

Development of a Prediction Model for Mortality in Patients with Positive Serology for Chagas Disease: Argen-CHAG Score

Desarrollo de un modelo de predicción para mortalidad en pacientes con serología positiva para Chagas: score Argen-CHAG

MARÍA VICTORIA CARVELLI¹, MARIO B. PRINCIPATO¹, JUAN A. ÁLVAREZ CASIANI¹, HYUN SOK YOO¹,
YHESICA MOREIRA CAMACHO¹, FLORENCIA L. MUSCHIETTI¹, MANUEL LAGO¹, ANALÍA PAOLUCCI¹, ALBERTO ADAN SUÁREZ¹,
JUSTO CARBAJALES¹

ABSTRACT

Background: Infection with *Trypanosoma cruzi*, the etiological agent of Chagas disease, is endemic in 21 countries in the Americas and affects more than 7 million people. With an annual incidence of 30 000 cases and 12 000 deaths, it remains a critical public health challenge. Despite its impact, prognosis remains difficult to establish, and the predictive tools available are limited and poorly validated. Although Rassi et al. developed a mortality prediction model in Brazil, there are significant differences in cardiac involvement between Brazil and Argentina, so there are no validated models for the Argentine population.

Objectives: This study aimed to evaluate predictors of long-term mortality in the population infected with *Trypanosoma cruzi* who attend a public hospital in the city of Buenos Aires, and to develop a prognostic score for this population.

Methods: It included patients aged over 18 years with positive serology for Chagas disease who were evaluated at the Cardiology Division Chagas Program of a public hospital in Buenos Aires. Participants underwent clinical evaluation, ECG, echocardiography, and 24-h Holter monitoring. Follow-up data were obtained by reviewing the Unified Medical Records of the City of Buenos Aires and through telephone interviews with patients or relatives.

A derivation group was established assessing prognostic clinical, electrocardiographic and echocardiographic variables related with time to death using a Cox proportional hazards model. Independent predictors of mortality were identified and a score was generated which was subsequently applied to a validation group. The model's predictive capacity for 5- and 8-year mortality was evaluated using ROC curves.

Results: Among a total of 603 patients, 422 were assigned to the derivation group and 181 to the validation group. During a median follow-up of 6.6 years, 63 deaths in the derivation group and 20 in the validation group were observed. Three independent predictors were found: age, left ventricular ejection fraction (these two variables were rescaled into several categories), and history of implantable cardioverter-defibrillator. Each was assigned a score proportional to the hazard ratio.

A risk score was calculated for each patient and divided into three categories: 1) low risk: score 0-4 points, 2) moderate risk: score 5-12 points, and 3) high risk: score \geq 13 points.

Survival was 12.5% at 6.3 years in the high-risk group, 67% at 8.75 years in the moderate-risk group, and 92% at 8.7 years in the low-risk group. The area under the curve for predicting death was 0.89 and 0.85 at 5 and 8 years, respectively.

Conclusion: The risk score proved highly effective, as it presented high prognostic accuracy based on only three predictors, which are easily accessible in clinical practice. This tool could contribute significantly to risk stratification and decision-making in resource-limited settings, especially in regions where the disease is endemic and existing models do not adequately reflect the local characteristics of the population.

Key words: Chagas - mortality - score - prognosis

RESUMEN

Introducción: La infección por *Trypanosoma cruzi*, agente causal de la enfermedad de Chagas, es endémica en 21 países de América y afecta a más de 7 millones de personas. Con una incidencia anual de 30 000 casos y 12 000 muertes, representa un problema de salud global. A pesar de su impacto, el pronóstico sigue siendo difícil de establecer y las herramientas predictivas disponibles son limitadas y poco validadas. Aunque Rassi et al. desarrollaron un modelo de predicción de mortalidad en Brasil, existen diferencias significativas en la afectación cardíaca entre Brasil y Argentina, por lo que no hay modelos validados para población argentina.

REV ARGENT CARDIOL 2025;93:413-422. <https://doi.org/10.7775/rac.v93.i6.20944>

SEE RELATED ARTICLE: REV ARGENT CARDIOL 2025;93:403-404. <https://doi.org/10.7775/rac.v93.i6.20965>

Received: 10/30/2025 – Accepted: 11/13/2025

Correspondence: xxxxx

This article won the 51st Argentine Congress of Cardiology Award



<https://creativecommons.org/licenses/by-nc-sa/4.0/>

©Revista Argentina de Cardiología

¹ Hospital General de Agudos JM Ramos Mejía, Autonomous City of Buenos Aires, Argentina

Objetivos: Evaluar predictores de mortalidad a largo plazo en población infectada por *Trypanosoma cruzi* que concurre al hospital público en la Ciudad de Buenos Aires, y desarrollar un score pronóstico para esta población

Material y métodos: Se incluyeron todos los pacientes mayores de 18 años con serología positiva para Chagas que consultaron al Programa de Chagas del Servicio de Cardiología de un Hospital Público de la Ciudad de Buenos Aires. Se les realizó evaluación clínica, ECG, ecocardiograma y Holter. El seguimiento se efectuó mediante la revisión de la historia clínica unificada del Gobierno de la Ciudad de Buenos Aires y contacto telefónico con los pacientes o sus allegados. Se recolectaron datos de mortalidad.

