Cardiac evaluation in adults with dengue virus infection by serial echocardiography

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Abstract

Background

Dengue virus infection (DVI) is a major health problem in many parts of the world. Its manifestations range from asymptomatic infections to severe disease. Although cardiac involvement has been reported in DVI, its incidence has not yet been well established.

Methods

From July 2016 to January 2018, patients hospitalized at the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, with dengue virus infection confirmed by positive NS1 or positive dengue immunoglobulin M findings, participated in the study. We characterized the incidence and change in cardiac function by serial echocardiography and levels of troponin-T and creatinine kinase-myocardial band (CK-MB) on the day of admission, the day of defervescence, the first day of hypotension (if any), and at 2-week follow-up.

Results

Of the 81 patients evaluated, 6 (7.41%) exhibited elevated biomarker levels. There was no difference in clinical presentation amongst dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) except the amount of bleeding. Cardiac involvement was found in 22% of patients: 3 (3.70%) had left ventricular systolic dysfunction, 3 (3.70%) had transient diastolic dysfunction, 6 (7.41%) had increased levels of at least one cardiac biomarker (troponin-T or CK-MB), and 6 (7.41%) had small pericardial effusion. Myocarditis was suspected in only two patient (with DHF); thus, myocarditis was uncommon in patients with dengue virus infection. Three patients developed DSS during admission and transfer to the intensive care unit.

Conclusion

Cardiac involvement in adults with dengue infection was found in 22.22% of cases, ranging from elevated cardiac biomarker, transient left ventricular systolic and diastolic dysfunction and pericardial effusion. We found that DHF was the significant risk factor for cardiac involvement ($p < 0.001$). Abnormalities in cardiac function had resolved spontaneously by the day of follow-up without specific treatment.

Background

Dengue virus infection (DVI) is a major health problem in more than 100 countries in tropical and subtropical regions. Approximately 96 million people develop DVI annually [21]. DVI has a broad clinical spectrum, according to the 2009 classification by the World Health Organisation (WHO), which includes asymptomatic to dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [3]. Cardiac complications are amongst the important consequences of DVI.

The actual incidence of, and details about, cardiac involvement are neither well-described nor well-defined. Among studies, the incidence of cardiac involvement in DVI varies from 15–40% [4, 6, 8, 9]. Various forms of cardiac involvement in DVI include transient atrioventricular block, relative bradycardia and myocarditis, and patients may develop acute pulmonary edema or cardiogenic shock [8, 9, 11]. Although severe cardiac complications, such as myocarditis, have been reported in the literature, their frequencies have still not been established. Dengue epidemics vary in severity, so previously reported frequencies may not represent an accurate assessment. Cardiac involvement in DVI must be better understood. In this

study, we aimed to characterise, describe and evaluate the dynamics of cardiac function using serial echocardiography in patients with different clinical manifestations of DVI over a period of several years. We also aimed to evaluate the risk factors of cardiac involvement in patients with DVI.

Methods

Ethical considerations

The study design was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University (Certificate No. MUTM 2016-005-02). Written informed consent was obtained from patients before enrolment into this study.

Study design

This prospective study focused on adult patients with dengue who were admitted to the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, between July 2016 and January 2018. The study's inclusion criteria were: (1) adults at least 18 years old; (2) having DVI confirmed by either a positive result of dengue non-structural protein 1 (NS1) testing or the presence of dengue immunoglobulin M (IgM) antibodies in acute-phase sera by enzyme-linked immunosorbent assay (ELISA). Patients who had had myocardial infarction within the previous month or history of cardiomyopathy were excluded from the study. Laboratory investigations, including complete blood count, blood chemistry, Troponin-T, CK-MB, ECG and 2D echocardiography, were performed on the day of admission, day of defervescence, the first day of hypotension (if any), and at 2-week follow-up. Patients' data, including demographic data, clinical presentation, and laboratory findings, were recorded in a pre-defined case-record form.

Definition of cardiac involvement

Cardiac involvement in this study was defined as one or more of the following:

1. Left ventricular systolic dysfunction
2. Transient diastolic dysfunction
3. Myocarditis, pericarditis, or pericardial effusion
4. Elevated levels of at least one cardiac biomarker (troponin-T or creatine kinase–myocardial band [CK-MB])

General definitions

An adult is defined as a person aged 18 years or older. Obesity [35] is defined as a BMI > 27.5 kg/m^2 and overweight is defined as a BMI > 23 kg/m^2, as adjusted for Asian population parameters. Severe transaminitis is defined as elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT), or both > 10x the upper normal limit.

Case definition of severe dengue

The WHO 2009 case definitions were used for severe DVI [10]. Severe dengue was classified as having: (1) severe plasma leakage that necessitated fluid resuscitation from shock, (2) severe clinical bleeding, defined as spontaneous bleeding from the mucosal area that needed blood transfusion or bleeding in the vital organs, (3) evidence of organ involvement, including heart failure or myocarditis, AST or ALT levels higher than 1000 U/L, and impaired consciousness. An adult was defined as a person aged 18 years or older.

Definition of severity of dengue fever

Patients who were confirmed DVI were classified, on the basis of WHO 1997 dengue case definition [3], into dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), based on clinical and laboratory criteria. Four cardinal features of DHF, as defined by the WHO, are as follows: (1) fever or history of fever lasting 2–7 days, occasionally biphasic, (2) hemorrhagic tendencies, evidenced by at least one of the following: positive tourniquet test; petechiae,

ecchymoses or purpura; bleeding from the mucosa, gastrointestinal tract, injection sites or other locations; hematemesis or melena, (3) thrombocytopenia (100,000 cells per mm^3 or less), (4) evidence of plasma leakage owing to increased vascular permeability shown by: an increase in hematocrit > 20% above average for age, sex and population; a decrease in hematocrit after intervention > 20% of baseline; signs of plasma leakage, such as pleural effusion, ascites or hypoproteinemia.

