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PREDICTIVE FACTORS FOR THE PROGRESSION OF CHRONIC CHAGAS CARDIOMYOPATHY IN PATIENTS WITHOUT LEFT VENTRICULAR DYSFUNCTION

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SUMMARY

The identification of predictors for the progression of chronic Chagas cardiomyopathy (CCC) is essential to ensure adequate patient management. This study looked into a non-concurrent cohort of 165 CCC patients between 1985 and 2010 for independent predictors for CCC progression. The outcomes were worsening of the CCC scores and the onset of left ventricular dysfunction assessed by means of echo-Doppler cardiography. Patients were analyzed for social, demographic, epidemiologic, clinical and workup-related variables. A descriptive analysis was conducted, followed by survival curves based on univariate (Kaplan-Meier and Cox's univariate model) and multivariate (Cox regression model) analysis. Patients were followed from two to 20 years (mean: 8.2). Their mean age was 44.8 years (20-77). Comparing both iterations of the study, in the second there was a statistically significant increase in the PR interval and in the QRS duration, despite a reduction in heart rates (Wilcoxon < 0.01). The predictors for CCC progression in the final regression model were male gender (HR = 2.81), Holter monitoring showing pauses equal to or greater than two seconds (HR = 3.02) increased cardiothoracic ratio (HR = 7.87) and time of use of digitalis (HR = 1.41). Patients with multiple predictive factors require stricter follow-up and treatment.

KEYWORDS: Chagas cardiomyopathy; Clinical progression; Prognosis; Cohort studies.

INTRODUCTION

Although it was first described over a century ago, Chagas disease (CD) still remains a relevant endemic ailment in Latin America as it threatens some 16 million people in the continent. As the transmission via vectors has been controlled in several countries, the clinical follow-up of the millions still infected remains an important challenge. Chronic Chagas cardiomyopathy (CCC) is the main morbidity resulting from CD[10]. Left ventricular dysfunction is the strongest predictive factor for morbidity and mortality in CCC[8,9]. The identification of markers for disease progression before the occurrence of ventricular dysfunction may allow for earlier treatment and better prognosis. Although this disease has been extensively studied, the natural history of CCC and its independent predictive factors in outpatients – examined through the most sophisticated non-invasive cardiovascular methods such as echo-Doppler cardiography (ECHO), Holter monitoring, and exercise testing (ET) – are not completely understood. Most previous studies resorted to simpler risk stratification methods, such as electrocardiography (ECG) and chest radiography, and were conducted based on small selected heterogeneous groups including Chagas patients with varied prognoses, some of them for a short period of time[23]. Some authors[26,31] have looked at earlier stage CCC patients, with differing findings on the ECG, no left ventricular dysfunction, and unnoticeable symptoms. Very few studies have measured prognostic factors of Chagas cardiomyopathy among asymptomatic Trypanosoma cruzi-infected persons[26].

This study aimed to identify the predictive factors for the progression of CCC in patients with no left ventricular dysfunction and to check if this progression is different in patients who have an ECG with abnormalities indicative of CCC when compared to one who have unspecific ECG abnormalities.

MATERIALS AND METHODS

Patients: This non-concurrent cohort study covered adult CCC patients with no left ventricular dysfunction living in the metropolitan area of Belo Horizonte seen at the Referral Center for Training on Infectious and Parasitic Diseases of the Hospital das Clínicas of the Federal University of Minas Gerais (HC-UFMG) for their first and return visits, between 1985 and 2010. Patients were not selected for gender, age range, ethnicity or social status. Ethics: this study was approved by the UFMG Research Ethics Committee (COEP-UFMG), as per process ETIC 347/09, and found to be in compliance with the 1975 Declaration of Helsinki. All the workup was carried out with the consent of the patients and the database was protected by user passwords granted only to the group of researchers.

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Enrollment criteria: proven diagnosis for CD by two positive conventional serologic test results for T. cruzi infection[32] having completed the initial assessment protocol (iteration 1) comprised of an interview, physical examination, chest radiography, ECG, and ECHO; being diagnosed with CCC (abnormal ECG); having undergone clinical assessment, ECG, and ECHO at least two years since the initial assessment (iteration 2); having the tests at iteration 1 done within ≤ 12 months.

Exclusion criteria: having other heart conditions (ischemic, hypertensive, congenital or valvular heart disease, alcoholic cardiomyopathy) referred or investigated through clinical and/or complementary tests, found at any stage of the follow-up; having left ventricular systolic or diastolic dysfunction on the ECHO on iteration 1; using a pacemaker (PM) or having ventricular tachycardia (VT) - de□ned as three or more consecutive premature ventricular complexes with a heart rate of more than 100 beats per minute - on the ECG at the initial assessment; patients with time intervals between tests > 12 months.

Cardiac non-invasive studies: They were all carried out as per the standard routines at HC-UFMG, from the preparation of the patients up to the interpretation of their results. All of them were conducted by personnel with previous experience of CCC and blind interpreted in relation to the clinical form of the disease. The date on which the □rst tests were done on the patients was considered as the patient's date of entry into the study.

Conventional resting 12-lead ECG: interpreted by two examiners using the diagnostic criteria for CCC3 accepted by the World Health Organization.

ECHO: Abnormal test results were characterized by LV (left ventricular) dysfunction and/or anomalous segmental contractility, in addition to the presence of apical aneurysm. Systolic dysfunction was considered when EF < 54% and classi□ed as mild to moderate (≥ 40%) and severe (< 40%), whereas diastolic disorder was characterized for dysfunction stages ≥ II (patients were classi□ed according to diastolic function patterns: normal, impaired relaxation known as stage I, pseudonormal pattern known as stage II and restrictive pattern known as stage III). Segmental disorder was de□ned as the presence of akinesia, hypokinesia or dyskinesia in a de□ned area.

