MEDWAVE
Peer Reviewed Medical Journal

REVIEWS

New perspectives on chagasic cardiomyopathy: A narrative review of genetics, magnetic resonance imaging and therapeutic alternatives

Jose Martin Velasco Hurtado[a,b]*, Dayannara Quispe Zavala[a], Chiara Vilela Luchini[a], Renzo Reineiro Rosales Gutiérrez[c]

[a]*Facultad de Medicina, Universidad Ricardo Palma, Lima, Perú;* [b]*Línea de Investigación en Atención Primaria de Salud, CPC SOCIMEP, Perú;* [c]*Servicio de Cardiología, Hospital Nacional Dos de Mayo, Lima, Perú*

ABSTRACT

Chagasic cardiomyopathy is the chronic manifestation of American trypanosomiasis. In endemic regions of Peru, delayed diagnosis remains a major public health concern. This review analyzes recent evidence (2020 to 2026) regarding the impact of genetic variants on severity, the utility of cardiac magnetic resonance imaging, and the efficacy of trypanocidal and advanced support treatment. A search was conducted in PubMed and Scopus, prioritizing clinical trials and meta-analyses. Current data challenge the direct relationship between parasite lineage and cardiac severity, highlighting the host inflammatory response as the primary driver. Diagnostically, cardiac magnetic resonance imaging surpassed echocardiography in identifying early fibrosis and defining arrhythmic risk. Regarding therapy, benznidazole use during the indeterminate phase reduced the risk of clinical progression (Relative Risk (RR) 0.35), challenging traditional palliative approaches. In conclusion, current evidence repositions etiological treatment as a viable preventive strategy and underscores the importance of cardiac magnetic resonance imaging for early clinical management.

KEYWORDS Cardiomiopatía Chagásica, Trypanosoma cruzi, Imagen por Resonancia Magnética, Biomarcadores, Insuficiencia Cardíaca, Chagas Cardiomyopathy, Magnetic Resonance Imaging, Biomarkers, Heart Failure.

INTRODUCTION

American trypanosomiasis, caused by the protozoan Trypanosoma cruzi and transmitted by triatomine bugs, is commonly known as Chagas disease. In Peru, Arequipa has had the highest prevalence for the past five years, with the adult population (ages 30 to 59) being the most affected [1].

Globally, it is estimated that more than 6 million people live with this infection, primarily in the 21 endemic countries of continental Latin America, where vector-borne transmission remains the predominant route. However, due to migration, it is estimated that nearly 32 million Latin American and Caribbean migrants currently reside in non-endemic countries—about 26 million in the United States and 5 million in Europe—which has extended the presence of the disease beyond its traditionally endemic area [2]. This global spread, combined with the typically asymptomatic course of the chronic phase, perpetuates delayed diagnosis and limits timely access to treatment, cementing Chagasic heart disease as a public health problem in both endemic and non-endemic areas.

The most serious aspect of Chagas disease is its ability to "hide," as it progresses asymptomatically after the acute phase and reappears later, when the body is no longer able to withstand the accumulated progressive and insidious damage. These changes can manifest between five and thirty years after the acute phase. It is estimated that this occurs in up to 40% of cases, while the remaining 60% progress through an indeterminate phase. Based on the global number of previously infected individuals, the number of patients with some form of visceral damage (gastrointestinal or cardiac) is estimated to be between 2.4 and 2.8 million [3]. In fact, it is estimated that Chagasic cardiomyopathy occurs in 20–30% of infected patients. Furthermore, according to a systematic review with meta-analysis, the risk of progression to cardiomyopathy is 1.9% per year in patients in the indeterminate stage and more than double that (4.6% per year) in the acute stage. In a Mexican study that performed serological tests on patients with dilated cardiomyopathy, it was shown that of the total 387 patients, 27

* **Corresponding author** 202220209@urp.edu.pe
Citation Velasco Hurtado JM, Quispe Zavala D, Vilela Luchini C, Rosales Gutiérrez RR. New perspectives on chagasic cardiomyopathy: A narrative review of genetics, magnetic resonance imaging and therapeutic alternatives. Medwave 2026;26(07):e3236
DOI 10.5867/medwave.2026.07.3236
Submitted May 2, 2026, **Accepted** Jul 20, 2026,
Published Aug 10, 2026
Postal address Jr Gregorio Paredes 273, Lima 15084, Perú

MAIN MESSAGES

- Chronic chagas heart disease has a high rate of underdiagnosis in Peruvian primary care, leading patients to seek care too late, when they already have advanced heart failure.
- This review analyzes recent evidence that challenges the exclusive role of parasite genotypes, positioning the host's inflammatory response as the primary determinant of disease severity.
- Limitations of this study include the lack of a systematic analysis of the articles regarding the risk of bias in the included studies, the use of only two databases, and methodological heterogeneity among the reviewed studies.

(6.9%) had Chagas heart disease, and that of these, 96.3% had congestive heart failure in functional class III or IV according to the New York Heart Association (NYHA) Functional Classification [4–6].

This disease burden is not distributed uniformly, in part because Trypanosoma cruzi is not a single pathogen. It has been discovered that this protozoan has seven distinct variants (TcI, TcII, TcIII, TcIV, TcV, TcVI, Tcbat), of which variants TcI–VI are the most genetically closely related to humans and are responsible for causing Chagas cardiomyopathy as well as abdominal visceromegaly [2] (Table 1).