Se generó un grupo de derivación en el que se evaluó el valor pronóstico de variables clínicas, electrocardiográficas y ecocardiográficas en relación con el tiempo a la muerte mediante el modelo de riesgos proporcionales de Cox. Se generó un score con los predictores independientes, que se aplicó en un grupo de validación. La capacidad predictiva del modelo en relación con la mortalidad a 5 y 8 años se evaluó mediante la curva ROC

Resultados: Se evaluaron 603 pacientes, de los cuales 422 fueron asignados al grupo de derivación y 181 al de validación. Durante una mediana de 6,6 años de seguimiento, se observaron 63 muertes en el grupo derivación y 20 muertes en el grupo validación. Entre los predictores estudiados, se encontraron tres predictores independientes: la edad, la fracción de eyección del ventrículo izquierdo (estas dos variables fueron reescaladas en varias categorías) y el antecedente de portar un cardiodesfibrilador implantable. Se asignó a cada uno un puntaje proporcional al Hazard ratio.

Se calculó el puntaje de riesgo para cada paciente y se dividió al mismo en tres categorías: 1) bajo riesgo: puntaje de 0 a 4, 2) moderado riesgo: puntaje 5 a 12, y 3) alto riesgo: puntaje igual a o mayor de 13 puntos.

Se observó una supervivencia de 12,5 % a 6,3 años en el grupo de alto riesgo, de 67 % a 8,75 años en el de moderado riesgo y de 92 % a 8,7 años en el grupo de bajo riesgo. El área bajo la curva para la predicción de muerte fue de 0,89 y 0,85 a 5 y 8 años respectivamente.

Conclusión: El puntaje de riesgo identificado mostró una gran eficacia, ya que presentó una alta certeza pronóstica basada en solo tres predictores, fácilmente accesibles en la práctica clínica. Esta herramienta podría contribuir significativamente a la estratificación del riesgo y a la toma de decisiones en contextos con recursos limitados, especialmente en regiones donde la enfermedad es endémica y los modelos existentes no reflejan adecuadamente las características locales de la población.

Palabras clave: Chagas - mortalidad - score - pronóstico

INTRODUCTION

Chronic infection with *Trypanosoma cruzi*, the etiological agent of Chagas disease, remains a critical public health challenge in Latin America. Current estimates suggest that over 7 million people are infected across 21 countries, with an annual incidence of approximately 30 000 new cases, 9000 of which result from vertical transmission. The disease accounts for roughly 12 000 deaths annually and has evolved into a global health threat due to increased migratory patterns. (1-4)

Although the chronic phase can remain asymptomatic for decades, up to 30% of patients eventually develop progressive cardiac complications, including complex arrhythmias, heart failure, dilated cardiomyopathy, and sudden cardiac death. (5-8)

Despite its significant clinical and socioeconomic burden, the prognosis for Chagas disease remains difficult to determine. Existing tools are limited and often lack adaptability to diverse clinical contexts. The Rassi score, developed in Brazil, is the most widely utilized model; however, its applicability outside Brazil is constrained by significant phenotypic and epidemiological variations across endemic regions. (9)

In Argentina, where Chagas remains a leading cause of cardiomyopathy and premature cardiovascular mortality in young adults, a locally calibrated risk model has yet to be established.

OBJECTIVE

The study aimed to identify long-term mortality predictors in a cohort of patients with chronic *Trypanosoma cruzi* infection at a public hospital in Buenos Aires and to develop a specific prognostic score for this population.

METHODS

This was a retrospective, single-center study. It consecutively included patients ≥ 18 years of age with confirmed positive serology for Chagas disease who attended the Cardiology Division Chagas Program at a public hospital in Buenos Aires. Each participant underwent a comprehensive evaluation, including clinical history, electrocardiogram (ECG), Doppler echocardiography, and 24-hour Holter monitoring.

Follow-up was performed by reviewing the unified electronic medical records of the Government of the City of Buenos Aires and through telephone contact with patients or their relatives. The primary endpoint was all-cause mortality.

Statistical analysis

Clinical and electrocardiographic variables, as well as echocardiographic left ventricular ejection fraction, were evaluated

To develop the score, patients were randomly divided into two groups a "Derivation" group, from which predictors were identified and selected to build the score, comprising 70% of the subjects, and a "Validation" group that assessed score performance.

Numerical variables are expressed as mean and standard deviation, using Student's t-test to compare between groups. Categorical variables are expressed as number of cases and the corresponding percentage, using the chi-square test to compare between groups. Time to all-cause death was identified as outcome.

The different variables were evaluated in the derivation group, initially using the univariate Cox regression model, with time to all-cause as outcome and each of the clinical variables, ECG, Holter monitoring and echocardiogram as predictors. All predictors with $p < 0.05$ were then used for the joint evaluation of their effect using a multivariate Cox regression model with backward selection strategy in the stepwise regression method. Subsequently, the predictors that in this analysis had an associated $p < 0.05$ were selected to build the score. To optimize score assignment numerical predictors were categorized into discrete groups.

Each independent predictor was assigned a weight proportional to its estimated hazard ratio. The score developed was then stratified into risk categories by estimating survival within the validation group using the Kaplan-Meier method. Finally, the model's predictive performance was assessed through the Area Under the ROC Curve (AUC) for 5- and 8-year mortality.

The analyses were performed using the survival (3.8-3 version), survminer (0.5.0 version), and survival ROC (1.0.3.1 version) packages of the R software (4.5.0 version, R Development Core Team/R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki (10) and approved by the institutional Teaching and Research Committee.

RESULTS

Among a total of 603 patients enrolled, 422 were assigned to the derivation group and 181 to the valida-

tion group. Mean age was 58 ± 12 years, 63% were female, and mean left ventricular ejection fraction (LVEF) was 56%. Baseline characteristics were comparable across both groups, except for a slightly older age in the validation group (Table 1).

Quantitative variables are presented as mean \pm standard deviation, and qualitative variables as n (%)

AF: atrial fibrillation; AVB: atrioventricular block; G: grade; ICD: implantable cardioverter-defibrillator; LAFB: left anterior fascicular block; LBBB: left bundle branch block; LPFB: left posterior fascicular block; LVEF: left ventricular ejection fraction; NYHA FC: New York Heart Association functional class; RBBB: right bundle branch block.