Dengue shock syndrome (DSS) as defined by all four criteria for DHF must be met, in addition to evidence of circulatory failure manifested by: rapid and weak pulse and narrow pulse pressure (< 20 mmHg or 2.7 kPa) manifested by hypotension for age and cold, clammy skin and restlessness or lethargy.

Cardiac enzymes

Troponin-T hs assay and CK-MB isoenzyme levels were determined for all dengue patients during hospitalization on day of admission, day of defervescence, and 2 weeks after discharge (early convalescence). Troponin-T was measured using with the Elecsys Troponin-T hs assay (Roche Diagnostics, Mannheim, Germany) and serum levels higher than 40 pg/mL were considered elevated. CK-MB was also measured by an enzyme-linked fluorescent assay (MyBioSource, San Diego, CA, USA) and serum levels detected by the assay ranged from 0.2 to 60 ng/mL. All tests were performed in batches after study completion and by clinicians without knowledge of the clinical diagnosis.

Chest radiography

Chest radiography was performed on the day of defervescence.

Echocardiography protocol

Using the Vivid E9 ultrasound platform (GE Healthcare, Chicago, IL, USA), a single cardiologist performed echocardiography from the time of patient enrolment into the study to the 2-week follow-up visit. All measurements were obtained daily, and the cardiologist had no knowledge of the laboratory results.

All images were recorded and analyzed according to a predefined method with the same software analysis system (GE Healthcare). Systolic and diastolic blood pressure and the results of electrocardiography (ECG) were recorded during the examination.

All echocardiographic images were recorded and reviewed by a single operator. Routine two-dimensional echocardiograms and colour-flow Doppler images were obtained in the standard parasternal long axis view, subcostal view, apical two-chamber views, and apical four-chamber views. The left ventricular walls and dimensions were measured in accordance with the guidelines of the American Society of Cardiology. Transmitral pulsed-wave Doppler velocities (peak E- and A-wave velocities) were measured in the apical four-chamber view with the sample volume positioned at the mitral valve. Tissue Doppler imaging of the left ventricle was performed with pulsed-wave Doppler assessment of the medial and lateral mitral valve annulus, peak tissue medial and lateral.

The diameter of the inferior vena cava was measured in the subcostal view. Pericardial effusion and other anatomical and functional findings were recorded when present.

Sample size calculation

To calculate the necessary sample size, we used the estimated prevalence described in a previous study [31], where the incidence of cardiac involvement was 37% among adults with dengue infection. Based on this information, a minimum sample size of 76 was deemed sufficient for this study, with an error of 30% at 95% confidence interval.

Statistical analysis

All data were analyzed using SPSS version 18.0 (IBM, Armonk, NY, USA). Qualitative variables were calculated as frequencies and percentages. Quantitative variables were calculated as medians and interquartile ranges (IQR), because the data distribution was skewed, even after the data were transformed in logarithmic functions. The chi-square test, Fisher's exact test and Mann-Whitney test, were performed. Factors demonstrating a univariate relationship ($p < 0.05$) with the outcome variable were included in the multiple logistic regression analysis to assess their effect on disease severity. Differences were considered significant at p-values of 0.05 or lower. A multivariate logistic regression model was used to determine the association of independent factors of cardiac involvement (adjusted odds ratio [OR] with 95% confidence interval). A forward stepwise method was used with entry at 0.05 and removal at 0.10. Variables were classified as statistically significant if their two-tailed p-value was less than 0.05.

Results

A total of 81 patients hospitalized with DVI between July 2016 and January 2018 were included in the study, as shown in Fig. 1

Characteristics of the patients

The mean age of the patients in this study was 33 years (SD 13 years; range, 20–46 years). All patients presented with typical clinical manifestations of DVI; symptoms had begun a median of 4 days earlier (IQR, 1 to 6 days). Of the 81 patients, 39 (48.15%) were classified as having dengue fever, 39 (48.15%) as having grade I or II DHF, and 3 (3.70%) as having grade III or IV DHF. DVI was confirmed by the detection of NS1 antigen in 71 patients (87.65%) and by the presence of specific IgM antibody in 37 (45.68%). Laboratory examination revealed troponin-T elevation in three patients (3.70%) and CK-MB elevation in five patients (6.17%), respectively. Thrombocytopaenia and mucosal bleeding were significantly different between patients with dengue fever and those with DHF. Mucosal bleeding occurred in 35 (43.21%) of the patients. Details of the clinical and laboratory characteristics of all 81 patients are shown in Table 1.

Table 1
Clinical and laboratory characteristics of 81 patients with dengue virus infection.

