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Chikungunya and the Heart

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Keywords
Chikungunya · Cardiac disease · Neglected tropical diseases

Abstract
Introduction: Neglected tropical diseases are a group of communicable diseases that occur in tropical and subtropical conditions and are closely related to poverty and inadequate sanitation conditions. Among these entities, chikungunya remains one of the most widely spread diseases. Although the main symptoms are related to a febrile syndrome, cardiovascular (CV) involvement has been reported, with short- and long-term implications. As part of the "Neglected Tropical Diseases and other Infectious Diseases involving the Heart" (NET-Heart) Project, the aim of this review is to compile all the information available regarding CV involvement of this disease, to help healthcare providers gain knowledge in this field, and contribute to improving early diagnosis, treatment, and prevention strategies. ***Methods:*** We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement in conducting and reporting this systematic review. The search was conducted using MEDLINE/PubMed, SciELO, and LILACS databases to identify any relevant studies or reviews detailing an association between chikungunya and cardiac involvement published from January 1972 to May 31, 2020. ***Results:*** Despite its mechanism not being fully understood, CV involvement has been described as the most frequent atypical presentation of chikungunya (54.2%). Myocarditis is the most prevalent CV complication. Different rhythm disturbances have been reported in 52% of cases, whereas heart failure was reported in 15% of cases, pericarditis in 5%, and acute myocardial infarction in 2%. Overall estimated CV mortality is 10%, although in patients with other comorbidities, it may increase up to 20%. In the proper clinical setting, the presence of fever, polyarthralgia, and new-onset arrhythmia suggests chikungunya virus-related myocarditis. ***Conclusion:*** Although most cases are rarely fatal, CV involvement in chikungunya infection remains the most frequent atypical presentation of this disease and may have severe manifestations. Timely diagnosis and appropriate management are necessary to improve patient outcomes. © 2021 S. Karger AG, Basel

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Introduction

Chikungunya disease is a mosquito-borne illness, caused by chikungunya virus (CHIKV), an enzootic RNA virus found in tropical, subtropical, and mild regions. It was first isolated from a febrile patient during an outbreak on the Makonde Plateau in the southern province of Tanzania (formerly Tanganyika) in 1952 [1, 2]. It is transmitted to human hosts through infectious bites by female *Aedes (A.)* spp. mosquitoes, specifically *A. albopictus* and *A. aegypti* [3], with variable geographic distributions [4].

Although this infection is commonly characterized by acute fever and severe and disabling arthralgia [1], older patients and those with comorbidities (such as obesity, autoimmune disorders, heart failure, and diabetes) have shown higher risk of developing systemic and severe forms of the disease [5]. Systemic forms are not common, but its incidence increases significantly during outbreaks [2]. Among these, cardiovascular (CV) involvement has been reported as the most frequent systemic manifestation [2]. Although rhythm abnormalities, pericardial involvement, and other mild complications have been described, CHIKV-related myocarditis remains as the most prevalent CV complication [2]. Early recognition is important as the acute presentation phase is associated with a high mortality rate and may progress to chronic dilated cardiomyopathy.

This review is part of the "Neglected Tropical Diseases and other Infectious Diseases involving the Heart" (NET-Heart) Project [6], an initiative of the "Emerging Leaders" section of the Interamerican Society of Cardiology (IASC). It aims to compile all the information available regarding CV involvement of this disease, to help healthcare providers gain knowledge in this field, and contribute to improving early diagnosis, treatment, and prevention strategies.

Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement in conducting and reporting this systematic review [7] (shown in PRISMA 2009 Checklist, see online suppl. material; see www.karger.com/doi/10.1159/000514206 for all online suppl. material). The search was conducted using MEDLINE/PubMed, SciELO, and LILACS databases to identify any relevant studies or reviews detailing an association between chikungunya and cardiac involvement published from January 1972 to May 31, 2020. MESH terms used were ("Chikungunya virus," "Chikungunya fever") and ("heart," "cardiac," "physiology and heart," "heart and disease," "myocarditis," "cardiomyopathy," "arrhythmias").

The initial selection of articles was made based on the following inclusion criteria: (i) randomized clinical trials, (ii) case series, (iii) observational studies, (iv) systematic and nonsystematic reviews, and (v) case reports. Only articles in English and those involving humans were included in the analyses. Articles were excluded if the full text was not accessible. Titles were screened by 2 blinded investigators (A.L.S.P. and J.I.C.). Discrepancy was solved by consensus. Kappa interobserver was determined. References for each selected article were also screened. Quality assessment of the selected articles was made using the Study Quality Assessment Tools developed by the National Heart, Lung, and Blood Institute [8] (shown in Table 1).

Results

From a total of 68 references obtained in the first search, 18 documents have been considered for this review: 1 meta-analysis, 2 systematic reviews, 6 nonsystematic reviews, 3 observational studies, 2 case series, and 4 case reports (shown in Table 1 and in Appendix 1). Kappa interobserver was 0.73. Among these articles, 14 were found directly through the literature search on databases and 4 through the review of references list (shown in Fig. 1).

Epidemiology

The virus is believed to have originated in Africa, and its subsequent spread to Asian countries likely occurred through shipping [1]. Before the year 2000, CHIKV outbreaks occurred sporadically; however, since 2000, the virus has re-emerged, causing outbreaks with more severe forms of disease than previously reported [3].

