Value of the Electrocardiographic (P Wave, T Wave, QRS) Axis as a Predictor of Mortality in 14 Years in a Population With a High Prevalence of Chagas Disease from the Bambuí Cohort Study of Aging

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We sought to investigate the prognostic value of the electrocardiogram (ECG) electrical axes (P wave, T wave and QRS) as predictors of mortality in the 14-year follow-up of the prospective cohort of all residents ≥60 years living in the southeastern Brazilian city of Bambuí, a population with high prevalence of Chagas disease (ChD). Baseline ECG axes were automatically measured with normal values defined as follows: P-wave axis 0° to 75°, QRS axis –30° to 90°, and T axis 15° to 75°. Participants underwent annual follow-up visits and death was verified using death certificates. Cox proportional hazards regression was used to assess the prognostic value of ECG axes for all-cause mortality, after adjustment for potential confounders. From 1,742 qualifying residents, 1,462 were enrolled, of whom 557 (38.1%) had ChD. Mortality rate was 51.9%. In multivariable adjusted models, abnormal P-wave axis was associated with a 48% (hazard ratio [HR] = 1.48 [95% confidence interval (CI) 1.16–1.88]) increased mortality risk in patients with ChD and 43% (HR = 1.43 [CI 1.13–1.81]) in patients without ChD. Abnormal QRS axis was associated with a 34% (HR = 1.34 [CI 1.04–1.73]) increased mortality risk in patients with ChD, but not in individuals without ChD. Similarly, in the ChD group, abnormal T-wave axis was associated with a 35% (HR = 1.35 [CI 1.07–1.71]) increased mortality, but not in patients without ChD. In conclusion, abnormal P-wave, QRS, and T-wave axes were associated with increased all-cause mortality in patients with ChD. Abnormal P-wave axis was associated with mortality also among those without ChD, being the strongest predictor among ECG variables. **(Am J Cardiol 2018;121:364–369)**

Abnormalities of the electrocardiogram (ECG) are known to be predictive of mortality in Chagas disease (ChD), as in other cardiomyopathies.[1,2] Patients with ChD and a normal baseline ECG have similar mortality as patients without the disease, confirming that this simple tool could have strong prognostic value.[1,3,4] However, there is still a lack of well-defined electrocardiographic predictors of mortality in ChD that could lead to early interventions. In this study, we sought to evaluate the prognostic value of abnormal axes of ECG wave forms (P-wave axis, QRS axis and T-wave axis) in the 14-year follow-up of the Bambuí Health and Aging Cohort Study (BHAS), a cohort conducted in Southeast Brazil in a population with high prevalence of ChD.

Methods

The BHAS was conducted in the southeastern Brazilian city of Bambuí (15,000 inhabitants), one of the oldest known endemic areas for ChD. Procedures used in the study and definitions of clinical variables were described in detail elsewhere.[5] Briefly, the baseline cohort population comprised all residents aged ≥60 years on January 1, 1997, identified by means of a population census. Baseline data were collected from February to May 1997, consisting of standardized interviews, blood and clinical tests, and ECG.[5,6] Diagnosis of ChD was made based on positive serology by 3 different methods, and patients with conflicting results were excluded. Participants underwent annual follow-up examinations in scheduled clinic visits and death certificates were verified. All participants signed an informed consent and authorized subsequent death certificate verification. The study was approved by the Institutional Review Board of the Fundação Oswaldo Cruz, Brazil.[5]

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All deaths from study enrollment until December 31, 2011 were included in this analysis. They were reported by relatives during the annual follow-up interview and ascertained through the Brazilian System of Information on Mortality, with the permission of the Ministry of Health. Death certificates were obtained for 98.9% of participants who died, allowing minimal loss of follow-up regarding vital status.

