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Original Research Article

A STUDY ON CLINICAL OUTCOMES AND 6 MONTH ECHOCARDIOGRAPHIC FOLLOW UP IN DENGUE MYOCARDITIS IN A TERTIARY CARE CENTRE

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Abstract

BACKGROUND: Dengue myocarditis is an underdiagnosed condition in our country and more so, in our region. Although this region is endemic for dengue, diagnosis of myocarditis has been challenging due to limited resources and underreporting. Hence, we studied clinical outcomes and echocardiographic abnormalities in dengue myocarditis and also, reported the follow up data.

OBJECTIVE: To study the clinical outcomes and 6 month echocardiographic follow up in dengue myocarditis in our region**.**

METHODS: A prospective observational study done at a tertiary care centre, we studied 168 dengue IgM positive patients referred to us with cardiac symptoms and diagnosed as myocarditis using the ESC 2013 diagnostic criteria from June 2022 to December 2022.

RESULTS: out of 168 dengue myocarditis patients, 62.5% were males. 44.6% of the patients belonged to the youngest group that is 12 – 20 years old. Troponin t was elevated in 88% of the patients.

Dyspnea was the most common symptom (83.9%). All patients had atleast one ECG abnormality, the most common being ST-T segment change. 18.4% patients had normal 2D ECHO while 69.6% patients had LV systolic dysfunction. Shock requiring IV inotropic therapy was high, noted in 31.5% and death occurred in 10.1%.

At 6 month follow up, 5.1% of discharged patients continued to have LV systolic dysfunction.

CONCLUSIONS:

Occurrence of Myocarditis is usually during the convalescence phase of Dengue illness that is, when fever subsides and it is more commonly seen in severe Dengue. Mortality is higher with severe Myocarditis. Cardiac biomarkers, ECG and 2D ECHO play an important role in the diagnosis of dengue myocarditis and there is no specific treatment for dengue myocarditis**.** Serial Echocardiography helps in assessing LV function recovery and prognostication**.**

Keywords: Dengue, Myocarditis, 2D Echocardiography, Shock, Mortality

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Introduction

Cardiac involvement has been seen in many viral infections like CMV, Coxsackie, Adenovirus, Influenza, Herpes Simplex, Zoster, Measles, HIV, dengue, etc. Dengue viral infection is an emerging major health problem affecting globally with more than 100 countries of tropical and sub-tropical regions of the world.[1]

Dengue fever is an arboviral disease caused by Flavivirus and transmitted by Aedes Aegypti mosquito. This mosquito bites daytime, breeds in and around human dwellings and capable of stinging many people in short span of time.[2] Dengue virus has 4 serotypes (DEN1, 2, 3, 4).
WHO in 1997 classified symptomatic dengue infection into Dengue Fever, Dengue Haemorrhagic Fever, and Dengue Shock Syndrome. In 2009, WHO revised and classified as Dengue with or without warning signs [Warning Signs: 1. Abdominal pain/tenderness, 2. Persistent Vomiting, 3. Clinical Fluid Accumulation, 4. Mucosal Bleeding, 5. Lethargy/Restlessness, 6. Liver Enlargement > 2 cm, 7. Increased Haematocrit and decreased Platelet count] and Severe Dengue [1. Severe Plasma Leakage leading to shock/respiratory distress, 2. Severe Bleeding, 3. Severe Organ Involvement: a. Liver – Elevated Enzymes, b. CNS – Altered consciousness, c. Heart – Myocarditis].[3,4]

An estimated 1-5% of dengue fever patients develop complications including capillary leak, coagulopathy and end organ failure.[5] Cardiac involvement in dengue infection is not uncommon, but is under-diagnosed as most cases are clinically mild and self-limited.[6] Cardiac manifestations in dengue include myocarditis, pericarditis, pericardial effusion and arrythmias.[7] The most common complication is myocarditis and it can mimic acute myocardial infarction.[8] Fatal complications of dengue myocarditis are heart failure, cardiogenic shock, arrythmias and death.[9]
This region has higher incidence and endemicity of dengue fever. Lower socio-economic standards and limited healthcare resources have led to Dengue related complications and deaths. Hence this study has been undertaken to evaluate dengue myocarditis and its outcomes.