Over a median follow-up of 6.6 years, 63 deaths occurred in the derivation group and 20 deaths in the validation group.

In the derivation group univariate Cox regression analysis, 9 predictors among all the variables

Table 1. Baseline population characteristics

| | GROUPS | | p |
|------------------------|--------------------|--------------------|-------|
| | Derivation (n=422) | Validation (n=181) | |
| Female | 274 (64.9) | 114 (62.9) | 0.716 |
| Age | 59.04 \pm 12.30 | 56.52 \pm 12.71 | 0.023 |
| NYHA FC | | | 0.954 |
| 1 | 367 (87.0) | 156 (86.2) | |
| 2 | 44 (10.4) | 21 (11.6) | |
| 3 | 9 (2.1) | 3 (1.7) | |
| 4 | 2 (0.5) | 1 (0.6) | |
| Hypertension | 133 (31.5) | 49 (27.1) | 0.321 |
| Diabetes | 49 (11.6) | 16 (8.8) | 0.388 |
| Smoking | 15 (3.6) | 2 (1.1) | 0.162 |
| Dyslipidemia | 37 (8.8) | 16 (8.8) | 1 |
| Coronary heart disease | 0 (0.0) | 0 (0.2) | 1 |
| LVEF | 56.06 \pm 13.26 | 56.94 \pm 12.87 | 0.455 |
| AF | 48 (11.4) | 13(7.2) | 0.156 |
| LBBB | 32 (7.6) | 7 (3.9) | 0.129 |
| RBBB | 59 (14.0) | 29 (16.0) | 0-656 |
| LAFB | 70 (16.6) | 35 (19.3) | 0.485 |
| LPFB | 4 (0.9) | 1 (0.6) | 0.999 |
| AVB 1G | 10 (2.4) | 6 (3.3) | 0.734 |
| AVB 2G Mobitz I | 1 (0.2) | 0 (0.0) | 1 |
| AVB 2G Mobitz II | 1 (0.2) | 0 (0.0) | 1 |
| AVB 3G | 2 (0.5) | 3 (1.7) | 0.328 |
| ICD | 27 (6.4) | 8 (4.4) | 0.446 |

Quantitative variables are presented as mean \pm standard deviation, and qualitative variables as n (%)

AF: atrial fibrillation; AVB: atrioventricular block; G: grade; ICD: implantable cardioverter-defibrillator; LAFB: left anterior fascicular block; LBBB: left bundle branch block; LPFB: left posterior fascicular block; LVEF: left ventricular ejection fraction; NYHA FC: New York Heart Association functional class; RBBB: right bundle branch block.

analyzed were significantly associated with mortality rate. functional class, history of implantable cardioverter-defibrillator (ICD), presence of atrial fibrillation, left bundle branch block, right bundle branch block, ventricular arrhythmias and age were related with increased mortality, while LVEF was inversely proportional to mortality (Table 2).

These variables were included in a multivariate Cox regression model, in which three remained as

independent predictors of mortality: age (HR 1.07; 95% CI 1.05–1.09; $p < 0.001$), LVEF (HR 0.94; 95% CI 0.92–0.96; $p < 0.001$) and history of ICD (HR 7.8; 95% CI 1.01–60.2; $p = 0.049$). (Table 3)

Next, the relationship between the continuous predictors LVEF and age was explored in order to divide them into categories that would simplify the construction of the score without affecting its predictive accuracy.

Table 2. Univariate Cox regression analysis u

| Predictor | HR | 95% CI | p |
|-----------------------------|------|------------|---------|
| LVEF | 0.93 | 0.91-0.94 | < 0.001 |
| Age | 1.08 | 1.05-1.11 | <0.001 |
| NYHA FC | 2.19 | 1.61-2.96 | <0.001 |
| ICD | 7.78 | 4.40-13.80 | <0.001 |
| AF | 3.77 | 2.17-6.52 | <0.001 |
| LBBB | 5.55 | 3.09-9.96 | <0.001 |
| RBBB | 2.01 | 1.13-3.59 | 0.018 |
| Coronary heart disease | 6.27 | 0.87-45.36 | 0.069 |
| Ventricular arrhythmia | 3.14 | 1.80-5.47 | 0.001 |
| Supraventricular arrhythmia | 0.37 | 0.13-1.01 | 0.052 |
| Hypertension | 1.22 | 0.73-2.04 | 0.441 |
| Diabetes | 1.73 | 0.90-3.31 | 0.099 |
| Smoking | 2.03 | 0.63-6.50 | 0.232 |
| Dyslipidemia | 1.22 | 0.52-2.80 | 0.664 |
| Female gender | 0.34 | 0.20-0.56 | <0.001 |
| LAFB | 1.74 | 0.96-3.01 | 0.066 |
| LPFB | 1.42 | 0.20-10.28 | 0.726 |
| AVB 1 G | 2.21 | 0.69-7.03 | 0.183 |

AF: atrial fibrillation; AVB: atrioventricular block; CI : confidence interval; G: grade; HR: hazard ratio; ICD: implantable cardioverter-defibrillator; LAFB: left anterior fascicular block; LBBB: left bundle branch block; LPFB: left posterior fascicular block; LVEF: left ventricular ejection fraction; NYHA FC: New York Heart Association functional class; RBBB: right bundle branch block.

