Acute Heart Failure in Patients with Chagas Cardiomyopathy: Results of the I Brazilian Heart Failure Registry (BREATHE)

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Abstract

Background: Although the clinical features of chronic Chagas' cardiomyopathy (CCC) have been well established, clinical data about the patients are scarce.

Objectives: The current analysis reports the results of the I Brazilian Heart Failure Registry (BREATHE) assessing baseline characteristics and clinical outcomes of patients with acute heart failure due to CCC.

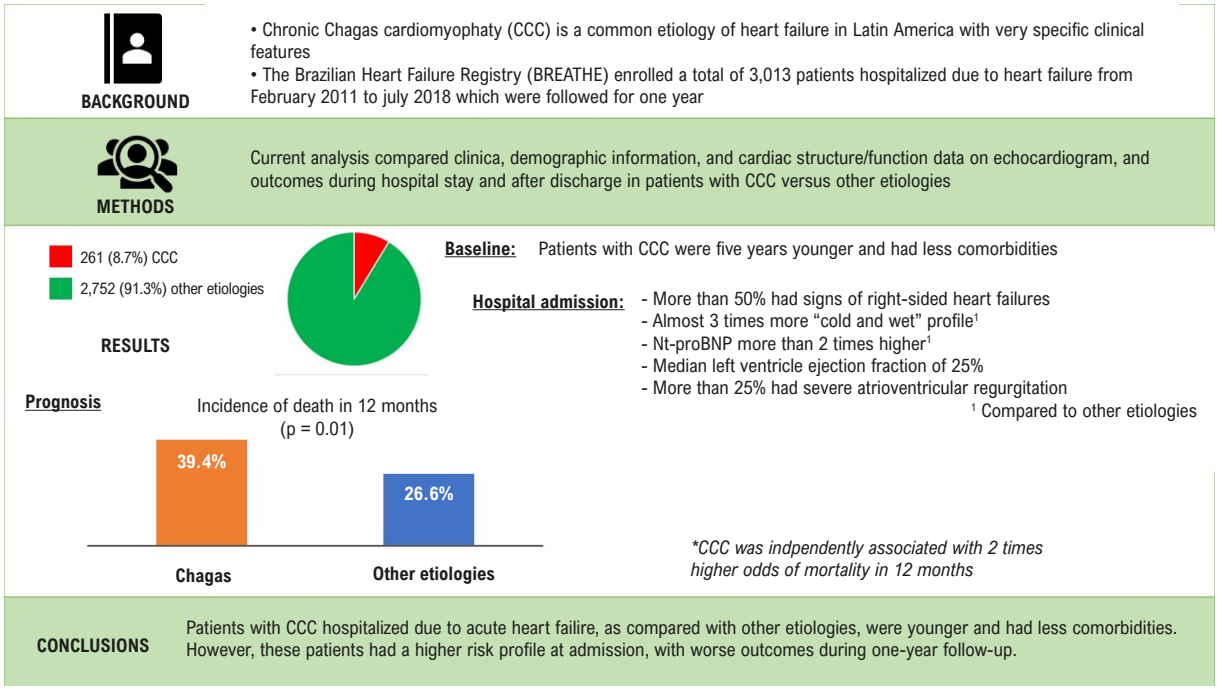
Methods: BREATHE enrolled a total of 3,013 adult patients hospitalized with acute heart failure. We analyzed comparatively 261 (8.7%) patients with chronic CCC and 2,752 (91.3%) patients with other etiologies. Clinical and demographic information, cardiac structure/function data on echocardiogram and outcomes during the hospital stay and after discharge were assessed in both groups. Uni and multivariate tests were performed and a p-value <0.05 was considered statistically significant.

Results: Patients with CCC presented lower systolic blood pressure (108.3 ± 26.1 vs 128.3 ± 30.3 mmHg, p<0.001) and left ventricle ejection fraction (25.4 [19 - 36]% vs 37 [27 - 54] %, p<0.001) with higher rates of jugular vein distension (54.8% vs 38.9%, p<0.001), hepatomegaly (47.9% vs 25.6%, p<0.001), and "cold and wet" clinical hemodynamic profile (27.2% vs 10.6%, p<0.001). Patients with CCC presented higher rate of the composite death or heart transplantation (17.4% vs. 11.1%, p=0.004), and higher cumulative incidence of death after 3 months (16.5% vs 10.8%, p=0.017), 6 months (25.3% vs 17.2%, p=0.006), and 12 months (39.4% vs 26.6%, p<0.001). Besides, CCC was independently associated with 12-month mortality risk with odds ratio = 2.02 (95% IC: 1.47-2.77).

Conclusion: Patients with CCC, hospitalized due to acute heart failure, in comparison to other etiologies, presented a higher risk profile that was associated with a poorer outcome during hospital stay and after discharge.

Keywords: Heart Failure, Chagas Disease, Chagas Cardiomyopathy, Dilated Cardiomyopathy.

