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REVIEW

Cardiovascular sequelae of dengue fever: a systematic review

Abdur Rahim[a], Ali Hameed[b], Uzma Ishaq [c], Jahanzeb Malik [d], Syed Muhammad Jawad Zaidi [e], Hajra Khurshid[f], Asmara Malik [g], Danish Iltaf Satti[h] and Hifza Naz[i]

[a]Department of Cardiology, Saidu Teaching Hospital Saidu Sharif, Swat, Pakistan; [b]Department of Cardiology, Punjab Institute of Cardiology, Lahore, Pakistan; [c]Department of Hematology, Foundation University Medical College Islamabad, Pakistan; [d]Department of Cardiology, Rawalpindi Institute of Cardiology, Rawalpindi, Pakistan; [e]Department of Medicine, Rawalpindi Medical University, Rawalpindi, Pakistan; [f]Department of Pathology, DHQ Hospital, Mirpur, Pakistan; [g]Department of Community Medicine, National University of Medical Sciences, Rawalpindi, Pakistan; [h]Department of Medicine, Shifa Tameer e Millat University, Islamabad, Pakistan; [i]Department of Medicine, Universita degli studi di Milano, Milan, Italy

ABSTRACT

Introduction: Dengue is one of the most important viral diseases globally and a majority of symptomatic infections result in a benign course. However, a small number of patients develop severe manifestations, including the cardiovascular (CV) manifestations, including myocardial impairment, arrhythmias, and fulminant myocarditis.

Areas covered: Electronic databases, including PubMed/MEDLINE, EMBASE, Scopus, and CINAHL were searched for articles incorporating CV manifestations of dengue fever (DF).

Expert opinion: Included studies involved 6,773 patients, and 3,122 (46.1%) exhibited at least one cardiac manifestation. Electrocardiogram (ECG) abnormalities (30.6%) included sinus bradycardia (8.8%), nonspecific ST-T changes (8.6%), ST depression (7.9%), and T-wave inversion (2.3%). Mechanical sequelae were present in 10.4%, including left ventricular (LV) systolic dysfunction (5.7%), and myocarditis (2.9%). Pericardial involvement was noted as pericarditis (0.1%), pericardial effusion (1.3%), and pericardial tamponade (0.1%). Apart from that, the cardiac injury was depicted through a rise in cardiac enzymes (4.5%). The spectrum of CV manifestations in dengue is broad, ranging from subtle ST-T changes to fulminant myocarditis and the use of contemporary techniques in diagnosing cardiac involvement should be employed for rapid diagnosis and treatment.

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KEYWORDS
Aedes aegypti; dengue shock syndrome; dengue hemorrhagic fever; pseudoaneurysm; myocarditis

1. Introduction

Dengue is one of the most important infectious diseases of temperate regions. The dengue virus is an RNA virus (single-stranded) consisting of 4 distinct serotypes (DENV 1–4) [1]. With the rate of geographic expansion of this vector-borne disease, it is estimated to infect 390 million people globally in 2022. Dengue is reported in more than 100 countries, with a high disease burden in South Asia and Latin America, and it is transmitted by mosquitos of the genus Aedes Aegypti [2].

It is classified into dengue fever (DF) and dengue hemorrhagic fever (DHF I/II). DHF grades III and IV are termed dengue shock syndrome (DSS). However, due to the inapplicability of these grades in various clinical scenarios, World Health Organization (WHO) revised the classification in 2009 to dengue with or without warning signs, or severe dengue [3]. While dengue infects adults and children equally, age seems to influence the clinical presentation of the disease. Bleeding complications and organ damage occurs more frequently in adults while shock is more common in children [4]. There is a propensity of severe disease with secondary co-infection with a different DENV serotype and severe manifestations mainly occur late in the disease course when the virus is being cleared from the body. Therefore, it suggests underlying immune-mediated pathophysiology [5].

Although most of the dengue infections are asymptomatic or present with mild symptoms, a proportion of patients (1%–5%) develop complications, including organ shutdown, bleeding, and plasma leakage from capillaries [6]. Dengue is divided into three stages of the disease progression: a febrile stage, lasting up to 7 days, during which the patient can experience high-grade fever, myalgias, headache, malaise, and vomiting; a critical phase, lasting 2–3 days, during which severe clinical manifestations become apparent; and recovery phase, for 2–5 days, when there is clinical improvement associated with resorption of leaked extracellular fluid. An increase in capillary permeability causes intravascular hypovolemia, leading to DSS. This is the most commonly known cardiovascular (CV) complication associated with dengue. However, various other CV manifestations have been reported, ranging from subtle electrocardiogram (ECG) changes to fulminant myocarditis, causing functional myocardial dysfunction and arrhythmias [7–94].

CONTACT Jahanzeb Malik heartdoc86@gmail.com Senior Registrar, Department of Cardiology, Rawalpindi Institute of Cardiology, Rawalpindi, Pakistan
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Article highlights

- Dengue is one of the most important viral diseases globally and it presents with variable disease course.
- Eighty-six articles involving 6,773 patients were extracted which demonstrated at least one cardiovascular manifestation in 3,122 (46.1%) patients.
- These manifestations can be a cause of hemodynamic collapse during the critical phase of capillary leakage.
- Use of conventional techniques in diagnosing cardiac involvement should be employed for rapid diagnosis and treatment in dengue fever.

This systematic review will cover the current incidence of various CV sequelae associated with dengue, and conclude with a discussion of expert opinion on current diagnostic and therapeutic options and future research directions.

2. Methods

2.1. Search strategy

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [95]. PRISMA flowchart is shown in Figure 1.

