Temporal changes in the clinical-epidemiological profile of patients with Chagas disease at a referral center in Brazil

Alejandro Marcel Hasslocher-Moreno[1], Roberto Magalhaes Saraiva[1], Pedro Emmanuel Alvarenga Americano do Brasil[1], Luiz Henrique Conde Sangenis[1], Sergio Salles Xavier[1], Andréa Silvestre de Sousa[1],[2], Gilberto Marcelo Sperandio-da-Silva[1], Fernanda de Souza Nogueira Sardinha Mendes[1], Andréa Rodrigues da Costa[1], Marcelo Teixeira de Holanda[1], Henrique Horta Veloso[1], Flavia Mazzoli-Rocha[1], Fernanda Martins Carneiro[1], Luciana Fernandes Portela[1] and Mauro Felippe Felix Mediano[1]

[1]. Fundação Oswaldo Cruz, Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, RJ, Brasil. [2]. Universidade Federal do Rio de Janeiro, Faculdade de Medicina, Rio de Janeiro, RJ, Brasil.

Abstract

Introduction: We aimed to describe the sociodemographic, epidemiological, and clinical characteristics of patients with chronic Chagas disease (CD) at an infectious disease referral center. Changes in patient profiles over time were also evaluated. Methods: This retrospective study included patients with CD from November 1986–December 2019. All patients underwent an evaluation protocol that included sociodemographic profile; epidemiological history; anamnesis; and physical, cardiologic, and digestive examinations. Trend differences for each 5-year period from 1986 to 2019 were tested using a nonparametric trend test for continuous and generalized linear models with binomial distribution for categorical variables. Results: A total of 2,168 patients (52.2% women) were included, with a mean age of 47.8 years old. White patients with low levels of education predominated. The reported transmission mode was vectorial in 90.2% of cases. The majority came from areas with a high prevalence (52.2%) and morbidity (67.8%) of CD. The most common clinical presentation was the indeterminate form (44.9%). The number of patients referred gradually decreased and the age at admission increased during the study period, as did the patients’ levels of education. Conclusions: The clinical profile of CD is characterized by a predominance of the indeterminate form. Regarding the patients who were followed up at the referral center, there was a progressive increase in the mean age and a concomitant decrease in the number of new patients. This reflects the successful control of vector and transfusion transmission in Brazil as well as the aging population of patients with CD.

Keywords: Chagas disease. Epidemiologic studies. Cohort studies.

INTRODUCTION

Chagas disease (CD) is considered a neglected tropical disease by the World Health Organization, with an estimated 6-7 million people infected worldwide. The implementation of CD vector and transfusion control programs in the 1980s significantly decreased the rate of disease transmission in Latin American countries. However, several challenges have hampered the effective implementation of disease surveillance due to new outbreaks of orally transmitted CD in endemic countries and the possibility of vertical transmission even in nonendemic areas. Integrated surveillance and healthcare interventions are now directed at a large contingent of patients already infected with Trypanosoma cruzi (T. cruzi), a significant portion of whom may develop chronic Chagas heart disease, a major determinant of morbidity and mortality. Owing to rapid globalization, CD cases are no longer restricted to Latin America, constituting a new challenge in the battle against this disease. In Brazil, the process of CD urbanization in the last decades of the 20th century has increased the number of patients with CD in urban cities, which has increased the demand for local health care services. This new urban context has also prompted the modification of the clinical-epidemiological profile of patients with CD, evidenced by changes in work activities, food consumption patterns, increased age, significant prevalence of comorbidities, and social determinants as a whole.

Corresponding author: Dr. Alejandro Marcel Hasslocher-Moreno. e-mail: alejandro.hasslocher@gmail.com https://orcid.org/0000-0002-5430-7222 Received 28 January 2021 Accepted 27 April 2021
The first national serological survey that evaluated the prevalence of CD in Brazil aimed to quantify the endemic transmission of CD. This study was conducted in rural areas of Brazil between 1975 and 1980, with an estimated national seroprevalence CD rate of 4.22%. A second national serological CD survey² conducted between 2001 and 2008 analyzed the seroprevalence in children aged up to five years, which only reported a CD serum positivity rate of 0.03%. The later survey highlighted the impact of the CD control measures implemented in previous decades, which led the Pan American Health Organization to grant Brazil an International Certificate of Elimination of CD transmission by Triatoma infestans and blood transfusions. In Brazil, the current estimated prevalence of CD is much lower than that reported in the 1970s. However, the estimates reported in previous studies on the prevalence of CD are imprecise and subject to criticism due to the lack of standardized data collection and heterogeneity in most of these estimates. Therefore, at present, the exact number of Brazilians with CD is unknown, although it is projected to be between 1 and 1.5 million people. Currently, new cases of CD in Brazil are mostly restricted to the Legal Amazon, with oral being the primary route of transmission, particularly through the consumption of a local fruit called açai when it is contaminated with T. cruzi.

