

Sex Differences in Patients Hospitalized for Syncope: Experience in University Hospital of Middle-income Country and with a Predominance of Chagasic Etiology

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Authors' contributions

This work was carried out in collaboration among all authors. Author RMFLS designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Authors JSP, DTGM, GVF, MAAC, PVAP and PADV collected data and managed the analysis of the study. Author LR managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Syncope is a common sign with an inpatient rate of up to 83%. Data on sex differences of patients with syncope in the emergency and hospitalization are scarce.

Aim: The present study aimed to verify sex differences regarding clinical profile, risk scores, causes of syncope and treatment modalities.

Study Design: This is a single center, prospective, observational study.

Place and Duration of Study: Department of Internal Medicine, Faculty of Medicine, Hospital das Clínicas, Federal University of Minas Gerais, Brazil, between February 2015 and February 2017.

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Methodology: We included 375 consecutive patients, 203 men and mean age of 52 years, hospitalized because of syncope. They underwent clinical evaluation, the laboratory tests, and the calculation of Martin, OESIL and EGSYS scores.

Results: 114 patients had chagasic cardiomyopathy. The causes of syncope due to arrhythmia were ventricular tachycardia in 127 patients (66.1% men), supraventricular in 117 (63.2% women) and bradyarrhythmias in 56 patients (66.1% men), $p < 0.0001$. Odds ratio for ventricular tachycardia in chagasic patients was 8.78 (95% IC: 5.33-14.46). Heart disease was predominant among men ($p = 0.001$), even among patients with Chagas' heart disease. Comparing male and female, median age was 57 versus 48 years ($p = 0.04$) and ejection fraction was 53 versus 58% ($p = 0.03$). Martin and OESIL scores were higher in males ($p < 0.0001$). There was no difference in treatment. Applying the receiver operating characteristic curve for ventricular tachycardia, Martin score had the largest area under the curve (0.84), $p < 0.0001$.

Conclusions: Men hospitalized for syncope were older, had more systolic ventricular dysfunction, and had higher Martin and OESIL scores. The main causes of syncope were ventricular tachycardia and bradyarrhythmias among men and supraventricular tachycardias among women.

Keywords: Syncope; sex difference; cardiac arrhythmia; ventricular tachycardia; chagas disease.

1. INTRODUCTION

Syncope is the sudden loss of consciousness, with spontaneous recovery, associated with cerebral hypoperfusion, with incapacity to maintain postural tone and that has a short duration of up to 20s [1,2]. It has an annual incidence of 6% and a prevalence of 42%, considering a life expectancy of 70 years [1,3]. In the general population, the annual number of episodes is 18.1 to 39.7 per 1,000 patients, with a significant increase in the incidence of syncope after 70 years of age, mainly due to cardiac etiology [2,3]. Male gender is one of the factors associated with cardiac syncope, as well as old age [2]. However, women with syncope are older and present physical injury more often [4].

Because of the morbidity and mortality of syncope, 40% of patients with syncope are hospitalized [1], reaching up to 83% hospitalization rate [5], with total costs of US \$ 1.6 billion [2]. Therefore, risk stratification is crucial in its initial rational approach. For this, risk scores have been recommended to predict the outcome of patients with syncope who have used hospital units, especially if applied prospectively [1,2,6]. Among the scores that use variables that are easy to obtain, through history, physical examination and electrocardiogram, there are the scores of Martin [7], OESIL [8] (Osservatorio Epidemiologico sulla Sincope nel Lazio) and EGSYS [9,10] (Evaluation of Guidelines in Syncope Study).

