P-Wave Dispersion and Left Atrial Volume Index as Predictors in Heart Failure

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Abstract

Background: **Studies have shown that P-wave dispersion (PWD) and left atrial volume index (LAVi) are predictors of cardiovascular events (CE).**

Objective: **To verify the prognostic value of PWD and LAVi for the occurrence of CE in patients with heart failure (HF).**

Methods: **This was a longitudinal prospective study of 78 consecutive patients with a mean age of 47.2 years, of which 52 were males. Patients had stable HF and underwent clinical evaluation, electrocardiogram and echocardiogram assessments, with a follow-up of 26.5 months.**

Results: **The means of the variables were: 50 ms for PWD and 35.5 mL/m² for LAVi. Considering PWD ≥ 40 ms and, as reference, LAVi ≥ 28 mL/m², the positive predictive value of PWD was 87.5% and the negative predictive value was 76.9%. During follow-up, 21 patients had CE. There was an association between left atrial measurements, left ventricular volumes, ejection fraction and CE. There was no association between PWD and CE. At the multivariate analysis, the left atrium and LAVi were predictors of events (p = 0.00 and 0.02). Through the operating characteristic curve for the variable stable CE, areas of 0.80 and 0.69 were obtained for LAVi (p = 0.00) and LAVi ≥ 28 mL/m² (p = 0.01). Survival curves (Kaplan-Meier) free of those events for LAVi ≥ 28 mL/m² and for Chagas disease etiology showed an odds ratio of 14.4 (p = 0.00) and 3.2 (p = 0.03). There was no difference in outcome between patients with ischemic and nonischemic heart failure.**

Conclusion: **PWD was not correlated to CE. LAVi was an independent predictor of CE, and chagasic patients showed worse outcomes. (Arq Bras Cardiol. 2013;100(1):67-74)**

Keywords: **Heart Failure; P Wave; Heart Atria; Electrocardiography; Atrial Fibrillation.**

Introduction

Heart failure (HF) is a serious public health problem and is considered pandemic in the XXI century, as it shows an increase in prevalence, with high morbidity — 83% of patients having at least one hospitalization and 43% with at least four hospitalizations after diagnosis. Despite advances in treatment and improved survival in recent decades, the annual mortality rates for heart failure are still high, reaching proportions of all deaths of 40.5% in men and 59.5% in women, considering all ages[1-3].

Thus, risk stratification in stable patients is important to predict events related to this disease, with the objective of achieving a more rational approach. Studies have demonstrated a correlation between P-wave measurements, obtained through the conventional and/or high-resolution electrocardiogram, and the occurrence or recurrence of atrial fibrillation (after electrical cardioversion or radiofrequency ablation)[4-7]; atrial arrhythmias in Brugada syndrome[8], and after cardiac transplantation[9]; hypertrophy and left diastolic dysfunction in hypertensive patients[10]; HF[11,12]; and improvement in ejection fraction after cardiac resynchronization therapy[13].

Other studies have shown that left atrial enlargement, mainly determined by the left atrial volume index (LAVi) is a predictor of cardiovascular events such as mortality; HF; hospitalization; need for heart transplantation; higher incidence of cerebrovascular accident (CVA) and atrial fibrillation; acute myocardial infarction; and coronary artery bypass surgery[14-17]. Considering the HF picture, the prognostic studies on P-wave measurements in conjunction with those of the left atrium are scarce[11,18], which motivated the present study. The main objective of this study is to correlate the P-wave measurements with left atrial volume and its index and verify the prognostic value of these measurements and other variables in stable patients with HF.

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Methods

This was an observational, longitudinal and prospective study. The study population consisted of 78 consecutive and stable patients with HF, regardless of the etiology, with atrial sinus rhythm, of both genders, aged 18 and older, who agreed to participate in the study. Both the research project and the informed consent form (ICF) were approved by the Ethics and Research Committee of the Universidade Federal de Minas Gerais (UFMG) (protocol number 270/06).