With globalization, the disease has spread to countries in the Northern Hemisphere, particularly in the United States and Spain. Because of this new geographic rearrangement of CD, studies describing the clinical and epidemiological profile of patients with chronic CD have been conducted in urban healthcare facilities in both endemic and nonendemic regions. Some of these facilities have also become reference centers for the treatment of CD that offer specialized care.

The Evandro Chagas Institute of Infectious Diseases of the Oswaldo Cruz Foundation (INI-Fiocruz), located in Rio de Janeiro, Brazil, is a national reference center for the treatment and research of infectious and tropical diseases covered by the Sistema Único de Saúde (SUS), the Brazilian National Health Service. INI-Fiocruz receives patients from various regions of the country and offers comprehensive and multidisciplinary care to patients with CD. To date, few studies have addressed the clinical and epidemiological profiles of the Brazilian population with chronic CD. The present study aimed to describe the clinical and epidemiological profiles of a historical cohort of patients with chronic CD followed up at the INI-Fiocruz.

**METHODS**

This was a retrospective descriptive study including patients diagnosed with chronic CD who were referred to the outpatient center of the INI-Fiocruz between November 1986 and December 2019. Clinical and epidemiological data were retrieved from the medical records.

After the serological diagnosis of chronic CD was confirmed by two simultaneous reactive serological techniques, all patients underwent an initial evaluation protocol, which included sociodemographic information (age, level of education, and race); epidemiological history (transmission mode, country and state of origin, time away from endemic area); clinical anamnesis; a physical examination focused on chronic CD-related cardiovascular and digestive signs and symptoms; a 12-lead electrocardiogram (ECG); and a two-dimensional Doppler echocardiogram. According to the presence of symptoms related to the digestive form of CD, the following examinations were performed: upper gastrointestinal endoscopy, esophagography, colonoscopy, and a contrast barium enema. The level of education was categorized based on the number of years of formal study as illiterate, < 9 years, or > 9 years. Race was self-reported and classified as white, black, mulatto, or indigenous.

Clinical forms of chronic CD were retrospectively classified according to the 2nd Brazilian Consensus on Chagas Disease. The cardiac form was classified into A, B1, B2, C, or D stages, and the digestive form was classified into megaesophagus, megacolon, or both megaesophagus and megacolon. Information about the region of origin was classified according to the prevalence and morbidity of chronic CD, which was based on serological data from national prevalence surveys and a national electrocardiographic survey. The prevalence was categorized as low (< 2%), medium (2%-4%), high (> 4%), and nonendemic (Rio de Janeiro and Espírito Santo), whereas the levels of morbidity by area were categorized as low (normal ECGs > 50%), high (normal ECGs < 50%), and nonendemic areas (Rio de Janeiro and Espírito Santo).

**Data analysis**

Descriptive statistics are presented as means (standard deviations) for continuous and absolute frequencies (percentages) for categorical variables. Trend differences for each 5-year period from 1986 to 2019 were tested using a nonparametric trend test for continuous (nptrend command in Stata 13.0) variables and using generalized linear models with binomial distribution for categorical variables (binreg command in Stata 13.0). The independent variable was the 5-year period, and the dependent variables were the binary classes of each categorical variable. The link choice was selected according to the lowest Bayesian information criterion. Statistical significance was set at a 2-tailed p-value of <0.05. All statistical analyses were performed using Stata software (version 13.0; StataCorp LP.; College Station, TX, USA).

**Ethics approval**

This study was approved by the INI-Fiocruz Research Ethics Committee (number CAAE:35748820.1.0000.5262) on September 2, 2020 and was carried out in accordance with the 1964 Declaration of Helsinki and its later amendments. The need for informed consent was waived considering the retrospective nature of the study.

**RESULTS**

The characteristics of the patients referred to the INI-Fiocruz are shown in Table 1. A total of 2,168 patients (52.2% women) were included from August 1986 to December 2019, with a mean age of 47.8 years (range, 13-88 years). The plurality self-reported as white (49.8%) and had < 9 years of education (80.5%). The reported transmission mode was vectorial in 90.2% of the patients. The majority, originating from Brazil (98.7%), were born in areas with high prevalence (52.2%) and morbidity (67.8%) of CD, mostly Minas Gerais and Bahia, and had moved away from endemic areas for >20 years (65.8%). The indeterminate form was the most
TABLE 1: Characteristics of patients admitted at the INI-Fiocruz (n=2,168).