Electronic databases, including PubMed/MEDLINE, EMBASE, Scopus, and CINAHL were searched (till November 2021) to identify primary references. All eligible studies, irrespective of the language were included in this review. The following search terms were used: ['Dengue [Mesh]' OR 'Dengue Hemorrhagic Fever [Mesh]' OR 'Dengue Virus [Mesh]'] AND ['Heart [Title/Abstract]' OR 'Cardiovascular Diseases [Title/Abstract/Mesh]' OR 'Myocarditis [Mesh/Abstract]' OR 'Pericarditis [Mesh/Abstract]' OR 'Cardiomyopathy [Mesh]' OR 'Atrioventricular Block [Title/Abstract/Mesh]' OR 'Atrial Fibrillation [Title/Abstract/Mesh]' OR 'Cardiac Arrhythmia [Title/Abstract/Mesh]' OR 'Myocardial Infarction [Title/

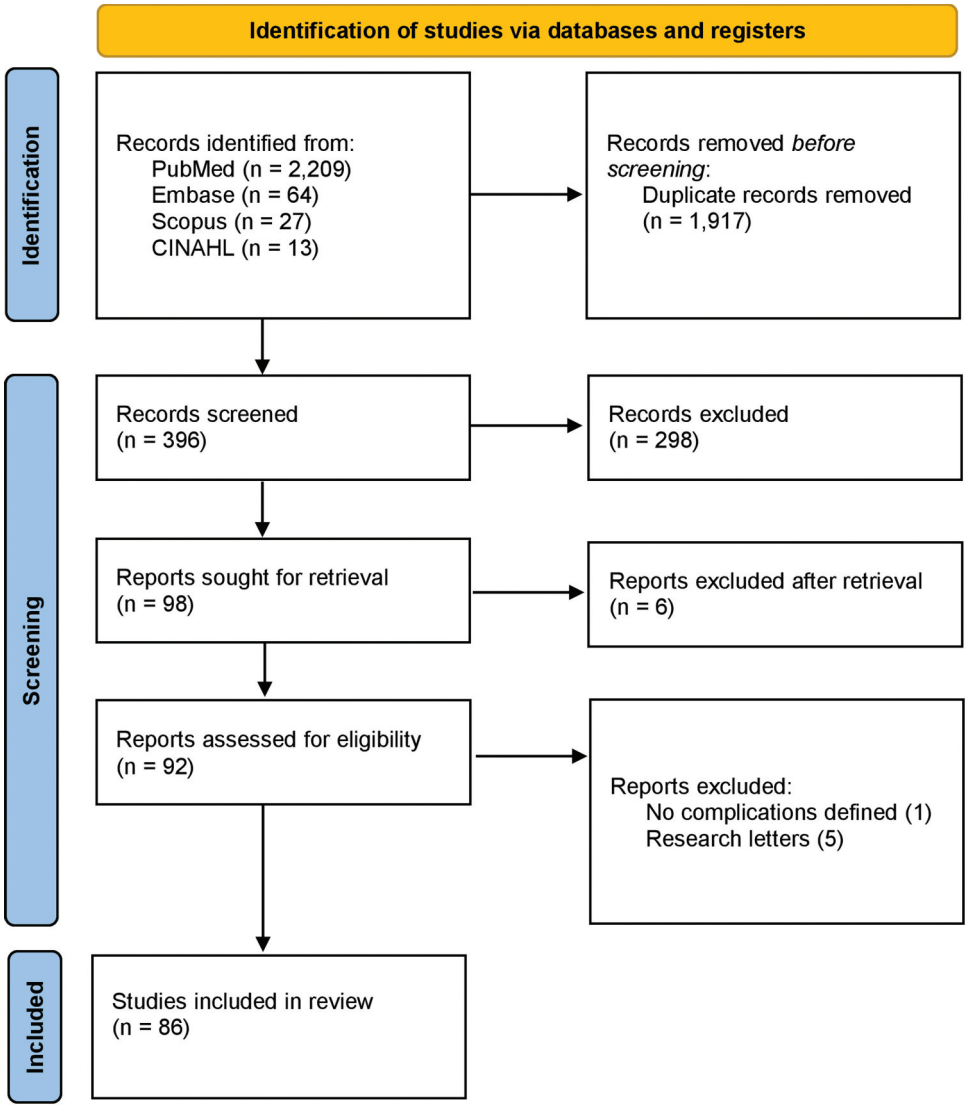

Figure 1. PRISMA flow chart

Abstract]' OR 'Echocardiography [Mesh]']. The authors searched all of the reference lists of the reviews in the relevant subject and Google Scholar to identify additional relevant studies.

2.2. Study selection

A web-based platform (Covidence) was used to integrate the two authors (S.M.J.Z. and J.M.) for reviewing the titles and abstracts of the articles independently. All duplicate articles were removed and studies were included after an agreement between the two authors. In case of a disagreement, a third author (U.I.) reviewed the article to resolve the impasse. For possible correlations, the full text was searched to determine the inclusion of the article.

All article types (randomized controlled trials [RCTs], observational studies [prospective or retrospective], case reports/series, letter to the editors) reporting CV manifestations of DF were included in this review. Abstracts, conference papers, animal experiments, machine prediction studies, and reviews were excluded.

2.3. Data extraction

Two reviewers (S.M.J.Z. and J.M.) extracted the data from the included studies mutually: (1) basic information of the studies, including author names, year of publication, study design, number of patients; (2) baseline characteristics such as comorbidities, the severity of DF, CV manifestations, diagnostic modalities, and study outcomes (if any). All conflicts in data extraction were resolved by the third reviewer (U.I.).

2.4. Risk of bias (quality) assessment

Quality assessment of all case reports or case series were assessed using the methodological quality and synthesis of case series and case reports and observational studies were assessed using the Newcastle-Ottawa scale [96].

2.5. Statistical analysis

For statistical analysis, Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA.) was used. The qualitative variables were presented as mean and standard deviation (SD) or median (Interquartile range) and quantitative variables were expressed in frequency (n). Percentages are depicted in Figure 2.

3. Results

The literature search identified 2,313 citations from the databases (PubMed/MEDLINE, EMBASE, Scopus, CINAHL). Of these, 396 were non-duplicated records and after application of the inclusion and exclusion criteria, 98 records were included for