After the ICF was signed, the patients underwent clinical evaluation and a conventional 12-lead surface electrocardiogram (ECG), a high-resolution electrocardiogram (HRECG), and a transthoracic echocardiography. We excluded patients with valvular heart disease, pregnant women, patients with congenital heart disease, those who had undergone heart transplantation, and terminally-ill patients.

The 12-lead ECG was performed at the speed of 50 mm/s and voltage of 20 mm/mV to allow measurement of the P-wave duration at the 12 leads and its dispersion (PWD), defined as the difference between its maximum and minimum values. The onset of the P-wave was defined as the point of the first visible upward departure of the trace from the bottom of the baseline for the positive waves, and as the point of the first downward departure from the top of the baseline for negative waves. The return of the bottom of the trace to the baseline in positive waves was considered to be the end of the P-wave[18]. After the recording, the measurements were performed by two trained and independent observers before the echocardiogram was performed; these were blinded to patients' clinical condition, so as to analyze interobserver variability.

A promediated ECG signal was acquired, amplified and filtered, after being obtained through orthogonal X, Y and Z leads (HRECG) with final noise < 0.5 microvolts and a number of ectopic beats lower than 1% of the total number of beats. The recording was acquired during a 16-minute monitoring using a digital multi-cardiographer, with patients in the supine position in a room with noise insulation. The signal evaluation was made after rigorous manual editing of recordings. The P-wave duration was measured manually from the onset to the end of the signal, which had an amplitude at least twice the noise level[19].

The patients also underwent an echocardiographic assessment performed simultaneously by two observers. Left atrial volume was obtained through the available software, using atrial measurements in the cephalocaudal, latero-lateral and oblique axes. The cutoff value used for left atrial volume index (LAVi) - left atrial volume/body surface area, was 28 mL/m^2 and 32 mL/m^2, according to literature references[14,20].

The mean follow-up duration was 26.5 ± 8.0 months. The clinical complications were recorded, as well as any hospitalizations.

Statistical Analysis

For data analysis, we used SPSS (Statistical Package for Social Sciences) software, release 14.0. The results were expressed as numbers and proportions for discrete variables, and measures of central tendency and dispersion for continuous variables. The Mann-Whitney test, the Kruskal-Wallis test, and the Chi-square or Fisher test were used, when appropriate, to compare differences between continuous and discrete variables, respectively. The correlation between variables was performed by Pearson's coefficient. Kappa agreement was used to analyze the interobserver variability. The operating characteristic curve was used to determine sensitivity and specificity for PWD and LAVi. Logistic regression analysis was used through the stepwise method, the dependent variable being the occurrence of cardiovascular events, considering the variables with $p \leq 0.10$ in the univariate analysis. Survival analysis was performed using the Kaplan-Meier curve, considering the measurement of LAVi ≥ 28 mL/m^2 and ≥ 32 mL/m^2 and HF etiology. The level of rejection of the null hypothesis was set at 0.05.

Results

The sample consisted of 78 patients, of which 52 (66.6%) were males and 26 (33.3%) females. The mean age was 47.2 ± 13.2 years, ranging from 19 to 71 years. The other clinical data are shown in Table 1. Concerning the etiology of the cardiomyopathy, 23 patients had idiopathic etiology; 17 had Chagas disease; 15 had ischemic etiology; nine patients were hypertensive; six had alcoholic etiology; five

Table 1 – Patient characteristics

Variables	Mean	Standard deviation	Minimum value	Maximum value
Previous FC	3.3	1.0	1.0	4.0
Current FC	1.7	0.6	1.0	3.0
Time of diagnosis (months)	59.6	54.6	3	240
Number of previous hospitalizations	2.0	2.54	0	13.0
BMI (kg/m^2)	24.9	5.43	13.9	43.6
BS (m^2)	1.73	0.2	1.0	2.3
HR (bpm)	77.6	15.3	50	120
SBP (mmHg)	111.6	17.7	78	162.9
DBP	106.4	18.7	70	164

FC: functional class; BMI: body mass index; BS: body surface; HR: heart rate in the supine position; bpm: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure.

had peripartum etiology; and two had dilated cardiomyopathy due to myocarditis. Regarding lifestyle, smoking habit was reported by 29 patients (37.2%), and alcohol consumption by 21 patients (26.6%).