| Variable                        | Mean (SD) Minimum-Maximum or Frequency (%) | Variable                        | Mean (SD) Minimum-Maximum or Frequency (%) |
|--------------------------------|--------------------------------------------|---------------------------------|--------------------------------------------|
| Age (years)                    | 47.8 (12.8) 13-88                          | Region of origin according to morbidity |                                            |
| Female sex                     | 1,132 (52.2)                               | Nonendemic Chagas disease       | 102 (4.7)                                 |
| Race                           |                                            | Low Chagas disease morbidity    | 596 (27.5)                                |
| White                          | 1,080 (49.8)                               | High Chagas disease morbidity   | 1,470 (67.8)                              |
| Mulatto                        | 815 (37.6)                                 | Time away from endemic area     |                                            |
| Black                          | 261 (12.0)                                 | None                            | 82 (3.8)                                  |
| Indigenous                     | 12 (0.6)                                   | 1 to 20 years                   | 577 (26.6)                                |
| Level of education             |                                            | >20 years                       | 1,426 (65.8)                              |
| Illiterate                     | 448 (20.7)                                 | Nonendemic area                 | 83 (3.8)                                  |
| < 9 years                      | 1,297 (59.8)                               | Clinical form (n=2,136)         |                                            |
| > 9 years                      | 423 (19.5)                                 | Indeterminate                   | 960 (44.9)                                |
| Transmission mode              |                                            | Cardiac                         | 924 (43.3)                                |
| Vectorial                      | 1,956 (90.2)                               | Digestive                       | 125 (5.9)                                 |
| Transfusion                    | 124 (5.7)                                  | Cardiodigestive                 | 127 (5.9)                                 |
| Vertical                       | 62 (2.9)                                   | Clinical cardiac stages\(^a\) (n=2,136) |                                            |
| Oral                           | 2 (0.1)                                    | None                            | 1085 (50.8)                               |
| Not identified                 | 24 (1.1)                                   | Stage A                         | 467 (21.9)                                |
| Country of origin              |                                            | Stage B1                        | 250 (11.7)                                |
| Brazil                         | 2,140 (98.7)                               | Stage B2                        | 108 (5.1)                                 |
| Other Latin American countries | 28 (1.3)                                   | Stage C                         | 206 (9.6)                                 |
| Region of origin according to prevalence |                        | Stage D                         | 20 (0.9)                                  |
| Nonendemic Chagas disease      | 102 (4.7)                                  | Clinical digestive presentation  |                                            |
| Low Chagas disease prevalence  | 260 (12.0)                                 | None                            | 1914 (88.3)                               |
| Medium Chagas disease prevalence | 674 (31.1)                              | Megaeosphagus                   | 160 (7.4)                                 |
| High Chagas disease prevalence | 1,132 (52.2)                               | Megacolon                       | 54 (2.5)                                  |
|                               |                                            | Megaeosphagus and megacolon     | 40 (1.8)                                  |

\(^a\)According to the 2\(^{nd}\) Brazilian Consensus on Chagas Disease\(^a\). Abbreviations: INI-Fiocruz: The Evandro Chagas Institute of Infectious Diseases of the Oswaldo Cruz Foundation; SD: standard deviation.

The common clinical presentation (44.9%), and stage A (21.9%) was the most common clinical presentation of the cardiac form. Only a minority of patients had digestive or cardiodigestive forms (11.7%), with 7.4% presenting with megaeosphagus, 2.5% with megacolon, and 1.8% with both megaeosphagus and megacolon.

The characteristics of patients referred to the INI-Fiocruz for each 5-year period are shown in Table 2. The number of patients referred increased from the 1986-1990 period (n=138) to the 2000-2004 period (n=569) and then gradually decreased until the 2015-2019 period (n=162). The age at the time of referral increased during all study periods (p<0.001). The number of white patients decreased over time (p<0.001), whereas the number of mulatto (p<0.001) and black (p<0.001) patients increased. Illiterate patients decreased over time (p=0.02), and those with >9 years of education increased (p=0.008). The vectorial and oral transmission modes increased over the study period (p<0.001 for both) while transfusion transmission decreased (p<0.001).

The percentage of patients that originated from low CD prevalence areas increased over the study period (p<0.001), while patients originating from high CD prevalence areas decreased (p<0.001). The same pattern was observed for the CD morbidity areas, with an increase in the percentage of patients who originated from low CD morbidity areas (p<0.001) and a decrease in patients from high CD morbidity areas (p<0.001). The number of patients who had moved away from an endemic area for <20 years increased (p=0.002) with a concomitant decrease of patients that had moved away for >20 years (p=0.005).

The clinical presentation characteristics also changed over the study period, with an increase in the digestive form (p<0.001) and a decrease in the indeterminate form (p<0.001). Considering the clinical cardiac stages, there was an increase in the percentage of patients admitted with stage C (p<0.001), however there were no changes observed in the other stages.
TABLE 2: Characteristics of patients admitted at the INI-Fiocruz for each 5-year period (n=2,168)

