

# Clinical and Echocardiographic Predictors of Mortality in Chagasic Cardiomyopathy - Systematic Review

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## Abstract

Diagnosis, prognosis and evaluation of death risk in Chagas cardiomyopathy still constitute a challenge due to the diversity of manifestations, which determine the importance of using echocardiography, tissue Doppler and biomarkers.

To evaluate, within a systematic review, clinical and echocardiographic profiles of patients with chronic chagasic cardiomyopathy, which may be related to worse prognosis and major mortality risk.

To perform the systematic review, we used Medline (via PubMed), LILACS and SciELO databases to identify 82 articles published from 1991 to 2012, with the following descriptors: echocardiography, mortality and Chagas disease. We selected 31 original articles, involving diagnostic and prognostic methods.

The importance of Chagas disease has increased due to its emergence in Europe and United States, but most evidence came from Brazil. Among the predictors of worse prognosis and higher mortality risk are morphological and functional alterations in the left and right ventricles, evaluated by conventional echocardiography and tissue Doppler, as well as the increase in brain natriuretic peptide and troponin I concentrations. Recently, the evaluations of dyssynchrony, dysautonomia, as well as strain, strain rate and myocardial twisting were added to the diagnostic arsenal for the early differentiation of Chagas cardiomyopathy.

Developments in imaging and biochemical diagnostic procedures have enabled more detailed cardiac evaluations, which demonstrate the early involvement of both ventricles, allowing a more accurate assessment of the mortality risk in Chagas disease.

## Introduction

Chagas disease remains a serious worldwide, economic and public health problem, endemic in South America and emergent in Europe and the United States<sup>1</sup>. The World

Health Organization (WHO), in 2013, estimated between 7 and 8 million people chronically infected with *Trypanosoma cruzi* in the world, most of them in 21 Latin American countries, among which more than 30% develop cardiac abnormalities and more than 10% digestive and neurological problems<sup>2</sup>. Additionally, the WHO estimated there are 25 million people at risk of contracting the disease<sup>3</sup>.

In Brazil, it is estimated that there are somewhere between 2 to 3 million infected individuals<sup>4</sup>, which makes it the third main cause of parasitic diseases after malaria and schistosomiasis, and the fourth cause of great damage among communicable diseases in America<sup>3</sup>.

In the acute phase of Chagas disease, cardiac involvement can occur in up to 90% of cases<sup>5</sup>. After six to eight weeks, most patients show recovery of the clinical picture<sup>6</sup>.

In the indeterminate phase, the infestation is only diagnosed by serological or parasitological tests, as there is no evidence of organ damage. Subclinical cardiac involvement may be demonstrated by imaging studies in some patients<sup>7</sup>. Symptoms will develop in the chronic phase, a long time after the first infestation, with cardiac involvement being mainly responsible for the reduction in life expectancy<sup>7</sup>.

Several physiopathological hypotheses have been implicated in myocardial damage, ranging from direct aggression by the parasite<sup>1,8</sup>, sympathetic and parasympathetic dysautonomia<sup>9</sup> and coronary microvascular abnormalities<sup>9</sup> to autoimmune processes<sup>10</sup>. The lack of definition of the physiopathology complicates the diagnosis and hence, the early implementation of treatment in patients with Chagas cardiomyopathy<sup>11</sup>. For these reasons, and because the mortality from Chagas cardiomyopathy is closely related to significant organ involvement, it becomes important to identify prognostic markers related to worse outcomes<sup>12</sup>.

This article aims to systematically review the clinical and echocardiographic profiles of patients with chronic Chagas' disease, which may be related to worse prognosis and mortality.

## Keywords

Chagas Cardiomyopathy / mortality; Prognosis; Chagas' Disease; Echocardiography.

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## Method

A systematic literature review was performed in the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed, Latin American and Caribbean Literature on Health Sciences (LILACS) and Scientific Electronic Library Online (SciELO). Using the descriptors: echocardiography, Chagas disease and mortality, the following were employed as inclusion criteria for the studies: being original; having as research subjects individuals diagnosed with Chagas disease; addressing diagnostic or prognostic methods

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of Chagas cardiomyopathy: detailing clear inclusion, exclusion and discontinuation (when relevant) criteria, and objectives for the research subjects, regardless of gender.

The search was not limited by period of time and language. Duplicate articles, those assessing interventions, those performed in patients aged zero to 10 years and in animals, *in vitro* experiments, case reports and editorials were excluded.

