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Short-term Mortality Risk Model in Chagas' Disease Heart Failure, a Comparison Etiology Public Healthcare Study

Modelo de Riesgo de Mortalidad a Corto Plazo en la Insuficiencia Cardíaca por Enfermedad de Chagas, un Estudio Comparativo de Etiología en el Ámbito de la Salud Pública

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SUMMARY

Introduction*: Chagas disease is an expanding etiology for heart failure (HF) worldwide. However, this variable is lacking in diffused mortality models by etiology.* **Objective***: to assess Chagas's heart failure mortality odds in a public health care center at a one-year follow-up.* **Methods***: A multivariate model containing clinical and laboratory data was used to construct a risk score. For comparison, we evaluated groups based on etiology: ischemic (n = 122), Chagas (n = 178), and non-ischemic (n = 249).* **Results***: After follow-up and 44 deaths (20.8 %, Chagas; 36.9 %, ischemic and 20.5 %, non-ischemic, p = 0.0017). The total group was characterized by four independent predictors: ß-blockers, statins, digoxin (dosages: 0.125 and 0.25 mg), and left ventricular diastolic diameter index. In Chagas, digoxin and ß-blockers, sodium, systolic blood pressure, and angiotensin-converting enzyme inhibitors (ACEis) (including combinations with ß-blockers). In ischemic: digoxin, left ventricle diastolic diameter index (LVDD/BMI), and hypothyroidism, and for non-ischemic: cholesterol and left ventricular diastolic volume (LVEVI). We obtain the following equation for each etiology:*

$\hat{S}(t) = [\hat{S}_0(t)]^{exp[-0.89*B\text{-}blocker-1.47*Statin+1.239*Digoxin(0.125)+Digoxin(0.25)+0.551*LVDD/BMI]}$

$\hat{S}(t) = [\hat{S}_0(t)]^{exp[-3.469*B\text{-}Blocker-2.663*ACEi - 4.456*B\text{-}blocker+ ACEi - 0.036*SBP-0.195+3.061*Digoxin}$

$\hat{S}(t) = [\hat{S}_0(t)]^{exp[-0.634*LVDD/BMI+1.652*Digoxin+1.834Hypothyroidsm]}$

$\hat{S}(t) = [\hat{S}_0(t)]^{exp[-0.024*Cholesterol+0.008*LVEVI]}$

Conclusions*: mortality predictors in heart failure outgoing patients are particular depending on the etiology. In Chagas, some drugs appear to have a superior benefit compared to other etiologies. This prognostic model shows the value for the public healthcare system beyond that supplied in the current clinical models.*

Keywords*: Heart failure, Chagas disease, public health, health policy, risk prediction.*

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RESUMEN

Introducción: *Chagas es una creciente etiología de insuficiencia cardíaca (IC) a nivel mundial. Sin embargo, la variable falta actualmente en los modelos de mortalidad difundidos por etiología.* **Objetivo**: *Evaluar las probabilidades de mortalidad por IC Chagásica en un centro de salud pública al año de seguimiento.* **Método**: *Se utilizó un modelo multivariante con datos clínicos y laboratoriales para construir una puntuación de riesgo. Para la comparación, se evaluaron grupos según la etiología: isquémica (n = 122), chagásica (n = 178) y no isquémica (n = 249).* **Resultados**: *Tras el seguimiento y 44 muertes (20,8 %, chagásicas; 36,9 %, isquémicas y 20,5 %, no isquémicas, p = 0,0017). Se identificaron cuatro predictores independientes en la población general: ß-bloqueadores, estatinas, digoxina (en las dosis: 0,125 y 0,25 mg) e índice de diámetro diastólico ventricular izquierdo. En Chagas, digoxina y ß-bloqueadores, sodio, presión arterial sistólica e inhibidores de la enzima convertidora de angiotensina (IECA), (incluyendo combinaciones con ß-bloqueadores). En isquémicos: digoxina, índice de diámetro diastólico del ventrículo izquierdo DdVI/IMC) e hipotiroidismo y en no isquémicos: colesterol y volumen telediastólico ventrícular izquierdo (VTdVI). Obteniéndose las siguientes ecuaciones por etiología:*

$$\hat{S}(t) = [\hat{S}_0(t)]^{exp[-0.89*B\text{-}bloqueador-1.47*Estatina+1.239*Digoxina(0.125)+Digoxina(0.25)+0.551*DdVI/IMC]}$$

$$\hat{S}(t) = [\hat{S}_0(t)]^{exp[-3.469*B\text{-}bloqueador-2.663*IECA - 4.456*B\text{-}bloqueador+IECA - 0.036*SBP-0.195+3.061*Digoxina}$$

$$\hat{S}(t) = [\hat{S}_0(t)]^{exp[-0.634* DdVI/IMC+1.652*Digoxina+1.834Hipotiroidismo]}$$

$$\hat{S}(t) = [\hat{S}_0(t)]^{exp[-0.024*Colesterol+0.008*VTdVI]}$$

Conclusiones: *los predictores de mortalidad, en pacientes ambulatoriales con IC, son particulares según la etiología. En Chagas, algunos fármacos parecen tener un beneficio superior en comparación con otras etiologías. Este modelo de pronóstico muestra un valor al sistema sanitario público más allá del que aportan los modelos clínicos actuales.*

Palabras clave: *Insuficiencia cardíaca, enfermedad de Chagas, salud pública, política sanitaria.*

INTRODUCTION

The continuous increase in the incidence of heart failure (HF) worldwide, maintaining it as a leading cause of mortality, has stimulated the creation of several predictive models intended to assess mortality odds at short- and mid-term follow-ups. New pharmacological drugs, for example, can change the variables in those models. However, there are drug-use limitations in low- and middle-income countries where clinical trials are more frequent in the private healthcare sector or sponsored by pharmaceutical companies. Otherwise, some gaps include understanding the impact of HF in the public sector. This awareness can vary from 29 % in the lower range in Indonesia, 36 % in the middle range in Brazil, and at the top (60 %) in Canada (1). Regarding outcomes, a known history of heart failure is that few patients with an established syndrome will have a good prognosis. Outpatient studies have shown a variety of outcomes, and mortality rates can be between 17 %-60 %, depending on the syndrome etiology (ischemic etiology been the worst outcome odd and drug-induced HF for minor aftermath (2).