Regarding comorbidities, nineteen patients had hypertension, 16 had diabetes mellitus, eight had hypothyroidism, and four had chronic kidney disease. In relation to drug treatment, 41 patients were taking angiotensin enzyme inhibitor; 24 used angiotensin receptor blocker; 59 used furosemide; 53 used spironolactone; 10 used thiazide; 50 used carvedilol; 3 used metoprolol; 47 used digoxin; 10 used aspirin; 11 used statin; and 15 used dicumarinic therapy.

ECG measurement means were obtained: P-wave duration in lead D2: 120.0 ± 14.6 ms; PWD: 50 ± 14.6 ms; duration of the P-wave at HRECG: 114.0 ± 20.8 ms (mean noise 0.3 ± 0.1 microvolt and number of acquired cycles = 975.6 ± 208.0). The interobserver variability in the P-wave measurements was performed by the Kappa test, with values of 0.69 for PWD, and 0.86 for the duration of the P-wave at the HRECG. It was considered an agreement between the two observers when the difference was ≤ 10 ms for the measurement of the P-wave through the conventional ECG, and ≤ 5 ms, at the HRECG.

Table 2 shows the measured means at the echocardiogram.

Association and correlation between variables

When applying the Kruskal-Wallis test for the analysis of variables in patients according to chagasic, ischemic, and other types of etiology, a p value of 0.015 was obtained for age (47.1, 56.2, and 44.6 years, respectively). There was no significant difference in relation to other variables, whether clinical, electrocardiographic or echocardiographic ones. Gender did not influence the etiology of heart failure (except for peripartum etiology).

Pearson's coefficients between the PWD and the echocardiographic variables, such as of the left atrial (LA) diameter, LA volume (LAV), and LAVi, as well as systolic and diastolic diameters of the left ventricle (LV) showed a p value of 0.00 for each of them (r = 0.47, 0.42, 0.37, 0.46, 0.40, respectively). There was no correlation between PWD and ejection fraction (EF), either by the Teicholtz method (p = 0.054) or the Simpson method (p = 0.153). Regarding the P-wave duration by the LAVi, p values were as follows: 0.001 for LA and LAV, and 0.024 for LAVi, with no correlation with the other echocardiographic measurements.

As for the LAVi and LV measurements, Pearson's coefficients were as follows, with a p value of 0.000: diastolic diameter, r = 0.62, and systolic diameter, r = 0.59, diastolic volume, r = 0, 53, and systolic volume, r = 0.60; mass, r = 0.46, and EF by both methods, Teicholtz and Simpson, r = 0.48 and 0.38, respectively.

Operating characteristic curve

When applying the operating characteristic curve for the stable variable of LAVi ≥ 28 mL/m², PWD showed an area under the curve of 0.67 and p = 0.015 to be the best measurement when compared with the others (P-wave duration at the ECG and HRECG). Considering PWD ≥ 40 ms as altered value, and LAVi ≥ 28 mL/m² as a reference standard value, the positive predictive value of PWD was 87.5% and the negative predictive value was 76.9%.

Clinical events

The following events were recorded during follow-up: hospitalization due to decompensated HF in six patients; atrial fibrillation in seven patients (symptomatic in three patients); CVA in three patients; ventricular tachycardia in seven patients; recovered sudden cardiac arrest in one patient; pulmonary embolism in one patient; and death from cardiac causes in seven patients. Two patients underwent cardiac resynchronization therapy, and four underwent heart transplantation.

