ORIGINAL RESEARCH ARTICLE

The course of patients with Chagas heart disease during episodes of decompensated heart failure

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Abstract

Aims   This study aimed to analyse the clinical presentation and prognosis of patients with Chagas cardiomyopathy and decompensated heart failure (HF), as compared with other aetiologies.

Methods and results   A prospective cohort of patients admitted with decompensated HF. We included 767 patients (63.9% male), with median age of 58 years [interquartile range 48.2–66.7 years]. Main aetiologies were non-Chagas/non-ischaemic cardiomyopathies in 389 (50.7%) patients, ischaemic disease in 209 (27.2%), and Chagas disease in 169 (22%). Median left ventricular ejection fraction was 26% (interquartile range 22–35%). Patients with Chagas differed from both patients with non-Chagas/non-ischaemic and ischaemic cardiomyopathies for a higher proportion of cardiogenic shock at admission (17.8%, 11.6%, and 11%, respectively, $P < 0.001$) and had lower blood pressure at admission (systolic blood pressure 90 [80–102.5], 100 [85–110], and 100 [88.2–120] mmHg, $P < 0.001$) and lower heart rate (heart rate 71 [60–80], 87 [70–102], and 79 [64–96.5] b.p.m., $P < 0.001$). Further, patients with Chagas had higher serum BNP level (1544 [734–3148], 1061 [465–239], and 927 [369–1455] pg/mL, $P < 0.001$), higher serum bilirubin (1.4 [0.922.44], 1.2 [0.77–2.19], and 0.84 [0.49–1.45] mg/dL, $P < 0.001$), larger left ventricular diameter (68 [63–73], 67 [58–74], and 62 [56.8–68.3] mm, respectively, $P < 0.001$), lower left ventricular ejection fraction (25 [21–30]%, 26 [22–35]%, and 30 [25–38]%, $P < 0.001$), and a higher proportion of patients with right ventricular function (48.8%, 40.7%, and 25.9%, $P < 0.001$). Patients with Chagas disease were more likely to receive inotropes than patients with non-Chagas/non-ischaemic and ischaemic cardiomyopathies (77.5%, 67.5%, and 62.5%, respectively, $P = 0.007$) and also to receive intra-aortic balloon pumping (30.8%, 16.2%, and 10.5%, $P < 0.001$). Overall, the rates of death or urgent transplant were higher among patients with Chagas than in other aetiologies, a difference that was driven mostly due to increased rate of heart transplant during hospital admission (20.2%, 10.3%, and 8.1%). The prognosis of patients at 180 days after hospital admission was worse for patients with Chagas disease as compared with other aetiologies. In patients with Chagas, age [odds ratio (OR) = 0.934, confidence interval (CI)$_{95\%}$ 0.901–0.982, $P = 0.005$], right ventricular dysfunction by echocardiography (OR = 2.68, CI$_{95\%}$ 1.055–6.81, $P = 0.016$), and urea (OR = 1.009, CI$_{95\%}$ 1.001–1.018, $P = 0.038$) were significantly associated with prognosis.

Conclusions   Patients with Chagas cardiomyopathy and decompensated HF have a distinct clinical presentation and worse prognosis compared with other aetiologies.

Introduction

Chagas disease is a clinical condition of growing epidemiological importance. In Latin America alone, it is estimated that 6 million people have been infected with *Trypanosoma cruzi*[1]

and an unknown number of individuals are silent carriers; more recently, migration has further contributed to the dissemination of the disease,[2] and currently 400 000 infected individuals are thought to live in non-endemic areas.[3] Importantly, it is estimated that up to 20–30% of the infected

individuals may eventually develop cardiac disease, and Chagas cardiomyopathy is reported to be the cause of heart failure (HF) in up to 25% of the HF cases in referral centres.[4]

Chronic Chagas cardiomyopathy is thought to have a distinct presentation when compared with other HF aetiologies. Patients with Chagas are younger and have less co-morbidities but have more frequently bradycardia, conduction abnormalities, arterial hypotension, right ventricular dysfunction, and thromboembolic events, among others.[4,5] Importantly, patients with chronic HF due to Chagas cardiomyopathy have worse prognosis as compared with other aetiologies; the all-cause mortality rates at 1, 5, and 10 years of follow-up are thought to be approximately 12%, 35%, and 60%, respectively,[6] and the 1 year all-cause mortality rate may be as high as 90% in patients with more severe forms of the disease.[7,8] However, it has been suggested that the risk factors found in patients with chronic HF and Chagas disease may differ from traditional HF risk factors,[9] with significant impact on mode of death[10] and response to therapeutic interventions,[11,12] further emphasizing the importance of the distinctive clinical features of this disease.

These clinical differences are the result of pathophysiologic, functional, and structural derangements found in patients after trypanosomal infection and may include a direct effect of the parasite on cardiac and neural cells, increased inflammatory and neurohumoral activation,[13] sympathetic denervation, and thrombogenic status,[14] among others.[5] Interestingly, many—if not all—of these factors are exacerbated during episodes of acute decompensated HF and, therefore, have the potential of further influencing the clinical presentation and prognosis of patients. Despite recent suggestions that the clinical presentation of patients with Chagas heart disease and decompensated HF may in fact differ from other aetiologies,[15] the clinical significance of these findings, especially in terms of the impact on risk stratification, therapy response, and prognosis, has not been sufficiently analysed.

We hypothesized that patients with Chagas cardiomyopathy may have a distinct presentation during episodes of decompensated HF influencing the prognosis, risk stratification, and response to therapy.

Methods

Objectives

The primary aim of our study was to evaluate the course of patients with Chagas disease during episodes of decompensated HF, as compared with other aetiologies. Further, we sought to investigate the presence markers associated with in-hospital prognosis; exploratory analysis was also performed for the prognosis after hospital discharge.

Study design

We analysed a prospective cohort of patients admitted to the Heart Institute (InCor) of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP; online registry 13713) with a diagnosis of acute decompensated HF. Our centre is a 535-bed tertiary academic hospital dedicated to cardiology and a referral institution for all regions of the country. The selection of patients was performed by means of active monitoring of the medical and administrative databases of our institution. The first inclusion occurred in August 2013, and the last was in January 2018. The study was approved by the Institutional Ethics Committee for Research Project Analysis, and patients were followed up for 180 days after hospital discharge.