Chest radiography: with images taken from two views: posteroanterior and lateral – using the cardiothoracic ratio (CTR) as reference and those patients with a CTR ≥ 0.50 were deemed as abnormal. Exercise Testing (ET): It was completed by patients for whom the test was not contraindicated. They were considered abnormal when any of the following were observed: ventricular arrhythmia, blood pressure alterations, chronotropic response, myocardial ischemia criteria - namely J-point depression (the point at which the QRS complex meets the ST segment) ≥ 1 mm, with a horizontal or downsloping ST segment with duration ≥ 0.80 seconds (sec); Y-point depression 80 milliseconds (msec) after point J ≥ 1.5 mm with an upsloping ST segment; J-point elevation ≥ 1 mm. 24-hour Holter monitoring: They were considered abnormal when any of the following were found: arrhythmias with complexity ≥ Lown 2[18], intra or atrioventricular conduction disorders, pauses of ≥ 2.0 seconds and changes in the ST segment matching myocardial ischemia criteria.

Categorization: After cardiac studies results had been analyzed, patients were divided into two groups at iteration 1: group 1 (G1): ECG with at least two unspeci□c abnormalities; and group 2 (G2): ECG with abnormalities indicative of CCC. Further on, considering ECG and ECHO, patients were independently categorized for CCC[8], taking the most abnormal test result into account, thus describing four stages: 1- ECG: at least two unspeci□c abnormalities (G1) – sinus bradycardia (HR > 40 bpm), low voltage, incomplete right bundle branch block (RBBB), left anterior hemiblock (LAHB), □rst-degree atrioventricular block (AV block), unspeci□c ST-T alterations. ECHO: normal. 2- ECG: abnormalities indicative of CCC (G2) – complete RBBB in association or not with LAHB, isolated monomorphic ventricular extrasystoles (VES), sinus bradycardia (HR ≤ 40 bpm), second-degree AV block, T primary alterations. ECHO: abnormal, but no ventricular dysfunction. 3- ECG: abnormalities indicative of CCC (G2) – polymorphic or sustained VES, electrically inactive area, sinus node dysfunction. ECHO: diastolic ventricular dysfunction or abnormal EF, however ≥ 40%. 4- ECG: abnormalities indicative of CCC (G2) – atrial □brillation (AF), complete AV block, left bundle branch block (LBBB), non-sustained ventricular tachycardia (NSVT) and PM at time 2. ECHO: diastolic ventricular dysfunction or EF < 40%.

Outcomes or response variables: worsening of the CCC scores and onset of left ventricular dysfunction.

Analyzed independent explanatory variables:

Social, demographic and epidemiologic variables: age; gender; ethnicity; intensity and duration of physical effort in previous and current occupations2; time spent in rural (RA) and CD endemic areas (EA); location and time spent at current residence; family history (FH) for CD, heart disease and sudden death – the last two occurring in family members aged 40 or less; drinking – weekly alcohol intake (in grams[29]) and period of abuse (in years); smoking (pack-year). Clinical variables: symptoms, thromboembolism, comorbidities, systemic hypertension, body mass index (BMI), speci□c complete etiologic treatment with benznidazole, CCC score, regular and continuous use (in years) of cardiovascular drugs for at least two years including: loop diuretics, hydrochlorothiazide (HCTZ), beta blockers, spironolactone, amiodarone, angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARBs). Cardiac non-invasive studies variables: abnormalities on ECG, chest radiography, ECHO, 24-hour Holter monitoring and on exercise testing.

Data collection tools and analysis: A structured questionnaire was completed during □rst and return visits and all codi□ed responses were entered into Microsoft Access. Statistical packages MINITAB for Windows 14.10, nQuery Advisor 4.0, SPSS 15.0 and EXCEL were used for data analysis purposes.

Descriptive analysis: Frequency distribution tables were used for nominal categorical variables, whereas central tendency (means, medians) and variability measures such as minimum, maximum, and standard deviation (SD) were used for numerical variables. McNemar's test was used to compare the variables resulting from initial and □nal ECG and ECHO tests, while the Wilcoxon test was adopted to compare continuous variables in paired data groups. Survival analysis: The outcomes considered for survival analysis were the worsening of CCC score over time and the onset of left ventricular dysfunction. CCC scores collected

at the beginning and end of the study were considered when calculating the worsening of the CCC score. CCC score worsening was de□ned as having a greater score at the end of the study than the one collected at the beginning. Patients categorized as stage 4 were excluded from the aforementioned analysis because it was impossible for them to receive a worse score at the end of the study. Univariate analysis the Kaplan-Meier estimator was used to build survival curves, alongside Cox's univariate model and the differences in survival between groups were assessed by the log-rank test. Multivariate analysis: The Cox regression model was used and a p-value of 0.20 was used to enter predictive variables into the Cox model and a 5% signi□cance level was adopted as a cutoff threshold for the variables to be considered in the model. A new □nal model using only variables obtained in univariate analysis with a p- value of 0.5 was performed in order to avoid "over□tting phenomena". A □nal model was considered adequate to be interpreted when cox proportional risk was tested by using a logarithm of cumulative risk function against time (in months) for each covariate.

Observations: A hazard ratio (HR) with a CI of 95% was calculated. A 5% signi□cance level was adopted in all analyses. Some data sets were strati□ed in accordance with the literature in order to explore them better.

Analysis of the sample strati□ed into ECG groups: In order to assess whether the intensity of the initial abnormality of the ECG could predict CCC progression, groups G1 and G2 were analyzed solely in relation to the onset of left ventricular dysfunction – as the ECG accounted for part of the CCC score, thus the outcome "worsening of the CCC scores" should not be considered. The detection power of the sample was calculated using a 95% CI[27].