Table 3. Multivariate Cox regression analysis

| Variable | HR | 95% CI | p |
|------------------------|-----------|-----------|--------|
| LVEF | 0.94 | 0.92–0.96 | <0.001 |
| Age | 1.07 | 1.05–1.09 | <0.001 |
| NYHA FC | 2.19 | 1.61-2.96 | <0.001 |
| 1.02 | 0.64–1.64 | 0.923 | <0.001 |
| ICD | 7.86 | 1.01–60.2 | 0.049 |
| AF | 1.31 | 0.72–2.38 | 0.372 |
| LBBB | 0.90 | 0.43-1.90 | 0.787 |
| RBBB | 1.72 | 0.92-3.24 | 0.090 |
| Ventricular arrhythmia | 0.20 | 0.03-1.52 | 0.120 |

AF: atrial fibrillation; CI: confidence interval; HR: hazard ratio ICD: implantable cardioverter-defibrillator; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; NYHA FC: New York Heart Association functional class; RBBB: right bundle branch block.

Figure 1 shows the survival function in relation to LVEF (A), which appeared to be nonlinear, and age (B), which appeared to be adequately linear. Therefore, the most appropriate partitioning of the LVEF and age scales was designed.

Age was divided into five categories: I) age < 40 years, II) age \geq 40 years and < 50 years, III) age \geq 50 years and < 60 years, IV) age \geq 60 years and < 70 years, and V) age > 70 years. It was analyzed as an ordinal scale, that is, the coefficient expresses the effect of changing from one category to the next.

LVEF was divided into four categories based on clinical evidence regarding its behavior in relation to prognosis and response to different treatments: I) LVEF \geq 53%, II) LVEF < 53% and \geq 40%, III) LVEF < 40% and \geq 30%, and IV) LVEF < 30%. It was analyzed as a multinomial scale, that is, the coefficient expresses the effect of each category I in relation to category I (baseline).

Table 4 shows Cox regression results with age and LVEF rescaled variables. Subsequently, the score variables are shown with their corresponding values (Table 5).

Figure 2 shows modeling of the relationship between survival function, time, and score values, where there is a marked difference in survival between the lowest values, with virtually zero mortality, and the highest values, with very high mortality.

The risk score for each patient was then calculated according to the values of each predictor, and the final score was divided into three categories: 1) low risk: score 0 to 4, 2) moderate risk: score 5 to 12, and 3) high risk: score \geq 13 points. The survival function was calculated in the derivation group to evaluate its discriminatory capacity between risk groups, and in the

validation group to evaluate the performance of the score in another similar group.

Figure 3 shows the Kaplan-Meier survival curves for each of the three risk categories defined by the score, both for the derivation group (Figure 3A) and for the validation group (Figure 3B), where the wide difference in survival between the categories and the similar behavior in both groups suggest adequate risk discrimination and reproducibility. In the validation group, consistent with the derivation group, mortality was 87.5% at 6.3 years in the high-risk group, 33% at 8.75 years in the moderate-risk group and only 8% at 8.7 years in the low-risk group (Figure 4)

Figure 5 shows the performance of the model evaluated using the area under the ROC curve (AUC) for all-cause mortality at 5 years. The AUC was 0.82 in the derivation group (Figure 5A) and 0.89 in the validation group (Figure 5B). At 8 years, the AUCs were 0.81 and 0.85, respectively.

DISCUSSION

Our study presents the Argen-CHAG score, developed in a large and representative cohort of patients with positive serology for *Trypanosoma cruzi* treated in the public health system of the City of Buenos Aires. The model was constructed based on three simple and accessible predictors—age, LVEF, and ICD history—and demonstrated excellent prognostic performance, with high and consistent discriminatory ability in both derivation and validation groups.

The score allows patients to be stratified into three clearly differentiated risk categories, with a net and clinically relevant mortality gradient. This classification can be very useful for identifying those who require closer follow-up, therapeutic intensification, or

Fig. 1. Survival probability as a function of LVEF (a) and age (B)

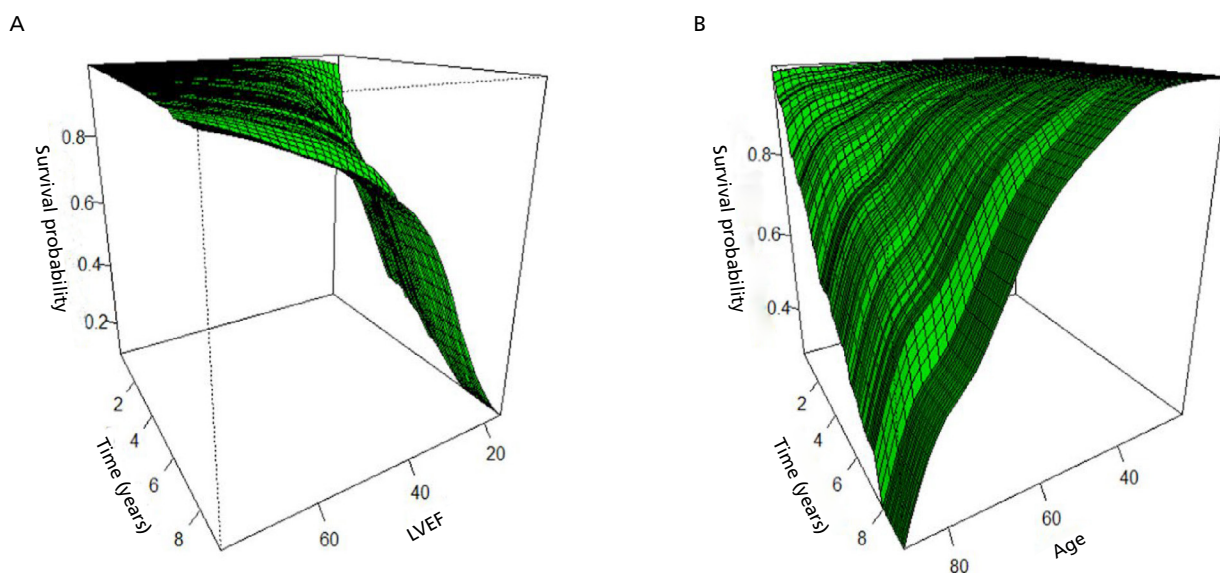


Table 4. Cox regression results with age and LVEF rescaled variables

| Variable | HR | 95% CI | p |
|--|-------|------------|---------|
| Age (every 10 years from age 40 onwards) | 2.28 | 1.70-3.06 | <0.001 |
| LVEF < 53-40 | 3.06 | 1.41-6.67 | 0.005 |
| LVEF < 40-30 | 6.41 | 3.19-12.88 | < 0.001 |
| LVEF < 30 | 11.41 | 5.20-25.01 | <0.001 |
| ICD | 1.84 | 0.89-3.80 | 0.099 |

