Cohort profile update: the main and new findings from the SaMi-Trop Chagas cohort

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ABSTRACT

The SaMi-Trop project is a cohort study conducted in 21 municipalities of endemic areas of Chagas disease, including 1,959 patients with chronic Chagas cardiomyopathy. In this article we updated the results of the project, adding information from the second cohort visit. *Trypanosoma cruzi*-seropositive patients were enrolled from the primary care Telehealth service in Minas Gerais State, Brazil. The eligibility criterium for the second visit was the participation in the baseline evaluation. Of 1,959 participants at the baseline assessment, 1,585 (79.9%) returned after two years for the second evaluation. The mortality rate was 6.7%, but varied from 0.9% to 18.2% when it was stratified by certain clinical characteristics. A lower age-adjusted NT-Pro-BNP level (less than 300) and a prior benznidazole treatment were associated with lower mortality. There was an improvement in most quality of life domain scores. Participants have also reported fewer signs and symptoms and greater use of medication. The second follow-up visit will be complete in Oct 2021.

KEYWORDS: Chagas disease. Neglected diseases. Chagas cardiomyopathy. Cohort studies.

INTRODUCTION

Chagas disease (ChD) is recognized by the World Health Organization as a neglected tropical disease, primarily affecting low-income populations in endemic areas. Millions of people are infected with *Trypanosoma cruzi* (*T. cruzi*), the causative agent, with most infected people living in Brazil and Argentina. In addition, migration has resulted in large numbers of infected individuals in non-endemic countries such as Spain, the United States, Canada, Australia and Japan. The control strategies of *T. cruzi* transmission implemented in the last 30 years have led to a reduction of approximately 10 million in the number of people living with ChD. Nevertheless, around 13% of the population in Latin America is at risk of infection, where ChD accounts for more than 600,000 disability-adjusted life-years annually.

ChD is related to poverty, poor socioeconomic conditions, and to a lower quality of life. In rural endemic areas, access to diagnosis and treatment is limited, resulting in a greater mortality. Thus, the identification of patients with chronic Chagas cardiomyopathy (CCC) is important to guide public policies’ and special attention is required in this scenario. Many studies have pointed to the need of a permanent
health care, as the morbidity and mortality are higher in patients with ChD. These patients have worse prognosis and higher mortality. A cohort study found that the mortality rate was 7.4 times higher in the group of patients with CCC compared with patients without cardiomyopathy.

The SaMi-Trop (Sao Paulo-Minas Gerais Tropical Medicine Research Center) project aims to build understanding on the mechanisms of the cardiomyopathy development, to find biomarkers of the disease evolution, and to better understand the pathophysiology and clinical consequences of ChD.

Clinical and laboratory markers predictive of severe and progressive ChD have been identified in the SaMi-Trop cohort, such as high age-adjusted brain-type natriuretic peptide (NT-Pro-BNP) levels, as well as symptoms of advanced heart failure. The SaMi-Trop cohort is one of the largest multicenter studies of ChD conducted in endemic areas in the world. It represents a major opportunity for research focused on ChD, generating knowledge that can be applied in the primary health care. To date, two visits were completed and the objective of this manuscript is to present the main results after six years of follow-up.

**MATERIALS AND METHODS**

The SaMi-Trop project is a prospective cohort study including ChD patients. It is organized and has been carried out by a network of collaborating scientists in Minas Gerais and Sao Paulo States, since 2013. The first study visit was in 2013-2014 (baseline) and the first follow-up (FU1) visit was performed in 2015-2016. The cohort was established to develop a prognostic algorithm, based on simple electrocardiogram (ECG) measurements in conjunction with clinical information and Brain Natriuretic Peptide (BNP) levels to predict the risk of disease progression and death in CCC patients, and also to be useful in the clinical management of such patients. In the second visit, some additional aims were included, namely: to test the clinical prediction rule developed during the first phase of the study, to expand the knowledge on the genetic basis of disease progression using a GWAS approach, to better understand how patients are being cared for by the health service, and to evaluate the level of health literacy and associated factors. This cohort study is conducted in 21 municipalities from Minas Gerais State, an endemic region for ChD. It is integrated with the Telehealth Network in Minas Gerais. This State-wide Telehealth program has the technological infrastructure to facilitate the acquisition, cloud storage, and automatic recognition of ECG patterns and echocardiogram (ECHO) images. The ECG reading center analyzes ECG using the Minnesota Code.