Central Illustration: Acute Heart Failure in Patients with Chagas Cardiomyopathy: Results of the I Brazilian Heart Failure Registry (BREATHE)



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Introduction

Chagas' disease (CD), caused by the protozoan parasite *Trypanosona cruzi*, is considered a major public health problem in the endemic Latin America area encompassing 21 countries, with current evidence of persistent vector-borne transmission in many regions.[1]Despite being a neglected disease, it represents one of the most important causes of heart failure (HF) and sudden death. The World Health Organization estimates that six to seven million people worldwide, mostly in Latin America, are infected with Trypanosoma cruzi and up to a third with chronic infection develop secondary cardiac disease.[2]

The recent recognition that new cases of acute CD are related to oral infestation in many areas of the Amazonian region indicates a perpetuation of CD transmission.[3] Moreover, due to globalization and migratory flows, CD is also an emergent disease in nonendemic countries, such as the United States of America, Canada, Spain, France, Switzerland, Italy, Japan, and other countries in Asia and Oceania.[4,5]

Cardiac involvement is the most frequent and severe manifestation of CD in the chronic phase, and Chronic Chagas' Cardiomyopathy (CCC) is associated with specific structural and functional cardiac changes that may differentiate it from other causes of dilated cardiomyopathy.[6] In particular, CCC patients present early and predominantly right ventricular failure, intense autonomic denervation, regional left ventricular myocardial fibrosis with development of aneurisms, mainly in the apex, with increased risk of intramural thrombi and cardioembolic events. CCC is also associated to severe ventricular arrhythmia and conduction system disease, with increased risk of sudden cardiac death.[7]

Single-center cohort studies with heart failure (HF) outpatients reported worse outcomes in CCC patients as compared to other etiologies.[8,9] Analysis of recent multicenter trials that enrolled patients with HF and CCC also showed higher cumulative mortality in comparison to other etiologies.[10] However, studies addressing the clinical characteristics and prognostic data of CCC patients hospitalized due to HF decompensation are scarce and, to the best of our knowledge, there is no prospective multicentric study with a representative cohort.[11-14]

Thus, the current analysis aimed to characterize clinical and laboratorial manifestations and outcomes at one year follow-up of patients hospitalized with acute decompensated HF (AHF) enrolled in the Brazilian Heart Failure Registry (BREATHE), comparing patients with CCC with patients with other etiologies of HF.

Methods

Study design and participants

The rationale and design for the BREATHE has been published previously.[15,16] In brief, BREATHE was an observational, prospective, multicenter study that included patients with AHF admitted in public and private hospitals from the five geographical regions of Brazil. The registry was designed to identify clinical characteristics and treatment gaps among patients with AHF in Brazil.[15,16] Information was collected at hospital discharge and at 90, 180, and 365 days.[15,16] The first phase of the study (February 2011 to December 2012) included 1263 patients and the second phase of the study (June 2016 to July 2018), BREATHE Extension, enrolled 1898 patients.[16]

Patients with age ≥18 years old, hospitalized with a primary definite diagnosis of AHF according to the Boston criteria (≥ 8 point-score) and that signed a free and informed consent form were included.[15,16] Patients who underwent myocardial revascularization procedures (coronary angioplasty or surgery) in the last month and patients with signs of HF secondary to sepsis were excluded.

The etiology was defined by the site investigator, but it was recommended that the diagnosis of CD should be confirmed by two different serological tests. Comorbidities were also identified by the physician during clinical practice. Patients with CCC were compared to other etiologies in terms of baseline characteristics, in-hospital data and clinical outcomes during 12 months of follow-up.

Variables included in the current analysis

Data were collected at admission, at discharge and during one year after discharge. At admission, information regarding demographics, relevant medical history (including etiology of HF and cause of decompensation), clinical characteristics at admission (including hemodynamic profile), concomitant medications, echocardiographic and laboratory data were collected. Echocardiographic and laboratory tests were performed according to local protocols. At hospital discharge, information regarding quality-of-care indicators, in-hospital cardiology procedures, and medication use were collected. Clinical follow-up visits were conducted at 90, 180, and 365 days to collect data on major cardiovascular events, cardiac procedures (e.g. heart transplantation), medication use, and laboratory tests reported by the investigators. Follow-up visits could take place in person during routine care or by telephone. The detailed information collected during each study was previously reported.[15,16]

In the current analysis, all information collected from admission to 365 days from BREATHE was assessed by comparing patients with and without CCC.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median and interquartile range as appropriate. The analysis of normally distributed continuous variables was performed using histograms. Comparison between groups was performed using unpaired Student's t-test for variables with normal distribution and the Wilcoxon-Mann-Whitney test for asymmetric distribution variables. Categorical variables were described as absolute and relative frequencies, groups were compared by Fisher's exact test. For clinical events, death from all causes, and hospitalization due to HF decompensation, the cumulative incidence was estimated, and the groups were compared using the cause-specific proportional odds model. The identification of independent predictors for death from any cause within 12 months after discharge was

performed using logistic regression models. Initially, univariate analysis was performed for baseline variables: etiology (CD or other causes), age, sex, heath care, previous myocardial infarction, arterial hypertension, previous stroke/transient ischemic attack, atrial fibrillation, depression, chronic kidney disease, diabetes mellitus, chronic obstructive pulmonary disease, smoking status, and combined use of beta-blockers, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) and spironolactone at hospital discharge. Variables with p-value < 0.15 were included in a multivariate analysis. We performed also a sensitivity analysis including echocardiographic data in a multivariate model for all-cause mortality.