In addition to the classic vector-borne route via triatomine bugs, the existence of an oral route of infection—through the consumption of food contaminated with Trypanosoma cruzi from infected mammals—has been known for several years. This route has been shown to be more efficient in transmission than the classic percutaneous route and is associated with a more severe clinical presentation and higher mortality [2].

However, it is now known that there is no significant relationship between a variant and the severity of cardiomyopathy as determined by clinical classification or standard echocardiographic variables. A study conducted in Brazil that sought to identify a relationship between the Discrete Typing Unit (DTU; TcI/TcII/TcVI) and disease severity found that patients infected with the TcV variant had higher levels of antibodies against the parasite in their blood, which is associated with a higher risk of death and incidence of cardiomyopathy. However, the sample size was small, and the findings were not specific to the severity scales for chronic Chagasic cardiomyopathy [7]. Another study suggests that this difficulty in establishing a relationship stems from the fact that most patients carry multiple discrete typing units simultaneously, each with distinct virulence and tissue tropism. For this reason, a single label for a discrete typing unit (e.g., "TcII") oversimplifies the infection and dilutes associations with the phenotype. Furthermore, the very low and fluctuating parasitemia in chronic disease means that genotyping often relies on a few clones detectable in the blood, which may not reflect the population in the cardiac tissue driving chronic Chagasic heart disease. Furthermore, host factors (immune response, genetics, comorbidities) likely interact with parasite diversity to determine disease progression, further complicating simple links between genotyping and disease severity [8].

Beyond parasite genetics, the most recent research adds another perspective on pathogenesis: circulating microRNAs such as miR-21, miR-146a/b, and miR-155 play a key regulatory role in fibrosis and inflammation in chronic Chagas cardiomyopathy [9,10]. Additionally, chronic exposure of cardiomyocytes to proinflammatory cytokines induces mitochondrial dysfunction that accelerates structural damage regardless of the infecting discrete typification unit [11].

Given this scenario, evidence published in recent years has challenged several classical paradigms regarding the pathophysiology, diagnosis, and treatment of Chagasic cardiomyopathy, warranting an updated, clinically oriented review. The objective of this narrative review is to analyze the evidence published between 2020 and 2026 along three main lines: the actual impact of the parasite's genetic variants on disease severity, the diagnostic utility of magnetic resonance imaging, and the efficacy of trypanocidal treatment in the different clinical phases.

METHODS

For this narrative review, a literature search was conducted in the MEDLINE/PubMed and Scopus databases, prioritizing evidence published between 2020 and 2026. MeSH terms and keywords such as "Chagas cardiomyopathy," "Trypanosoma cruzi DTU," "cardiac magnetic resonance," and "heart failure therapies" were used.

We included randomized clinical trials, systematic reviews, meta-analyses, and clinical practice guidelines published in English, Spanish, or Portuguese, with the full text available, that addressed at least one of the three main areas of this review:

a. The role of genetic variants of the parasite and the host's immune response in the pathogenesis of Chagasic heart disease.

b. The diagnostic performance of cardiac magnetic resonance imaging compared to other imaging methods.

c. The efficacy and safety of trypanocidal treatment and therapies targeting heart failure in Chagas disease.

Isolated case reports, letters to the editor, conference abstracts without full-text availability, and studies conducted exclusively in animal models without a direct clinical correlate were excluded. The main variables analyzed included the parasite lineage or discrete typing unit, markers of the host's immuno-inflammatory response (cytokines, microRNAs), the diagnostic performance of cardiac magnetic resonance

Table 1. *T. cruzi* variants and clinical manifestations.

	Chronic manifestations		Mode of transmission	
Variant	Cardiomyopathy	Abdominal visceromegaly	Vertical	Food
TcI	X	X	?	X
TcII	X	X	X	?
TcIII	X	?	?	X
TcIV	X	X	?	X
TcV	X	X	X	?
TcVI	X	X	X	X
Tcbat	?	?	?	?

T.cruzi: Trypanosoma cruzi. X: Does this variant cause that clinical manifestation or is it transmitted through that route, according to the reviewed literature. ?: There is currently no knowledge or evidence regarding this variant.
Source: Prepared by the authors of this study.

imaging, and therapeutic outcomes (relative risk of clinical progression, changes in biomarkers, mortality, and arrhythmic risk). The selection prioritized evidence with the greatest impact and relevance to current medical practice, and the findings were organized into three thematic areas: pathophysiology, diagnosis, and treatment.

DEVELOPMENT

Pathophysiology

At the cellular level, Trypanosoma cruzi evades destruction by escaping the endolysosome. Upon transitioning to its amastigote phase, it activates the inflammasome and nuclear factor κB. This induces the release of interleukin-12, interleukin-18, and interferon γ, promoting the differentiation of Th1 lymphocytes that attempt to destroy the parasite using reactive oxygen and nitrogen species. However, it has been shown that patients who develop Chagas cardiomyopathy maintain significantly higher levels of anti-Trypanosoma cruzi antibodies than those in the indeterminate phase. This persistence facilitates cross-reactivity between parasitic antigens and proteins on the surface of cardiomyocytes, leading to autoimmune myocarditis that attacks healthy cells and accounts for the degeneration, inflammation, and progressive fibrosis [3,6,12].