CI: confidence interval; HR: hazard ratio; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction.

Table 5. Argen- CHAG variables with their corresponding scores

| Variable | Category | Score |
|-------------|----------|-------|
| ICD | Present | 2 |
| | Absent | 0 |
| Age (years) | < 40 | 0 |
| | 40-49 | 2 |
| | 50-59 | 4 |
| | 60-69 | 6 |
| | ≥ 70 | 8 |
| LVEF % | ≥ 53 | 0 |
| | 40-52 | 3 |
| | 30-39 | 6 |
| | <30 | 12 |

ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction;

Fig. 2. Modeling of the survival probability, time and score relationship

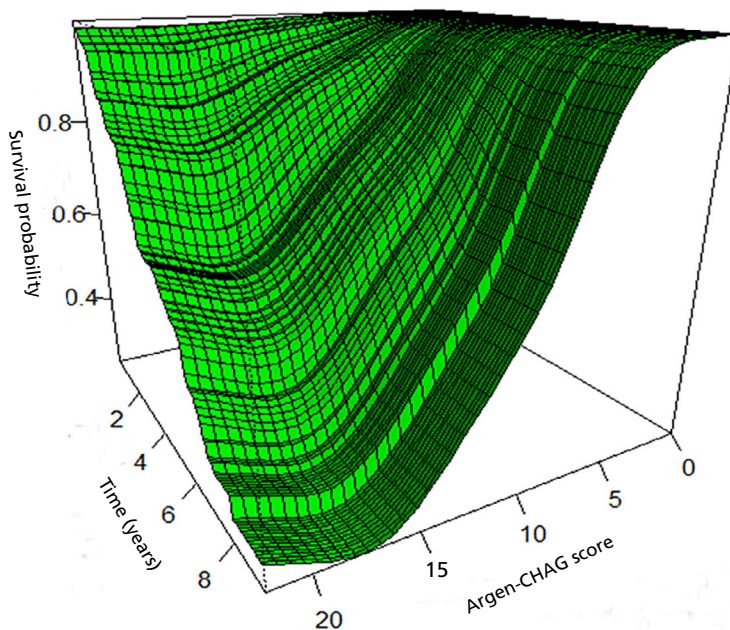


Fig. 3. Kaplan -Meier curves for each of the three score categories in both groups. A, Survival in the derivation group. B Survival in the validation group.

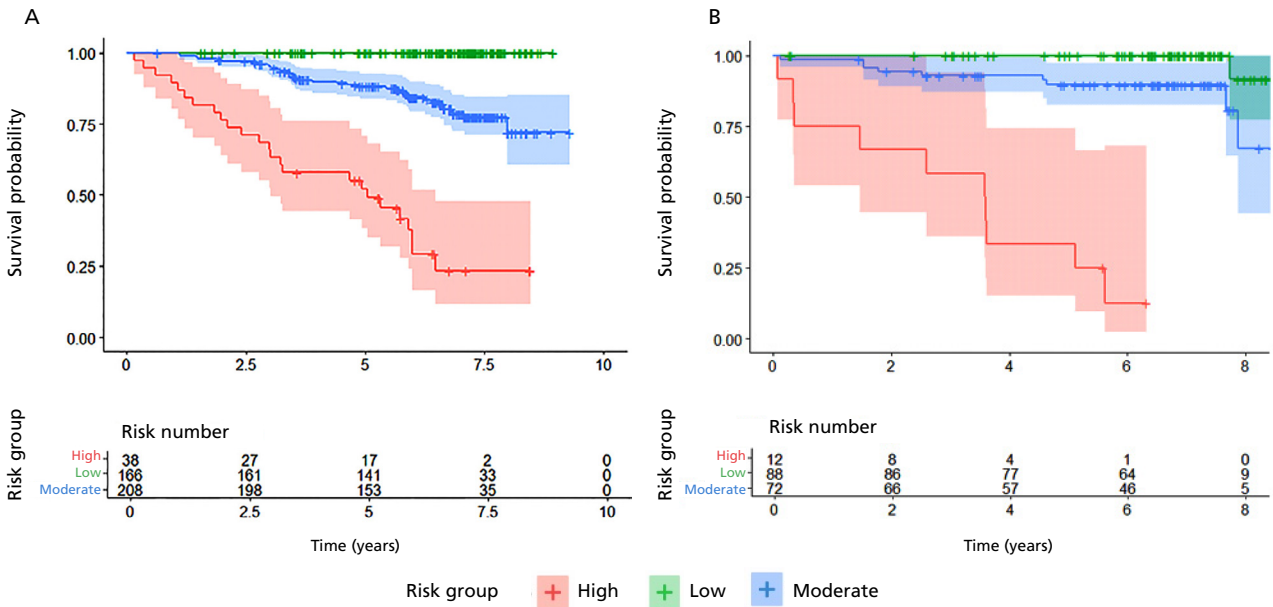
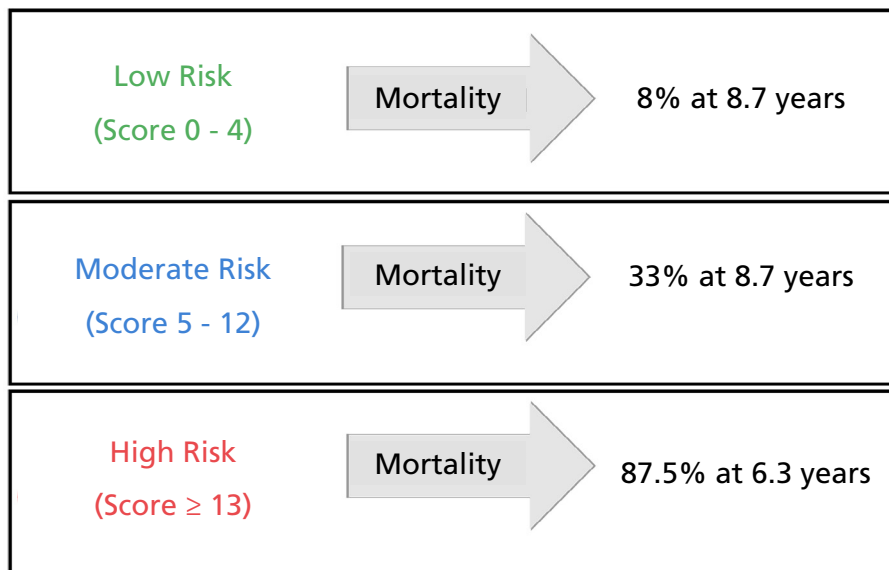


