Chagas disease: morbidity profile in an endemic area of Northeastern Brazil

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ABSTRACT

Introduction: This study evaluated the clinical forms and manifestation severities of Chagas disease among serologically reactive individuals from Western Rio Grande do Norte (Northeastern Brazil). **Methods**: This cross-sectional study included 186 adults who were evaluated using electrocardiography, echocardiography, chest radiography, and contrast radiography of the esophagus and colon. A clinical-epidemiological questionnaire was also used. **Results**: The indeterminate, cardiac, digestive, and cardiodigestive clinical forms of Chagas disease were diagnosed in 51.6% (96/186), 32.2% (60/186), 8.1% (15/186) and 8.1% (15/186) of the participants, respectively. Heart failure (functional classes I-IV) was detected in 7.5% (14/186) of the participants, and 36.4% (24/66), 30.3% (20/66), 15.2% (10/66), 13.6% (9/66), and 4.5% (3/66) of the patients were at stage A, B1, B2, C, and D, respectively. Dilated cardiomyopathy and electrocardiographic changes were detected in 10.2% (19/186) and 48.1% (91/186) of the participants, respectively. Apical aneurysm was diagnosed in 10.8% (20/186) of the participants, and other changes in the segmental myocardial contractility of the left ventricle were diagnosed in 33.9% (63/186) of the participants. Megaesophagus (groups I-IV) was observed in 7% (13/186) of the participants, megacolon (grades 1-3) was detected in12.9% (24/186) of the participants, and both organs were affected in 29.2% (7/24) of the megacolon cases. **Conclusions**: We detected various clinical forms of Chagas disease (including the digestive form). Our findings indicate that clinical symptoms alone may not be sufficient to exclude or confirm cardiac and/or digestive damage, and the number of patients with symptomatic clinical forms may be underestimated.

Keywords: *Trypanosoma cruzi*. Chagas disease. Chagasic cardiomyopathy. Megaesophagus. Megacolon.

INTRODUCTION

Chagas disease (ChD) remains a major public health challenge in Latin America, where it currently affects 5.7 million individuals, with the largest numbers observed in Argentina, Brazil, and Mexico[1]. The clinical manifestations of ChD exhibit regional variations that are associated with different factors and are related to the parasite and/or host as the main cause of the chronic phase of the disease[2]. The digestive form is considered common in central Brazil and Chile, although it is practically non-existent in Venezuela and Central America[3].

The forms of ChD are usually estimated based on clinical signs and symptoms, and without performing esophagus and colon contrast radiography, due to the difficulty of performing these exams. Therefore, in northeastern Brazil, an initial diagnosis of the digestive form has typically been based on the signs and symptoms of intestinal constipation and/or evidence of fecalomas[4]. In contrast, the indeterminate form is characterized by the absence of symptoms that are compatible with ChD, and common diagnostic testing is not normally performed, such as conventional serology,12-lead electrocardiography, and radiography of the chest, esophagus, and colon[5]. In endemic areas, 50-70% of patients present with the indeterminate clinical form and 2-5% of these individuals evolve to a known clinical form, with approximately 20-30% of patients developing the cardiac form, 5-8% developing the esophageal form, and 4-6% developing the intestinal form[6][7][8]. The high mortality rateis due to chronic ChD cardiomyopathy (CCC), which is characterized by manifestations that include complex arrhythmias, heart failure, and thromboembolic

events[9]. The digestive form is characterized by digestive symptoms of megaesophagus and/or megacolon, which are due to inflammation and fibrosis of the esophagus and/or colon that results in destruction of the autonomic nervous system and subsequent organ dysfunction[10].

The first scientific description of *Trypanosoma cruzi* infection in the State of Rio Grande do Norte (RN) reported a prevalence of 15.5%[11]. More recent data support an estimated seroprevalence of 6.5% for chagasic infection in the Western mesoregion of RN, although that study did not examine the clinical forms of ChD[12]. Therefore, the present study aimed to characterize the different clinical forms of ChD, its evolution among seroreactive individuals from different municipalities in western RN, and its association with disease severity.

METHODS

Study area

The State of RN is located in Northeastern Brazil, and consists of 167 municipalities that are distributed throughout East, Agreste, Central, and West mesoregions. The present study was performed in the West mesoregion, which covers >40% of RN's surface area (53,077.3km²) **(Figure 1)**.This area was selected because a previous seroepidemiological survey was performed in this region during 2007-2009, and reported an estimated ChD prevalence of 6.5%[12].