| Variable | 1986-1989 (n=138) | 1990-1994 (n=295) | 1995-1999 (n=498) | 2000-2004 (n=569) | 2005-2009 (n=307) | 2010-2014 (n=199) | 2015-2019 (n=162) | p-value
|----------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|---------
| Age (years) | 44.3 (10.6) | 45.3 (12.0) | 45.9 (11.3) | 46.3 (12.2) | 49.7 (14.1) | 53.5 (12.9) | 57.1 (12.9) | <0.001
| Female sex | 22 (73) | 19 (65) | 16 (84) | 13 (84) | 15 (87) | 19 (85) | 21 (88) | 0.04
| Race | 71 (51.8) | 168 (57.0) | 252 (50.60) | 283 (49.7) | 158 (51.5) | 116 (58.3) | 84 (51.9) | 0.93
| Level of education | 32 (23.2) | 52 (17.6) | 141 (28.3) | 110 (19.3) | 50 (16.3) | 34 (17.1) | 29 (17.9) | 0.02
| Transmission mode | 86 (62.3) | 182 (61.7) | 268 (53.8) | 350 (61.5) | 209 (68.1) | 117 (58.8) | 85 (52.2) | 0.87
| Country of origin | 20 (14.5) | 61 (20.7) | 89 (17.9) | 109 (19.2) | 48 (15.6) | 48 (24.1) | 48 (29.6) | 0.008
| Region of origin according to prevalence | 119 (86.2) | 254 (86.1) | 435 (87.4) | 525 (92.3) | 285 (92.8) | 189 (95.0) | 149 (92.0) | <0.001
| Nonendemic Chagas disease | 16 (11.6) | 29 (9.8) | 45 (9.0) | 16 (2.8) | 8 (2.6) | 3 (1.5) | 7 (4.3) | <0.001
| Low Chagas disease prevalence | 1 (0.7) | 8 (2.7) | 13 (2.6) | 24 (4.2) | 9 (2.9) | 4 (2.0) | 3 (1.9) | 0.81
| Medium Chagas disease prevalence | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | <0.001
| High Chagas disease prevalence | 2 (1.5) | 4 (1.4) | 5 (1.0) | 4 (0.7) | 5 (1.6) | 3 (1.5) | 1 (0.6) | 0.84
| Region of origin according to morbidity | 135 (97.8) | 289 (98.0) | 491 (98.6) | 565 (99.3) | 302 (98.4) | 197 (99.0) | 161 (99.4) | 0.15
| Nonendemic Chagas disease area | 3 (2.2) | 6 (2.0) | 7 (1.4) | 4 (0.7) | 5 (1.6) | 2 (1.0) | 1 (0.6) |<0.001
| Medium Chagas disease area | 7 (5.1) | 17 (5.8) | 58 (11.7) | 74 (13.0) | 42 (13.7) | 38 (19.1) | 24 (14.8) | <0.001
| Low Chagas disease morbidity area | 37 (26.8) | 93 (31.5) | 137 (27.5) | 186 (32.7) | 101 (32.9) | 56 (28.1) | 64 (39.5) | 0.04
| High Chagas disease morbidity area | 89 (64.5) | 167 (56.6) | 284 (57.0) | 278 (48.9) | 150 (48.9) | 97 (48.7) | 67 (41.4) | <0.001
| Time away from endemic area | 5 (3.7) | 18 (6.1) | 19 (3.8) | 31 (5.5) | 14 (4.6) | 8 (4.0) | 7 (4.3) | 0.78
| Clinical form (n=2,136) | 111 (80.4) | 210 (71.2) | 349 (70.1) | 379 (66.6) | 198 (64.5) | 127 (63.8) | 96 (59.3) | <0.001
| Indeterminate | 56 (40.6) | 135 (45.8) | 264 (53.0) | 280 (51.2) | 107 (35.9) | 66 (33.3) | 52 (32.1) | <0.001
| Cardiac | 68 (49.3) | 142 (48.1) | 204 (41.0) | 221 (40.4) | 140 (47.0) | 81 (40.9) | 68 (42.0) | 0.20
| Digestive | 6 (4.3) | 12 (4.1) | 14 (2.8) | 26 (4.8) | 23 (7.7) | 28 (14.2) | 16 (9.9) | <0.001
| Cardiovascular | 8 (5.8) | 6 (2.0) | 16 (3.2) | 20 (3.6) | 28 (9.4) | 23 (11.6) | 26 (16.0) | <0.001
| Clinical cardiac stages* (n=2,136) | 36 (26.1) | 58 (19.7) | 104 (20.9) | 129 (23.6) | 66 (22.2) | 33 (16.7) | 41 (25.3) | 0.93
| Stage A | 17 (12.3) | 45 (15.3) | 48 (9.6) | 48 (8.8) | 40 (13.4) | 32 (16.2) | 20 (12.4) | 0.59
| Stage B | 13 (9.4) | 16 (5.4) | 26 (5.2) | 21 (3.8) | 17 (5.7) | 8 (4.0) | 7 (4.3) | 0.10
| Stage C | 9 (6.5) | 21 (7.1) | 39 (7.8) | 38 (6.0) | 44 (14.8) | 30 (15.2) | 25 (15.3) | <0.001
| Stage D | 1 (0.7) | 8 (2.7) | 3 (0.6) | 5 (0.9) | 1 (0.3) | 1 (0.5) | 1 (0.6) | 0.07
| Clinical digestive presentation | 8 (5.8) | 14 (4.8) | 19 (3.8) | 26 (4.8) | 35 (11.4) | 33 (16.6) | 25 (15.4) | <0.001
| Megacolon | 3 (2.2) | 3 (1.0) | 8 (1.6) | 12 (2.1) | 7 (2.3) | 10 (5.0) | 11 (6.6) | <0.001
| Megaesophagus and megacolon | 3 (2.2) | 1 (0.3) | 3 (0.6) | 10 (1.8) | 9 (2.9) | 8 (4.0) | 6 (3.7) | 0.001