The Martin score used 4 risk variables for the multivariate analysis (electrocardiogram - ECG - abnormal, history of ventricular arrhythmia, heart

failure and age >45 years), with a score of 1 for each, to predict the occurrence of cardiac arrhythmia or arrhythmia death for one year [7]. The OESIL score considered 4 variables, each is worth 1 point (abnormal ECG, history of cardiovascular disease, absence of prodromes and age > 65 years) to predict mortality in one year [8]. Through the EGSYS score, 6 predictors of mortality were considered, with the following score: +4, if palpitations before syncope; +3, if abnormal ECG and/or structural heart disease; +3, if syncope during exertion; +2, if syncope occurs in the supine position; -1, if the presence of autonomic prodromes; -1, if there are predisposing and / or precipitating factors [9].

The main objective of this study was to verify sex differences regarding clinical profile, risk scores, causes of syncope and treatment modalities. The secondary objective was to assess the performance of risk scores for the causal factor of syncope. Knowledge of those characteristics can help identify targets for quality improvement intervention and reveal particularities in a tertiary institution in a middle-income country.

2. PATIENTS AND METHODS

This is a prospective, observational study of 375 consecutive patients, 203 men and mean age of 52 years, hospitalized because of syncope, of both sexes and all ages. Patients were included during the 24-month period (between February 2015 and February 2017). During this period there were a total of 36,000 admissions. Patients whose cause of syncope was vasovagal by initial evaluation using the clinical method were excluded. The research project was approved by

the research ethics committee of the institution. All patients and/or legal guardians gave informed consent and signed a written consent form for participation in this study. All data analyzed were anonymized.

Patients underwent clinical evaluation, the laboratory tests, according to its indication, and the calculation of Martin, OESIL and EGSYS scores. The calculation of scores was done by researchers enabled without the knowledge of the cause of syncope. The electrocardiographic interpretation was done by a cardiologist. The treatment was done by the attending physicians of the patients, without the influence of the researchers. The hospital where this study was conducted is one of the accredited health establishments for the implantable electronic cardiac device procedure.

2.1 Statistical Analysis

For statistical analysis, the Statistical Package for Social Sciences (SPSS, Inc. Chicago, IL, USA) version 14.0 was used. The results were expressed in numbers and proportions, for categorical variables, and in measures of central tendency (median) and interquartile ranges, for continuous variables. Chi-square test and Fisher's exact test, as appropriate, were used to study possible associations between categorical variables. The Mann-Whitney and Kruskal-Wallis tests were used to compare continuous variables. These non-parametric tests were used because there was no normal distribution by the Kolmogorov-Smirnov test. Spearman rank correlation was used to test the association between one ranked variable and one measurement variable. Analysis of receiver operating characteristic curves were used to assess the ability of diagnostic scores to cause syncope. The level of statistical significance was 5%.

3. RESULTS

3.1 Baseline Characteristics of the Participants

The median age of patients was 52.0 years, ranging from 12 to 90 years, 25 and 75 percentiles of 39 and 67 years, respectively. The medians of blood pressure and heart rate at the time of admission were 120/70 mmHg (ranging from 80/43 to 210/115) and 70.0 bpm (between 30 and 188). 114 patients had chagasic cardiomyopathy, 31 hypertensive heart disease,

39 coronary artery disease, 20 dilated cardiomyopathy of other etiologies, 20 valvular heart disease (mitral valve prolapse in 11, rheumatic mitral valve disease in 6, and aortic stenosis in 3 patients). Other etiologies of heart disease were observed in 21 patients, such as hypertrophic cardiomyopathy, congenital heart disease, arrhythmogenic right ventricular dysplasia and Brugada syndrome. One hundred and thirty patients (34.6%) had no heart disease. Left ventricular ejection fraction had a median of 0.56 (ranging from 0.10 to 0.84), with 25 and 75 percentiles of 0.37 and 0.66; respectively. The medians were 2.0 for Martin score and also for OESIL score and 4.0 for EGSYS score.

3.2 Causes of Syncope

The causes of syncope due to arrhythmia detected by conventional electrocardiogram, telemetric or Holter monitoring were ventricular tachycardia (VT) in 127 patients, supraventricular in 117 and bradyarrhythmias in 56 patients.

