

ORIGINAL ARTICLE

Development and Validation of a Risk Score for Predicting Death in Chagas' Heart Disease

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ABSTRACT

BACKGROUND

Chagas' disease is an important health problem in Latin America, and cardiac involvement is associated with substantial morbidity and mortality. We developed a model to predict the risk of death in patients with Chagas' heart disease.

METHODS

We retrospectively evaluated 424 outpatients from a regional Brazilian cohort. The association of potential risk factors with death was tested by Cox proportional-hazards analysis, and a risk score was created. The model was validated in 153 patients from a separate community hospital.

RESULTS

During a mean follow-up of 7.9 years, 130 patients in the development cohort died. Six independent prognostic factors were identified, and each was assigned a number of points proportional to its regression coefficient: New York Heart Association class III or IV (5 points), evidence of cardiomegaly on radiography (5 points), left ventricular systolic dysfunction on echocardiography (3 points), nonsustained ventricular tachycardia on 24-hour Holter monitoring (3 points), low QRS voltage on electrocardiography (2 points), and male sex (2 points). We calculated risk scores for each patient and defined three risk groups: low risk (0 to 6 points), intermediate risk (7 to 11 points), and high risk (12 to 20 points). In the development cohort, the 10-year mortality rates for these three groups were 10 percent, 44 percent, and 84 percent, respectively. In the validation cohort, the corresponding mortality rates were 9 percent, 37 percent, and 85 percent. The C statistic for the point system was 0.84 in the development cohort and 0.81 in the validation cohort.

CONCLUSIONS

A simple risk score was developed to predict death in Chagas' heart disease and was validated in an independent cohort.

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CHAGAS' DISEASE IS DUE TO A PARASITIC infection with *Trypanosoma cruzi*. It is transmitted to humans through the feces of infected bloodsucking insects in areas in which the disease is endemic and, occasionally, by nonvectorial mechanisms such as blood transfusion. Chagas' disease is a serious problem in most Latin American countries, with 18 million persons chronically infected and approximately 200,000 new cases each year.¹ Cardiac involvement is the main cause of death.² The clinical course of Chagas' heart disease is variable, and the identification of patients at risk for death remains a challenge. Previous reports³⁻¹³ demonstrated that many individual characteristics predict an unfavorable prognosis. However, the results of different studies have been somewhat inconsistent; for example, there is controversy over whether nonsustained ventricular tachycardia is an independent predictor of death.^{9,10} Moreover, the previous studies have not been validated with the use of independent databases.

We conducted a long-term follow-up study in a large group of well-characterized patients with Chagas' disease and cardiac involvement. Our main objective was to develop a risk score derived from the combination of independent predictors of death. The validity of this risk score was then tested in a separate cohort of patients.

METHODS

PATIENTS

Hospital São Salvador is a nontertiary regional referral center located in Goiânia in central Brazil; the patient population includes both rural and urban residents, who are seen without regard to economic status. From a clinical database of patients with Chagas' disease evaluated at this hospital between December 1986 and December 1991, those with chronic cardiac involvement were retrospectively considered for inclusion in our analysis. The local ethics committee approved the protocol and waived the need for written informed consent.

The diagnosis of Chagas' disease required at least two positive serologic tests for antibodies against *T. cruzi* (complement fixation, indirect hemagglutination, indirect immunofluorescence, or enzyme-linked immunosorbent assay) together with the typical electrocardiographic¹⁴ or echocardiographic¹⁵ findings of Chagas' heart disease.

Patients who met any of the following a priori criteria were excluded because of a high risk of death and the confounding effects of other risks for death: age over 70 years, sustained ventricular tachycardia or ventricular fibrillation, an implanted cardiac pacemaker, and associated ischemic, hypertensive, or valvular heart disease. Data from the remaining patients, who are referred to as the development cohort, were used to develop the clinical risk score.

NONINVASIVE STUDIES

At the time of enrollment in the database, all patients underwent a clinical assessment, 12-lead electrocardiography, chest radiography, 24-hour ambulatory electrocardiographic (Holter) monitoring, an assessment of heart-rate variability, exercise testing, and echocardiography. Electrocardiographic abnormalities were classified according to the modified Minnesota code adapted for Chagas' disease.¹⁶ Left ventricular function was evaluated by visual estimation from the echocardiogram, and the ejection fraction was classified as normal or as mildly, moderately, or severely reduced. Similarly, left ventricular end-diastolic diameter was classified as normal or as mildly, moderately, or greatly increased. The presence of regional wall-motion abnormalities, apical aneurysm, or intracavitary thrombus was also recorded. Cardiomegaly, as determined by chest radiography, was defined by a cardiothoracic ratio of more than 0.50. The total numbers of premature ventricular complexes and episodes of nonsustained ventricular tachycardia (defined as three or more consecutive premature ventricular complexes with a heart rate of more than 100 beats per minute) were determined from the Holter monitor.

