analysis was run to predict whether NT-proBNP variation was dependant on independent factors like changes in values of total CK, CK-MB and TROP-T or not. Of all these variables only TROP-T significantly predicted NT-proBNP rise as a late effect of dengue myocarditis (p<0.05) [Table/Fig-4].

Sl No.	Parameters versus NT-proBNP (µg/L)	Correlation coefficient (R-value)*
1	Total CK (U/L) vs NT-proBNP (µg/L)	-0.197
2	CK-MB (U/L) vs NT-proBNP (µg/L)	0.174
3.	Trop T (ng/mL) vs NT-proBNP (µg/L)	0.443

**[Table/Fig-2]:** Correlation between the biochemical parameters in dengue fever with myocarditis.

CK: Creatine kinase; CK-MB: Creatine kinase-muscle brain; Trop T: Troponin T; NT-BNP: N-Terminal pro brain natriuretic peptide

\*Pearson's correlation analysis



**[Table/Fig-3]:** Scatter plot to correlate Trop T with NT-proBNP values. NT-proBNP values have been converted and expressed in terms of ng/mL

		R	R square	Adjusted R square	Std. error of the estimate		
<b>Model summary</b>		0.47	0.23	0.16	151.68		
<b>ANOVA</b>		<b>Sum of squares</b>	<b>df</b>	<b>Mean square</b>	<b>F</b>	<b>Sig.</b>	
Regression		247111.28	3	82370.43	3.580	0.02*	
Residual		828264.31	36	23007.34			
Total		1075375.6	39				
Coefficients	Unstandardised coefficients		Standardised coefficients		95.0% Confidence interval for B		
	B	Std. error	Beta	t	Sig.	Upper bound	Lower bound
(Constant)	-345.1	1336.19		-0.25	0.79	-3054.94	2364.8
Total CK	5.12	7.27	0.191	0.70	0.48	-9.62	19.87
CK-MB	-16.98	14.56	-0.301	-1.17	0.25	-46.52	12.56
TROP-T	1602.3	537.506	0.484	2.981	0.005	512.284	2692.5

**[Table/Fig-4]:** Multiple regression analysis for biochemical parameters in dengue fever with myocarditis.

a: Dependent Variable: NT-proBNP

b: Predictors: (Constant), Total CK, CK-MB, TROP-T

R: Multiple correlation coefficient; R<sup>2</sup>: Coefficient of determination; Adjusted R Square: Adjusts for nonsignificant predictors; Std. Error of the Estimate: Measure of the accuracy of predictions

\*Analysis of variance (ANOVA), Multiple Regression Analysis

## DISCUSSION

Myocarditis is a common complication of severe dengue infection. However, data about prevalence and characterisation of myocarditis among Indian population in dengue are still lacking. Several studies have reported cardiac involvement in dengue including myocarditis and heart failure [10-12]. In 2005, an epidemic showed high

incidence of myocarditis [13]. Myocarditis is an especially common cause of death in patients with severe dengue [16,17]. Prevalence of myocarditis in dengue was reported from 9% to 15% [18,22,23]. This variation in prevalence of myocarditis in dengue may result from differences in host genetic factors and type of dengue serotype circulating in a region, which may modify the resultant host inflammatory responses. Also, separate temporal patterns of circulating serotypes might predispose to particular dengue immune status that causes more severe cardiac manifestation when there is a secondary infection.

In dengue, damage to myocardial cells occurs due to direct viral invasion of the myocardium and derangement of calcium storage in the infected cells [24]. The clinical spectrum varies from nonspecific electrocardiographic abnormalities to sudden cardiac arrest [25,26]. Cardiac arrhythmia and heart failure are very common. Accordingly, dengue patients developing myocarditis have different diagnostic and laboratory performances. The treatment of viral myocarditis varies by clinical presentation.