MATERIALS AND METHODS

This study was done at Dept. Of Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Kalaburagi. Patients were enrolled from June 2022 to December 2022 and were followed up for 6 months. Confirmed Dengue patients who had cardiac symptoms, ECG changes and/or hemodynamic instability were referred to our centre for further evaluation and management. All patients underwent ECG, 2D ECHO and Troponin T.

The patients were subjected to daily monitoring of ECG, CBC, RFT, LFT. ECG was performed using a 6 channel *BPL Cardiart 9108* machine. 2D ECHO was done using *Vivid iq, GE Medical systems* ultrasound equipment. All standard ECHO views were used. Troponin T was measured using standardized enzyme linked assay *(Elecsys Troponin T hs, ROCHE Diagnostics,* Germany). 2D ECHO was done at admission, and then on follow up at 1 month, 3 month and 6 month intervals.

Definition of Myocarditis

Diagnostic criteria for clinically suspected myocarditis (2013 ESC RECOMMENDATIONS).
Clinical presentations
Acute chest pain, pericarditic, or pseudo-ischaemic New-onset (days up to 3 months) or worsening of dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs Subacute/chronic (>3 months) or worsening of dyspnoea at rest or exercise, and/or

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fatigue, with or without left and/or right heart failure signs Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death Unexplained cardiogenic shock

Diagnostic criteria :

I. ECG/Holter/stress test features

Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia

II. Myocardiocytolysis markers

Elevated TnT/TnI

III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)

New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi

IV. Tissue characterization by CMR

Oedema and/or LGE of classical myocarditic pattern

Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis ≥ 50%); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.). Suspicion is higher with higher number of fulfilled criteria

[a]If the patient is asymptomatic ≥2 diagnostic criteria should be met.

INCLUSION CRITERIA:

- Age greater than 12 years.
- Dengue NS1 Antigen/Ig M positive patients with cardiac symptoms, hemodynamic instability, ECG and/or 2D ECHO findings, fulfilling the criteria for definition of Acute Myocarditis according to the ESC 2013 recommendations (mentioned above). [10]

EXCLUSION CRITERIA:

- Patients with previous history of Heart failure, Valvular Heart disease, Congenital Heart disease, Ischemic Heart disease, Cardiomyopathies.
- Patients with Acute Coronary Syndrome

STATISTICAL ANALYSIS

The data collected from the selected patients were recorded in a Master Chart using Microsoft Excel. The analysis of the tabulated data was doneby using SPSS 16 software tool. With the help of this software tool, percentages, means, standard deviations and 'p' values were calculated. For consolidated dataChi Square test was used to test the significance of difference between variables.Any 'p' value less than 0.05 was considered to denote significant relationship among the tested variables.

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RESULTS AND OBSERVATIONS

AGE STRATIFIED CHARACTERISTICS OF OUR STUDY POPULATION

	< 20 Yrs (n=75)	Yrs (n=42)	>60 Yrs (n=51)	Total (N=168)
Male Gender	49	31	25	105
Female gender	26	11	26	63
Diabetes Mellitus	0	12	34	46
Hypertension	0	15	37	52
Obesity	0	13	10	23
Smoking	8	17	11	36
Troponin T Elevation	69	37	42	148

In this study of 168 patients conducted, 105were male and 63 were female. The youngest patient was 12 years old, and the oldest was 72 years of age.

Highest number of patients came under the age group of < 20 years (44.6%), followed by > 60 years age group (30.4%) and the lowest were in the 20 to 60 years age group (25%).
As expected, traditional comorbidities like Hypertension, Diabetes and Obesity were noted to be higher in the latter two groups.

Troponin T elevation was noted in 148 (88%) patients on admission.

SYMPTOM PROFILE:

	< 20 Y (n=75)	– 60 Y (n=42)	>60 Y (n=51)	Total (N=168)	P value
Fever	21	9	15	45	0.09
Fatigue	48	21	33	102	0.01
Dyspnea	63	35	43	141	0.01
Palpitations	13	8	11	32	0.55
Chest pain	11	5	7	23	0.29
Syncope	1	0	1	2	0.61

Dyspnea was the most common symptom in our study, noted in 83.9% of patients. Fatigue was

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second most frequent symptom (60.7%) followed by fever (26.7%).