*According to the 2nd Brazilian Consensus on Chagas Disease (2015)\textsuperscript{4.1, 4.2}. Abbreviations: INI-Fiocruz: The Evandro Chagas Institute of Infectious Diseases of the Oswaldo Cruz Foundation; SD: standard deviation.
DISCUSSION

The INI-Fiocruz is a reference center for CD that provides diagnostic interpretation for patients referred from blood banks, primary and secondary care units, private health services, or by spontaneous demand, and it offers integral and multidisciplinary clinical care to patients with CD. In the present study, most patients were long-time residents of the metropolitan region of the state of Rio de Janeiro and who had been away from endemic areas for many years. Although patients lived in Rio de Janeiro, most were migrants from 19 Brazilian states, predominantly from Bahia and Minas Gerais, which constitutes almost 50% of the studied cohort. A study conducted in the 1960s that evaluated natural-born Brazilian citizens with chronic CD residing in the city of Rio de Janeiro reported the same prevalence. A similar profile was reported in a study published by Ianni et al. 20 of patients living in the city of São Paulo, indicating the migratory profile of the CD-infected population. Dias et al. 28 studied the status of chronic CD in the Northeastern region and reported that the state of Bahia had the highest prevalence of the disease in the region, which is similar to that of the state of Minas Gerais. They also discussed the social causes of the strong emigration to large urban centers in the Southeastern region, which justifies the significant number of people from Minas Gerais and Bahia in the present cohort. Besides, 1.3% of the patients come from other South American countries, predominantly from Bolivia, a country with a prevalence rate of 4.4% for chronic CD among migrants. 29

The vector route is the most probable transmission mechanism. The majority of patients reported living in rural areas in houses made of mud and straw and were aware of the triatomine bug, while some even reported intradomicile coexistence with the insect, yet only a few remembered that they had been bitten. Most patients claimed that they were unaware that the triatomine bug was a health risk. This finding indicates the knowledge deficit regarding CD among these patients, which reinforces why most of them do not consider living with triatomine bugs as a threat to their health. Several studies on transmission mechanisms have also reported the vector route as the primary route of disease transmission. 12, 13, 20

This cohort showed a slight predominance of women (52.2%), characterizing a balanced cohort in terms of sex and reflecting the distribution of men and women in the Brazilian population, which is 51% women and 49% men according to the Brazilian Institute of Geography and Statistics. In previous studies, women accounted for 46% to 84% of the total study population. 13-17, 20-23, 34, 36, 37

In the center where this study was conducted, white patients predominated (49.8%). Gontijo et al. 20 reported the predominance of mulattos (43%) in Minas Gerais, while Gasparim et al. 13 reported 51.1% of whites in Paraná, suggesting ethnic differences by geographic location. Most patients (59.8%) had low levels of education. This is attributed to the origin of the patients, usually born in rural areas without access to formal education. Gontijo et al. 20 showed that 84% of patients examined in a reference outpatient clinic in Belo Horizonte, Brazil were either illiterate or semi-illiterate. Pereira et al. 34 reported that 40.2% of patients in a reference center in Fortaleza were illiterate. The number of white patients decreased over time, whereas the number of mulatto and black patients increased. The number of illiterate patients decreased and those with >9 years of education increased. These data suggest that the Brazilian population of low socioeconomic strata has gained access to both health services and formal education in the last few decades.

The mean age of the patients was 47.8 years old. Field studies performed between 1960 and the early 2000s reported a progressive increase in the mean age of patients with chronic CD over time, from less than 25 to 45 years. 11-13 Studies on the clinical epidemiological profile of patients with chronic CD in urban centers reported that the mean age showed the same increasing trend in the last decades, ranging from 37.7 to 67.5 years. 12, 13, 15, 20, 22. Studies conducted in endemic regions of the Northern Hemisphere, where patients migrated from South America, especially Bolivia and Central America, reported younger patients with chronic CD with a mean age ranging from 28.5 to 47 years. 16-18, 34-37, reflecting the lack of CD vectorial transmission control in their countries of origin and that CD vectorial transmission remained active in rural areas. The present study showed a progressive increase over time in the age of patients who were included in the study cohort during the 5-year intervals of the study period, with the mean age increasing from 44.3 to 57.1 years. Following the increase in the age of patients with CD, there was an inverse decrease in the number of new patients requesting care at the INI-Fiocruz. An ascending temporal curve was observed between 1986 and 1994, stabilizing between 1995 and 2004, and decreasing in 2005. This behavior may reflect the successful control of vector transmission by Triatoma infestans as well as by blood transfusions in Brazil; however, this may also indicate the decrease in migration from rural to urban areas verified in recent decades due to the decreased economic power of urban cities consequently attracting fewer people.