### Data Analysis

Article selection was performed in three steps. Firstly, the titles were read and the ones that did not fit any of the study inclusion criteria were excluded. Secondly, summaries of the selected studies in the first step were read and, likewise, the ones that did not fit at least one of the inclusion criteria were excluded. In the third step, all studies that were not excluded in previous studies were read in full to select the ones that would be included in this review.

A total of 52 articles were found in the MedLine database via PubMed using the descriptors, of which 13 were excluded after reading the title and eight after reading

the abstracts. The remaining 31 articles were read in full and 12 were excluded and 19 included in the review. A total of 30 articles were located in the SciELO and LILACS databases, six of which were excluded after reading the abstracts and 11, after reading the full article; one of these was a duplicate, resulting in the selection of 12 articles. Thus, 31 articles were included in this review, published between 1991 and 2012 (Figure 1).

For a better presentation of the results, we chose to classify methodologically articles selected by the variables: author, year, country, sample size, mean age of the subjects, presence of criteria for subject selection (inclusion and exclusion), of comparison group and results (Chart 1).

### Results

Regarding temporal distribution, there was a marked prevalence of publications in the past decade, with only two publications having been published in the penultimate decade (1990-1999)<sup>13-14</sup>. Another important point to be considered is the absolute hegemony of studies carried out in Brazil (77%