In Hospital Course:

	< 20 Yrs (n=75)	**20-60Yrs (n=42)**	**>60 Yrs (n=51)**	**Total (n=168)**	**P value**
Thrombocytopenia requiring Platelet transfusion	31	14	20	65	0.03
Renal Dysfunction	31	13	18	62	0.01
Raised Liver enzymes	33	10	21	64	0.01
Major Bleed	2	1	1	4	0.77
Shock requiring Inotropic support	29	9	15	53	0.01
Mechanical Ventilation	14	3	6	23	0.01
Mortality	12	0	5	17	0.01

During the course of hospital stay, the patients were monitored for the presence of bleeding manifestations like skin rashes, epistaxis, gum bleeding, hemoptysis, hematuria, bleeding PV, melena and major bleeds like intracranial hemorrhage and major Gastrointestinal bleed.
Among the 168 patients, 54 (32.1%) patients had bleeding manifestations. The most common form of bleeding occurred in the form of skin bleeding followed by gum bleeding followed by melena.
Thrombocytopenia was seen in 163 (97%) patients but platelet transfusion was required in 65 (38.7%) patients.
Intracranial hemorrhage was noted in 3 patients and Hematemesis in 1 patient who was <20 years old.
Hypotension was noted in 110 (65.5%) patients. Among them, 57 patients improved with Fluid resuscitation and other supportive care. Shock which was refractory to IV fluids and required IV inotropic support was noted in 53 (31.5%) patients.
Mortality was seen in 17 (10.1%) patients in our study. 7 patients came gasping and they all died within the first 5 hours of admission. All 3 patients with intracranial hemorrhage died. 1 patient had refractory Ventricular arrhythmia and died. The other 6 deaths occured due to Cardiogenic Shock. There was no mortality in the age group of 20 to 60 years. However, the age group of <20 years had the highest mortality with 12 deaths (16% of study population).

ECG ABNORMALITIES:

ECG Abnormalities	**No. of Patients (n)**	**Percentage (%)**
Junctional Bradycardia	10	5.9%
1st Degree AV Block	12	7.1%
Bundle branch block	15	8.9%
ST-T Changes	118	70.2%
Ectopics	18	10.7%
Supraventricular Tachycarrhythmia	7	4.1%
Ventricular Tachyarrhythmia	3	1.7%

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In our study, tachycardia (Sinus - 113, Supraventricular - 7 and Ventricular – 3) was seen in 123 (73.2%) patients whereas 23 (13.6%) patients had bradycardia (Sinus, Junctional, AV Blocks). 22 (13.1%) patients had normal heart rate.

Most common ECG finding was ST-T change(s) which include ST depression, St elevation, T inversion. ST depression was noted in 76 (45.2%) patients and ST elevation was noted in 15 (8.9%) patients

ECHOCARDIOGRAPHY FINDINGS ON ADMISSION:

Echo Findings	**No. of Patients (n)**
LV Systolic Dysfunction Mild (EF 40-55%) Moderate (EF 30-40%) Severe (EF < 30%)	117 70 20 27
LV Diastolic Dysfunction (in absence of systolic dysfunction)	20
RV Dysfunction	15
Pericardial Effusion	39
Normal	31

ECHO FINDINGS ON ADMISSION STRATIFIED ACCORDING TO AGE

Echo Findings	Age (< 20 Yrs)	Age (20-60 Yrs)	Age (> 60 Yrs)
LV Systolic Dysfunction: Mild Moderate Severe	59(n) 35(20.8%) 9(5.3%) 15(8.9%)	23(n) 15(8.9%) 4(2.3%) 4(2.3%)	35(n) 20(11.9%) 7(4.1%) 8(4.7%)
LV Diastolic Dysfunction (Without Systolic dysfunction)	2(1.1%)	6(3.5%)	12(7.1%)
RV Dysfunction	9(5.3%)	2(1.1%)	4(2.3%)
Pericardial Effusion	20(11.9%)	8(4.7%)	11(6.5%)
Normal	9(5.3%)	16(9.5%)	6(3.6%)