Study population and protocol

A total of 215 individuals from 15 municipalities were invited to participate in this cross-sectional study between 2011 and 2013. However, only 186 individuals (23-78 years old) were ultimately included, as various patients were excluded due to disabilities, unwillingness to be examined, and other heart pathologies (e.g., ischemic, valvular, and hypertensive heart disease). Among the 186 included individuals, 83 individuals (38 men and 45 women) had participated in the previous seroepidemiological survey[12], and 103 individuals (54 men and 49 women) had spontaneously demanded testing at the ChD outpatient clinic of the State University of Rio Grande do Norte. The patients who spontaneously demanded testing generally presented with two or more previous reactive serological tests for *T. cruzi* (e.g., at blood banks or primary health centers), and had been instructed to seek treatment at our outpatient clinic. Very few patients spontaneously demanded testing due to clinical symptoms.

All patients completed the same clinical-epidemiological questionnaire, which evaluated their lifestyle and concomitant diseases, and underwent a physical examination. Heart failure was classified according to the New York Heart Association criteria[13] and categorized according to the American College of Cardiology/American Heart Association classifications that were adapted for ChD[14][15].

Plain posteroanterior and lateral chest radiography were performed to evaluate the cardiac silhouette, signs of pulmonary
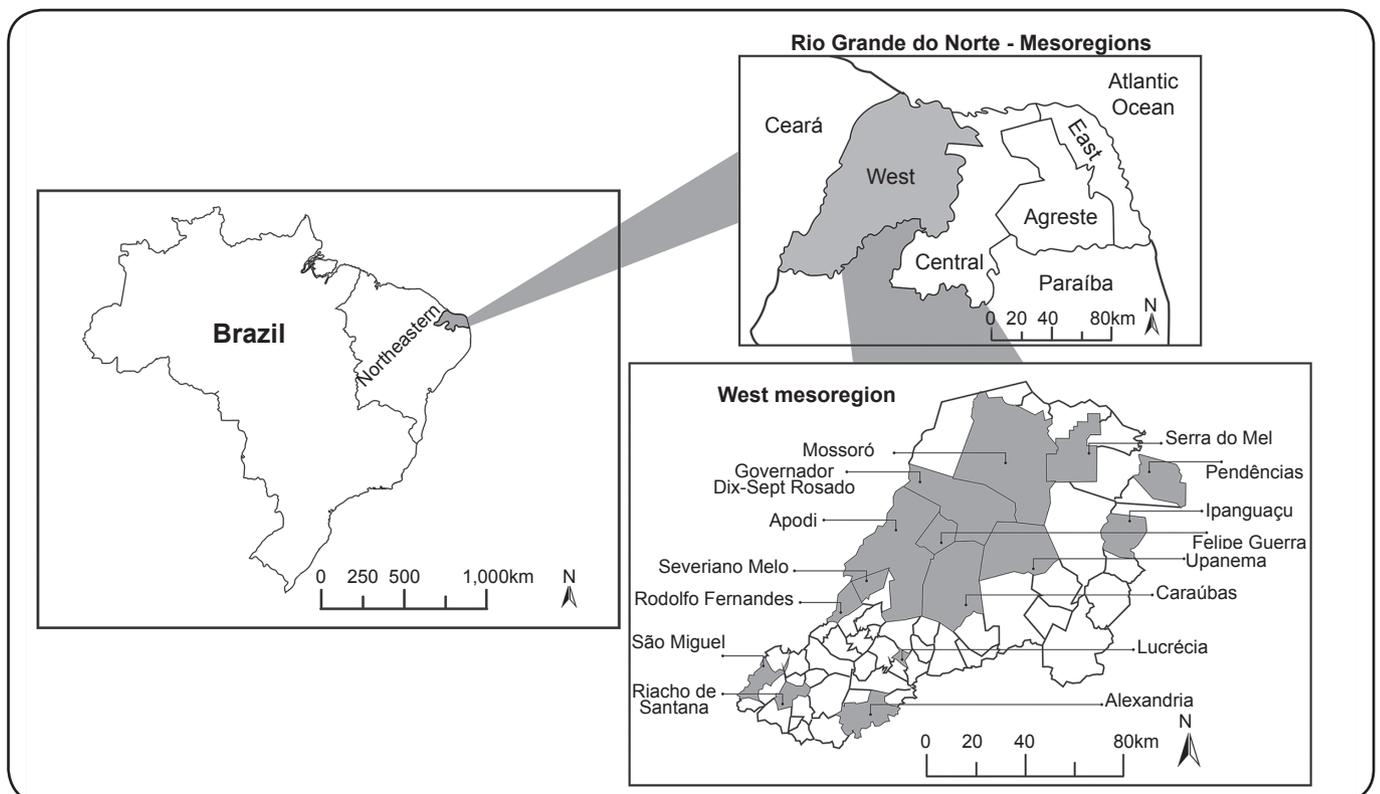