Targeted therapy for acute heart failure is critical for recovery [27,28] as approximately 20% of those who developed dengue haemorrhagic fever have a left ventricular ejection fraction of less than 50% [29]. In dengue, a mediators like TNF- $\alpha$  and nitric oxide have been reported to be altered. Cytokine release activates matrix metalloproteinase which disrupts cardiac scaffolding of collagen and elastin protein causing dilated cardiomyopathy [30,31]. NT-proBNP is an established surrogate marker of heart failure and this is inversely correlated to ejection fraction. Study conducted upon 100 heart failure patients clearly showed that there exists a strong negative correlation between NT-proBNP concentration and LVEF (p<0.004). A cut-off value of 940 pg/mL for NT-proBNP predicted LVEF <30%, with a sensitivity and the specificity of 89.8% and 71.4%, respectively [32]. This is evident in study results in terms of decreased cardiac ejection fraction in cases and simultaneous high serum NT-proBNP levels compared to controls. In study on patients with myocarditis, presence of viral genomes in the myocardium like parvovirus, parvovirus B19, HHV-6 and Epstein-Barr virus, were associated with an increased hs-TnT level compared to those with myocarditis but without evidence of viral genomes [33]. In the present study, serum Trop T levels in cases were significantly raised in comparison to controls. Serum levels of cardiac enzymes CK and

CK-MB were found to be significantly elevated in cases with respect to controls. These findings are in contrast to data obtained by other workers, who reported that during the course of myocarditis, the laboratory markers of myocardial cell damage, such as CK and CK-MB levels were often within the normal range [34,35]. But the present study finding is in accordance with some other researchers

[36,37]. These findings are important because raised CK, CK-MB and Trop T levels suggest injury to myocardial tissue. Yacoub S et al., stated that cardiac biomarker elevation and marked changes on ECHO or ECG are evidence of widespread myocyte infection and damage in fulminant cases of dengue myocarditis [38]. Among dengue patients with elevated cardiac biomarker Troponin I, Miranda CH et al., had reported that 10% (8 patients) patients presented with clinical manifestations suggestive of cardiac involvement, such as acute heart failure in 4 patients, chest pain in 3 patients, and hypotension and shock in 3 patients [30]. Findings from the study suggest that only a small number of dilated cardiomyopathy cases (n=3) had developed ventricular tachyarrhythmia. Among the cardiac biomarkers only Trop T had some correlation with NT-Pro BNP [Table/Fig-3]. This suggests importance of Trop T estimation over prescribing a total cardiac profile testing in suspected viral myocarditis cases. Absence of a strong linear relationship makes the authors believe that the timing of the two events of myocardial injury and the resultant heart failure varies in individuals. Trop T is showing as significant predictor for the detection of myocardial involvement in dengue as depicted in multivariate regression analysis. Trop T assays are well suited for early diagnosis of myocarditis [39].

In a middle aged adult progressive dyspnea had developed only after two weeks of serological confirmation. The ejection fraction of these cases is reported to become normal in due course of time [40]. Diagnoses of cardiac involvement in viral disease are still based on elevated biomarkers of cardiac injury along with ECG and ECHO findings [41]. Established role of measurement of anti-heart antibodies or endomyocardial biopsy on a routine basis for diagnosis and evaluation is lacking. A small number of cases present with fulminant myocarditis causing cardiogenic shock and resulting in multiorgan failure [42]. Recognition of this phenomenon is of utmost importance as aggressive management is potentially life-saving [43].

### Limitation(s)

In the present study, some methodological limitations exist. The study was conducted in a Tertiary Care Hospital and is primarily a cross sectional study. However, in India, most people visit district, sub divisional and lower-tier hospitals for treatment. This particular study population comprised of only Dengue infected persons. Other patients with a history of pre-existing heart disease with previous echocardiographic abnormality were excluded from the study. Hence, results of this study might not reflect the true picture of the population as a whole. In addition, subjects were not divided according to Dengue serotypes because it is not definite that infection by a particular serotype predispose to myocarditis. Lastly, variations in age groups, co-morbidities, and study design might be additional factors causing separate manifestations and incidences but it was the limitation of the study.

### CONCLUSION(S)

This study demonstrates diagnostic characteristics of dengue associated myocarditis. Data from the present study shows that cardiac biomarkers are elevated in dengue myocarditis and hence should be measured routinely in conjunction with other function tests in early diagnosis and management. Estimation of Trop T is reliable point of care testing to diagnose myocarditis among Dengue patients, though the results should be substantiated with further research in a larger multicentric population.

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**PLAGIARISM CHECKING METHODS:** [\[Jan H et al.\]](#)

- Plagiarism X-checker: Aug 22, 2020
- Manual Googling: Nov 09, 2020
- iThenticate Software: Dec 14, 2020 (19%)

**ETYMOLOGY:** Author Origin**AUTHOR DECLARATION:**

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 17, 2020**Date of Peer Review: **Sep 03, 2020**Date of Acceptance: **Nov 10, 2020**Date of Publishing: **Dec 15, 2020**