Genetic advances reveal that the two groups of genes responsible for the greatest pathogenicity are those of Trypanosoma cruzi itself (which confer resistance to elimination and dissemination) and variants in the host's innate immune system (polymorphonuclear cells and monocyte-derived cells). In these patients, macrophages lack negative regulation of interferon-γ and interleukin-18 production, leading to increased differentiation of Th1 lymphocytes [3].

Recent research has shown that mitochondria play an important role in the progression of this disease. The cytokines interferon-γ and tumor necrosis factor-α induce mitochondrial dysfunction and nitro-oxidative stress in cardiomyocytes, rather than activating their energy metabolism. Specifically, tumor necrosis factor-α reduces the expression of subunits of complex I of the electron transport chain, increasing reactive oxygen species and decreasing adenosine triphosphate. This is exacerbated by a decrease in adenosine triphosphate synthase (complex V) and creatine kinase in Chagas-affected cardiac tissue. This results in a myocardium that is structurally incapable of sustaining its energy demands [3,13,14].

This triggers a "perfect storm" of cellular damage, in which, although the cell attempts to compensate for energy demand, the lack of counterregulation triggers the production of reactive oxygen and nitrogen species. Chronic oxidative stress perpetuates damage to the organelle's DNA and compromises the permeability of its membrane, further reducing the availability of adenosine triphosphate. The drop in energy directly impacts ionic homeostasis, particularly magnesium- and calcium-dependent pumps, impairing the electrophysiological stability of the myocardium, which explains the subsequent onset of conduction disturbances and the ventricular remodeling characteristic of the disease [15].

Diagnosis

The diagnosis of Chagas disease depends on the clinical stage. In the acute stage, parasitemia is high, so direct microscopy to observe trypomastigotes or PCR is recommended. In the chronic stage, the scarcity of the parasite renders these tests less useful. For this stage, the World Health Organization (WHO) recommends performing two serological tests using different methodologies (for example, enzyme-linked immunosorbent assays combined with indirect immunofluorescence or indirect hemagglutination; or non-conventional methods such as chemiluminescent microparticle immunoassay/electrochemiluminescent immunoassay). In the event of conflicting results, a new blood sample should be collected using the same techniques and, if possible, a third technique [12,16–18].

In addition to etiological diagnosis, troponin and, especially, NT-proBNP have demonstrated high sensitivity (area under the curve 88.54%) for detecting patients with early diastolic dysfunction, which allows for optimized management before progression to severe heart failure. Among inflammatory cytokines, interleukin-1β stands out as a powerful predictor of mortality. Furthermore, recent evidence highlights the use of circulating microRNAs (miR-95-3p and miR-130b-3p) as

diagnostic, prognostic, and differential biomarkers for other heart diseases [18–20].

Various methods for evaluating cardiovascular abnormalities are described, ranked according to their practical utility. Echocardiography is essential for structural and functional monitoring. Its clinical value is not limited to confirming cardiomegaly in advanced stages; rather, it allows us to detect early markers to initiate or adjust heart failure therapy. Notable among these are diastolic dysfunction—considered an early hallmark of the disease—and segmental contractility abnormalities. A characteristic finding is the presence of aneurysms at the apex and in the inferior and inferolateral walls. Furthermore, this structural study must be repeated without fail upon the onset of new symptoms or clinical decompensation [12,21].

Alongside structural evaluation, rhythm analysis is essential. The electrocardiogram serves as an initial screening tool, as its abnormalities often precede symptoms. For accurate interpretation, the Brazilian Consensus on Chagas Disease provides a framework, defining characteristic abnormalities such as complete right bundle branch block (often associated with left anterior hemiblock), atrioventricular blocks, ventricular extrasystoles, and electrically inactive zones. Due to the progressive and predominantly arrhythmogenic nature of the disease, the electrocardiogram is used both for clinical follow-up and for predicting the risk of sudden death. Therefore, it should be systematically supplemented with a 24-hour Holter monitor in all patients with an established diagnosis, regardless of their apparent severity [12,22].

For a more in-depth evaluation, cardiac magnetic resonance imaging has become the gold standard for tissue characterization. Through gadolinium late enhancement, which not only detects fibrosis in the lateral-basal and mid-basal walls but also allows for distinguishing the classic intramyocardial or epicardial Chagas disease pattern from scars of ischemic origin. This makes it possible to identify patients at high risk for malignant arrhythmias and sudden death, even when they retain a normal ejection fraction, which justifies interventions such as the implantation of an automatic implantable defibrillator [23].

In addition to guiding therapy, cardiac magnetic resonance imaging can detect myocardial involvement in up to 25% of patients classified as having indeterminate forms of the disease [21]. Furthermore, in patients from non-endemic areas with cardiomyopathy of unknown origin, this pattern of fibrosis strongly directs the diagnostic suspicion toward a Chagas etiology [12,17]. However, its clinical indication must be rational; due to its high cost and limited availability, its use should be prioritized in patients with dysfunction of unclear cause or those whose risk stratification is uncertain using other methods [24–26].