Potential participants were identified from the list of patients managed by the Telehealth Network, a program designed to support the primary care in Minas Gerais State. The inclusion criteria in the baseline were patients aged 18 years or more, who self-reported ChD and abnormal alterations from the previous ECG recorded in a text report. All surviving baseline participants were invited to participate in the FU1 visit. Eligible patients were selected based on the ECG results performed in 2011–2012 by the Telehealth Network. The exclusion criteria included pregnancy or breastfeeding, and any life-threatening disease with an ominous prognosis that suggested a life expectancy of less than two years. More details regarding the eligible population, sample size, and other procedures can be found in the previously published paper.

All participants evaluated in the baseline were contacted by telephone or letter and were invited to participate in the FU1. The FU1 protocol included a questionnaire, a blood collection to repeat the NT-proBNP measurement, an ECG and an ECHO. The ECHO was not performed in the baseline. Two new groups of questions were included in the questionnaire: a set of questions regarding the use of health services, and the SALPHA instrument to evaluate the health literacy. The death certificates of participants who died before FU1 were obtained from the local health system. We repeated the serology test for participants with inconclusive or missing baseline T. cruzi serology results and 25 additional participants were included for serology testing in FU1. These participants were not included in the baseline because their blood samples were not available. The categorical variables were presented as percentages, and a test for equality matched pairs was performed to compare participants in both visits.

**RESULTS**

The SaMi-Trop cohort has been conducted in 21 municipalities in the North of Minas Gerais State, Brazil. In the baseline visit, 1,959 T. cruzi-seropositive participants were enrolled, but we subsequently included 25 additional participants because their serological results became available. In this way, the final number of participants in the first follow-up was 1,585. Table 1 shows the distribution of sociodemographic and clinical variables according to the final status on FU1. The overall mortality was 6.7%, but the mortality rate varied from 0.9% to 18.2% when it was stratified according to clinical characteristics. The mortality was higher in older people (more than 50 years old), those with New York Heart Association (NYHA) functional classification of II or more, presence of Chagas cardiomyopathy and
individuals with major ECG alterations. Regarding other clinical characteristics, those who died were associated with more coagulation problems in the baseline evaluation compared to those who survived (3.83% vs 6.9%), more renal disease (7.6% vs 10.3%), infarction (4.23% vs 15.2%), hypertension (64.4% vs 73.8%), more use of amiodarone (21.6% vs 47.2%), and more pacemakers (5.3% vs 14.6%). Conversely, a lower NT-Pro-BNP level (less than 300) and prior benznidazole treatment were associated with lower mortality.13,15 These results corroborate other studies.21

Table 2 presents a comparison of sociodemographic variables at baseline and on FU1. Most variables remained stable between visits, except for the self-perception of health. Most of the participants were women (67.9%), aged 50 years or more (78.4%), that self-declared mixed skin color (58.8%), and low education level (79.4%). Clinical variables in both visits are shown in Table 3. According to the Short Assessment of Health Literacy for Portuguese-speaking Adults (SAHLPA), a health literacy tool, 74% were classified as illiterate and 21.8% as having inadequate health literacy. There was an improvement in most quality of life domains. Better quality of life and clinical characteristics were associated with better medical care and treatment of ChD.13 Fifteen percent of participants presented LV systolic dysfunction according to the ECHO findings.

Table 4 shows the prevalence of some comorbidities, behavioral characteristics, medication use as well as signs and symptoms at baseline and FU1 visits. The proportion of participants reporting high serum cholesterol levels fell by 11.4% (40.1% vs 28.7%), but there was an increase of 29.2% in those reporting hypertension. Five new cases of leishmaniasis were registered among the participants. The proportion of subjects reporting current tobacco smoking decreased from 7.3% to 5.8%. The proportion of participants with no regular medications reduced from 30.1% to 23.5%, and those taking at least one medicine increased from 36.4% to 38.6%. The proportion of participants classified as making use of polypharmacy (more than 5 medications) increased by 2.9% (6.0% vs 8.9%). The main medications accounting for this increase were angiotensin receptor blockers (ARBs) (28.4% vs 33.3%) and aspirin (26.2% vs 29.5%). Medications that were prescribed less frequently at FU1 were angiotensin converting enzyme (ACE) inhibitors (28.6% vs 23.3%), amiodarone (22% vs 13.4%), digoxin (7.2% vs 5.1%) and hydralazine (4.3% vs 3.8%).