Fig. 4. Stratification of mortality risk according to the ARGEN-CHAG score, showing low, moderate and high-risk categories, together with mortality during follow-up.



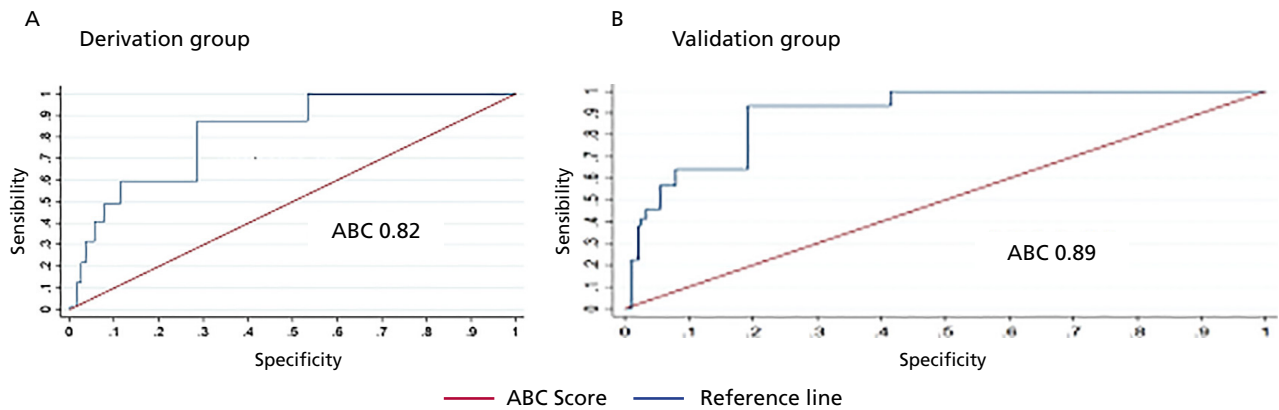
consideration of devices, while recognizing those at low risk, which avoids the overuse of resources. Thus, the model not only predicts but also offers a practical framework for clinical decision-making and resource optimization in contexts with high prevalence and structural limitations.

In Argentina, Chagas disease continues to be a significant cause of heart failure and sudden death. (11,12) Chronic Chagas cardiomyopathy (CCM) is as-

sociated with alarmingly high mortality, even higher than that observed in other forms of dilated cardiomyopathy. In a recent meta-analysis that included 37 studies and 17 949 patients, Gómez-Ochoa et al. demonstrated that patients with CCM have an almost twofold higher risk of mortality compared with those with non-ischemic and non-chagasic cardiomyopathies. (13)

The higher mortality rate of CCM can be explained

Fig. 5. Model performance: ROC curves to predict 5-year mortality for the Argen-CHAG score.



AUC: Area under the curve.

by its particular pathophysiology, characterized by persistent myocardial inflammation, diffuse transmural fibrosis, diffuse myocardial fibrosis, malignant ventricular arrhythmias, and a high thromboembolic burden. Added to this is the absence of randomized clinical trials demonstrating the advantage of specific therapies in this population, suggesting that the benefit of conventional treatments for heart failure may not be comparable to those observed in other etiologies. (13-15) In the recently published PARACHUTE-HF study, sacubitril valsartan, compared with enalapril, generated a greater reduction in natriuretic peptide values, without reducing cardiovascular mortality or the incidence of hospitalization for heart failure. (16)

Moreover, a systematic review and meta-analysis by Cucunubá et al. aimed to evaluate whether Chagas disease induces higher mortality compared with a control population with similar symptoms. This analysis included 25 studies with 10 638 patients and 53 346 person-years of follow-up, showing that *Trypanosoma cruzi* infection is associated with significantly higher mortality. The overall relative risk (RR) of death in patients with Chagas disease was 1.74 (95% CI 1.49–2.03) compared with uninfected individuals, with an annual mortality rate of 18% versus 10%, and an attributable risk of 42.5%. This excess mortality was observed in all clinical stages, although annual rates increased with severity (2% in asymptomatic patients, 16% in moderate-patients, and 43% in severe patients). However, a relevant limitation is the absence of studies conducted in Argentina. (17)

The Rassi score, published in 2006, represented a key progress in the prognostic stratification of Chagas disease. This model was developed from a Brazilian hospital cohort that initially included 424 patients, although the multivariate analysis was performed on 331 patients with complete data for all the variables evaluated. Patients were followed up for an average of 7.9 years to assess mortality. (9) However, its appli-

cation has significant limitations outside the original context. First, the score was built with patients in advanced stages of the disease, which limits its extrapolation to populations with earlier or different clinical presentations. Furthermore, although the model performed well in Brazil, there are important differences in the manifestation and evolution of cardiac involvement between Brazil and Argentina, which reduces its validity for the Argentine population and highlights the need for locally validated prognostic tools.