At the baseline examination, a standard digitally recorded 12-lead ECG (Hewlett-Packard MI700A, Palo Alto, California) was obtained at rest. ECGs were centrally read at the Epidemiological Cardiology Research Center located at Wake Forest School of Medicine, Winston-Salem, North Carolina. ECGs were analyzed by experienced cardiologists and visually inspected for technical errors before being classified by the Minnesota Code criteria.[5,6] The P (excluding individuals in atrial fibrillation or flutter), QRS, and T axes were obtained from the ECG printouts. Normal values were defined as (1) P wave between 0° and 75°,[7] (2) QRS complex between −30° and 90°,[8] and (3) T wave between 15° and 75°.[9,10]

Statistical analysis was performed using SPSS software version 23.0 for Mac OSX (IBM Corp., Chicago, Illinois) and the R software (The R Foundation for Statistical Computing, Vienna, Austria). The distribution pattern of the variables was assessed with the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation or median and interquartile range. Categorical variables were expressed as absolute values and percentages. The between-group comparison was performed using the Student *t* test for continuous variables with normal distribution and the Mann-Whitney test for those with non-normal distribution. The comparison of categorical variables was performed using Fisher's exact test.

Multivariable Cox proportional hazards regression was used to examine the association between baseline ECG axes with all-cause mortality in those with and without ChD separately as well as total population. Models were adjusted as follows: model 1, unadjusted; model 2, adjusted for age and gender; model 3, adjusted for variables in model 2 plus cardiovascular risk factors (total cholesterol or high-density lipoprotein, diabetes mellitus, body mass index, smoking, systolic arterial pressure and hypertension treatment); model 4, adjusted for variables in model 3 plus major ECG abnormalities (defined as previous definite or possible myocardial infarction, complete intraventricular blocks, supraventricular and ventricular premature beats, significant abnormalities of the ST segment and T wave, atrial fibrillation and flutter, supraventricular tachycardia, other arrhythmias, conduction abnormalities, pacemaker rhythm, QT prolongation, left ventricular hypertrophy)[6]; and model 5, adjusted for variables in model 4 plus serum B-type natriuretic peptide (BNP) levels.

Analysis of interaction between ECG axis abnormalities, ChD status, and residue test by the Schoenfeld[11] method were performed to assure the validity of the models. Kaplan-Meier curves were built for the total population, patients with and without ChD.

Results

From the 1,742 residents of Bambuí aged 60 years and older, 1,606 were enrolled. Of these, 280 were excluded for incomplete information and 17 for conflicting serological results, leaving 1,462 for this analysis, being 557 (38.1%) seropositive for *Trypanosoma cruzi* infection. The baseline characteristics of these patients are described in Table 1.

Table 1
Baseline characteristics of patients without and with Chagas disease

Characteristics	Chagas disease		p-value
	NO (N = 905)	YES (N = 557)	
Age (years, median (Q1 – Q3))	67 (63–73)	68 (64–74)	**0.041**
Male	391 (43.2%)	181 (32.5%)	**<0.001**
Creatinine (mg/dL, median (Q1 – Q3))	0.85 (0.74–0.99)	0.85 (0.75–0.97)	0.79
Total cholesterol (mg/dL median (Q1 – Q3))	227 (200–262)	229 (200–266)	0.62
High density lipoprotein (mg/dL, median (Q1 – Q3))	46 (38–56)	49 (40–58)	**0.001**
Diabetes mellitus	152 (16.8%)	57 (10.3%)	**0.001**
Body mass index (Kg/m^2, median (Q1 – Q3))	25.4 (22.3–28.3)	23.9 (20.8–27.3)	**<0.001**
Smoking	166 (18.3%)	98 (17.6%)	0.73
Systolic blood pressure (mmHg, median (Q1 – Q3))	136 (124–161)	133 (119–149)	**0.003**
Antihypertensive use	457 (50.5%)	285 (51.2%)	0.83
B-type natriuretic peptide (pg/dL, median (Q1 – Q3))	64 (35–112)	119.5 (63–207)	**<0.001**

Bold: $p < 0.05$.

The median follow-up time was 154 (79 to 179) months, equating to 15,725 person-years. Loss to follow-up was minimal. In years 1 and 14, it was 1.7% and 7.9%, respectively. All-cause mortality in years 1 and 14 was 4.6% and 51.9%, respectively. The ChD group had higher BNP levels and greater proportion of male patients. Otherwise, demographic and clinical differences between groups were subtle. Most ECG abnormalities, including abnormalities of the ECG axis, were more frequent in patients with ChD (Table 2); abnormal P-wave axis: 13% versus 20%, $p < 0.001$; abnormal QRS axis: 16% versus 41%, $p < 0.001$; abnormal T-wave axis: 37% versus 47%, $p < 0.001$.