Participants reported less frequently “prolonged faintness or dizziness” (21.9% vs 11.4%), but had more “difficulty breathing when lying down” (39.1% vs 42.5%).
Table 1 - Sociodemographic and clinical variables according to the status of the patients in the second follow-up visit (FU1): participated, died, or lost to follow-up.

| Variables                        | Valid N* | Participated in FU1 N (%) | Lost to follow-up N (%) | Died N (%)  |
|----------------------------------|----------|---------------------------|-------------------------|-------------|
| Gender                           | 1,984    | 1,585 (79.9)              | 265 (13.4)              | 134 (6.7)   |
| Female                           | 1,334    | 1,076 (80.7)              | 183 (13.7)              | 75 (5.6)    |
| Male                             | 650      | 509 (78.3)                | 82 (12.6)               | 59 (9.1)    |
| Age                              | 1,984    | 1,585 (79.9)              | 265 (13.4)              | 134 (6.7)   |
| < 50 years                       | 489      | 408 (83.4)                | 67 (13.7)               | 14 (2.9)    |
| 50 - 74 years                    | 1,227    | 1,005 (81.9)              | 142 (11.6)              | 80 (6.5)    |
| > 74 years                       | 268      | 172 (64.2)                | 56 (20.9)               | 40 (14.9)   |
| Household members                 | 1,984    | 1,585 (79.9)              | 265 (13.4)              | 134 (6.7)   |
| 1-3                              | 1,128    | 885 (78.5)                | 161 (14.3)              | 82 (7.3)    |
| 4-6                              | 717      | 588 (82.0)                | 84 (11.7)               | 45 (6.3)    |
| 7-17                             | 139      | 112 (80.6)                | 20 (14.4)               | 7 (5.0)     |
| Family monthly income**          | 1,950    | 1,553 (79.6)              | 264 (13.6)              | 130 (6.7)   |
| > US$327                         | 1,036    | 835 (80.6)                | 139 (13.4)              | 62 (6.0)    |
| ≤ US$327                         | 914      | 718 (78.6)                | 126 (13.8)              | 70 (7.6)    |
| Skin color                        | 1,974    | 1,578 (79.9)              | 265 (13.4)              | 131 (6.6)   |
| Mixed                            | 1,155    | 928 (80.3)                | 141 (12.2)              | 86 (7.4)    |
| White                            | 433      | 339 (78.3)                | 65 (15.0)               | 29 (6.7)    |
| Black                            | 352      | 282 (80.1)                | 55 (15.6)               | 15 (4.3)    |
| Others                           | 34       | 29 (85.3)                 | 4 (11.8)                | 1 (2.9)     |
| Self-reported years of schooling  | 1,950    | 1,555 (79.7)              | 264 (13.5)              | 131 (6.7)   |
| Illiterate                       | 670      | 508 (75.8)                | 92 (13.7)               | 70 (10.4)   |
| 1 to 4 years                     | 862      | 721 (83.6)                | 94 (10.9)               | 47 (5.4)    |
| 5 to 8 years                     | 320      | 242 (75.6)                | 66 (20.6)               | 12 (3.8)    |
| Other                            | 98       | 84 (85.7)                 | 12 (12.2)               | 2 (2.1)     |
| Marital status                   | 1,977    | 1,580 (79.9)              | 265 (13.4)              | 132 (6.7)   |
| Married or living with partner    | 1,251    | 1,022 (81.7)              | 154 (12.3)              | 75 (6.0)    |
| Widower                          | 458      | 342 (74.7)                | 71 (15.5)               | 45 (9.8)    |
| Single                           | 177      | 143 (80.8)                | 28 (15.8)               | 6 (3.4)     |
| Divorced                         | 91       | 73 (80.2)                 | 12 (13.2)               | 6 (6.6)     |
| Previous use of benznidazole     | 1,979    | 1,581 (79.9)              | 264 (13.3)              | 134 (6.8)   |
| No                               | 1,335    | 1,055 (79.0)              | 180 (13.5)              | 100 (7.5)   |
| Yes                              | 498      | 420 (84.3)                | 64 (12.8)               | 14 (2.8)    |
| Do not know                      | 146      | 106 (72.6)                | 20 (13.7)               | 20 (13.7)   |
| NYHA functional classification    | 1,966    | 1,570 (79.9)              | 264 (13.4)              | 132 (6.7)   |
| I                                | 1,065    | 895 (84.0)                | 126 (11.8)              | 44 (4.1)    |
| II or more                       | 901      | 675 (74.9)                | 138 (15.3)              | 88 (9.8)    |
| Chagas cardiomyopathy            | 1,910    | 1,523 (79.7)              | 259 (13.6)              | 128 (6.7)   |
| Absent                           | 799      | 668 (83.6)                | 114 (14.3)              | 17 (2.3)    |
| Present                          | 1,111    | 855 (77.0)                | 145 (13.0)              | 111 (10.0)  |
| NT-proBNP level                  | 1,950    | 1,553 (79.6)              | 263 (13.5)              | 134 (6.7)   |
| < 300 pg/mL                      | 1,369    | 1,167 (85.2)              | 174 (12.7)              | 28 (2.1)    |
| ≥ 300 pg/mL                      | 581      | 386 (66.4)                | 89 (15.3)               | 106         |
| ECG result                       | 1,934    | 1,547 (80.0)              | 259 (13.4)              | 128 (6.6)   |
| Minor                            | 476      | 392 (82.3)                | 70 (14.7)               | 14 (3.0)    |
| Normal                           | 332      | 285 (85.8)                | 44 (13.2)               | 3 (0.9)     |
| Major                            | 1,126    | 870 (77.3)                | 145 (12.9)              | 111 (9.9)   |