Studies on the clinical form of CD conducted in urban areas have shown that the cardiac form predominates, with a prevalence ranging from 56% to 66%. 12, 16, 22, 24. Few studies have reported a higher incidence of the indeterminate form, varying between 56% and 81.6%. 67, 20. These differences in the prevalence of clinical forms are attributed to the profile of the healthcare unit. CD reference centers usually receive asymptomatic donors from blood banks, asymptomatic family members of patients under follow-up at the institution, and spontaneous demand for serological diagnosis, which tends to mirror the epidemiological reality of the disease in which the indeterminate forms predominate. Symptomatic patients are expected in secondary and tertiary care units, which involve the management of patients with more complex cases. Therefore, cases of the cardiac and digestive forms are more prevalent in these units. In the present study, the indeterminate form was the most prevalent (44.9%). The digestive form, either isolated or associated with heart disease, had a prevalence of 11.8%, which is within the range of the mean prevalence of this clinical form (9%-41%) presented in other studies. 12, 15, 17, 19, 20, 22. Regarding the cardiac and cardiodigestive forms, the most common cardiac stage was stage A (44.4%), which, if associated with the indeterminate form, would account for 65.8% of the cohort, with normal left ventricular systolic function on the ECG indicating patients with long-term benign prognoses.

In this cohort, although the indeterminate form was common among all patients throughout the study period, it occurred mainly
between 1995 and 2004. Before and after this period, the cardiac form was more prevalent in newly diagnosed patients. Until 1994, the cardiac form reflected patients coming from areas with active vector transmission and with higher CD prevalence and morbidity. After the mid-2000s, although there was an increased number of patients coming from areas of lower CD morbidity, they tended to be older with several comorbidities such as systemic arterial hypertension, dyslipidemia, diabetes mellitus, and ischemic heart disease. These comorbidities usually lead to cardiac changes that are reflected in the ECG and may mimic the electrocardiographic changes of Chagas heart disease leading patients to be classified as having the cardiac form of the disease\textsuperscript{13}. The progressive increase in the presence of mega forms of CD over time may also be related to the aging patients in the CD cohort justified by the gradual progression of neuronal degeneration associated with the disease\textsuperscript{10}.

The INI-Fiocruz cohort is mostly comprised of patients who migrated from various Brazilian regions, which may partially increase the representativeness of the total CD-infected population in Brazil, characterized by a predominance of the indeterminate clinical form of the disease. In addition, the progressive decrease in the number of new patients who entered the cohort over the past few years possibly reflects the success of the vector transmission control by \textit{Triatoma infestans} and by the transfusion route in recent decades in Brazil. We also observed the gradual aging of patients with chronic CD.

**AUTHORS’ CONTRIBUTION**

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AMH-M and PEAAB was responsible for the study concept. AMH-M, PEAAB, SSX, ASS, RMS, LHCS, GMSS, FCM, LFP, MTH, HHV, ARC, FSNS, FMR, FMC and MFFM was responsible for acquisition, analysis or interpretation of data. AMH-M was responsible for drafting the manuscript. MFFM was responsible for the study responsibility for the integrity of the data and the accuracy of the data analysis. AMH-M and PEAAB was responsible for the study concept. AMH-M was responsible for acquisition, analysis or interpretation of data. AMH-M and PEAAB was responsible for the study concept. AMH-M, PEAAB, SSX, ASS, RMS, LHCS, GMSS, FCM, LFP, MTH, HHV, ARC, FSNS, FMR, FMC and MFFM was responsible for acquisition, analysis or interpretation of data. AMH-M was responsible for drafting the manuscript. MFFM was responsible for the study responsibility for the integrity of the data and the accuracy of the data analysis. AMH-M and PEAAB was responsible for the study concept.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**FINANCIAL SUPPORT**