Characteristic	Total (*N* = 81)	DF (*n* = 39)	DHF (*n* = 42)	p-value
Sex				0.418
Female	44 (54.32%)	23 (58.97%)	21 (50.00%)	
Male	37 (45.68%)	16 (41.03%)	21 (50.00%)	
Age	32.95 ± 13.56	33.79 ± 14.46	32.17 ± 12.8	0.592
Body mass index	22.77 ± 4.93	21.99 ± 4.71	23.5 ± 5.07	0.170
Obesity	24 (29.63%)	10 (25.64%)	14 (33.33%)	0.449
Overweight	9 (11.11%)	3 (7.69%)	6 (14.29%)	0.345
Underlying diseases	12 (14.81%)	5 (12.82%)	7 (16.67%)	0.626
Mucosal bleeding	35 (43.21%)	12 (30.8%)	23 (54.76%)	0.029*
Fever duration (days; median [IQR 1–6])	3.83 ± 1.17	3.95 ± 1.05	3.71 ± 1.27	0.371
Clinical classification				
Dengue fever	39 (48.15%)	39 (100%)	0 (0%)	< 0.001*
DHF, grade I or II	39 (48.15%)	0 (0%)	39 (92.86%)	< 0.001*
DHF, grade III or IV	3 (3.70%)	0 (0%)	3 (7.14%)	0.089
Diagnostic test				
NS1 antigen	71 (87.65%)	33 (84.61%)	38 (90.48%)	0.423
IgM antibody	37 (45.68%)	18 (46.15%)	19 (45.24%)	0.934
Laboratory finding (mean ± standard deviation)				
Low platelet count	45.43 ± 31.53	53.64 ± 26.91	37.81 ± 33.84	0.023*
Characteristic	**Total (*N* = 81)**	**DF (*n* = 39)**	**DHF (*n* = 42)**	**p-value**
Maximum AST, U/L	424.34 ± 1275.99	162.25 ± 198.37	672.63 ± 1744.98	0.081
Maximum ALT, U/L	203.55 ± 492.6	104.39 ± 98.64	297.5 ± 671.51	0.088
Troponin-T elevation	3 (3.70%)	0 (0%)	3 (7.10%)	0.089
CK-MB elevation	5 (6.17%)	0 (0%)	5 (11.90%)	0.026*
Cardiac involvement	18 (22.22%)	1 (2.56%)	17 (40.48%)	< 0.001*
Severe dengue virus infection	9 (11.11%)	1 (2.56%)	8 (19.05%)	0.018*

* Statistically significant (Chi-square test)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase– myocardial band; DF, dengue fever; DHF, dengue hemorrhagic fever; IgM, immunoglobulin M; IQR, interquartile range.

Comparison between patients with and without elevated cardiac biomarkers

In the majority of patients (75 [92.5%]), cardiac biomarker levels were not elevated. There was no significant difference in age, sex, duration of fever, underlying disease(s), white blood cell count, hemoglobin, hematocrit, platelet count or creatinine level between these patients and those in whom the levels were elevated.

Patients whose biomarker levels were elevated had significantly more cardiac involvement in DVI ($p < 0.001$). Characteristics of patients with increased levels of troponin-T, CK-MB or both, and of patients with normal levels, are listed in Table 2.

Table 2
Comparison between patients with and without elevation in biomarker levels.

Characteristics	With biomarker elevation ($n = 6$)	Without biomarker elevation ($n = 75$)	p-value
Age (years)	28.67 ± 6.22	33.29 ± 13.95	0.156
Male sex	5 (83.33%)	32 (42.67%)	0.054
Dengue fever	0 (0%)	39 (52%)	0.014*
Dengue hemorrhagic fever	6 (100%)	36 (48%)	0.014*
Grade I or II	4 (66.67%)	35 (46.67%)	0.345
Grade III or IV	2 (33.33%)	1 (1.33%)	< 0.001*
Underlying diseases	2 (33.33%)	10 (13.33%)	0.185
Fever duration (days; mean ± standard deviation)	3.5 ± 1.38	3.85 ± 1.16	0.480
White blood cell count (cells/mm^3)	6225 ± 3115.95	4988 ± 2403.99	0.325
Hemoglobin (g/dL)	13.58 ± 2.36	13.65 ± 1.75	0.935
Hematocrit (%)	38.42 ± 6.73	40.07 ± 4.71	0.426
Platelet count (per microlitre)	56666.67 ± 30826.4	65733.33 ± 85941.11	0.799
Creatinine (mg/dL)	1.1 ± 0.75	0.75 ± 0.21	0.304
No. patients with cardiac involvement	6 (100%)	12 (16%)	< 0.001*
* Statistically significant (Chi-square test)			

Evaluation of patients with cardiac involvement

Of the 81 patients with DVI, 18 (22.22%) had cardiac involvement (Fig. 2): 3 (3.70%) had left ventricular systolic dysfunction, 3 (3.70%) had transient diastolic dysfunction, 6 (7.41%) had increased levels of at least one cardiac biomarker (troponin-T or CK-MB), and 6 (7.41%) had small pericardial effusion. Of the 42 patients with DHF, 17 (40.5%) had cardiac involvement. We found that cardiac involvement was more common in DHF than in dengue fever.

ECG revealed that of the 81 patients, 78 (96.30%) had sinus rhythm; of these, 65 (80.25% of the total) had a normal heart rate, 6 (7.41%) had tachycardia, 5 (6.17%) had bradycardia, and 2 (2.47%) had sinus arrhythmia. Of the three patients with abnormal rhythm, two (2.47% of the total) had junctional rhythm and one (1.23%) had premature ventricular contractions (Table 3).

Table 3
Electrocardiographic finding at the time of admission.

Rhythm	Number (*N* = 81)
Normal sinus rhythm	65 (80.25%)
Sinus tachycardia	6 (7.41%)
Sinus bradycardia	5 (6.17%)
Sinus arrhythmia	2 (2.47%)
Premature ventricular contraction	2 (2.47%)
Junctional rhythm	1 (1.23%)

Evaluation of patients with biomarker elevation

Clinical, laboratory and echocardiographic characteristics of the six patients (7.41%) with elevated levels of cardiac biomarkers are listed in Table 4. Four (4.94%) patients presented with clinical manifestations of cardiac involvement: myocarditis in two patients, acute heart failure with shock in one patient, and shock in one patient. Two patients had suspected myocarditis. These patients were young (33 and 37 years) and presented without underlying disease. Myocarditis was confirmed by depressed left ventricular ejection fraction (LVEF) in echocardiography, and elevated cardiac enzymes (Troponin-T and CK-MB). Dengue myocarditis is not common, and cardiac enzyme(s) may not be elevated among some dengue patients with cardiac involvement but without myocarditis.