In the Western Hemisphere, CHIKV was initially identified on Saint Martin Island in October 2013, and from this point, it spread rapidly to countries and territories in the Americas [4]. CHIKV has been identified in over 60 countries in Asia, Africa, Europe, and the Americas (CHIKV; Centers for Disease Control and Prevention [Internet]. Available from: https://www.cdc.gov/chikungunya/geo/index.html. Consulted July 2020) (shown in Fig. 2).

Alvarez et al. [2], described CV involvement in 54.2% of cases, based on reports from different areas, including the USA, France, Sri Lanka, Malaysia, Colombia, and India. Postmortem studies in patients diagnosed with idiopathic dilated cardiomyopathy showed viral infiltration of myocytes in 66% of cases [2].

La Reunion, an island in the Macareñas Archipelago in the Indian Ocean, reported an overall outbreak

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Table 1. Characteristics of included studies

Reference	Quality assessment	Type of study	Patients	Sex (*n*)	Main findings
Obeyeskere and Hermon [10]	Fair	Case series	10 patients, median age 40 years	F (8)	Myocarditis was diagnosed in all patients
				M (2)	Patients presented chest pain (70%), crepitations (20%), palpitations (50%), dyspnea (50%), hepatomegaly (30%), ankle edema (30%), pleural effusion (10%), anasarca (10%), cardiac constriction (10%), congestive heart failure (70%), cardiomegaly (70%), and gallop rhythm (50%)
					EKG changes included: Sinus bradycardia (10%), AV conduction disturbances (30%), atrial fibrillation, atrial ectopic beats (10%), ventricular ectopic beats (40%), and repolarization changes (90%)
Mendoza et al. [11]	Good	Prospective multicenter observational study	83 patients, mean age 54 years	F (44)	Patients presented palpitations (34.9%), dyspnea (34.9%), chest pain (34.9%), and SCD (2.4%)
				M (39)	Rhythm disturbances occurred in 52% of the patients; bradyarrhytmia (29%) was the most common finding
Villamil-Gómez et al. [12]	Fair	Case series	42 patients, median age 60 years	F (22)	All patients presented chest pain and palpitations
				M (20)	EKG disturbances were observed in 71.4% of patients
					Repolarization disturbances were the most frequent finding (21.4%)
					Other alterations included left ventricular hypertrophy (20%), U waves (13.3%), and poor R wave progression at precordial leads (10%)
					All patients had more than 1 EKG alteration
Simon et al. [17]	Good	Case report	1 patient, 21 years	F	Travel-acquired myopericarditis (Reunion Island)
					Patient presented prolonged chest pain, ST segment elevation in the anteroseptal region, and increase in troponin I level
					MRI showed pericardial effusion and subepicardial LGE in apical and apical-lateral LV segments, and RV free wall as well
Farias et al. [18]	Fair	Case report	1 patient, 28 years	M	Case of myocarditis related to CHIKV and DENV coinfection
					Cardiogenic shock (LVEF 36%, diffuse hypokinesia, and pericardial effusion)
					Initial management with inotropes infusion, with positive response
					Patient discharged 11 days after admission with new echocardiogram showing LVEF 70% and persistence of pericardial effusion
Mirabel et al. [19]	Good	Case report	1 patient, 19 years	M	Episode of acute myocarditis
					EKG with frequent ventricular premature beats and diffuse ST changes
					Increased levels of troponin and NT-proBNP
					Diagnosis confirmed by LGE MRI and high titles of anti-CHIKV antibodies
Kularatne et al. [20]	Fair	Prospective single-center observational study	120 patients, median age 34 years	F (70)	Description of cardiac complications during 2005 DENV outbreak
				M (50)	Expands information about CV involvement in arbovirus-related infection
Torres and Leopoldo Códova [21]	Poor	Case series	4 patients	F (2)	All patients had CHIKV infection confirmed by RT-PCR
				M (2)	Case 1: fatal case of a 75-year-old man with diagnosis of multi-organ failure and septic shock
					Cases 2 and 3: Fatal cases of a 53-year-old woman and 65 year-old-man, with diagnosis of thrombocytopenia and distributive shock
					Case 4: a 32-year-old splenectomized woman with myocarditis and mixed shock, discharged from hospital after 12 days
Gonzalez Carta et al. [23]	Good	Prospective multicenter observational study	280 patients, mean age 59 years	F (167)	30% of patients developed palpitations
				M (113)	Prevalence of arrhythmias was 45%, including bradyarrhythmia (33%) and atrial fibrillation (6.6%)
					The triad of fever, polyarthralgia, and new-onset arrhythmia may suggest CHIKV related myocarditis

NA, not assessed; EKG, electrocardiogram; SCD, sudden cardiac death; MRI, magnetic resonance imaging; LGE, late gadolinium enhancement; LV, left ventricle; RV, right ventricle; CHIKV, chikungunya virus; DENV, dengue virus; LVEF, left ventricle ejection fraction; CV, cardiovascular; CVD, CV disease.