Table 2 – Echocardiographic measurements

Variables	Mean	Standard deviation	Minimum value	Maximum value
LA (mm)	43.5	7.8	28	61
LAV (ml)	67.2	34.7	26	173
LAVi (ml/m²)	37.5	22.5	15.7	115.3
LVDD (mm)	67	9.7	54	97
LVSD (mm)	56.5	11.1	33	83
LVEDV (ml)	239	78.7	128	528
LVESV (ml)	160	69.9	44	345
LV systolic volume (ml)	83	31.4	29.5	254
EF (Teicholz) %	37.4	12.8	13	68
EF (Simpson) %	37.0	11.7	12	63
LV Mass (grams)	203	91.4	96	535

LA: anteroposterior left atrial diameter; LAV: left atrial volume; LAVi: LAV index; LV: left ventricle; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LVEDV: LV-end diastolic volume; LVESV: LV-end systolic volume; EF: ejection fraction; LV: left ventricle.

Twenty-one patients had one or more of these events during a follow-up of 26.5 ± 8.0 months. There was no patient loss to follow-up; however, the follow-up period comprised between 15 days and 35 months, according to the occurrence of cardiovascular events.

Table 3 shows the comparison of the clinical, electrocardiographic, and echocardiographic variables by means of univariate analysis using the Mann-Whitney test between the groups of patients with and without cardiovascular events.

When applying the characteristic operating curve, considering the occurrence of cardiovascular events as the stable variable, the variable LAVi showed an area under the curve of 0.80 ($p = 0.000$, 95% confidence interval of 0.69 to 0.90); the best cutoff was 29.3 mL/m^2, of which sensitivity was 94.7% and specificity was 55.4%.

At the stepwise multivariate analysis, only the variables LA and LAVi were significant, with $p = 0.001$ and $p = 0.022$, respectively.

Survival curves

Using the Kaplan-Meier method and considering the occurrence of events as prognostic basis, survival curves were constructed in relation to variables LAVi ≥ 28 mL/m^2, LAVi ≥ 32 mL/m^2, and the Chagasic and non-Chagasic and ischemic and nonischemic etiologies. The Log rank test (Mantel-Cox) was applied to compare the curves. The data found were plotted in Figures 1, 2, and 3. During follow-up, 13 (47.0%) patients with heart failure due to Chagas disease had cardiovascular events *versus* eight (21.3%) non-Chagasic ones. Considering the ischemic etiology, only two patients (14.2%) had events *versus* 29.6% of patients with nonischemic etiology of HF, with no statistical difference.

Discussion

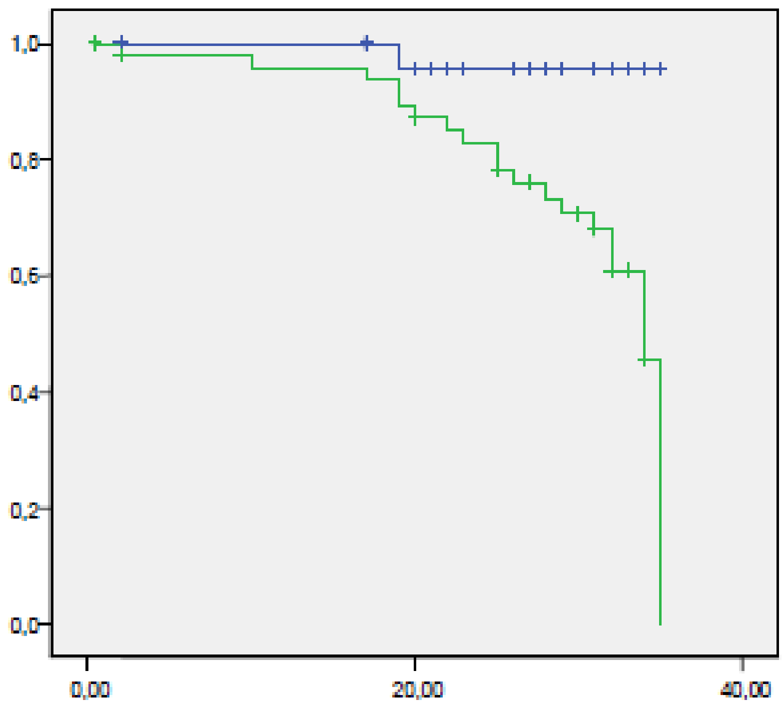
The main finding of this study was the correlation between LAVi and cardiovascular events, with that measure being an independent predictor of outcome of patients with HF with an odds ratio of 14.4 for LAVi ≥ 28 mL/m^2 and 18.0 for LAVi ≥ 32 mL/m^2. Furthermore, patients with HF due to Chagas disease had a lower event-free survival compared to non-Chagasic ones.