Table 4
Characteristic of patients with elevated level of biomarkers (troponin-T or CK-MB).

Demographic				Clinical				Echocardiography	
No.	Age (y)	Sex	Symptom duration (days)	Classification	Cardiac manifestation	CK-MB level	Troponin-T	Depressed LVEF	Pericardial effusion
1	19	Male	3	DHF	None	323	< 50	No	No
2	26	Male	4	DHF	Shock	15.8	< 50	No	No
3	30	Male	6	DHF	None	1.4	50–100	No	No
4	29	Male	2	DHF/DSS	Shock, heart failure	19	< 50	No	Yes
5	37	Male	3	DHF	Myocarditis	18.2	1344	Yes	No
6	33	Female	3	DSS	Myocarditis	9.78	1210	Yes	Yes

CK-MB, creatine kinase–myocardial band; DHF, dengue haemorrhagic fever; DSS, dengue shock syndrome; LVEF, left ventricular ejection fraction.

Independent factors associated with cardiac involvement

Univariate analysis revealed the following independent variables: age, male sex, overweight, obesity, underlying disease, DHF, severe transaminitis, and severe dengue. Categorical variables were placed into the model with entry at 0.05 and removal at 0.10 and were scored with ‘no’ as the reference category. In this way, two variables were eliminated: severe transaminitis and obesity. Eventually, DHF was identified as the only risk factor for the development of cardiac involvement in DVI ($p < 0.001$; Table 5).

Table 5
Independent associated factors for cardiac involvement, according to univariate and multivariate analyses.

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	1 (0.96 to 1.04)	0.872		
Male sex	3.04 (1.01 to 9.15)	0.048*	2.97 (0.85 to 10.42)	0.089
Overweight	1.3 (0.45 to 3.75)	0.627		
Obesity	1.51 (0.41 to 5.56)	0.532		
Underlying	1.96 (0.52 to 7.47)	0.322		
DHF	25.84 (3.23 to 206.63)	0.002*	22.99 (2.78 to 190.26)	0.004*
Severe dengue	5.67 (1.34 to 24.07)	0.019*	2.6 (0.52 to 12.84)	0.242
Severe transaminitis	0.27 (0.07 to 1.04)	0.056		

CI, confidence interval; DHF, dengue haemorrhagic fever; OR, odds ratio.

All patients had a follow-up examination during early convalescence (< 2 weeks after discharge). Trends towards improvement from day of defervescence to convalescent phase were found for LVEF, stroke volume, and cardiac index, in cases of dengue fever and dengue hemorrhagic fever (Table 6).

Table 6
Comparison between cardiac function on day of admission (day 1), day of defervescence (day 2: critical period) and on day of 2-week follow-up (day 3).

Cardiac function	Dengue fever					Dengue hemorrhagic fever				
	Day 1	Day 2	Day 3	p-value D1 VS D2	p-value D2 VS D3	Day 1	Day 2	Day 3	p-value D1 VS D2	p-value D2 VS D3
Heart rate	81.14 ± 15.28	70.09 ± 10.25	73.42 ± 11.71	< 0.001*	0.072	79.32 ± 11.27	70.43 ± 13.85	74.65 ± 10.01	< 0.001*	0.066
MV flow E-wave velocity	0.88 ± 0.2	0.86 ± 0.17	0.91 ± 0.17	0.066	0.064	0.83 ± 0.21	0.83 ± 0.2	0.94 ± 0.17	0.797	0.001*
MV flow deceleration time	179.27± 35.81	184.2 ± 36.85	175.71 ± 36.33	0.880	0.514	169.43 ± 45.64	194.06 ± 48.06	175.73 ± 38.84	0.023*	0.392
MV flow A-wave velocity	0.64 ± 0.18	0.58 ± 0.22	0.63 ± 0.18	0.002*	0.022*	0.61 ± 0.17	1.59 ± 6.56	0.71 ± 0.2	0.342	0.379
MV annulus E-wave velocity	1.5 ± 0.54	2.25 ± 3.4	1.79 ± 1.21	0.246	0.500	1.48 ± 0.54	1.63 ± 0.58	1.42 ± 0.46	0.065	0.053
e´	0.12 ± 0.04	0.13 ± 0.07	0.13 ± 0.08	0.385	0.890	0.11 ± 0.03	0.1 ± 0.03	0.12 ± 0.03	0.587	0.051*
E/e´	8.01 ± 2.09	8.09 ± 2.49	8.42 ± 2.42	0.797	0.295	8.34 ± 2.56	8.38 ± 2.02	8.35 ± 2.35	0.840	0.938
a´	0.09 ± 0.02	0.07 ± 0.02	0.09 ± 0.02	0.009*	0.001*	0.08 ± 0.03	0.08 ± 0.03	0.08 ± 0.03	0.345	0.202

a´, late (atrial) diastolic mitral annular velocity; e´, early diastolic mitral annular velocity; E/e´, ratio of peak early mitral inflow velocity to early diastolic mitral annular velocity; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MV, mitral valve.