Finally, other diagnostic modalities play specific second-line roles. Chest X-rays retain their prognostic utility, with an elevated cardiothoracic index serving as an independent predictor of mortality. Meanwhile, the 2023 guidelines from the Brazilian Society of Cardiology (SBC) also describe other methods, such as nuclear medicine, coronary CT angiography, or cardiac catheterization, whose primary clinical indication is to rule out concomitant obstructive coronary artery disease. These tools should be reserved for patients with a high clinical probability of ischemic heart disease or for those in whom cardiac magnetic resonance imaging is contraindicated [17].

Treatment

Chagas disease, with appropriate early detection and therapeutic management during its acute phase, can prevent subsequent complications such as Chagasic cardiomyopathy. Compared to other cardiomyopathies that also cause heart failure, this complication carries an approximately twofold higher risk of mortality [24].

Treatment for Chagas disease can be divided according to its phases: in the acute phase, etiological (trypanocidal) treatment is administered to eliminate the pathogen, and in the chronic phase, treatment focuses primarily on preventing or managing the complications of the disease, with an emphasis on preventing sudden death [17].

Acute phase

The Pan American Health Organization (PAHO) and the Brazilian Society of Cardiology recommend benznidazole as the first-line treatment; in cases of resistance or intolerance, nifurtimox is indicated as the second-line treatment. Dosages vary depending on the patient's weight and the stage of the disease [17,26].

Treatment can be used in all age groups; however, in special cases such as pregnant women, it is contraindicated during the first trimester due to its high teratogenic risk, and only symptomatic management of the patient is performed. Furthermore, administering treatment during the second trimester does not guarantee that the newborn will be free of malformations, perinatal mortality, or congenital Chagas disease. For this reason, the risks and benefits must be weighed to justify proceeding with treatment [17].

In cases of congenital infection, PAHO and the Brazilian Society of Cardiology recommend benznidazole as the first-line treatment and nifurtimox as an alternative, regardless of whether the diagnosis was made in the first few weeks or 9 months after birth [17,26] (Table 2).

Some adverse effects of benznidazole that may occur in approximately 50% of cases include dermatitis, skin rashes, nausea, vomiting, diarrhea, paresthesia, and arthralgia; a rarer effect is significant leukopenia due to a decrease in segmented neutrophils. Therefore, monitoring via routine complete blood counts is necessary 21 days after the start of treatment [17,25].

As for nifurtimox, the average incidence of its adverse effects is 85%, and they frequently include gastrointestinal intolerance, arthralgia, and skin reactions. It should be noted that this medication is sometimes better tolerated than benznidazole, as susceptibility to these drugs varies depending on the strain of Trypanosoma cruzi [17,25].

Table 2. Chagas treatment in congenital cases.

Congenital cases		
Drug	**Dose**	**Frequency**
1° option: Benznidazol	5 to 10 mg/kg/day (oral). Maximun dose: 300 mg/day	Divided into 2 to 3 daily doses for 60 days
2° option: Nifurtimox	10 to 15 mg/kg/day (oral)	Divided into 2 to 3 daily doses for 60 days

mg/kg/day: milligrams per kilogram per day. mg/day: miligrams per day.
Source: Prepared by the authors based on Marin-Neto JA et al. [17] and PAHO [26].

Chronic phase

In this phase, parasitemia levels are undetectable, and two clinical forms may occur: asymptomatic or indeterminate, and symptomatic or determined. The majority (approximately 60 to 70%) are asymptomatic, and about 30 to 40% present with cardiac, gastrointestinal, or mixed (cardiogastrointestinal) manifestations [17,25]. In the recent chronic phase, treatment is recommended for asymptomatic children, adolescents, and adults up to age 50, provided there are no contraindications; nifurtimox should not be used [17,26]. For women with chronic infection who are of childbearing age (between 15 and 49 years), treatment with benznidazole is recommended to prevent the transmission of congenital Chagas disease [17,26].

Patients diagnosed with chronic Chagasic heart disease should undergo annual clinical evaluations, including a thorough medical history and physical examination, always accompanied by a chest X-ray and an electrocardiogram to identify the presence of new cardiac abnormalities. Management involves both pharmacological and non-pharmacological approaches. These approaches focus on alleviating the symptoms of heart failure and reducing the parasite burden with benznidazole only in cases of recent chronic phase with low risk according to the Rassi score. However, the use of this drug should be limited, as it is highly toxic and its effectiveness in this phase is limited [17,27].

In a study conducted on laboratory mice examining the use of curcumin or aspirin in combination with benznidazole for the treatment of heart disease, the results showed that it can reduce inflammation and cardiac fibrosis, as curcumin has cardioprotective effects due to its anti-inflammatory and antioxidant properties. However, there is not yet sufficient information to support its therapeutic use; nevertheless, it is important to note that research is ongoing to identify new effective natural remedies [27,28] (Table 3).

Management of heart failure and ventricular dysfunction

Treatment is primarily directed at patients with mildly reduced (41–54%) and reduced (≤40%) left ventricular ejection fraction. Furthermore, dosing should be individualized and based on clinical judgment, taking into account the benefits and harms to the patient [17].

Pharmacological therapy medications

Diuretics should be used in cases where the left ventricular ejection fraction is reduced or mildly reduced, as their benefit is evident in controlling systemic or pulmonary congestion associated with heart failure. Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce morbidity in patients with heart failure and a reduced left ventricular ejection fraction. The greater the degree of ventricular dysfunction, the greater the benefit of the medication.