In the final adjusted model, abnormalities of the P-wave, QRS, and T-wave axes increased the risk of mortality in the ChD group (48% P-wave axis, 34% QRS axis, and 35% T-wave axis). In the non-ChD group, only abnormalities of the P-wave axis increased mortality risk in the final model (43% increase), whereas the QRS axis was predictive only in the unadjusted model, and the T-wave axis lost significance after adjustment for BNP (Table 3).

For the total study population, there was a significant association between abnormalities of the ECG axes (P-wave, QRS, and T-wave) and mortality in the final adjusted models. However, interaction analysis with ChD status was significant for abnormalities of the T-wave axis (abnormal T-wave axis: hazard ratio [HR] = 1.11 (95% confidence interval [CI] 0.92 to 1.35), $p = 0.277$; abnormal T-wave axis × ChD: HR = 1.33 [95% CI 1.06 to 1.66], $p = 0.012$) and QRS axis (abnormal QRS axis: HR = 0.97 [95% CI 0.76 to 1.24],

Table 2
Electrocardiographic abnormalities of patients without and with Chagas disease

Electrocardiographic abnormalities	Chagas disease		p-value
	NO (N = 905)	YES (N = 557)	
Rhythm			
Sinus rhythm	789 (87.2%)	395 (70.9%)	**<0.001**
Sinus tachycardia	21 (2.3%)	10 (1.8%)	0.58
Sinus bradycardia	22 (2.5%)	28 (5.0%)	**0.02**
Frequent premature ventricular beats	37 (4.1%)	60 (10.1%)	**<0.001**
Frequent premature supraventricular beats	50 (5.5%)	60 (10.8%)	**<0.001**
Atrial fibrillation and flutter	17 (1.9%)	34 (6.1%)	**<0.001**
Pacemaker rhythm	0	6 (1.1%)	**0.003**
Intraventricular conduction			
Left bundle branch block	18 (2.0%)	18 (3.2%)	0.164
Right bundle branch block	30 (3.3%)	123 (23.2%)	**<0.001**
Left anterior fascicle block and right bundle branch block	8 (0.9%)	51 (9.2%)	**<0.001**
Incomplete left bundle branch block	52 (5.7%)	24 (4.3%)	0.28
Incomplete right bundle branch block	22 (2.4%)	31 (5.6%)	**0.002**
Atrioventricular conduction			
First degree atrioventricular block	17 (1.9%)	36 (6.8%)	**<0.001**
Second degree atrioventricular block	0	0	N/A
Third degree atrioventricular block	1 (0.1%)	3 (0.5%)	0.16
Myocardial ischemia			
Previous myocardial infarction definitive or probable	29 (3.2%)	33 (5.9%)	**0.02**
Major alterations on ST segment	119 (13.0%)	63 (11.3%)	0.30
Minor alterations on ST segment	518 (57.2%)	266 (47.8%)	**<0.001**
ST segment elevation	14 (1.5%)	5 (0.9%)	0.29
Other abnormalities			
Left ventricular hypertrophy	35 (3.9%)	11 (2.0%)	**0.046**
Short PR interval	2 (0.2%)	5 (0.9%)	0.12
Major prolongation of the QT interval	19 (2.1%)	35 (5.9%)	**<0.001**
Minor prolongation of the QT interval	23 (2.5%)	36 (6.5%)	**<0.001**
Low amplitude QRS	16 (1.8%)	14 (2.5%)	0.35
QRS left axis deviation	120 (13.3%)	163 (29.3%)	**<0.001**
QRS right axis deviation	10 (1.1%)	29 (5.2%)	**<0.001**

Bold: $p < 0.05$.

$p = 0.805$, abnormal QRS axis × ChD: HR = 1.48 [95% CI 1.10 to 1.97], $p = 0.009$), suggesting that the increased mortality associated with these variables in the overall population was influenced by the ChD group. Interaction was not significant for abnormalities of the P-wave axis (abnormal P-wave axis: HR = 1.36 [95% CI 1.09 to 1.69], $p = 0.007$; abnormal P-wave axis × ChD: HR = 1.17 [95% CI 0.89 to 1.54], $p = 0.261$).

Unadjusted Kaplan-Meier curves for all-cause mortality associated with abnormal ECG axes are depicted in Figure 1.