Values are presented as means ± standard deviations. p-values correspond to paired *t* tests

Cardiac function	Dengue fever					Dengue hemorrhagic fever				
	Day 1	Day 2	Day 3	p-value D1 VS D2	p-value D2 VS D3	Day 1	Day 2	Day 3	p-value D1 VS D2	p-value D2 VS D3
LVEF	68.9 ± 5.77	69.4 ± 9.28	72.12 ± 7.63	0.822	0.022*	69.17 ± 8.58	68.68 ± 7.08	71.35 ± 6.82	0.835	0.086
LVOT mean velocity	0.59 ± 0.13	0.55 ± 0.13	0.57 ± 0.12	0.081	0.063	0.57 ± 0.12	0.52 ± 0.13	0.58 ± 0.13	0.087	0.024*
Atrioventricular mean velocity	0.88 ± 0.18	0.78 ± 0.14	0.83 ± 0.18	0.005*	0.018*	0.83 ± 0.14	0.82 ± 0.28	0.83 ± 0.18	0.187	0.619
Left atrial diameter	3.44 ± 0.48	3.43 ± 0.43	3.47 ± 0.4	0.664	0.402	3.34 ± 0.54	3.53 ± 0.47	3.56 ± 0.48	0.026*	0.894
Cardiac index	3.54 ± 1.18	2.98 ± 0.89	3.27 ± 0.95	0.003*	0.039*	3.26 ± 0.83	2.9 ± 0.84	3.29 ± 1.03	0.064	0.030*
Stroke volume	69.47 ± 16.88	69.22 ± 18.14	71.56 ± 22.01	0.596	0.093	67.9 ± 16.22	69.79 ± 20.97	74.11 ± 19.03	0.429	0.233

a´, late (atrial) diastolic mitral annular velocity; e´, early diastolic mitral annular velocity; E/e´, ratio of peak early mitral inflow velocity to early diastolic mitral annular velocity; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MV, mitral valve.

Values are presented as means ± standard deviations. p-values correspond to paired *t* tests

Discussion

In our study, evidence of myocardial involvement was found in 22% of patients who were hospitalized, among whom clinical manifestations ranged in severity from mild elevation of cardiac biomarker levels to myocarditis. Fortunately, these cardiac abnormalities were transient and did not necessitate specific treatment. Impairment of systolic function, characterized by a left ventricular ejection fraction of less than 45%, was found in other studies of severe dengue [4, 9, 16]. In another case report of 102 paediatric patients with DHF, 10 patients had fulminant myocarditis that necessitated early inotropic drug support for acute heart failure [13]. Prospective studies have reported various incidences of abnormal cardiac involvement in dengue: myocarditis in 15–27% of cases [6, 8, 12, 15, 20, 33] and functional cardiac abnormalities in up to 40% [4, 31, 34].

In contrast to these findings, myocarditis was suspected in two of our patients on the basis of clinical information, elevation of cardiac enzyme levels, and minimal depression of left ventricular ejection fraction. The difference in the incidence of myocarditis in other reports may be related to dengue severity, which can vary year by year; this study was conducted during a year when severe dengue was not prevalent. Our results are compatible with those of a report of dengue cases in Southeast Asia [7, 27] and a report from Sri Lanka [8]. Wichmann et al. [12] showed that 25% of patients with dengue had elevated levels of one or more cardiac biomarkers, such as myoglobin, CK-MB, troponin-T, N-terminal pro B-type natriuretic peptide, and heart-type fatty acid-binding protein. Myocardial involvement may result from a direct effect of the dengue virus or from cytokine-induced immune damage, in which high circulatory levels of pro-inflammatory cytokines cause depression of myocardial function [1, 2]. Another potential mechanism is regional vulnerability to coronary hypoperfusion [29]. Patients with elevated levels of cardiac biomarkers showed more inflammatory activity, such as higher white blood cell counts, but these findings were not statistically significant compared with previous studies [23].

Cardiac involvement in dengue, although often mild, can be severe, progressing to heart failure, according to several reports [4, 17, 32]. Cardiac and hemodynamic parameters are affected by cardiac function, volume status and autonomic responses [29]. Functional cardiac involvement in dengue was found to involve both diastolic and systolic function and was related to severity of plasma leakage [29]. Echocardiographic findings of myocardial injury in DVI have been demonstrated [9, 20, 23, 24, 30]. We found that abnormalities in cardiac parameters were related to the severity of DVI. Decreases in left ventricular ejection fraction, cardiac index and left ventricular diastolic inflow, and elevations in systemic vascular resistance in DHF are likely to be affected by reduced intravascular volume [29]. We found decreases in mitral valve early wave peak velocities, early diastolic mitral annular velocity (e´), left ventricular outflow tract mean and cardiac index in DHF. Lower e´ in this study may reflect diastolic dysfunction, as in previous studies [28, 29]. Cardiac functional assessment with the use of tissue Doppler imaging parameters revealed that e´ was significantly decreased in patients with severe dengue, which may reflect impaired left ventricular relaxation and diastolic defects [18, 29].

Fatal dengue-related myocarditis has also been reported. In a study of adult and paediatric cases in Brazil, the incidence of myocarditis amongst patients with clinical manifestations or elevated biomarker levels was approximately 15% [19]. In a subset of these cases, echocardiographic or magnetic resonance imaging (MRI) findings were abnormal [12, 15]. When dengue-related myocarditis occurs, good supportive care with optimal intravascular volume and maintenance fluid is crucial. According to many studies, myocarditis is transient and self-limiting. In particular, dengue with suspected cardiac involvement should not be treated with iatrogenic fluid overload [16, 19]. The decrease in heart rate on the day of defervescence that has been observed in DVI is attributed to increased parasympathetic activity [26]. In this study, we found that patients with severe DVI are likely to be at risk of cardiac involvement; however, the numbers of patients categorized by severity were small. Further studies are needed to evaluate the risk factors. We found that DHF was one of the associated risk factors for the development of cardiac involvement in DVI. This finding will increase physicians' awareness of the possibility of cardiac involvement in patients with DHF.

This study had some limitations. First, we studied a population at only a single center in Thailand; our data may not be representative of all patients with dengue. Second, we studied hospitalized adults with DVI during a period when few cases of myocarditis related to dengue were reported; hence, the results may not be all patients with DVI. Third, we used cardiac biomarker elevation and serial echocardiography to screen for myocarditis in patients with DVI, but these are not ideal screening tools. Cardiac MRI is more sensitive than echocardiography for subclinical myocarditis, but is very expensive.