*25 participants were included because their serology at the baseline was lost, but they tested positive in the FU1 visit; **Dollar conversion is from July 2013 (US$ 1.00 = R$ 2.23).
Table 2 - Sociodemographics, health satisfaction, and use of health service variables in the SAMI-TROP cohort at baseline and at the 2-years follow-up visit.

| Variables                  | Baseline |           | Follow-up 1 |           |
|----------------------------|----------|-----------|-------------|-----------|
|                            | Valid N  | N (%)     | Valid N     | N (%)     |
| Gender                     | 1,959    | 1,584     |             |           |
| Female                     | 1,323 (67.5) | 1,076 (67.9) |           |           |
| Male                       | 626 (32.5) | 508 (32.1)   |           |           |
| Age (years)                | 1,959    | 1,584     |             |           |
| < 50                       | 499 (25.6) | 342 (21.6)   |           |           |
| 50 - 74                    | 1,223 (62.6) | 1,016 (64.1) |           |           |
| > 74                       | 231 (11.8) | 226 (14.3)   |           |           |
| Household members          | 1,953    | 1,584     |             |           |
| 1-3                        | 1,106 (56.6) | 884 (55.8)   |           |           |
| 4-6                        | 709 (36.3) | 588 (37.1)   |           |           |
| 7-17                       | 138 (7.1) | 112 (7.1)    |           |           |
| Family monthly income      | 1,940    | 1,577     |             |           |
| > US$327                   | 1,037 (53.1) | 849 (53.8)   |           |           |
| ≤ US$327                   | 916 (46.9) | 728 (46.1)   |           |           |
| Skin color                 | 1,950    | 1,578     |             |           |
| Mixed                      | 1,144 (58.6) | 928 (58.8)   |           |           |
| White                      | 426 (21.8) | 339 (21.5)   |           |           |
| Black                      | 348 (17.8) | 282 (17.9)   |           |           |
| Others                     | 32 (1.8)  | 29 (0.2)    |           |           |
| Years of schooling         | 1,950    | 1,579     |             |           |
| Illiterate                 | 670 (34.4) | 521 (33.0)   |           |           |
| 1 to 4                     | 862 (44.2) | 732 (46.4)   |           |           |
| 5 to 8                     | 320 (16.4) | 242 (15.3)   |           |           |
| Other                      | 98 (5.0)  | 84 (5.3)     |           |           |
| Marital status             | 1,953    | 1,580     |             |           |
| Married or living with partner | 1,238 (63.4) | 1,022 (64.7) |           |           |
| Widower                    | 449 (23.0) | 342 (21.6)   |           |           |
| Single                     | 176 (9.0)  | 143 (9.0)    |           |           |
| Divorced                   | 90 (4.6)  | 73 (4.7)     |           |           |
| Health satisfaction        | 1,076    | 480       |             |           |
| Not at all satisfied       | 231 (21.4) | 126 (20.7)   |           |           |
| Partially satisfied        | 232 (21.6) | 181 (29.6)   |           |           |
| Very satisfied             | 613 (57.0) | 302 (49.7)   |           |           |
| Health service used        | Not collected |           |             |           |
| Public                     |           | 1,043 (66.9) |           |           |
| Private                    |           | 354 (22.7)   |           |           |
| Health Insurance           |           | 18 (1.2)     |           |           |
| None                       |           | 143 (9.2)    |           |           |