In patients with HF, the LA area is considered an important marker of prognosis, and its increase is related to mortality and hospitalization due to worsening of HF, regardless of age, functional class, ejection fraction and restrictive filling pattern, as shown in a meta-analysis of 18 studies, with a total sample of 1157 patients[16]. In this same study, the LA index was obtained through the ratio of the LA area and body surface in 721 patients, demonstrating that values ≥ 9.85 cm^2/m^2 had an odds ratio of 2.35. There was no analysis of P-wave measurements or LA volume.

Table 3 – Comparison of variable means between the group of patients with no cardiovascular events and the group of patients with cardiovascular events

Variables	Group with no events	Group with events	p
Age (years)	47.6	46.2	0.82
Current FC	1.6	2.0	0.03
Time of diagnosis (months)	54.9	67.4	0.19
Number of previous hospitalizations	1.6	2.8	0.27
LA (mm)	43.3	47.2	0.04
LAV (ml)	62.6	96.1	0.00
LAVi (ml/m^2)	36.2	59.4	0.00
LV diastolic diameter (mm)	67.2	72.8	0.00
LV systolic diameter (mm)	53.5	61.8	0.00
LV-end diastolic volume (ml)	238.6	281.6	0.01
LV-end systolic volume (ml)	148.6	194.1	0.00
LV systolic volume (ml)	90.0	87.3	0.13
LV EF (Teicholz) %	40.1	29.9	0.00
LV EF (Simpson) %	38.4	32.9	0.02
LV Mass (g)	218.7	227.5	0.27
PD (ms)	46.8	53.0	0.17
PD2 (ms)	113.6	117.0	0.34
DP ≥ 40 ms (number of patients)	32	13	0.48
PECGAR (ms)	112.7	116.5	0.87

FC: functional class; LAVi: left atrial volume index; LV: left ventricle; EF: ejection fraction; PD: P-wave dispersion; PD2: P-wave duration at D2 lead; PECGAR: P-wave duration at ECGAR.



Time (months)	2	19	22	26	31	32	34
Cumulative number of patients with events	2	5	7	11	14	16	17
Cumulative percentage of survival (%)	95.8	89.4	85.0	75.9	68.0	60.8	45.6

Figure 1 – *Cumulative probability of event-free survival of patients in relation to the variable LAVi ≥ 28 ml/m2.*
Horizontal axis: time in months; vertical axis: cumulative probability of survival; LAVi: left atrial volume index; LAVi blue curve < 28 ml/m²; LAVi green curve ≥ 28 ml/m². Odds ratio 14.4; p = 0.008 (95% confidence interval: 1.18 - 116.3).