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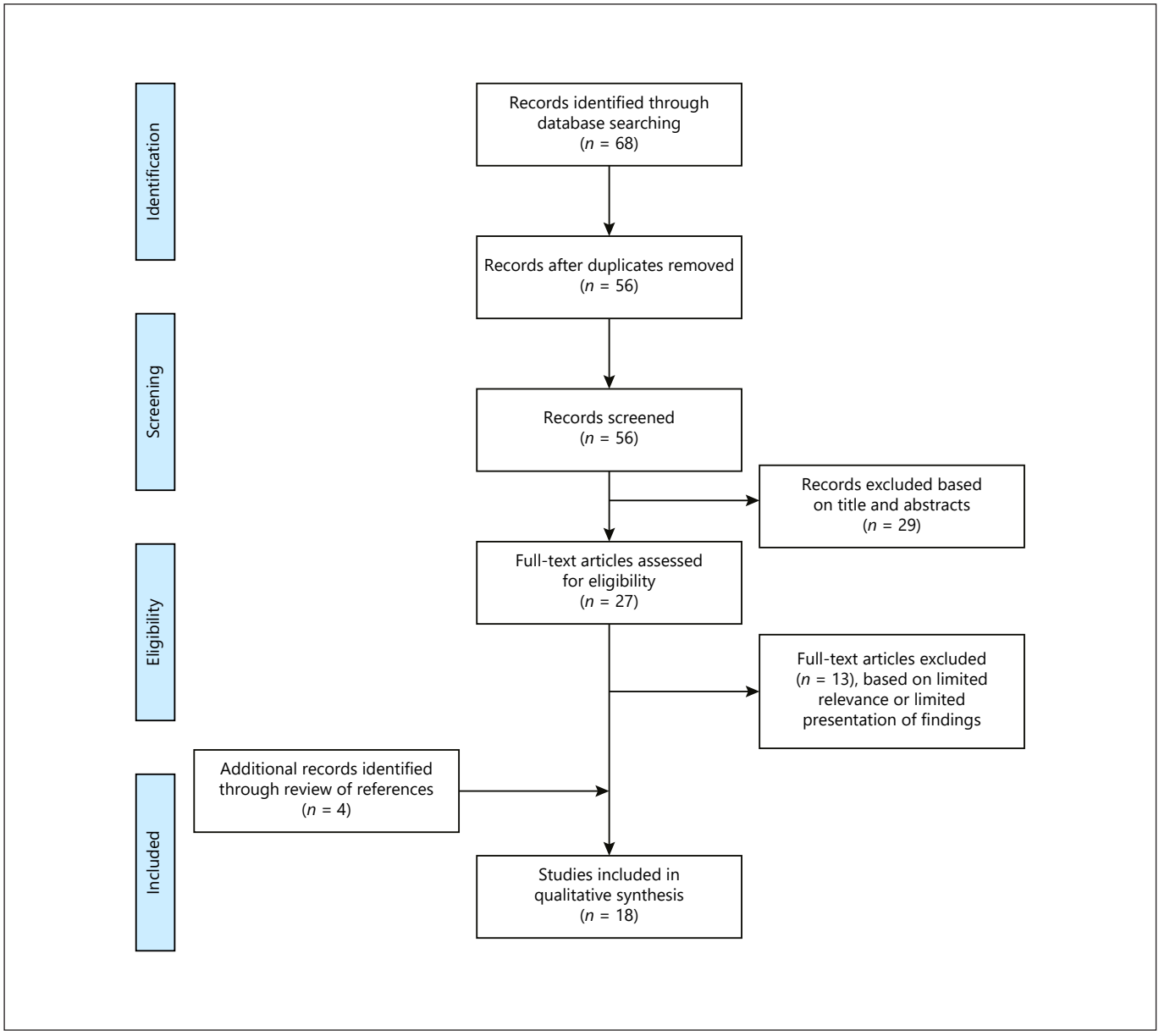

Fig. 1. PRISMA flow diagram [6]. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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mortality of 10% [2, 3]. Interestingly, heart failure was reported in 15% of cases, myocarditis and pericarditis in 5%, and acute myocardial infarction in 2%; among all deaths, CV mortality represented 22% of the total [2].

Pathophysiology and Cardiac Involvement

After an *Aedes mosquito* bites an infected human (shown in Fig. 3a), CHIKV replicates in the female mosquito's salivary glands [2]. When this infected mosquito bites a human host, CHIKV replicates at the site of inoculation in fibroblasts and possibly macrophages [4]. Once in the bloodstream, CHIKV enters the plasma membrane of the cell, mainly by endocytosis, through a