Patients who were able to exercise adequately and for whom the test was not contraindicated underwent an exercise test on a bicycle ergometer or a treadmill, according to the Bruce protocol or a modified Bruce protocol. To better assess the behavior of ventricular arrhythmias during exercise, the stress test in these patients was administered during the last hour of Holter monitoring. Heart-rate variability was also assessed from the Holter-monitor recording (after exclusion of the last hour of recording for those undergoing an exercise test) and defined as the standard deviation of all normal-to-normal RR intervals (SDNN).

TREATMENT AND FOLLOW-UP

Patients with complex ventricular arrhythmias were treated with amiodarone (200 to 400 mg per day). Patients with congestive heart failure received digoxin, diuretics, angiotensin-converting-enzyme (ACE) inhibitors, or a combination. Patients with atrial fibrillation, previous embolic episodes, or apical aneurysm with thrombus received aspirin or oral anticoagulants, and those with severe bradyarrhythmias received pacemakers.

The date of entry into the study was defined as the date on which noninvasive testing began. Patients were followed until death or until the last ambulatory visit in 1997 or 1998. The cause of death was ascertained by reviewing the medical record, questioning relatives involved in the patient's care, and examining the death certificate. A death was classified as sudden if it occurred within one hour after a change in symptoms, was unwitnessed in a patient whose condition had been stable, or occurred during sleep; as due to progressive heart failure if it occurred after a documented period of symptomatic or hemodynamic deterioration; as due to other cardiovascular causes; or as due to noncardiovascular causes.

STATISTICAL ANALYSIS

Categorical variables are presented as numbers and percentages, and continuous variables are presented as means \pm SD. The significance of baseline differences was determined by the chi-square test, Fisher's exact test, or the unpaired t-test, as appropriate. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

Survival was estimated by the Kaplan–Meier method, and differences in survival between groups were assessed by the log-rank test. Univariate and multivariate Cox proportional-hazards models were used to determine the contribution of these variables. If the Pearson's correlation coefficient between variables was 0.60 or more, only the variable judged to be clinically more important was entered into the multivariate model. Finally, to develop a practical prognostic score, we assigned the risk factors identified by multivariate analysis weighted points proportional to the β regression coefficient values (rounded to the nearest integer). A risk score was then calculated for each patient, and the population was divided into three categories: patients at low risk, patients at intermediate risk, and patients at high risk for death.

A second set of patients was selected from another clinical database of patients with Chagas' disease who were seen in the outpatient clinic of a government referral center (Hospital Evandro Chagas, Rio de Janeiro). Patients in this database who had been enrolled between April 1990 and September 2001 were retrospectively screened according to the same inclusion and exclusion criteria as those used for the development cohort. The same clinical and laboratory data were available for analysis in both cohorts, with the exception of exercise testing for the evaluation of ventricular arrhythmias. This second group of patients is referred to as the validation cohort.

For both the development and the validation cohorts, Kaplan–Meier survival curves for patients in the three risk groups were generated to illustrate the partitioning of the risk of death. The predictive accuracy of the scoring system was examined by calculating the C statistic¹⁷ and by determining the difference between the prognostic groups in the probability of death within 5 and 10 years, calculated as $(P_{\text{high}} - P_{\text{low}}) \div 100$, where P_{high} is the predicted probability of death for a patient in the group with the worst prognosis, and P_{low} is the corresponding value for a patient in the group with the best prognosis.¹⁸

RESULTS**PATIENTS' CHARACTERISTICS AND OUTCOMES**

A total of 521 patients from the Hospital São Salvador database were initially evaluated for inclusion in the development cohort. Of these, 97 were excluded: 30 were over 70 years old, 20 had sustained ventricular tachycardia or fibrillation, 36 had an implanted cardiac pacemaker, and 18 had cardiovascular disease in addition to that related to Chagas' disease. (Some patients had more than one exclusion criterion.) The final sample consisted of 424 patients. Their baseline characteristics are shown in Table 1; data on some variables were missing for some patients.