Conclusions

In this study, the prevalence of cardiac involvement in adults with DVI was 22%; manifestations included elevated levels of cardiac biomarkers, transient left ventricular systolic and diastolic dysfunction, and pericardial effusion. The functional abnormality was transient and resolved spontaneously by day of follow-up without specific treatment. Myocarditis in patients with DVI was uncommon. We found that DHF is one of the risk factors for the development of cardiac involvement

in DVI. Echocardiography is the investigation of choice for evaluating hemodynamic status in patients with DVI, especially in severe cases.

Abbreviations

a´: late (atrial) diastolic mitral annular velocity; ALT:Alanine aminotransferase; AST:Aspartate aminotransferase; BMI:Body mass index; CI:Confidence intervals; CK-MB:Creatinine kinase-myocardial band; DVI:Dengue virus infection; DF:Dengue hemorrhagic fever; DSS:Dengue shock syndrome; e´:early diastolic mitral annular velocity; ECG:Electrocardiography; E/e´:ratio of peak early mitral inflow velocity to early diastolic mitral annular velocity; ELISA:enzyme-linked immunosorbent assay; IgM:Immunoglobulin M; IQR:Inter-quartile range; LVOT:left ventricular outflow tract; LVEF:Left ventricular ejection fraction; MRI:Magnetic resonance imaging; MV:Mitral valve; NS1 antigen:Non-structural protein 1 antigen; OR:Odds rato; WHO:World Health Organization.

Declarations

Competing interests

The authors declare that they have no competing interests

Authors' contributions

CM contributed to the conception, study design, data collection, data analysis, data interpretation, and with writing and preparing the manuscript. BH contributed to the conception, study design, and data collection. SM contributed the conception, study design, data interpretation. AH contributed to caring for patients with dengue, data collection. AP contributed the conception, data analysis with writing and preparing the manuscript. SM contributed the conception, data collection, data analysis with writing and preparing the manuscript. WP contributed to the conception, study design, writing and preparing the manuscript. WH contributed to the conception, study design, data collection and preparing the manuscript.

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References

1. Hober D, Poli L, Roblin B, Gestas P, Chungue E, Granic G, et al. Serum levels of the tumor necrotic factor-alpha (TNF-alpha), interleukin-6 (IL-6), and interleukin-1 beta (IL-1 beta) in dengue-infected patients. Am J Trop Med Hyg. 1993;48:324–31.
2. Hober D, Delannoy AS, Benyoucef S, Groote DD, Wattre P. High levels of sTNFR p75 and TNF alpha in dengue-infected patients. Microbiol Immunol. 1996;40:569–73.
3. Dengue Hemorrhagic Fever:diagnosis, treatment, prevention and control.2nd ed.World Health Organization; 1997.
4. Wali JP, Biswas A, Chandra S, Malhotra A, Aggarwal P, Handa R, et al. Cardiac involvement in dengue haemorrhagic fever. Int J Cardiol. 1998;64:31–6.

5. Khongphatthanayothin A, Suesaowalak M, Muangmingsook S, Bhattarakosol P, Pancharoen C. Hemodynamic profiles of patients with dengue hemorrhagic fever during toxic stage: an echocardiographic study. Intensive Care Med. 2003;29:570–4.
6. Promphan W, Sopontammarak S, Pruekprasert P, Kajornwattanakul W, Kongpattanayothin A. Dengue myocarditis. Southeast Asian J Trop Med Public Health. 2004;35:611–3.
7. Khongphatthanayothin A, Lertsapcharoen P, Supachokchaiwattana P, Satupan P, Thongchaiprasit K, Poovorawan Y, et al. Hepatosplanchnic circulatory dysfunction in acute hepatic infection: the case of dengue hemorrhagic fever. Shock. 2005;24:407–11.
8. Kularatne SA, Pathirage MM, Kumarasiri PV, Gunasena S, Mahindawanse SI. Cardiac complications of a dengue fever outbreak in Sri Lanka, 2005. Trans Royal Soc Trop Med Hyg. 2007;101:804–8.
9. Khongphatthanayayothin A, Lertsapcharoen P, Supachokchaiwattana P, La-Orkhun V, Khumtonvong A, et al. Myocardial depression in dengue hemorrhagic fever: prevalence and clinical description. Pediatr Crit Care Med. 2007;8:524–9.
10. Dengue, guidelines for diagnosis, treatment, prevention and control:World Health Organization, 2009.
11. Lee CH, Teo C, Low AF. Fulminant dengue myocarditis masquerading as acute myocardial infarction. Int J Cardiol. 2009;136:e69–71.
12. Wichmann D, Kularatne S, Ehrhardt S, Wijesinghe S, Brattig NW, Abel W, et al. Cardiac involvement in dengue virus infections during the 2004/2005 dengue fever season in Sri Lanka. Southeast Asian J Trop Med Public Health. 2009;40:727–30.
13. Salgado DM, Panqueba CA, Castro D, Vega R, Rodriguez JA. Myocarditis in children affected by dengue hemorrhagic fever in a teaching hospital in Columbia. Rev Salud Publica (Bogota). 2009;11:591–600.
14. Wichmann D, Kularatne S, Ehrhardt S, Wijesinghe S, Brattig NW, Abel W, et al. Cardiac involvement in dengue virus infections during the 2004/2005 dengue fever season in Sri Lanka. Southeast Asian J Trop Med Public Health. 2009;40:727–370.
15. Salgado DM, Eltit JM, Mansfield K, Panqueba C, Castro D, Vega MR, et al. Heart and skeletal muscle are targets of dengue virus infection. Pediatr Infect Dis J. 2010;29:238–42.
16. Lee IK, Lee WH, Lin JWW, Yang KD. Acute myocarditis in dengue hemorrhagic fever: a case report and review of cardiac complications in dengue-affected patients. Int J Inf Dis. 2010;14:e919–22.
17. Gupta VK, Godpayle AK. Subclinical cardiac involvement in dengue hemorrhagic fever. J Indian Acad Clin Med. 2010;11:107–11.
18. Yacoub S, Griffiths A, Chau TT, Simmons CP, Wills B, Hien TT, et al. Cardiac function in Vietnamese patients with different dengue severity grades. Crit Care Med. 2012;40:477–83.
19. Seppelt IM, Orde SR. Why guess when you can see? Heart function and fluid management in dengue shock. Crit Care Med. 2012;40:675–6.
20. Miranda CH, Borges Mde C, Matsuno AK, Vilar FC, Gali. Volpe LG GJ, et al. Evaluation of cardiac. involvement during dengue viral infection. Clin Infect Dis. 2013;57(6):812–9.
21. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, et al. The global distribution and burden of dengue. Nature. 2013;496:504–7.
22. Marques N, Gan VC, Leo YS. Dengue myocarditis in Singapore: two case reports. Infection. 2013;41:709–14.
23. Miranda CH, Borges Mde C, Schmidt A, Pazin-Filho A, Rossi MA, Ramos SG, et al. A case presentation of a fatal dengue myocarditis showing evidence for dengue virus-induced lesion. Eur Heart J Acute Cardiovasc Care. 2013;2:127–30.
24. Saldarriaga C, Roncancio G, González N, Fortich F. Cardiac manifestations of dengue. Report of a series of cases during the dengue epidemic of 2010 in Columbia. Rev Colomb Cardiol. 2013;20:366–9.