RESULTS

Patients were considered as lost when there was a failure to establish communications with patients after at least three phone calls on different days and at different times, sending a letter, and attempting to contact the patient's neighbors (Fig. 1). The lost group was similar to the excluded and studied ones, there was no statistically signi□cant difference between these groups.

Descriptive analysis:

Social, demographic and epidemiologic pro□le of the patients: the mean age of patients was 44.8 years (20-77 years) (SD = 10.6); mainly born in RA (97.0%) and residing in CD EA (88.5%) for a mean of 16 years (SD = 8.7). Most patients have lived away from RA and EA for a mean of 23.4 years (SD = 11.1). At the start of the study, patients had been involved in intense (49%) occupational physical effort for a mean of 14.6 years. Mean alcohol intake was 194.9 grams/week for 21.5 years (SD = 474.1 g/week), median 60 grams/week for 20 years; smoking history was quanti□ed at a mean of 18.4 pack-years (SD = 16.3).

Clinical pro□le: Most patients were asymptomatic (63.6%). Systemic hypertension was the most prevalent comorbidity (21.8%) in iteration 1; incidence increasing to 28.5% in iteration 2, an increase which was also seen in the use of cardiovascular drugs, going from 30.3 in iteration 1 to 43.6% in iteration 2. The increase was statistically signi□cant in both cases (McNemar's: $p < 0.01$). Prevalence rates of the stages of CCC reduced from 49.7% (iteration 1) to 39.4% (iteration 2) in stage 1; from 42.4% to 40.6% in stage 2; while an increase from 6.7% to 13.3% was noticed in stage 3 and from 1.2% to 6.7% in stage 4.

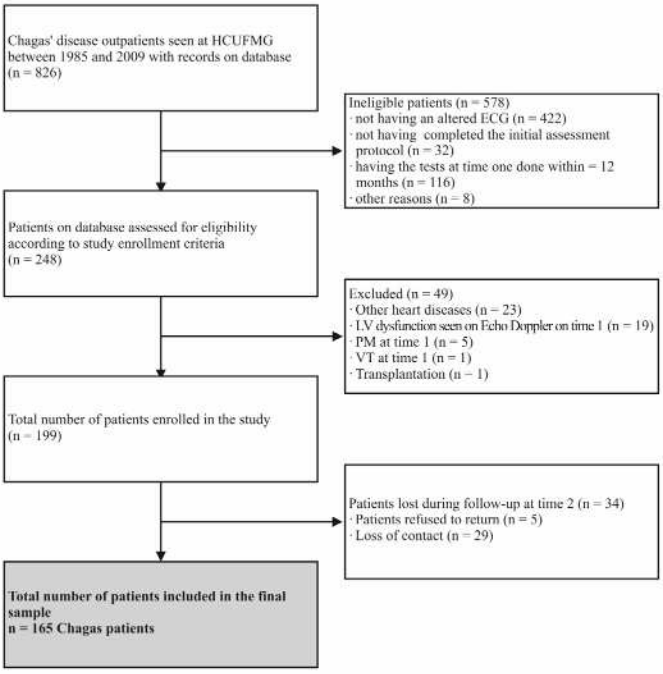

Fig. 1 - Work□ow from the study 'Predictive factors for chronic Chagas cardiomyopathy patients without left ventricular dysfunction', CD Outpatient ward/HC-UFMG.

Cardiac non-invasive studies: ECG (Table 1) and ECHO (Table 2) explanatory variables were described and compared in both iterations of the study. They show a statistically signi□cant (p-value Wilcoxon Test < 0.01) increase in both PR interval (56.4% of the patients) and QRS duration (40.8%), and in the reduction of heart rate (57.6%) all in iteration 2 of the study.

One-hundred patients underwent ET (61%), and 142 (86%) the 24-hour Holter monitoring.

Follow-up: More than 91% of the patients survived until the end of the study, while seven deaths were observed (4.5% lethality rate), two of which (28.6%) were due to sudden death, two (28.6%) due to decompensated CCC and three (42.8%) due to causes unrelated to CD. Eight (4.8%) patients were lost for over a year after completing the protocol in iterations 1 and 2 of the study. The minimum follow-up time in the study was two and the maximum was 20 years (mean = 8.2; DP = 3.2). The worsening of the CCC score was observed in 37 (22.7%) patients, while □ve (3.1%) improved their scores and 121 (74.2%) remained stable.

Analysis of the outcome "worsening of the CCC scores": In univariate analysis, all studied and statistically signi□cant explanatory variables are shown in the tables and □gures below (Table 3, Table 4 and Table 5 and Fig. 2, 3, 4, 5). In multivariate analysis, three adequate models were obtained, the □rst using the variables that had $p < 0.20$ and the others using variables that had $p < 0.5$ in the univariate analysis. The best □nal model was one of the $p < 0.5$ variables. It presented HR estimates with a more stable and shorter CI of 95% and showed the following remaining variables to be signi□cant: male gender, pauses ≥ 2 seconds on Holter,

Table 1
Descriptive comparative analysis of ECG variables. CD patients. HC-UFMG

Variable		Time 1		Time 2	
		Occurrences (n)	Percentage (%)	Occurrences (n)	Percentage (%)
1st degree AV block*	No	150	90.9	136	82.4
	< 230 msec	14	8.5	17	10.3
	≥ 230 msec	1	0.6	12	7.3
Sinus bradycardia*	< 60 bpm	62	37.6	69	41.8
Complete RBBB	No	113	68.5	108	65.5
	yes	52	31.5	57	34.5
Inomplete RBBB	No	153	92.7	152	92.1
	yes	12	7.3	13	7.9
Isolated VES	No	150	90.9	154	93.3
	yes	15	9.1	11	6.7
LAHB	No	117	70.9	117	70.9
	yes	48	29.1	48	29.1
Unspeci□c ST alterations	No	142	86.1	137	83.0
	yes	23	13.9	28	17.0
Rhythm	sinus	164	99.4	158	95.8
	multifocal atrial	1	0.6	-	-
	AF			2	1.2
	PM			5	3.0
2nd degree AV block - grade I	No	163	98.8	164	99.4
	yes	2	1.2	1	0.6
LBBB	No	163	98.8	162	98.2
	yes	2	1.2	3	1.8
Low voltage	yes	3	1.8	3	1.8
NSVT	yes			1	.6

* p-value McNemar's test < 0.05.

