

# Dengue Fever-Related Cardiac manifestation in Ibn-Sina Hospital Mukalla, Hadhramout, Yemen

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## ABSTRACT

**Objective:** This study was done to evaluate cardiac manifestation of dengue fever (DF) and its severity in a patient admitted in Ibn-Sina Hospital Mukalla, Hadhramout. **Materials and Methods:** This study was done for patients admitted in the medical department during the dengue outbreak from November 2015 to February 2016. A total of 147 patients with a clinical diagnosis of DF, DF with warning signs (WD), and severe dengue were included in the study. Data were collected from patient's files and cardiac assessment according to history and clinical examination and electrocardiogram, chest X-ray. Cardiac biomarkers and echocardiography were done in little cases. **Results:** From a total of 147 patients, male was 89 (60.5%), with male to female ratio 1.6:1. The most common age group affected was 13–35 years (84.35%), with a mean age of 27.56 years (SD ± 12.03). The most common clinical features were fever (100%), myalgia and arthralgia (99.3%), headache (98.6%), abdominal pain (56.46%), and persisting vomiting (51.7%), where bleeding account (28.57%). Cardiac manifestations occur in the form of sinus tachycardia (39.4%), hypotension (18.37%), pulmonary congestion (6.8%), bradycardia (4.08%), and pericardial effusion (2.7%). There was a close correlation between cardiac features and dengue severity. The refractory shock was one presentation of 10 death cases of patients including in this study. **Conclusions:** There is a significant cardiac manifestation of DF, although not so common. The common were tachycardia, hypotension, pericardial effusion, and bradycardia with a strong correlation with dengue severity. Unexplained abnormalities of rhythm may indicate early warning signs of DF.

**Key words:** Dengue fever, dengue shock syndrome, Mukalla, Yemen

## INTRODUCTION

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. In the past 50 years, the incidence has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings. Dengue fever (DF) is one of the world's major re-emerging infections. The number of cases reported annually to the World Health Organization (WHO) ranged from 0.4 to 1.3 million in the decade 1999–2005. As an infectious disease, the number of cases varies substantially from year to year.<sup>[1]</sup>

Dengue virus belongs to the genus *Flavivirus*, family *Flaviviridae*. It is composed of single-stranded RNA and has four antigenically related but distinct serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). It transmitted by the bite of *Aedes aegypti*, a domestic mosquito that feeds almost entirely on humans, mainly during daylight hours.<sup>[2]</sup> Dengue transmission usually occurs during the rainy season when the temperature and humidity are conducive for the build-up of the vector population breeding in secondary habitats as well as for longer mosquito survival.<sup>[1,2]</sup>

Infection with a dengue virus serotype can produce a spectrum of clinical illness, ranging from asymptomatic or may cause undifferentiated febrile illness (viral syndrome),

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DF, or dengue hemorrhagic fever (DHF) including dengue shock syndrome (DSS).<sup>[2]</sup>

The WHO 2009 guidelines classify patients into three groups; dengue without warning signs, DF with warning sign (WD), and severe dengue (SD).<sup>[1]</sup>

The hallmark of DHF is the increased vascular permeability resulting in plasma leakage, contracted intravascular volume, and shock in severe cases. The leakage is unique in that there is selective leakage of plasma in the pleural and peritoneal cavities, and the period of leakage is short (24–48 h).<sup>[2,3]</sup> The increase in capillary permeability that occurs in some patients, and can cause intravascular hypovolemia and shock, is the best known cardiovascular complication associated with dengue.

Although the vast majority of DENV infections are either asymptomatic or result in fairly mild disease, an estimated 1–5% of patients presenting to hospital develop complications, including organ impairment, bleeding, and plasma leakage from the capillaries. In severe cases, leakage can result in potentially fatal cardiovascular collapse; that is, DSS.<sup>[4]</sup>

The clinical course of dengue is divided into three distinct phases: A febrile phase, lasting 3–7 days, during which the patient typically experiences sudden onset high fever, headache, myalgias, vomiting, and malaise; a critical phase, lasting 2–3 days around defervescence, when severe clinical manifestations become apparent in a minority of patients; and a recovery phase, lasting 2–5 days, when clinical improvement occurs in association with resorption of extravascular fluid Figure 1.<sup>[5]</sup>