25. Limkittikul K, Brett J, L'Azou M.Epidemiological trends of dengue disease in Thailand (2000–2011):a systematic literature review.Halstead SB, ed.PLOS Negl Trop Dis.2014; 8: e3241.
26. Carter R 3rd, Hinojosa-Laborde C, Convertino VA. Heart rate variability in patients being treated for dengue viral infection: new insights from mathematical correlation of heart rate. Front Physiol. 2014;5:46.
27. Yacoub S, Wertheim H, Simmons CP, Screaton G, Wills B. Cardiovascular manifestations of the emerging dengue pandemic. Nat Rev Cardiol. 2014;11:335–45.
28. Wan SH, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. J Am Coll Cardiol. 2014;63:407–16.
29. Tawatchai Kirawittaya I-K, Yoon, Sineewanlaya Wichit2, S, Green, et al.Evaluation of cardiac involvement in children with dengue by serial echocardiographic studies.PLoS Negl Trop Dis 2015;9: e0003943.
30. Shivanthan MC, Navinan MR, Constantine GR, Rajapakse S. Cardiac involvement in dengue infection. J Infect Dev Ctries. 2015;9:338–46.
31. Arora M, Patil RS. Cardiac manifestation in dengue fever. J Assoc Phys India. 2016;64:40–4.
32. Li Y, Hu Z, Huang Y, Li J, Hong W, Qin Z, et al. Characterization of the myocarditis during the worst outbreak of dengue infection in China. Medicine. 2016;95:e4051.
33. Papalkar PV, Sarode RR, Acharya S, Kumar S. Cardiac manifestations in dengue. Indian J Med Spec. 2019;10:30–4.
34. Kalakutakar A, Suresh H, Ashok G. Study of cardiac manifestations in dengue fever. Int J Curr Microbiol App Sci. 2019;8:636–44.
35. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet, 2004 Jan 10; 363(9403), 157–163. doi: 10.1016/S0140-6736(03) 15268–3.