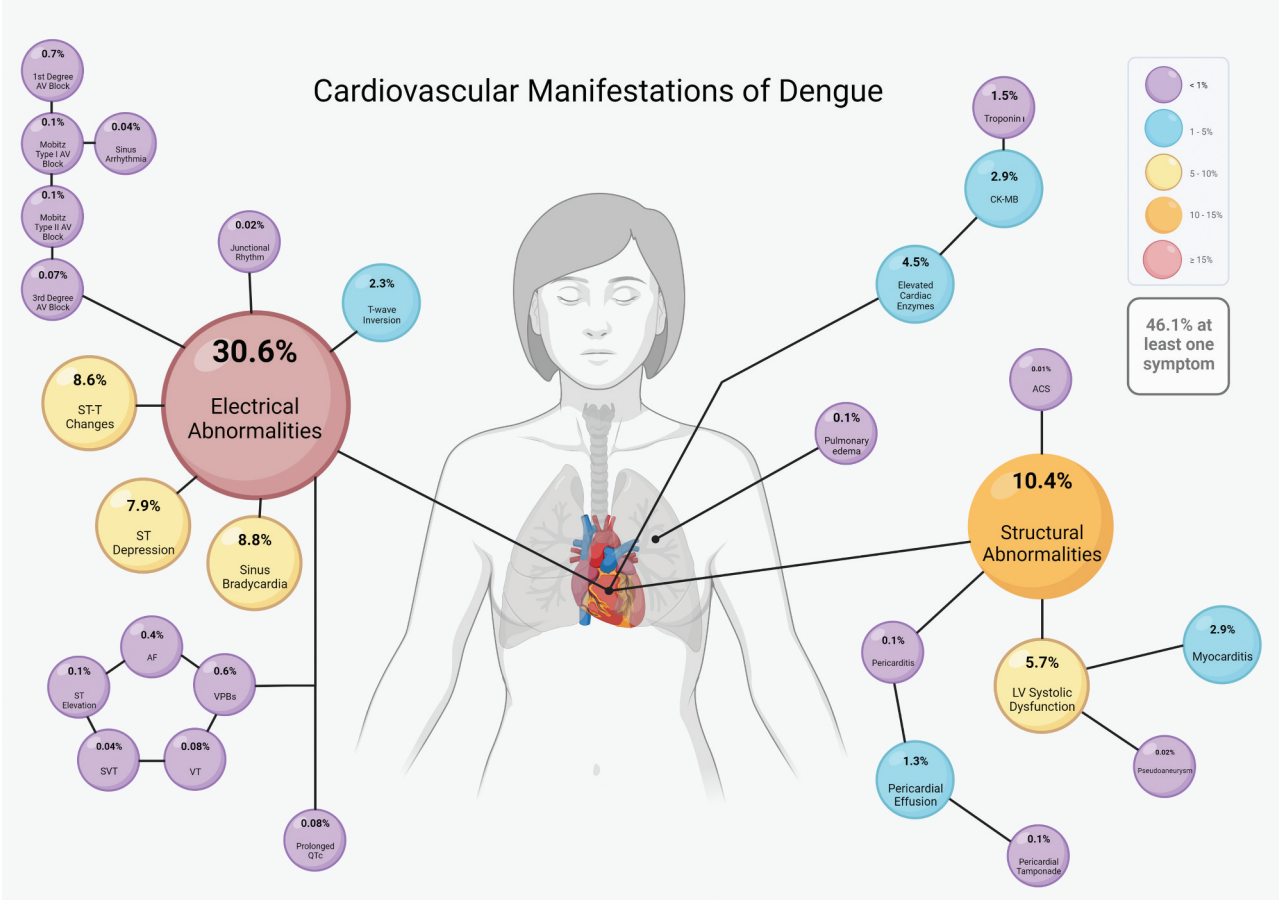

Figure 2. Cardiovascular manifestations of dengue. This image was created [by J.M.] from biorender.com

Table 1. Study characteristics.

Study (year)	References	Design (participants)	Country	Comorbid conditions	Clinical symptoms	Diagnostic modality	Cardiovascular manifestation (n)	Outcomes	Quality assessment
Kabra et al. (1998)	7	Prospective cohort (54)	India	NR	DF (21) DHS (13) DSS (20)	Echo	• LV dysfunction [EF < 50% (9), < 35% (3)]	EF improved after 2 months	5
Wali et al. (1998)	8	Prospective cohort (17)	India	NR	DSS (17)	ECG Echo Radionucleotide ventriculography	• LV dysfunction [EF < 40% (7) Global hypokinesia (12)] • ECG changes [ST depression (5)]	EF and ECG changes improved after 3 weeks	6
Khongphatthallayothin et al. (2000)	9	Case series (2)	Thailand	NR	DF (2)	ECG	• Mobitz type I AVB (2)	Spontaneous resolution	6
Velosa et al. (2003)	10	Case report (1)	Brazil	NR	DHS (1)	ECG	• AF (1)	No episode of AF on low dose amiodarone (200 mg)	5
Kularatne et al. (2006)	11	Case series (3)	Sri Lanka	NR	DSS (3)	ECG Echo	• LV dysfunction (3) • ECG changes [ST depression, T wave inversion (3)]	Spontaneous resolution	6
Khongphatthallayothin et al. (2007)	12	Prospective cohort (91)	Thailand	NR	DF (30) DHS (36) DSS (25)	Echo	• LV dysfunction [EF < 50% (11), <40% (5)]	NR	6
Kularatne et al. (2007)	13	Prospective cohort (120)	Sri Lanka	NR	DF (45) DHF (75)	ECG Echo	• ECG changes [ST depression, T wave inversion (75)] • Sinus bradycardia (21)	NR	6
Lateef et al. (2007)	14	Case-control (39)	Singapore	MVP (1) DF MR (1)	DF (39)	ECG	• Sinus bradycardia (39)	NR	7
Mahmod et al. (2009)	15	Case report (1)	Malaysia	NR	DF (1)	ECG	• AF (1)	Resolution after 1 month on amiodarone	7
Salgado et al. (2009)	16	Prospective cohort (102)	Columbia	NR	DSS (102)	Echo	• Myocarditis (11) • Tachy-arrhythmias [VT (1), SVT (1)] • Sinus bradycardia (100) • Pericardial effusion (2) • AF (1)	NR	5
Wichmann et al. (2009)	17	Prospective cohort (133)	Sri Lanka	NR	DF (133)	Cardiac enzymes	• Elevated cardiac enzymes [Myoglobin (60), CK-MB (17), Troponin I (1), h-FABP (7), NT pro-BNP (25)]	NR	7
Goh et al. (2010)	18	Case report (1)	Singapore	NR	DSS (1)	ECG Echo	• ECG changes [ST-elevation (1)] • Pericardial effusion (1)	Death	6
Kaushik et al. (2010)	19	Case report (1)	India	NR	DF (1)	ECG	• 3rd AVB (1)	Spontaneous resolution	5
Kumar et al. (2010)	20	Case report (1)	USA	Lupus nephritis HTN	DSS (1)	Echo Pericardiocentesis	• Pericardial tamponade (1)	Spontaneous resolution	6
Lee et al. (2010)	21	Case report (1)	Taiwan	NR	DSS (1)	ECG Echo Cardiac enzymes	• ECG changes [ST depression (1)] • LV dysfunction (1) • Myocarditis (1) • Acute heart failure (1) • Elevated cardiac enzymes [Troponin I (1)]	Spontaneous resolution	4
Tayeb et al. (2010)	22	Case report (1)	France	HTN	DHF (1)	ECG Echo Coronary angiogram Cardiac MRI	• ECG changes [T wave inversion (1)]	Resolution after aspirin and colchicine	5

(*Continued*)

Table 1. (Continued).