All analyses were performed using the statistical program R 4.1.1 (R Core Team, 2023); a p-value <0.05 was considered statistically significant.

Results

Baseline clinical and demographic characteristics

A total of 3,013 patients were included in the BREATHE (both phases): 261 patients with CCC (8.7%) and 2.752 patients (91.3%) with other etiologies for heart failure. Most of the non-CCC patients presented ischemic heart disease (32.4%), hypertension (21.2%), valvular heart disease (15.4%) and idiopathic dilated cardiomyopathy (15.0%).

Patients with CCC were younger, with higher proportion of blacks, and lower rate of risk factors for atherosclerotic disease, as hypertension, diabetes, hypercholesterolemia, and tobacco use (Table 1). The frequency of other comorbidities, as depression and chronic obstructive pulmonary disease was higher in the group without CD. However, the rate of previous stroke was higher in CCC patients. A higher proportion of NYHA functional class III or IV was observed in CCC patients but no significant difference in chronic renal disease prevalence. Regarding medications in use before admission, CCC patients exhibited lower rate of aspirin, statins, but higher rates of betablockers, loop diuretics, spironolactone and amiodarone use (Table S1).

Clinical presentation at hospital admission

Regarding the clinical presentation at hospital admission for AHF, CCC patients in comparison to other etiologies presented a higher prevalence of signs and symptoms of systemic congestion, like jugular vein distension and hepatomegaly, but without a statistically significant difference in terms of signs of pulmonary congestion, as pulmonary rales. Blood pressure and heart rate values were also significantly lower in CCC patients (Table 2).

The non-invasive Stevenson clinical/hemodynamic "C" profile (cold and wet) was more prevalent in CCC (27.2%) than in other etiologies (10.6%). Conversely, the "B" profile (warm and wet) was more prevalent in patients with other etiologies (72.8%) than in CCC patients (59.8%). Non-adherence was the most common cause of decompensation in both groups, but infection was more commonly related to non-CCC etiologies (Table 2).

In the blood tests performed according to physician's discretion, patients with CCC presented higher levels of creatinine and urea, with more pronounced reduction in estimated glomerular filtration rate. In addition, CCC patients presented lower serum sodium levels, higher bilirubin levels and higher hemoglobin compared to other etiologies (Table 2).

Evaluation of cardiac function and remodeling by transthoracic echocardiogram was performed within the first 24 hours after admission in 29.9% of CCC and 41.5% of non-CCC patients, showed that CCC patients presented lower left ventricle ejection fraction (LVEF), larger left ventricular systolic and diastolic dimensions, larger left atrium diameter, and higher prevalence of severe mitral and tricuspid regurgitation, as compared to patients with other etiologies (Table 2). Severe tricuspid and mitral regurgitation were present each one in more than one quarter of the patients.

Medications and procedures during hospitalization

Regarding the medications used during hospitalization, higher proportion of CCC patients received betablockers, loop diuretics, spironolactone, and digoxin (Table S2). However, vasodilators were less prescribed in CCC patients (4.6% vs. 9.9%). Inotropic agents, mainly dobutamine, were more frequently prescribed in CCC patients (23.8%) in comparison to non-CCC patients (6.8%), p < 0.0001.

Quality indicators of evidence-based therapies

Among patients with ejection fraction ≤ 40%, at discharge, the use of beta-blockers was lower in CCC patients compared to other etiologies (Table S2). There was no significant difference in other medications at discharge, except for amiodarone and digoxin that were more frequently prescribed in CCC patients (Table S2).

Nonpharmacologic recommendations including dietary counseling, instructions about correct drug usage, physical activity and smoke cessation were similar in patients with CCC and other etiologies (Table S2). Explanations about worsening symptoms were less common in patients with CCC (61.9% vs 69.8%)

Clinical outcome

There was no significant difference concerning in-hospital mortality (13.6% vs. 10.7%; p=0.17) (Figure 1) but there was a higher rate of heart transplantation in CCC in comparison with non-CCC patients (4.7% vs. 0.6%; p < 0.001). The rates of pacemaker cardiac resynchronization therapy/implantable cardioverter device use were also higher in CCC while valve surgery rates were lower in this population (Table 3).

After discharge, CCC patients presented significantly higher cumulative incidence of the composite death or heart transplantation (17.4% vs. 11.1%, p=0.004), and higher cumulative incidence of death after three months (16.5% vs. 10.8%, p=0.017), 6 months (25.3% vs. 17.2%, p=0.006), and 12 months (39.4% vs. 26.6%, p<0.001) (Figure 1). In a multivariate analysis, CCC was independently associated with 12-month mortality risk (Odds ratio = 2.02 [95% CI: 1.47;2.77]) (Table 4).