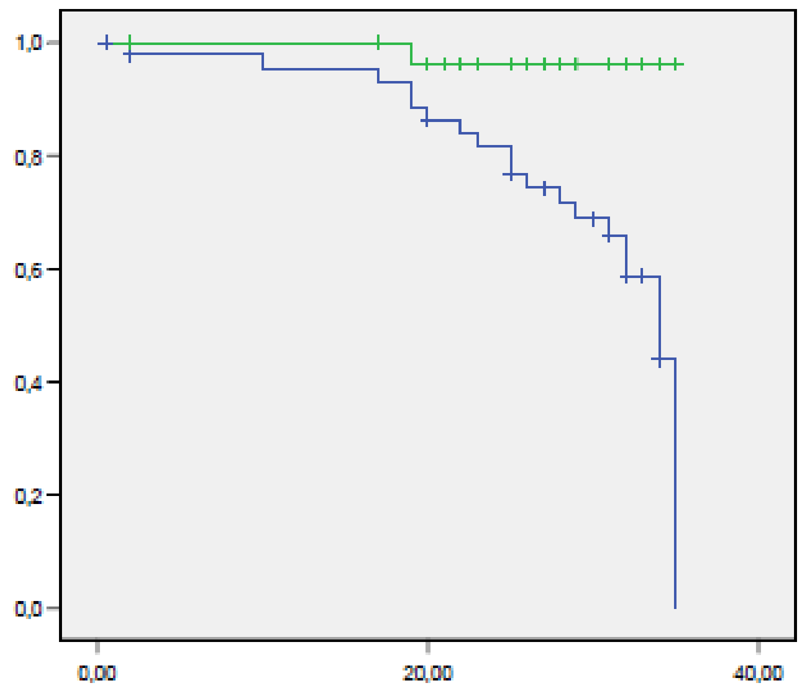
Another important study by the same author[21], which was performed by measuring LAVi in 102 patients with dilated cardiomyopathy, found that this measurement was also associated with mortality and need for heart transplantation. The best cutoff for the maximum value of LAVi was 68.5 mL/m², with a sensitivity of 65% and an odds ratio of 3.8. However, in this study 12% of patients were in atrial fibrillation. Thus, the present study showed an association, correlation and independent prognostic value of LAVi, which are consistent with the literature.

However, the relevant aspects of our study were the use of values considered to be of lesser magnitude in the literature for cardiovascular events (28 mL/m² [20] and 32 mL/m² [14]), a sample in which all patients had HF and sinus rhythm, and the inclusion of other etiologies in addition to ischemic and idiopathic etiologies. Additionally, P-wave measurements were carried out by ECG, obtaining its dispersion, and by HRECG, which was not performed in other studies that assessed the subject.

P-wave abnormalities are associated with increased LA, hypertension in this chamber, disturbances of intra-atrial conduction or a combination of all these elements. The LA remains directly exposed to increased LV end-diastolic pressure, which results in increased intra-atrial pressure to maintain adequate flow, thus increasing the tension in the atrial walls and causing dilation and stretching of myocardial fibers. In patients with HF, it has been demonstrated that P-wave duration at the HRECG depends more on the intra-atrial pressure than on LA size[19].

However, in this study, in spite of the correlation between PWD and P-wave duration at the HRECG and LA measurements, and the positive predictive value of 87.5% for PWD ≥ 40 ms in relation to LAVi ≥ 28 mL/m², Pearson's coefficient was < 0.50, suggesting a moderate degree of statistical linear dependence between these variables. This finding may also be related to the low sensitivity of ECG in relation to echocardiography in regard to LA overloads, or the lower cutoff value for the LAVi on which it was based. There was no correlation between PWD and EF due to homogeneity of the sample, which consisted of patients with HF and mean EF of 37% by Simpson's method.

Analyzing the clinical data when comparing variables between the groups with and without events, we observed that variables traditionally correlated with poor prognosis[1,2], such as functional class and LA size and LV size and its EF, also showed this association in the univariate analysis. However, at the multivariate analysis, only variables LA and LAVi were independent predictors of cardiovascular events.



Time (months)	2	19	22	26	31	32	34
Cumulative number of patients with events	1	11	14	14	16	16	16
Cumulative percentage of survival (%)	95.5	71.6	66.6	66.6	58.6	58.6	58.6

Figure 2 – *Cumulative probability of event-free survival of patients in relation to the variable LAVi ≥ 32 ml/m2.*
Horizontal axis: time in months; vertical axis: cumulative probability of survival. LAVi blue curve < 32 ml/m2; LAVi green curve ≥ 32 ml/m2. Odds ratio 18.0; p = 0.003 (95% confidence interval: 2.24 – 114.1).