Among the other hospitalized patients, after laboratory tests, including clinical pathology testing, echocardiogram, Holter monitoring, electrophysiological study, head-up tilt testing, duplex carotid scan and neurological evaluation, structural cardiomyopathy was considered as causes of syncope in 18 patients (because low output), neurally mediated syncope in 44 and carotid stenosis in one patient. The cause of syncope was not identified in 3.2% of patients. The proportions of the main causes of syncope are shown in Fig. 1.

VT as a cause of syncope occurred in 16% of patients with hypertensive cardiomyopathy, 20.1% of those with ischemic heart disease, 59% of chagasic patients and 10.3% of those with dilated cardiomyopathy due to other etiologies ($p < 0.00001$). Odds ratio for VT in chagasic patients was 8.78, 95% confidence interval 5.33 to 14.46.

3.3 Sex Differences

There was a statistical difference between the sexes regarding the cause of syncope due to arrhythmia. The percentage of 63.2% of patients with supraventricular tachycardia as a cause of syncope was women. Among the patients with syncope due to VT, 66.1% were men. Odds ratio for VT in men was 2.12, 95% confidence interval 1.36 to 3.30. Among those with syncope due to bradyarrhythmia, 66.1% were men. Data on the comparison between genders and statistical analysis are shown in Table 1.

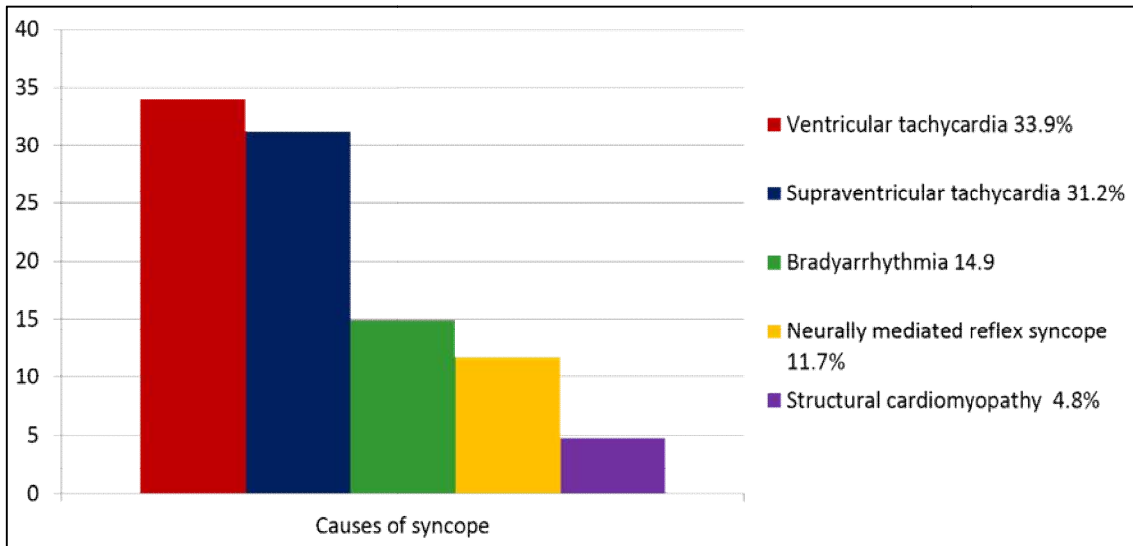


Fig. 1. Proportion of the main causes of syncope in the study population

Table 1. Comparison between sexes regarding clinical and laboratory variables, risk scores and causes of syncope