It is postulated that dengue rarely affects the heart. Medical literature has reports of isolated cases of atrioventricular conduction disorders (junctional rhythm and atrioventricular block), supraventricular arrhythmias, and myocarditis. On the other hand, the ventricular dysfunction associated with the acute phase of DHF has been described by several authors and is probably underdiagnosed in clinical practice.<sup>[6]</sup>

Yemen is also affected by the increasing frequency and geographic spread of epidemic dengue, and the number of cases has risen since the major DEN-3 epidemic that occurred in the Western Al-Hudaydah Governorate in 2005.<sup>[1]</sup> In 2008, dengue affected the Southern Province of Shabwa.<sup>[1]</sup> DF has emerged as one of the major public health problems in Hadhramout in recent years. The reported dengue outbreak in Hadramout (2010) indicates the potential threat of dengue as a public health issue.<sup>[7]</sup> DENV-3 was confirmed to be the cause of an outbreak of DHF in Al-Mukalla in 2010.<sup>[8]</sup>

This study will highlight the cardiac features in hospitalized patients with DF in Mukalla city – Hadhramout and it is a relation to severity.

## MATERIALS AND METHODS

This descriptive retrospective study was done at Ibn-Sina general Hospital – Mukalla – Hadhramout. Patients admitted during the dengue outbreak from mid November 2015 to end of February 2016 were the target population in the study.

A total of 147 patients (90 males and 57 females) diagnosed as DF admitted in the medical department were included in the study. Those cases were chosen out of a total 254 cases admitted at this period, 107 cases were excluded due to: Hospitalization <1 day, confused diagnosis, cases, not complete essential investigation and patient with a history of cardiac disease or cardiac drugs interfere with electrocardiography (ECG) reading.

Patients information taking from their files including history and physical examination, rapid tests for dengue IgM and IgG dengue or non-structural protein1, complete blood count, and liver function test including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), ECG, chest X-ray, and abdominal ultrasonography. Cardiac enzymes and echocardiography done in selected cases as requested by treating doctors.

Patient was subgrouped in decades to four groups (13–25 years, 26–35 years, 36–45 years, and >45 years).

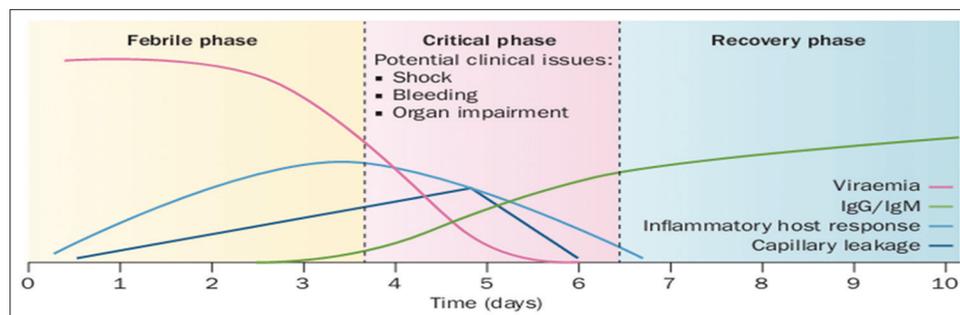


Figure 1: The clinical course of dengue<sup>[5]</sup>

DF was defined in our hospital according to the new WHO classification of DF proposed by tropical disease research (TDR) and was published in the WHO TDR 2009 dengue guidelines to three groups: (1). DF without warning signs (dengue DF), (2) WD, and (3) SD [Table 1].

Cardiac feature considered in this study was pulse rate (tachycardia or bradycardia), blood pressure, cardiac and lungs auscultations, elevation of AST or, abnormal rhythm on ECG, and cardiac enzymes, creatine kinase isoenzyme MB (CKMB) and Troponin, and echocardiography if done.

All data were entered and analyzed using SPSS (21 version) and Microsoft Office Excel 2010.

## RESULTS

Among the 147 studied cases, male to female ratio was 1.6:1 (90 M: 57 F). Their ages ranged from 13 years to 70 years with a mean age of 27.56 years (SD + 12.03) and most age group affected is between 13 and 25 years ( $n = 90, 61.22\%$ ).