Inclusion and exclusion criteria

We included patients over 18 years of age admitted with a diagnosis of acute decompensated HF and ejection fraction less than 50% as measured by echocardiography. We excluded patients hospitalized for less than 24 h and patients with cardiogenic shock or decompensated HF during the post-operative period after heart surgery. For the purpose of the present analysis, HF aetiology was categorized into three groups: Chagas cardiomyopathy, ischaemic cardiomyopathy, and non-Chagas/non-ischaemic cardiomyopathy.

Analysed variables

Data were obtained from medical records, including demographic information, epidemiological data, pathological history, reason for hospitalization, presence and duration of HF-related symptoms, aetiologic diagnosis of HF or cardiomyopathy, physical examination, and electrocardiographic and echocardiographic data. The estimation of right ventricular function was based on subjective analysis; for the purpose of present analysis, the presence of right ventricular dysfunction was defined as echocardiographic dysfunction estimated as moderate or severe, and the absence of right ventricular dysfunction was defined as echocardiographic dysfunction estimated as mild or absent. The occurrence of death and heart transplantation since hospital admission up to 180 days after hospital discharge was registered.

Statistical analysis

Categorical variables are described as absolute value and percentage; continuous variables are described as median ± interquartile range [IQR] 25–75%. For non-normal distribution of variables, the non-parametric Mann–Whitney

U test was used. Comparison of proportions between groups was performed with the χ^2 test. In order to correct for multiple comparisons, the step-down Bonferroni–Holm procedure was applied to each set of measurements. Both adjusted and unadjusted *P*-values are reported. Multivariable analysis was performed with logistic regression; all variables with clinical significance were entered in the model. Survival was estimated by using the Kaplan–Meier method, and differences in survival between groups were assessed with the log-rank test. *P*-values less than 0.05 were considered significant. In order to analyse the prognosis of patients in the follow-up, a Cox regression model was performed for the occurrence of the combined endpoint of death, heart transplant, and hospital readmission; all variables with clinical significance were entered in the model. Statistical analysis was performed using SPSS for Windows Version 11.0.

Results

Baseline characteristics

We included 767 patients admitted with decompensated HF from August 2013 through January 2018 (*Table 1*); 80 (10.4%) had the diagnosis of *de novo* HF. Patients were predominantly male (63.9%), and the median age was 58 years (IQR 48.2–66.7 years). Main aetiologies were non-Chagas/non-ischaemic cardiomyopathy in 389 (52.4%) patients, ischaemic heart disease in 209 (27.2%), and Chagas disease in 169 (22%). Median left ventricular (LV) ejection fraction was 26% (IQR 22–35%). Inotropes were used in 523 (68.2%) and intra-aortic balloon pump in 137 (17.9%) patients; 224 (29.2%) died during hospital admission, and 91 (11.9%) were transplanted.

Comparison of clinical and complementary variables

When clinical characteristics were analysed according to the aetiology (*Table 2*), we found that patients with Chagas disease, as well as patients with non-Chagas/non-ischaemic cardiomyopathy, were younger as compared with patients with ischaemic heart disease (ages 57 [IQR 46.2–64.7], 55 [43–65], and 64 [57–71] years old, respectively, $P < 0.001$) and had a higher proportion of female patients (42.6%, 39.1%, and 25.4%, respectively, $P < 0.001$). Importantly, patients with Chagas differed from both patients with non-Chagas/non-ischaemic cardiomyopathy and patients with ischaemic cardiomyopathy for a higher proportion of individuals with syncope at admission (20.2%, 12.6%, and 11.5%, respectively, $P = 0.028$), lower proportion of diabetes mellitus (13%, 26%, and 55.8%, respectively, $P < 0.001$) and arterial

Table 1 Clinical characteristics of patients

Clinical characteristics	Total
	Median [IQR]/*N* (%)
Number of patients	767
Gender	
Female	277 (36.1)
Male	490 (63.9)
Age (years)	58 [48.2–66.7]
Co-morbidities	
Arterial hypertension	402 (52.4)
Diabetes mellitus	239 (31.2)
Atrial fibrillation	279 (36.4)
HF aetiology	
Non-ischaemic/non-Chagas	389 (50.7)
Ischaemic heart disease	209 (27.2)
Chagas heart disease	169 (22)
Medications	
Beta-blocker	625 (81.5)
ACEi/ARB	503 (65.6)
Hydralazine/nitrate	559 (72.9)
Spironolactone	440 (57.4)
Diuretics	601 (78.4)
Digoxin	182 (23.7)
Warfarin	201 (26.2)
Acetylsalicylic acid	251 (32.7)
Cardiac devices	
ICD	59 (7.7)
CRT-D	41 (5.3)
Admission diagnosis	
Progressive HF	461 (60.1)
Cardiogenic shock	98 (12.8)
Arrhythmia/syncope	83 (10.8)
ACS	31 (4.0)
Others	94 (12.3)
Physical examination	
Congestion	628 (81.8)
Hypoperfusion	277 (36.1)
SBP (mmHg)	100 [84–111.5]
Heart rate (b.p.m.)	80 [68–98]
Laboratory findings (serum)	
Creatinine (mg/dL)	1.64 [1.21–2.38]
Urea (mg/dL)	75 [49–113]
Sodium (mEq/L)	137 [133–140]
Potassium (mEq/L)	4.4 [4.0–4.9]
BNP (pg/dL)	1069 [474–2028]
Echocardiographic findings	
LV ejection fraction (%)	26 [22–35]
RV dysfunction	289 (37.7)
Prognosis	
Inotropes	523 (68.2)
IABC	137 (17.9)
Dialysis	113 (14.7)
In-hospital mortality	224 (29.2)
Urgent heart transplant	91 (11.9)

ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CRT-D, cardiac resynchronization therapy in association with a defibrillator; HF, heart failure; IABC, intra-aortic balloon; ICD, intracardiac defibrillator; IQR, interquartile range; LV, left ventricle; RV, right ventricle; SBP, systolic blood pressure.