Variables	Male gender (N=203) Median (Q1 - Q3) or proportion	Female (N=172) Median (Q1 - Q3) or proportion	p-value
Age (years)	57.0 (40.0 – 69.0)	48.0 (39.0 – 65.0)	0.04
HR (bpm)	67.5 (60.0 – 76.0)	72.0 (62.0 – 84.0)	0.002
Left ventricular ejection fraction (%)	53.0 (35.5 – 64.0)	58.0 (39.7 – 68.0)	0.03
Left ventricular ejection fraction <55% (percentage of patients)	41.4	24.6	0.001
Martin score	2.0 (2.0 – 3.0)	1.0 (1.0 – 2.7)	<0.0001
OESIL score	2.0 (2.0 – 3.0)	2.0 (1.0 – 3.0)	<0.0001
EGSYS score	5.0 (3.0 – 7.0)	4.0 (3.0 – 7.0)	0.80
Causes of syncope due arrhythmia			<0.0001
- 300 patients (percentage of patients)	66.1	33.9	
- Ventricular tachycardia	36.8	63.2	
- Supraventricular tachycardia	66.1	33.9	
- Bradyarrhythmias			

HR: Heart rate (at hospital admission); bpm: Beats per minute; Q1: First quartile - 25th percentile; Q3: Third quartile - 75th percentile. Chi-square and Mann-Whitney tests

Among the 130 patients without structural heart disease, 61.5% were women. There was a predominance of heart disease among men (p=0.001), with hypertensive etiology (70.9% of men), ischemic (79.4%), dilated (65%) and chagasic (57.0%). Among those with valvular heart disease, 65% were women. When comparing patients with and without structural heart disease, the cause of syncope was structural heart disease in 83.3% of the men (p=0.0006, Fisher's exact test). Spearman correlation between gender and causes of syncope and baseline heart disease presented p

<0.0001 for both and p=0.001 for left ventricular ejection fraction <55%.

There was a difference in risk scores in relation to sex. Regarding Martin score, the proportion of men was 23.7%, 39.4%, 62.6%, 68.4% and 65.4% for the score 0, 1, 2, 3 and 4, respectively (p <0.0001). As for OESIL score, the proportion of men was 33.37%, 40.5%, 61.3%, 62% and 76.2% for the scores 0, 1, 2, 3 and 4, respectively (p <0.0001). There was no predominance of sex regarding the EGSYS score, which ranged from -2 to 12.

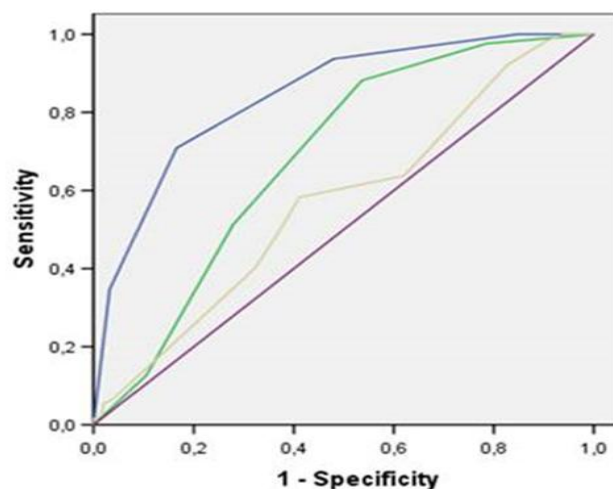


Fig. 2. Receiver operating characteristic curve for Martin, OESIL and EGSYS scores, considering ventricular tachycardia as cause of syncope. Abscissa axis: Sensitivity; coordinate axis: 1 - Specificity. Line in blue color: Martin score; green line: OESIL Score; brown line: EGSYS score; Reference line in lilac