None to declare

**ORCID**

Alejandro Marcel Hasslocher-Moreno: 0000-0002-5430-7222

Roberto Magalhaes Saraiva: 0000-0002-2263-4261

Pedro E. A. Americano do Brasil: 0000-0002-6700-2268

Luiz Henrique Conde Sangenis: 0000-0002-5948-6282

Sergio Salles Xaver: 0000-0002-9337-0363

Andréa Silvestre de Sousa: 0000-0001-8266-4801

Gilberto Marcelo Sperandio-da-Silva: 0000-0002-0468-4417

Fernanda de Souza Nogueira S. Mendes: 0000-0003-2033-1715

Andrêa Rodrigues da Costa: 0000-0002-5033-4856

Marcelo Teixeira de Holanda: 0000-0002-3125-6610

Henrique Horta Veloso: 0000-0002-2743-6555

Flavia Mazzoli-Rocha: 0000-0003-0972-194X

Fernanda Martins Carneiro: 0000-0002-3544-9671

Luciana Fernandes Portela: 0000-0001-8961-468X

Mauro Felipe Felix Mediano: 0000-0001-6369-3631

**REFERENCES**

1. WHO. Chagas disease (American trypanosomiasis). 2020.
2. Workshop on Chagas disease. Workshop on Epidemiology and Social Determining Factors of Chagas Disease. Basic information for surveillance and control policy in Latin America. Mem Inst Oswaldo Cruz. 2007;102(Suppl. 1):5-10.
3. Santos-Filho JCL, Vieira MC, Xavier IGG, Maciel ER, Rodrigues Junior LF, Curvo EOV, et al. Quality of life and associated factors in patients with chronic Chagas disease. Trop Med Int Health. 2018;23(11):1213-22.
4. Xavier IGG, Vieira MC, Rodrigues Junior LF, Sperandio da Silva GM, da Silva PS, de Holanda MT, et al. Prevalence of metabolic syndrome and associated factors among patients with chronic Chagas disease. PLoS ONE. 2021;16(4):e0249116.
5. Camargo ME, Silva GR da, Castilho EA de, Silveira AC. Inquérito sorológico da prevalência de infecção chagásica no Brasil, 1975/1980. Rev Inst Med Trop São Paulo. 1984;26(4):192-204.
6. Luquetti AO, Passos ADC, Silveira AC, Ferreira AW, Macedo V, Prata AR. O inquérito nacional de soroprevalência de avaliação do controle da doença de Chagas no Brasil (2001-2008). Rev Soc Bras Med Trop. 2011;44(supl II):108-21.
7. Dias JCP. Doença de Chagas: sucessos e desafios. Cad Saude Publica. 2006;22(10):2020-1.
8. Martins-Melo FR, Ramos AN, Alencar CH, Heukelbach J. Prevalence of Chagas disease in Brazil: a systematic review and meta-analysis. Acta Trop. 2014;130:167-74.
9. WHO. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. 2015.
10. Ministério da Saúde (BR), Secretaria de Vigilância em Saúde. Boletim Epidemiológico 36: Panorama da doença de Chagas no Brasil. 2019.
11. Gascon J, Bern C, Pinazo M-J. Chagas disease in Spain, the United States and other non-endemic countries. Acta Trop. 2010;115(1):22-7.
12. Bruscasto A, Pereira MB, Archilhi MD, Teodoro TM, Almeida EA de, Martins LC, et al. Using a Chagas disease hospital database: a clinical and epidemiological patient profile. Rev Soc Bras Med Trop. 2018;51(6):831-5.
13. Gasparim AZ, Fontes CER, Rossoni DF, Toledo MJ de O. Epidemiological and clinical profile of patients with Chagas disease in the Central-North area of Paraná, Southern Brazil. Rev Soc Bras Med Trop. 2018;51(2):225-30.
14. Pereira L dos S, Freitas EC, Fidalgo ASO de BV, Andrade MC, Cândido D da S, Silva Filho JD da, et al. Clinical and epidemiological profile of elderly patients with Chagas disease followed between 2005-2013 by pharmaceutical care service in Ceará state, northeastern Brazil. Rev Inst Med Trop Sao Paulo. 2015;57(2):145-52.
15. Bozelli CE, Araújo SM de, Guilherme ALF, Gomes ML. Perfil clinico-epidemiológico de pacientes com doença de Chagas no Hospital Universitário de Maringá, Paraná, Brasil. Cad Saude Publica. 2006;22(5):1027-34.

16. Zheng C, Quintero O, Revere EK, Oey MB, Espinoza F, Puiius YA, et al. Chagas Disease in the New York City Metropolitan Area. Open Forum Infect Dis. 2020;7(1):1.

17. Acosta IC, Pérez-Tanoira R, Prieto-Pérez L, Úbeda AC, Álvarez Álvarez B, Antoranz PA, et al. Chagas' heart disease: Descriptive analysis of 141 patients in a hospital of Madrid, Spain. Travel Med Infect Dis. 2020;101690.

18. Navarro M, Berens-Riya N, Hohnerlein S, Seiringer P, von Saltzern C, Garcia S, et al. Cross-sectional, descriptive study of Chagas disease among citizens of Bolivian origin living in Munich, Germany. BMJ Open. 2017;7(1):e013960.

19. Muñoz J, Prat JG i, Gállego M, Gimeno F, Treviño B, López-Chejade P, et al. Clinical profile of Trypanosoma cruzi infestation in a non-endemic setting: Immigration and Chagas disease in Barcelona (Spain). Acta Trop. 2009;111(1):51-5.

20. Gontijo ED, Rocha MOC, Oliveira UT. Perfil clinico-epidemiológico de chagásicos atendidos em ambulatório de referência e proposição de modelo de atenção ao chagásico na perspectiva do SUS. Rev Soc Bras Med Trop. 1996;29(2):101-8.