hypertension (30.2%, 50.4%, and 74.2%, respectively, $P < 0.001$), and higher proportion of patients with admission diagnosis of cardiogenic shock (17.8%, 11.6%, and 11%, respectively, $P < 0.001$) or arrhythmias and syncope (18.9%, 6.7%, and 12%, respectively, $P < 0.001$); additionally, patients with Chagas were more likely to have a lower blood pressure

Table 2 Clinical characteristics of patients according to aetiology

Clinical characteristics	Chagas Median [IQR]/N (%)	Non-Chagas/non-ischaemic Median [IQR]/N (%)	Ischaemic Median [IQR]/N (%)	P-value	Adjusted P-value
Number of patients	169	389	209		
Gender					
Female	72 (42.6)	152 (39.1)	53 (25.4)***	<0.001	0.003
Male	97 (57.4)	237(60.9)	156 (74.6)		
Age (years)	57 [46.2–64.7]	55 [43–65]	64 [57–71]***	<0.001	<0.001
Duration of symptoms	8 [3–31]	14 [4–31]++	7 [2–28.9]	0.015	0.06
Symptoms at presentation				0.028	0.084
Chest pain	41 (24.6)	105 (27.2)	71 (34.1)	0.09	0.09
Orthopnoea	91 (53.8)	214 (55)	88 (42.1)	0.008	0.04
PND	78 (46.2)	198 (51)	77 (36.8)*	0.004	0.024
Syncope	34 (20.2)	49 (12.6)++	24 (11.5)*	0.028	0.08
Co-morbidities					
Arterial hypertension	51 (30.2)	196 (50.4)+++	155 (74.2)***	<0.001	<0.001
Diabetes mellitus	22 (13)	101 (26)+	116 (55.8)***	<0.001	<0.001
Dyslipidaemia	28 (16.9)	76 (19.8)	117 (57.1)***	<0.001	<0.001
Atrial fibrillation	69 (41.6)	146 (38.2)	64 (30.8)*	0.074	0.074
Previous VT/VF	30 (17.8)	29 (7.5)++	39 (18.8)	<0.001	<0.001
Admission diagnosis		+++	***		
Progressive HF	89 (52.7)	267 (68.6)	105 (50.2)		
Cardiogenic shock	30 (17.8)	45 (11.6)	23 (11)		
Arrhythmia/syncope	32 (18.9)	26 (6.7)	25 (12)	<0.001	<0.001
ACS	2 (1.2)	8 (2.1)	21 (10)		
Others	16 (9.5)	43 (11.1)	35 (16.7)		
Physical exam					
Congestion	135 (79.9)	333 (85.6)	159 (76.1)	0.012	0.0024
Hypoperfusion	78 (46.2)	140 (36.5)+	59 (28.2)***	0.002	0.006
SBP (mmHg)	90 [80–102.5]	100 [85–110]+++	100 [88.2–120]***	<0.001	<0.001
Heart rate (b.p.m.)	71 [60–86]	85 [70–102]+++	79 [64–96.5]**	<0.001	<0.001
Mitral regurgitation	68 (40.2)	121 (31.2)	40 (19.2)***	<0.001	0.0011
Tric. regurgitation	16 (9.5)	30 (7.7)	15 (7.2)	0.79	0.79
Previous medications					
ACEi/ARB	121 (71.6)	254 (65.3)	128 (61.2)*	0.107	0.146
Beta-blocker	150 (88.8)	317 (81.5)+	158 (75.6)*	0.005	0.02
Hydralazine/nitrate	40 (23.7)	99 (25.4)	69 (33)*	0.073	0.146
Spironolactone	107 (63.3)	228 (58.3)	105 (50.2)*	0.03	0.09
Diuretics	139 (82.2)	315 (81)	147 (70.3)**	0.004	0.02
Digoxin	42 (24.9)	113 (29)	27 (12.9)**	<0.001	<0.001
Warfarin	54 (32)	110 (28.3)	37 (17.7)**	0.003	0.018
Acetylsalicylic acid	33 (19.5)	94 (24.2)	124 (59.3)***	<0.001	<0.001
Amiodarone	58 (34.3)	57 (14.7)+++	30 (14.4)***	<0.001	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; HF, heart failure; IQR, interquartile range; PND, paroxysmal nocturnal dyspnoea; SBP, systolic blood pressure; VF, ventricular fibrillation; VT, ventricular tachycardia.

Valvular murmurs estimate as moderate/severe.

*P < 0.05.

**P < 0.01.

***P < 0.001 for Chagas vs. ischaemic.

+P < 0.05.

++P < 0.01.

+++P < 0.001 for Chagas vs. non-Chagas/non-ischaemic.

at admission (systolic blood pressure 90 [80–102.5], 100 [85–110], and 100 [88.2–120] mmHg, respectively, P < 0.001) and a lower heart rate (heart rate 71 [60–80], 87 [70–102], and 79 [64–96.5] b.p.m., respectively, P < 0.001). Except for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, all other medications that patients received prior to hospital admission differed among groups.

Regarding laboratory findings, the presentation of patients with Chagas cardiomyopathy differed from other aetiologies and was remarkable for higher serum BNP level (1544 [734–3148], 1061 [465–239], and 927[369–1455] pg/mL, respectively, P < 0.001) and higher serum bilirubin (1.4 [0.92–2.44], 1.2 [0.77–2.19], and 0.84 [0.49–1.45] mg/dL, respectively, P < 0.001), among others (Table 3).