FIGURE 1 - A map of Brazil with the State of Rio Grande do Norte, the Western mesoregion (in gray), and the municipalities that were evaluated.

congestion, and cardiothoracic ratio. The patient's clinical form was classified based on the assumption that a cardiothoracic ratio of >0.5was abnormal[16]. Contrast radiography of the esophagus was performed to classify the esophagus into four groups[17],and contrast radiography of the colon was performed as previously described[18]. The diameter of the rectum was measured in the right lateral decubitus position, and the sigmoid colon was measured in the dorsal decubitus position, or in the ventral decubitus position if necessary[19].The sigmoid colon was classified into four grades (0-3)[20], with some modifications.

A portable electrocardiography device (EP3 2008; Dixtal®, Brazil) was used for 12-lead electrocardiography. All electrocardiographic recordings were evaluated by the same examiner, and scored based on the Minnesota Code that was modified and adapted for ChD[21].

All Doppler echocardiography examinations were performed by the same examiner, using conventional views and their variations (Vivid e®; General Electric, Milwaukee, WI). Linear measurements of the cardiac chambers and left ventricle ejection fraction were visually estimated and confirmed. The cardiac chambers were evaluated according to the recommendations of the American Society of Echocardiography[22]. Simpson's modified method[23] was used when changes in segmental contractility were observed, and the Teichholz formula[24] was used in the absence of any changes.

Statistical analysis

This study used a convenience sample. Data were reported as mean ± standard deviation (SD).The proportions of the ChD forms were compared before and after the completion of contrast radiography. The chi-square test was used to analyze the associations between the clinical forms of ChD and the patients' age; testing type (seroepidemiological survey vs. spontaneous demand); symptoms of palpitations, dysphagia, and constipation; and the associations between dysphagia and megaesophagus and constipation and megacolon, after the completion of contrast radiography. The prevalence ratios (PRs) and their respective confidence intervals (CIs) were calculated for the associated data. The parametric Student t test was used to evaluate the differences between the mean values of the sigmoid colon and rectum measurements for men and women. Differences were considered significant at a p-value of ≤0.05, and all analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 20.0; SPSS Inc. Chicago, IL, USA).

Ethical considerations

Informed consent for this study was obtained from all participants, and the study's design was approved by the Research Ethics Committee of the State University of Rio Grande do Norte (protocol no. 027.2011). All experiments were performed in accordance with the human experimental guidelines of the Brazilian Ministry of Health and the Declaration of Helsinki.

RESULTS

All participants were from rural areas and were currently residing or had previously resided in packed-earth houses;

agricultural work was the predominant occupation. Approximately 50.5% of the participants were women, the mean age was 49 ± 12 years, and >70% of patients were illiterate or only had access to elementary/middle school education (which was not always completed) (**Table 1**). The indeterminate, cardiac, digestive, and cardiodigestive forms of ChD were observed in 51.6% (96/186), 32.2% (60/186), 8.1% (15/186), and 8.1% (15/186) of the participants, respectively. Based on only digestive symptoms (no contrast radiography),the proportions were 59.1%, 33.3%, 3.3%, and 4.3% for the indeterminate, cardiac, digestive, and cardiodigestive forms of ChD, respectively.

When we compared the prevalence ratios of the radiography-confirmed and estimated clinical forms, significant differences for the digestive form (PR: 2.45; 95% CI: 2.18-2.73) and the cardiodigestive form (PR: 1.88; 95% CI: 1.61-2.16). There were no significant differences for the indeterminate form (PR: 0.87; 95% CI: 0.60-1.15) or the cardiac form (PR: 0.97; 95% CI: 0.69-1.24). We also did not observe any significant differences when we compared the testing types (seroepidemiological survey vs. spontaneous demand) among the various age groups (p = 0.6385) (**Table 2**).

Chest radiography revealed cardiomegaly in 10.2% (19/186) of the participants, which provided a sensitivity of 25.3% (19/75) for identifying heart involvement in the cardiac and cardiodigestive clinical forms.