Discussion

Our study showed that, in patients older than 60 years, abnormalities of the P-wave axis were predictive of increased mortality both in the ChD group and in the non-ChD group. Conversely, although T-wave and QRS complex axes were associated with increased mortality in the ChD group, they were not predictive of increased mortality for those without ChD. Our findings highlight the prognostic relevance of variables reported in ECG printouts, one of the least expensive and most available complementary tests.

The association between abnormal P-wave axis and mortality in patients with and without cardiomyopathies is in accordance with previous studies.[12,13] P-wave axis is influenced by atrial anatomy and factors associated with the propagation of electrical stimuli. Its alterations are presumably electrocardiographic markers of subjacent atrial pathology, including inflammation and fibrosis—known to be associated with ChD—or structural remodeling leading to arrhythmogenic substrate.[12,14] It may also be a sign of ventricular dysfunction/overload resulting in remodeling,[14] and has been associated with other morbid conditions of the elderly, such as subjacent pulmonary disease and atrial fibrillation,[12–14] even in the absence of established structural heart disease.

Our findings that an abnormal T-wave axis predicted mortality in patients with ChD are consistent with published evidence involving individuals with chronic ChD.[15] This association was true even for borderline deviations.[15] Similarly, T-wave alternans and T-wave amplitude variability have also been associated with prognosis in ChD as early markers of repolarization impairment.[16,17] The mechanism of these changes is not clear in our population, but other studies have suggested the importance of the altered T-wave axis as an early marker of myocardial damage.[18–20] It is also speculated that T-wave abnormalities reflect disturbances of the ventricular repolarization that might be linked to the functional substrate of tachyarrhythmias in patients with ChD.[15] However, the true biologic meaning and the use of the T-wave axis in predicting overall cardiovascular risk remain unclear. Our conclusions about its predictive value—especially without concomitant ST changes—are underpowered and limited to patients with ChD.

Our data lead to similar assumptions for abnormalities of the QRS axis, which was not a consistent predictor of mortality in patients without ChD and in the total population. Previous studies have demonstrated the association between QRS axis deviations and mortality in elderly patients with heart failure and in patients with previous left bundle branch block.[21,22] An association with myocardial scarring has also been demonstrated, and it is proposed that scar-related histological findings, observed in ischemic and nonischemic myocardial damage, alter the electrical properties of the myocardium and its homogeneity and lead to QRS axis abnormalities.[22,23] In a large cohort, a related repolarization abnormality (QRS/T angle in the frontal plane) was associated with incident heart failure, markedly in the presence of other bundle branch blocks.[24] Our findings, however, do not support this predictive performance for patients without ChD and denotes a clear interaction between the predictive effect or QRS axis abnormalities and ChD status.

The results of this study may help future advances in risk stratification of ChD and elderly patients. Frontal electrocardiographic axes can be automatically estimated from printouts and are less prone to inaccuracies related to noise and artifacts than most of the ECG variables. The acknowledgment of these easily recognizable axes might provide additional information beyond that available from other ECG measurements, help identify patients at greater mortality risk,

Table 3
Multivariable Cox proportional hazards models: abnormal P-wave axis, abnormal QRS axis, and abnormal T-wave axis and all-cause mortality, adjusted for covariables