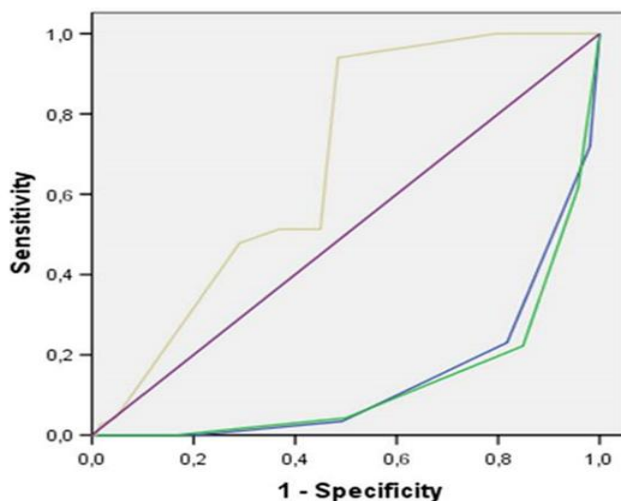


Fig. 3. Receiver operating characteristic curve for Martin, OESIL and EGSYS scores, considering supraventricular tachycardia as the cause of syncope

Table 2. Comparison between specific treatment modalities

Variables	Pacemaker implantation	ICD	Antiarrhythmic and/or ablation	p-value
Age (years): median (Q1-Q3)	66.5 (44.5-74.3)	63.0 (54.0-72.0)	46.0 (34.0-58.0)	<0.0001
Sex (number of patients): male/female	22/16	95/93	26/17	0.41
Left ventricular ejection fraction (%): median (Q1-Q3)	58.0 (46.3-61.5)	36.5 (26.7-53.0)	56.0 (37.0-66.0)	<0.0001
Martin score: median (Q1-Q3)	2.0 (2.0-2.0)	4.0 (3.0-4.0)	1.0 (1.0-3.0)	<0.0001
OESIL score: median (Q1-Q3)	3.0 (2.0-4.0)	3.0 (2.0-3.0)	1.0 (1.0-2.0)	<0.0001
EGSYS score: median (Q1-Q3)	3.0 (3.0-5.3)	5.0 (3.0-7.0)	6.0 (4.0-7.0)	<0.0001

ICD: Implantable cardioverter-defibrillator; Chi-square and Kruskal-Wallis tests; Q1: 25th percentile; Q3: 75th percentile

A total of 269 patients underwent a specific treatment, with pacemaker implantation in 38, cardioverter-defibrillator (ICD) in 43, and use of antiarrhythmic and/or ablation in 188 patients. The comparison between these treatment modalities and the variables are shown in Table 2. For other patients, there were changes in their medications, according to the guidelines recommended by the literature [1,2,6].

3.4 Receiver Operating Characteristic Curve Analysis

Using the analysis of receiver operating characteristic curve for VT variable as the cause of syncope, Martin score had the largest area under the curve, of 0.84 ($p < 0.0001$, 95% confidence interval 0.80-0.88). The data referring to scores are plotted in Fig. 2. Martin score ≥ 2 was observed in 93.7% of patients with VT (negative predictive value of 100%).

Considering supraventricular tachycardia as cause of syncope, the area under the curve above baseline was only for EGSYS score of 0.67, with $p < 0.0001$ (95% confidence interval 0.62-0.73) (Fig.3). The negative predictive value was 88.9% and a positive predictive value of 64.5% for EGSYS score ≥ 3.5 .

For bradycardia as cause of syncope, the area under the curve above baseline for OESIL score was 0.73, with $p < 0.0001$ (95% confidence interval 0.66-0.79), resulting in a negative predictive value of 89.4% and a positive predictive value of 70.1% for the best cutoff point, which was 1.5.

4. DISCUSSION

Epidemiological data show differences in prevalence and risk between sexes. For example, men have a higher prevalence of coronary heart disease, myocardial infarction, heart failure, aortic stenosis. However, women have a higher prevalence of arterial hypertension, a higher lifetime risk of stroke (especially with atrial fibrillation) and a higher risk of cardiac events due to prolonged QT interval. In addition, women are less subject to cardiovascular operations and procedures, such as cardiac catheterization, coronary artery bypass, percutaneous coronary intervention, implantable defibrillators. Therefore, total cardiovascular disease and stroke costs are lower in women's care [11]. Regarding vasovagal syncope, the cumulative incidence at age 60 is 42% for women and 32% for men. Among those

with postural tachycardia syndrome, more than 75% are women [12]. As previously mentioned, male gender is one of the factors associated with cardiac syncope [2]. Other data as cause of syncope and risk stratification scores in relation to sex were not well studied in patients hospitalized for syncope.