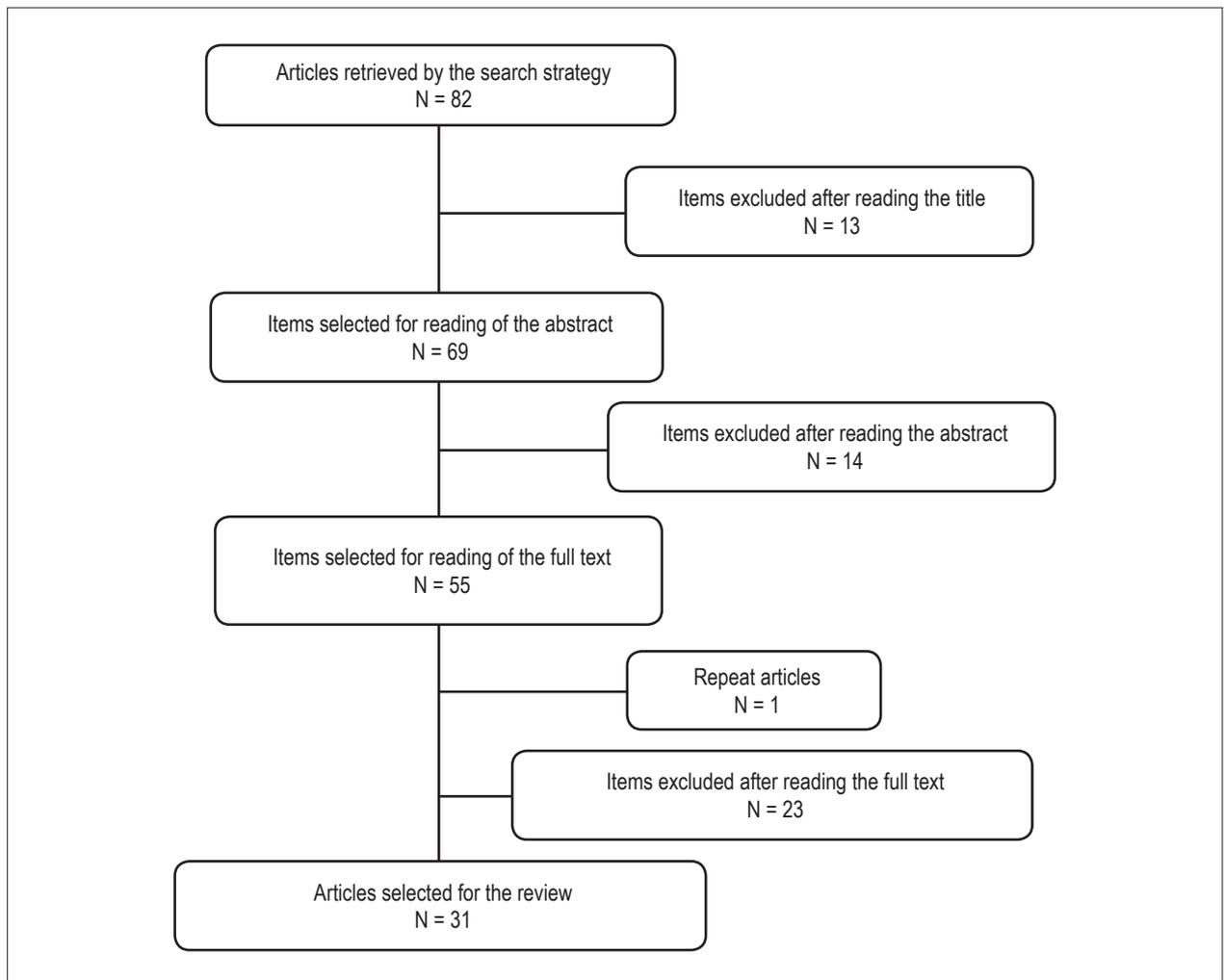


Figure 1 – Flow chart of the number of articles found and selected after applying the inclusion and exclusion criteria

Chart 1 – Methodological classification of selected articles

Author	Year	Country	Type of study	N. of patients	Mean age (years) (range)	Selection criteria	Group of comparison	Results
Guerrero et al. <sup>13</sup>	1991	Venezuela	Cohort	269	> 18	Yes	Yes	The higher prevalence of complex ventricular arrhythmias in chronic Chagasic patients, compared to those with primary dilated cardiomyopathy, exposes Chagasic patients to a worse prognosis.
Marin-Neto et al. <sup>14</sup>	1998	Brazil	Prospective	45	With digestive tract abnormalities = 39.4 ± 10.7 Without abnormalities = 42.4 ± 11.9	Yes	Yes	Dysautonomia is evident in chagasic patients with the digestive form, but not with the indeterminate form. There is no causal association with early myocardial damage, apparent only in patients with impaired right ventricular function, which appears to be the mechanism for the predominance of systemic over pulmonary congestion when heart failure occurs.
Barros et al. <sup>15</sup>	2001	Brazil	Prospective	40	Not informed	Yes	Yes	TDI allowed the identification of higher isovolumic contraction of the septal wall in chagasic patients with the indeterminate form.
Barros et al. <sup>16</sup>	2002	Brazil	Prospective	30	39.9 ± 9.9	Yes	Yes	TDI allows early identification of the RV dysfunction (increased isovolumic contraction of the septal and lateral walls).
Barros et al. <sup>17</sup>	2003	Brazil	Prospective cross-sectional	77	Control: 35.8 ± 10.6 Chagasic com normal ECG: 40.7 ± 8.5 Chagasic with abnormal ECG: 43.9 ± 11.1	Yes	Yes	Tissue Doppler imaging (TDI) identifies early contractility abnormalities.
Arias et al. <sup>18</sup>	2003	Brazil	Prospective cross-sectional	60	> 18	Yes	Yes	Troponin levels are elevated in different clinical presentations of Chagas' disease and detect early inflammation.
Nunes et al. <sup>19</sup>	2004	Brazil	Prospective cross-sectional	74	47.5 ± 12.9 (22-73)	Yes	No	RV dysfunction was significantly associated with LV involvement and pulmonary hypertension, which was more correlated with RV overload than to contractility.
Viotti et al. <sup>20</sup>	2004	Argentina	Cohort	849	> 18	Yes	No	Echocardiography determines the prognosis of chronic Chagasic patients without congestive heart failure (CHF).
Talvani et al. <sup>21</sup>	2004	Brazil	Prospective cross-sectional	81	43.5 ± 11.1	Yes	Yes	High levels of brain natriuretic peptide (BNP) in Chagasic patients detect heart failure (HF) or severe HF manifestations, generating arrhythmias.
Rocha et al. <sup>22</sup>	2004	Brazil	Cohort	60	47 ± 13	Yes	No	Left atrial volume (LAV) was an important predictor of death in Chagas disease.
Freitas et al. <sup>23</sup>	2005	Brazil	Cohort	1220	13 ± 72 (45)	Yes	No	Chagasic etiology in HF patients was the main prognostic factor for mortality.
Melo et al. <sup>24</sup>	2005	Brazil	Transversal	25	62.7 ± 7.7 chronic 42.2 ± 11.7 asymptomatic	Yes	Yes (Chagas asymptomatic x symptomatic)	BNP increases with worsening functional class and cardiac area.
Pazin-Filho et al. <sup>25</sup>	2006	Brazil	Prospective cross-sectional	59	37-76 > 55	Yes	No	In time, slight alterations in the left ventricular ejection fraction (LVEF) lead to the worsening of global LV systolic function.
Rassi Jr et al. <sup>26</sup>	2006	Brazil	Cohort	424	47 ± 11	Yes	Yes	Development of death risk assessment in chagasic cardiomyopathy based on six factors
Chaves et al. <sup>27</sup>	2006	Colombia	Prospective cross-sectional	430	Md = 40.5 (IQR = 36-45)	Yes	Yes	Comparing controls, stage I and stage II using tissue Doppler, it is possible to identify, in stage II, the greater relaxation time, lower velocity of A wave, higher E/A ratio, lower pulmonary A velocity, greater pulmonary/mitral A velocity ratio, greater annulus A wave velocity, and the RV shows increased tricuspid A wave velocity and isovolumic contraction time.