Study (year)	References	Design (participants)	Country	Comorbid conditions	Clinical symptoms	Diagnostic modality	Cardiovascular manifestation (n)	Outcomes	Quality assessment
Koshy et al. (2012)	23	Case report (1)	India	Pregnancy	DSS (1)	ECG Echo	• ECG changes [ST-T changes (1)] • Myocarditis (1) • LV dysfunction [EF < 30% (1)]	Spontaneous resolution	6
Yacoub et al (2012)	24	Prospective cohort (79)	Vietnam	NR	DF (22) DHF (42) DSS (15)		• Pericardial effusion (1) • LV dysfunction (57)	NR	4
Miranda et al. (2013)	25	Prospective cohort (81)	Brazil	NR	DF (78) DSS (3)	ECG Echo Cardiac enzymes Cardiac MRI	• LV dysfunction [EF < 30% (3)] • Elevated cardiac enzymes (12) • Pericardial effusion (1)	NR	6
Clara Saldarriaga et al. (2013)	26	Prospective cohort (7)	Columbia	IHD	DF (4) DSS (3)	ECG Echo	• Sinus bradycardia (3) • AF (1) • 3rd AV block (1) • Pericardial effusion (1) • ACS (1) • Acute heart failure (2)	NR	7
Miranda et al. (2013)	27	Case report (1)	Brazil	NR	DSS (1)	Histology	• Myocarditis (1)	Death	4
Tarique et al. (2013)	28	Prospective cohort (116)	Pakistan	NR	DF/DHF (61) DSS (55)	ECG	• Sinus bradycardia (18) • Tachyarrhythmia (7) • ECG changes [ST depression (7)]	NR	6
Patra et al. (2013)	29	Case report (1)	India	NR	DSS (1)	ECG Echo	• Myocarditis (1) • ECG changes [ST elevation (1)] • Elevated cardiac enzymes (1)	Lost to follow-up	7
Sengupta et al. (2013)	30	Prospective cohort (20)	India	NR	DSS (20)	Speckle tracking echo	• LV dysfunction	NR	8
Bendwal et al. (2014)	31	Case report (1)	India	NR	DSS (1)	Echo Periocardiocentesis	• Pericardial tamponade (1)	Resolution after Pericardiocentesis	6
Madhavan et al. (2014)	32	Case report (1)	India	NR	DSS (1)	Echo Cardiac CT	• Pseudoaneurysm (1)	NR	4
Nimmagadda et al. (2014)	33	Prospective cohort (150)	India	NR	NR	ECG Echo	• Myocarditis (5) • AF (1) • Conduction abnormalities (9)	NR	6
Samat et al. (2014)	34	Case report (1)	Malaysia	NR	DF (1)	ECG	• Mobitz type I AVB (1)	Spontaneous resolution	5
Zea et al. (2014)	35	Case report (1)	USA	NR	DHF (1)	ECG Echo CXR Cardiac enzymes	• Myocarditis (1)	Spontaneous resolution	5
Tahir et al. (2015)	36	Case report (1)	USA	HTN Tuberculosis Family Hx of IHD	DSS (1)	Echo	• LV dysfunction (1) • Myocarditis (1)	Death	7
Arora et al. (2015)	37	Prospective cohort (120)	India	NR	NR	ECG Echo Cardiac enzymes	• Myocarditis (45) • AVB (6) • Elevated cardiac enzymes [Troponin I (32), CK-MB (40)]	NR	6
Jayaprakash et al. (2015)	38	Case report (1)	India	NR	DSS (1)	ECG Echo Cardiac MRI	• Pseudoaneurysm (1) • ECG changes [St elevation (1)] • Pericardial effusion (1)	Spontaneous resolution	5

(*Continued*)

Table 1. (Continued).

Study (year)	References	Design (participants)	Country	Comorbid conditions	Clinical symptoms	Diagnostic modality	Cardiovascular manifestation (n)	Outcomes	Quality assessment
Kirawittaya et al. (2015)	39	Prospective cohort (181)	Thailand	NR	DF (119) DSS (62)	Echo	• LV dysfunction (50)	NR	6
Li et al. (2015)	40	Prospective (1782)	China	NR	NR	ECG Echo Cardiac enzymes	• LV dysfunction (139) • ECG changes (449) • Elevated cardiac enzymes (247)	NR	7
Mohammed et al. (2015)	41	Case report (1)	India	NR	NR	ECG Echo	• Tachy-arrhythmia [VT (1)]	Resolution after treatment with amiodarone	6
Neki et al. (2015)	42	Case report (1)	India	Pregnancy	DSS (1)	ECG Echo	• ECG changes [ST segment depression (1)] • Myocarditis (1)	Lost to follow-up	6
Nigam et al. (2015)	43	Case report (1)	India	NR	DF (1)	ECG Echo	• Mobitz type II AVB (4)	Spontaneous resolution	6
Ramanathan et al. (2015)	44	Case report (1)	Singapore	NR	DSS (1)	ECG Echo Cardiac MRI	• LV dysfunction (1) • Myocarditis (1) • ECG changes [hyperacute T waves (1)]	Spontaneous resolution	7
Abrar et al. (2016)	45	Case report (1)	India	NR	DSS (1)	Echo	• Myocarditis (1) • LV dysfunction (1)	Death	6
Dhariwal et al. (2016)	46	Case report (1)	India	NR	DHF (1)	ECG	• 3rd degree AVB (1)	Spontaneous resolution	6
Chou et al. (2016)	47	Case report (1)	Taiwan	DM HTN		ECG Echo Cardiac enzymes Coronary angiogram	• ECG changes [T wave inversion, prolonged QTc, sinus bradycardia] • LV dysfunction (1) • Elevated cardiac enzymes [troponin I (1)]	Spontaneous resolution	6
Yante et al. (2016)	48	Case series (10)	Indonesia	NR	DF (10)	ECG	• Sinus arrhythmia (3) • Sinus bradycardia (3) • First degree AVB (2) • Mobitz type I AVB (1)	Spontaneous resolution	5
Krishnan et al. (2016)	49	Prospective (60)	India	NR	DF (60)	ECG Echo	• Sinus bradycardia (43)	NR	5
Ku et al. (2016)	50	Case report (1)	Taiwan	Recent travel history	DSS (1)	ECG Echo Cardiac enzymes Coronary angiography	• LV dysfunction (1) • ST-T changes (1) • Myocarditis (1)	Death	5
Manya et al. (2016)	51	Case report (1)	India	NR	DSS (1)	ECG	• Mobitz type II AVB (1)	Spontaneous resolution	4
Pothapregada et al. (2016)	52	Prospective cohort (254)	India	NR	NR	ECG Echo	• Myocarditis (5) • Pericardial effusion (3) • Tachy-arrhythmias (3)	Spontaneous resolution	4

(*Continued*)

Table 1. (Continued).