Regarding echocardiographic parameters (Table 4), patients with Chagas disease showed increased remodelling parameters, as indicated by larger LV diameter (68 [63–73], 67 [58–74], and 62 [56.8–68.3] mm, respectively, P < 0.001); additionally, ventricular function was more pronouncedly reduced among patients with Chagas, as indicated by lower LV ejection fraction (25 [21–30]%, 26 [22–35]%, and 30

Table 3 Laboratory characteristics of patients according to aetiology

	Chagas	Non-Chagas/non-ischaemic	Ischaemic		Adjusted
	Median [IQR]/N (%)	Median [IQR]/N (%)	Median [IQR]/N (%)	P-value	P-value
Number of patients	169	389	209		
Creatinine (mg/dL)	1.58 [1.23–2.22]	1.58 [1.16–2.42]	1.78 [1.3–2.41]	0.168	0.84
Urea (mg/dL)	71 [49–100]	74 [47–116]	80 [51–125]	0.327	0.99
Sodium (mEq/L)	137 [133–140]	136 [133–140]	138 [135–140]	0.02	0.22
eGFR	44.7 [28.1–58.9]	45.4 [26.1–64.5]	36.8 [25.5–52.7]*	0.03	0.27
Potassium (mEq/L)	4.4 [4.0–4.8]	4.4 [3.9–5.0]	4 [4–4.9]	0.99	0.99
BNP (pg/dL)	1545 [734–3148]	1061 [465–239][+++]	927 [369–1455]***	<0.001	<0.001
Leucocytes	7210 [5680–8990]	7825 [527–10 269][+]	8715 [6285–11 557]***	<0.001	0.015
Haemoglobin	13 [12–14.5]	13 [11–15]	13 [12–14]	0.69	0.99
Cholesterol (mg/dL)	127 [110–169]	135 [111–169][+]	133 [106.7–165.2]	0.675	0.99
Triglycerides (mg/dL)	72 [55–93]	83 [61–110][+]	93 [65–129]**	0.001	0.02
Glycaemia (mg/dL)	103 [85.5–120]	102 [88–125]	122 [102–160]***	<0.001	<0.001
Bilirubin (mg/dL)	1.4 [0.92–2.44]	1.2 [0.77–2.19]	0.84 [0.49–1.45]***	<0.001	0.048
GGT (mg/dL)	217 [119–358]	151 [96–274.8][++]	145 [62–246]***	<0.001	0.026
AST (mg/dL)	37 [22–80]	33 [22–80]	31 [21–62]	0.130	0.84
ALT (mg/dL)	39 [24–74.3]	34 [25–61.5]	31 [22–54]*	0.035	0.28
Albumin (mg/dL)	3.1 [2.77–3.5]	3 [2.6–3.4]	3 [2.3–3.45]	0.025	0.25
HbA1c (%)	6.1 [5.7–6.6]	6.1 [5.7–6.7]	6.3 [5.8–7.85]	0.12	0.84

ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimate glomerular filtration rate; GGT, gamma-glutamyl transferase; HbA1c, glycated haemoglobin; IQR, interquartile range.
*P < 0.05.
**P < 0.01.
***P < 0.001 for Chagas vs. ischaemic.
+P < 0.05.
++P < 0.01.
+++P < 0.001 for Chagas vs. non-Chagas/non-ischaemic.

Table 4 Echocardiographic findings according to aetiology

	Chagas	Non-Chagas/non-ischaemic	Ischaemic		Adjusted
Clinical characteristics	Median [IQR]/N (%)	Median [IQR]/N (%)	Median [IQR]/N (%)	P-value	P-value
Number of patients	169	389	209		
Septum (mm)	8 [8–9]	9 [8–11][+++]	9 [8–10]***	<0.001	0.06
LV posterior wall (mm)	8 [7–9]	9 [8–10][+++]	9 [8–10]***	<0.001	0.02
LVDD (mm)	68 [63–73]	67 [58–74]	62 [56.8–68.3]***	<0.001	0.0015
LVEF (%)	25 [21–30]	26 [22–35][+]	30 [25–38]***	<0.001	0.0015
LA (mm)	49 [45–54]	50 [45–55]	49 [45–53]	0.27	0.54
PASP (mmHg)	45 [35–52]	48 [39–57][++]	48 [37.8–60]*	0.011	0.045
RV dysfunction (%)[a]	81 (48.8)	156 (40.7)[+]	52 (25.9)***	<0.001	<0.001
Mitral regurgitation (%)[a]	114 (67.5)	211 (54.2)[+]	106 (50.7)**	0.009	0.045
Tricuspid regurgitation (%)[a]	103 (60.9)	179 (46)[++]	73 (34.9)***	<0.001	<0.001
Intracavitary thrombus (%)	13 (8)	27 (7.3)	13 (6.5)	0.85	0.85

DD, diastolic diameter; EF, ejection fraction; IQR, interquartile range; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; RV, right ventricle.
[a]Estimated as moderate or severe.
*P < 0.05.
**P < 0.01.
***P < 0.001 for Chagas vs. ischaemic.
+P < 0.05.
++P < 0.01.
+++P < 0.001 for Chagas vs. non-Chagas/non-ischaemic.

[25–38]%, P < 0.001) and a higher proportion of patients with right ventricular function estimated as moderately or severely reduced (48.8%, 40.7%, and 25.9%, P < 0.001).

Invasive haemodynamic evaluation was available in 187 (24.4%) and showed (*Table 5*) that patients with Chagas disease, when compared with patients with dilated and ischaemic aetiologies, had lower heart rate (88 [70–99], 104 [93–110], and 95.5 [90.5–106.8] b.p.m., P < 0.001) and lower systolic pulmonary pressure (47 [35–59], 50 [42–61], and 60 [41.5–70.5] mmHg, P = 0.0018).

In-hospital interventions and prognosis

Patients with Chagas disease were more likely to receive inotropes than patients with dilated and ischaemic cardiomyopathies (77.5%, 67.5%, and 62.5%, respectively, $P = 0.007$) and also to receive intra-aortic balloon pumping (30.8%, 16.2%, and 10.5%, respectively, $P < 0.001$). The rates of death or urgent transplant were higher among patients with Chagas than in other aetiologies (*Figures 1 and 5*); the higher

mortality was mostly linked to the higher heart transplant rate during hospital admission: 52 (30.8%) patients with Chagas died and 34 (20.2%) were transplanted, 104 (26.7%) patients with dilated cardiomyopathies died and 40 (10.3%) were transplanted, and 68 (32.5%) patients with ischaemic cardiomyopathy died and 17 (8.1%) were transplanted. The prognosis of patients at 180 days after hospital admission was also worse for patients with Chagas disease as compared with other aetiologies (*Figures 2 and 5*).