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ECHO FINDINGS OF PATIENTS AT FOLLOW UP (Comparison between admission and follow up):

Echo Parameters	Group I Follow up 0	1m	3m	6m	Group II Follow up 0	1m	3m	6m	Group III Follow up 0	1m	3m	6m
LV Systolic Dysfunction	n=59	8	5	1	n=23	6	5	2	n=35	8	6	5
Mild	n=35	0	0	0	n=15	0	0	0	n=20	0	0	0
Moderate	n=9	5	2	0	n=4	3	2	0	n=7	5	3	2
Severe	n=15	3	3	1	n=4	3	3	2	n=8	3	3	3
LV Diastolic Dysfunction (Without Systolic dysfunction)	N=2	0	0	0	N=6	4	2	2	N=12	10	10	10
RV Dysfunction	N=9	3	3	1	N=2	1	1		N=4	1	1	1
Pericardial Effusion	N=20	0	0	0	N=8	0	0	0	N=11	2	0	0

Group I : Age group 12 - 20 years
Group II : Age group 20 – 60 years
Group III : Age group > 60 years

LV systolic dysfunction was noted in 117 (69.6%) patients. It was the most common Echocardiographic abnormality observed across all age groups. All patients with LV systolic dysfunction had global hypokinesia, none of them had any regional wall motion abnormality.
Isolated LV diastolic dysfunction was observed in 11.9% patients, most commonly seen in Group III.
RV dysfunction was observed in 8.9%.
Pericardial effusion was seen in 23.2 % of patients. All of the effusions were mild, none had features of tamponade.
Out of all patients, 17 died during hospital stay; 151 were discharged home. 31 patients who had normal ECHO went on to have uneventful course and normal ECHO at 6 months after discharge.

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All patients with mild LV Systolic dysfunction had normal LV function at 1 month of follow up.
At 6 month follow up:

1. Among patients (total N=20) with Moderate LV systolic dysfunction, 2 out of 7 (28.5%) patients in Group III continued to have LV Systolic dysfunction.
2. Among discharged patients (N=10) with Severe LV systolic dysfunction, 1 patient (33.3%) of group I, 2 patients (50%) of group II, 3 patients (100%) of group III continued to have LV systolic dysfunction.

Also, it was noted that patients with moderate LV Systolic dysfunction recovered later than those patients who had mild LV dysfunction.
At 6 month follow up, RV Dysfunction persisted in 3 (20%) patients who had concomitant baseline severe LV systolic dysfunction

Pericardial effusion resolved in all patients by 1 month in group I and group II; and by 3 months in group III.

DISCUSSION

Dengue viral infection is a global health problem with morbidity and mortality. More than 40% of the world's population live in dengue endemic areas and WHO estimates that about 2.5 billion people in 100 countries are at risk of infection and around 100 million people are infected by dengue virus every year. In majority of infected people, dengue is a self-limiting disease and resolves in 5 to 7 days. Approximately, 500,000 people develop severeform leading to about 20,000 deaths annually.[11,12]
The incidence of cardiac involvement in dengue infection varies from 15 to 40% [13,14,15,16] and can be in the form of rhythm disturbances, myocarditis, pericarditis, pericardial effusion. Myocarditis, considered to be an uncommon complication, has varied clinical presentations from chest pain, dyspnea, palpitations, syncope, cardiogenic shock to death. [9]
The mechanism of myocardial damage in dengue could be the release of inflammatory mediators and/or direct action of the virus itself on cardiomyocytes.[17] The fulminant course was associated with intense interstitial edema, several multifocal areas of necrosis and diffuse inflammatory infiltration. The myocytolytic necrotic areas were replete with viral particles, therefore providing detailed histological evidence of a possible direct viral action on cardiomyocytes.[18] Cardiac rhythm disturbances have been described during dengue myocarditis such as bradycardia, ectopics, AV blocks, atrial fibrillation, supraventricular tachycardia and ventricular tachycardia. These arrhythmias are associated with syncope and even sudden death.[19,20,14,21,22,23]

In our study, 62.5% were males and 37.5% were females. Males were more commonly affected than females by myocarditis in our study (p 0.01).
Most patients presented with platelet count less than 1 lakh.