Study (year)	References	Design (participants)	Country	Comorbid conditions	Clinical symptoms	Diagnostic modality	Cardiovascular manifestation (n)	Outcomes	Quality assessment
Shareef et al. (2016)	53	Case report (1)	Bangladesh	DM HTN	DSS (1)	ECG Echo Cardiac enzymes Coronary angiogram	• ECG changes [ST elevation (1)] • LV dysfunction (1) • Myocarditis (1)	Spontaneous resolution	5
Sheetal et al. (2016)	54	Prospective (100)	India	CRF (4) HTN (11) DM (2) Hereditary spherocytosis (1)	NR	ECG Echo Cardiac enzymes	• ECG changes [VPBs (1), ST-T changes (11), AVB (1)] • Pericardial effusion (3)	Spontaneous resolution	6
Virk et al. (2016)	55	Case report (1)	USA	NR	DSS (1)	ECG Echo	• 3rd degree AVB (1) • VT (1)	Spontaneous resolution	8
Fernandes et al. (2017)	56	Case report (1)	Brazil	Post C-section Pregnancy	DSS (1)	Echo	• Pericardial tamponade (1)	Resolved after pericardiocentesis	6
Yadav et al. (2017)	57	Cross-sectional (100)	India	NR	NR	ECG Echo	• Sinus bradycardia (60) • First degree AVB (11) • VPBs (15)	NR	5
Girdhar et al. (2017)	58	Cross-sectional (211)	India	NR	NR	ECG Echo Cardiac enzymes	• Elevated troponin I (12) • LV dysfunction (28) • Sinus bradycardia (18) • ST-T changes (28)	NR	4
Hussain et al. (2017)	59	Retrospective (128)	Pakistan	NR	DSS (128)	ECG Echo	• LV dysfunction [global hypokinesia (24), EF < 40% (24)] • AF (2) • VT (1)	NR	6
Kumar et al. (2017)	60	Case report (1)	India	NR	DF (1)	ECG	• Junctional bradycardia (1)	Spontaneous resolution	6
Mukhopadhyay et al. (2017)	61	Prospective cohort (50)	India	NR	NR	ECG Echo	• Sinus bradycardia (14) • ST-T changes (2) • 1st degree AVB (3) • 2nd degree AVB (1) • LV dysfunction (3) • Pericardial effusion (2)	NR	5
Palangasinghe et al. (2017)	62	Case report (1)	Sri Lanka	NR	DSS (1)	ECG Echo Pericardiocentesis	• Pericardial effusion (1)	Resolution on corticosteroids	7
Rivillas et al. (2017)	63	Prospective cohort (60)	Columbia	HTN (11)	NR	ECG Echo	• Myocarditis (3) • Pericarditis (2) • AF (14) • 1st degree AVB (27) • Sinus bradycardia (23)	NR	6

(*Continued*)

Table 1. (Continued).

Study (year)	References	Design (participants)	Country	Comorbid conditions	Clinical symptoms	Diagnostic modality	Cardiovascular manifestation (n)	Outcomes	Quality assessment
Siddapa et al. (2017)	64	Prospective cohort (39)	India	NR	NR	ECG Echo CK-MB	• ST-T changes (7) • SVT (2) • LV dysfunction (4) • Pericardial effusion (2)	NR	6
Vuppali et al. (2018)	65	Case report (1)	India	NR	DSS (1)	Echo	• Myocarditis (1) • LV dysfunction (1)	Resolution after 15 days on ECMO support	5
Lakshman et al. (2018)	66	Prospective cohort (50)	India	NR	NR	Echo Cardiac enzymes	• LV dysfunction (8) • Elevated cardiac enzymes (11) • T wave inversion (2) • Prolonged QTc (5) • AVB (2)	NR	4
Ruhella et al. (2018)	67	Retrospective (221)	India	NR	NR	ECG	• Sinus bradycardia (39) • ST-T changes (9)	NR	4
Shah et al. (2018)	68	Case report (1)	USA	NR	DSS (1)	Echo Right heart catheterization	• LV dysfunction (1) • Pericardial tamponade (1)	Complete resolution at 6 weeks	6
Gunda et al. (2019)	69	Prospective (60)	India	NR	NR	ECG Echo	• Myocarditis (2) • AF (1) • 3rd AVB (1) • 1st degree AVB (1)	NR	7
Agarwal et al. (2019)	70	Case report (1)	India	NR	DSS (1)	ECG Echo	• Myocarditis (1) • LV dysfunction (1) • Pericardial tamponade (1)	Resolution after 10 days on ventilator	5
Biswas et al. (2019)	71	Case report (1)	India	NR	DSS (1)	ECG Echo Pericardiocentesis	• Myocarditis (1) • LV dysfunction (1) • ST elevation (1) • Pericardial tamponade (1)	Spontaneous resolution	6
Buntubatu et al. (2019)	72	Prospective cohort (50)	Indonesia	NR	DF (15) DHF (12) DSS (23)	ECG Echo	• Myocarditis (39) • Elevated cardiac enzymes [CK-MB (35), Troponin I (12)] • Sinus bradycardia (4)	NR	6
Dakeek et al. (2019)	73	Retrospective (147)	Yemen	NR	DF (7) DHF (64) DSS (76)	ECG Echo	• Pericardial effusion (4) • Sinus bradycardia (7) • CCF (10)	15 patients dies, rest recovered completely	6
Datta et al. (2019)	74	Cross-sectional (120)	India	NR	NR	ECG Echo	• Sinus bradycardia (8) • LV dysfunction (4) • Pericardial effusion (2) • AF (2) • Mobitz type II AVB (2)	All had normal recovery after 2 weeks	7
Bhatt et al. (2020)	75	Prospective cohort (182)	India	NR	DHF (85) DSS (60)	ECG Echo Cardiac enzymes	• Elevated cardiac enzymes (27) • Myocarditis (13)	Five deaths in the study population	7

(*Continued*)

Table 1. (Continued).