Cardiac syncope presents a proportion of 10%, reaching up to 35% in the emergency units [13]. Because of their mortality [3], hospitalization of patients with this cause is imperative. In the study in question, after comprehensive investigation, 84.8% of the patients hospitalized for syncope presented cardiac cause, 80% of the total for arrhythmia, demonstrating that hospital admission was appropriate. A recent study with 362 patients evaluated in the emergency unit presented a rate of 69% hospitalization and the readmission rate in one year was 18% among those who were discharged from the emergency room [14].

A prospective cohort study of 4064 patients from 5 emergency units demonstrated that cardiac arrhythmia syncope is the leading cause of hospitalization in adult patients with syncope, reaching 84.2% of 165 hospitalized patients. Furthermore, arrhythmia was the most common serious adverse event after discharge directly from the emergency unit or hospital [15]. Among the arrhythmias, the correlation between the syncope symptom and VT record, supraventricular tachycardia (with heart rate ≥ 160 bpm) or asystole ≥ 3 s is considered a gold standard for diagnosis [1]. Syncope can occur in 15% of cases in patients with supraventricular tachycardia [16] and among those who present this arrhythmia while driving, syncope can occur in 14% and pre-syncope in 50% of cases [17].

There was no patient with pulmonary embolism as a cause of syncope, in agreement with the literature, which reported a prevalence of up to 0.55% among 1,671,944 patients treated in the emergency room with syncope [18]. Regarding reflex syncope, its prevalence was lower in the study population (11.7%), compared to that in the literature, between 30% and 40% [2,3,19]. This proportion of the literature refers to the diagnosis made in the emergency; therefore, the proportion was higher because the diagnosis of the cause of syncope in this study was made after hospitalization. Another distinct finding was the proportion of unexplained syncope lower than reported in the literature, which is between 37% and 41% [2,3,19,20]. In these studies, there was investigation with laboratory tests, including

invasive, of patients admitted to the emergency room with syncope. However, in the study in question, the patients were submitted to a more comprehensive investigation, which made it possible to identify the cause of syncope in its majority.

Among men, there was a predominance of VT and bradyarrhythmia as causes of syncope, and in women, supraventricular tachycardias predominated in line with what has already been demonstrated in the literature regarding these arrhythmias [11,21]. Also according to the bibliographic data [11,22], there was a predominance of cardiomyopathy, especially ischemic etiology and ventricular dysfunction in men, and valvular heart disease, most of them due to mitral valve prolapse, in women. These presentations explain the age difference between sexes and reflected in higher scores of Martin and OESIL in men.

Because the region where the research was developed to be an endemic area for Chagas disease, 46.5% of patients with structural heart disease had chagasic cardiomyopathy, predominantly in men. It has been reported a worse prognosis of this heart disease in men [23], evidencing greater ventricular remodeling and myocardial fibrosis [24]. In chronic Chagas cardiomyopathy, most probable causes of syncope, mainly recurrent, is VT which represents 43% of the causes of syncope [25].

Another aspect of interest between the sexes was the difference in heart rate at admission, higher in women. A meta-analysis including 63,612 participants, of whom 31,970 were women, demonstrated that resting heart rate was higher in women [26].

The specific treatment modalities presented data of compliance with the literature. The pacemaker implantation was performed in older patients by increased conduction disorders with advancing age [11,27]. The reduced left ventricular ejection fraction is one of the determinants of ICD implantation. Syncope is one of the predictors of mortality in patients with ventricular dysfunction, including in patients with ICD [2,27-29]. Regarding sex, there was no difference in relation to the treatment modality in the study in question. Although the guidelines [2,27,28] present the same recommendations for implanting electronic cardiac devices independent of sex, there are differences regarding the indication of ICD, with a proportion below that

appropriate for women, which has been decreasing over time [30]. However, the influence of sex on pacemaker implantation was observed in the mode of stimulation, especially in elderly women [31].

