EDITORIAL

Prognostic Stratification in Chagas Cardiomyopathy: Precision Medicine Adapted to the Local Real-World Setting

Estratificación pronóstica en cardiopatía chagásica: hacia una medicina de precisión adaptada a la propia realidad

LUIS EDUARDO ECHEVERRÍA[1,2]

> *"..... The world was so recent that many things lacked names, and to mention them, it was necessary to point at them with a finger."*
> **One Hundred Years of Solitude.**
> **Gabriel García Márquez**

Until Carlos Chagas identified it just over a century ago, the disease caused by the flagellate protozoan *Trypanosoma cruzi* had no name. Although anthropological evidence documents the presence of Chagas disease (CD) in the Americas for more than nine millennia, (1) the first documented clinical case in Argentina was recorded only 100 years ago. (2) Renowned local scientists, such as Salvador Mazza and Cecilio Romaña, made fundamental contributions to the global epidemiological understanding of the infection. (3) The subsequent description of the chronic cardiac form of the CD consolidated its public health impact. (4) Today, barely a century later, Argentina remains one of the major global epicenters of the disease and, according to most estimates, ranks as the country with the second highest number of cases worldwide. (5)

CD represents one of the most complex and persistent challenges in cardiology in Argentina and the rest of Latin America, and its most feared complication, chronic Chagas cardiomyopathy (CCC), is associated with higher mortality than that observed in other causes of heart failure, (6) which places a considerable burden on health systems, particularly in resource-limited settings. (7) This excess mortality is driven by complex pathophysiological mechanisms, including persistent myocardial inflammation, extensive fibrosis, autonomic dysfunction, and malignant ventricular arrhythmias. (8) In this context, appropriate risk stratification is not merely an academic exercise, but rather a central tool for defining the intensity of follow-up, prioritizing interventions, and optimizing resource allocation.

Establishing the prognosis of CCC has historically been challenging. The indeterminate phase may last for years, and the transition to clinical disease occurs with marked variability in structural, arrhythmic, and functional phenotypes. In this context, although prognostic models are available, their performance tends to decline when applied to populations different from those in which they were developed, particularly in terms of calibration and clinical utility. A paradigmatic example is the Rassi score, derived from a Brazilian cohort, which was published more than two decades ago and remains the most widely used model in clinical practice, demonstrating adequate discriminatory capacity in certain populations. (9) Despite this, it has relevant limitations that constrain its current applicability. It was developed in a historical context in which both the therapeutic arsenal and the availability of devices were considerably more limited; therefore, it does not incorporate the impact of contemporary management strategies. Furthermore, it relies on tools currently considered suboptimal for cardiovascular assessment, such as chest radiography for the evaluation of cardiomegaly. Finally, and perhaps most importantly, its application in other countries and healthcare systems across the region cannot be assumed to be universal or automatic but rather requires rigorous external validation before widespread adoption. In this scenario, validation of the model in the rest of Latin America or the development of a region-specific score emerge as a necessary alternative.

In this issue of the Argentine Journal of Cardiology, María Carvelli and colleagues opt for the latter

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Correspondence: Dr. Luis Eduardo Echeverria. luisedo10@gmail.com

[1] Cardiology Service, Heart Failure and Heart Transplant Unit, Fundación Cardiovascular de Colombia, Floridablanca, Colombia
[2] Universidad de Santander, Bucaramanga, Colombia

approach and present a prognostic stratification tool developed specifically for the local context: the Argen-CHAG score. (10) This model was derived and validated in a contemporary cohort of 603 adults with serological tests positive for CD treated within the public health system of the City of Buenos Aires, of whom 422 comprised the derivation cohort and 181 the validation cohort. During a median follow-up of 6.6 years, the score demonstrated robust predictive capacity for all-cause mortality over the medium and long term. The score was constructed using three independent predictors: age, left ventricular ejection fraction, and history of implantable cardioverter-defibrillator (ICD) placement, identified through multivariate analysis and weighted according to their prognostic contribution. The selection of these variables is not based solely on statistical criteria but rather coherently reflects the main pathophysiological determinants of CCC, integrating the impact of cumulative structural myocardial damage, the temporal progression of the disease, and the presence of a malignant arrhythmic substrate associated with a high risk of fatal outcomes.

Despite its remarkable simplicity, the Argen-CHAG score demonstrated high and consistent discriminatory capacity in both the derivation and validation cohorts, with areas under the curve greater than 0.8 for the prediction of 5- and 8-year mortality. Stratification into three risk categories allowed the identification of clearly differentiated mortality gradients, ranging from a favorable prognosis in low-risk patients to extremely high mortality in those classified as high risk. This robust and reproducible performance reinforces the clinical value of the model and its potential usefulness in routine clinical practice.

However, several weaknesses should be acknowledged. The score was derived from a single-center retrospective study within the public healthcare system, which entails an inherent risk of residual confounding, selection bias, and limitations related to historical data. Although the cohort is representative of real-world clinical practice, this limits its immediate generalizability to other settings. Furthermore, although the model has robust internal validation, it has not yet been evaluated in external cohorts, particularly from other national centers, making a subsequent multicenter validation phase desirable before widespread adoption. Finally, the inclusion of a history of ICD placement should be interpreted with caution, as it likely reflects the underlying severity of the disease and the presence of a malignant arrhythmic substrate rather than an independent causal effect on mortality.

Despite these considerations, the Argen-CHAG score marks a milestone in Chagas cardiomyopathy research and stands as a benchmark for the region. In this way, unlike the protagonists of García Márquez's masterpiece, populations historically condemned to a hundred years of solitude and oblivion now have a new tool for risk stratification and, perhaps, a second chance on Earth.

Conflicts of interest

None declared

(See authors conflicts of interest forms on the website).

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