Study (year)	References	Design (participants)	Country	Comorbid conditions	Clinical symptoms	Diagnostic modality	Cardiovascular manifestation (n)	Outcomes	Quality assessment
da Costa et al. (2020)	76	Case report (1)	Brazil	NR	DSS (1)	Echo	• Pericardial tamponade (1)	Spontaneous resolution	5
Dandeniya et al. (2020)	77	Case report (1)	Sri Lanka	NR	DSS (1)	ECG Echo	• St elevation (1) • Myocarditis (1)	Spontaneous resolution	6
Menwal et al. (2020)	78	Cross-sectional (60)	India	NR	DF (19) DHF (39) DSS (2)	ECG Echo	• ECG changes [sinus bradycardia (6), ST elevation (4)] • DF LV dysfunction (4)	NR	8
Nadkarni et al. (2020)	79	Cross-sectional (75)	India	NR	DF (75)	ECG Echo	• Acute heart failure (3)	NR	5
Shah et al. (2020)	80	Prospective cohort (320)	India	NR	NR	ECG Echo	• Myocarditis (56) • LV dysfunction (42) • Global hypokinesia (32) • Pericardial effusion (3) • ECG changes [Sinus bradycardia (63), 1st degree AVB (6), 2nd degree AVB (1), AF (2), ST elevation (4), VT (2)	NR	4
Shakya et al. (2020)	81	Retrospective (256)	India	NR	DF (179) DSS (77)	Echo	• Pericardial effusion (1) • Myocarditis (1)	NR	5
Sukhwani et al. (2020)	82	Cross-sectional (58)	India	NR	DF (49) DHF (7) DSS (2)	ECG Echo	• ECG changes [T wave inversion (8), sinus bradycardia (7), ST-T changes (9)] • LV dysfunction (1) • Pericardial effusion (1)	NR	5
Talreja et al. (2020)	83	Cross-sectional (70)	India	NR	NR	ECG	• Sinus bradycardia (32) • 1st degree AVB (10) • VPBs (8)	NR	7
Shanbhag et al. (2021)	84	Cross-sectional (100)	India	NR	DF (60) DHF (25) DSS (15)	ECG Echo	• Sinus bradycardia (4) • Pericardial effusion (30) • LV dysfunction (2)	NR	7
Abhinaya et al. (2021)	85	Cross-sectional (130)	India	NR	DF (56) DHF (52) DSS (22)	ECG Echo	• ECG changes (62) • Pericardial effusion (23) • LV dysfunction (4) • Elevated CK-MB (95)	NR	6
Adams et al. (2021)	86	Case report (1)	Columbia	Non-Hodgkin's Lymphoma	DSS (1)	ECG Echo Cardiac MRI	• ST elevation (1) • LV dysfunction (1) • Global hypokinesia (1)	Spontaneous resolution	5
Cabrera-Rego et al. (2021)	87	Prospective cohort (427)	Cuba	NR	DF (360) DHF (44) DSS (23)	ECG Echo	• ECG changes [Sinus bradycardia (59), VPBs (17), 1st degree AVB (6), AF (2)] • Pericarditis (7) • Pericardial effusion (4) • Myocarditis (1)	NR	7

(*Continued*)

Table 1. (Continued).

Study (year)	References	Design (participants)	Country	Comorbid conditions	Clinical symptoms	Diagnostic modality	Cardiovascular manifestation (n)	Outcomes	Quality assessment
Lee et al. (2021)	88	Retrospective (60)	Taiwan	HTN (32) DM (30) CKD (20) CAD (15)	NR	NR	• Acute heart failure (2) • LV dysfunction (2)	NR	8
Mansanguan et al. (2021)	89	Prospective cohort (81)	Thailand	HTN (3) DM (2) Dyslipidemia (3)	DF (39) DHF/DSS (42)	ECG Echo Cardiac enzymes	• Pericardial effusion (6) • Myocarditis (2) • Elevated cardiac enzymes (4) • LV dysfunction (3) • ECG changes [Sinus bradycardia (5), VPBs (2), Junctional rhythm (1)]	NR	7
Naqvi et al. (2021)	90	Case report (1)	Pakistan	NR	DF (1)	ECG Echo	• AF (1)	Spontaneous resolution	7
Papalkar et al. (2021)	91	Cross-sectional (60)	India	NR	DF (51) DHF (7) DSS (2)	ECG Echo	• ECG changes [Sinus bradycardia (9), prolonged PR (1), ST-T changes (5)] • LV dysfunction (4) • Pericardial effusion (2)	NR	7
Raghu et al. (2021)	92	Prospective cohort (100)	India	NR	NR	ECG Echo Cardiac enzymes	• ECG changes [Sinus bradycardia (15), T wave inversion (10), ST-T changes (4), AVB (5)] • LV dysfunction (6) • Elevated cardiac enzymes (15)	NR	6

retrieval. Twelve records were excluded after retrieval and eligibility criteria, and a total of 86 studies were included for this review. Study characteristics and quality are delineated in Table 1. Eighty-six studies include 38 case reports, 3 case series, 5 retrospective studies, 10 cross-sectional, 1 case-control, and 29 prospective cohort studies. Majority of the studies were from India (n = 43), Sri Lanka (n = 5), Brazil (n = 5), USA (n = 5), Taiwan (n = 4), Thailand (n = 4), and Pakistan (n = 3). This is demonstrated in Figure 3.

Abbreviations: atrioventricular [AV]; atrial fibrillation [AF]; ventricular premature beats [VPBs]; ventricular tachycardia [VT]; supraventricular tachycardia [SVT]; corrected QT interval [QTc]; acute coronary syndrome [ACS]; left ventricle [LV] Cardiovascular manifestations

Included studies were published between 1998 and 2021, involving 6,773 dengue patients. In 3,122 (46.1%) patients, at least one cardiac manifestation was evident. This is stratified in Figure 2.

3.1 Study selection and characteristics

The most common manifestations were ECG abnormalities (30.6%), which included sinus bradycardia (8.8%), nonspecific ST-T changes (8.6%), ST depression (7.9%), and T-wave inversion (2.3%). Rhythm abnormalities included ventricular premature beats (VPBs) (0.6%), atrial fibrillation (AF) (0.4%), ventricular and supraventricular tachycardia (VT, SVT) (0.08%, 0.04%, respectively). 0.08% had prolonged QTc and 0.1% ST-segment elevation. Among atrioventricular blocks (AVBs), 0.7% had 1st degree, 0.1% Mobitz type I and type II, while 0.07% had 3rd-degree AVBs. 0.04% had sinus arrhythmia and 0.02% presented with junctional rhythm.