The medications taken after the initial evaluation were digitalis (12.3 percent of patients), diuretics (15.6 percent), ACE inhibitors (1.9 percent), amiodarone (35.1 percent), beta-blockers (0.2 percent), and antithrombotic agents (1.4 percent). At the last visit, the percentages of patients taking these medications were 22.9, 36.1, 21.9, 71.9, 2.4, and 14.9 percent, respectively. No patient received cardiac-resynchronization ther-

apy or a cardiac transplant; 66 patients (15.6 percent) received a pacemaker; and 1 patient (0.2 percent) received a cardioverter–defibrillator.

Follow-up data were available for 411 patients (97.0 percent). During a mean follow-up of 7.9 ± 3.2 years (range, 9 days to 11.7 years), 130 patients (30.7 percent) died. Eighty-one deaths (62.3 percent) were sudden, 20 (15.4 percent) were due to progressive heart failure, 12 (9.2 percent) were due to other cardiovascular causes (mainly stroke), and 16 (12.3 percent) were due to noncardiovascular causes. The cause of death could not be determined in one patient (0.8 percent). The clinical characteristics of the survivors and nonsurvivors are compared in Table 1.

SURVIVAL ANALYSIS AND RISK-SCORING SYSTEM

We used the univariate Cox regression model to test the ability of potential baseline risk factors

to predict the risk of death. Table 1 shows that several variables were associated with a higher risk of death. To identify independent predictor variables, we performed multivariate analysis using the stepwise Cox proportional-hazards model. Variables in this analysis were dichotomized for ease of use in the subsequent risk score.

Because multivariate analysis requires a complete set of variables for each patient, missing data from one or more noninvasive tests restricted the analysis to 331 patients (78.1 percent). However, there were no significant differences in baseline characteristics or survival between patients with complete data and those with missing data, with the exception of cardiomegaly on chest radiography, which was significantly more frequent in the group with missing data.

After the exclusion of variables with a low prevalence or exhibiting multicollinearity, 15 vari-

Table 1. Population Characteristics of the Development Cohort and Crude Association of Potential Prognostic Determinants with Death.*

Characteristic	All Patients (N=424)	Survivors (N=294)	Nonsurvivors (N=130)	P Value†	Hazard Ratio (95% CI)‡
Demographic and clinical					
No. of patients with data	424	294	130		
Age — yr	47±11	46±11	51±11	<0.001	NA
Age >48 yr — no. (%)	205 (48.3)	124 (42.2)	81 (62.3)	<0.001	2.06 (1.45–2.93)
Male sex — no. (%)	247 (58.3)	151 (51.4)	96 (73.8)	<0.001	2.33 (1.57–3.44)
Palpitations — no. (%)	126 (29.7)	93 (31.6)	33 (25.4)	0.19	0.75 (0.51–1.18)
Syncope — no. (%)	27 (6.4)	14 (4.8)	13 (10.0)	0.04	2.06 (1.16–3.66)
NYHA class III or IV — no. (%)	44 (10.4)	4 (1.4)	40 (30.8)	<0.001	13.92 (9.36–20.70)
Electrocardiographic					
No. of patients with data	424	294	130		
Isolated RBBB — no. (%)	79 (18.6)	62 (21.1)	17 (13.1)	0.05	0.60 (0.36–0.99)
Isolated LAFB — no. (%)	56 (13.2)	41 (13.9)	15 (11.5)	0.60	0.85 (0.49–1.45)
RBBB plus LAFB — no. (%)	103 (24.3)	75 (25.5)	28 (21.5)	0.44	0.85 (0.56–1.30)
LBBB — no. (%)	30 (7.1)	11 (3.7)	19 (14.6)	<0.001	3.07 (1.88–5.01)
PVCs — no. (%)	158 (37.3)	103 (35.0)	55 (42.3)	0.15	1.28 (0.91–1.82)
Q waves — no. (%)	28 (6.6)	10 (3.4)	18 (13.8)	<0.001	3.72 (2.25–6.14)
ST-T changes — no. (%)	118 (27.8)	70 (23.8)	48 (36.9)	0.005	1.73 (1.21–2.47)
1st or 2nd degree AV block — no. (%)	38 (9.0)	19 (6.5)	19 (14.6)	0.007	2.00 (1.31–3.06)
Low QRS voltage — no. (%)	38 (9.0)	17 (5.8)	21 (16.2)	0.001	2.57 (1.61–4.10)
Atrial fibrillation or flutter — no. (%)	13 (3.1)	2 (0.7)	11 (8.5)	<0.001	5.43 (2.91–10.13)
Radiologic					
No. of patients with data	396	273	123		
Cardiomegaly — no. (%)	120 (30.3)	37 (13.6)	83 (67.5)	<0.001	9.22 (6.29–13.51)
Pulmonary congestion — no. (%)	23 (5.8)	1 (0.4)	22 (17.9)	<0.001	10.70 (6.58–17.38)