Table 5 Haemodynamic findings according to aetiology

Clinical characteristics	Chagas Median [IQR]/N (%)	Non-Chagas/non-ischaemic Median [IQR]/N (%)	Ischaemic Median [IQR]/N (%)	P-value	Adjusted P-value
Number of patients	52	90	45		
Heart rate (b.p.m.)	88 [70–99]	104 [93–110][+++]	95.5 [90.5–106.8]*	<0.001	<0.001
Systolic systemic AP (mmHg)	94 [8–9]	96 [87–105.5]	100 [90–111.7]	0.26	0.99
Mean systemic AP (mmHg)	70.5 [65.3–78.8]	72 [67–80]	67.5 [61.5–83]	0.30	0.99
Systolic pulmonary AP (mmHg)	47 [35–59]	50 [42–61]	60 [41.5–70.5]*	0.018	0.126
Mean pulmonary AP (mmHg)	35 [25–42.5]	36 [29.8–42]	40 [30–48]*	0.056	0.34
Wedge pressure (mmHg)	24 [17–28.8]	25 [18.5–30]	22 [16–32]	0.408	0.99
Right atrium pressure (mmHg)	14 [10–19.2]	13 [9–19]	12.5 [8–16.8]	0.464	0.99
Cardiac output (L/min)	3.6 [3–4.3]	4 [2.9–5.1]	4.25 [3.3–5.3]*	0.078	0.39

AP, arterial pressure; IQR, interquartile range.
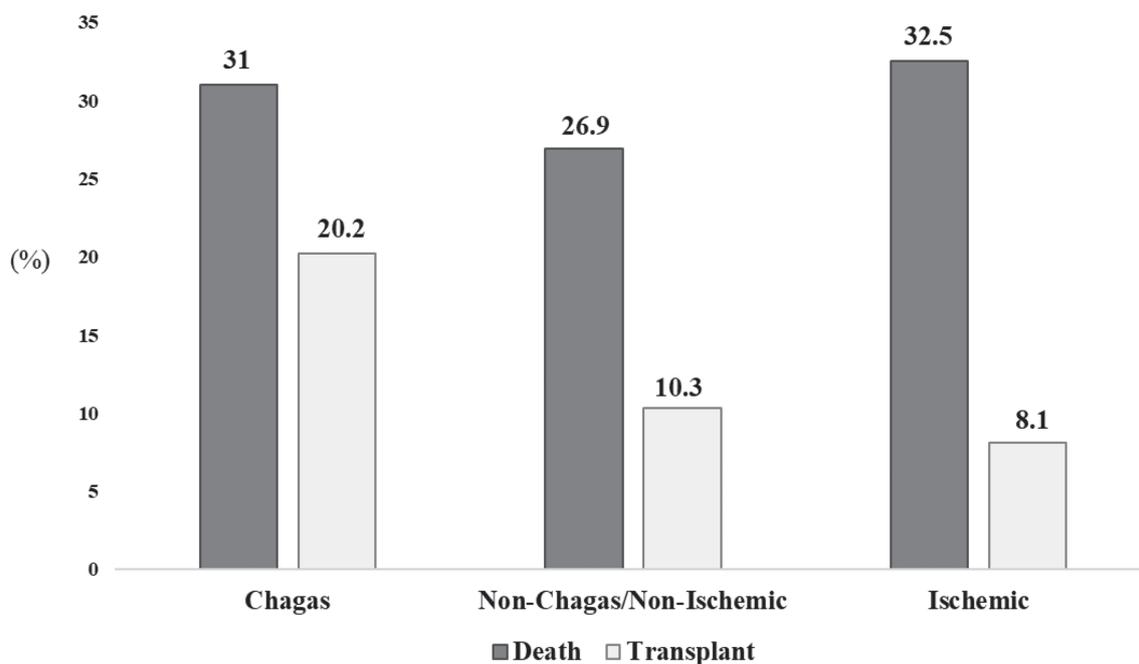*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$ for Chagas vs. ischaemic.
+$P < 0.05$.
++$P < 0.01$.
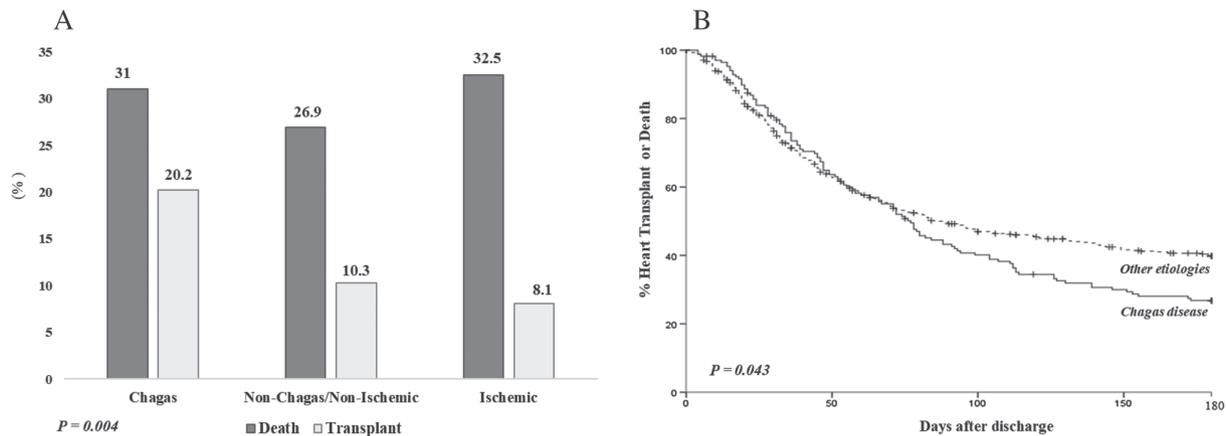+++$P < 0.001$ for Chagas vs. non-Chagas/non-ischaemic.