3.2 Structural abnormalities

Mechanical sequelae were present in 10.4%, including left ventricular (LV) systolic dysfunction (5.7%), and myocarditis (2.9%) in a majority of the cases. Pericardial involvement was noted as pericarditis (0.1%), pericardial effusion (1.3%), leading to pericardial tamponade (0.1%). Two patients (0.02%) developed pseudoaneurysms and 1 patient had an acute coronary syndrome (0.01%) as ST-elevation myocardial infarction (STEMI) and acute heart failure (AHF) occurred in 0.1%.

3.3 Markers of cardiac injury

Apart from that, the cardiac injury was depicted through a rise in cardiac enzymes (4.5%). CK-MB was elevated in 2.9% and Troponin I in 1.5% of the patients.

4. Discussion

CV manifestations of dengue viral illness are uncommon and mostly related to the severe nature of the disease [5]. Our study showed that there is an extremely wide spectrum of CV abnormalities associated with dengue that range from electrical abnormalities (mainly sinus bradycardia) to very severe and life-threatening mechanical abnormalities (mainly myocarditis and LV dysfunction). A prospective study from Columbia conducted on 102 patients with severe dengue viral infection elucidated that 98% of the patients showed at least one of the CV complications [sinus bradycardia, myocarditis, or pericardial effusion] [16]. Studies also suggest that severe dengue viral illness is also indirectly involved in myocardial injury [17,25]. A prospective cohort study on 133 patients showed that nearly 27% of the patients had clinical myocarditis and the patients that succumbed to the disease had histological evidence of myocarditis with interstitial edema, inflammatory cell infiltration, and necrosis [17]. Similarly, another study from Brazil concluded that severe DF causes mild-to-moderate elevation of cardiac enzymes [25]. The limitations of these studies are that the authors included only hospitalized patients with severe nature of illness which increased the prevalence of cardiac abnormalities in such patients.

There is complex pathophysiology that explains the various cardiovascular manifestations in DF. Changes in vascular endothelial membrane leading to endothelial dysfunction due to the release of inflammatory cytokines in severe dengue along with direct injury to cardiac myocytes are a few possible explanations [17,35]. The development of CV abnormalities in dengue fever depends on multiple factors of which age, viral load, immunity, disease severity, and comorbidities are the most important [17,43]. Studies with microscopic examination of the CV system have suggested minute histological changes in vascular myocytes that suggest endothelial wall disruption due to dysfunction of glycocalyx [27,93]. In severe dengue, hypoproteinemia and low levels of albumin causes glycocalyx dysfunction [93]. Moreover, an increased viral load and NS1 antigen bind to the heparan sulfate which is important for the maintenance of the integrity of the glycocalyx [67,90,91]. Therefore, viremia during severe disease is associated with more adverse CV manifestations. Some studies have also hypothesized high levels of NS1 antigen as the culprit of endothelial dysfunction, vascular impairment, and damage to the components of vascular and cardiac myocytes (including actin and cadherin) [66,67]. All these mechanisms explain the capillary fluid leakage and development of dengue shock syndrome. The direct injury to cardiac myocytes by NS1 antigen explains the elevation of cardiac enzymes and myocarditis in these studies [17,25]. On the contrary, some studies suggest an exaggerated immune response (release of inflammatory cytokines and chemokines) in DSS as a possible mechanism of cardiac injury and elevation of cardiac enzymes [75,78,80].

The CV manifestations of dengue can be asymptomatic or it may lead to fatal complications [81]. There is a wide spectrum of clinical signs and symptoms which suggest CV involvement. These include palpitations, chest pain, pleural pain, pulmonary edema, hypotension, irregular pulse, dehydration, deranging central venous pressures, and pedal edema [47,49]. These signs and symptoms can present in early dengue fever or late stages of DHF or DSS [27,93]. Myocarditis has been reported as the most common cardiac complication following severe dengue infection that can causemortality if not treated early [17,25,60]. Tachycardia, severe hypotension not responding to fluids, fever, cardiomegaly on chest X-ray and tachypnea are classic features that suggest myocarditis[32,33]. Aggressive vital

