Original Paper

European Neurology

Eur Neurol 2018;79:177–184
DOI: 10.1159/000488033

Received: January 31, 2018
Accepted: February 27, 2018
Published online: March 14, 2018

Mortality and Stroke Recurrence in a Rehabilitation Cohort of Patients with Cerebral Infarcts and Chagas Disease

Vinícius Viana Abreu Montanaro[a] Thiago Falcão Hora[a] Creuza Maria da Silva[b]
Carla Verônica de Viana Santos[b] Maria Inacia Ruas Lima[b]
Edson Marcio Negrão[a] Daniele Sebestyan Martins Ribeiro[a]
Eleonora Maria de Jesus Oliveira[a] Gabriel R. de Freitas[c]

[a]SARAH Network of Rehabilitation Hospitals, Brasília, Brazil; [b]Neurological Rehabilitation Program, SARAH Network of Rehabilitation Hospitals, Brasília, Brazil; [c]Universidade Federal Fluminense, and D'Or Institute for Research and Education, Rio de Janeiro, Brazil

Keywords
Chagas disease · Ischemic stroke · Mortality · Recurrence

Abstract
Background: Chagas disease is related to ischemic stroke (IS), although few epidemiological studies have evaluated the associated mortality and recurrence. Our objective is to determine factors associated with mortality and recurrence of IS in patients with IS and Chagas disease. ***Methods:*** We retrospectively studied data obtained from electronic medical records of patients admitted at SARAH Hospitals across Brazil between 2009 and 2013. Using Cox regression analysis for mortality and logistic regression for recurrence, we assessed primary population characteristics and statistical associations between risk factors and outcomes. ***Results:*** We analyzed 279 patients who were followed up until 2016. The mean age at stroke onset was 61 with a 10% frequency of death. Multivariate analysis assessing mortality demonstrated that the associated factors were age at stroke (hazard ratio [HR] 1.04), initial modified Rankin Scale (mRS; HR 20.91), bladder dysfunction (HR 2.51), diabetes mellitus (DM; HR 3.64), and alcoholism (HR 3.37). Multivariate analysis assessing recurrence demonstrated that the associated factors were age at ictus (OR 0.96), cognitive deficit (OR 0.44), initial mRS (OR 1.84), cardioembolic etiology (OR 2.47), and female sex (OR 2.73). ***Conclusions:*** Cardiac conditions did not correlate with mortality or recurrence. Age was a protective factor against recurrence, probably due to cumulative risk of IS over time, while initial mRS was associated with both outcomes. Treating diseases such as DM and bladder dysfunction, and early treatment to reduce the initial mRS could potentially prevent both outcomes; also, establishing a correct etiological diagnosis is important.

KARGER

E-Mail karger@karger.com
www.karger.com/ene

Vinicius Viana Abreu Montanaro
SARAH Network of Rehabilitation Hospitals
SHMS 501 bloco A Asa sul
Brasília (Brazil)
E-Mail vinicius_montanaro@yahoo.com.br

Introduction

Chagas disease is a vector-borne illness caused by the *Trypanosoma cruzi* parasite. It is the third most common parasitic infection worldwide and a major health problem in non-endemic regions [1–3]. The disease can initially manifest as an acute febrile illness characterized by fever, headache, facial edema, and the classic *Romaña* sign, which can last between 6 and 12 weeks. A chronic form of infection can occur in approximately 40% of cases [4]. This form is characterized by cardiac involvement including arrhythmias and cardiomyopathy [5].

A close relationship between Chagas disease and ischemic stroke (IS) has been widely described in literature based on autopsy reports [6], as well as case-control and cohort studies [7, 8] – all these showing increased prevalence of IS, especially during the chronic stage of the disease. However, few studies have focused on identifying factors associated with stroke recurrence or mortality in these patients [9–11].

To date, limited long-term follow-up data are available [11]. However, determining such factors could potentially help with identifying management strategies to prevent recurrence and define prognosis in these patients. Identifying possible targets to reduce death or recurrence outcomes in these patients could lead to the establishment of new guidelines for their management, which presently remains dependent on extrapolation of knowledge and incomplete information [12].

We aimed to determine risk factors and clinical findings associated with the recurrence of IS and mortality in patients diagnosed with Chagas disease.