Continuation

Benchimol Barbosa <sup>28</sup>	2007	Brazil	Cohort	50	34-74	Yes	No	In the male gender, pathological Q wave, ventricular extrasystoles, ventricular tachycardia and abnormal echocardiogram (diastolic and systolic dysfunction and apical aneurysm) are markers of poorer prognosis.
Barbosa et al. <sup>29</sup>	2007	Brazil	Prospective cross-sectional	59	48 ± 11	Yes	No	The pro-BNP levels remained a strong correlation with LVEF and duration indices of diastolic dysfunction of left atrial volume, as well as with the more severe forms of the disease, allowing their differentiation from the moderate forms.
Nunes et al. <sup>30</sup>	2008	Brazil	Cohort	158	48 ± 12	Yes	No	Evaluation of systolic and diastolic function using the Tei index (myocardial performance index) and CF showed to be useful prognostic tool in Chagasic cardiomyopathy.
Villas-Boas et al. <sup>31</sup>	2008	Brazil	Prospective cross-sectional	38	51.3 ± 1.6 for chagasic and 53.3 ± 2.3 for control patients	Yes	Yes	The concentration of BNP is increased and correlates with heart failure (direct), functional class (direct) natremia (reverse), blood pressure (reverse), right atrial pressure, R/L ventricular dysfunction, TNF-alpha (demonstrating inflammatory characteristic of the disease).
Nunes et al. <sup>32</sup>	2009	Brazil	Cohort	192	48 ± 12	Yes	No	LAV provides powerful information to predict mortality regardless of clinical and echocardiographic data.
Del Castillo et al. <sup>33</sup>	2009	Brazil	Prospective cross-sectional	40	55 ± 10	Yes	Yes	Based on the principle of speckle tracking and employing the assessment of intramyocardial velocity gradients, they identified the reduction in the percentage of deformation (X-strain) and the rate of deformation (strain rate) of the infero-lateral left ventricular wall in Chagas patients unidentifiable by clinical data or conventional echocardiography.
Terzi et al. <sup>34</sup>	2010	Brazil	Prospective cross-sectional	62	58	Yes	No	Chagasic patients with normal LVEF and normal electrocardiogram had a significant frequency of contractile alterations related with arrhythmias and reduced LVEF.
Pereira Nunes et al. <sup>35</sup>	2010	Brazil	Cohort	287	Chagasic: 48.3 ± 12 Idiopathic: 49.6 ± 15.9	Yes	Yes	Identification of Chagasic etiology resulted in poor prognosis in patients with HF, regardless of clinical and echocardiography data.
Nunes et al. <sup>36</sup>	2010	Brazil	Cohort	65	48.6 ± 9.1	Yes	No	RV dysfunction is an important determinant, regardless of exercise capacity, and the systolic valvular velocity of this ventricle was associated with the peak volume of O2 consumed, regardless of age, gender and echocardiographic parameters.
Garcia-Alvarez et al. <sup>37</sup>	2010	Spain	Cohort	54	20-58 (mean 37)	Yes	Yes (4 groups)	The identification of diastolic dysfunction can be achieved by increasing BNP, which correlates with functional class (NYHA), TNF-alpha, PS, endothelin, ANP and reduction in the percentage of longitudinal and radial deformation to assess contractility.
Duarte et al. <sup>38</sup>	2011	Brazil	Cohort	56	56 ± 10	Yes	No	Although high prevalence of intraventricular dyssynchrony and moderate interventricular dyssynchrony was demonstrated among Chagasic patients, especially in patients without a pacemaker, dyssynchrony did not show to be a risk factor for poor prognosis.
Valerio et al. <sup>39</sup>	2011	Spain	Descriptive	100	38.2 ± 10.2	Yes	No	The fact that Spain has become a center of migration of Latin Americans in Europe has aroused the concern of Chagas disease becoming an important cause of cardiomyopathy in health services.