In addition, survival rates at 1, 5, and 10 years of patients with their first diagnosis are described as 81.3 % (95 % CI 80.9-81.6), 51.5 % (95 % CI 51.0-52.0), and 29.5 % (95 % CI 28.9-30.2) in a primary care population, respectively, with no improvement over time (3). Moreover, a wide range of articles describe independent predictors for heart failure. Still, we want to point out that most of the models used (such as the Seattle model) (4) were designed from randomized trials as DIG (5); however, using variables commonly used in outpatient setups. Although many factors seem important, the prognosis predicted for both populations (hospital and ambulatory) could differ (6).

Latin American patients also present some unique features that these models still need to consider. One of them is Chagas etiology, an issue that is underexplored in the American College of Cardiology/American Heart Association guidelines, (7) a growing problem in developed countries (8), and for instance, justifying models that compare those predictors based on this added etiology.

Ancillary, there are some particular concerns regarding the treatment of Chagas patients; for example, there are initial reports that show higher use of anti-arrhythmic drugs and up to 20 % fewer ß-blockers when compared with patients with heart failure from other etiologies (9) which could eventually lead to a different prognosis. A lack of ß-blockers in this scenario further increased the mortality odds for these patients

by fourfold (10). Among the reasons mentioned above was low drug availability by public health care centers, a much different situation at our Institution where ß-blockers use was encouraged. Furthermore, it is a challenge for us to make life-saving decisions in an ambulatory state characterized by patients with advanced heart failure, with some of them on a list for heart transplantation and usually optimized therapy.

Study design

We consecutively enrolled selected patients receiving optimized treatment derived from cohorts of HF patients, including Chagas' heart disease (Figure 1), at the Heart Institute's (InCor) ambulatory heart failure and transplant unit. The local Ethics Committee approved this project. The Heart Failure and Heart Transplantation Clinic accepted patients for assessment of their status, treatment optimization, and evaluation for potential surgical treatment of HF.

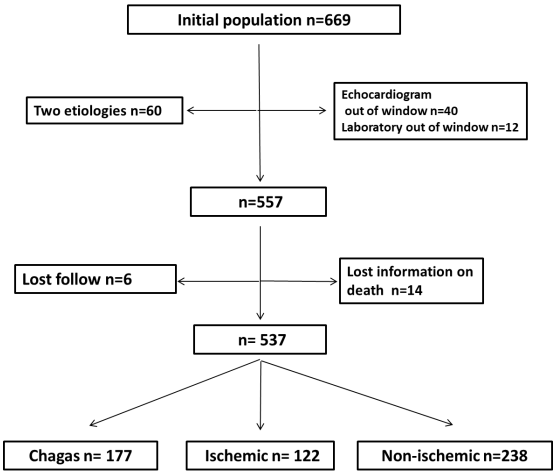

Figure 1. Patient selection flow chart.

Eligible patients were ≥18 years old, had chronic HF of at least six months, were followed at our outpatient clinic, and did not participate in any other institutional protocol. Exclusion criteria included researchers' inability to monitor the patient due to the patient's lack of transportation, living too far away, and social or communication problems. Concerning clinical data we excluded: myocardial infarction or unstable angina within 6 months before randomization, cardiac surgery or angioplasty within 6 months of randomization, hospitalized patients, severe renal/hepatic/neurological/ pulmonary or any systemic disease that could confuse the interpretation of results and influence expected survival, planned surgical procedure or other procedure that could influence follow-up, potential or definite pregnancy, poor life expectancy independently of the HF syndrome, mechanical prosthetic valves, estrogen therapy, coagulopathy, active chronic infection, two or more suspected etiologies for HF, arrhythmogenic right ventricular cardiomyopathy/dysplasia, left ventricle non-compaction, conduction system disease, ion channelopathies, primary restrictive nonhypertrophied cardiomyopathy, non-chagasic myocarditis, stress ("Tako-Tsubo") cardiomyopathy, peripartum (postpartum) cardiomyopathy, secondary cardiomyopathies, congenital heart disease, lack of echocardiogram or another cardiac imaging method for diagnosis within six months, or laboratory tests more than one month, before inclusion.

The ischemic etiology was defined in the presence of cardiac dilatation and myocardial dysfunction as a direct consequence of coronary artery disease confirmed by cardiac catheterization. Nonischemic cardiomyopathy as a cause of HF was defined by dilatation and myocardial dysfunction that could not be explained by genetic primary cardiomyopathies, valvar heart disease, primary restrictive nonhypertrophied cardiomyopathy, myocarditis, stress ("Tako-Tsubo") cardiomyopathy, myocardial dysfunction secondary to prolonged periods of supraventricular or ventricular tachycardia, peripartum (postpartum) cardiomyopathy, and secondary cardiomyopathies according the American Heart Association classification of the cardiomyopathies (11).

Valvular heart disease was diagnosed in the presence of cardiac dilatation and myocardial dysfunction secondary to primary valvular disease. The diagnostic criteria for Chagas' disease were accepted based on a combination of epidemiological data, clinical history, physical examination, EKG, echocardiogram, and positive serologic tests for anti-T. *cruzi*, compatible clinical syndrome, and no evidence of any other cause for cardiomyopathy, in accordance with current guidelines (12). Coronary arteriography was normal in all Chagas' disease HF patients who had at least two positive serologic tests (ELISA, indirect immunofluorescence, and indirect hemagglutination). Patients did not receive anti—*T. cruzi*—specific drug treatment. Patients with subclinical and clinical hypothyroidism received treatment after diagnosis based on laboratory results (TSH, T3, and T4 values).