Methods

Ours was a retrospective study using data obtained from the electronic medical records of the patient cohort who presented with IS and concomitant Chagas disease. These patients were admitted between January 2009 and December 2013 to several rehabilitation hospitals which are public, open access, and quaternary health institutions located across 8 cities in Brazil, attending patients all over the country. Our study protocol was approved by the Ethics Committee of the SARAH Network of Hospitals, and the need for patient consent was waived by the committee.

We analyzed data pertaining to all patients admitted during this time period with a dual diagnosis of IS and Chagas disease. Chagas disease was confirmed using 2 different serological tests (enzyme-linked immunosorbent and hemagglutination assay). Inclusion criteria for this study were evaluation of patients during the stated period at the SARAH Network of Rehabilitation Hospitals, a diagnosis of Chagas disease, and of IS confirmed using neuroimaging (CT) or (MRI). Exclusion criteria were conflicting serological results and age <18.

Data recorded included vascular risk factors (dyslipidemia, hypertension, obesity, diabetes mellitus [DM], history of smoking and alcoholism up to 1 year prior to the diagnosis of IS), neurological deficit, and disability evaluated using the modified Rankin Scale (mRS) and medical treatment regimens employed for secondary prevention (none, antiplatelet agents, or anticoagulants). All these variables are routinely acquired during admission of patients in the rehabilitation program. We also evaluated the recurrence of IS, the presence of hemorrhagic transformation, history of hemorrhagic stroke, age at stroke onset, evidence of atrial fibrillation (AF) on an electrocardiogram (ECG), evidence of systolic dysfunction on a transthoracic echocardiogram (TTE), cognitive dysfunction, and bowel or bladder dysfunction following the IS.

Etiological investigation of patients included a battery of tests such as TTE, chest radiograph, ECG, neuroimaging (MRI or CT), noninvasive intracranial vascular studies (MR angiography, CT angiography, and transcranial Doppler), transesophageal echocardiography, and 24-h Holter monitoring, which were performed at the discretion of the attending neurologist responsible for the patient's care.

Data related to the assessment of cognitive dysfunction comprised an altered Mini-Mental State Examination, which is routinely performed at our hospitals, adjusting for low scores for age and level of schooling in the Brazilian population [13]. Overt dementia syndrome with patients showing dependence in activities of daily living, not due to motor deficit, was also considered among the relevant variables. If cognition was not feasibly accessible (due to aphasia), the subject was considered not having it, as long as they maintained independence in activities of daily living and did not perform poorly on an executive function test such as the trail making test [14] (also routinely evaluated at our rehabilitation program). Bladder (incontinence or retention) and bowel (constipation or incontinence) dysfunction after stroke were also assessed.

Stroke etiology was classified by 2 independent neurologists using a computerized system (available at https://ccs.mgh.harvard.edu/ccs_title.php) based on the Stop Stroke Study Causative Classification System (SSS-CCS) Trial of ORG 10172 in Acute Stroke Treatment (TOAST) [15–16]. This score was found to be superior to the classical TOAST criteria in these patients [17]. Disagreements between investigators were resolved through discussion and consensus.

The Instituto de Pesquisa Clínica Evandro Chagas/Fundação Oswaldo Cruz (IPEC\FIOCRUZ) risk of embolism score (a score ranging from 0 to 5 that stratifies risk of cerebral embolism in Chagas disease) was used to identify the risk of embolic stroke. To analyze the IPEC/FIOCRUZ embolic score, patients were divided into 2 groups: those with a score <3 and those with a score ≥3. This cutoff value is often used for the prescription of anticoagulants [18].

For strokes of undetermined etiologies, we used the embolic stroke of undetermined source criteria, which is a clinical construct developed in 2014 to classify strokes of undetermined etiologies including non-lacunar strokes, those associated with absence of extra- or intracranial stenosis ≥50%, absence of major cardioembolic sources to explain embolism, and strokes not attributable to any specific cause [19].

The mRS was determined using information contained in the patient records at admission and at the last consultation in 2016,

if the patient had presented for a last consultation approximately a year prior to the beginning of this study. If not, a Portuguese validated telephone evaluation was used to determine the score [20]. Patients were divided into 2 groups for comparison: those with a score ≤3 and those with a score >3.

Mortality was determined by death occurred during the rehabilitation program or after discharge by the aforementioned telephone contact. Recurrence was determined by 2 neurologists and was defined by the occurrence of a new ictus or history of more than one ictus episodes prior to admission in the rehabilitation program, the condition having a correlation with a new lesion in the neuroimaging.