These may be replaced with angiotensin II receptor antagonists if the patient has poor tolerance to the angiotensin-converting enzyme inhibitor. In congenital cases, it is best to proceed with slow titration to avoid symptomatic hypotension. The use of beta-blockers is widely recommended for heart failure with a reduced left ventricular ejection fraction due to their ability to improve symptoms. However, if severe ventricular arrhythmia is present alongside heart failure, amiodarone is required. Based on clinical judgment, the antiarrhythmic drug should be prioritized over the beta-blocker, as the combination could cause bradycardia and/or QT interval prolongation. Spironolactone may be used with or without an angiotensin-converting enzyme inhibitor, an angiotensin II receptor antagonist, or beta-blockers, as it has been proven to reduce the risk of death. However, its use is not recommended if the patient has a glomerular filtration rate (GFR) below 30 microliters per minute per 1.73 square meters, a serum creatinine level greater than 2.5 micrograms per deciliter, or a serum potassium level greater than 5 milliequivalents per liter. Some preliminary studies suggest the use of sacubitril/valsartan, which has better vasodilatory efficacy than an angiotensin-converting enzyme inhibitor, as it demonstrates a significant reduction in the NT-proBNP biomarker, thereby improving patient survival rates. Furthermore, its recommendation grade is B, and it can be used as an alternative treatment [17,25,29].

Ivabradine is a drug that, by selectively blocking the If pacemaker current (funny current) in the sinus node, reduces the rate of diastolic depolarization, resulting in a reduction in heart rate without altering blood pressure, myocardial contractility, or intracardiac electrical conduction. It also has a recommendation grade of B and is useful when the heart rate is elevated and it is no longer possible to increase the beta-blocker dose.

In clinical practice, digoxin is used in combination with other medications to optimize its effect in cases of atrial fibrillation with a high ventricular response. However, caution must be exercised regarding its dosage, as the drug's therapeutic window is narrow, making adverse effects such as bradyarrhythmias, atrioventricular blocks, or other manifestations more likely to occur.

Table 3. Treatment according to phase (acute or chronic).

Acute phase		
Drug	**Dose according to weight**	
	≤40kg	>40kg
1° option: Benznidazol	7.5 to 10 mg/kg/day (oral)	5 to 7 mg/kg/day (oral)
	In both cases, the dose should be divided into 2 to 3 daily doses for 60 days. Maximum dose: 300 mg/day	
2° option: Nifurtimox	10 to 15mg/kg/day (oral)	8 to 10 mg/kg/day (oral)
	In both cases, they should be divided into 2 to 3 daily doses for 60 days	
Recent chronic phase		
Benznidazol	7.5mg/kg/day (oral)	5mg/kg/day (oral)
	In both cases, they should be divided into 2 to 3 daily doses for 60 days	

≤less than or equal to. >, greater than. kg, kilograms. mg/kg/d, milligrams per kilogram per day. mg/d, milligrams per day.
Any recent chronic infection (including in children 12 years of age or younger) and any chronically diagnosed infection requires a comprehensive general evaluation of the patient and a formal referral from the treating physician.
Source: Prepared by the authors based on Marin-Neto JA et al. [17] and PAHO [26].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors lead to a better prognosis for patients with kidney failure, heart failure, and reduced left ventricular ejection fraction, due to their mechanism of action, which promotes osmotic diuresis, natriuresis, and "weight loss." Furthermore, they have a recommendation grade of B [17].

Heart transplantation is a nonpharmacological treatment option for refractory heart failure that improves quality of life and increases patient survival. It is strongly recommended for chronic Chagas heart disease and is contraindicated only if the patient has megacolon or megaesophagus, which increases the likelihood of postoperative complications.

Finally, the use of pacemakers is indicated in patients with sinus node fibrosis, as this condition can cause intraventricular, atrioventricular, and right bundle branch blocks [17,25].

DISCUSSION

This review identifies three key findings. First, recent evidence calls into question the appropriateness of classifying patients solely based on discrete typing units, as this shifts the etiopathogenic focus from variants of Trypanosoma cruzi to the host's immunoinflammatory response. Second, cardiac magnetic resonance imaging is established as the method with the highest diagnostic yield, not only because it is capable of detecting subclinical fibrosis, but also because it allows for differentiating between Chagas-related and ischemic causes and identifying candidates for an implantable cardioverter-defibrillator. Third, treatment with benznidazole during the recent indeterminate phase is beneficial for reducing the risk of clinical progression.

The reviewed studies agree that the parasite's variants or discrete typing units cannot adequately explain the severity of chronic Chagasic heart disease. The fact that multiple clones of Trypanosoma cruzi coexist in the same patient, each with different degrees of virulence and tissue tropism, undermines any simple correlation between a discrete typing unit label and the clinical phenotype. In contrast, host-focused mechanisms—such as the persistence of anti-Trypanosoma cruzi antibodies, mitochondrial dysfunction induced by interferon γ/tumor necrosis factor-α, molecular mimicry with cardiomyocyte proteins, and the regulatory function of circulating microRNAs, provide a more robust explanation for the progression to cardiomyopathy regardless of the infecting genotype. This convergence of different lines of evidence is what lends greater strength to this paradigm shift.