Table 1 – Demographic and clinical characteristics of the study population

Characteristics		Chagas' Cardiomyopathy n=261 (8.7%)	Other etiologies n=2752 (91.3%)	p
Demographic				
	Age (years), mean ± SD	60.6 ± 13.9	65.7 ± 15.7	<0.001
	Female gender, n (%)	101 (38.7)	1082 (39.3)	0.897
Education level				0.001
	Not literate/Some elementary school, n (%)	152 (58.5%)	1343 (48.8%)	
	Elementary school/Some high school, n (%)	60 (23.1%)	614 (22.3%)	
	Completed high school, n (%)	40 (15.4%)	535 (19.4%)	
	Complete College or higher degree, n (%)	8 (3.1%)	260 (9.4%)	
Service category				0.003
	Public Healthcare, n (%)	213 (81.6%)	1991 (72.3%)	
	Private, n (%)	9 (3.4%)	201 (7.3%)	
	Health insurance, n (%)	39 (14.9%)	560 (20.3%)	
Race				<0.001
	White, n (%)	114 (43.7)	1637 (59.5)	
	Black, n (%)	145 (55.5)	1070 (38.8)	
	Other, n (%)	2 (0.8)	45 (1.7)	
Clinical				
Heart failure etiology	Ischemic heart disease, n (%)	-	892 (32.4)	
	Hypertension, n (%)	-	583 (21.2)	
	Idiopatic n (%)	-	414 (15.0)	
	Valve disease, n (%)	-	425 (15.4)	
	Other, n (%)	-	438 (15.9)	
Comorbidities	Hypertension n (%)	111 (42.5)	2142 (77.8)	<0.001
	Diabetes, n (%)	40 (15.3)	1094 (39.8)	<0.001
	Hypercholesterolemia n (%)	47 (18.0)	1134 (41.2)	<0.001
	Previous Stroke, TIA n (%)	44 (16.9)	338 (12.3)	0.04
	Chronic renal disease, n (%)	48 (18.4)	596 (21.7)	0.236
	Atrial fibrillation	77 (29.5)	803 (29.2)	0.943
	COPD, n (%)	23 (8.8)	461 (16.8)	0.001
	Depression, n (%)	18 (6.9)	378 (14.0)	0.001
	Sedentary, n (%)	105 (77)	902 (81)	0.319
	Smoking, n (%)	13 (5)	272 (9.9)	0.001
	Alcoholism (%)	42 (16.1)	489 (17.8)	0.552
NYHA Functional class				<0.001
	I, n (%)	2 (0.9)	28 (1.2)	
	II, n (%)	7 (3.1)	198 (8.7)	
	III, n (%)	86 (37.7)	1024 (44.9)	
	IV, n (%)	133 (58.3)	1029 (45.2)	

History of arrhythmia				<0.001
	Sustained ventricular tachycardia, n (%)	8 (21.6%)	11 (2.9%)	
	Non sustained ventricular tachycardia, n (%)	2 (5.4%)	3 (0.8%)	
	Ventricular fibrillation, n (%)	0 (0%)	6 (1.6%)	
	Atrial fibrillation, n (%)	18 (48.6%)	338 (89.2%)	
	Complete atrioventricular block, n (%)	9 (24.3%)	21 (5.5%)	

COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association.

Table 2 – Clinical and laboratorial characteristics at hospital admission

Characteristic	Chagas' cardiomyopathy n=261	Other etiologies n = 2752	p
Clinical evaluation			
Dyspnea, n (%)	253 (96.9%)	2615 (95.2%)	0.224
Jugular vein distension, n (%)	143 (54.8)	1071 (38.9%)	<0.001
Hepatomegaly, n (%)	125 (47.9)	704 (25.6%)	<0.001
Pulmonary rales, n (%)	164 (62.8)	1865 (67.8)	0.112
Ankle edema, n (%)	198 (75.9)	1974 (71.7)	0.172
SBP, mean ± SD (mmHg)	108.3 ± 26.1	128.3 ± 30.3	<0.001
DBP, mean ± SD (mmHg)	68.7 ± 16.3	77.5 ± 18.0	<0.001
HR, mean ± SD (bpm)	77.3 ± 22.1	88.5 ± 23.2	<0.001
Body weight, mean ± SD (Kg)	66.8 ± 14.6	74.4 ± 18.2	<0.001
Clinical hemodynamic profile			
A – Warm-and-dry	25 (9.6%)	363 (13.2%)	<0.001
B – Warm -and-wet	156 (59.8%)	2004 (72.8%)	
C – Cold-and-wet	71 (27.2%)	293 10.6%)	
L – Cold-and-dry	9 (3.4%)	92 (3.3%)	
Trigger for decompensation			
Infection, n (%)	32 (12.3%)	609 (22.2%)	<0.001
Valve disease, n (%)	4 (1.5%)	305 (11.1%)	<0.001
Non-adherence, n (%)	66 (25.4%)	770 (28.0%)	0.385
Excessive sodium intake, n (%)	33 (12.7%)	222 (8.1%)	0.014
Arrhythmia, n (%)	38 (14.6%)	383 (13.9%)	0.779
Pulmonary embolism, n (%)	1 (0.4%)	15 (0.5%)	1.000
Cardiac arrest, n (%)	2 (0.8%)	3 (0.1%)	0.062
Others, n (%)	107 (41.2%)	748 (27.2%)	< 0.001
Blood Biochemical analysis			
Creatinine (mg/dL), median [quartiles]	1.4 [1.1 – 1.8]	1.2 [1.0 – 1.7]	0.001
Estimated Glomerular filtration rate (MDRD) , median [quartiles]	51.9 [37.1 - 62.9]	53.9 [36.9 - 72.9]	0.04
Urea (mg/dL), median [quartiles]	60.5 [43.0 - 91.0]	56.0 [41 - 86]	0.035
Sodium (mg/dL), median [quartiles]	136.0 [134.0 – 139.0]	138.0 [135.0 – 141.0]	<0.001
Potassium (mg/dL), median [quartiles]	4.4 [3.9 – 4.9]	4.4 [4.0 – 4.8]	0.894
Glucose (mg/dL); median [quartiles]	103 [85 - 126]	119 [96 - 159]	<0.001