We initially evaluated 669 suitable patients who were living in the state of São Paulo and were able to manage their own drug treatment to have optimal follow-up. The patients were evaluated retrospectively from a database because we had difficulty obtaining sufficient cases not included in interventional trials by the Institution despite the 700/month mean patient influx at the unit. We withdrew 112 patients from the study because of two etiologies prevalence (n = 60), echocardiography was performed more than six months window before entering the study (n=40), and 12 patients had more than a month window for laboratory results at baseline follow-up.

Death information reports from 14 patients could not be retrieved, and six cases could not be followed. The remaining 537 patients were divided into three groups based on etiology: Chagas (n = 177), ischemic (n = 122), and non-ischemic (n = 238). The non-ischemic group contains different etiologies (idiopathic (57.6 %), valvar (4.6 %), hypertensive (37 %), and hypertrophic (0.8 %).

Baseline characteristics are shown in Table 1 and were limited to historical, physical, and routine laboratory results. The ejection fraction was acquired through echocardiographic techniques, radionuclides, or angiographic measures. All patients had depressed left ventricle ejection fraction (mean 27 ± 11 %), with 42.5 % in NYHA class III and IV. Only 13.1 % of the patients had AF, with the highest prevalence in Chagas (16 %).

The following variables were chosen for univariate analysis: age, sex, BMI, etiology, systolic blood pressure (SBP), height, drug used; Angiotensin-converting-enzyme inhibitors (ACEIs), Spironolactone, Calcium antagonist, Hydrochlorothiazide, Furosemide, ß-blockers, Angiotensin II receptor blockers (ARBs), Statins, Hydralazine, Nitrates, Levothyroxine, Amiodarone, Digoxin), laboratory results: Sodium, Creatinine, Cholesterol, Hemoglobin and Lymphocytes. Electrocardiographic data included Left Bundle Branch Block (LBBB) and Right Bundle Branch Block (RBBB), pacemaker use, atrial fibrillation (AF), and echocardiographic measures. Since hypothyroidism had a respectable 14 % prevalence in the total population, it was also included in the general analysis and by group, showing a prevalence of 16.8 % in Chagas, 12.6 % in ischemic 12.7 %, and 12.7 non-ischemic groups respectively. Additionally, we partitioned and analyzed some variable combinations in the model: patients taking ß-blockers without ACEIs, ACEIs without ß-blockers, and both drugs combined, an index based on body weight mass and height. Furthermore, we constructed a drug dosage classification based on the principal medications used for each category, such as enalapril for ACEIs, carvedilol for ß-blockers, losartan for ARBs, and furosemide as a diuretic. The drugs used were part of the Unified Health System (SUS) [Sistema Único de Salud].

Table 1. Baseline characteristics of the population and for groups.

	Total	Chagas	Ischemic	Others
Age (years)	51 ± 11	51 ± 11	51± 9	49 ± 12
Sex (male) %	69.1 %	64.4 %	73.8 %	70.2 %
BMI	26 ± 5	24 ± 4	25 ± 4	26 ± 5
SBP (mmHg)	109 ± 20	103 ± 18	114 ± 22	111 ± 19
NYHA class *				
I	14.7 %	10.4 %	18.3 %	19.7 %
II	42.9 %	34.1 %	87.3 %	44.4 %
III	29.9 %	37 %	39.4 %	27.8 %
IV	12.6 %	18.5 %	21.1 %	8.1 %
Medications				
ACEIs	72.3	63.8	75.4	76.9 %
Spironolactone	65.7	67.2	58.2	68.5 %
Calcium antagonist *	9.7	4.5	11.5	12.6 %
Hydrochlorothiazide	19.7	20.3	17.2	20.6 %
Furosemide	79.3	81.4	77.9	78.6 %
ß-blockers	83.1 %	72.3 %	89.3 %	87.8 %
ARBs *	15.8 %	18.1 %	12.3 %	16 %
Statins *	23.6 %	12.4 %	47.5 %	19.7 %
Hydralazine	11.2 %	10.2 %	11.5 %	11.8 %
Amiodarone *	14 %	19.2 %	11.5 %	11.3 %
Digoxin *	50.7 %	37.3 %	46.7 %	62.6 %
Laboratory				
Sodium (mg/dL)	138 ± 4	138 ± 3	139 ± 3	138 ± 4
Creatinine (mg/dL) *¨	1.2	1.20	1.23	1.10
Cholesterol (mg/dL) *¨	178	169	182	184
Hemoglobin (g/L) *¨	14	13.4	14	14
White blood cells (mm^3) *¨	7.7	6.5	7.3	7.3
Lymphocytes %¨	25	26	24	25
Electrical activity				
AF	13.1 %	16 %	8.2 %	13.5 %
LBBB	26.1 %	17.8 %	23.8 %	33.5 %
RBBB *	18.6 %	36.9 %	9.8 %	9.9 %

Abbreviations: BMI: Body mass index, ACEIs: Angiotensin-Converting Enzyme inhibitors, SBP: Systolic blood pressure, LBBB: Left Bundle Branch Block, RBBB: Right Bundle Branch Block, *: p value<0.05, ¨: Nonparametric analysis (median values).

Additionally, we seek to know about a special group of patients with large left ventricular diastolic diameter or "big hearts," set as a cutoff point of 8 cm of left ventricle end-diastole diameter (LVEDD), and different combinations of left ventricular diastolic diameter index based on body mass index (BMI) and height (LVEDD/BMI and LVEDD/height).

Statistical analysis

The sample size accounted for a 12 % Chagas prevalence in the ambulatory with 85 % statistical power and an alpha of 0.05. All tests were bicaudate. As a result, we initially estimated a population of 580 patients ± 5 %. The Shapiro-Wilk test gauged the normality distribution of the population. Standard deviations helped describe quantitative variables. The Chi-Square test gauged qualitative variables and continuous variables between the three groups using one-way ANOVA, helping with a Kruskal variant depending on the normality test results. Cox proportional-hazards stepwise models determined the contribution of these variables. The Kaplan-Meier method estimated survival probability.