Contrast radiography revealed megaesophagus in 7% (13/186) of the participants, with group I observed in 7 (53.8%) patients, group II observed in 4 (30.8%) patients, group III observed in 1 (7.7%) patient, and group IV observed in 1 (7.7%) patient. No significant sex-related differences between the megaesophagus groups were observed (p = 0.27) (**Figure 2A**). Dysphagia was diagnosed in 6.5% (12/186) of the participants, and patients with megaesophagus II and III reported that dysphagia limited their quality of life. However, this symptom did not discriminate between patients that had normal esophageal radiography findings with dysphagia and patients in the megaesophagus group I who did not have dysphagia (p = 0.07). Approximately 5% of the participants complained of occasional dysphagia, despite exhibiting normal esophageal radiography findings. However, patients with the digestive and cardiodigestive forms exhibited the greatest probability of having dysphagia (PR: 3.2; 95% CI: 2.07-4.33; p=0.006), compared to patients who had the indeterminate form. Esophageal radiography revealed three characteristic features: significant dilatation and elongation of the esophagus, food debris due to achalasia of the lower esophagus (the rat's tail sign; even in patients who had fasted for 12h), and folding over the diaphragm (**Figure 2B**).

Colon contrast radiography revealed megacolon in 12.9% (24/186) of the participants, with grade 1 observed in 17 (70.8%) patients, grade 2 observed in 6 (25%) patients, and grade 3 observed in 1 (4.2%) patient. Both sexes exhibited similar distributions (p = 0.42) (**Figure 2C**). Constipation was detected in 8.6% (16/186) of the participants, although this symptom did not discriminate between patients with grade 0 or grade 1 sigmoid colon (p = 0.23). Approximately 7% of the participants

TABLE 1 - Epidemiological variables from 186 individuals with reactive conventional serology results for *Trypanosoma cruzi*.

Variables	Number	Percentage
Sex		
male	92	49.5
female	94	50.5
Educational level		
illiterate	12	6.5
elementary/middle school, completed or incomplete	126	67.7
high school, completed or incomplete	34	18.3
college/university, completed or incomplete	14	7.5
Occupation		
farmer/cattle farmer	121	65.1
housewife	20	10.8
merchant	1	0.5
other	44	23.6
Knowledge of the triatomine insects		
yes	163	87.6
no	23	12.4
Dwelling in packed-earth house		
yes	140	75.3
no	46	24.7
Blood transfusion		
yes	9	4.8
no	177	95.2
Blood donor		
yes	26	14.0
no	160	86.0

TABLE 2 - Distribution of clinical forms according to age and testing type among 186 patients with chronic-phase Chagas disease.

Age range, years	Testing	Clinical form									
		indeterminate		cardiac		digestive		cardiodigestive		Total	
		n	%	n	%	n	%	n	%	n/T	%
20–29	SS	4	33.3	2	16.7	1	8.3	1	8.3	8/12	66.7
	SD	2	16.7	2	16.7	0	0.0	0	0.0	4/12	33.3
30–39	SS	9	26.5	4	11.8	1	2.9	0	0.0	14/34	41.2
	SD	12	35.3	7	20.6	1	2.9	0	0.0	20/34	58.8
40–49	SS	12	23.1	7	13.5	2	3.8	2	3.8	23/52	44.2
	SD	16	30.8	11	21.2	2	3.8	0	0.0	29/52	55.8
50–59	SS	9	20.0	6	13.4	1	2.2	1	2.2	17/45	37.8
	SD	13	28.9	10	22.2	3	6.7	2	4.4	28/45	62.2
60–69	SS	8	24.2	3	9.1	1	3.0	2	6.1	14/33	42.4
	SD	9	27.2	5	15.2	2	6.1	3	9.1	19/33	57.6
70–79	SS	2	20.0	1	10.0	1	10.0	3	30.0	7/10	70.0
	SD	0	0.0	2	20.0	0	0.0	1	10.0	3/10	30.0