Hb (g/dL), median [quartiles]	13.1 [11.4 - 14,1]	12.5 [11.0 – 13.9]	0.027
Bilirubin (mg/dL), median [quartiles]	2.7 [1.6 - 4]	1.1 [0.7 – 1.8]	0.001
NT-ProBNP (pg/ml); median [quartiles]	12022 [3012 - 287850]	5380.5 [2538.8 - 13080.8]	0.067
BNP (pg/ml); median [quartiles]	1591 [681 - 3838.2]	851 [434.5 - 1520.5]	0.062
Echocardiogram (first 24 h)	78/261 (29.9%)	1142/2752 (41.5%)	<0.001
LVDD (mm), median [quartiles]	65 [57 – 72.8]	59 [51 - 66]	<0.001
LVSD (mm), median [quartiles]	58 [45 – 65.8]	48 [34 - 57]	<0.001
LVEF (%), median [quartiles]	25.4 [19.0 – 36.0]	37 [27.0 – 54.0]	<0.001
LAD (mm), median [quartiles]	48 [43 - 53]	46 [42 - 52]	0.075
Severe mitral valve regurgitation, n (%)	21/78 (26.9%)	138/1128 (12.2%)	0.001
Severe tricuspid regurgitation, n (%)	20/78 (25.6%)	114/1128 (10.1)	<0.001
ECG			
Sinus rhythm, n (%)	35 (34%)	803 (57.4%)	<0.001
Atrial fibrillation, n (%)	33 (32%)	466 (33.3%)	0.829
Left bundle branch block, n (%)	12 (11.7%)	267 (19.1%)	0.066
Pacemaker, n (%)	36 (35%)	105 (7.5%)	<0.001

SBP: systolic blood pressure; DBP: dyastolic blood pressure; HR: heart rate; Hb: hemoglobin; LVDD: left ventricle diastolic diameter; LVSD: left ventricle systolic diameter; LVEF: left ventricle ejection fraction; LAD: left atrium diameter; ECG: electrocardiogram.