RESULTS

Within the twelve-month follow-up period, only forty-four patients died (8.2 %). In univariate analysis, initial mortality predictors for the general population were demographic characteristics, BMI, hydrochlorothiazide, ß-blockers, digoxin, statins, hemoglobin, sodium, and lymphocyte percentage. All indexes based on BMI and height were also associated with mortality along with Left ventricle end-diastole diameter (LVEDD) above 8 cm. The BMI-based index showed the most relevant association in the total group ($p < 0.001$).

Mortality between drug use

In the general population, digoxin showed the highest mortality-related risk (HR: 5.157, CI95:2.299-11.569, $p<0.001$), followed by furosemide, whereas ß-blockers, hydrochlorothiazide, and statins had protective odds (Table 2). Furthermore, ACEIs, ARBs, nitrates, hydralazine, amiodarone, and levothyroxine were not associated with mortality. Regarding laboratory predictors, sodium, hemoglobin, and lymphocyte percentages were related to mortality odds.

ß-blockers, used by 83.1 % of the sample, showed that mortality significantly decreased by almost 70 % in univariate analysis, $p < 0.001$ (Table 2). Their beneficial effect was present in all groups initially (Table 3,4,5), in drug combinations (Table 6), and later upheld after adjusted multivariate analysis only in the general population and Chagas (Table 7).

Contrary to the drugs alone, the combination of ACEIs and ß-blockers had superior beneficial effects in this population (Table 6). Enalapril alone or stratified in doses lacked an association with mortality. Moreover, mortality hazards were dose-related for furosemide and digoxin, but carvedilol had a mixed result, with the best protective effect at the intermediate dose (Table 6).

Electric activity-related markers

LBBB and RBBB, AF, and pace marker device did not show mortality associations in any of the groups studied in univariate analysis (Tables 3,4,5) or multivariate (Table 7).

General population

The independent predictors were ß-blockers, statins, LVEDD/BMI index, and digoxin. Notwithstanding the low dose, Digoxin had a dose-related hazard, which only showed a statistical trend in the total population (Table 7).

The following formula gives the first score for the total population:

$$\hat{S}(t) = [\hat{S}_0(t)]^{exp[-0.89*B\text{-}blocker-1.47*Statin+1.239*Digoxin(0.125)+Digoxin(0.25)+0.551*LVDD/BMI]}$$

Chagas group

Chagas' one-year mortality was the highest among the groups based on Kaplan-Meir survival curves, $p < 0.0017$ (Figure 2), and one-hundred-day days mortality rates were similar amongst groups. As expected, Chagas patients used fewer statins and calcium channel blockers than the other groups. Chagas patients use more amiodarone than others.

In univariate analysis (Table 3), digoxin, furosemide, SBP, sodium, hemoglobin, and low ejection fraction (EF) were associated with mortality odds, and ß-blockers exhibited a protective effect in these patients (HR: 0.291, $p = 0.009$). Furosemide, used in 79.3 % of patients, exhibited dosage-related mortality only for Chagas etiology, with an odd non-significant at a dose less than 40 mg; however, it was significant at 40-80 mg with 8.7 odds, $p = 0.045$ and higher hazard (12.4, $p = 0.029$) for doses above 80mg on univariate analysis (Table 3) but without effect after adjusted analysis (Table 7).

Table 2. Univariate predictors of survival in the general population.

	Univariate Hazard Ratio			
	HR	95 % CI	P	Wald x^2
Demographic				
Age	1.002	(0.976 - 1.028)	0.884	0.021
Sex (male)	0.815	(0.420 - 1.583)	0.546	0.365
BMI	0.908	(0.841 - 0.980)	0.014	6.096
NYHA class	1.213	(0.860 - 1.712)	0.670	1.213
Etiology			0.172	
SBP	0.979	(0.961 - 0.998)	0.029	4.791
LVEDD>8 cm	3.015	(1.553 - 5.855)	0.001	10.621
LVEDD / BMI	1.951	(1.441 - 2.642)	0.000	18.666
LVEDD / height	1.032	(1.010 - 1.055)	0.004	8.212
EF	1.013	(0.988 - 1.037)	0.312	1.021
Hypothyroidism	1.110	(0.468 - 2.629)	0.813	0.056
Atrial Fibrillation	1.759	(0.844 - 3.668)	0.132	2.270
Medications				
ACEIs	1.389	(0.668 - 2.89)	0.379	0.774
Spironolactone	1.614	(0.815 - 3.193)	0.169	1.888
Calcium antagonist	0.408	(0.099 - 1.685)	0.215	1.536
Hydrochlorothiazide	0.298	(0.092 - 0.961)	0.043	4.106
Furosemide	1.670	(0.706 - 3.951)	0.243	1.363
ß-blockers	0.296	(0.161 - 0.543)	<0.001	15.464
ARBs	0.510	(0.182 - 1.425)	0.199	1.650
Statins	0.143	(0.035 - 0.591)	0.007	7.220
Hydralazine	1.099	(0.433 - 2.790)	0.842	0.040
Nitrates	0.981	(0.415 - 2.321)	0.965	0.002
Levothyroxine	1.781	(0.702 - 4.519)	0.224	1.476
Amiodarone	1.038	(0.439 - 2.454)	0.933	0.007
Digoxin	5.157	(2.299 - 11.569)	<0.001	15.840
Laboratory				
Sodium	0.938	(0.896 - 0.982)	0.006	7.412
Creatinine	1.011	(0.838 - 1.221)	0.905	0.014
Cholesterol	1.001	(0.994 - 1.008)	0.843	0.039
Hemoglobin	0.833	(0.711 - 0.975)	0.023	5.161
Lymphocytes	1.000	(0.999 – 1.000)	0.089	2.889
Lymphocytes %	0.957	(0.925 - 0.990)	0.011	6.476
Electric activity				
LBBB	0.736	(0.354 - 1.532)	0.413	0.671
RBBB	1.231	(0.592 - 2.562)	0.578	0.310
Pacemaker device	0.872	(0.270 - 2.818)	0.819	0.052

Abbreviations: BMI: Body mass index, SBP: systolic blood pressure, LVEDD, Left ventricle end-diastolic diameter, ACEIs: Angiotensin-Converting Enzyme inhibitors, EF: Ejection fraction, ARBs: Angiotensin 2 receptor blockers, LBBB, Left bundle branch block, RBBB, right bundle branch block.