ables found to be of prognostic significance by univariate analysis were entered into the multivariate model: New York Heart Association (NYHA) class III or IV, cardiomegaly, nonsustained ventricular tachycardia, segmental or global wall-motion abnormality, atrial fibrillation or flutter, Q waves, left bundle-branch block, male sex, an age of more than 48 years, low QRS voltage, an SDNN of less than 100 msec, first- or second-degree atrioventricular block, ST-T changes, syncope, and right bundle-branch block. The variables were entered in descending order of significance on the basis of the value of chi-square Wald statistics.

Six variables maintained their prognostic significance after multivariate analysis (Table 2 and Fig. 1): NYHA functional class III or IV, cardiomegaly on chest radiography, segmental or global wall-motion abnormality on echocardiography,

nonsustained ventricular tachycardia on 24-hour Holter monitoring, low QRS voltage on electrocardiography, and male sex. All these variables were also strong predictors of the risk of death from cardiovascular causes and sudden death from cardiac causes, except for male sex, which was of borderline significance for the prediction of death from cardiovascular causes, and low QRS voltage, which was of borderline significance for the prediction of sudden death from cardiac causes. These associations did not change significantly after adjustment for medication use.

To calculate a risk score, we assigned each of the six prognostic variables a number of points that was proportional to its regression coefficient (Table 2). A score was calculated for each patient by adding together the points corresponding to his or her risk factors. The patients were then divided into 16 subgroups on the basis of the score,

Table 1. (Continued.)

Characteristic	All Patients (N=424)	Survivors (N=294)	Nonsurvivors (N=130)	P Value†	Hazard Ratio (95% CI)‡
Echocardiographic					
No. of patients with data	354	251	103		
Increased LVEDD — no. (%)	133 (37.6)§	55 (21.9)	78 (75.7)	<0.001	7.97 (5.07–12.54)
Segmental or global WMA — no. (%)¶	167 (47.2)¶	80 (31.9)	87 (84.5)	<0.001	8.53 (5.00–14.56)
Apical aneurysm — no. (%)	37 (10.5)	25 (10.0)	12 (11.7)	0.64	1.09 (0.60–2.00)
Intracavitary thrombus — no. (%)	7 (2.0)	3 (1.2)	4 (3.9)	0.20	2.34 (0.86–6.35)
24-Hr Holter monitoring					
No. of patients with data	424	294	130		
Frequent PVCs — no. (%)	191 (45.0)	106 (36.1)	85 (65.4)	<0.001	2.95 (2.05–4.23)
Nonsustained VT — no. (%)**	197 (46.5)††	97 (33.0)	100 (76.9)	<0.001	5.74 (3.81–8.66)
Heart-rate variability					
No. of patients with data	374	262	112		
SDNN <100 msec — no. (%)	83 (22.2)	46 (17.6)	37 (33.0)	0.001	1.93 (1.30–2.86)

* Plus-minus values are means ±SD. NA denotes not applicable, RBBB right bundle-branch block, LAFB left anterior fascicular block, LBBB left bundle-branch block, PVCs premature ventricular complexes, AV atrioventricular, LVEDD left ventricular end-diastolic diameter, WMA wall-motion abnormality, VT ventricular tachycardia, and SDNN standard deviation of normal-to-normal RR intervals.

† P values are for the comparison of survivors with patients who died and were calculated by the unpaired t-test for mean age and by the chi-square test or Fisher's exact test, as appropriate, for the other variables.

‡ Hazard ratios with corresponding 95 percent confidence intervals (CIs) were calculated by univariate Cox regression analysis and are for the comparison of survivors with patients who died.

§ Increased LVEDD was mild in 47 percent, moderate in 31 percent, and severe in 22 percent of patients. According to observations from our laboratory, mildly, moderately, and severely increased LVEDDs correspond to values of 55 through 65 mm, 66 through 75 mm, and greater than 75 mm, respectively.