Figures

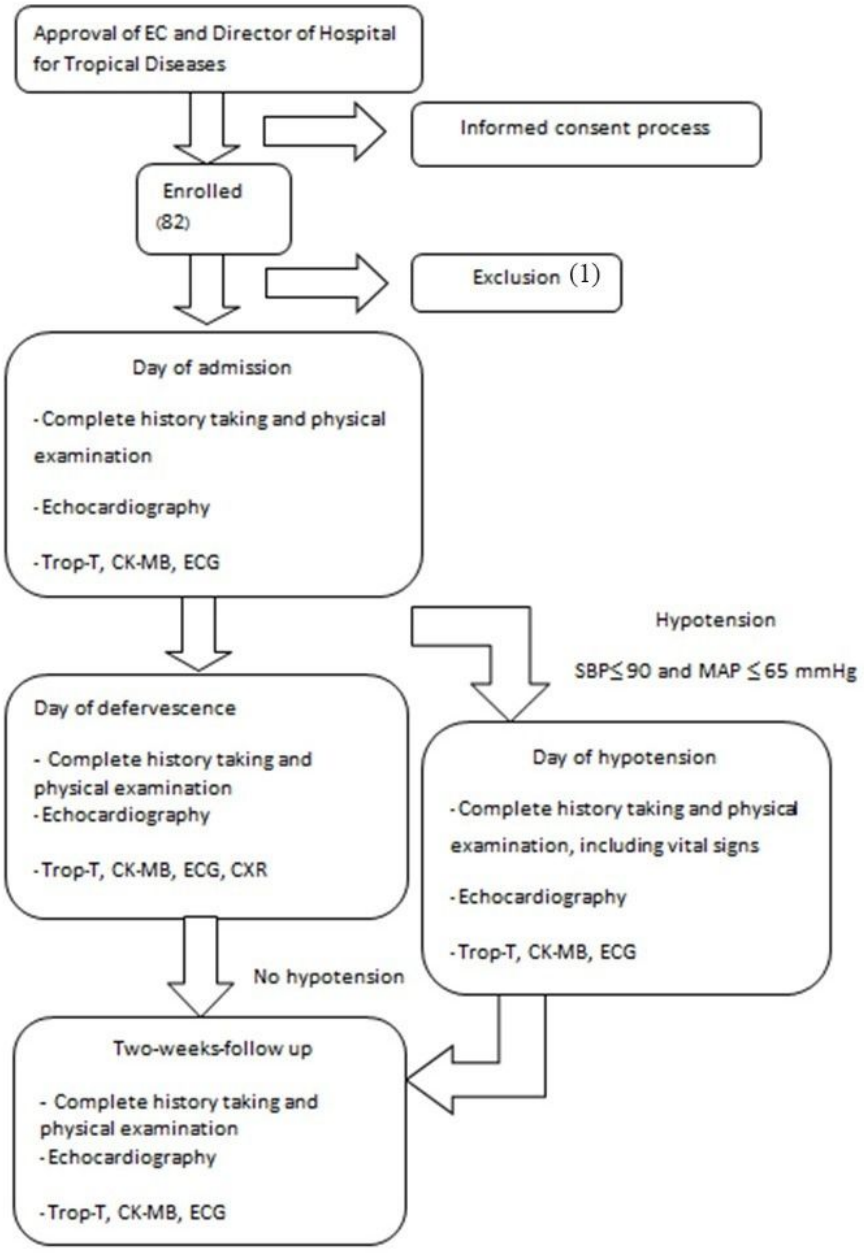

Figure 1

Study flow chart. Trop-T, Troponin-T; CK-MB, creatine kinase–myocardial band; ECG, Electrocardiography

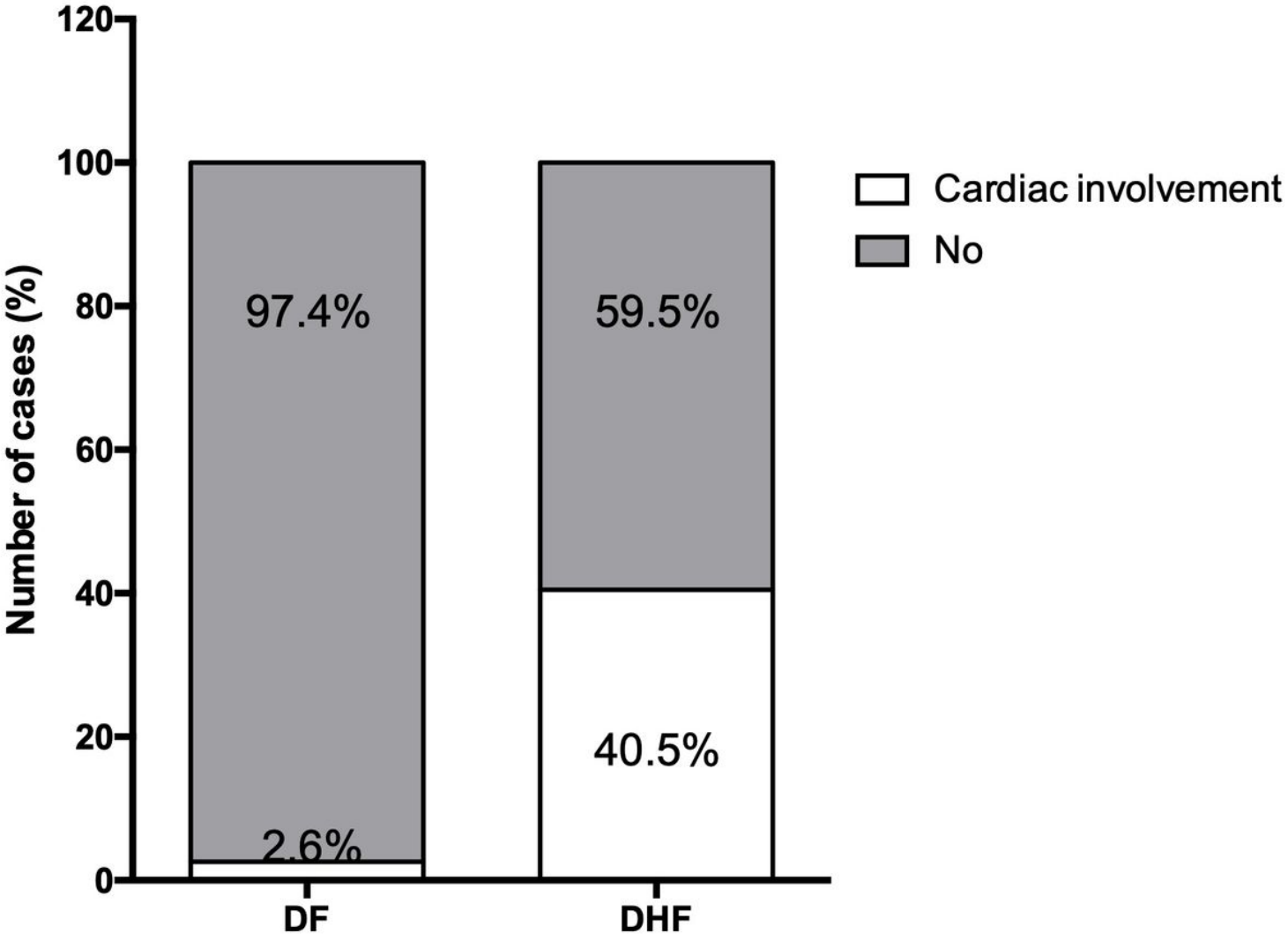

Figure 2

Percentages of DF/DHF patients with and without cardiac involvement. DF, dengue fever; DHF, dengue haemorrhagic fever