SS: seroprevalence survey; **SD:** spontaneous demand; **n:** number of patients; **T:** total number of patients in the age range.
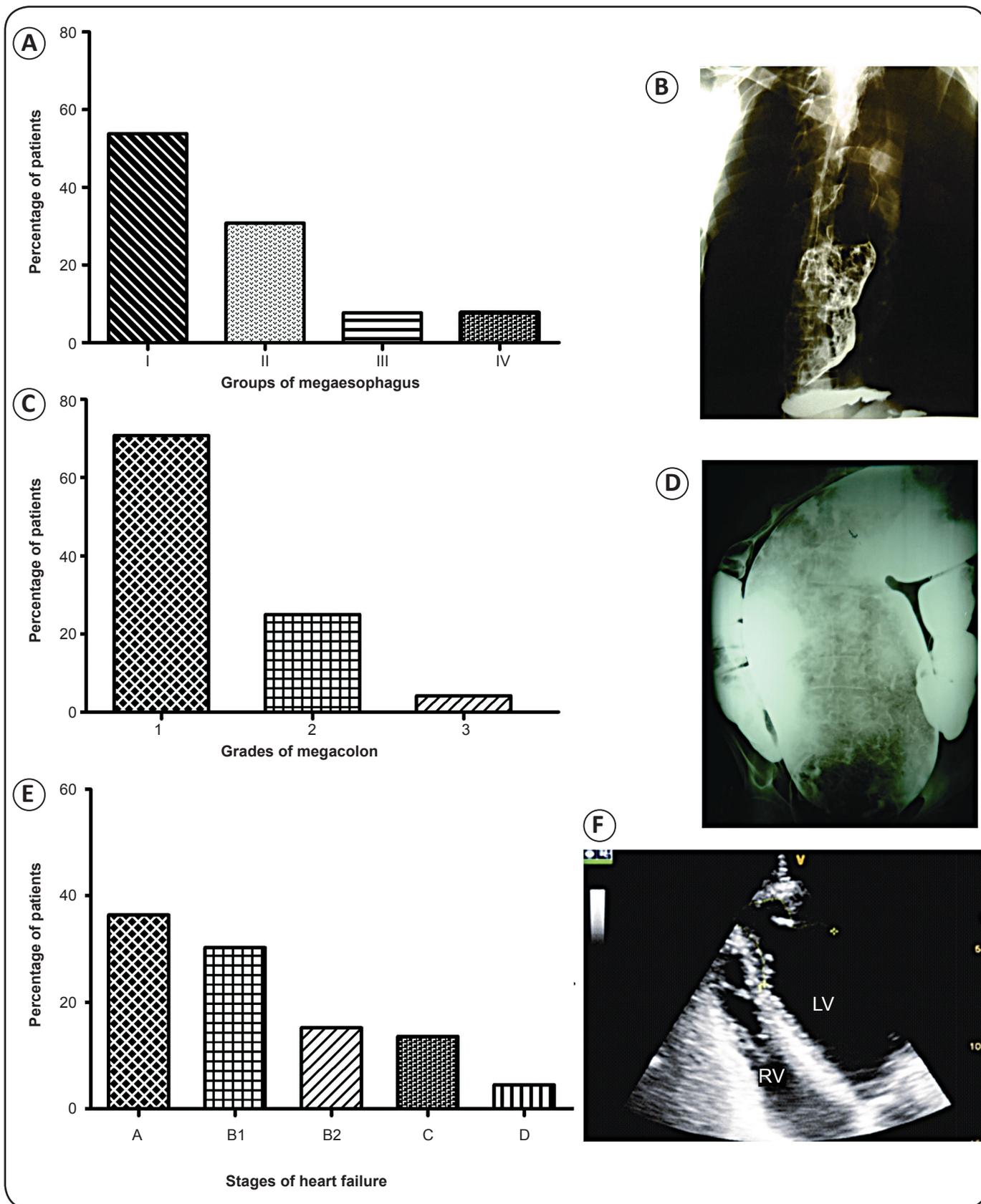
FIGURE 2 - The clinical evolution of Chagas disease. A. Patients were categorized into different groups of megaesophagus, and B. A contrast radiography image of the characteristic esophagus appearance is shown. C. Patients were categorized into different grades of megacolon, and D. A contrast radiography image of the characteristic colon appearance is shown. E. Patients were categorized according to heart failure stage, and F. Echocardiography reveals a characteristic left ventricle apical aneurysm. **LV**: left ventricle; **RV**: right ventricle.

with grade 0 sigmoid colon also experienced constipation. In contrast, patients with the digestive/cardiodigestive forms exhibited a high probability of constipation (PR: 2.56; 95% CI: 1.24-3.87; p = 0.001), compared to patients who had the indeterminate form. The smallest sigmoid colon diameter was 2.5cm, the largest diameter was 19.0cm, and the mean diameter was 4.9 ± 1.8cm. The smallest rectum diameter was 3.0cm, the largest diameter was 15.0cm, and the mean diameter was 5.7 ± 1.4cm. Among the patients with different megacolon grades, 7 patients also exhibited megaesophagus. Colon contrast radiography revealed significant dilatation of the sigmoid colon and rectum in patients with chronic constipation, and abdominal palpation revealed the presence of fecal impaction (**Figure 2D**).