¶ WMA was exclusively regional in 14 percent, mildly global in 29 percent, moderately global in 19 percent, and severely global in 38 percent of patients. According to observations from our laboratory, mildly, moderately, and severely depressed ejection fractions correspond to values of 0.55 through 0.45, 0.44 through 0.30, and less than 0.30, respectively.

|| Frequent PVCs were defined as more than 1000 PVCs per 24 hours.

** Ventricular tachycardia was defined by a heart rate of more than 100 beats per minute.

†† Patients who had nonsustained VT on a treadmill exercise test were also included.

Table 2. Multivariate Cox Proportional-Hazards Analysis of the Development Cohort and Scoring System.*

Risk Factor	Prevalence (N=331)	Hazard Ratio (95% CI)	P Value	β Regression Coefficient	Points†
NYHA class III or IV — no. (%)	33 (10.0)	4.05 (2.46–6.67)	<0.001	1.40	5
Cardiomegaly — no. (%)	89 (26.9)	3.43 (2.06–5.72)	<0.001	1.23	5
Segmental or global WMA — no. (%)	155 (46.8)	2.46 (1.26–4.79)	0.008	0.90	3
Nonsustained VT — no. (%)	160 (48.3)	2.15 (1.28–3.62)	0.004	0.77	3
Low QRS voltage — no. (%)	28 (8.5)	1.87 (1.03–3.37)	0.039	0.62	2
Male sex — no. (%)	200 (60.4)	1.72 (1.06–2.81)	0.030	0.54	2

* Because data for some variables were missing for some patients, the final sample used in the multivariate analysis consisted of 331 patients, 98 of whom died. CI denotes confidence interval, WMA wall-motion abnormality, and VT ventricular tachycardia.

† Assignment of points to risk factors was based on a linear transformation of the corresponding β regression coefficient. The coefficient of each variable was divided by 0.54 (the lowest β value, corresponding to male sex), multiplied by a constant (2), and rounded to the nearest integer.

which ranged from 0 to 20. Survival estimates for the 16 subgroups were used to define 3 groups with significantly different prognoses: a low-risk group (0 to 6 points), an intermediate-risk group (7 to 11 points), and a high-risk group (12 to 20 points) (Table 3 and Fig. 2).

CHARACTERISTICS OF THE VALIDATION COHORT

From a database of 1053 patients with Chagas' disease treated at another institution, 153 were selected who met the same inclusion and exclusion criteria as the development cohort. The mean age of the patients in this validation cohort was 48 years (range, 22 to 70), 56 (36.6 percent) were men, and 97 (63.4 percent) were women. Most of the patients (85.0 percent) were in NYHA functional class I or II. At presentation, 28.8 percent of the patients had cardiomegaly and 39.9 percent had segmental or global wall-motion abnormalities. Forty-four patients (28.8 percent) had nonsustained ventricular tachycardia during initial 24-hour Holter monitoring. Data on exercise testing for evaluation of ventricular arrhythmias were not available for this cohort.

The medications being taken at the last visit were digitalis (13.7 percent of patients), diuretics (35.3 percent), ACE inhibitors (54.9 percent), amiodarone (27.5 percent), beta-blockers (12.4 percent), and antithrombotic agents (17.6 percent). No patient received cardiac-resynchronization therapy or a cardiac transplant, 16 patients (10.5 percent) received a pacemaker, and 5 patients (3.3 percent) received a cardioverter-defibrillator. During a mean follow-up of 7.7 ± 4.0 years, 35 patients

(22.9 percent) died. The majority of deaths (57.1 percent) were sudden.

VALIDATION OF THE RISK SCORE

Classification of the development cohort according to risk score resulted in the assignment of 61.3 percent of the patients to the low-risk group, 18.7 percent to the intermediate-risk group, and 19.9 percent to the high-risk group (Table 3). The results were similar for the validation cohort: 65.4 percent of the patients were in the low-risk group, 19.6 percent in the intermediate-risk group, and 15.0 percent in the high-risk group.

In the development cohort, the 10-year mortality rates for the low-, intermediate-, and high-risk groups were 10 percent, 44 percent, and 84 percent, respectively (Table 3 and Fig. 2). The difference in the probability of death between the high-risk and the low-risk groups was 0.61 at 5 years and 0.74 at 10 years, with a C statistic of 0.84 (95 percent confidence interval, 0.79 to 0.89). In the validation cohort, the 10-year mortality rates for the low-, intermediate-, and high-risk groups were 9 percent, 37 percent, and 85 percent, respectively (Table 3 and Fig. 2). The difference in the probability of death between the high-risk and the low-risk groups was 0.53 at 5 years and 0.76 at 10 years, and the C statistic was 0.81 (95 percent confidence interval, 0.72 to 0.90).