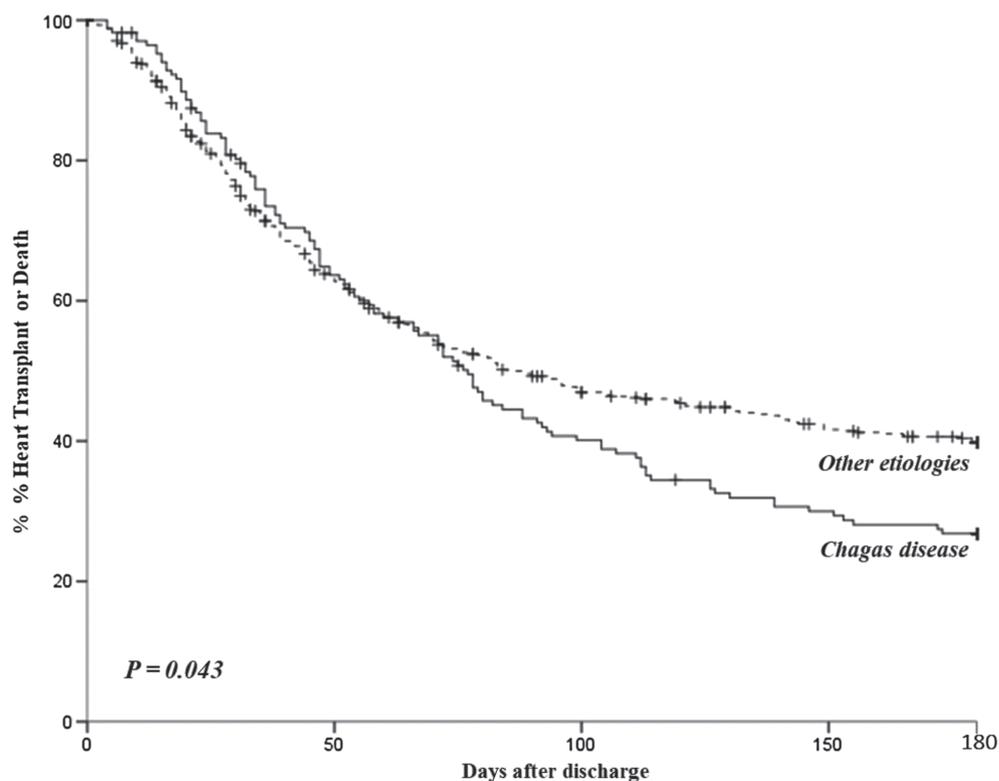**Figure 1** In-hospital prognosis according to aetiology.

$P = 0.003$ for the comparison Chagas vs Ischemic
$P = 0.004$ for the comparison Chagas vs Non-Chagas/Non-Ischemic

Figure 2 Central illustration. Prognosis of patients with Chagas cardiomyopathy compared with other aetiologies after an episode of acute decompensated heart failure. (A) In-hospital prognosis according to aetiology. (B) Kaplan–Meier curve depicting the survival of patients according to aetiology at 180 days of follow-up.

Figure 3 Kaplan–Maier curve depicting the survival of patients according to aetiology at 180 days of follow-up.
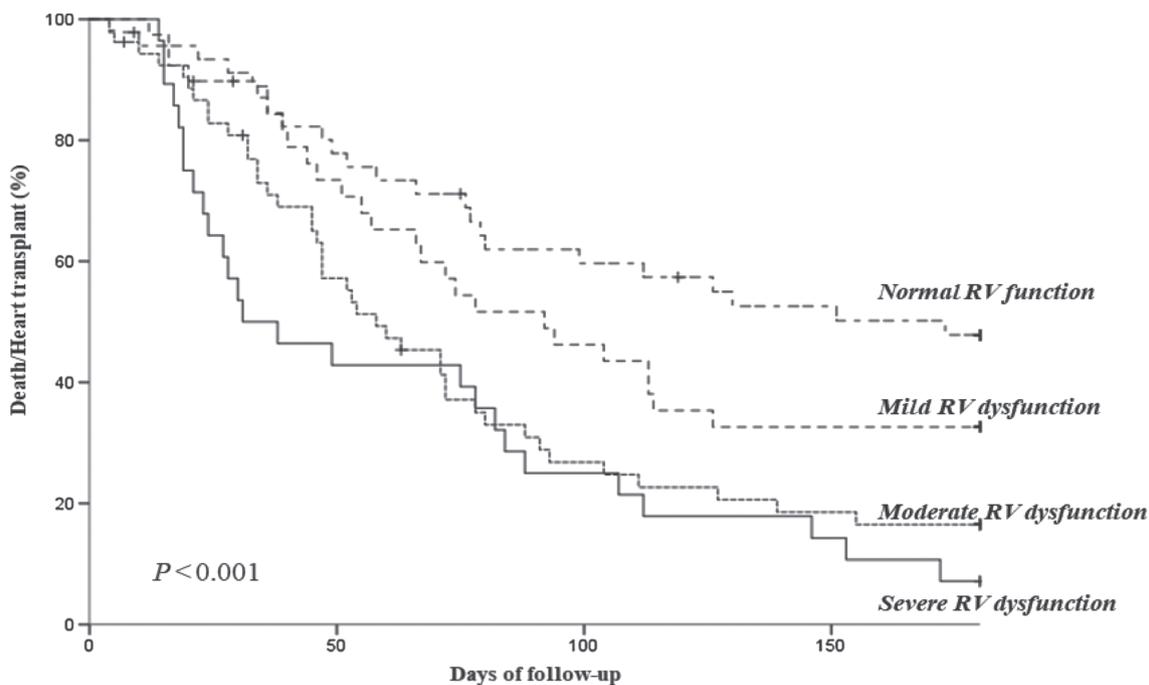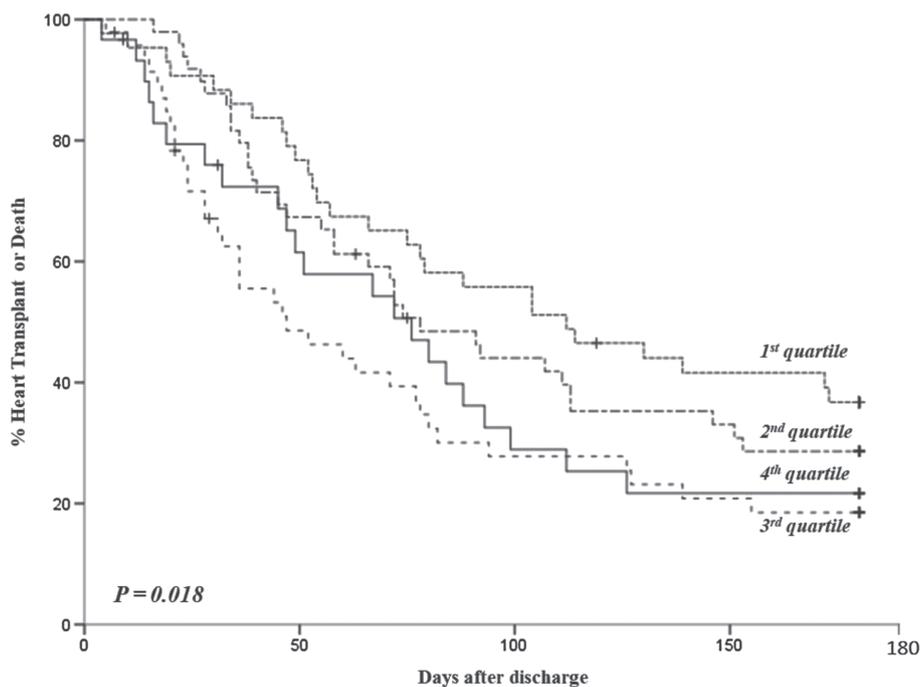