Others in skin colors include Asian (n=27) and Native Americans (n=5); others in the educational level included: elementary school (n=81) and graduate school (n=17); Dollar conversion is from July 2013 (US$ 1.00 = R$ 2.23).

"inability to climb two flights of stairs" (38.9% vs 63.1%), "pain when swallowing food" (17.8% vs 30.8%) and megaesophagus (6.1% vs 11.4%).

In order to compare the variation between visits, we only selected patients who participated in both visits (Table 5). Use of ACE inhibitors and amiodarone reduced significantly (22.2% vs 14.3%), and the use of ARBs (26.8% vs 33.4%) and aspirin (25.1% vs 29.5%) increased. Most signs and symptoms reduced significantly except for night-time dyspnea, pedal edema in the morning and those related to megaesophagus. Twenty-seven (1.2%) participants received a new pacemaker.

DISCUSSION

SaMi-Trop is one of the largest multi-center cohort studies of ChD disease in the world, and has led to a number of important scientific contributions to the understanding
Our results suggest that participation in SaMi-Trop improved the medical care of the participants. Specifically, the access to laboratory tests was improved and participants were re-evaluated by a cardiologist and underwent an ECHO assessment. This allowed for the diagnosis of both, ChD and the general health status. Furthermore, the SaMi-Trop project team conducted many meetings in the municipalities that participated in the study, with health professionals and government officials. The project has also raised the profile of the Telehealth system and provided training for physicians. One of the aspects of the project is the ethical commitment to patients: patients with more severe disease were scheduled for consultation with a physician or specialist for evaluation at a primary health care unit and received further care. All patients received information regarding ChD and self-care strategies. According to our results, the demographic profile is similar to the one of participants from other studies conducted in other regions. Around 50% of our participants were classified as class 1 according to the NYHA functional classification, which means they have no significant symptoms. In the general population, the left ventricular function was preserved with a median for the ejection fraction of 63%. Only 13% presented LV systolic dysfunction characterized by an ejection fraction of less than 50%.

The study brings new information regarding how patients use health services and how they are able to understand health information and advice. The proportion of patients who reported the use of a private health service was high (22.7%), compared to the general population in Brazil. Considering the lower level of family income, around 53% receive less than US$400 per month, but this information requires further attention and will be discussed with the local health planners to better understand the underlying reasons. Another important observation was that almost 100% of the participants were considered not able to understand simple information regarding their health. Using a standardized questionnaire to evaluate the health literacy

Table 3 - Clinical variables, health literacy and quality of life in the SAMI-TROP cohort at baseline and at the 2-years follow-up visit.