Despite the established algorithms for the approach of patients with syncope in the emergency units [32], there is still uncertainty about the risk stratification and, therefore, for adequate indication of hospitalization. Easy-to-obtain scores validated by prospective studies that allow estimating the cause of syncope may be useful to improve care and use of diagnostic tools, guiding the need for hospitalization, based on the short- and long-term prognosis [1,2,33]. There is influence of clinical judgment (including electrocardiographic interpretation), of the medical professional (if clinical, emergency physician, cardiologist) and there is heterogeneity of the assisted population, according to the level of complexity of the hospital [32,34].

In the study population, all scores were statistically significant for VT as cause of syncope, with a larger area under receiver operating characteristic curve for the Martin score and with high predictive values, either positive or negative. This score, which includes 4 predictors through multivariate analysis, was developed with 252 patients and validated in 374 patients in the tertiary hospital emergency unit. Patients with 4 predictors presented cardiac arrhythmia or arrhythmia death in 80.4% of cases during one year after the emergency, documented by cardiac monitoring or electrophysiological study [7]. The OESIL score presented a sample of 270 patients and was validated with 328 patients who went to the emergency room due to syncope in 5 hospitals [8]. The EGSYS score was performed in 14 general hospitals in Italy with 261 patients and was validated with 256 patients and similar to OESIL it was a predictor of mortality [9]. Because the purpose of these scores, Martin score showed greater predictive value for VT. A study with 200 patients showed that OESIL score identified patients with low risk for cardiac syncope with a negative predictive value of 97.8% if this score was less than 2 [35]. This finding is corroborated by other sources, including meta-analysis, demonstrating different quality of study methods [2,36]. As the OESIL score includes age > 65 years among its variables and atrioventricular conduction disturbances increase with age [11,27], the area

under the curve was higher for this score in relation to the bradyarrhythmias in the present study.

About the EGSYS score [9], it allows identifying cardiac syncope cause if it is at least 3. External validation of this score demonstrated a sensitivity of 56% in a population of 231 patients, that is, less than the initial study, which was 92% [37]. Another study using this score with 198 patients with cardiac syncope demonstrated a sensitivity of 86% for that cutoff point [38]. Thus, this score was useful for differentiating patients with cardiac cause those patients with noncardiac causes of syncope [39], but without specifying the etiology of cardiac syncope. The usefulness of syncope units is added to risk stratification by clinical judgment and scores, allowing for a greater proportion of diagnosis, patient satisfaction, shorter hospital stay and cost reduction [6,13,14,40-43]. Recent meta-analysis of 6 studies including 458 patients, with equal distribution between the sexes, demonstrated a high diagnostic rate in syncope units. This rate was 67.3% with a length of stay of 28.2 h [44]. As a complement, risk scores - with prognostic risk stratification more easily remembered [45] - can assist in medical decision on emergency for admission of patients in the syncope units or their hospitalization.

4.1 Limitations

The proportion and management of patients with syncope in the emergency units vary among physicians and institutions. This may interfere with the reproduction of the results, which were obtained in a tertiary hospital in a middle-income country and in an endemic area of Chagas disease, but without syncope unit. Furthermore, the study was performed with patients in hospital units.

5. CONCLUSIONS

Men hospitalized for syncope were older, had more systolic ventricular dysfunction, and had higher Martin and OESIL scores. The main causes of syncope were VT and bradyarrhythmias among men and supraventricular tachycardias among women. VT presented an odds ratio of 8.78 as a cause of syncope among patients with Chagas cardiomyopathy.

CONSENT

The authors declare that written informed consent was obtained from the patients.

ETHICAL APPROVAL

All authors declare that the research was approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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