Table 2
Descriptive comparative analysis of ECHO variables. CD Outpatient ward/HC-UFMG

Variable		Time 1		Time 2	
		Occurrences (n)	Percentage (%)	Occurrences (n)	Percentage (%)
LV □nal diastol.[a] diameter	normal	151	91.5	137	83.0
	altered	14	8.5	28	17.0
LV*[c] □nal systol.[b] diamater	normal	155	93.9	134	81.2
	altered	10	6.1	31	18.8
Ejection fraction	normal	165	100.0	144	87.3
	53 to 40%			17	10.3
	<40%			4	2.4
Shortening fraction	normal	144	87.3	136	82.4
	altered	21	12.7	29	17.6
Contractility alterations	absent	148	89.7	131	79.4
	global dysf.[d]	1	0.6	9	5.5
	segmental dysf.[d]	16	9.7	25	15.2
Diastolic function alteration	absent	133	80.6	75	45.7
	grade I dysf.[d].	32	19.4	85	51.8
	grade II dysf.[d]	-	-	4	2.4
Degenerative* valve disorders	no	158	95.8	140	84.8
	yes	7	4.2	25	15.2

a: diastol: diastolic; b: systol: systolic; *c: p-value McNemar's test < 0.05; d: dysf: dysfunction.

Table 3
Univariate analysis for outcome 'worsening of CCC scores'. CD Outpatient ward/HC-UFMG

Variable	Absolute # (n) / relative # (%) or stratification	Worsening incidence (%)	p-value[a]	HR	95% CI for HR	
					Lower limit	Upper limit
Female gender	yes (103/62.4)	13.7		1.00		
	no (62/37.6)	37.7	0.010	2.59	1.25	5.36
Age	< 50 years (112/67.8)	21.9		1.00		
	≥ 50 years (53/32.2)	24.5	0.024	2.18	1.11	4.26
Caucasian ethnicity	no (112/67.9)	21.8		1.00		
	yes (53/32.1)	24.5	0.615	1.19	0.60	2.36
Permanence at RA	<10 years (41/24.8)	31.1		1.00		
	≥ 10 years (124/75.2)	19.5	0.079	0.55	0.28	1.07
Permanence at EA	< 10 years (34/20.6)	24.4		1.00		
	≥ 10 years (131/79.4)	15.6	0.363	0.64	0.25	1.66
Currently resides at RA	no (160/97)	22.2		1.00		
	yes (05/3)	40.0	0.012	6.54	1.50	28.50
Currently resides at EA	no (140 /84.8)	20.3		1.00		
	yes (25/15.2)	36.0	0.002	3.39	1.56	7.40
Remains currently at RA or EA	< 10 years (163/98.2)	10.7		1.00		
	≥ 10 years (2/1.2)	25.2	0.071	2.99	0.91	9.77
FH of Chagas' disease	yes (127/77)	21.6		1.00		
	no (38/23)	23.0	0.912	1.05	0.47	2.32
FH of heart disease	yes (74/44.8)	22.2		1.00		
	no (91/55.2)	23.3	0.656	0.86	0.45	1.66
FH of sudden death	yes (59/35.8)	22.1		1.00		
	no (106/64.2)	24.1	0.839	1.05	0.63	1.77
Physical effort at current job	mild (36/21.8) + moderate(48/29.1)	25.3		1.00		
	intense (67/40.6)+ VI[b] (14/8.5)	20.0	0.183	0.64	0.33	1.24
Time at current job	< 10 years (42/25.5)	19.1		1.00		
	≥ 10 years (123/74.5)	25.3	0.318	1.42	0.72	2.80
Physical effort previous job	mild (11/8.9) /moderate (33/26.8)	18.2		1.00		
	intense (49/39.8) / VI[b](30/24.4)	22.1	0.362	1.48	0.64	3.45
Time at previous job	< 10 years (112/67.9)	19.5		1.00		
	≥ 10 years (53/32.1)	24.2	0.359	1.48	0.64	3.44
Drinking present/past	yes (75/45.5)	18.0		1.00		
	no (90/54.5)	28.4	0.438	1.30	0.67	2.51
Smoking present/past	yes (58/35.2)	23.4		1.00		
	no (107/64.8)	21.4	0.639	0.84	0.41	1.72
Thrombo-embolics	no (159/96.4)	22.8				
	yes (6/3.6)	20.0	0.564	0.556	0.08	4.08
Comorbidities	no (117/70.9)	25.2				
	yes (48/29.1)	16.7	0.941	0.97	0.44	2.14
Systemic hypertension	no (129/78.2)	23.6				
	yes (36/21.8)	19.4	0.617	1.24	0.54	2.84
BMI	↓ weight (9/5.5)	12.5	0.714			
	normal (92/55.8)	22.8	0.845	1.22	0.16	9.20
	↑ weight (47/28.5)	21.7	0.784	1.33	0.17	10.51
	obese (17/10.3)	29.4	0.485	2.15	0.25	18.51

Table 3
Univariate analysis for outcome 'worsening of CCC scores'. CD Outpatient ward/HC-UFMG (cont.)