Table 3. Univariate predictors of survival for Chagas.

	Univariate Hazard Ratio			
	HR	95 % CI	P	Wald x^2
Demographic				
Age	0.982	(0.940 - 1.026)	0.411	0.675
Sex (male)	1.104	(0.428 - 2.847)	0.838	0.042
BMI	0.976	(0.854 - 1.115)	0.715	0.133
NYHA class	1.192	(0.678 - 2.097)	0.542	0.372
SBP	0.945	(0.916 - 0.975)	<0.001	12.306
LVDD>8cm	1.992	(0.457 - 8.677)	0.359	0.842
LVEDD / BMI	1.032	(0.430 - 2.473)	0.944	0.005
LVEDD/ height	0.995	(0.898 - 1.102)	0.923	0.009
EF	1.037	(1.000 - 1.075)	0.052	3.784
Hypothyroidism	0.340	(0.468 - 2.552)	0.294	1.102
Medications				
ACEIs	1.077	(0.404 - 2.869)	0.883	2.216
Spironolactone	1.753	(0.577 - 5.326)	0.322	2.802
Calcium antagonist	1.454	(0.193 - 10.932)	0.716	0.010
Hydrochlorothiazide	0.516	(0.119 - 2.246)	0.378	0.499
Furosemide	1.809	(0.416 - 7.869)	0.429	0.266
Reference			0.007	12.085
<40 mg	2.188	(0.274 - 17.493)	0.460	0.545
40-80 mg	8.712	(1.048 - 72.400)	0.045	4.015
>80 mg	12.380	(1.286 - 119.145)	0.029	4.744
ß-Blockers	0.291	(0.115 - 0.738)	0.009	6.759
ARBs	0.816	(0.236 - 2.820)	0.748	0.103
Statins	0.041	(0.000 - 19.164)	0.308	1.039
Hydralazine	1.452	(0.334 - 6.316)	0.619	0.247
Nitrates	2.040	(0.590 - 7.047)	0.260	1.270
Levothyroxine	0.046	(0.000 - 444.434)	0.510	0.433
Amiodarone	1.964	(0.700 - 5.515)	0.200	0.010
Digoxin	5.689	(1.872 - 17.286)	0.002	9.401
Laboratory				
Sodium	0.819	(0.728 - 0.922)	0.001	10.918
Creatinine	0.964	(0.700 - 1.328)	0.822	0.051
Cholesterol	1.001	(0.990 - 1.011)	0.896	0.017
Hemoglobin	0.737	(0.567 - 0.958)	0.022	5.216
Lymphocytes	1.000	(0.999 - 1.000)	0.284	1.148
Lymphocytes %	0.974	(0.929 - 1.021)	0.271	1.214
Electric activity				
LBBB	1.411	(0.464 - 4.286)	0.544	0.368
RBBB	0.814	(0.306 - 2.170)	0.681	0.168
Pacemaker device	0.812	(0.187 - 3.530)	0.781	0.077
AF	1.986	(0.708 - 5.570)	0.192	1.698

Abbreviations: BMI, Body mass index, SBP: systolic blood pressure, EF: Ejection fraction, ACEIs: Angiotensin-Converting Enzyme inhibitors, ARBs: Angiotensin 2 receptor blockers, LVEDD, Left ventricle end-diastolic diameter, LBBB, Left bundle branch block, RBBB, right bundle branch block, AF: Atrial fibrillation.

Table 4. Univariate predictors of survival in ischemic

	Univariate Hazard Ratio			
	HR	95 % CI	P	Wald 2
Demographic				
Age	1.003	(0.942 - 1.067)	0.933	0.007
Sex (male)	0.244	(0.031 - 1.888)	0.176	1.827
BMI	0.908	(0.841 - 0.980)	0.014	2.555
NYHA class	0.953	(0.485 - 1.872)	0.889	0.020
SBP	1.000	(0.976 - 1.025)	0.996	0.000
LVEDD > 8cm	3.015	(1.553 - 5.855)	0.001	5.015
LVEDD / BMI	1.951	(1.441 - 2.642)	<0.001	8.826
LVEDD / height	1.032	(1.010 - 1.055)	0.004	4.791
EF	0.973	(0.919 - 1.030)	0.345	0.890
Hypothyroidism	3.115	(0.826 - 11.756)	0.094	2.812
Atrial Fibrillation	1.112	(0.142 - 8.687)	0.919	0.010
Medications				
ACEIs	3.432	(0.443 - 25.580)	0.238	1.394
Spironolactone	1.045	(0.332 - 3.291)	0.941	0.006
Calcium antagonist	0.040	(<0.001 - 68.920)	0.398	0.714
Hydrochlorothiazide	0.410	(0.053 - 3.177)	0.394	0.728
Furosemide	3.346	(0.432 - 25.918)	0.248	1.337
ß-blockers	0.572	(0.125 - 2.613)	0.472	0.518
ARBs	0.041	(<0.001 - 75.641)	0.045	0.695
Statins	0.208	(0.046 - 0.949)	0.043	4.113
Hydralazine	0.724	(0.094 - 5.612)	0.758	0.095
Nitrates	0.277	(0.036 - 2.149)	0.220	1.507
Levothyroxine	5.302	(1.430 - 19.658)	0.013	6.223
Amiodarone	0.696	(0.090 - 5.395)	0.729	0.120
Digoxin	3.620	(0.980 - 13.373)	0.054	3.723
Laboratory				
Sodium	0.971	(0.813 - 1.161)	0.750	0.102
Creatinine	1.348	(0.495 - 3.667)	0.341	
Cholesterol	1.013	(1.001 - 1.025)	0.041	4.192
Hemoglobin	0.916	(0.688 - 1.220)	0.550	0.358
Lymphocytes	1.000	(0.999 - 1.001)	0.652	0.204
Lymphocytes %	0.951	(0.889 - 1.017)	0.144	2.138
Electric activity				
LBBB	0.315	(0.041 - 2.441)	0.269	1.222
RBBB	1.993	(0.426 - 9.098)	0.374	0.792
Pacemaker device	1.649	(0.213 - 12.78)	0.632	0.229

Abbreviations: BMI: Body mass index, EF: Ejection fraction, ACEIs: Angiotensin-Converting Enzyme inhibitors, ARBs: Angiotensin 2 receptor blockers, LVEDD: Left ventricle end-diastolic diameter, LBBB: Left bundle branch block, RBBB: right bundle branch block.