The literature consistently identifies cardiac magnetic resonance imaging as the most effective method for tissue characterization, outperforming echocardiography in the detection of subclinical fibrosis in up to 25% of patients classified as having indeterminate forms. A particularly relevant finding from the current evidence is that the late gadolinium enhancement pattern can not only detect fibrosis but also distinguish between the intramyocardial or epicardial pattern characteristic of Chagas disease and scars of ischemic origin, and identify patients at high risk for arrhythmias even when they retain a normal left ventricular ejection fraction. This finding is consistent with reports from other sources indicating that sudden arrhythmic death may be the first clinical manifestation of chronic Chagasic cardiomyopathy, and that there is still limited evidence regarding the optimal timing for prescribing implantable devices in this population. In conjunction with serum biomarkers (NT-proBNP, troponin, interleukin-1β, circulating microRNAs), the evidence supports a stepwise stratification model, which includes initial screening with an electrocardiogram and echocardiography, biomarkers to detect early diastolic dysfunction, as well as cardiac magnetic resonance imaging only for cases with greater diagnostic uncertainty or questionable arrhythmic risk.

The finding that benznidazole in the indeterminate phase reduces the probability of clinical progression (relative risk 0.35) reopens the debate regarding the optimal timing for etiological therapy, which has traditionally been reserved for the acute phase. This is consistent with the discussion in the supplementary literature, which notes that, although the trial evaluating benznidazole for interrupting trypanosomiasis (Benznidazole Evaluation for Interrupting Trypanosomiasis, BENEFIT) did not demonstrate a benefit of this drug in advanced chronic Chagasic heart disease, observational studies do show a benefit in terms

of survival and disease progression for patients with mild to moderate disease. A common problem with this line of evidence is that most clinical trials on etiological treatment have not included patients with established chronic Chagasic heart disease, meaning that the existing evidence focuses on earlier stages of the disease [30].

Regarding the treatment of heart failure, a large portion of the pharmacological recommendations (angiotensin-converting enzyme inhibitors, beta-blockers, spironolactone, sacubitril/valsartan, SGLT2 inhibitors) are derived from guidelines applied to other cardiovascular diseases rather than from trials specifically designed for chronic Chagas heart disease. This is a structural limitation that also affects nonpharmacological interventions such as nutritional support or cardiac rehabilitation, as well as emerging strategies such as curcumin, for which evidence to date comes primarily from animal models.

Limitations

The most obvious limitation of our narrative review is inherent to its design, as we did not conduct a systematic analysis of the articles to assess the risk of bias in the included studies. Another limitation is the use of only two databases and the publication period (2020 to 2025), as well as the methodological heterogeneity among the reviewed studies, which limits the ability to draw definitive conclusions.

CONCLUSIONS

Based on the above, we conclude that chronic Chagas heart disease is now understood to be a disease determined primarily by the host's inflammatory response, rather than by the parasite's lineage or variants. Furthermore, cardiac magnetic resonance imaging and timely etiological treatment during the indeterminate phase represent the tools with the greatest potential to modify the clinical course of the disease.

The management of Chagas heart disease requires structured follow-up programs and health policies that ensure equitable access to timely diagnosis and treatment to ensure proper adherence, taking cost-benefit considerations into account.

However, the lack of clinical trials specifically designed for patients with chronic Chagasic heart disease and the reliance on guidelines adapted from other diseases remain the most significant obstacles to implementing these strategies in routine medical practice.

Contributor roles JMVH, DQZ, CVL, and RRRG contributed to the conceptualization, literature review, drafting of the original manuscript, and critical review of the final manuscript. All authors approved the final version for submission.

Competing interests The authors declare that they have no conflicts of interest regarding the subject matter of this article.

The authors state that there were no external sources of funding for this study.

Statement on the use of artificial intelligence models The Gemini large language model (Google) was used exclusively as a tool to assist with grammar and spelling checks and to improve the writing style of the Spanish text during the draft preparation phase. All scientific content, literature review, synthesis of empirical data, and conclusions were generated, reviewed, and verified in their entirety by the human authors, who assume sole responsibility for the integrity and accuracy of the manuscript.

Ethics This does not apply because it is a narrative review of publicly available literature that does not involve the direct participation of human subjects or the use of primary data.

Data sharing statement No primary data were generated in this work. All analyzed information comes from published, publicly available sources, whose full references can be found in the References section.

Language of submission Spanish.

Peer review and provenance Unsolicited. Peer-reviewed by two external reviewers, both using a double-blind review process.