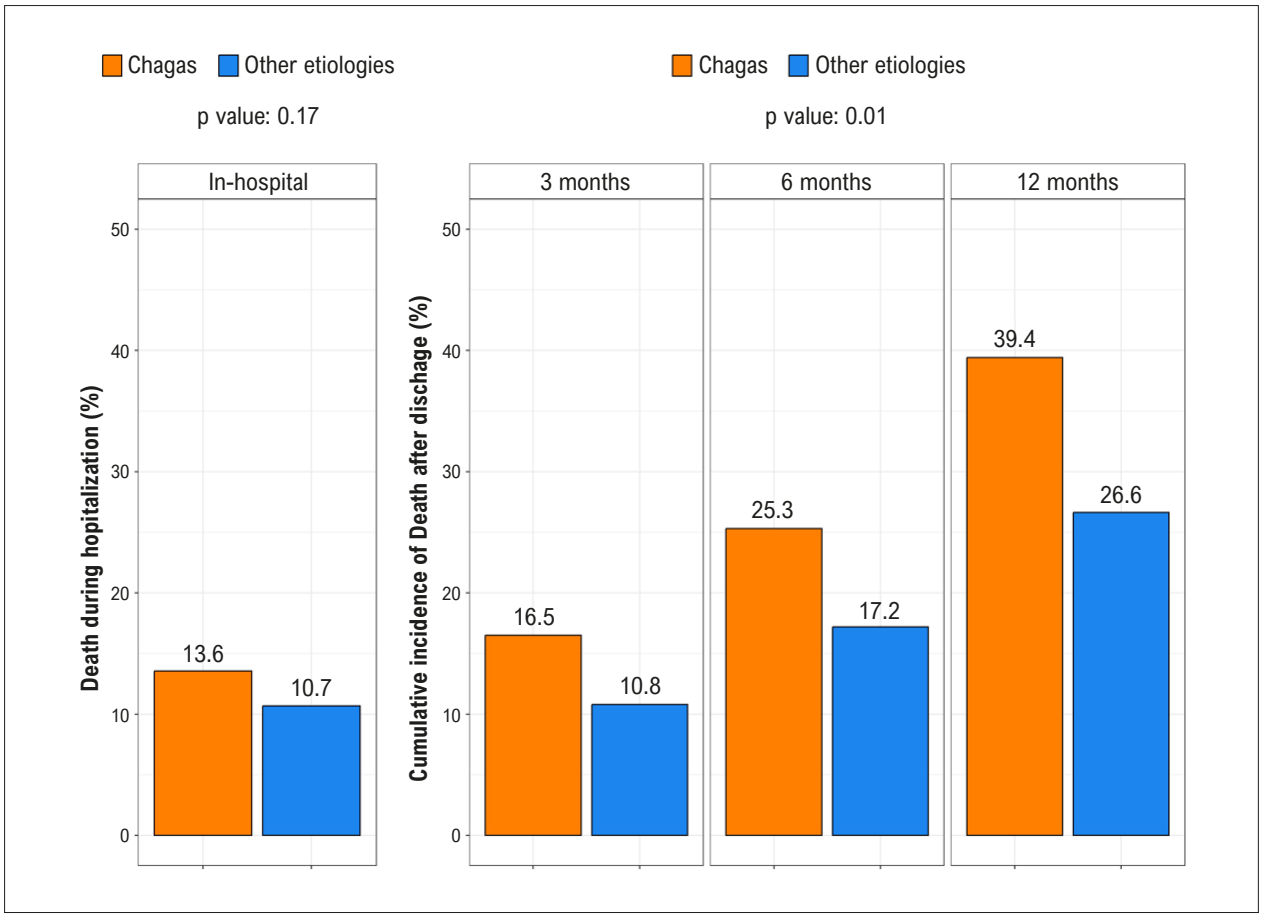

Figure 1 – *In-hospital mortality and cumulative incidence of mortality after discharge, in both groups.*

Table 3 – Outcomes and procedures/interventions during hospitalization

	Chagas' Cardiomyopathy (n=261)	Other Etiologies (n=2752)	p value
First 24h mortality, n (%)	0/261 (0%)	37/2752 (1.3%)	0.071
In-hospital mortality, n (%)	35/258 (13.6%)	289/2704 (10.7%)	0.174
Hospital stay (days), median [quartiles]	12 [6 - 30.8]	12 [6 - 25]	0.902
Procedures/interventions (total)	40/258 (15.5%)	232/2667 (8.7%)	0.001
CABG, n (%)	1/258 (0.4%)	19/2667 (0.7%)	1
Valve surgery, n (%)	1/258 (0.4%)	96/2667 (3.6%)	0.003
PCI, n (%)	4/258 (1.6%)	57/2667 (2.1%)	0.653
ICD/CRT implantation, n (%)	11/258 (4.3%)	22/2667 (0.8%)	<0.001
Pacemaker implantation, n (%)	14/258 (5.4%)	37/2667 (1.4%)	<0.001
Heart Transplantation, n (%)	12/258 (4.7%)	15/2667 (0.6%)	<0.001

CABG: coronary artery bypass graft surgery; PCI: percutaneous coronary intervention; ICD: implantable cardioverter device; CRT: cardiac resynchronization therapy.

Table 4 – Univariate and multivariate analysis for all-cause mortality after discharge

Variable	Univariate		Multivariate	
	Odds Ratio [95% IC]	p value	Odds Ratio [95% IC]	p value
Chagas' cardiomyopathy	1.791 [1.322; 2.414]	<0.001	2.025 [1.475; 2.771]	<0.001
Age (5 years increase)	1.064 [1.033; 1.098]	<0.001	1.086 [1.050; 1.125]	<0.001
Female gender	0.894 [0.742; 1.077]	0.240		
Private institution hospitalization	0.581 [0.470; 0.715]	<0.001	0.483 [0.385; 0.603]	<0.001
Previous myocardial infarction	1.150 [0.938; 1.407]	0.177		
Arterial hypertension	0.984 [0.801; 1.214]	0.881		
Previous stroke/TIA	1.246 [0.955; 1.617]	0.101	1.074 [0.816; 1.404]	0.607
Atrial fibrillation	1.172 [0.963; 1.423]	0.111	1.169 [0.954; 1.432]	0.130
Depression	0.904 [0.692; 1.170]	0.448		
Chronic renal failure	1.462 [1.181; 1.808]	<0.001	1.393 [1.114; 1.739]	0.003
Diabetes Mellitus	1.174 [0.975; 1.412]	0.090	1.127 [0.927; 1.370]	0.228
COPD	1.340 [1.055; 1.694]	0.015	1.188 [0.929; 1.515]	0.167
Tobacco use	1.103 [0.911; 1.334]	0.315		
Triple therapy at discharge (ACEi/ARB, betablocker, MRA)	0.811 [0.670; 0.980]	0.031	0.855 [0.701; 1.041]	0.120

Variables showing p value < 0.15 in the univariate analysis were candidates for the multivariate analysis. TIA: transient ischemic attack; COPD: chronic obstructive pulmonary disease; ACEi: angiotensin converter enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist.

Despite a higher risk of all-cause readmission, we found no difference among groups in the cumulative incidence of re-hospitalization for decompensated HF at three, six or 12 months considering death as a competing risk (Figure 2). Echocardiographic data available was not included as an independent variable in the multivariate model (Table S3).

The Central Illustration summarizes the main findings described above.