| Variables                                      | Baseline | N (%) | Follow-up 1 | N (%) |
|------------------------------------------------|----------|-------|-------------|-------|
| Previous use of benznidazole                   | 1,955    |       | 1,561       |       |
| No                                             | 1,320    | 67.5  | 1,055       | 66.7  |
| Yes                                            | 492      | 25.2  | 420         | 26.6  |
| Do not know                                    | 143      | 7.3   | 106         | 6.7   |
| NYHA functional classification                  | 1,931    |       | 1,560       |       |
| I                                              | 1,059    | 54.8  | 895         | 56.5  |
| II or more                                     | 872      | 45.2  | 689         | 47.5  |
| ProBNP level                                   | 1,955    |       | 1,518       |       |
| < 300 pg/mL                                    | 1,368    | 70.2  | 1,068       | 69.2  |
| ≥ 300                                          | 581      | 29.8  | 474         | 30.8  |
| ECG result                                     | 1,910    |       | 1,487       |       |
| Minor                                          | 326      | 17.1  | 291         | 19.0  |
| Normal                                         | 473      | 24.8  | 315         | 21.1  |
| Major                                          | 1,111    | 58.2  | 905         | 59.9  |
| Echocardiographic findings (median/IQ)          | Not collected |       | 1,564       |       |
| LV end-diastolic diameter (mm)                  |          |       | 48 (45-52)  |       |
| LV end-systolic diameter (mm)                   |          |       | 31 (29-36)  |       |
| LV ejection fraction (%)                        |          |       | 63 (57-66)  |       |
| LV systolic dysfunction                         |          |       |              |       |
| No                                             |          |       | 1,357       | 87    |
| Yes                                            |          |       | 203         | 13    |
| Health literacy - SAHLPA                        | Not collected |       | 1,557       |       |
| Illiterate                                      |          |       | 1,159       | 74    |
| Inadequate health literacy                      |          |       | 339         | 21.8  |
| Adequate health literacy                        |          |       | 59          | 3.84  |
| Quality of life domains                         | 625      |       | 609         |       |
| Physical                                       | 57.84    | (15.32)| 60.7        | (17.6) |
| Psychological                                   | 65.98    | (12.85)| 65.4        | (15.5) |
| Social relationships                            | 73.17    | (13.99)| 72.9        | (16.1) |
| Environment                                     | 57.66    | (12.26)| 59.8        | (14.6) |
helped to correct the underestimation of the education level self-reported by the patients. It is well known that inadequate health literacy can be a barrier to self-reported and treatment of diseases, therefore health professionals must adopt strategies to minimize these effects that can be harmful to the health due to inadequate literacy.\textsuperscript{33,34}

In our cohort, those patients who died presented a higher proportion of comorbidities, more use of amiodarone, and...
functional class II or higher classification, and more pacemakers. This was expected because these patients were likely to have more severe disease. Among those patients who participated in both visits (baseline and follow-up 1), we found that many of them had reduced the use of amiodarone. One possible explanation is that they were examined by a cardiologist and the prescribed medication was probably reviewed. Another possible explanation is that the side effects of the medicine have motivated the patients to discontinue the medication. Stein et al. found that patients taking amiodarone presented side effects which vary from 10.6% to 61.1%, and 7.68% discontinued the

### Table 5 - Statistical comparison of medications, signs and symptoms in the SaMi-Trop cohort for paired patients that participated in both visits. N=1,560.