The CHA_2DS_2-VASc score after the stroke was determined using data from electronic patient records to assess variables (congestive heart failure noted on TTE, age, sex, diabetes, hypertension, history of stroke/TIA/thromboembolism, and vascular disease). Values ≥2 were considered to be associated with a potentially high risk of embolism. This is a score used to determine the risk of embolism in AF and more recently in patients without AF [21–23].

All variables (excluding the recurrence of IS in determining the recurrence outcome) were used to assess recurrence and mortality outcomes. These variables were chosen based on previous evidence demonstrating their correlation with occurrence and/or severity of stroke in patients diagnosed with Chagas disease [9–12, 24–25]. The prevalence of ECG findings commonly observed in those diagnosed with Chagas disease (right bundle block and/or repolarization abnormalities) did not differ between the groups; thus, they were not analyzed.

Statistical Analyses

All statistical analyses were performed using the SPSS IBM® version 23 program. Continuous variables were expressed as means with standard deviation for normally distributed variables and as median and interquartile ranges for non-normally distributed variables. The Students *t* test and the Mann-Whitney test were used for comparisons. Categorical variables were expressed as proportions and compared with the chi-square test or the Fisher exact test. The Kappa coefficient was used as a measure of agreement/concordance between the 2 neurologists who determined the etiological diagnosis.

For evaluating the mortality outcome, we used the previously mentioned baseline variables to test the robustness of any association, using mortality at 14 years as the dependent variable. Additional models applied for data analysis included univariate analysis using the Kaplan-Meier method and the log-rank test. The Cox regression model was used for multivariate analysis of all variables showing a *p* value ≤0.2 using univariate analysis. Survival curves for statistically significant factors were calculated. To determine if independent variables were constantly proportional with time, we used graphics to depict variables (log-minus-log) showing non-crossing curves for statistically significant variables.

A multiple logistic regression analysis model was used to analyze the same variables (excluding recurrence of IS to evaluate recurrence rates). Variables showing a *p* value ≤0.2 were evaluated using multivariate analysis. The OR was used to measure the association derived from logistic regression analysis. *p* values ≤0.05 were considered significant using multivariate analysis for both mortality and recurrence. A confidence interval of 95% was relevant to all analyses.

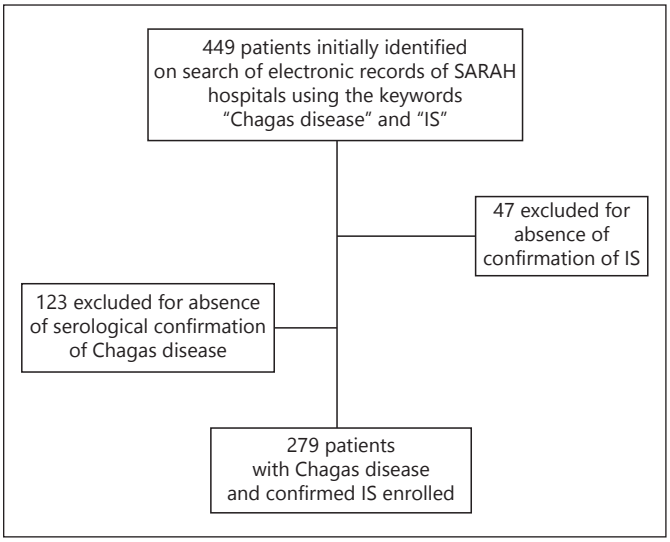

Fig. 1. Flowchart showing patient selection using electronic patient records from the SARAH Network of Rehabilitation Hospitals between 2009 and 2013 . IS, ischemic stroke.

Results

We selected 449 patients from among the SARAH Network database. We excluded 170 patients (123 who did not show serological evidence of Chagas disease and 47 who did not show evidence of IS using neuroimaging). All of them were admitted for stroke rehabilitation and 75% discovered Chagas disease during etiological investigation in our service. We analyzed 279 patients with follow-up until 2016 (mean follow-up 6.1 years; Fig. 1). The average age at stroke onset was 61, mean time from ictus to hospitalization was 3.1 years, and 65% were women. There was a 10% incidence of death in the cohort. Recurrence occurred at a medium time of 1.5 years after stroke. The kappa coefficient was 0.9 (*p* value 0.03, 95% CI 0.77–0.95) with respect to etiological evaluation performed by the 2 neurologists.