Table 5. Univariate predictors of survival in the non-ischemic group

	Univariate Hazard Ratio			
	HR	95 % CI	P	Wald x2
Demographic				
Age	1.013	(0.969 -1.060)	0.565	0.332
Sex (male)	0.918	(0.288 - 2.928)	0.886	0.021
BMI	0.887	(0.786 - 1.001)	0.052	3.772
NYHA class	1.320	(0.724 - 2.405)	0.365	0.819
SBP	0.994	(0.963 - 1.026)	0.715	0.133
LVEDD > 8cm	4.892	(1.715 - 13.953)	0.003	8.816
LVEDD / BMI	3.415	(1.802 - 6.471)	<0.001	14.181
LVEDD / height	1.124	(1.024 - 1.235)	0.014	5.996
LVEDD	1.005	(1.002 - 1.008)	0.003	8.793
EF	1.015	(0.977 - 1.055)	0.444	0.585
Hypothyroidism	1.197	(0.268 - 5.347)	0.814	0.055
Medications				
ACEIs	1.697	(0.380 - 7.581)	0.489	0.479
Spironolactone	2.847	(0.637 - 12.722)	0.171	1.877
Calcium antagonist	0.487	(0.064 - 3.721)	0.488	0.481
Hydrochlorothiazide	0.035	(0.000 - 9.006)	0.236	1.404
Furosemide	0.980	(0.273 - 3.514)	0.976	0.001
ß-blockers	0.230	(0.077 - 0.687)	0.008	6.938
ARBs	0.391	(0.051 - 2.993)	0.336	0.817
Statins	0.035	(0.000 - 8.845)	0.234	1.414
Hydralazine	1.245	(0.279 - 5.564)	0.774	0.083
Nitrates	0.769	(0.280 - 5.594)	1.252	0.086
Levothyroxine	1.941	(0.434 - 8.675)	0.385	0.754
Amiodarone	0.041	(0.000 - 47.382)	0.375	0.788
Digoxin	43.575	(0.494 - 3846.387)	0.375	2.726
Laboratory				
Sodium	0.958	(0.885 - 1.036)	0.280	1.166
Creatinine	1.073	(0.687 - 1.674)	0.757	0.095
Cholesterol	0.984	(0.680 - 1.000)	0.054	3.715
Hemoglobin	0.893	(0.670 - 1.890)	0.438	0.603
Lymphocytes	0.999	(0.998 - 1.000)	0.192	1.703
Lymphocytes %	0.933	(0.872 - 0.998)	0.044	4.042
Electric activity				
LBBB	0.797	(0.250 - 2.542)	0.702	0.147
RBBB	0.842	(0.110 - 6.443)	0.868	0.027
Pacemaker device	0.046	(0.000 - 1437.000)	0.559	0.341
AF	1.729	(0.482 - 6.200)	0.400	0.707

Abbreviations: BMI: Body mass index, SBP: systolic blood pressure, LVEDD: Left ventricle end-diastolic diameter, EF: Ejection fraction, ACEIs: Angiotensin-Converting Enzyme inhibitors, ARBs: Angiotensin 2 receptor blockers, LBBB: Left bundle branch block, RBBB: right bundle branch block.

Table 6. Drug dosage and drug combination in the general population (multivariate analysis)

	Hazard Ratio General population			
General population	HR	95 % CI	P	Wald2
ß-blockers / ACEIs			0.001	17.209
ACEIs	0.554	(0.159 - 1.927)	0.353	0.863
ß-blockers	0.135	(0.034 - 0.540)	0.005	8.009
ß-blockers + ACEIs	0.195	(0.058 - 0.656)	0.008	6.988
Enalapril			0.568	2.021
< 10 mg	0.811	(0.242 - 2.719)	0.734	0.115
10-20 mg	0.595	(0.280 - 1.263)	0.177	1.826
> 20 mg	0.720	(0.339 - 1.530)	0.393	0.729
Carvedilol			0.124	5.766
< 25 mg	0.740	(0.228 - 2.402)	0.616	0.252
25-50 mg	0.320	(0.126 - 0.816)	0.017	5.690
> 50 mg	0.000	(0.000 - 2.830)	0.962	0.002
Furosemide			0.020	9.877
< 40 mg	1.541	(0.581 - 4.086)	0.385	0.755
40-80 mg	2.820	(0.993 - 8.003)	0.051	3.792
> 80 mg	4.820	(1.470 - 15.798)	0.009	6.741
Digoxin			<0.001	19.971
0.125 mg	2.371	(0.694 - 8.100)	0.168	2.371
0.25 mg	6.014	(2.660 - 13.595)	0.000	6.014

Abbreviations: ACEIs: Angiotensin-converting enzyme inhibitors.

Table 7. Multivariate analysis for the population and groups

	Multivariate Hazard Ratio			
General population	HR	95 % CI	P	Wald2
ß-blockers	0.411	(0.215 - 0.783)	0.007	7.315
Statins	0.230	(0.054 - 0.972)	0.046	3.994
Digoxin			0.001	14.437
0.125 mg	3.451	(0.861 - 13.831)	0.080	3.058
0.25 mg	7.175	(2.518 - 20.444)	0.000	13.604
LDDVE/BMI	1.735	(1.228 - 2.450)	0.002	9.784
Chagas				
Digoxin	21.359	(2.78 - 164.123)	0.003	8.659
ACEIs	0.070	(0.004 - 1.155)	0.063	3.457
ß-blockers	0.031	(0.002 - 0.580)	0.020	5.406
ß-blockers + ACEIs	0.012	(0.001 - 0.251)	0.005	8.064
PAS	0.965	(0.939 - 0.992)	0.011	6.393
Na	0.823	(0.712 - 0.952)	0.009	6.914
Ischemic				
Digoxin	5.219	(1.101 - 24-728)	0.037	4.333
Hypothyroidism	6.256	(1.508 - 25.96)	0.012	6.376
LVEDD/BMI	1.885	(1.244 - 2.856)	0.003	8.937
Non-ischemic				
Cholesterol	0.976	(0.958 - 0.996)	0.016	5.782
LVEDV	1.008	(1.002 - 1.014)	0.006	7.568

Abbreviations: DDVE: BMI: Body mass index, ACEIs: Angiotensin-converting enzyme inhibitors, LVEDD: Left ventricle end-diastolic diameter, LBBB: Left bundle branch block, RBBB: right bundle branch block.