Discussion

The main results of our analysis show that CCC patients hospitalized with AHF, in comparison to other HF etiologies,

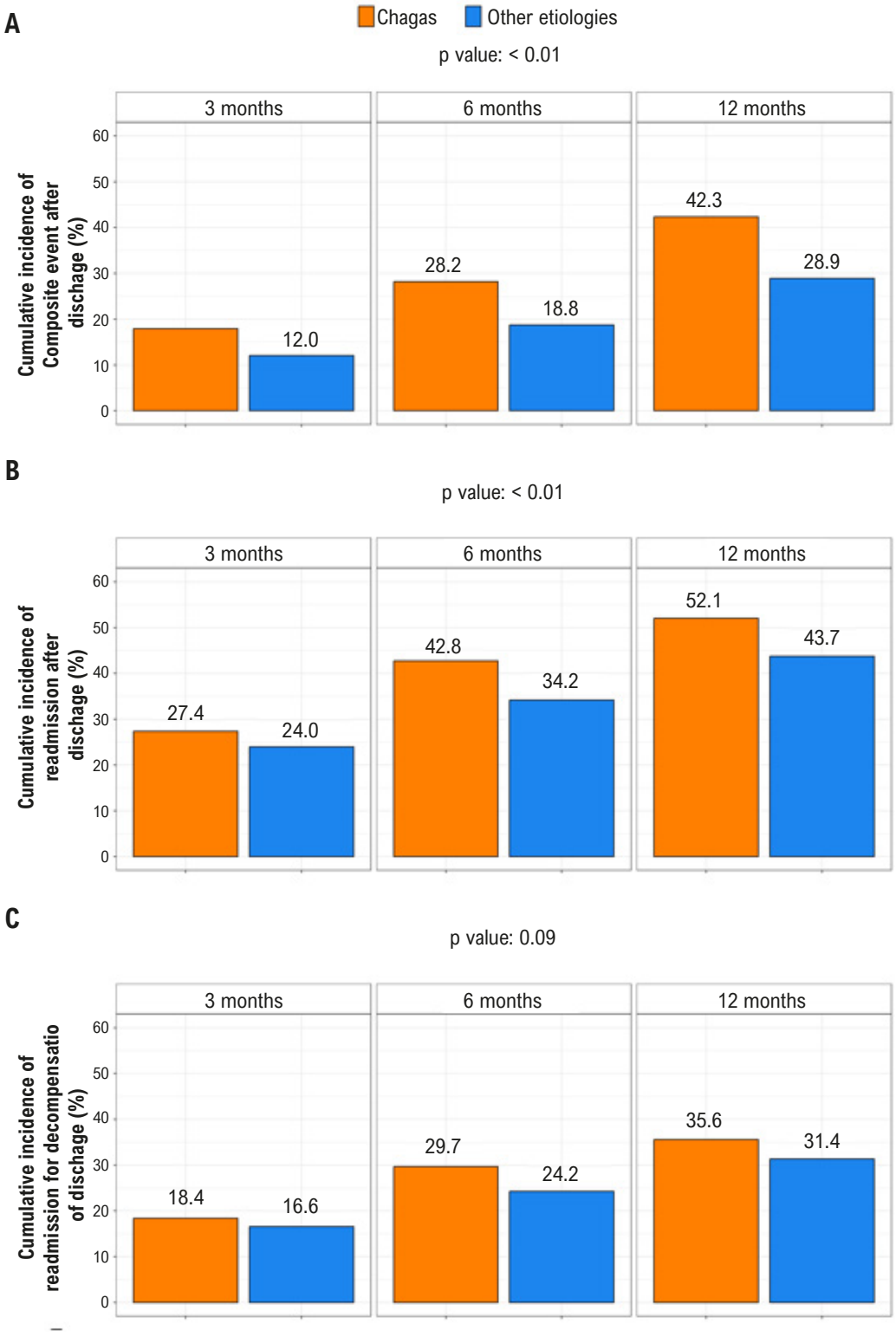

Figure 2 – *Cumulative incidence of composite event included all-cause death, myocardial infarction, stroke, cardiac arrest (Panel A), re-hospitalization (Panel B), and re-hospitalization for heart failure decompensation after discharge at three, six and 12 months of follow-up in both groups (considering death from all causes as a competitive risk).*

present more prominent findings of systemic congestion, with more severe renal and hepatic dysfunction, and usually with cold-and-wet hemodynamic profile. Also, these patients have a higher need for inotropes during hospitalization, and more severe structural and functional cardiac changes in echocardiographic assessment. In addition to these characteristics, it was also identified poorer outcomes during hospitalization and after hospital discharge among patients with CCC.

Our study population reflects differences of patients with CCC including a higher proportion of black race. Nevertheless, this variable was self-reported, and the percentage of mixed race was lower than previous reports.[17] Beyond race, the BREATHE also showed that patients with CCC were younger, and had a lower prevalence of cardiovascular risk factors as hypertension, smoking, diabetes and hypercholesterolemia, commonly related to ischemic heart disease, more prevalent in non-CCC patients. Despite this clinical profile of lower risk for cardiovascular events, CCC patients had a higher prevalence of history of stroke. This finding reinforces CCC as a main risk factor for cardioembolic stroke in patients with HF, with an important relation to apical aneurysm, left ventricular disfunction and ECG abnormalities.[18-20] Strategies to reduce the risk of stroke in patients with CCC should be explored in clinical trials.[18-21]