A TTE was performed in 100% of patients, an ECG was performed in all, a CT in 54%, an MRI in 38%, and both a CT and MRI in 8%. We investigated approximately 15% of patients who showed a high risk of thrombophilia, and found a positive result in 4% of these patients. We found that the prevalence of cognitive deficit at admission was 33%, bladder dysfunction was 25%, and bowel dysfunction was 19%. We classified 61% of patients as belonging to the embolic stroke of undetermined source category, which corresponds to 85% of patients with undetermined etiology according to the SSS/CCS TOAST. The most common ECG findings were ventricular repolarization

Table 1. Baseline characteristics of all patients and survivors and non-survivors to study the mortality outcome

Baseline characteristics	N = 279	Survivors (*n* = 251)	Non-survivors (*n* = 28)	*p* value
Age, years	60.9	60.5 (12.41)	67.2 (10.94)	0.005
Recurrence	71 (25)	62 (25)	9 (32)	0.391
Hemorrhagic stroke	14 (5)	13 (5)	1 (3)	0.833
Epilepsy	42 (15)	39 (15)	3 (10)	0.481
Hemorrhagic transformation	25 (9)	24 (10)	1 (4)	0.539
Statin use	159 (57)	144 (57)	15 (54)	0.700
Anticoagulant use	49 (17)	47 (18)	2 (7)	0.188
Cognitive deficit	93 (33)	76 (30)	17 (61)	0.020
ESUS	172 (62)	154 (61)	18 (64)	0.762
Bowel dysfunction	53 (19)	40 (16)	13 (46)	<0.000
Bladder dysfunction	72 (26)	58 (23)	14 (50)	0.002
Cardioaortic embolic etiology	150 (54)	134 (53)	16 (57)	0.705
Undetermined etiology	57 (20)	54 (21)	3 (11)	0.179
IPEC\FIOCRUZ score ≥3	61 (22)	57 (23)	4 (14)	0.222
Modified Rankin Scale >3	142 (51)	115 (46)	27 (98)	<0.000
SAH	208 (75)	186 (74)	22 (96)	0.607
Systolic dysfunction	47 (17)	44 (17)	3 (11)	0.269
DM	58 (21)	46 (18)	12 (43)	0.002
AF	41 (15)	36 (14)	5 (18)	0.618
CHA_2DS_2-VASc score	224 (80)	197 (78)	27 (96)	0.024
Gender, Female	182 (65)	161 (64)	21 (75)	0.253
Dyslipidemia	144 (52)	126 (50)	18 (64)	0.157
Smoking history	90 (32)	80 (32)	10 (26)	0.680
Alcoholism	91 (32)	79 (32)	12 (43)	0.223
Obesity	16 (6)	15 (6)	1 (4)	0.604
Antiplatelet drug use	207 (74)	183 (73)	24 (86)	0.142

ESUS, embolic stroke of undetermined source; SAH, systemic arterial hypertension; DM, diabetes mellitus; AF, atrial fibrillation; IPEC\FIOCRUZ, Instituto de pesquisa Evandro Chagas\Fundação Oswaldo Cruz. Values are expressed in *n* (%).

abnormalities (20%) and AF (12%). Primary TTE findings were ventricular diastolic dysfunction (35%) and a normal exam (24%). The use of secondary prophylaxis (anticoagulants or antiplatelet agents) was reported by 91% of patients. Although most strokes were secondary to cardioaortic embolism, most patients did not receive anticoagulant prophylaxis (only 30% reported such use).

Mortality Outcome

Patients were divided into 2 groups: survivors (90%) and non-survivors (10%). A female predominance was observed in both groups (64 vs. 75% respectively). Stroke etiologies showed a similar frequency between the groups, and both groups showed primarily cardioembolic etiology, which was almost identical (52 vs. 53% respectively). Transesophageal echocardiography was not performed in the non-survivors group and Holter monitoring was performed only in 1 patient from this group. Dilated cardiomyopathy frequencies did not differ from both the surviving and non-surviving groups and the recurrence and non-recurrence groups (15 and 16% and 18 and 19% respectively). Thus, these variables were not included in the multivariate analysis. Table 1 summarizes the findings in both groups.