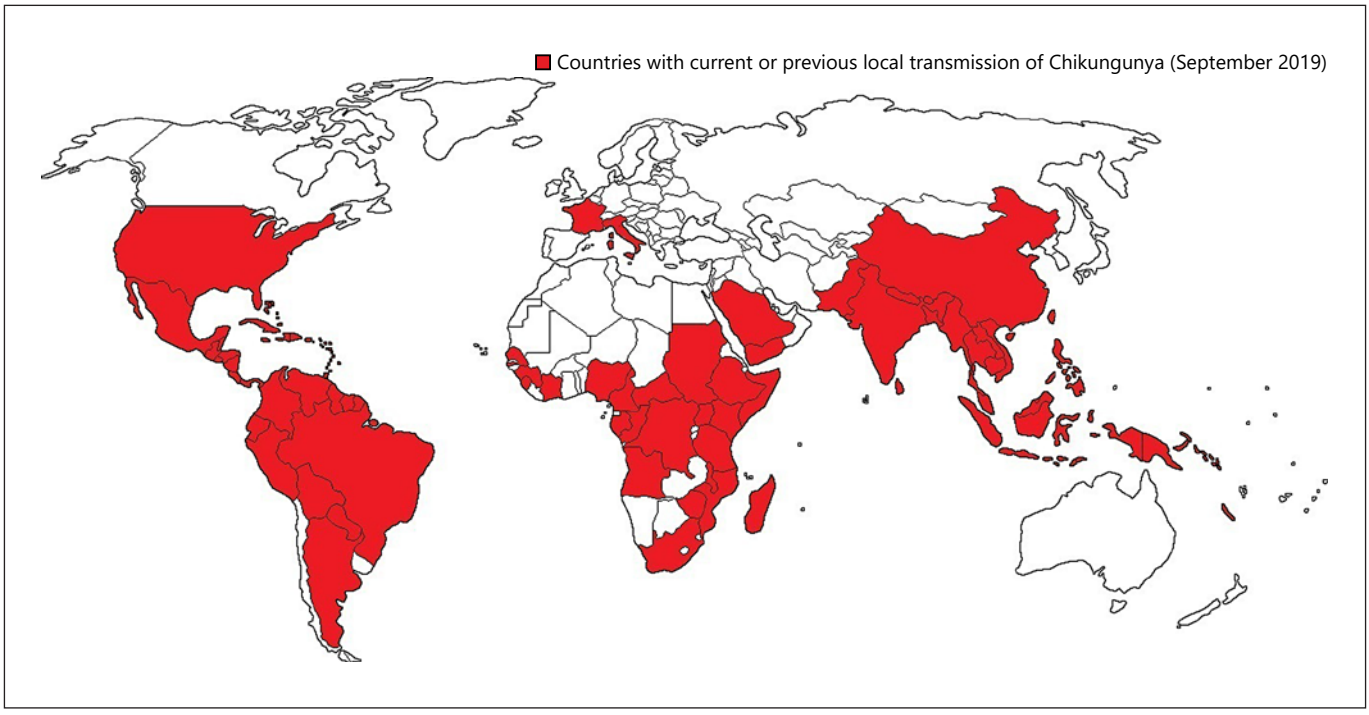

Fig. 2. Countries and territories where chikungunya cases have been reported (as of September 17, 2019).