According to hospital and WHO dengue classification, 76 (51.7%) patients were diagnosed as severe SD; 64 (43.5%) patients diagnosed as WD, and 7 (4.8%) patients as SD Figure 2.

Fever was the most common clinical presentation, occurring in all patients on presentation. There was no specific pattern of fever; other clinical features in order of frequency are summarized in Table 2.

The most common signs are tachycardia, and hypotension and other signs are shown in Table 3. Investigations are shown in Table 4. With low platelet  $< 100000 \text{ mm}^3$  was the most common, followed by elevation of AST, ALT more than 40 U, and low albumin  $< 3.5 \text{ mg/dl}$ .

Regarding cardiac features of DF, we found that tachycardia was the most common and occurs in about 58 patients (39.4%) of all patient; seven patients in WD group and 51 in SD group. Other features are hypotension, pulmonary rales, bradycardia, and pedal edema, as shown in Table 2.

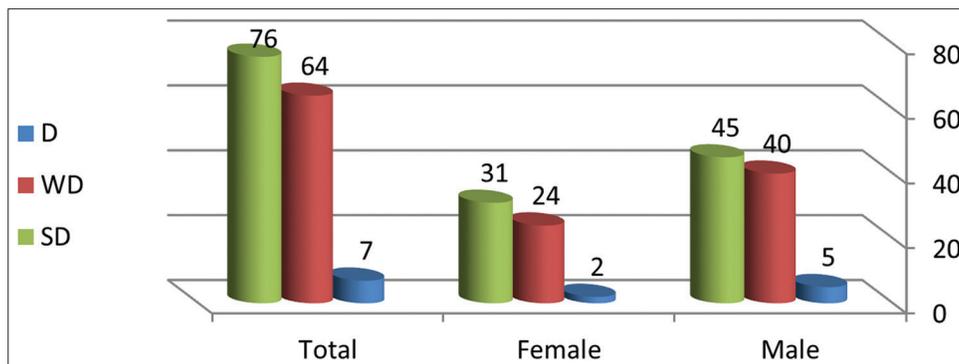
The most cardiac findings in investigations were AST enzyme elevation, pericardial effusion, and elevation of CKMB. Pericardial effusion was found in female patients only from all patients done to them echocardiography (6 patients), and CK-MB commonly found in female more than male. NO evidence of conduction defect or myocarditis was finding in all cases.

From 76 patients (51.7%) diagnose as SD, 51 patients (67.1% of all patient with SD) have sinus tachycardia

**Table 1: WHO classification of dengue fever 2009**

DF	Dengue fever with warning signs	Severe dengue fever
Live in/travel to dengue-endemic area	DF plus warning signs	1. Severe plasma leakage leading to Shock (DSS)
Fever and two of the following criteria:	Abdominal pain or tenderness	Fluid accumulation with respiratory distress
Nausea and vomiting	Persistent vomiting	2. Severe bleeding
Rash	Clinical fluid accumulation	As evaluated by a clinician
Aches and pains	Mucosal bleed	3. Severe organ impairment
Tourniquet test+ve	Lethargy; restlessness	Liver: AST or ALT $\geq 1000$
Leukopenia	Liver enlargement $> 2 \text{ cm}$	CNS: Impaired consciousness
Any warning sign	Laboratory: Increase in HCT concurrent with rapid decrease in platelet count	Heart and other organs

DF: Dengue fever



**Figure 2: Classification of dengue patients according to the severity**

**Table 2: Symptoms of dengue fever according to sex**

Clinical manifestations	M & (%)	F & (%)	Total & (%)
Fever	90 (61.2)	57 (38.8)	147 (100)
Myalgia and arthralgia	89 (60.5)	55 (37.4)	144 (97.9)
Headache	88 (59.9)	55 (37.4)	143 (97.3)
Retro-orbital pain	83 (56.5)	55 (37.4)	138 (93.9)
Abdominal pain and tenderness	48 (32.7)	35 (23.8)	83 (56.5)
Persisting vomiting	47 (32)	29 (19.7)	76 (51.7)
Bleeding	27 (18.4)	15 (10.2)	42 (28.6)