Risk stratification

A logistic regression analysis for adverse in-hospital composite outcome (death plus heart transplantation) was performed (*Table 6*). All variables with clinical significance were entered in the model, including age, systolic arterial pressure, urea serum level, BNP level at hospital admission, pulmonary systolic pressure as measured by echocardiography, and presence of right ventricular dysfunction and LV ejection fraction by echocardiography. We found that in patients with Chagas heart disease, age [odds ratio (OR) = 0.941, confidence interval (CI)$_{95\%}$ 0.901–0.982, $P = 0.005$], presence of right ventricular dysfunction estimated as moderate or severe at echocardiography (OR = 2.68, CI$_{95\%}$ 1.055–6.81, $P = 0.025$),

Figure 4 Rate of death and urgent heart transplant according to the presence of right ventricular (RV) dysfunction in echocardiography in patients with Chagas disease.

Figure 5 Rate of death and urgent heart transplant in patients with Chagas disease according to the urea quartiles at admission.

Table 6 Logistic regression analysis for adverse in-hospital composite outcome (death plus heart transplantation) according to aetiology

Variable	Chagas cardiomyopathy			Other aetiologies		
	OR	IC$_{95\%}$	P-value	OR	IC$_{95\%}$	P-value
Age	0.941	0.901–0.982	0.005	1.007	0.989–1.025	0.456
Systolic arterial pressure	0.988	0.963–1.014	0.361	0.975	0.964–0.987	<0.001
Urea	1.009	1.001–1.018	0.038	1.002	0.998–1.007	0.295
BNP	1.117	0.672–1.858	0.669	1.545	1.177–2.029	0.002
Pulmonary systolic pressure	0.968	0.939–1.011	0.164	1.018	1.000–1.035	0.045
Right ventricular dysfunction	2.68	1.055–6.810	0.016	1.316	0.783–2.11	0.3
Left ventricular ejection fraction	1.009	0.957–1.064	0.735	0.972	0.974–0.999	0.041

CI, confidence interval; OR, odds ratio.
The odds ratios in the logistic regression correspond to one-unit increase in the covariate.

and serum urea (OR = 1.009, CI$_{95\%}$ 1.001–1.018, P = 0.038) were significantly associated with prognosis. In patients with other aetiologies, the variables associated with prognosis were arterial systolic pressure (OR = 0.975, CI$_{95\%}$ 0.964–0.987, P < 0.001), LV ejection fraction (OR = 0.972, CI$_{95\%}$ 0.974–0.999, P = 0.041), and BNP level (OR = 1.545, CI$_{95\%}$ 1.177–2.029, P = 0.002). In order to investigate the significance of these variables only for mortality, we performed a logistic regression analysis for the occurrence of in-hospital death. In patients with Chagas, the serum urea was associated with increased mortality (OR = 1.011, CI$_{95\%}$ 1.001–1.021, P = 0.026), and in patients with other aetiologies, the arterial systolic pressure (OR = 0.974, CI$_{95\%}$ 0.962–0.987, P < 0.001), age (OR = 1.023, CI$_{95\%}$ 1.002–1.043, P = 0.03), serum BNP (OR = 1.768, CI$_{95\%}$ 1.293–2.417, P < 0.001), and the pulmonary systolic pressure (OR = 1.022, CI$_{95\%}$ 1.002–1.041, P = 0.028) were associated with mortality.

We further analysed these variables in a Cox regression model for events in the follow-up (death, heart transplant, and hospital readmission); we found that age (HR 0.98 [0.962–0.999], P = 0.042), right ventricular dysfunction (HR 1.672 [1.034–2.705], P = 0.036), and urea (HR 1.004 [1.001–1.008], P = 0.012) were independently associated with prognosis in the first 180 days of follow-up (*Appendix A* and *Figures 4* and *5*).

Discussion

The analysis of this cohort of 767 patients showed that patients with Chagas cardiomyopathy have a distinctive clinical during episodes of HF decompensation, as indicated by younger age, higher proportion of female gender, lower frequency of co-morbidities such as diabetes mellitus and arterial hypertension, higher proportion of patients with cardiogenic shock and syncope at admission, and lower blood pressure and heart rate. Further, patients with Chagas had more frequently markers of advanced cardiac disease at presentation, as suggested by a higher BNP level, increased LV dimension, and worse biventricular function in the echocardiogram. Most importantly, patients with Chagas aetiology had a higher death rate and heart transplant during hospital stay as well as at 180 days after hospital discharge. Prognostic markers were also distinct in patients with Chagas and were mostly associated with right ventricular function. The major strength of the present study was the inclusion of a significant number of patients with Chagas disease during episodes of decompensated HF, a clinical scenario scarcely explored in previous studies; it also presents a thorough examination of the patients, including clinical, haemodynamic, echocardiographic, and prognostic information.