Model: P-wave axis	Total population (HR (95% CI))	With Chagas disease (HR (95% CI))	Without Chagas disease (HR (95% CI))
P-wave axis and all-cause mortality			
P wave axis	2.08 (1.79–2.41)	2.06 (1.65–2.56)	1.95 (1.57–2.41)
Adjusted for sex and age	1.77 (1.52–2.05)	1.7 (1.36–2.12)	1.66 (1.34–2.06)
Adjusted for sex, age and cardiovascular risk factors	1.58 (1.34–1.85)	1.52 (1.2–1.93)	1.48 (1.18–1.87)
Adjusted for sex, age, cardiovascular risk factors and ECG abnormalities	1.51 (1.28–1.77)	1.46 (1.15–1.85)	1.46 (1.16–1.84)
Adjusted for sex, age, cardiovascular risk factors, ECG abnormalities and B-type natriuretic peptide	1.47 (1.25–1.74)	1.48 (1.16–1.88)	1.43 (1.13–1.81)
QRS axis and all-cause mortality			
QRS axis	1.58 (1.36–1.84)	1.62 (1.31–2.02)	1.32 (1.04–1.69)
Adjusted for sex and age	1.35 (1.15–1.58)	1.48 (1.19–1.85)	1 (0.78–1.28)
Adjusted for sex, age and cardiovascular risk factors	1.38 (1.18–1.62)	1.56 (1.24–1.97)	1.03 (0.79–1.32)
Adjusted for sex, age, cardiovascular risk factors and ECG abnormalities	1.21 (1.02–1.43)	1.3 (1.01–1.66)	0.98 (0.75–1.26)
Adjusted for sex, age, cardiovascular risk factors, ECG abnormalities and B-type natriuretic peptide	1.22 (1.03–1.44)	1.34 (1.04–1.73)	0.99 (0.76–1.28)
T-wave axis and all-cause mortality			
T wave axis	1.67 (1.45–1.92)	1.72 (1.39–2.14)	1.57 (1.29–1.89)
Adjusted for sex and age	1.66 (1.44–1.91)	1.62 (1.3–2.01)	1.63 (1.34–1.97)
Adjusted for sex, age and cardiovascular risk factors	1.46 (1.26–1.7)	1.52 (1.21–1.9)	1.36 (1.11–1.67)
Adjusted for sex, age, cardiovascular risk factors and ECG abnormalities	1.29 (1.1–1.51)	1.37 (1.09–1.73)	1.25 (1.01–1.55)
Adjusted for sex, age, cardiovascular risk factors, ECG abnormalities and B-type natriuretic peptide	1.26 (1.08–1.48)	1.35 (1.07–1.71)	1.21 (0.97–1.51)

ECG = electrocardiogram; HR = hazard ratio (for each model).

and speculatively allow early therapeutic interventions. Although our findings are preliminary, we believe that the strong association between abnormalities of the P-wave axis and mortality, in the overall cohort and in patients with ChD, is consistent and should be further evaluated for integral application as a cardiovascular risk marker in the future. It has not yet been shown, however, if such abnormalities are early markers of subclinical disease—when interventions are more effective—or associated with already established structural damage (e.g., overload, fibrosis), either primary or secondary.

Previous studies have shown that patients with ChD appear to have an increased mortality risk compared with other cardiomyopathies in similar clinical stages. The risk factors for mortality are not well-defined for this population as for other cardiomyopathies,[25] highlighting the need for recognition of new prognostic markers. Considering the great prevalence of ChD in underserved areas, the deeper investigation of the ECG axes—an inexpensive and universal tool even in underdeveloped countries—becomes even more relevant.[26] Besides the findings in the ChD group, our cohort included elderly patients regardless of previous cardiovascular disease, which allows the extrapolation of the findings of the non-ChD population for this age range and reinforces the importance of detailed ECG analysis also for the care of the elderly.

Our study has some other significant strengths. It is, to the best of our knowledge, the longest follow-up of patients with ChD and the first to evaluate specifically the ECG axes as predictors of mortality in a population with such high prevalence of the disease. Also, the limited sample size of most follow-up studies involving ChD populations reinforces the importance of the data from the 557 enrolled in the BHAS, which has the unique feature of being a community-based cohort, allowing particular epidemiological and sociodemographic insights.

Our study has also some limitations. At first, our follow-up mortality data were obtained from a national registry, with no adjudication for the specific cause of death. In a cohort of elderly patients, the distinction between cardiac and non-cardiac causes could provide better prognostic insights, although cardiovascular diseases are the leading cause of death among Brazilians.[27] Other health conditions, such as respiratory diseases, are prevalent among the elderly and may be mediators between ECG axis abnormalities—noticeably P wave—and mortality. Also, some variables with known prognostic implications were not systematically collected: left ventricular ejection fraction —strongly associated with cardiovascular mortality—was not available for inclusion in the multivariable mortality models. We believe, however, that the results remain valid, once we used the BNP levels—with marked inverse correlation with left ventricular ejection fraction and mortality in cardiomyopathies[28,29]—as a reliable surrogate for left ventricular function. Finally, only baseline data were available for most variables, including ECG and laboratory results. The changes of such variables—markedly the ECG axes—over the follow-up period could also provide valuable prediction information for clinical outcomes.

In conclusion, we demonstrated that in a cohort of patients followed up for 14 years, abnormalities of the ECG axes had significant prognostic value. Abnormalities of the QRS axis and T-wave axis were associated with increased all-cause mortality in patients with ChD. Noticeably, abnormal P-wave axis was the strongest predictor of mortality among the ECG axis variables in the total population, even after adjustment for potential confounders.