Variable	Absolute # (n) / relative # (%) or stratification	Worsening incidence (%)	p-value[a]	HR	95% CI for HR	
					Lower limit	Upper limit
CTR	normal (144/87.3)	16.8				
	altered (21/12.7)	65.0	0.000	6.419	3.213	12.823
Ventricular arrhythmia grade on ET	Lown 0 (63/63)	17.5				
	Lown 1- 4 (37/37)	36.1	0.041	2.36	1.04	5.39
Top HR on ET	normal (81/81)	26.3				
	altered (19/19)	15.8	0.418	0.61	0.18	0.418
Blood pressure on ET	normal (26/26)	24.7				
	altered (74/74)	23.1	0.587	0.77	0.30	1.98
AHA functional class on ET	I (27/27)	25.9	0.651			
	II (44/44)	25.6	0.513	0.68	0.21	2.17
	III+IV (29/29)	20.7	0.871	1.09	0.40	2.96
cond.[c] dis.[d] AV/ IV Holter	no (79/55.6)	26.6				
	yes (63/44.4)	18.0	0.111	0.55	0.26	1.15
pauses ≥ 2 sec. on Holter	no (133/93.7)	21.4				
	yes (9/6.3)	44.4	0.043	2.99	1.04	8.64
SV[e] arrhythmia on Holter	no (107/75.4)	22.9				
	yes (35/24.6)	22.9	0.384	1.46	0.62	3.40
Ventricular arrhythmia complexity on Holter	0 and 1 (74/52.1)	16.4				
	2 to 4 (68/47.9)	29.9	0.056	2.05	0.98	4.28
Sustained VA[f] (pairs) on Holter	no (100/70.4)	16.2				
	yes (42/29.6)	39.0	0.004	3.09	1.42	6.72
NSVT on Holter	no (124/87.3)	18.7				
	yes (18/12.7)	52.9	0.003	1.47	1.14	1.90

a *: Cox's univariate model; b: VI: very intense; c: cond.: conduction; d: dis.: disorders; e: SV: supraventricular; f: VA: ventricular arrhythmia.

Table 4
Univariate analysis for outcome 'worsening of CCC scores'. CD Outpatient ward/HC-UFMG. Drinking (weekly alcohol intake and time of abuse) and smoking (pack-year)

Worsening of CCC scores	Estimation	Weekly alcohol intake (in grams)	Time of drinking abuse (in years)	Smoking (pack-year)
No	Quartile 1	22.0	12.0	458.5
	Median	58.0	21.0	1160.0
	Quartile 3	157.5	27.5	4042.5
Yes	Quartile 1	20.0	13.5	603.0
	Median	66.0	20.0	1020.0
	Quartile 3	197.0	27.0	4028.0
	p - value*	0.979	0.959	0.598
	HR	1.00	1.00	1.01
	95% CI to HR	[0.99; 1.01]	[0.96; 1.04]	[0.97; 1.05]

(*): Cox's univariate model.

Table 5
Univariate analysis of time (in years) patients have taken cardiovascular drugs for outcome 'worsening of CCC scores'. CD Outpatient ward/HC- UFMG

Variable	p-value*[a]	HR	95% CI to HR	
			Lower limit	Upper limit
Loop diuretics	0.036	1.17	1.01	1.36
HCTZ[b]	0.276	0.92	0.79	1.07
Digitalis	0.000	1.47	1.23	1.77
B-blockers	0.449	0.45	0.06	3.52
Spironolactone	0.004	1.42	1.12	1.80
ACEi/ARBs	0.030	1.13	1.01	1.26
Amiodarone	0.320	1.08	0.93	1.25

*[a]: Cox's univariate model; b: HCTZ: hydrochlorothiazide.

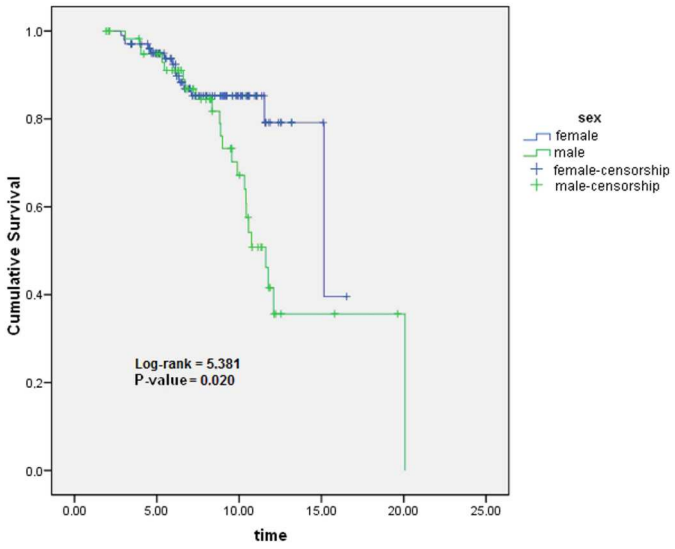

Fig. 2 - Kaplan-Meier estimator for time (in years) until the worsening of CCC scores by gender, CD Outpatient ward/HC-UFMG.

increased CTR, and time of use of digitalis (Table 6). The Median survival time to CCC score worsening was 15.15 (8.91-21.39) years (standard error = 3.18; 95% CI).

Analysis of the outcome "onset of left ventricular dysfunction": Even after including the variables that had $p < 0.20$ in the univariate analysis (Table 7), an adequate final regression model was not attained for multivariate analysis.

Analysis of sample stratified into ECG groups: 88 (53%) patients were categorized into group 1 (G1) and 77 (47%) into group 2 (G2). Left ventricular dysfunction was seen in 11 (12.5%) patients in G1 and in 13 (16.9%) in G2. Univariate analysis did not reveal a statistically significant difference between both groups (HR = 0.89) for the onset of left ventricular dysfunction (p = 0.788; 95% CI: 0.39-2.02). Relative risk (RR) was 1.4 and calculated sample detection power found to be 12.23%.