DISCUSSION

Chagas' disease is a heterogeneous entity with wide variation in clinical course and prognosis.

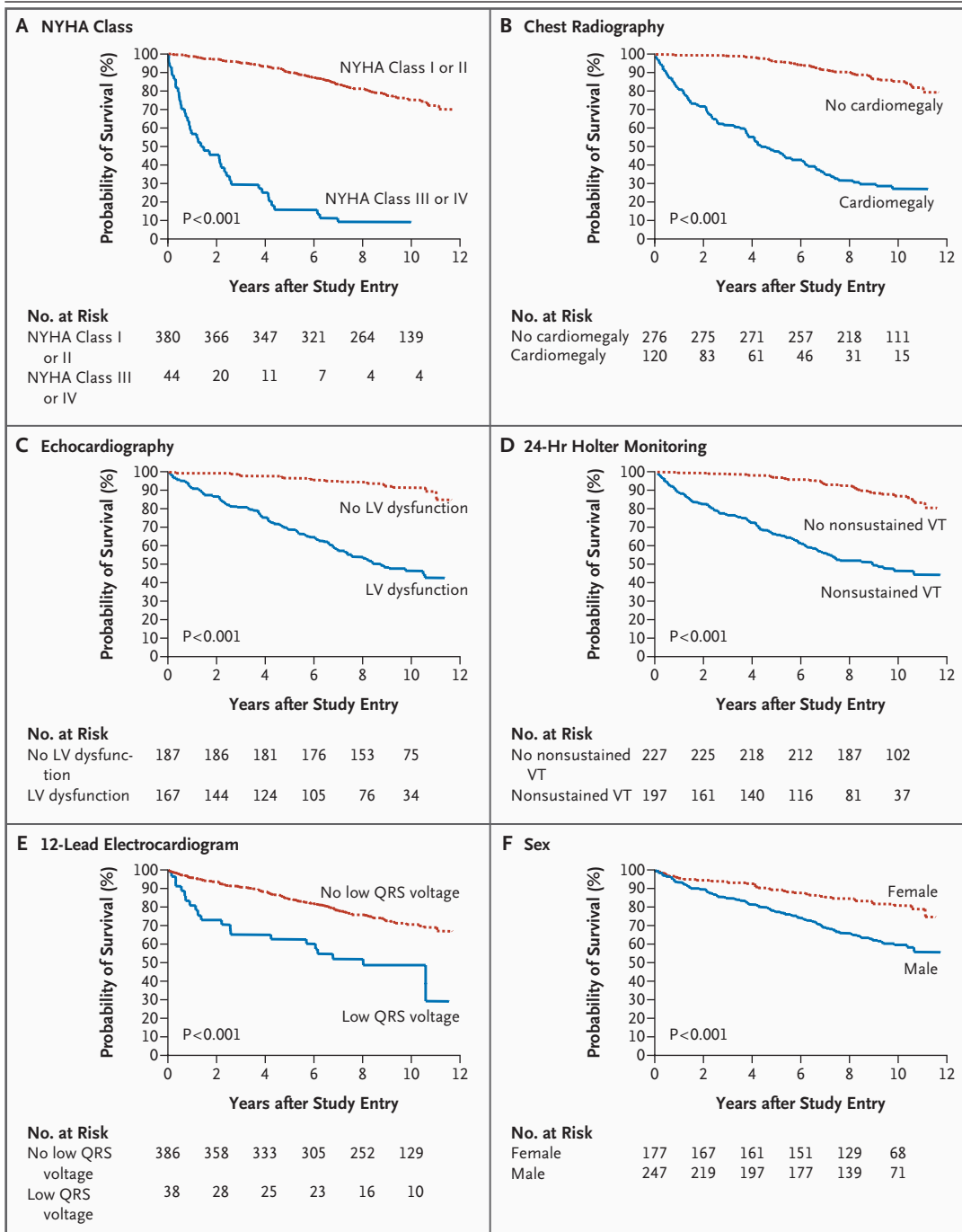


Figure 1. Kaplan–Meier Survival Curves for Six Variables That Were Significantly Associated with Outcome in Multivariate Analysis.