**Table 3: Signs of dengue fever according to sex**

Signs	M & (%)	F & (%)	Total & (%)
Tachycardia	28 (12.2)	30 (12.9)	58 (39.4)
Hypotension	13 (8.8)	14 (9.5)	27 (18.3)
Pulmonary rales	7 (4.8)	3 (2)	10 (6.8)
Bradycardia	5 (3.4)	2 (1.4)	7 (4.8)
Pedal edema	4 (2.7)	2 (1.4)	6 (4.1)
Tourniquet test	4 (2.7)	2 (1.4)	6 (4.1)

**Table 4: Investigation of dengue fever according to sex**

Test	M & (%)	F & (%)	Total & (%)
Platelet <100,000 mm <sup>3</sup>	80 (54.4)	46 (31.2)	126 (85.6)
AST	39 (26.5)	30 (20.4)	69 (46.9)
ALT	31 (21.1)	27 (18.4)	58 (39.5)
S. albumin <3.5	19 (12.9)	14 (9.5)	33 (22.4)
Ascites	14 (9.5)	8 (5.4)	22 (14.9)
Pleural effusion	14 (9.5)	7 (4.8)	21 (14.3)
Hematocrit >20% of base line	4 (2.7)	2 (1.4)	6 (4.1)
Pericardial effusion	0	4 (2.7)	4 (2.7)
CK-MB	1 (0.68)	3 (2.04)	4 (2.72)

(<100 beats/min); from them 27 patients with hypotension and the remaining 24 patients with normal temperature and blood pressure. Seven patients (9.2% of all SD patients) have sinus bradycardia (<60 beats/min), all of them with normal temperature and blood pressure; the remaining has normal heart rate.

Hypotension second cardiac feature and occurs in 35.5% (27 patients) of all SD cases. Both sinus tachycardia and hypotension occurred more in females than males. Other features percentages are shown in Figure 3.

All cardiac manifestations were found in SD except small percent of patients with tachycardia which found in WD and SD [Table 5], with  $P = 0.072$  and  $0.099$  for tachycardia and hypotension ( $P < 0.05$ ), which means that cardiac features closely correlated with SD.

Most patients in this study discharged; while 10 (6.8%) out 147 were died. All died patients admitted as SD (7 males and 3 females), most significant features at presentations of death cases were: Thrombocytopenia < 100,000 mm<sup>3</sup> 80% (8 cases); elevated level of liver enzymes more than two-folds 60% (6 cases); leukopenia < 4000 mm<sup>3</sup> 60% (6 cases); disturbed level of consciousness and convulsions 50% (5 cases); and refractory shock 40% (4 cases), Figure 4.

## DISCUSSION

Cardiac involvement in DF is not rare. The involvement is more in severe forms of the disease. Although most of them are transient and self-limiting, a proper diagnosis must be made early to avoid devastating complications.

Our study investigated the clinical characteristics and cardiac manifestations in patients with dengue virus infection during the epidemic of Hadhramout-Mukalla city 2015–2016. This retrospective study showed male more affection than female, and a younger age of DF (mean  $27.56 \pm 12.03$  years), and elderly status was rarely involved. This consistent with literature that state classic dengue is more commonly seen among older children, adolescents, and adults,<sup>[9]</sup> and those findings were also seen in Saudi Arabia,<sup>[10,11]</sup> Pakistan,<sup>[12-14]</sup> and Hong Kong<sup>[15]</sup> but opposite to a study done in India,<sup>[16]</sup> in which children were the most affected group.

In this study, the patient’s symptoms, high-grade fever, myalgia, arthralgia, headache, ret orbital pain, abdominal pain, vomiting, and bleeding manifestation were the most common presenting symptoms ordered according to frequency, which was also observed in other studies in our country<sup>[17]</sup> and other the regions with different frequencies<sup>[10,11,15]</sup> except the bleeding manifestation which was less common in our study (28.6%) than others, but within the range of a systematic review that reported an incidence of 22–93% bleeding episodes of different severity in different studies.<sup>[18,19]</sup>

Regarding cardiac features, tachycardia was a most common finding in most of our patients, including in the study. Tachycardia is present in the absence of fever, which is the state in a critical phase of DF in our study and also found in other study like in India but with less frequency.<sup>[20]</sup> Tachycardia may be occur as compensation for hypotension and shock, which occurred in half patients (27 patients) presented with it.