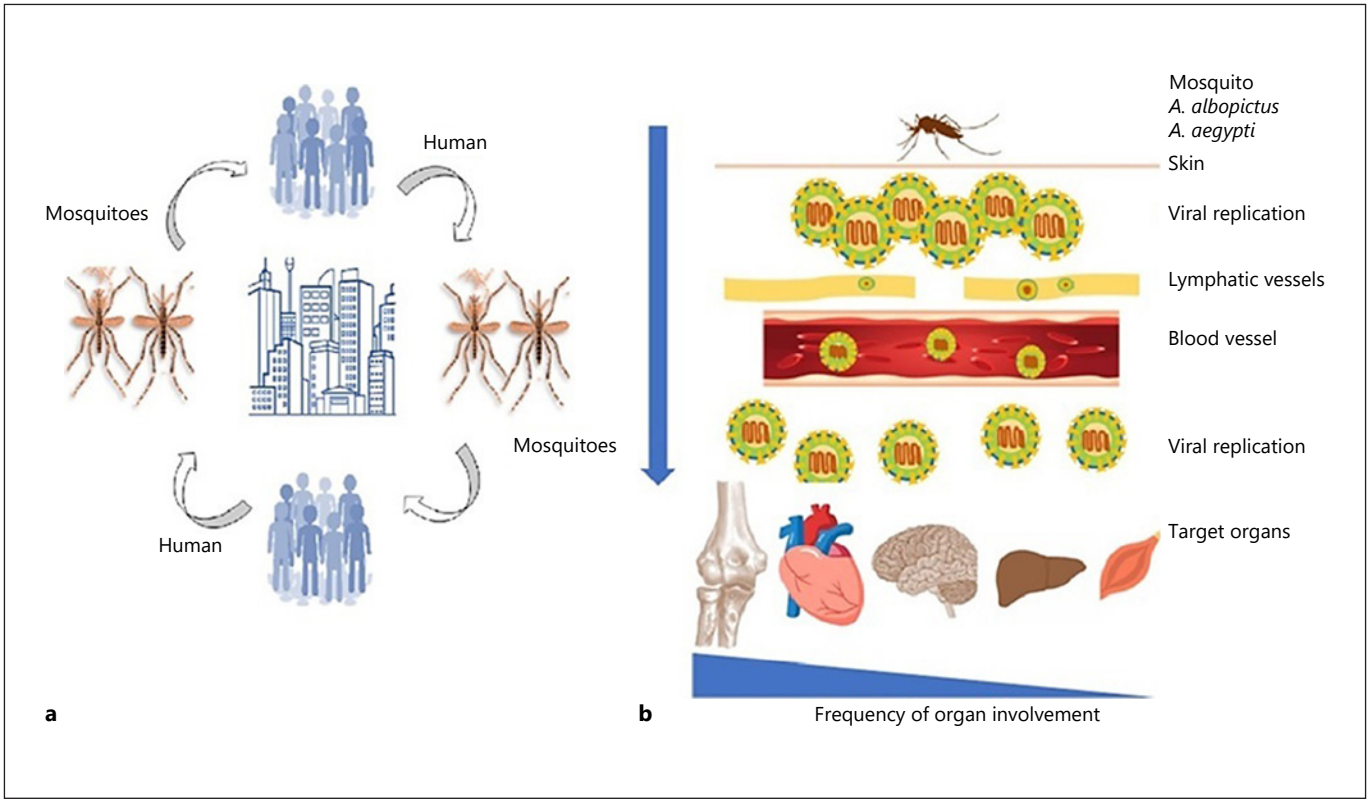

Fig. 3. Chikungunya transmission (**a**) and replication (**b**) cycle in humans.

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pH-dependent mechanism, which culminates in the formation of fusion pores and the release of the nucleocapsid in the cytosol [3].

The result of the inflammatory response matches with elevation of immune mediators, followed by infiltration of immune cells into infected joints and surrounding tissues [4, 8]. Patients with acute and chronic CHIKV infection have high concentrations of pro-inflammatory cytokines such as interferon α, interferon γ, interleukin 6, IP-10, and chemoattractant protein of monocytes [4, 9]. The virus spreads through the lymphatic vessels to the bloodstream, allowing it to reach various sites of replication, most commonly lymphoid organs, skin, and other tissues such as muscle, peripheral joints, and tendons, and less frequently the brain, heart, or liver (shown in Fig. 3b) [4, 8].

The mechanism of CV involvement is not clearly understood [10]. Viruses can directly damage the myocardium or cause a hypersensitivity response or an autoimmune reaction [10]. CHIKV penetrates myocytes and generates direct damage to muscle fibers, increasing the inflammatory response and leading to secondary damage due to hypersensitivity and necrosis [2]. These alterations can be long-lasting and make cardiac tissue more vulnerable to recurrent damage from other microorganisms, favoring the transition from myocarditis to dilated cardiomyopathy [2, 10]. Complete recovery depends, among other factors, on the degree of myocardial damage [10].

Symptoms

Stages of the disease after incubation have been divided into (i) acute (<3 weeks after infection), (ii) post-acute or subacute (3–12 weeks after infection), and (iii) chronic (>12 weeks after infection) [2]. Not all patients develop the full 3 stages [1, 2].

The incubation time is 2–4 days (on average), followed by an abrupt onset of high fever, severe myalgias, and arthralgias, often associated with headache, photophobia, and skin rash [2, 4]. The joint pain can be so intense that patients may have difficulty standing upright, adopting a characteristic "bent over" position (shown in online suppl. Video 1). Approximately 3–25% of individuals with serological evidence of infection have no obvious symptoms [1, 2].

Obeyeskere and Hermon [10] first reported a total of 10 patients with positive serological evidence for dengue virus and CHIKV, with consistent myocarditis findings. Some of these patients recovered successfully, but others developed complications such as cardiomegaly and arrhythmias. Since then, there have been several reported cases of myocarditis, heart failure, and dilated cardiomyopathy associated with CHIKV [10].

Mendoza et al. [11] conducted an observational, multicenter study in patients with CHIKV myocarditis during an outbreak in Venezuela. A total of 83 patients were evaluated, 39 were men, with a median age of 54 years. All patients presented with fever and polyarthralgia; 29 patients developed palpitations, dyspnea, or chest pain; and 2 presented with sudden cardiac death. Rhythm disturbances occurred in 52% of patients: bradyarrhythmias (33%), atrial fibrillation (6%), nonsustained atrial tachycardia (9%), ventricular tachycardia, and sudden death (1%) [11]. Villamil-Gómez et al. [12] described repolarization disorders as the most frequent finding (21%).

A 3-stage CV progression pattern has been proposed: the first phase is described as pre-congestive, and usually, there are no obvious CV symptoms; the second phase is known as the arrhythmic phase because the myocardial injury and inflammatory process do not allow proper functioning of the conduction system [2, 10]. After the acute and subacute stages, the most affected patients will develop congestive heart failure, with involvement of the left chambers more frequently [2, 10].

In a systematic review, Alvarez et al. [2] showed that the most frequent symptoms that suggest cardiac involvement in CHIKV-infected patients includes chest pain, fatigue, dyspnea, palpitations, edema, and vagal symptoms. The most common signs include hypotension, tachycardia and/or tachypnea, crepitation in the pulmonary bases, irregular pulse, and gallop rhythm, among others [10, 11]. In the proper epidemiological context, the triad of fever, polyarthralgia, and new-onset arrhythmia suggests CHIKV-related myocarditis [11].

Diagnosis

Chikungunya diagnosis is based on clinical presentation and epidemiological context. In the first 3–5 days from onset of symptoms, high CHIKV titers are present in the blood, resulting in a viremia that can be detected by RT-PCR with excellent sensitivity and specificity [13]. After this initial period, IgM titration with ELISA-like methods is widely used and recommended for diagnosis [14]; however, up to 6% of dengue-infected patients could have anti-CHIKV IgM due to cross-over antibodies [15]. After 3 months, anti-CHIKV IgG dosage is recommended [16]; its presence does not determine active infection but only previous contact with this virus.