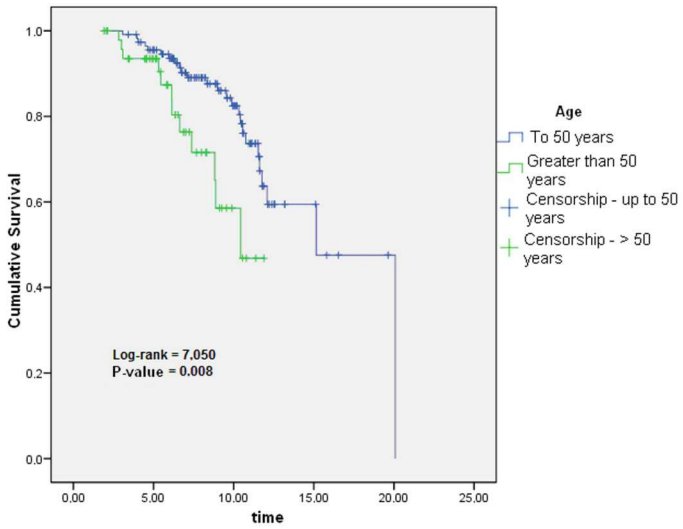

Fig. 3 - Kaplan-Meier estimator for time (in years) until the worsening of CCC scores by age range, CD Outpatient ward/HC-UFMG.

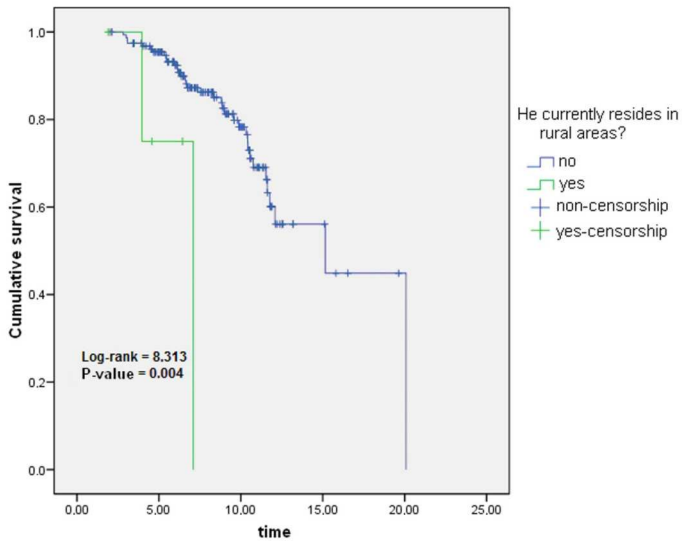

Fig. 4 - Kaplan-Meier estimator for time (in years) until the worsening of CCC scores for those currently residing in rural areas, CD Outpatient ward/HC-UFMG.

DISCUSSION

Chagas disease is a complex heterogeneous illness with wide variation in clinical course and prognosis. The advantages of the present study include the homogeneous sample of patients at earlier stages of CCC with no left ventricular dysfunction, having minimal abnormalities on ECG, examined through noninvasive risk markers that can be routinely measured, the duration of follow-up (mean 8.2 years), and the use of multivariate methods of statistical analysis. This study demonstrated that the variables finally found to be predictive factors for CCC progression for both outcomes - worsening of the CCC scores and the onset of left ventricular dysfunction – were male gender, living in rural areas, time of use of digitalis and increased cardiothoracic ratio.

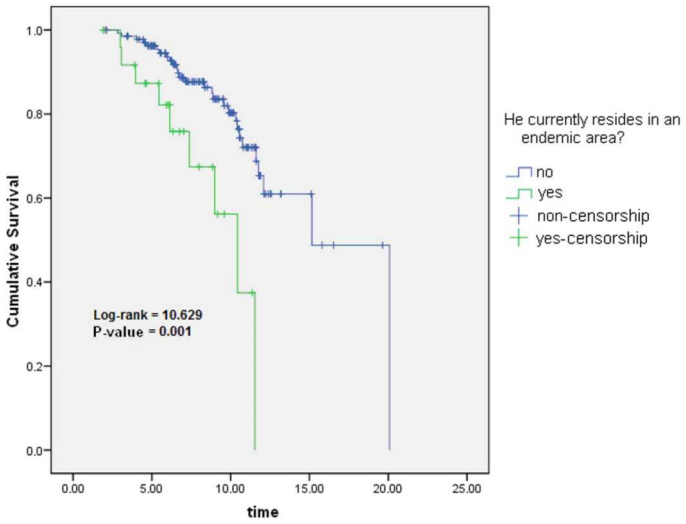

Fig. 5 - Kaplan-Meier estimator for time (in years) until the worsening of CCC scores for those currently residing in endemic areas, CD Outpatient ward/HC-UFMG.

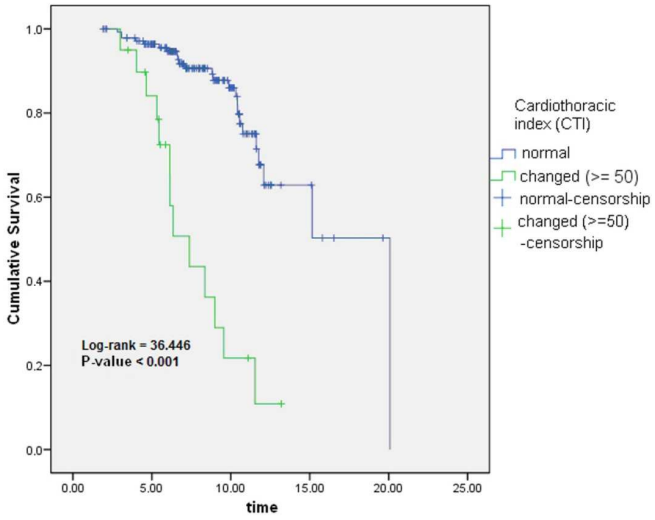

Fig. 6 - Kaplan-Meier estimator for time (in years) until the worsening of CCC scores based on CTR. CD Outpatient ward/HC-UFMG.