Hypotension and shock are the second common finding. It considered a common finding in SD (dengue hemorrhagic/

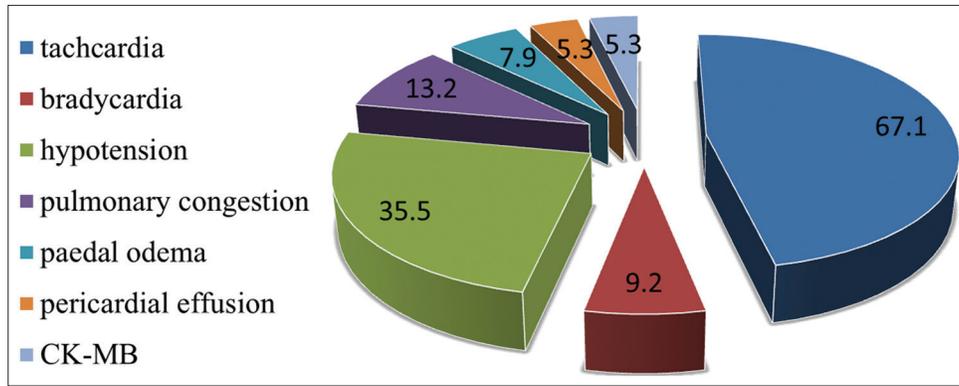


Figure 3: Cardiac features of severe dengue fever

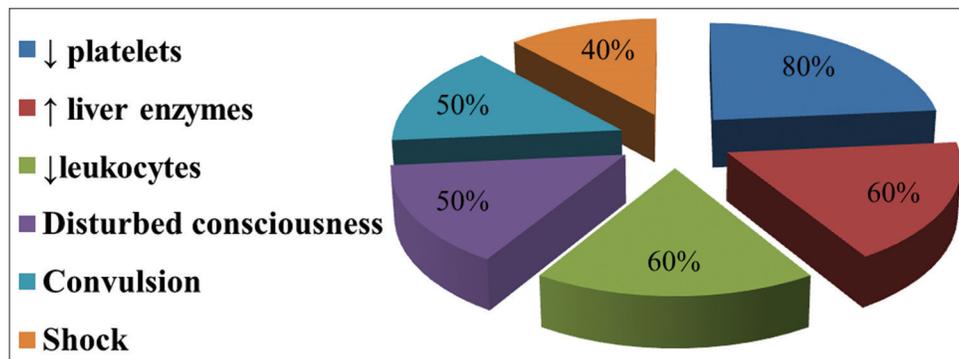


Figure 4: Common features of death cases

Table 5: Correlation of cardiac features with dengue severity

Cardiac features	No. of patients with WD	No. of patients with SD	P-value
Tachycardia	7	51	0.072
Hypotension	0	27	0.099
Pedal edema	0	10	0.472
Bradycardia	0	4	0.256

WD: dengue fever with warning signs, SD: severe dengue

DSS). It has been reported as a risk factor for mortality with or without a bleeding history. Vascular collapse (shock) was present in 27 (18.3%) of our cases, without the association of major bleeding, and refractory shock was the most important cause of death in literature<sup>[21]</sup> and in our study. Shock is an alarming presentation in patients with dengue virus infection and as an indicator of the severity.<sup>[22]</sup>

Although shock in DHF/DSS has been attributed largely to decreased intravascular volume due to capillary leakage of plasma into the interstitial space, a few recent studies have reported that it may be due to cardiac involvement.<sup>[23]</sup>

Pulmonary congestion presented by pulmonary rales was one of clinical finding in our study. This finding is mentioned in

one study in India.<sup>[20]</sup> We cannot attribute this finding due to cardiac affection because no complete cardiac investigations were done such as cardiac biomarkers and echocardiography in all cases, taking in consideration volume overload as a possible cause of this finding.