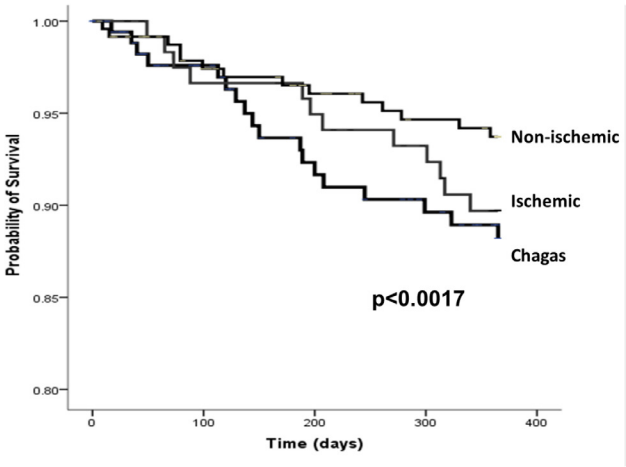

Figure 2. Survival probability in heart failure according to etiology.

In multivariate analysis, sodium (diuretic-dependent) was an independent predictor in this population (HR: 0.823, p < 0.009). ß-blockers enhanced their benefits when stratified onward with ACEIs when compared to the drugs alone. SBP maintained its favorable odds in the multivariate model (Table 7). Otherwise, digoxin showed the highest hazard risk (HR:21.359, CI95 % 2.78-164.123), resulting in the following formula:

$$\hat{S}(t) = [\hat{S}_0(t)]^{exp[-3.469*B\text{-}Blocker-2.663*ACEIs - 4.456*B\text{-}Blocker+ACEIs - 0.036*SBP-0.195+3.061*Digoxin}$$

Ischemic group

Statins, levothyroxine, enlarged LVEDD, and indexes based on weight and height were associated with mortality in univariate analysis (Table 4). Digoxin and hypothyroidism displayed a non-statistical significance in univariate analysis crossing the null hypothesis; nonetheless, they appeared as independent predictors in the multivariate model (HR: 5.219, p = 0.037, HR: 6.256, p=0.012,) respectively (Table 7). LVEDD/BMI index retained its initial mortality risk and with the resulting formula score:

$$\hat{S}(t)=[\hat{S}_0(t)]^{exp[-0.634*LVDD/BMI+1.652*Digoxin+1.834Hypothyroidsm]}$$

Non-ischemic group

In univariate analysis, mortality predictors were ß-blockers, hypothyroidism, LVEDD above 8 cm, BMI, and LVEDD-related measures (Table 5). Cholesterol exhibited a trend but revealed associated with mortality in the multivariate analysis, accompanied only by LVEDD (Table 7), leading to the formula:

$$\hat{S}(t) = [\hat{S}_0(t)]^{exp[-0.024*Cholesterol+0.008*LVEVI]}$$

DISCUSSION

Evaluation and treatment of patients with heart failure before entering an ambulatory system aim to cover mortality odds at short- and long-term follow-ups. One-year mortality risk is the first step in this endeavor. Unfortunately, it is frequently the case that when new pharmacology treatments are available for HF, a significant part of the population stops participating in observational studies after access to these treatments is gained.

Otherwise, risk score models must adapt to a wide range of etiologies to achieve their legitimate usefulness. Using Chagas disease as a comparison model provides us with a one-of-a-kind chance for targeted health policy in the

public sector. The likelihood that patients from the other groups (ischemic and non-ischemic) participate in clinical trials explained the high prevalence of Chagas cases enrolled in the ambulatory unit, a reason for exclusion criteria from this research population.

Moreover, independent predictors could differ from several trials, mainly due to the percentage of specific drug use. They might explain how drug classes such as ACEIs were not related to mortality in the multivariate analysis in this study. The PRAISE trial (13) that validated the results of five trials to compose the SEATTLE score showed similar results (14). Consequently, drug hazard estimates came from the data set and were not added, although suitable for predicting heart failure mortality (15). They were perhaps granted due to the widespread use of ACEIs in concurrent therapy and the fact that it does not increase mortality rates. Regarding the hydralazine-nitrate combination, an article examined the advantages of the drug combination above standard therapy, which appeared to be limited to the ethnic group of African Americans (16). Furthermore, in a larger group of 6 800 individuals, nitrates failed to show positive effects at 12 months but did influence mortality at 36 months with an HR: 1.18, CI95:1.06-1.32 (5).

This work emphasized the additional benefit of particular medications dependent on etiology. For example, lack of use of ß-blockers was a poor prognosis associated with Chagas (10); however, the study authors reported a low 34 % use of ß-blockers, compared to the 72.3 % observed in this study. As a result, such drugs that were not available to everyone in the past are frequently introduced and encouraged, fortunately positively improving outcomes. The same theory can also be true for drug combinations emerging as independent predictors in some groups, as was the case for ACEIs and ß-blockers in Chagas patients with an impressive protective odd. In the COPERNICUS trial (17), which evaluated 2 289 patients, carvedilol reduced mortality in severe heart failure. It is worth noting that both placebo and interventional groups had a high prevalence of ACEI use, suggesting that if there is a beneficial effect from this combination of drugs, it could overlap in the study.