The dichotomized variables were NYHA class III or IV (vs. class I or II) (Panel A), presence (vs. absence) of cardiomegaly on chest radiography (Panel B), presence (vs. absence) of segmental or global wall-motion abnormality on echocardiography (Panel C), presence (vs. absence) of nonsustained ventricular tachycardia on 24-hour Holter monitoring (Panel D), presence (vs. absence) of low QRS voltage on electrocardiography (Panel E), and male (vs. female) sex (Panel F). LV denotes left ventricular, and VT ventricular tachycardia.

Table 3. Risk of Death at 5 and 10 Years in the Development and Validation Cohorts, According to Risk Category.*

Risk Category	Development Cohort (N=331)			Validation Cohort (N=153)		
	No. (%)	Death at 5 Yr % (95% CI)	Death at 10 Yr % (95% CI)	No. (%)	Death at 5 Yr % (95% CI)	Death at 10 Yr % (95% CI)
Low	203 (61.3)	2 (0–5)	10 (5–14)	100 (65.4)	0	9 (2–16)
Intermediate	62 (18.7)	18 (8–28)	44 (31–57)	30 (19.6)	15 (1–28)	37 (16–59)
High	66 (19.9)	63 (51–75)	84 (74–93)	23 (15.0)	53 (31–75)	85 (63–100)
		<i>difference in probability of death†</i>			<i>difference in probability of death†</i>	
		0.61	0.74		0.53	0.76
C statistic (95% CI)‡		0.84 (0.79–0.89)			0.81 (0.72–0.90)	

* The risk category was calculated by adding the points for each of the following risk factors: male sex (2 points), low QRS voltage on the electrocardiogram (2 points), nonsustained ventricular tachycardia on 24-hour Holter monitoring (3 points), segmental or global wall-motion abnormality on the echocardiogram (3 points), cardiomegaly on chest radiography (5 points), and NYHA class III or IV (5 points). The prognostic index was categorized in three groups: low risk (0 to 6 points), intermediate risk (7 to 11 points), and high risk (12 to 20 points). CI denotes confidence interval.

† The difference in the probability of death between the high- and the low-risk groups was calculated by the formula $(P_{\text{high}} - P_{\text{low}}) \div 100$.

‡ The C statistic for overall score is reported.