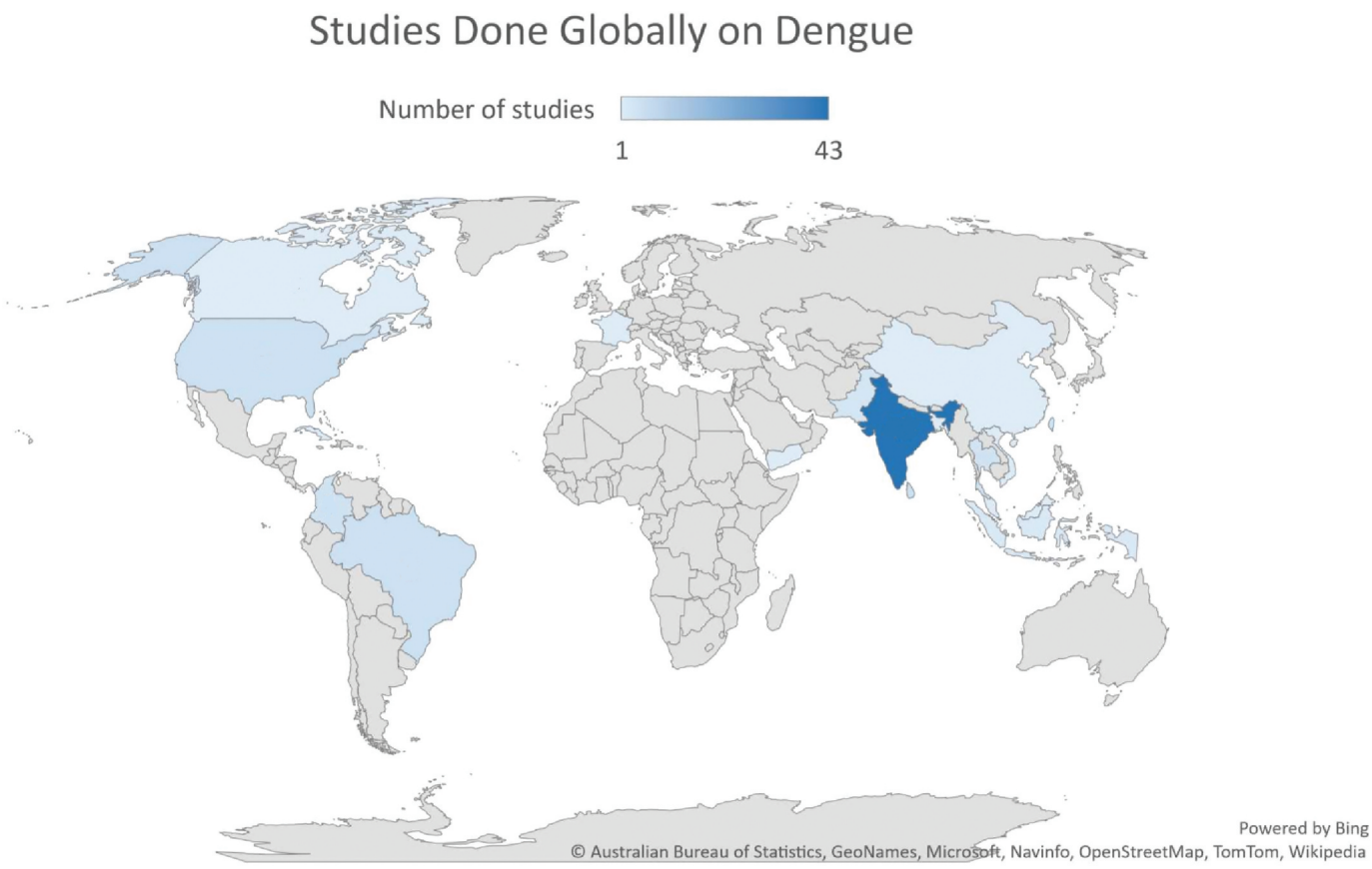

Figure 3. World map showing distribution of included studies

monitoring , serial hematocrit measurement, and timely assessment of the clinical signsprevent CV complications in DF.

A number of cardiac rhythm abnormalities are associated with dengue. Most of these changes range from asymptomatic ECG abnormalities and fatal arrhythmias [8–10]. In DF, various arrhythmias have been reported, includingatrial fibrillation, ST segment changes, Mobitz type I, Mobitz Type II, third-degree heart block, T wave changes, and sinus bradycardia. T wave changes mainly include hyperacute T-waves and T-wave inversions [9, 13, 44, 47, 51, 66, 71, 80, 83, 87]. Other CV abnormalities include pericarditis, pericardial effusion, cardiac tamponade, pseudoaneurysm, and cardiac failure [83,85].

Several diagnostic modalities, including hematology and biochemistry [cardiac enzyme profile, baseline investigations, serial hematocrit measurement] and radiography [chest X-rays, transthoracic echocardiography, cardiac MRI scan, late gadolinium scan] are used to confirm CV involvement in dengue [93]. However, the clinical correlation of CV symptoms along with laboratory and radiological investigations is critical [94].

5 Conclusion

The spectrum of CV manifestations in dengue is extremely broad and ranges from subtle ST-T changes to fulminant myocarditis. It can cause hemodynamic collapse during capillary leakage and can be fatal for patients with severe dengue. Use of conventional techniques, including ECG and transthoracic echocardiography in diagnosing cardiac involvement should be employed in guidelines for rapid diagnosis and treatment of DF. Medications that prolong QT interval should be avoided to prevent an exacerbation of ongoing arrhythmias. More studies in the form of RCTs and meta-analyses are required so that appropriate guideline can be curated for optimal management of CV complications in dengue.

6 Expert Opinion

Diagnosis of CV manifestations of dengue can be difficult as many arrhythmias or underlying CV pathology can be asymptomatic. Therefore, we suggest that initial ECG and echocardiography should be performed, especially in patients with moderate-to-severe DF. However, if a patient develops any of the CV signs and symptoms with a confirmed diagnosis of dengue on RT-PCR, dengue serology, or NS1 antigen testing, an ECG can be very helpful in determining the underlying arrhythmias in mild cases as well. If the ECG is normal, the patient should be clinically reassessed even after recovery because subtle ECG changes can occur after the recovery [46,48,55]. If the symptomatic patient has an abnormal ECG, transthoracic echocardiography is recommended to evaluate valvular abnormalities, pericardial involvement, or myocarditis. In the case of normal transthoracic echocardiography, cardiac magnetic resonance imaging is recommended [94]. Timely detection of myocardial injury during DF should be the core objective of the clinician and a holistic approach

using clinical correlation with laboratory parameters are an absolute necessity for the management of DF.

CV manifestation during DF should be treated with conservative management and supportive care [87,93,94]. Inotropic support, supplementary oxygen, and an equilibrium between the use of diuretics and intravenous fluids can help in better management of dengue patients with CV abnormalities. Even though the electrical abnormalities in dengue fever are insufficiently investigated, a` timely assessment of electrolyte abnormalities (especially potassium and calcium) can help reduce mortality [57,76,93,94]. The use of QT prolonging drugs should be avoided during DF.

The study quality in this review was not an exclusion criteria as most of the studies were performed in third world countries [25,94]. Most of these countries have poor health infrastructure, and very limited resources for research activities. As a result, a larger proportion of the infected patients develop severe form of the disease and a high incidence of CV manifestations. Moreover, most of the studies included only hospitalized patients where the patients already had developed severe dengue and thereafter, CV complications. Moreover, there is a paucity of RCTs to assess treatment options for optimal management of DF.

To our knowledge, a systematic review by Araiza-Garaygordobil et al. included 28 studies enumerating CV manifestations of DF. It discussed dengue as a neglected tropical disease causing a global economic burden, especially in the continent of Africa and South America. Ours is an updated systematic review after exhaustive literature search to extract every possible CV sequela reported in the literature. We included 86 articles, mostly reported from the Indian subcontinent, and discussed the epidemiology, clinical characteristics, pathophysiology, diagnosis, and treatment regarding CV manifestations of dengue. Our study also necessitates the need for the incorporation of conventional diagnostic techniques [ECG and TTE] to diagnose cardiac involvement in dengue. Further studies in the form of meta-analyses and RCTs are required to further delineate the course of CV complications in DF.

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Author contribution

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ORCID

Uzma Ishaq http://orcid.org/0000-0001-9515-3664
Jahanzeb Malik http://orcid.org/0000-0002-9343-4187
Syed Muhammad Jawad Zaidi http://orcid.org/0000-0002-3513-6974
Asmara Malik http://orcid.org/0000-0002-4175-7689

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