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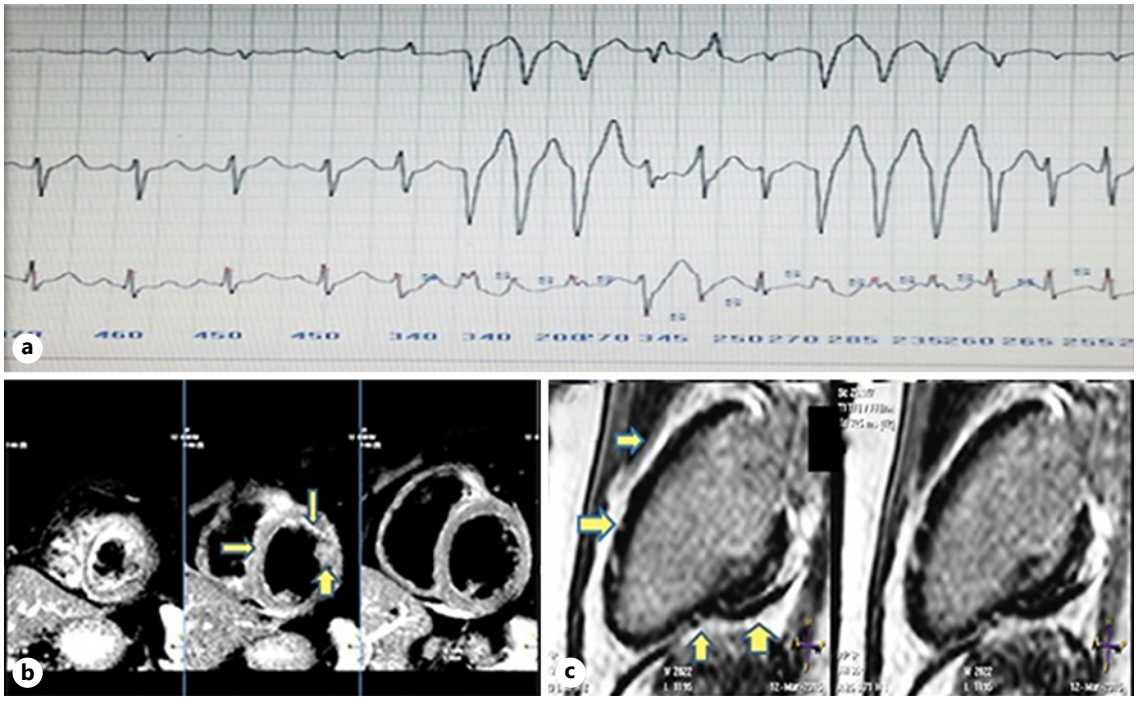

Fig. 4. a Twenty-three-year-old male patient with diagnosis of chikungunya disease presenting with fever, polyarthralgia, and palpitations. Nonsustained ventricular tachycardia is seen in Holter EKG. **b**, **c** Cardiac MRI performed on a 70-year-old male patient with chikungunya-related myocarditis. **b** T2 sequence shows lateral and diffuse myocardial edema (yellow arrows). **c** LGE of lateral, inferior, and septal epicardium (yellow arrows). LGE, late gadolinium enhancement; EKG, electrocardiogram.

Early recognition of CV involvement is paramount to avoid fatal outcomes [11]. Clinical suspicion remains essential for diagnosis and should be confirmed with cardiac enzyme quantification (troponin and NT-proBNP, if possible), electrocardiogram (EKG), and appropriate imaging tools, which are, unfortunately, not always available in some regions.

Considering EKG abnormalities have been described from 35 to 75% of patients infected with CHIKV [2], this widely available test is a fundamental diagnostic tool. Prolonged monitoring with Holter EKG can improve detection of rhythm disorders (shown in Fig. 4a).

Echocardiographic findings are inconsistent and not specific for CHIKV. Wall motion abnormalities, ventricular enlargement, and different degrees of ejection fraction impairment have been described [17, 18]. Pleural and pericardial effusions are less frequent but have been reported as well [17]. Contrast-enhanced magnetic resonance imaging may show multiple subepicardial and midwall intramyocardial foci with increased signal intensities on both early and delayed gadolinium-enhanced images, which typically does not correspond to an epicardial coronary artery distribution (shown in Fig. 4b, c). Although all these findings support a diagnosis of myocarditis, they are not specific for chikungunya [17, 19]. An algorithm to guide the suspicion of CHIKV-related CV involvement can be found in Figure 5.

Treatment

There is no specific vaccine or treatment for chikungunya, and treatment of CV involvement remains controversial. There is consensus that interventions should be done in the early stages of the disease and aimed at avoiding heart failure and cardiogenic shock. Supportive measures, such as strict cardiac monitoring, oxygenation, and inotropic drugs when necessary, are highly encouraged.