Heart failure functional classification revealed that 7.5% (14/186) of the participants had dyspnea, with 8 (57.1%) of these patients being class I, 2 (14.3%) patients being class II, 1 (7.1%) patient being class III, and 3 (21.5%) patients being class IV. The stage classification that was adapted for ChD revealed that 36.4% (24/66) of patients were in stage A, 30.3% (20/66) of patients were in stage B1, 15.2% (10/66) of patients were in stage B2, 13.6% (9/66) of patients were in stage C, and 4.5% (3/66) of patients were in stage D (**Figure 2E**). Symptoms of palpitation at rest were identified in 15% (28/186) of the participants, and echocardiography in the modified apical view revealed left ventricular aneurysm in patients with chagasic cardiomyopathy and stage C heart failure (**Figure 2F**).

Although electrocardiographic changes are not always suggestive of cardiac ChD, these changes were detected in 48.9% (91/186) of the participants, although they were not associated with any specific cardiac symptoms. Right bundle branch block (RBBB) was present in 30.8% (28/91) of the patients with electrocardiographic changes. Low-amplitude signals in the QRS complex were identified in 27.5% (21/91) of these patients, and the association of RBBB with left anterior fascicular block (LAFB) was observed in 17.6% (16/91) of these patients (**Figure 3**).

Echocardiography revealed left and right ventricle systolic dysfunction in 14% (26/186) and 7% (13/186) of the participants, respectively. Among the 26 patients with left ventricle systolic dysfunction, the dysfunction was discrete in 42.3% (11/26) of the patients, moderate in 50% (13/26) of the patients, and severe in 7.7% (2/26) of the patients. Changes in the left ventricle segment contractility were observed in 33.9% (63/186) of the participants, with 46.7% (28/60) of patients having the cardiac form, 66.7% (10/15) of patients having the cardiodigestive form, 22.9% (22/96) of patients having the indeterminate form, and 20% (3/15) of patients having the digestive form. The most frequently affected left ventricle segment was the apex (31/63; 49.2%), which was followed by the posteroinferior segment (21/63; 33.3%) and global involvement (4/63; 6.3%). Left ventricular apical aneurysm was detected in 10.8% (20/186) of the participants, and 55% (11/20) of these patients had the cardiac form, 20% (4/20) of
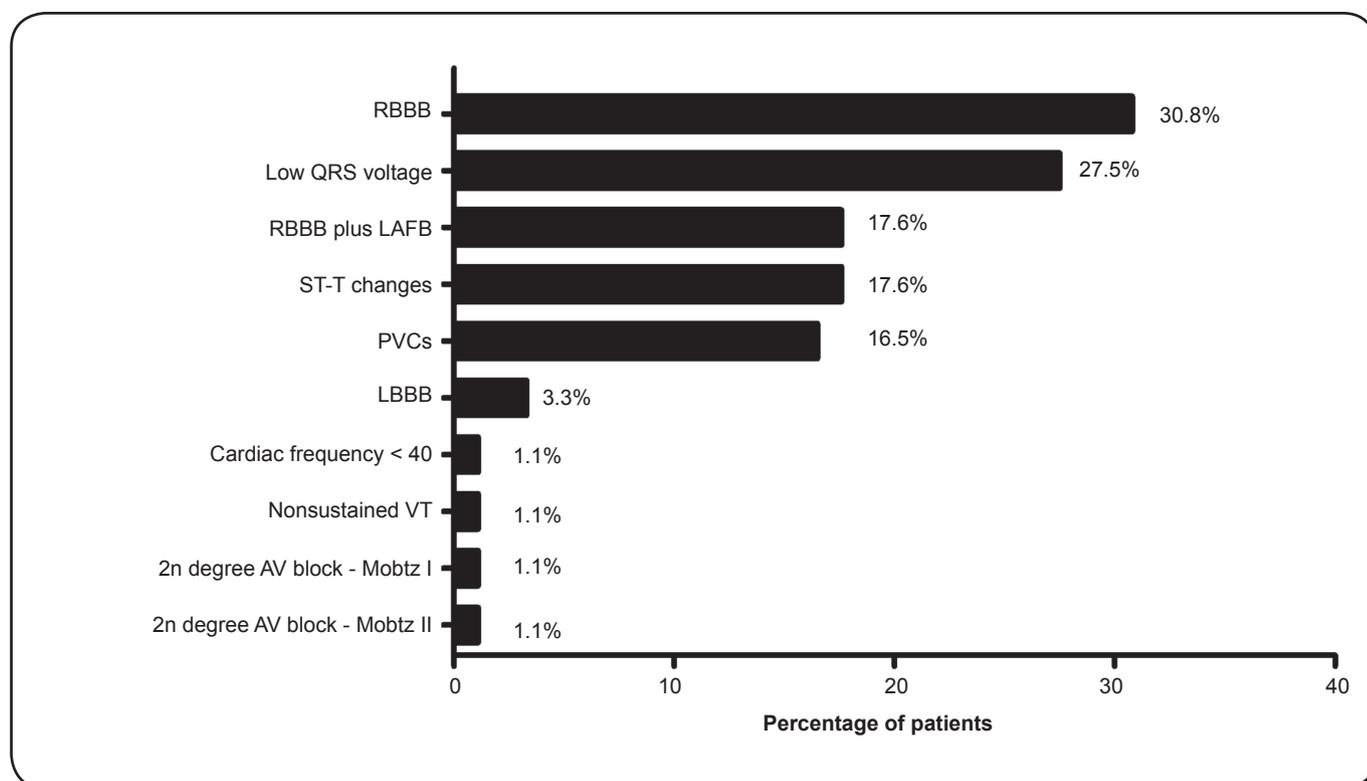
FIGURE 3 - Distribution of the ten most frequent electrocardiographic changes among 91chagasic patients. Note: more than one change was possible in the same patient. **RBBB:** right bundle branch block; **LAFB:** left anterior fascicular block; **PVCs:** premature ventricular complexes; **LBBB:** left bundle-branch block; **VT:** ventricular tachycardia; **2n:** second; **AV:** atrioventricular.