The association of DF with relative bradycardia has already been well established and is certainly not a new finding in many kinds of literature. It is one clinical finding in our study with (4.8%) of all patient, but it was the high frequency in India<sup>[20,24]</sup> and Singapore.<sup>[25]</sup> The relationship of relative bradycardia to the cardiac problem is unknown. Further, studies could consider the relative importance of immune and neural mechanisms and also any direct cardiac pathology in the etiology of dengue-associated relative bradycardia.<sup>[25]</sup>

Pedal edema is one finding in this study, although in a low percentage of patients, and it may be due to volume overload or due to the effect of cardiac in DF. This finding is found in an Indian study with high percentage of 13.3%.<sup>[20]</sup>

Echocardiography was done in only 6 cases as requested by treating doctors and 4 of them have had pericardial effusion, all of them female. Pericardial effusion is usually associated with dengue severity associated with pleural effusion, ascites, and thickened gallbladder.<sup>[26]</sup> It may be

subclinical and discovered by the radiological method.<sup>[26]</sup> This may explain the low percentage of pericardial effusion in comparing with others due to routine chest X-ray and abdominal ultrasonography for all cases admitted with SD and WD.

Cardiac biomarker was one of consistent finding in DF and the main biomarker was myoglobin, troponin T, NT-proBNP, and/or heart-type fatty acid binding protein levels (h-FAB P).<sup>[27]</sup> In our study, due to low resources this marker not available except CK-MB and troponin and done in specific cases (due to it is expensive) as ordered by treating doctors. We found that CK-MB was elevated in 4 cases requested for them. Most studies found elevated cardiac enzymes (Troponin and CK-MB) in a significant portion of patients.<sup>[20,26,27]</sup> AST used as hepatic biomarker, and can be used as non-specific cardiac enzymes (It was used before new specific biomarkers emerge).<sup>[23]</sup> AST was found in higher proportions of our patients (64.9%) and was more than ALT (39.5%) which is more specific for hepatic injury, and this may indicate subclinical cardiac involvement going with study indicating elevation of non-specific biomarker more than specific one.<sup>[23]</sup>

In our study, there is no evidence of rhythm abnormalities or conduction abnormalities and block, which were mentioned in different studies.<sup>[20,24,27,23]</sup> Furthermore, myocarditis is one medical challenging of dengue feature, there was no documented case in our study, may be due to subclinical appearance, and cardiac biomarker and echocardiography are not done as routine investigations unless clinically indicated and done only in 6 cases. However, we can consider unexplained tachycardia and bradycardia as early indications for subclinical myocarditis.<sup>[28]</sup>

All cardiac features were found in SD and too little extent WD, indicating correlation with of cardiac features with DF severity and may consider unexplained tachycardia and bradycardia and cardiac biomarker as warning signs to DF and this correlate to the finding of a study in India.<sup>[24]</sup>

The outcomes of DF in most cases were good, except for 10 death cases. The death cases mostly presented with altered mental status, convulsion, shock states, low platelet count, and elevated liver enzymes which might be regarded as predictive manifestations for SD fever and death as seen in other literature.<sup>[29]</sup>

Finally, our study has some limitations: (1) No attention to cardiac manifestations in files of cases, (2) cardiac biomarkers and other cardiac evaluations not done routinely in severe cases of DF, and (3) due to our political, social, and low resources in our situations that limit complete evaluation of cases.

## CONCLUSIONS

In our evaluations of 147 cases, admitted in our hospital with DF, we found 76 cases with SD. The most common cardiac abnormalities noted were rhythm abnormalities of which the most common was sinus tachycardia and bradycardia. Of all the patients admitted, 4 cases underwent echocardiographic study; all of them had mild to severe pericardial effusion. AST was done in all patients and was positive in the majority of them (64.9%), while CK-MB is done in limited cases and positive in 4 cases.

Among SD, fluid accumulation causing respiratory distress (mainly pericardial effusion) was found to have a significant correlation with the cardiac manifestations. There is a strong correlation between cardiac manifestations and severity of DF.

Our message from this study is that cardiac evaluation by history, examination, and cardiac biomarkers and echocardiography should be performed in patients with dengue, particularly in those with severe disease and refractory shock, to detect cardiac complications and tailor their management.

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