Highest number of patients belonged to age group of < 20 years (44.6%). Our study also shows that Myocarditis occurs more commonly at extremes of age, in which Dengue illness manifests most severely, which is concurrent with *Wallace H G et al*. [9,24,25]
Comorbidities like Hypertension, Diabetes and Obesity were noted in Group II and Group III patients.

Dyspnea was the most common symptom, it was noted in 83.9% of our study population. This is in contrast to other studies,[26,27] which showed fatigue and fever as more common symptoms.

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This is because our study population consisted of only patients who were referred to us with cardiac symptoms. Also, Myocarditis occurs during the convalescent phase when fever would have subsided in many of the cases.

Out of 168 patients, 54 (32.1%) had bleeding manifestations of which 4 patients had major bleed. 65 patients (38.7%) had thrombocytopenia requiring platelet transfusion. This incidence is much higher when compared to other studies[27] as our study population consisted of severe Dengue.

110 patients had hypotension out of which, 53 patients (48.2%) required IV Inotropic therapy. Hypotension was high in our study, as most patients with severe dengue and myocarditis were referred to us. The number of patients who remained in shock despite fluid resuscitation is also higher compared to other studies. This is because 1) of more serious illness in our study population and 2) 47 (40.2%) patients had moderate to severe LV systolic dysfunction warranting judicious titration of IV fluids and inotropes.

Prevalence of tachycardia was high in our study compared to other studies as more patients presented in heart failure or hypotension and shock.[27,28]

The most common ECG abnormality was changes in ST-T segment, which is concurrent with previous studies.[28]

The most common 2D ECHO finding was LV Systolic Dysfunction (69.6%). This is high compared to other studies[27,28] as our study patients were referred for dengue with cardiac symptoms. 31 (18.4%) patients had no abnormality on 2D ECHO but these patients were diagnosed with Myocarditis based on ECG and Troponin assay. 2D ECHO abnormalities were more commonly observed in extremes of age which inturn, correlate with severity of Dengue.

On follow up, all patients with mild LV systolic dysfunction had normal 2D ECHO at 1 month. At 6 month follow up, 2 out of 20 (10%) patients with moderate LV systolic dysfunction continued to have LV systolic dysfunction; rest improved. Whereas 6 out of 10 (60%) discharged patients with severe LV Systolic Dysfunction continued to have LV Systolic Dysfunction.
All 17 patients who died had severe LV Systolic dysfunction on admission.

LIMITATIONS

As there is unavailability of Cardiac MRI (Magnetic Resonance Imaging) and Endomyocardial biopsy in our region, these were not considered to define Myocarditis in our study.
Cardiac MR imaging could have picked cardiac abnormalities in 31 patients who had normal 2D ECHO in our study.
As ours is a single centre study of patients referred to our centre, we cannot know the actual incidence and outcome of dengue myocarditis in the community.

CONCLUSIONS

Dengue virus affects more than 100 million people worldwide and approximately 0.5% develop cardiac manifestations.
Occurrence of Myocarditis is usually during the convalescence phase of Dengue illness that is, when fever subsides and it is more commonly seen in severe Dengue.

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Cardiac involvement can be in the form of rhythm disturbances, myocarditis and pericarditis/pericardial effusion. Cardiac symptoms in dengue patients may range from being asymptomatic to mild symptoms to acute heart failure, cardiogenic shock and death.
Mortality is higher with severe Myocarditis as evident by all deaths occurring in patients with severe LV Dysfunction.
Cardiac biomarkers, ECG and 2D ECHO play an important role in the diagnosis of dengue myocarditis. No specific treatment exists for treatment of dengue myocarditis. Fluid resuscitation, inotropic support, ventilator support and guideline directed treatment of heart failure were used based on LV systolic function and patient's clinical condition. Serial Echocardiography helps in assessing LV function recovery and prognostication.
The cornerstone in the management of dengue myocarditis is early detection, timely treatment and continuous monitoring and thus saving lives.

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