these patients had the cardiodigestive form, 20% (4/20) of these patients had the indeterminate form, and 5% (1/20) of these patients had the digestive form. Right ventricular apical aneurysm was diagnosed in 5.4% (10/186) of the participants.

DISCUSSION

Studies regarding chronic ChD in endemic areas have typically been conducted by stratifying the clinical forms using the patients' clinical symptoms, and without the use of contrast radiography. This is the first study to characterize the clinical forms of ChD and the severity of its clinical manifestations among patients with chronic infection in Western RN. Our findings revealed that very few participants were <30 years old, which is likely due to recent improvements in rural dwellings, vector control programs[25], and population movement into more urban areas. The small number of participants who were >60 years old may be explained by the evolution of the indeterminate form in to a known clinical form (e.g., the cardiac form), which would increase the risk of fatal complications[26].

We did not observe any significant difference in the clinical forms according to the testing type for each age range. However, the indeterminate form of ChD was predominant (>50% of the participants), which confirms the findings of other studies that examined outpatients[27] [28] [29]. Nevertheless, the characterization of ChD is difficult in rural populations, as many small Brazilian towns do not have the equipment for classic barium enema radiography[19]. Therefore, most authors have not radiographically examined the colon, and have assumed that treatment of the digestive manifestations of ChD should be directed to the symptomatic and more advanced forms[30]. This approach likely results in underestimation of the prevalences for the digestive and cardiodigestive forms. Thus, clinical symptoms (e.g., dysphagia and constipation) are insufficient to identify patients with early-stage digestive and cardiodigestive forms. In this context, early identification of digestive lesions can motivate lifestyle changes (e.g., in hygiene and diet) and indicate multidisciplinary care, which might prevent progression to a more severe form of ChD.

Megaesophagus was detected at different stages in the present study, which supports the data from other Brazilian regions[31] and studies that reported high prevalences of the digestive form in central Brazil and other South American countries[32]. Although cases of grade 2-3 megacolon were diagnosed in the present study, the majority of cases were grade 1 with a sigmoid colon diameter of >5.0cm. Using the same technique, but only considering megacolon with a sigmoid colon diameter of ≥7.0cm, resulted in a lower prevalence[33]. Thus, all patients with grade 2-3 megacolon had ChD, although patients with grade 1 megacolon may or may not exhibit intestinal involvement of ChD. Various factors may be involved in the genesis of the digestive form, which include intrinsic denervation that is triggered by *T. cruzi* along the nerve plexus of the esophagus and intestine, which and which can result in denervation of the autonomic parasympathetic system[34]. This denervation affects these organs' functions, and especially those

of the esophagus and sigmoid colon, which require coordination to propel their contents through their distal sphincters. The climax of megaesophagus and megacolon is the decompensated stage of the disease[35], which can be triggered by various parasite strains[36] or a cross-reaction between *T. cruzi* antigens and the host tissues[37].

The most important clinical presentation of chronic ChD is CCC, which has been detected in patients with similar morbidity rates through different endemic areas of Brazil and Colombia[38] [39]. However, lower morbidity rates are observed in other endemic regions of Latin America[40] [41]. In the present study, cardiomegaly was exclusively present with the cardiac and cardiodigestive forms, which is in agreement with previously reported data[42] [43]. However, the low sensitivity of chest radiography for identifying cardiac involvement is related to the right ventricle being one of the cardiac chambers that is most affected by CCC[44]. As this is the most anterior chamber of the heart, its enlargement may not noticeably increase the cardiothoracic ratio, which precludes the identification of the cardiomegaly.