We expected benefits from amiodarone, but they were unrelated to mortality in any of the groups. In addition, we did not explore dose combinations with ß-blockers, which are known to prevent arrhythmic death due to ventricular tachyarrhythmias in heart failure patients (18). Notably, amiodarone, a class III drug, also exhibits ß-blocker properties. Similar results were obtained for atrial fibrillation, bundle branch blocks, and pacemaker devices, perhaps because of the low percentage prevalence and small sample size.

A decreased EF was an independent mortality predictor in a systematic literature review of Chagas disease. In eleven studies analyzed, cardiac function was estimated by either an echocardiogram or cineventriculogram (19). In this study, only a tendency was observed in the Chagas group. Different ways to assess cardiac function could also explain why, in non-ischemic, left ventricular end-diastolic volume and not left ventricular end-diastolic diameter was the independent predictor, considering that one is derived from the other.

Digoxin use was associated with poor outcomes and observed in both doses (low and standard dose) for the general group and Chagas. Some authors where investigated a population in the use of digoxin and sinus rhythm, initially enrolled in the Digitalis Investigation Group trial and found no influence over mortality at 12 months (5); we had 50.7 % of the population on digoxin, and it was used in 70.5 % of patient with AF. We noted that digoxin use was in concordance with the European Task Force jointly with the Heart Failure Association, which maintains digoxin when ß-blockers fail, acknowledging that high plasma levels are associated with mortality and its effectiveness is limited with increased sympathetic drive (20). Furthermore, we emphasized that a broad confidence interval was detected in the results, a phenomenon observed in a small sample. Although digoxin exerts a positive inotropic effect at higher doses (0.25 mg or more), its neurohormonal activity is achieved at lower doses. Still, none of the doses herein studied were beneficial regarding mortality, at least in the short term. However, a post hoc analysis from a DIG trial found a

one-year mortality reduction in patients using 0.125 mg compared to 0.25 mg in a population that lacked ß-blockers, which could eventually affect the results (21).

According to a previous report (22), statins were also associated with lower mortality in the general group and similarly in the ischemic group. Nevertheless, the results were not seen in the third group (formed mainly by idiopathic and hypertensive etiologies) or the Chagas group. This outcome persisted in multivariate only for the general group.

Though cholesterol levels were lower in the Chagas group, they were only associated with mortality in the third group. Furthermore, in other studies with larger populations, as observed in the CORONA trial, the authors failed to show the benefits of using statins (23). The culprit's reasons included a depletion of the CoQ10 molecule the mitochondria need to produce adenosine triphosphate, a precious molecule in heart failure patients. Its depletion by statins could be up to 51 % (24). None of our patients were taking CoQ10, a non-approved FDA supplement that has shown benefits despite suboptimal levels in some trials with small populations (25). Moreover, some scientists have expressed concern about statin-induced cardiomyopathy, which occurs after an average of six years (26).

Thyroid function, in the ischemic, emerged as a new factor. However, it is necessary to define this group's authentic relevance. It is relevant to remember that thyroid function assessment was not a routine exam in our study, and its prevalence could be fold-enhanced. To address the problem, up to 20 % of the population could have subclinical hypothyroidism that could affect cardiac output and blood volume (27). Furthermore, it is equally documented that appropriate TSH monitoring could be lower as the patient worsens the NYHA class and has a longer time between levels of measurement while receiving amiodarone (28), suggesting appropriate routine measuring of this hormone. The effects of this study on helping discriminate patients with poor prognosis in the short term will also aid organizational management structures, especially in the public health system, by affecting decisions regarding high complexity procedures like the use of implantable ventricular assistance or heart transplant itself, where patient selection includes optimized medical treatment, severely depressed ventricular function and a high chance to be on continuous inotropic drugs in the incoming months. In this sense, with this toolset of formulas, we hope to be aiding in the groundwork to build a better assessment for treating Chagas' disease and heart failure in an outgoing setting.

Study limitations and advantages

Patients were analyzed in an ambulatory setting where some variables were unavailable as routine (neuro markers and other metabolic markers), which could have impacted the scores. We found it challenging to find patients to enroll principally because of the actual ongoing institutional interventional trials and its retrospective observational design. According to some authors, a short follow-up period may obscure some drug benefits (5). As unique leverage, the outpatient setting using drugs provided by the national public health program helps the gap in policymaker knowledge. This work aligns with studies to raise awareness between patients, caregivers, the healthcare system, and society (1). Furthermore, the cost-effectiveness related to using medications provided by the National Unified Health System (SUS) can be worthwhile when outcomes are compared with cutting-edge therapies like sacubitril/valsartan versus enalapril in the PARADIGM-HF trial, where the first group needed to complete 36 months, equivalent to 9 months beyond the mean follow-up to have a sensitive benefit (29). Regarding the published mortality risk score in Chagas HF, it is worth considering two studies, none compared other etiologies simultaneously. The first covered a two-year follow, considering pivotal clinical data, medications used for Chagas disease, and HF (the SaMi-Trop cohort study placed in the endemic area) (30). The second one had a longer follow-up, a mean of 7.9 years, but without comparing drug treatment and using a point score based mainly on electrocardiographic findings (31). Consequently, this research is the first to acknowledge comparative etiologies in outpatient settings, a first evidence step considering one-year

mortality, and an introduction for future clinical trials in the field.

CONCLUSIONS

Our results show that CDHF has distinct predictors of one-year survival compared to other etiologies in the same clinical setting. *B*-blockers alone or in combinations with ACEIs are more effective for CDHF than considering other etiologies simultaneously. Dose stratification and hypothyroidism odds brought new insights into risk scores, and we suggest their consideration in future models. Furthermore, the assimilation of these new predictive variables in this comparative way should have an incremental value, helping organizational management structures in the public health system beyond that supplied by other clinical models. In this way, we envision this concept, especially for low and middle-income countries with characteristics found in Latin America and Chagas disease prevalence and where there is a great need to systematize heart failure population public health adapted to the cost-effectiveness of resource allocation.

Declaration of Generative AI and AI-assisted technologies in the writing process

This work used only AI-assisted technology (Grammarly) to improve readability and language.

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