Continuation

Nunes et al. <sup>40</sup>	2012	Brazil	Prospective endpoint	232	48 ± 12	Yes	Yes (survivors and deaths)	Using tissue Doppler imaging, they identified risk factors for death: functional class III and IV, increased RV Tei, increased left atrial volume index and interaction of LV ejection fraction and E / E ' index and protectors: E / E ' ratio and reduction in LV ejection fraction.
Vasconcelos and Junqueira <sup>41</sup>	2012	Brazil	Prospective cross-sectional	15 controls and 13 chagasic	controls = 40-46 chagasic = 35-49	Yes	Yes	The sympathetic and parasympathetic depressions with preserved balance were associated with heart rate variability and increased left ventricular systolic diameter in Chagasic patients with cardiomyopathy, indicating that these depressions may precede and be independently more severe than ventricular dysfunction, with no causal association between this depression and dysfunction.
Del Castillo et al. <sup>42</sup>	2012	Brazil	Prospective cross-sectional	20	54.8 ± 13.5	Yes	Yes	Employing the speckle tracking technique, it was possible to prove reduction of twisting and torsional deformation of myocardial fibers in Chagas cardiomyopathy, thus differentiating it from ventricular hypertrophy.
Melo et al. <sup>43</sup>	2010	Brazil	Cross-sectional	150	G1:51.02 ± 1.256 G2: 54.88 ± 0.8787	Yes	Yes	It was demonstrated that both groups had increased inflammatory activity, but there were no indications of greater prothrombotic status among chagasic patients.

Legend: ANP: Atrial Natriuretic Peptide, BNP: brain natriuretic peptide; DTI: Doppler tissue imaging (Image by tissue Doppler), CF: cardiac function, LVEF, left ventricular ejection fraction, HF: Heart failure; NYHA: New York Heart Association; O2: oxygen; Tei: myocardial performance index, TNF: Tumor Necrosis Factor; LAV: left atrial volume, RV: right ventricle, LV: left ventricle.

of those included in this review)<sup>4,6-9,11,12,14-19,21-26,28-36,38,40-43</sup>. Among the five studies performed in other countries, three were carried out in Latin America<sup>13,20,27</sup> and two in Europe<sup>37,39</sup>.

Regarding the use of comparison groups, it was observed that in 18 articles (58%) the authors used the design of comparisons between groups<sup>8,13-18,21,24,26,27,31,35,37,33,40-41,43</sup>. It is also interesting to note the predominance of adult patients in the selected studies, with only one study including adolescent chagasic patients<sup>23</sup>.

As for the addressed topics, 10 articles considered prognostic factors of mortality and risk of disease progression using echocardiography<sup>13,19,22,23,26,28,30,32,35,36</sup>, five studies assessed left ventricular ejection fraction (LVEF)<sup>20,25,29,34,39</sup>, alone or together with prognostic factors, seven articles assessed systolic and diastolic ventricular function with tissue Doppler<sup>15-17,27,33,36,40</sup>, five assessed concentrations of brain natriuretic peptide (BNP)<sup>21,24,29,31,37</sup>, one study assessed the prognostic value of troponin concentrations<sup>18</sup>, one study evaluated ventricular dyssynchrony<sup>38</sup>, two studies assessed cardiac dysautonomia<sup>14,41</sup>, two studies used two-dimensional echocardiography to assess ventricular deformation (strain, strain rate and twisting)<sup>33,42</sup> and one study addressed the proinflammatory and prothrombotic factors in Chagas disease<sup>43</sup>.

## Discussion

The predominance of publications over the last ten years may be related to the fact that in past decades, the prognosis for Chagas disease relied almost exclusively on clinical predictors of mortality, which could be evaluated solely during patient follow-up. This means that the preventive

process was restricted to the tertiary level, when treatment aimed only to improve quality of life, as the entire spectrum of cardiomyopathy was already established<sup>7</sup>. With the technological development of ultrasound devices, which allow performing more detailed tests capable of providing valuable information on the physiopathology and prognosis of Chagas cardiomyopathy and establish hemodynamic correlation, studies have become more comprehensive.