Another notable limitation is the absence of variables derived from Doppler echocardiography in the original model. In recent years, this shortcoming has been one of the most questioned points, given that Doppler echocardiography is currently a fundamental tool, accessible in most health centers, with a consolidated prognostic value in the evaluation of cardiac function and structural heart diseases. (8,19) Finally, Rassi's model did not consider the inclusion of implantable devices, such as ICD, which are a current mainstay in the management of patients at high risk for ventricular arrhythmias and sudden death. (19-21)

Other recent studies have attempted to refine prognostic prediction in specific subgroups. Pereira et al. evaluated 117 CCM patients with ICD, observing a high incidence of appropriate therapies and a mortality rate of 6.2% person-years, predominantly due to refractory heart failure. In the multivariate analysis, secondary prevention, LVEF <30%, and intermediate Rassi score were associated with the occurrence of appropriate therapies, while functional class IV, LVEF <30%, and age >75 years were predictors of mortality. However, this was a single-center study, with a predominance of secondary prevention and a long inclusion period (2003-2021), which may have introduced heterogeneity in clinical management. (22)

Peixoto et al. developed and validated a specific prognostic score for CCM patients with pacemaker, a subgroup that was underrepresented in previous studies. They included 555 patients with an average

follow-up of 3.7 ± 1.5 years and a cumulative mortality rate of 18%. They identified six independent predictors of mortality (right ventricular dysfunction, functional class III-IV, chronic kidney disease, left ventricular end-systolic diameter >44 mm, atrial fibrillation, and radiographic cardiomegaly) and classified patients into risk categories with mortality rates of 8%, 20.4%, and 51%. Although its clinical applicability is high, the study was single-center, without external validation, and with a visual assessment of right ventricular function, which may limit its reproducibility. (23)

This evidence reinforces the need to develop specific and locally validated prognostic tools, especially in contexts such as Argentina, where epidemiological, clinical, and socioeconomic characteristics differ from those observed in the Brazilian cohorts predominant in the literature. In addition, the country under study may reflect a differential distribution of *T. cruzi* genotypes, which are believed to influence disease progression and, therefore, mortality. This biological heterogeneity, coupled with differences in access to and quality of healthcare systems, reinforces the notion that scores derived from other populations cannot be directly extrapolated to the Argentine context, justifying the development of specific prognostic models such as the one presented here. (24)

Limitations

The retrospective nature of the study does not allow us to rule out the presence of residual confounding factors inherent in a non-randomized observational design.

CONCLUSION

Chagas disease continues to be a significant cause of morbidity and mortality, and there is lack of prognostic tools adapted to the Argentine reality. In this scenario, the ARGEN-CHAG model emerges as a simple, accurate, and easy-to-apply prognostic tool, developed from a representative cohort of the Argentine public health system. Its high discriminatory power, based on only three easily assessed clinical predictors, positions it as a valuable resource for optimizing risk stratification, guiding therapeutic decisions, and improving the follow-up of patients with Chagas disease in our country.

Acknowledgments

Our deepest and most sincere thanks go to the patients with Chagas disease who participated in this study, as their contribution and that of their families was essential to perform this work. Therefore, we hope to continue generating evidence that will allow us to improve the follow-up and care of this group of patients.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