Table 6
Multivariate analysis of time until the worsening of CCC scores. CD Outpatient ward/HC-UFMG

Variable	Ratio	Standard error	Wald's test	p-value	HR	95% CI to HR	
						Lower limit	Upper limit
Male gender	1.03	0.39	6.99	0.008	2.81	1.31	6.03
Pauses ≥ 2 seconds on Holter	1.11	0.55	4.07	0.044	3.02	1.03	8.83
CTR ≥ 0.50	2.06	0.42	24.51	<0.001	7.87	3.48	17.82
Time taking digitalis (years)	0.35	0.11	10.15	0.001	1.41	1.14	1.75

Resorting to univariate analysis, this paper – as did other important longitudinal studies – has revealed the following as statistically signi□cant variables found to be predictive factors for CCC worsening as an outcome: male gender[12,14], age > 50 years[20,25,28]; CTR ≥ 0.50[13,14,22,25]; time of use of digitalis[30], identi□cation of ventricular arrhythmias in the ET[24] categorized from Lown 1 to 4; Holter monitoring showing pauses equal to or greater than two seconds, and ventricular arrhythmia – sustained and non-sustained VT[22,24]. A statistically signi□cant □nding – time taking cardiovascular medication – may be related to more severe cases of CCC (patients who needs treatment) as well as the variable "time of use of digitalis". However, this study was not designed to discuss such □ndings.

Upon looking into patients' current residential addresses in RA and CD EA two interesting issues surface: (1) the impact of exposure to reinfection in rural and endemic areas upon the deterioration of the patient's clinical status. The progressive decrease in morbidity and mortality seen in CD in all controlled endemic areas was clearly predicted by DIAS[11], who observed this in Bambuí, Minas Gerais, Brazil, where a pioneering effort was made to systematically eradicate the vector insect. The author attributed the decrease to the cessation of exogenous reinfections, probably by the same strain, responsible for the more severe cases of CD. And (2): access to healthcare services is more precarious in rural areas. It is clear that patients followed up at CD specialized care centers or at cardiology outpatient wards have greater access to therapy, enhanced compliance to treatment, better quality of life, and live longer, as the therapeutic arsenal used to treat heart failure from Chagas disease is highly effective and bene□cial for the patient's survival and quality of life, in addition to reducing hospitalization rates.

It was observed that patients with abnormal CTR have almost a 13-fold risk of this outcome happening, a very high risk, con□rming the important predictive value of chest radiography. When evaluating a patient with abnormal CTR, attention should be turned to their adequate treatment as soon as possible. Less than one fourth of the patients with CCC had abnormal CTR, stressing the diagnostic value of ECG, due to its signi□cant sensitivity in detecting abnormalities in early stage CCC[8,28]. Although ECG unspeci□c abnormalities can commonly occur in the elderly as a result of atherosclerosis, hypertension, ischemia etc., the presence of electrocardiographic repolarization abnormalities increase sensitivity for the diagnosis of acute Chagas disease[1]. Those abnormalities seem to persist. Some longitudinal studies have found unspecific abnormalities in the ECG to be independent predictive factors for worse prognoses and the progression of CCC[15,22,25], which reinforces the point

Table 7
Univariate comparison of ECG and CTR variables in both iterations of the study for outcome 'onset of ventricular dysfunction on ECHO'. CD Outpatient ward/HC-UFMG

Variable			Incidence of ventricular dysfunction on ECHO (%)	p-value*[a]	HR	95% CI to HR	
						Lower limit	Upper limit
TIME 1	PR interval* (msec)	≤ 200	14.02				
		> 200 & < 230	21.4	0.772	1.20	0.36	4.02
	HRate* (bpm)	< 60	17.5				
		≥ 60 & < 100	9.7	0.321	0.62	0.25	1.58
	QRS duration* (msec)	< 120	14.4				
		≥ 120	14.8	0.324	0.64	0.26	1.55
	RBBB + CRBBB	no	13.9				
		yes	15.6	0.352	0.67	0.28	1.57
	CRBBB	no	15.0				
		yes	13.5	0.212	0.56	0.22	1.40
TIME 2	PR interval* (msec)	≤ 200	11.8	0.169			
		> 200 & < 230	17.6	0.871	1.11	0.32	3.82
		≥ 230	41.7	0.061	2.62	0.96	7.19
	HRate* (bpm)	< 60	14.7				
		≥ 60 & < 100	14.5	0.612	0.81	0.36	1.83
	QRS duration* (msec)	< 120	11.3				
		≥ 120	19.1	0.852	1.08	0.47	2.49
	RBBB + CRBBB	no	13.7				
		yes	15.7	0.586	0.79	0.34	1.83
	CRBBB	no	14.8				
		yes	14.0	0.225	0.57	0.23	1.41
	CTR	normal	8.3				
		altered	57.1	0.000	12.73	5.34	30.33

a*: Cox's univariate model.

that ECG unspeci□c abnormalities are prevalent from acute phases of the disease. In the present study, a statistically signi□cant difference between both groups (G1 and G2) for the onset of left ventricular dysfunction was not found, which can be explained by two ideas: the possibility that both groups were not really particularly different, thereby not allowing the authors to lessen the risk of patients with more than one unspeci□c abnormalities in the ECG progress CCC, and the low calculated sample detection power found to be 12.23% in the present study.