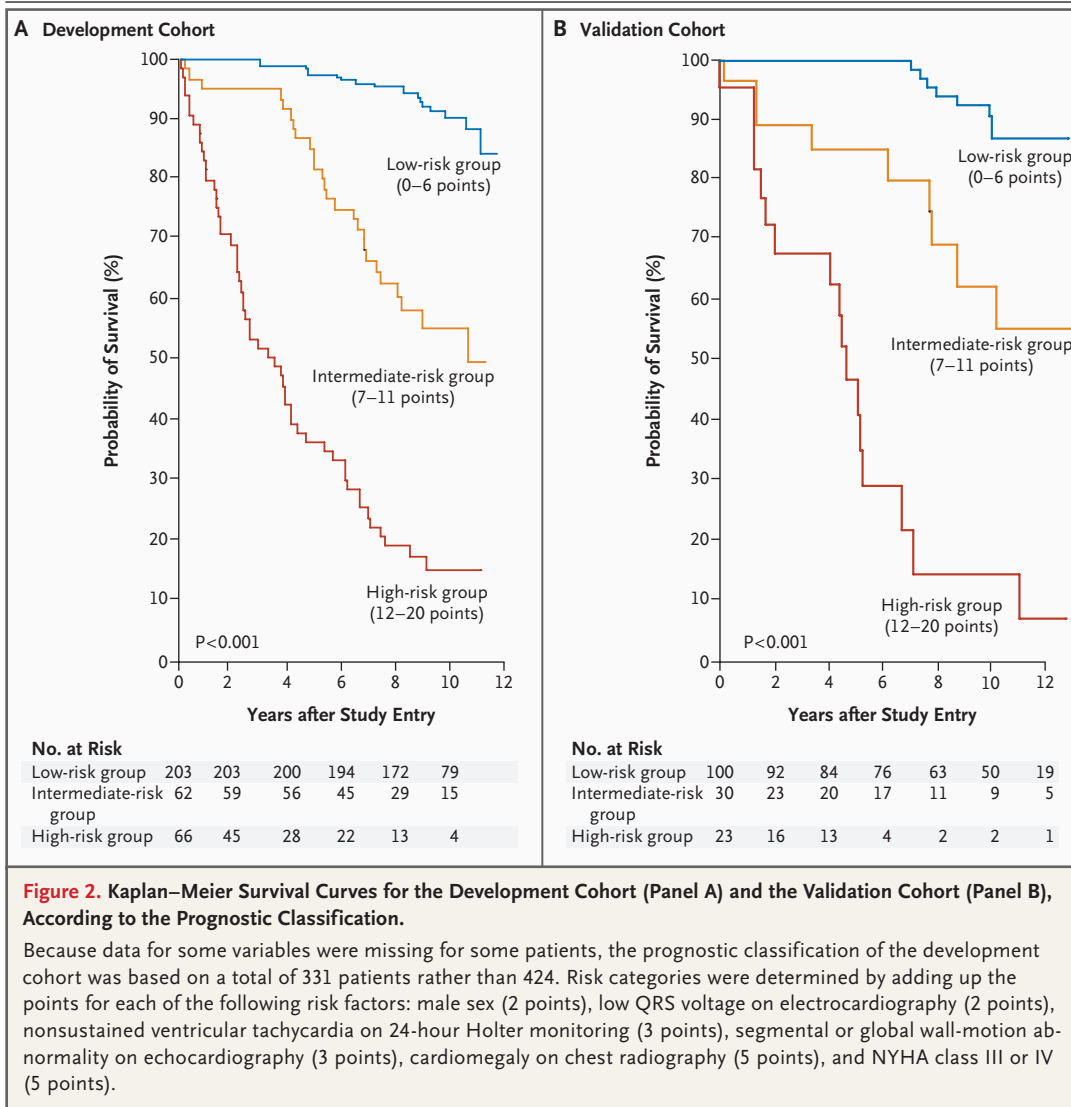
Our study demonstrates that the long-term risk of death among patients with chronic Chagas' heart disease is predicted by the presence of six clinical features. In descending order of importance, these features are NYHA class III or IV, cardiomegaly on chest radiography, segmental or global wall-motion abnormalities on echocardiography, nonsustained ventricular tachycardia on Holter monitoring, low QRS voltage on electrocardiography, and male sex. A risk score derived by combining points for each of these features accurately classified patients into subgroups at low, medium, and high risk for death. In the development cohort, the 10-year mortality rates in these three groups were 10 percent, 44 percent, and 84 percent, respectively. The respective figures in the validation cohort were 9 percent, 37 percent, and 85 percent. Patients in the high-risk group could potentially benefit the most from aggressive therapies, including the implantation of a defibrillator, cardiac resynchronization, and heart transplantation.

Death related to Chagas' disease usually results from cardiac involvement and rarely from non-cardiovascular causes, such as megaesophagus or megacolon. Progressive cardiac failure was the principal cause of death in studies performed at a tertiary referral center.⁹ However, we found that most of the deaths (more than 60 percent) were

sudden, a finding similar to that obtained in population-derived samples.¹⁹ The overall mortality rate was 3.9 percent per year, and the rate of sudden death was 2.4 percent per year.

The strengths of our study include the duration of follow-up (mean, 7.9 years), the examination of noninvasive risk markers that can be routinely measured, and the use of multivariate methods of statistical analysis. In addition, our risk model was validated in an independent data sample.

Our model has several limitations. First, selection bias might have occurred because we excluded patients with missing data and restricted the multivariate analysis to the 331 patients who had complete data on all the variables. In addition, we used dichotomized variables. Although this strategy simplifies the creation of a risk score, the use of continuous variables has the potential to provide more refined information. Second, we could not assess the effect of therapy on survival because treatment was not controlled, but varied according to the manifestations and severity of disease and changed during follow-up. However, the fact that adjustment for medication use did not significantly alter the results suggests that potential confounding on the basis of treatment effects was minimal. Third, the model did not include some previously described important prog-



nostic variables, such as ventricular repolarization variables determined by electrocardiography¹⁹ or inducibility of ventricular tachyarrhythmias determined by invasive electrophysiologic methods.²⁰ Finally, although we believe that the patients in the development and validation cohorts were representative of outpatients with Chagas' heart disease in other areas of Brazil and South and Central America, further investigation involving this population is desirable.

In conclusion, we developed a risk score based

on six clinical factors that predicts long-term mortality in outpatients with Chagas' heart disease. The score was validated in an independent sample of patients from a different site. These findings may be useful to clinicians for predicting individual survival probabilities and directing therapy, to researchers for designing and interpreting clinical trials, and to policymakers for allocating limited health care resources.

Dr. Little reports having served as a consultant to Guidant. No other potential conflict of interest relevant to this article was reported.

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