As for the near hegemony of studies performed in South America, particularly in Brazil, one possible explanation is that our country constitutes a true source of specialized centers and researchers who, for decades, have been devoted to research on Chagas disease, mainly concerning the factors that alone or combined, may be involved with worse prognosis and increased mortality. Among these are Rassi Jr et al.<sup>26</sup>, Nunes et al.<sup>19,30,32,35,36,40</sup>, Marin-Neto et al.<sup>14</sup>, Barbosa<sup>28</sup>, Barbosa et al.<sup>29</sup>.

Another possible explanation for the increase in publications in the last decade was the dissemination of *T. cruzi* beyond the limits of Central and South America. The immigration of Latin Americans resulted in the diagnosis of patients with the indeterminate form, who were blood donors, especially in Europe<sup>39</sup>, arousing concerns given the frequency at which Chagas cardiomyopathy became an important diagnostic issue in health services, which were not used to managing these patients<sup>39</sup>.

This concern is also found in other countries, especially with the objective of providing primary and secondary disease prevention<sup>26</sup>.

Studies with group comparison<sup>13-18,21,24,26,27,31,33,35,37,40,41</sup> aimed to evaluate the clinical, hemodynamic and evolution

aspects of Chagas cardiomyopathy, while those aimed to identifying morphological and functional characteristics related to prognosis and mortality did not employ this methodology<sup>19,20,22,23,25,28-30,32,34,36,38,39</sup>. The identification of the predominance of publications aimed to investigate adult patients (between the third and fourth decades of life), when compared to those involving adolescents, seems justified by the physiopathology of the disease. In the chronic phase, symptoms of organ involvement most often manifests after 10 to 30 years since the first infestation. That is why Chagas cardiomyopathy in adolescents is a rarer event, for which the acute phase is the most frequent in epidemiological studies<sup>23</sup>. It is appropriate to stress that, in cases of vertical transmission of the disease, children and adolescents may exhibit signs of early cardiac impairment, but these cases have been the subject of underreporting, reinforcing the scarcity of cases also in adolescence<sup>23</sup>.

In addition to the involvement of young adults, chronic Chagas cardiomyopathy constitutes a serious public health problem, as it is a major cause of heart failure with a high mortality rate<sup>23</sup>. This fact, which persists a century after the first description of the disease, has motivated many studies on prognostic factors of mortality and risk of disease progression, among which 10 were included in this review<sup>10,17,19,20,23,25, 27,29,31,37</sup>. All these studies recognize the importance of identifying the chagasic etiology of heart failure, given its destructive and overwhelming role due to incessant myocarditis, caused by extensive myocardial fibrosis, as well as being responsible for complex ventricular arrhythmias, which may explain poorer prognosis of chagasic patients when compared to patients with primary dilated cardiomyopathy<sup>13,34</sup>.

Emphasizing the importance of the etiological diagnosis of heart failure in the context of Chagas disease, another study, which compared 224 patients with chagasic cardiomyopathy and 63 with idiopathic dilated cardiomyopathy, showed that only the identification of Chagas disease conferred poor prognosis for patients with heart failure, regardless of clinical and echocardiographic data<sup>35</sup>.

In addition to heart failure, other studies have shown that right ventricular involvement may be useful for risk stratification of Chagas cardiomyopathy. The myocardial performance index (Tei index), assessed by echocardiography, adds significant prognostic information and allows analysis of systolic and diastolic function of the right ventricle (RV), very useful and effective in patients with Chagas heart disease<sup>30</sup>. Another index used to evaluate RV systolic function is the tricuspid annular plane systolic excursion (TAPSE), capable of providing more reliable information<sup>33</sup>.

Thus, the RV morphological and functional characteristics were also the subject of a study including 74 patients<sup>19</sup>, demonstrating that such changes are associated with significant left ventricular involvement and pulmonary hypertension, contributing to poor prognosis of Chagas disease and also acting as an independent determinant of reduced exercise capacity<sup>36</sup>. Among the left ventricular alterations, the presence of apical aneurysm, impaired left ventricular function and ventricular extrasystoles also acted as predictors of poor prognosis<sup>28</sup>, associated with increased left atrial volume, regardless of the clinical data and conventional

echocardiographic parameters<sup>20,22,32</sup>. Left ventricular wall motion abnormalities in patients with normal systolic function were shown to be a predictor of ventricular function deterioration in chagasic patients with normal ECG and no symptoms or physical signs<sup>25</sup>.