Although only 21.7% of the sample patients had Chagas disease, a worse prognosis was observed for this group, with an odds ratio of 3.2 for cardiovascular events compared to non-Chagasic patients. This worse outcome is in agreement with literature data[22], and this poor prognosis is attributed to greater hemodynamic impairment, greater magnitude of systolic dysfunction and humoral and inflammatory activation.

In relation to the entire population of the present study, we observed a cardiac mortality rate of 8.9% during the mean period of 2.2 years. Data in Brazil showed an annual mortality rate of 6.3% of patients with HF, reaching a value as high as 11% in those older than 80 years[1].

Statistical data from the American Heart Association showed an annual mortality rate of 4.9% for those aged at least 20 years, reaching a rate of 50% in five years[3]. Among those patients with HF who were hospitalized and were discharged, the overall mortality was 26% during a follow-up of 9.9 months, with 10.7% mortality due to HF[23]. Therefore, the mortality rate of our patients was similar or lower than those in the literature, according to differences in study population, whether outpatient or after hospital discharge, different functional classes, age range and etiologies.

Conclusion

P-wave dispersion was not correlated with the occurrence of cardiovascular events in this series of patients with HF. LAVi was an independent predictor of occurrence of these events, with an odds ratio of 14.4 for LAVi ≥ 28 mL/m² and 18.0 for LAVi ≥ 32 mL/m². Patients with heart failure due to Chagas' disease had lower event-free survival compared to those patients without Chagas' disease, with an odds ratio of 3.2.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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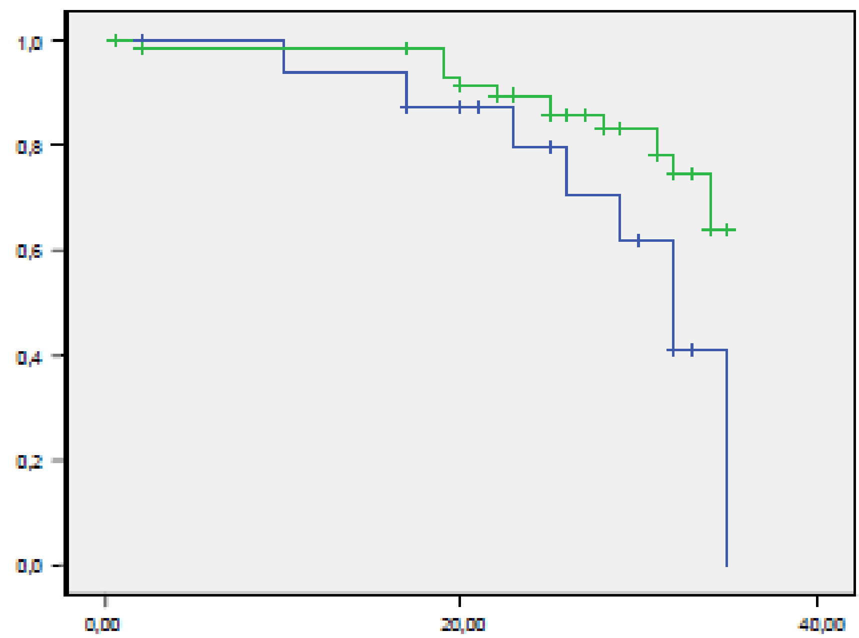

Time (months)	2	19	22	26	31	32	34
Cumulative number of patients with events	1	8	8	9	11	11	11
Cumulative percentage of survival (%)	98.3	85.7	85.7	83.3	78.1	78.1	78.1

Figure 3 – *Cumulative probability of event-free survival of patients in relation to the Chagasic and Non-chagasic etiologies*
Horizontal axis: time in months; vertical axis: cumulative probability of survival. Blue curve: Chagasic etiology; green curve: Non-chagasic etiology. Odds ratio 3.2; p = 0.036 (95% confidence interval: 1.05 – 10.18).

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