REFERENCES

1. Centro Nacional de Epidemiologia, Prevención y Control de Enfermedades - MINSA. Reporte de Casos de Enfermedad de Chagas, Perú 2000-2025. Lima, Perú: Ministerio de Salud; 2025.
2. Cucunubá ZM, Gutiérrez-Romero SA, Ramírez J-D, Velásquez-Ortiz N, Ceccarelli S, Parra-Henao G, et al. The epidemiology of Chagas disease in the Americas. Lancet Reg Health Am. 2024;37. https://doi.org/10.1016/j.lana.2024.100881
3. Frade AF, Guérin H, Nunes JPS, Silva LFSE, Roda VM de P, Madeira RP, et al. Cardiac and Digestive Forms of Chagas Disease: An Update on Pathogenesis, Genetics, and Therapeutic Targets. Trentini A, editor. Mediators Inflamm. 2025;2025. https://doi.org/10.1155/mi/8862004
4. Chadalawada S, Sillau S, Archuleta S, Mundo W, Bandali M, Parra-Henao G, et al. Risk of Chronic Cardiomyopathy Among Patients With the Acute Phase or Indeterminate Form of Chagas Disease: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3. https://doi.org/10.1001/jamanetworkopen.2020.15072
5. González-Zambrano H, Amaya-Tapia G, Franco-Ramos MC, López León-Murguía OJ. Prevalencia de cardiopatía chagásica en la miocardiopatía dilatada. ACM. 2021;91: 4513. https://doi.org/10.24875/ACM.20000042
6. Santos É, Menezes Falcão L. Chagas cardiomyopathy and heart failure: From epidemiology to treatment. Rev Port Cardiol (Engl Ed). 2020;39: 279–289. https://doi.org/10.1016/j.repc.2019.12.006
7. Xavier E de MS, Araujo PF, Pedras JRS, Gonçalves T da S, de Souza NN, Ferreira AM, et al. Genetic diversity of Trypanosoma cruzi in individuals with chronic Chagas disease in the Northern Minas Gerais and Vale do Jequitinhonha regions, Minas Gerais, Brazil. Gerais M, LI BrazilM, editors. PLoS Negl Trop Dis. 2025;19: e0013627. https://doi.org/10.1371/journal.pntd.0013627
8. Carlier Y, Dumonteil E, Herrera C, Waleckx E, Tibayrenc M, Buekens P, et al. Coinfection by multiple *Trypanosoma cruzi*

clones: a new perspective on host-parasite relationship with consequences for pathogenesis and management of Chagas disease. Lodoen MB, editor. Microbiol Mol Biol Rev. 2025;89: e0024224. https://doi.org/10.1128/mmbr.00242-24