| Variables                             | Baseline | Follow-up 1 | P-value* |
|---------------------------------------|----------|-------------|----------|
|                                       | N (%)    | N (%)       |          |
| **Medication in use (Yes)**           |          |             |          |
| ACEa (n=1,512)                        |          |             |          |
| No                                    | 1,081 (71.5) | 1,155 (76.4) |          |
| Yes                                   | 431 (28.5)  | 357 (23.6)  | 0.000    |
| ARBs (n=1,513)                        |          |             |          |
| No                                    | 1,107 (73.2) | 1,008 (66.6) |          |
| Yes                                   | 406 (26.8)  | 505 (33.4)  | 0.000    |
| Aspirin (n=1,513)                     |          |             |          |
| No                                    | 1,104 (74.9) | 1,067 (70.5) |          |
| Yes                                   | 379 (25.1)  | 446 (29.5)  | 0.003    |
| Amiodarone (n=1,368)                  |          |             |          |
| No                                    | 1,064 (77.8) | 1,172 (85.7) |          |
| Yes                                   | 304 (22.2)  | 196 (14.3)  | 0.000    |
| **Self-reported signs and symptoms (Yes)** |          |             |          |
| Heartbeat racing or beating abnormally (n=1,501) |          |             |          |
| No                                    | 546 (36.4)  | 680 (45.3)  |          |
| Yes                                   | 955 (63.6)  | 821 (54.7)  | 0.000    |
| Prolonged faintness or dizziness (n=1,513) |          |             |          |
| No                                    | 1,182 (78.1) | 1,339 (88.5) |          |
| Yes                                   | 331 (21.9)  | 174 (11.5)  | 0.000    |
| Problems on electrocardiogram (n=1,527) |          |             |          |
| No                                    | 602 (39)    | 730 (47.8)  |          |
| Yes                                   | 925 (61)    | 797 (52.2)  | 0.000    |
| Heartbeat racing at rest (n=1,501)    |          |             |          |
| No                                    | 711 (47.4)  | 908 (60.5)  |          |
| Yes                                   | 790 (52.6)  | 593 (39.5)  | 0.000    |
| Irregular heartbeat (n=1,501)          |          |             |          |
| No                                    | 808 (53.8)  | 929 (61.9)  |          |
| Yes                                   | 693 (46.2)  | 572 (38.1)  | 0.000    |
| Awake during the night unable to breathe (n=1,501) |          |             |          |
| No                                    | 982 (65.4)  | 923 (61.5)  |          |
| Yes                                   | 519 (34.6)  | 578 (38.5)  | 0.008    |
| Swelling or puffiness of the feet (morning) (n=1,501) |          |             |          |
| No                                    | 1,116 (74.3) | 1,059 (70.5) |          |
| Yes                                   | 385 (25.7)  | 442 (29.5)  | 0.005    |
| Pacemaker (n=1,501)                   |          |             |          |
| No                                    | 1,420 (94.7) | 1,393 (92.8) |          |
| Yes                                   | 81 (5.3)    | 108 (7.2)   | 0.000    |
| Megaoesophagus (n=1,501)              |          |             |          |
| No                                    | 1,414 (94.2) | 1,328 (88.5) |          |
| Yes                                   | 87 (5.8)    | 173 (11.5)  | 0.000    |

*Test the equality of matched pairs (Wilcoxon matched-pairs test); ^ACE = Angiotensin converting enzyme; ^ARBs = Angiotensin receptor blockers.
drug. We observed that 27.2% of the patients reported a previous use of benznidazole, but the use was more frequent among individuals with better demographic conditions and a longer time since the CD diagnosis. The use of benznidazole was beneficial to reduce the parasitemia and the mortality rate according to our results. In another cohort study, treatment with benznidazole was associated with a decrease in ChD progression from the indeterminate form to the cardiac one and also a decrease in the risk of cardiovascular events.

A limitation out of our study was the number of participants lost to follow-up; 13% of subjects did not participate in the FU1 visit. We believe this was due to the high degree of disease severity of the participants and the challenges of working in a remote region of Minas Gerais State. Another limitation is that the ECHO results are available only for the first follow-up visit so that some comparisons were not possible. However, the ECHOs will be repeated for all the participants in the second follow-up visit.

CONCLUSION

In conclusion, our results confirmed that abnormal NT-proBNP level adjusted by age as a strong predictor of death, which reinforces that benznidazole should be strongly considered in the treatment of chronic ChD, and the quality of life is worse in these patients. Additionally, we detected, as expected, a greater use of some medicines such as ARBs and aspirin and a higher mortality rate among those who have more severe disease. The SaMi-Trop project has also started its second visit (follow-up 2), before its interruption due the COVID-19 pandemic, and its contribution to fill some gaps in the knowledge regarding ChD progression is very important.

Some positive findings in our study need to be highlighted, such as the fact that the project enabled the training of human resources, gave technical support for the local primary health care in order to improve the medical care provided to the patients, and should improve medical assistance as well as the management of treatment which will probably contribute to improve the quality of life of the patients. These findings reinforce the importance of adequate financial support from governments to help Chagas patients to have access to healthcare.

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AUTHORS’ CONTRIBUTIONS

CDLO, CCS, ALPR and ECS were responsible for study concept, analyzed and interpreted the data, drafted and revised the manuscript, and approved the final version. LCO, LN, NDQ, AMF, ECN, ALB, LB, DSH and ALR have substantially contributed to the drafting of the article or revising it critically for important intellectual content; and have given the final approval of the version to be published.

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