Another finding from this analysis that would be useful for clinical practice is related to clinical presentation at the hospital admission. CCC patients as compared to non-CCC patients presented higher rates of jugular vein distension and hepatomegaly, but similar rates of pulmonary rales and dyspnea, representing higher intensity of systemic over lung congestion. These physical examination abnormalities are probably related to more severe right ventricle dysfunction.[22,23] This aspect agrees with previous studies reporting that right ventricular dysfunction is an early finding in the clinical course of CCC and is frequently more evident than left ventricular dysfunction.[22,23] In addition, it is also conceivable that higher systemic venous pressures in CCC patients is the probable mechanism associated to the higher levels of creatinine, denoting a cardiorenal syndrome secondary to more severe renal congestion.[24] We also observed increased bilirubin levels and a higher rate of hepatomegaly in the physical examination, probably reflecting more severe hepatic lesion secondary to pronounced systemic congestion. Thus, these results indicate higher rates of target-organ dysfunctions associated with more severe visceral congestion in CCC patients, abnormalities classically associated with worse outcomes in AHF patients.[24,25]

Patients with CCC had a higher risk profile during admission including a higher proportion of "C" hemodynamic profile, as consequence of higher rate of inotropic use and lower blood pressure. This hemodynamic profile is also one explanation for more frequent organ dysfunction (renal, hepatic) among patients with CCC. Other risk markers included reduced levels of serum sodium, probably reflecting severe hypervolemia and a dilutional mechanism. Higher rates of loop diuretic, spironolactone, digoxin and betablocker in this group also indicates more advanced disease than other etiologies. One in four patients with CCC had severe tricuspid regurgitation which may be a potential target for new transcatheter approaches that could also be tested in patients with CD, especially due to the high frequency of systemic congestion. All these clinical, laboratory and echocardiographic characteristics reflect in worse clinical outcomes during hospital stay and after discharge. The absence of statistical difference regarding re-hospitalization may reflect competing risks related to a higher risk of death after discharge in CCC patients. Studies assessing the performance of models for prognosis prediction of patients with HF[26] should also consider etiology, especially in countries with higher prevalence of CCC.

Study limitations

The follow-up time of one year after hospitalization limits the evaluation of later complications, especially all-cause mortality. We could not perform survival analysis of time to event since the specific date of the event was not collected. In addition, even considering the statistical adjustment of variables in multivariate analysis, some variables related to the clinical outcome may not be included in the model due to absence of systematic data collection as echocardiogram data which had limited information. Nevertheless, the current analysis reflects the evaluation of variables commonly available in clinical practice and indicates an important prognosis implication of CCC etiology both during hospitalization and after discharge. Finally, we had few patients in the north of Brazil and all the sites had minimal infrastructure for clinical research. Thus, these findings could be different in some regions with more limited resources.

Conclusion

Patients with Chagas cardiomyopathy hospitalized due to AHF, in comparison to other etiologies, presented with different clinical characteristics and a higher risk profile that was associated with a poorer outcome during hospital stay and after discharge. Specific approaches are warranted to improve outcomes among patients with Chagas cardiomyopathy hospitalized due to AHF.

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Author Contributions

Conception and design of the research: Barros e Silva PGM, Albuquerque DC, Lopes RD, Nogueira PR, Freitas Jr AF, Simões MV; Data collection: Barros e Silva PGM, Albuquerque DC, Nogueira PR, Freitas Jr AF, Nascimento CV, Mady C, Santos ES, Hernandes ME, Rivera MAM, Souza Neto JD, Rabelo A, Canesin MF, Reis H, Armstrong AC, Hoffmann C, Santos RHN, Jesuino IA, Rohde LE, Moura LZ, Marcondes-Braga FG, Mesquita ET,[4] Figueiredo Neto JA, Mourilhe-Rocha R, Beck-da-Silva L, Oliveira Junior MT, Simões MV; Analysis and interpretation of the data: Barros e Silva PGM, Albuquerque DC, Lopes RD, Nogueira PR, Freitas Jr AF, Nascimento CV, Mady C, Santos ES, Hernandes ME, Rivera MAM, Souza Neto JD, Rabelo A,

Canesin MF, Reis H, Armstrong AC, Hoffmann C, Santos RHN, Jesuino IA, Rohde LE, Moura LZ, Marcondes-Braga FG, Mesquita ET,[4] Figueiredo Neto JA, Mourilhe-Rocha R, Beck-da-Silva L, Oliveira Junior MT, Simões MV; Statistical analysis: Barros e Silva PGM; Obtaining financing: Barros e Silva PGM, Albuquerque DC; Writing of the manuscript: Barros e Silva PGM; Critical revision of the manuscript for content: Albuquerque DC, Lopes RD, Nogueira PR, Freitas Jr AF, Nascimento CV, Mady C, Santos ES, Hernandes ME, Rivera MAM, Souza Neto JD, Rabelo A, Canesin MF, Reis H, Armstrong AC, Hoffmann C, Santos RHN, Jesuino IA, Rohde LE, Moura LZ, Marcondes-Braga FG, Mesquita ET,[4] Figueiredo Neto JA, Mourilhe-Rocha R, Beck-da-Silva L, Oliveira Junior MT, Simões MV.

Potential conflict of interest

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Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital do Coração under the protocol number CAAE: 53595816.8.0000.0060. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Data Availability

The underlying content of the research text is contained within the manuscript.

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*Supplemental Materials

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