The evaluation of several mutually related indices demonstrates their potential in determining prognostic factors of mortality and risk of disease progression<sup>27</sup>, as emphasized in the paper of Rassi Jr. et al.<sup>26</sup>, which described six risk factors and attributed a score to constitute a simple and validated score. It should be noted that this score was gradually increased by the adding of other factors identified by echocardiography and tissue Doppler imaging.

Mitral annular tissue Doppler, an established modality of echocardiographic assessment of ventricular diastolic and systolic function, disclosed early abnormalities of myocardial contractility<sup>15-17</sup>, thus enabling a previous cardiac planning, regarding the institution of early measures to preserve left ventricular function. It also showed to be effective in predicting RV systolic function, correlated with peak oxygen uptake, regardless of the influence of gender and age or other echocardiographic parameters<sup>36</sup>. Additionally, the E / E' ratio showed high prognostic value for mortality in patients with mild or moderate left ventricular dysfunction<sup>40</sup>. Tissue Doppler imaging constitutes an easy and reproducible way of systolic and diastolic assessment that must be increasingly used, as it is superior to conventional echocardiography<sup>17</sup>, identifying overall contractile abnormalities, especially in patients at the indeterminate phase of Chagas disease and with normal ECG<sup>15</sup>.

Other studies have sought to determine the prognostic markers of cardiac function in Chagas disease. Among them, BNP, a neurohormone of specific cardiac origin, has been the subject of five studies, with the aim of associating its concentration to cardiac dysfunction<sup>21,24,29,31,37</sup>, with discordant results.

Talvani et al.<sup>21</sup>, by correlating BNP levels to ventricular function indices in chagasic patients, showed that because it was a simple, fast, relatively inexpensive method, it should be used for diagnosis of heart failure in these patients, to identify the increased risk of severe arrhythmias, sudden death and reduced survival.

Additionally, they recommended the use of a cutoff lower than 60 pg/mL to characterize patients with low risk of severe chagasic cardiomyopathy, for which echocardiography was not necessary. A study carried out in 2005, however, despite confirming the correlation between high concentrations of BNP and cardiac involvement in Chagas disease, did not confirm it when considered ejection fraction. This study showed that individuals with the indeterminate form of Chagas disease had serum BNP levels similar to those found in the general population, i.e., it did not contribute to the diagnosis of this clinical form<sup>24</sup>.

Subsequent studies, however, have supplemented the significance of BNP measurement in patients with Chagas disease and were also compared to those results. They demonstrated that the assessment of systolic and diastolic functions of the left ventricle and right atrial pressure, together with serum BNP levels, helps to stratify the risk of cardiovascular event development, facilitating the diagnosis of Chagas cardiomyopathy<sup>21,29,31</sup>.

Some studies contrasted to the findings of Melo et al.<sup>24</sup>, by identifying a strong correlation between BNP levels and ejection fraction<sup>29</sup>, as well as the validity of BNP to identify patients in the indeterminate form of Chagas disease<sup>37</sup>. The differences between the findings can be attributed to increased sensitivity and specificity of the test used for BNP measurement, verified since 2006, in response to its large-scale use in many countries.

Considering Chagas disease in the context of inflammatory diseases, another biomarker of heart muscle injury has been evaluated in chagasic patients - troponin I. In chagasic individuals, the concentration of troponin I has been identified in the chronic and indeterminate forms, allowing early detection of myocardial inflammation and consequently, secondary prevention of this injury<sup>18</sup>. More recent studies have sought prognostic markers of myocardial damage degree and, consequently, risk of death, based on physiological processes. In this context, a study has addressed ventricular dyssynchrony<sup>38</sup>, while another<sup>41</sup> sought to update cardiac dysautonomia, of which importance in Chagas disease had already been highlighted in 1998<sup>14</sup>.

As for the dyssynchrony in chagasic cardiomyopathy, a cohort assessed by echocardiography showed high intraventricular and moderate interventricular prevalence and found that, despite the high prevalence, this phenomenon may not affect prognosis as it is independent from the changes in QRS. The importance of this finding is that dyssynchrony, being a segmental alteration secondary to the presence of areas of fibrosis associated with chronic diffuse inflammatory process, does not behave as a risk factor. However, the authors left the significance of dyssynchrony open to discussion and suggested studies with larger samples so that the evaluation of poor prognosis can be supplemented by other factors<sup>38</sup>.