REFERENCES

- Nunes MC, Dones W, Morillo CA, Encina JJ, Ribeiro AL; Council on Chagas Disease of the Interamerican Society of Cardiology. Chagas disease: an overview of clinical and epidemiological aspects. *J Am Coll Cardiol* 2013;62:767-76. <https://doi.org/10.1016/j.jacc.2013.05.046>
- Schmunis GA, Yadon ZE. Chagas disease: a Latin American health problem becoming a world health problem. *Acta Trop* 2010;115:14-21. <https://doi.org/10.1016/j.actatropica.2009.11.003>
- Lee BY, Bacon KM, Bottazzi ME, Hotez PJ. Global economic burden of Chagas disease: a computational simulation model. *Lancet Infect Dis* 2013;13:342-8. [https://doi.org/10.1016/S1473-3099\(13\)70002-1](https://doi.org/10.1016/S1473-3099(13)70002-1)
- Requena-Méndez A, Aldasoro E, De Lazzari E, Sicuri E, Brown M, Moore DA, et al. Prevalence of Chagas disease in Latin-American migrants living in Europe: a systematic review and meta-analysis. *PLoS Negl Trop Dis* 2015;9:e0003540. <https://doi.org/10.1371/journal.pntd.0003540>
- Prata A. Clinical and epidemiological aspects of Chagas disease. *Lancet Infect Dis* 2001;1:92-100. [https://doi.org/10.1016/S1473-3099\(01\)00065-2](https://doi.org/10.1016/S1473-3099(01)00065-2)
- Cunha-Neto E, Chevillard C. Chagas disease cardiomyopathy: immunopathology and genetics. *Mediators Inflamm* 2014;2014:683230. <https://doi.org/10.1155/2014/683230>
- Nunes MCP, Beaton A, Acquatella H, Bern C, Bolger AF, Echeverría LE, et al. Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American Heart Association. *Circulation* 2018;138:e169-e209. <https://doi.org/10.1161/CIR.0000000000000599>
- Bonney KM, Luthringer DJ, Kim SA, Garg NJ, Engman DM. Pathology and pathogenesis of Chagas heart disease. *Annu Rev Pathol* 2019;14:421-47. <https://doi.org/10.1146/annurev-pathol-020117-043711>
- Rassi A Jr, Rassi A, Little WC, Xavier SS, Rassi SG, Rassi AG, et al. Development and validation of a risk score for predicting death in Chagas' heart disease. *N Engl J Med* 2006;355:799-808. <https://doi.org/10.1056/NEJMoa053241>
- World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA* 2013;310:2191-4. <https://doi.org/10.1001/jama.2013.281053>
- Gómez-Ochoa SA, Rojas LZ, Echeverría LE, Muka T, Franco OH. Global, regional, and national trends of Chagas disease from 1990 to 2019: comprehensive analysis of the Global Burden of Disease Study. *Glob Heart*. 2022;17:59. <https://doi.org/10.5334/gh.1150>
- Echeverría LE, Morillo CA. American trypanosomiasis (Chagas disease). *Infect Dis Clin North Am* 2019;33:119-34. <https://doi.org/10.1016/j.idc.2018.10.015>
- Gómez-Ochoa SA, Serrano-García AY, Hurtado-Ortiz A, Aceros A, Rojas LZ, Echeverría LE. A systematic review and meta-analysis of mortality in chronic Chagas cardiomyopathy versus other cardiomyopathies: higher risk or fiction? *Rev Esp Cardiol (Engl Ed)* 2024;77:843-50. <https://doi.org/10.1016/j.rec.2024.02.014>
- Issa VS, Amaral AF, Cruz FD, Ayub-Ferreira SM, Chizzola PR, Souza GE, et al. Beta-blocker therapy and mortality of patients with Chagas cardiomyopathy: a subanalysis of the REMADHE prospective trial. *Circ Heart Fail* 2010;3:82-8. <https://doi.org/10.1161/CIRCHEARTFAILURE.109.882035>
- Shen L, Ramires F, Martínez F, Bodanese LC, Echeverría LE, Gomez EA, et al. Contemporary characteristics and outcomes in Chagasic heart failure compared with other nonischemic and ischemic cardiomyopathy. *Circ Heart Fail* 2017;10:e004361. <https://doi.org/10.1161/CIRCHEARTFAILURE.117.004361>
- Lopes RD, Bocchi EA, Echeverría LE, Demacq C, de Barros E Silva PGM et al; Prevention and Reduction of Adverse Outcomes in Chagasic Heart Failure Trial Evaluation (PARACHUTE-HF) Investigators. Sacubitril/Valsartan vs Enalapril in Heart Failure Due to Chagas Disease: An Open-Label, Multicenter Randomized Clinical Trial. *JAMA* 2025:e2519808. <https://doi.org/10.1001/jama.2025.19808>
- Cucunubá ZM, Okuwoga O, Basáñez MG, Nouvellet P. Increased mortality attributed to Chagas disease: a systematic review and meta-analysis. *Parasit Vectors* 2016;9:42. <https://doi.org/10.1186/s13071-016-1315-x>

18. Acquatella H, Asch FM, Barbosa MM, Barros M, Bern C, Cavalcante JL, et al. Recommendations for multimodality cardiac imaging in patients with Chagas disease: a report from the American Society of Echocardiography in collaboration with the InterAmerican Association of Echocardiography (ECOSIAC) and the Cardiovascular Imaging Department of the Brazilian Society of Cardiology (DICSBC). *J Am Soc Echocardiogr* 2018;31:3-25. <https://doi.org/10.1016/j.echo.2017.10.019>
19. Rassi D, Vieira ML, Arruda AL, Hotta VT, Furtado RG, Rassi DT, et al. Echocardiographic parameters and survival in Chagas heart disease with severe systolic dysfunction. *Arq Bras Cardiol* 2014;102:245-52. <https://doi.org/10.5935/abc.20140003>
20. Sarabanda AV, Marin-Neto JA. Predictors of mortality in patients with Chagas cardiomyopathy and ventricular tachycardia not treated with implantable cardioverter-defibrillators. *Pacing Clin Electrophysiol* 2011;34:54-62. <https://doi.org/10.1111/j.1540-8159.2010.02896.x>
21. Barbosa MPT, Rocha MOC, Oliveira AB, Lombardi F, Ribeiro ALP. Efficacy and Safety of Implantable Cardioverter-defibrillators in Patients with Chagas Disease. *Europace* 2013;15:957-62. <https://doi.org/10.1093/europace/eut011>
22. Pereira FTM, Rocha EA, Gondim DSP, Almeida RLF, Pires Neto RDJ. Predictors of appropriate therapies and death in patients with implantable cardioverter-defibrillator and chronic Chagas heart disease. *Arq Bras Cardiol* 2024;121:e20230337. <https://doi.org/10.36660/abc.20230337i>
23. de Lima Peixoto G, de Siqueira SF, Nishioka SAD, Pedrosa AA, Teixeira RA, Costa R, et al. Mortality risk score for patients with Chagas cardiomyopathy and pacemaker. *PLoS Negl Trop Dis* 2024;18:e0012114. <https://doi.org/10.1371/journal.pntd.0012114>
24. Messenger LA, Miles MA, Bern C. Between a bug and a hard place: *Trypanosoma cruzi* genetic diversity and the clinical outcomes of Chagas disease. *Expert Rev Anti Infect Ther* 2015;13:995-1029. <https://doi.org/10.1586/14787210.2015.1056158>