In the present study, the most prevalent abnormalities found in ECG are in accordance with the literature[19] as well as the presence of ECG alterations being an independent predictive factor for poor prognosis of CCC[14,20,22,25]: QRS width was associated with mortality, as seen in the papers by RIBEIRO et al.[24]. A PR interval ≥ 0.16 seconds was shown to be an independent predictive factor[15]. Some papers have indicated that increased – and not reduced – heart rates are a predictive factor for mortality, but such a □nding, albeit not correlated to the worst prognosis in several longitudinal studies, has been frequently reported in clinical settings in association with heart disease progression and severe sinus bradycardia (HR under 40 bpm).

Concerning ECHO, stage I diastolic dysfunction was the most prevalent abnormality found in both iterations of the study, further supporting the □nding seen in the literature that it may occur even in Chagas patients without heart disease and precede systolic dysfunction in CCC4. Some authors[13] have described increased LV diastolic diameter as a predictive factor for poor prognosis of CCC, while PETTI et al.[20] correlated increased □nal LV diastolic diameter to death.

The authors' data show that occupational reorientation is needed as the disease progresses to cardiac involvement, but many factors act as barriers to successfully □nding a new career: the limits imposed upon the patient by the disease's clinical manifestations and complications[8,16], the lack of specialized training seen among CD patients due to adverse socioeconomic circumstances, the migration from rural areas to urban regions – where the types of jobs available differ tremendously, the stigma that haunts those diagnosed with CD – even when the diagnosis is not accompanied by occupational disability.

In the present study, a significant share of the patients were overweight (BMI > 25) or obese (BMI > 30) due to their lifestyle and a third of them had comorbidities, with systemic hypertension ranking highest. However, the prevalence rate of systemic hypertension in the studied population, made up exclusively of CD patients, was lower than

that found for the Brazilian population in general within the same age range[7]. In spite of some controversy, there are publications to further support this finding[17]. This study, however, was not designed to this aim. The statistically significant increase in the incidence of systemic hypertension and in the use of cardiovascular drugs between iterations 1 and 2 of the study supports the verification of its increased prevalence rates as patient age increases while CCC progresses, giving both diseases a summational character. Some patients took inadequately prescribed digitalis, despite the authors' efforts to convince patients and doctors of other services to stop it once it was not indicated. Increased CTR can result in a lack of opportunity of ready access to ACE inhibitor (this drug was first prescribed about ten years after the beginning of the study).

Low lethality rates in this paper relate to the overall status of the patients in the study. Mean follow-up was long enough to ensure that time was plenty for events to unfold, with regard to the onset of left ventricular dysfunction and CCC progression. Four patients died due to Chagas disease during the follow-up in this study, two due to sudden death and two due to heart failure requiring internation. Nowadays, there is a noticeable displacement of deaths to older patients, mainly among those from 50 to 79 years old[21]. More than 50% of the internations due to Chagas disease in Brazil occurred among this population. Heart failure is the main cause of hospitalization (approximately 50%) of the South American population and it presents high mortality especially in patients with Chagas etiology[6].

The limitations of the present study: selection bias might have occurred because patients with missing data were excluded and the multivariate analysis was restricted to the 165 patients who had complete data on all the variables. Although the authors believe that the patients in this cohort were representative of outpatients with Chagas heart disease in other areas of Brazil, further investigations involving this population are desirable. Patients with minimal abnormalities in their ECG were studied, thus it was necessary to define as G1 (group 1) and stage 1 those patients with two or more unspecific abnormalities, despite the low calculated sample detection power hindering the authors' ability to draw certain conclusions. The authors could not assess the effect of therapy because treatment was not controlled in the study. The loss of follow-ups was more than 5%, although these patients and those excluded were statistically similar.

Conclusion: The identification of factors associated with the progression of CCC is essential to adequate patient management. In the present study the most important predictors were: male gender, Holter monitoring showing pauses equal to or greater than two seconds, time of use of digitalis and increased cardiothoracic ratio. Several other potential prognostic factors were pointed out in the univariate analysis, which will also contribute to the improvement in CCC patients care.

AUTHORS CONTRIBUTIONS

Silvana de Araújo Silva, Eliane Dias Gontijo and Carlos Faria Santos Amaral: Study design; collection, analysis, and interpretation of data; writing of the paper; and decision to submit it for publication. João Carlos Pinto Dias: interpretation of data; writing of the paper; and decision to submit it for publication. Camila Gomes de Souza Andrade: collection, writing of the paper.

RESUMO

Preditores da evolução da cardiopatia chagásica crônica em pacientes sem disfunção ventricular esquerda

A identificação de preditores da progressão da cardiopatia chagásica crônica (CCC) é essencial ao manejo adequado do paciente. Estudo coorte não concorrente de 165 pacientes portadores de CCC entre 1985-2010 quanto a preditores independentes da evolução da CCC. Os desfechos foram piora da classificação da CCC e surgimento de disfunção ventricular esquerda ao ecoDopplercardiograma. Variáveis sócio-demográficas, epidemiológicas, clínicas e propedêuticas foram estudadas e realizadas análise descritiva, análise de sobrevida com análise univariada (Kaplan-Meier e modelo univariado de Cox) e multivariada (modelo de regressão de Cox). O seguimento foi de dois a 20 anos, com média de 8,2 anos. A média de idade dos pacientes foi de 44,8 anos (20-77 anos). Comparando ambos os tempos do estudo, no tempo 2 houve significância estatística do aumento do intervalo PR e da duração do QRS, além da redução da frequência cardíaca (Wilcoxon < 0,01). Os preditores da evolução da CCC no modelo final de regressão foram sexo masculino (HR = 2,81), pausas iguais ou maiores que dois segundos ao Holter (HR = 3,02), aumento do índice cardiotorácico (HR = 7,87) e tempo de uso de digital (HR = 1,41), destacando-se necessidade de seguimento e tratamento mais rigoroso para os chagásicos que cumulam estes fatores.

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