In 1998, Marin-Neto et al.<sup>14</sup>, based on the premise that the digestive form of Chagas disease is characterized by autonomic dysfunction, essential for the development of megaesophagus and megacolon, admitted that this dysfunction could be involved in ventricular alterations of Chagas cardiomyopathy. Cardiac autonomic function was evaluated using angiography with Tc-99m labeled RBCs, demonstrating that patients with the digestive form had pronounced parasympathetic cardiac injury and right ventricular dysfunction in the absence of diagnosed left ventricular dysfunction. However, cardiac autonomic dysfunction was absent in the indeterminate forms, even in the presence of similar right ventricular involvement<sup>14</sup>. The importance of this pioneering study was to demonstrate the possibility that the presence of severe right ventricular involvement can constitute the only cardiac dysfunction in asymptomatic chronic chagasic patients with no other clinical signs of cardiac involvement<sup>14</sup>.

Fourteen years later, a period in which echocardiography was improved by the technological development of equipment and programs (software), allowing early evaluation of morphological and functional disorders, cardiac autonomic function in asymptomatic chronic Chagas cardiomyopathy started to be investigated once again in more detail<sup>41</sup>.

Cardiac autonomic dysfunction, characterized by marked depression of autonomic modulation of heart rate variability

with preserved vagosympathetic balance, was verified regardless of the standing position of the patient. The association of autonomic dysfunction with normality of most ventricular echocardiographic variables suggests that dysautonomia must be a primary phenomenon that may precede ventricular mechanical changes. Thus, its assessment may constitute a precursor of ventricular dysfunction<sup>41</sup>.

Recently, new echocardiographic tools have been employed to allow earlier diagnosis of ventricular alterations in chagasic patients, as, although echocardiography is considered adequate for analysis of ventricular contractility and regional myocardial function, it does not allow ventricular deformation assessment. Two-dimensional X-strain echocardiography is an easy-to-apply technique that allows differentiating passive from active deformation of the ventricular cavity walls, through the assessment of tangential and longitudinal deformation. Del Castillo et al.<sup>33</sup>, using X-strain and strain rate determination, showed the presence of significant reduction in the percentage of deformation and the rate of deformation of the infero-lateral left ventricular wall of patients with Chagas disease, especially in the middle and apical portions, regions that show segmental contractility alterations in the cardiac form of Chagas disease.

This study was improved<sup>42</sup> with the use of the speckle tracking technique, which allows determination of basal and apical myocardial rotation, as well as the twisting, i.e., the angular difference resulting from the clockwise rotation of the apical region and of the basal in the counterclockwise direction, during ventricular systole. These new echocardiographic parameters were employed<sup>42</sup> in the differentiation of chagasic patients and those with left ventricular hypertrophy. By identifying the reduction in global longitudinal strain, radial strain, twisting and myocardial rotation in patients with chagasic cardiomyopathy, as well as the increase in these parameters in ventricular hypertrophy, the authors<sup>42</sup> recommend the use of this modality as a differentiation tool.

In addition to the search for new methodologies for cardiac function assessment, the association between inflammatory and prothrombotic activity in Chagasic cardiomyopathy has been investigated in an attempt to better characterize the disease, as to attain better care of these patients<sup>43</sup>. Such studies are relevant to the elucidation of the damage of chronic Chagas cardiomyopathy, so that it will no longer be included in the group of neglected diseases, considering that after 100 years of its discovery, it is still a serious public health problem. Chronic Chagas disease still leads individuals to heart failure as result of the disease, incapacitating them for work and for life, increasing public expenses, notably with incapacity to lead a productive life, cardio-stimulation (pacemakers, implantable cardioverter-defibrillators and cardiac resynchronizers), drug therapy and heart transplantation.

## Conclusion

The evidence shown in this review allows us to state that the possibility of early etiological diagnosis of chronic chagasic cardiomyopathy has increased over time, enabling us to predict the reduction of mortality in these patients.

By demonstrating that ventricular impairment, not only left as it has been emphasized, but also right, occurs since the indeterminate phase of the disease, when symptoms are mild and do not prevent patients from performing activities of daily living, opens up new possibilities that can translate in prolonged life with quality.

New methods of cardiac assessment for the detailing of ventricular impairment, associated with the use of prognostic scores for risk of death in the future tend to be incorporated into cardiologic routine, facilitating the differential diagnosis of Chagas cardiomyopathy while still in its early phase.

### Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical

analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Pereira Júnior CB, Markman Filho B; Obtaining financing: Markman Filho B.

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