21. Mendes JR, Silva J da, Costa TP de C, Farias RC de, Alves FV, Melo FSM, et al. Cases of Chronic Chagas Disease in the State of Piauí according to the Public reference Laboratory in Health in the Period of 2013-2017. Int J Adv Res Sci Eng Technol. 2020;7(3):416-20.

22. Mendonça RM, Rocha AM da, Andrade MS, Silva AB dos S. Doença de Chagas: serviço de referência e epidemiologia. Rev Bras Promoc Saude. 2020;33(9364):1-12.

23. Zanella LGF de ABD, Galiano IW, Martins CPA, Tokumo MO, Suzuki RB, Chagas FEB, et al. Clinical and epidemiological profile of patients in the chronic phase of Chagas disease treated at a reference center in the Southeast region of Brazil. Rev Fac Med. 2020;68(3).

24. Dias JCP, Ramos Jr AN, Gontijo ED, Luqueti A, Shikanai-Yasuda MA, Coura JR, et al. 2nd Brazilian Consensus on Chagas Disease, 2015. Rev Soc Bras Med Trop. 2016;49(suppl 1):3-60.

25. Gonzalves JGF, Prata A, Dias JCP, Macêdo V. The electrocardiographic survey. Rev Soc Bras Med Trop. 2011;44:40-6.

26. Coura JR. Contribuição ao estudo da doença de Chagas no Estado da Guanabara. Rev Bras Malariol Doencas Trop. 1966;18(9):9-83.

27. Ianni BM, Arteaga E, Frimm C de C, Barreto ACP, Mady C. Chagas' Heart Disease: Evolution Evaluation of Electrocardiographic and Echocardiographic Parameters in Patients with the Indeterminate Form. Arq Bras Cardiol. 2001;77(1):59-62.

28. Dias JCP, Machado EMM, Fernandes AL, Vinhaes MC. General situation and perspectives of Chagas disease in Northeastern Region, Brazil. Cad Saude Publica. 2000;16:13-34.

29. Shikanai Yasuda MA, Sátolo CG, Carvalho NB, Atala MM, Ferrufino RQ, Leite RM, et al. Interdisciplinary approach at the primary healthcare level for Bolivian immigrants with Chagas disease in the city of São Paulo. PLoS Negl Trop Dis. 2017;11(3):e0005466.

30. Ventura-Garcia L, Roura M, Pell C, Posada E, Gascon J, Aldasoro E, et al. Socio-cultural aspects of Chagas disease: a systematic review of qualitative research. PLoS Negl Trop Dis. 2013;7(9):e2410.

31. Macedo V. Influência da exposição à reinfeccão na evolução da doença de Chagas. Estudo longitudinal de 5 anos. Rev Pat Trop. 1976;5:33-116.

32. Coura JR, Abreu LL de, Pereira JB, Willcox HP. Morbidity in Chagas' disease: IV. Longitudinal study of 10 years in Pains and Iguauma, Minas Gerais, Brazil. Mem Inst Oswaldo Cruz. 1985;80(1):73-80.

33. Castro C, Prata A, Macedo V. A follow-up period of 13 years prospective study in 190 chagasic patients of Mambai, Goiás, State, Brazil. Rev Soc Bras Med Trop. 2001;34(4):309-18.

34. Jackson Y, Pula DV de M, Finckh A, Chizzolini C, Chappuis F. Chagas disease and systemic autoimmune diseases among Bolivian patients in Switzerland. Mem Inst Oswaldo Cruz. 2018;113(4).

35. Sayama Y, Furuji Y, Takakura A, Ishinoda M, Matsumoto C, Taira R, et al. Seroprevalence of Trypanosoma cruzi infection among at-risk blood donors in Japan. Transfusion. 2019;59(1):287-94.

36. Repetto EC, Zachariah R, Kumar A, Angehen A, Gobbi F, Anselmi M, et al. Neglect of a Neglected Disease in Italy: The Challenge of Access-to-Care for Chagas Disease in Bergamo Area. PLoS Negl Trop Dis. 2015;9(9):e0004103.

37. Meymandi SK, Forsyth CJ, Soverow J, Hernandez S, Sanchez D, Montgomery SP, et al. Prevalence of Chagas Disease in the Latin American-Born Population of Los Angeles. Clin Infect Dis. 2017;64(9):1182-8.

38. Hasslocher-Moreno AM, Salles Xavier S, Magalhães Saraiva R, Conde Sangenis LH, Teixeira de Holanda M, Horta Veloso H, et al. Progression Rate from the Indeterminate Form to the Cardiac Form in Patients with Chronic Chagas Disease: Twenty-Two-Year Follow-Up in a Brazilian Urban Cohort. Trop Med Infect Dis. 2020;5(2):1-5.

39. Ghoshal UC. Pathogenesis of achalasia cardia. World J Gastroenterol. 2012;18(24):3050.