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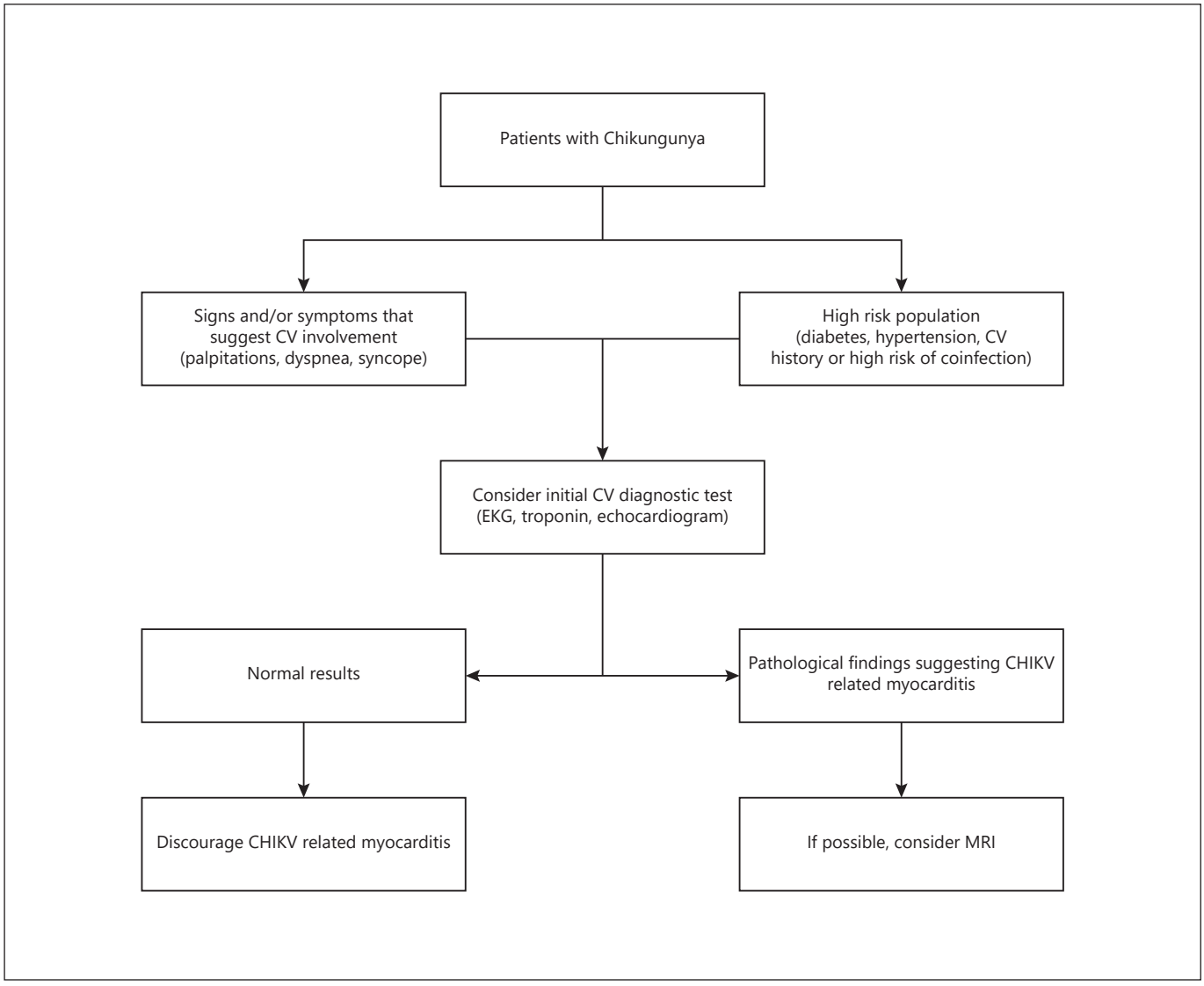

Fig. 5. Proposed algorithm to guide diagnosis of CV involvement in CHIKV patients. CV, cardiovascular; EKG, electrocardiogram; CHIKV, chikungunya virus; MRI, magnetic resonance imaging.

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Intravenous hydrocortisone has been proposed as an efficient treatment in CHIKV myocarditis, but there are concerns about its use, considering that benefit in terms of mortality remains unclear [18]. Empirical interventions, like excessive fluid administration and fresh frozen plasma, are discouraged [20]. In severe and refractory cases, a left ventricular assist device may be useful [21], although technical features, availability, and costs restrain its use. Although there are several scientific groups working on developing a vaccine, results are still far from being successful [22].

Discussion

Most chikungunya cases are typically self-limited. The severe presentation of the disease may include an atypical systemic syndrome, in which different organs are affected by an extra-articular intense inflammatory response [2].

Cardiac compromise is not frequent in isolated episodes, but countries where these viruses have epidemic potential should be alarmed about this condition, especially when outbreaks take place and in the presence of

coinfections with other ARBV [2]. CHIKV-related myocarditis is the most frequent CV presentation of this disease, and it is paramount to consider it early for two main reasons. First, due to complications that may develop in the acute or subacute phase, CV involvement remains the leading cause of death in these patients [23]. Cardiogenic shock, heart failure, and fatal arrhythmias are more frequent in these stages, especially in patients with other diseases such as diabetes, in whom it has been reported up to a 20% risk of mortality [5]. Second, progressive evolution into chronic dilated cardiomyopathy and subsequent clinical deterioration has been described; therefore, a long-term cardiology follow-up is essential in this population [2].