The participants with ChD exhibited all functional classifications and stages of heart failure, although the patients were predominantly functional class I and stage A, which is characteristic of an outpatient sample. However, the presence of patients in functional classes III-IV and stages C-D indicates that ChD in this region is more severe than findings from northern Brazil[45]. In this context, CCC is associated with a worse prognosis and a survival rate that is one-half of the rates for cardiomyopathies of non-inflammatory etiology (e.g., dilated cardiomyopathy and ischemic heart disease)[46]. Studies in Brazil and Venezuela have also reported that higher functional classes are associated with higher mortality rates among patients with CCC[47] [48], with sudden death, heart failure, and ischemic stroke being the main mechanisms of death in patients with ChD[49] [50].

Our findings regarding electrocardiographic changes, such as RBBB and LAFB, are in agreement with the previous studies and are the most characteristic changes of the disease in endemic areas[51]. The higher prevalence of RBBB, compared to left bundle branch block, is likely related to the anatomy of the heart's conduction system, as in the classical description[52]. The right branch of the His-Purkinje system is long, slender, and presents a large intramyocardial course, while the left branch has many sub-branches and takes a subendocardial course along its entire length. Ventricular arrhythmia has been previously described[53], and may be caused by cardiac conduction system lesions that are related to the degree of ventricular dysfunction and to the increased risk of cardiovascular death[54].

Changes in segmental myocardial contractility were predominantly in the left ventricular apex and posterior basal segment, even in patients with the indeterminate form, which confirms the findings of previous studies[55] [56]. Interestingly, the indeterminate form was assigned to patients who fulfilled the related criteria in the present study, even if they exhibited contractility segmental changes during echocardiography. However, we believe that these patients should be classified as having the cardiac form, as this classification may facilitate the

use of more effective prophylactic and/or therapeutic measures. Furthermore, left ventricular apical aneurysm was more common in this study than the reported frequency in central Brazil[43], and was less common than the reported frequency in southeastern Brazil[57]. Although left ventricular apical aneurysm is not characteristic of the cardiac form, it was more common among patients with this clinical form, which may be related to its severity and the increased risk of ischemic stroke and/or death among these patients[58] [59].

Unfortunately, the factors that determine the variability of the clinical forms of ChD, pathogenesis, and patterns of development remain unclear. It is possible that these changes may be associated with the wide geographical dispersion of homogeneous *T. cruzi* genotypes from different parasite sources and groups that have been identified throughout the municipalities of RN[60]. As a result, the forms of chronic ChD seem to be directly associated with discrete typing units of *T. cruzi*, which might explain the observed differences in the expression of anti-inflammatory and pro-inflammatory cytokines, and the specific immune responses[61]. Furthermore, this variability may depend on tissue-specific responses and the intensities of the parasitism, inflammatory response, and immune response[62] [63]. Moreover, familial aggregation of CCC cases has been well documented, which suggests that genetic components are involved in patients' susceptibility to cardiomyopathy[64].

In conclusion, among patients from Western RN, we believe that approximately one-quarter of patients who are diagnosed with the indeterminate form of ChD should be considered to potentially have the cardiac form or silent heart disease. This approach would decrease the prevalence of the indeterminate form and alter the therapeutic management of these patients, which might subsequently reduce the prevalence of more severe complications. Furthermore, patients' clinical symptoms may not be sufficient to confirm or rule out a diagnosis of cardiac and/or digestive involvement in chronic ChD. Moreover, isolated digestive and cardiodigestive forms were detected in both symptomatic and asymptomatic patients, with different groupings and grades of megaesophagus and megacolon. Thus, while ignoring any potential underdiagnosis, approximately one-third of patients were diagnosed with the cardiac form of ChD, which involved different types and degrees of atrioventricular and ventricular block, several segmental contractility alterations, and varying degrees of heart failure. These findings indicate that the cardiac form may be the most relevant form of chronic ChD, as it was responsible for more severe clinical outcomes. Nevertheless, prospective cohort studies are needed to confirm our findings in this endemic area, especially among patients with the indeterminate form. Furthermore, studies are needed to evaluate the potential immunological, clinical, and/or genetic markers from the host and/or parasite, which may contribute to improving the prognosis of these clinical manifestations. Moreover, interventional studies are needed to examine the etiology of, and damage due to ChD- related manifestations in the cardiovascular and digestive systems.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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