Disclosures

The authors have no conflicts of interest to disclose.

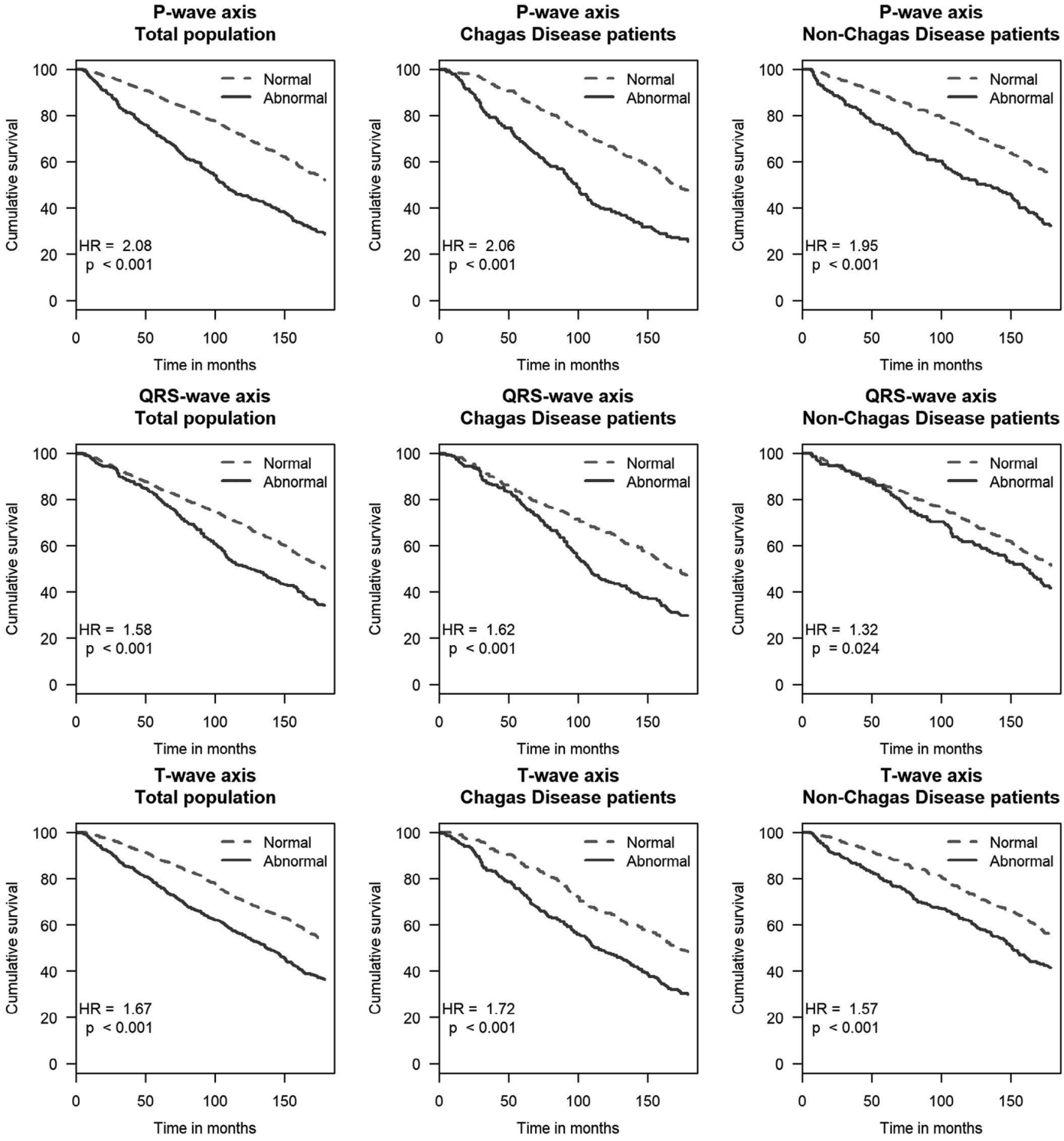

Figure 1. Unadjusted Kaplan-Meier curve: P-wave axis and mortality, QRS axis and mortality, and T-wave axis and mortality.

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