As this disease often mimics dengue fever and CHIKV circulates in regions where dengue virus is endemic, it has been postulated that the incidence of CHIKV infection is much higher than reported [13]. Low clinical suspicion, unavailability of diagnostic methods (and lack of a systematic algorithm), and lack of vaccine and standardized treatments for arbovirus-induced cardiomyopathy hinder CHIKV management and affect prognosis.

With CV disease-associated mortality being higher in low-income countries, an important component of the burden of CV disease in these regions may be attributed to neglected tropical diseases [6]. Therefore, although these entities have remained forgotten among the global health priorities, a growing awareness of their importance in the world's lower middle-income countries is needed. Strategies such as early diagnosis, integrated surveillance, sustainable vector control, and continuous research for future vaccine implementation are necessary in the short-term future [24].

It is crucial to consider that the obstacles to accessing healthcare services may make it difficult to fulfill the usual recommendations. In this adverse scenario, alternative and specific algorithms for neglected tropical disease might be necessary.

Medical training programs and the improvement of the diagnostic equipment of health centers in affected areas are also essential to encourage early CV involvement and to prevent undesirable complications. Limitations of this review may include the low number of previous studies about this subject, the low number of patients included in the selected articles, and short-term follow-ups. Hence, it is difficult to make conclusions about the real long-term impact of CV involvement. Future prospective studies with long-term follow-ups are needed.

Conclusion

Fifty years after the first description of CHIKV-related myocarditis, this mosquito-borne disease remains an unsolved worldwide health problem. Although chikungunya is not generally a lethal disease, CV involvement is identified as the cause of death in most cases. Better public health policies along with more affordable and reproducible strategies should be considered to facilitate early diagnosis, guide effective treatment, and help mitigating damage.

Statement of Ethics

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement in conducting and reporting this systematic review.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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The authors did not receive any funding.

Author Contributions

Ana L. Sauce, Juan I. Cotella, Clara I. Saldarriaga, Gonzalo Emanuel Pérez, Juan M. Farina, and Adrian Baranchuk: contributed to the desing and implementation of the research. Ana L. Sauce, Juan I. Cotella, Fernando Wyss, Alvaro Sosa Liprandi, and Ana G. Múnera: contributed to the analysis of the data. Ana L. Sauce, Juan I. Cotella, Clara I. Saldarriaga, Gonzalo Emanuel Pérez, Juan M. Farina, Ivan Mendoza, Bryce Alexander, and Adrian Baranchuk: contributed to the writing and review of the manuscript.

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Appendix 1

Prior Reviews and Systematic Reviews Included

Reference	Study design	Studies included	Main findings
Burt et al. [1]	Nonsystematic review	Nonspecified	General aspects of CHIKV infection Information on virus-host interactions, immunological responses, and potential antiviral therapies and vaccines
Alvarez et al. [2]	Systematic review	40 articles selected 54.2% at least mentioned CHIKV CV compromise within the systemic compromise Only 21.4% of the resulting articles focused solely and exclusively on CV findings	CV involvement was categorized as common (40–59%) Risk of CV involvement often rises in patients with predisposing conditions and during large outbreaks Rhythm disturbances were frequent (71%) Myocarditis is often fatal, and there is no specific treatment Persistence of abnormal imaging studies after initial CV involvement and association to long-term increase in cardiomyopathy
Thiberville et al. [3]	Non-systematic review	Nonspecified	Atypical cases (including CV involvement) were estimated at 0.3% during the Reunion Island outbreak Among atypical cases 36% were considered severe, 14% were admitted to an ICU, and 10% died
Burt et al. [4]	Nonsystematic review	Nonspecified	Severe CHIKV infection can present with myocarditis Death from CHIKV infection is rare and occurs in fewer than one in 1,000 individuals
Badawi et al. [5]	Systematic review and meta-analysis	11 studies with a total of 2,773 patients	Hypertension, diabetes, and previous CVD were the most prevalent comorbidities in severe forms of CHIKV (20–30%) 20% higher risk for developing severe forms of CHIKV in diabetic patients (including CV involvement)
Silva and Dermody [9]	Nonsystematic review	Nonspecified	Overall CHIKV mortality: 0.1% In recent epidemics, more atypical and severe symptoms have been observed, including myocarditis Atypical symptoms are most prevalent among vulnerable groups (neonates, elderly, and underlying comorbidities)
Jain et al. [13]	Nonsystematic review	Nonspecified	CHIKV often mimics dengue fever It circulates in regions where dengue virus is endemic; hence, the incidence of CHIKV infection is much higher than reported It suggests that CHIKV virulence is higher than previous epidemics
Harapan et al. [16]	Systematic review	24 studies	The estimated incidence rate of 36.2 CHIKV cases per 100,000 person-year Asymptomatic infection ranges from 3.2 to 82.1% Seroprevalence of IgG antibodies among residents living in post-outbreak areas is about 3 times higher than that in residents in nonoutbreak areas
Wenxi et al. [22]	Nonsystematic review	Nonspecified	General description of CHIKV infection Provides information about CHIKV-host interactions and host immune response Provides information on vaccine research and development

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