Some particular characteristics of the present cohort should be acknowledged. Firstly, patients tended to be young (58 [48.2–66.7] years) and with a higher proportion of male patients (63.9%); the in-hospital mortality was high (29.2%), as well as the frequency of inotropic therapy and heart transplantation, which reflect the fact that our institution is a tertiary referral centre that cares for high-risk patients. These findings contrast with reports from other studies. Data from the ADHERE registry that included patients from the USA showed a mean age of 72 years, a higher prevalence of female patients, ischaemic heart disease as the main aetiology, and in-hospital mortality of 4%.[16] Similarly, the reported mean age from the European registry was 70 ± 13 years with a majority of male patients; the total in-hospital mortality rate was 3.8%.[17] Data from the Brazilian Registry of patients with decompensated HF showed mean age of 64 years, a predominance of male patients, and in-hospital mortality of 12.6%.[18] These differences may be mostly due to the inclusion of a high proportion of patients with Chagas.[19] There are few other studies on the patients with Chagas heart disease in the scenario of acute decompensation; data derived from studies with patients with chronic HF indicate that patients with Chagas may have a worse prognosis as compared with other aetiologies.[13,20] In the setting of decompensated HF, a recent study compared the prognosis of patients with Chagas cardiomyopathy with that of patients with other aetiologies; no

difference was found regarding in-hospital mortality, but patients with Chagas had a higher rate of hospital readmission.[21] Additionally, it should be noticed that our centre is a tertiary hospital dedicated to cardiology that care for patients with advanced HF, with a higher expected mortality compared with that in community hospitals. In this sense, a majority of our patients received inotropes during their hospital stay (68.2%), and a significant proportion received either an intra-aortic balloon (17.9%) or dialysis (14.7%).

One important finding was the reported higher rate of the outcomes of death or heart transplant during hospital stay, as well as at 180 days of follow-up after hospital discharge among patients with Chagas disease. This difference was driven mostly by a higher rate of heart transplantations as compared with other aetiologies. Other studies have explored the association between HF aetiology and outcomes, and most previous comparisons from the USA and Europe have indicated a lower survival among patients with ischaemic heart disease.[22–24] In this respect, studies from areas where Chagas disease is an endemic condition have reported a worse prognosis among patients with Chagas, including excessive mortality and higher rates of readmission.[25] Our findings confirm that patients with Chagas have a worse prognosis during episodes of decompensated HF; different mechanisms have been proposed for this worse prognostic found in patients with Chagas, and most information comes from patients with chronic Chagas cardiomyopathy.[13] Possible mechanisms reported may include an increased rate of right ventricular dysfunction, ventricular arrhythmias, and conduction abnormalities as well as higher rate of thromboembolic events.[11,26]

In the present analysis, we sought to identify clinical markers associated with clinical outcomes during hospital admission among patients with Chagas aetiology, and we found that a younger age, presence of significant right ventricular dysfunction by echocardiography, and renal function were independently associated with the occurrence of death or heart transplant. Previous studies have identified clinical markers in populations where the ischaemic aetiology is more frequent, and reported variables associated with worse prognosis in the setting of acute HF include arterial blood pressure, renal function, and LV function, among others.[27,28] The importance of the right ventricular function in patients with chronic Chagas disease had been previously demonstrated; pathology findings suggest that the right ventricle is involved early during the course of the disease[29]; more recently, studies using magnetic resonance imaging[30] and speckle-tracking echocardiography[31] have further confirmed these findings. However, the clinical and prognostic relevance of right ventricular involvement in the setting of acute decompensated HF had not been previously reported. Similarly, the clinical relevance of renal dysfunction among patients with Chagas had been reported in patient with chronic HF,[32] but its significance in the decompensated patient had

not yet been studied. The presence of increasing age as a protective prognostic marker probably reflects the increased chance of younger patients to be admitted to a heart transplant protocol, reaching, thus, one of the studied outcomes. Finally, it is possible to consider that the socio-economic conditions differ in patients with Chagas disease as compared with other aetiologies and may modulate the clinical presentation of the disease with access to therapy and better prognosis.[33]

There are limitations in the present study that should be acknowledged; we included a limited number of patients compared with other HF patient cohorts, and despite the continuous surveillance of patients admitted to our institution, we cannot exclude the possibility of loss of patients at inclusion; therefore, the possibility of selection bias cannot be excluded. Additionally, as clinical data were obtained from medical records, heterogeneity regarding information from anamnesis and physical examination cannot be excluded. Information about the treatment that patients were receiving on the day they had the haemodynamic measurements performed could not be retrieved; therefore, the results of the haemodynamic study may have been influenced by therapeutic interventions, such as inotropic therapy and presence of intra-aortic balloon. Finally, some particular characteristics of our centre (a tertiary academic institution dedicated to cardiology) and of our population (younger age and the high-risk patient profile) may hinder the applicability of our results to other populations.

Conclusions

Our results indicate that during episodes of decompensated HF, patients with Chagas cardiomyopathy have a distinct clinical presentation and worse prognosis as compared with other aetiologies; reduced right ventricular function and impaired renal function are important prognostic markers. These results should be taken into consideration in the clinical and therapeutic approach to patients with Chagas hospitalized for HF.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Appendix A: Cox regression model for events in the follow-up in patients with Chagas disease

Variable	HR	CI$_{95\%}$	*P*-value
Age	0.980	0.962–0.999	0.042
Right ventricular dysfunction	1.672	1.034–2.705	0.036
Urea	1.004	1.001–1.008	0.012
Pulmonary systolic pressure	1.008	0.989–1.028	0.398
BNP	1.073	0.81–1.421	0.623
Systolic arterial pressure	0.996	0.984–1.007	0.443
Left ventricular ejection fraction	0.992	0.962–1.022	0.589

CI, confidence interval; HR, hazard ratio.
The hazard ratios in the logistic regression correspond to one-unit increase in the covariat