9. Villar SR, Herreros-Cabello A, Callejas-Hernández F, Maza MC, Del Moral-Salmoral J, Gómez-Montes M, et al. Discovery of circulating miRNAs as biomarkers of chronic Chagas heart disease via a small RNA-Seq approach. Sci Rep. 2024;14. https://doi.org/10.1038/s41598-024-51487-9
10. Ribeiro HG, Galdino OA, de Souza KSC, Rosa Neta AP, Lin-Wang HT, Cunha-Neto E, et al. Unraveling the role of miRNAs as biomarkers in Chagas cardiomyopathy: Insights into molecular pathophysiology. PLoS Negl Trop Dis. 2024;18. https://doi.org/10.1371/journal.pntd.0011865
11. Gómez-Ochoa SA, Bautista-Niño PK, Rojas LZ, Hunziker L, Muka T, Echeverría LE. Circulating MicroRNAs and myocardial involvement severity in chronic Chagas cardiomyopathy. Front Cell Infect Microbiol. 2022;12. https://doi.org/10.3389/fcimb.2022.922189
12. Pino-Marín A, Medina-Rincón GJ, Gallo-Bernal S, Duran-Crane A, Arango Duque ÁI, Rodríguez MJ, et al. Chagas Cardiomyopathy: From Romaña Sign to Heart Failure and Sudden Cardiac Death. Pathogens. 2021;10: 505. https://doi.org/10.3390/pathogens10050505
13. Nunes JPS, Andrieux P, Brochet P, Almeida RR, Kitano E, Honda AK, et al. Co-Exposure of Cardiomyocytes to IFN-γ and TNF-α Induces Mitochondrial Dysfunction and Nitro-Oxidative Stress: Implications for the Pathogenesis of Chronic Chagas Disease Cardiomyopathy. Front Immunol. 2021;12: 755862. https://doi.org/10.3389/fimmu.2021.755862
14. Nunes JPS, Roda VM de P, Andrieux P, Kalil J, Chevillard C, Cunha-Neto E. Inflammation and mitochondria in the pathogenesis of chronic Chagas disease cardiomyopathy. Exp Biol Med (Maywood). 2023;248: 2062–2071. https://doi.org/10.1177/15353702231220658
15. Principato M, Carvelli MV, Paolucci AG, Miranda S, Keller GA, Lago M, et al. Cytokine Profiles and Inflammatory Implications in Chagas Disease: Associations with Ventricular Function and Conduction Disorders. Medical Sciences. 2025;13: 309. https://doi.org/10.3390/medsci13040309
16. Suárez C, Nolder D, García-Mingo A, Moore DAJ, Chiodini PL. Diagnosis and Clinical Management of Chagas Disease: An Increasing Challenge in Non-Endemic Areas. Res Rep Trop Med. 2022;13: 25–40. https://doi.org/10.2147/RRTM.S278135
17. Marin-Neto JA, Rassi A Jr, Oliveira GMM, Correia LCL, Ramos AN Júnior, Luquetti AO, et al. Diretriz da SBC sobre Diagnóstico e Tratamento de Pacientes com Cardiomiopatia da Doença de Chagas – 2023. Arq Bras Cardiol. 2023;120: e20230269. https://doi.org/10.36660/abc.20230269
18. Antonietti L, Mariani J, Martínez MJ, Santalla M, Vensentini N, Kyle DA, et al. Circulating microRNAs as biomarkers of Chagas cardiomyopathy. Front Cardiovasc Med. 2023;10. https://doi.org/10.3389/fcvm.2023.1250029
19. Echeverría LE, Gómez-Ochoa SA, Rojas LZ, García-Rueda KA, López-Aldana P, Muka T, et al. Cardiovascular Biomarkers and Diastolic Dysfunction in Patients With Chronic Chagas Cardiomyopathy. Front Cardiovasc Med. 2021;8. https://doi.org/10.3389/fcvm.2021.751415
20. Rodrigues AB, da Gama Torres HO, Nunes M do CP, de Assis Silva Gomes J, Rodrigues AB, Pinho LLN, et al. Biomakers in Chronic Chagas Cardiomyopathy. Microorganisms. 2022;10. https://doi.org/10.3390/microorganisms10081602
21. Torres RM, Correia D, Nunes M do CP, Dutra WO, Talvani A, Sousa AS, et al. Prognosis of chronic Chagas heart disease and other pending clinical challenges. Mem Inst Oswaldo Cruz. 2022;117. https://doi.org/10.1590/0074-02760210172
22. Hasslocher-Moreno AM, Saraiva RM, Silva Júnior TL da, Xavier SS, Sousa AS de. Exploring the Historical Background and Clinical Implications of Electrocardiogram in the Context of Chagas Disease Research. Rev Soc Bras Med Trop. 2023;56: 0506. https://doi.org/10.1590/0037-8682-0506-2023
23. Ali SH, Khan UN, Chandupatla N, Abdullah Y, Mahmoud M, Merie A, et al. The Pivotal Role of Cardiac Magnetic Resonance Imaging in Diagnosing Chronic Chagas Cardiomyopathy. JACC Case Rep. 2025;30. https://doi.org/10.1016/j.jaccas.2025.103948
24. Gómez-Ochoa SA, Serrano-García AY, Hurtado-Ortiz A, Aceros A, Rojas LZ, Echeverría LE. A systematic review and meta-analysis of mortality in chronic Chagas cardiomyopathy versus other cardiomyopathies: higher risk or fiction? Rev Esp Cardiol (Engl Ed). 2024;77: 843–850. https://doi.org/10.1016/j.rec.2024.02.014
25. Montalvo-Ocotoxtle IG, Rojas-Velasco G, Rodríguez-Morales O, Arce-Fonseca M, Baeza-Herrera LA, Arzate-Ramírez A, et al. Chagas Heart Disease: Beyond a Single Complication, from Asymptomatic Disease to Heart Failure. J Clin Med. 2022;11. https://doi.org/10.3390/jcm11247262
26. Organización Panamericana de la Salud. Síntesis de evidencia: Guía para el diagnóstico y el tratamiento de la enfermedad de Chagas. Rev Panam Salud Pública. 2021;28: 1. https://doi.org/10.26633/RPSP.2020.28
27. Llerena-Velastegui J, Lopez-Usina A, Mantilla-Cisneros C. Advances in the Understanding and Treatment of Chronic Chagas Cardiomyopathy. Cardiol Res. 2024;15: 340–349. https://doi.org/10.14740/cr1665
28. Imperador CHL, Scarim CB, Bosquesi PL, Lopes JR, Cardinalli Neto A, Giarolla J, et al. Resveratrol and Curcumin for Chagas Disease Treatment-A Systematic Review. Pharmaceuticals (Basel). 2022;15. https://doi.org/10.3390/ph15050609
29. Skibicka K, Wesołowska W, Skibicki T, Bujak R. Angiotensin Receptor-Neprilysin Inhibition in Chagas Cardiomyopathy: Clinical Practice Update. J Educ Health Sport. 2025;85: 65615. https://doi.org/10.12775/JEHS.2025.85.65615
30. Mediano MFF, Saraiva RM, Molina I, Mendes F de SNS. Addressing challenges and advancing treatment strategies for Chagas cardiomyopathy. The Lancet. 2024;404: 915–917. https://doi.org/10.1016/S0140-6736(24)00751-7

Nuevas perspectivas en la cardiopatía chagásica: genética, resonancia magnética y posibles alternativas terapéuticas. Una revisión narrativa

RESUMEN

La cardiopatía chagásica es la forma crónica de la tripanosomiasis americana. En regiones endémicas peruanas, el diagnóstico tardío persiste como un grave problema de salud pública. Esta revisión analiza la evidencia reciente (2020 a 2026) sobre el impacto de las variantes genéticas en la severidad, la utilidad de la resonancia magnética cardíaca y la eficacia del tratamiento tripanocida y de soporte avanzado. Se realizó una búsqueda en PubMed y Scopus, priorizando ensayos clínicos y metaanálisis. Los datos actuales cuestionan la relación directa entre el linaje del parásito y la severidad cardíaca, destacando la respuesta inflamatoria del huésped como factor principal. Para el diagnóstico, la resonancia magnética cardíaca superó a la ecocardiografía para identificar fibrosis precoz y definir el riesgo de arritmias. Respecto a la terapéutica, el uso de benznidazol en fase indeterminada redujo el riesgo de progresión clínica (riesgo relativo 0,35), desafiando el enfoque paliativo tradicional. En conclusión, la evidencia reposiciona al tratamiento etiológico como una estrategia preventiva viable y subraya la importancia de la resonancia magnética cardíaca para el manejo temprano.