Univariate analysis showed that age at stroke onset, alcoholism, initial mRS, diabetes, cognitive deficit, bladder dysfunction, bowel dysfunction, and a CHA_2DS_2-VASc score ≥2 were significantly associated with the outcome, considering a *p* value <0.1. All other variables showed a similar proportion in both, the survivor and non-survivor groups. When only AF patients were analyzed, the mean CHA_2DS_2-VASc scores did not differ between the groups.

The multivariate Cox regression model showed that only age at stroke onset, alcoholism, diabetes, initial mRS, and bladder dysfunction remained significant (Table 2). Survival graphics showing non-crossing curves with respect to these variables are shown in Figure 2.

Table 2. Assessment of factors associated with mortality

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Antiplatelet drug use	0.36 (0.124–1.045)	0.060		
Cognitive deficit	2.356 (1.096–5.067)	0.028		
Bowel dysfunction	2.846 (1.341–6.042)	0.006		
Bladder dysfunction	2.570 (1.220–5.412)	0.013	2.517 (1.140–5.559)	0.022
Initial mRS >3	28.585 (3.882–210.463)	0.001	20.910 (2.814–155.372)	0.003
Stroke, age, years	1.055 (1.018–1.093)	0.003	1.049 (1.008–1.092)	0.019
DM	3.206 (1.513–6.790)	0.002	3.647 (1.656–8.030)	0.001
Gender, female	2.065 (0.878–4.861)	0.097		
CHA_2DS_2-VASc	5.846 (0.794–43.069)	0.083		
Alcoholism	2.098 (0.985–4.473)	0.055	3.376 (1.496–7.622)	0.003

HR, hazard ratio; mRS, modified Rankin Scale; DM, diabetes mellitus.

Recurrence Outcome

To evaluate the recurrence outcome, we used the same variables that we analyzed for the mortality outcome. We found that (higher) age at stroke onset was a protective factor because every additional year reduces the risk of stroke by 4.4%. Cognitive deficit was also found to be a protective factor. Initial mRS, female sex, and cardioaortic embolic etiology were risk factors for recurrence. While univariate analysis found that anticoagulant use was a significant protective factor, no such result was found using multivariate analysis (Table 3).

Discussion

Multiple studies [5, 6] have described a correlation between IS and Chagas disease. However, the epidemiology, etiology, prognosis, and factors associated with mortality and recurrence of IS in these cases remain poorly understood [2, 11, 23]. Although few studies have evaluated factors associated with cardioembolic etiology [2, 6, 9, 23], to our knowledge, ours is the first study to analyze factors associated with stroke recurrence and mortality outcomes.

Our study found that factors associated with mortality were DM, alcoholism, initial mRS, age at stroke onset, and bladder dysfunction. Diabetes is a classical factor associated with higher mortality in cases presenting with IS, demonstrating a greater than twofold increase in the risk of death, as reported by a previous study [26]. The higher risk of death observed in diabetic patients is attributed to a higher risk of cardiovascular outcomes including myocardial infarction [26].

Alcoholism is a risk for hypertension, AF, cardiomyopathy, and DM, which explains its contribution to a higher mortality rate [27–28]. A study has demonstrated a J-shaped association between alcohol intake and stroke morbidity and mortality [29]. A higher initial mRS could correlate with a greater degree of medical complications, which explains its association with a higher mortality. Older patients showed a higher risk of mortality, probably attributable to a lower life expectancy and possible medical complications.

The prevalence of bladder dysfunction in our study patients did not differ from other stroke populations [30, 31]. There is a higher prevalence of urinary tract infection and bacteriuria, which contribute to bladder dysfunction in stroke patients [31], and medical complications arising from these could explain their association with mortality in this setting. Previous epidemiological studies reveal a 35% prevalence of arrhythmias and heart dysfunction in deaths related to Chagas disease, although these were not necessarily the cause of death [32]. Our study did not find an association between cardiac abnormalities and mortality, suggesting that individual risk factors and functional status post stroke (evaluated by mRS), are more strongly associated with the risk of death compared to organ involvement caused by Chagas disease.

Using multivariate analysis, we found that older age was a protective factor with respect to stroke recurrence. The risk of IS is cumulative in nature. Thus, it seems plausible that older patients show a lower risk of recurrence because the lesser the number of years they live, the lower their risk of recurrence. Another possible explanation is that some very old patients may have died before enter-

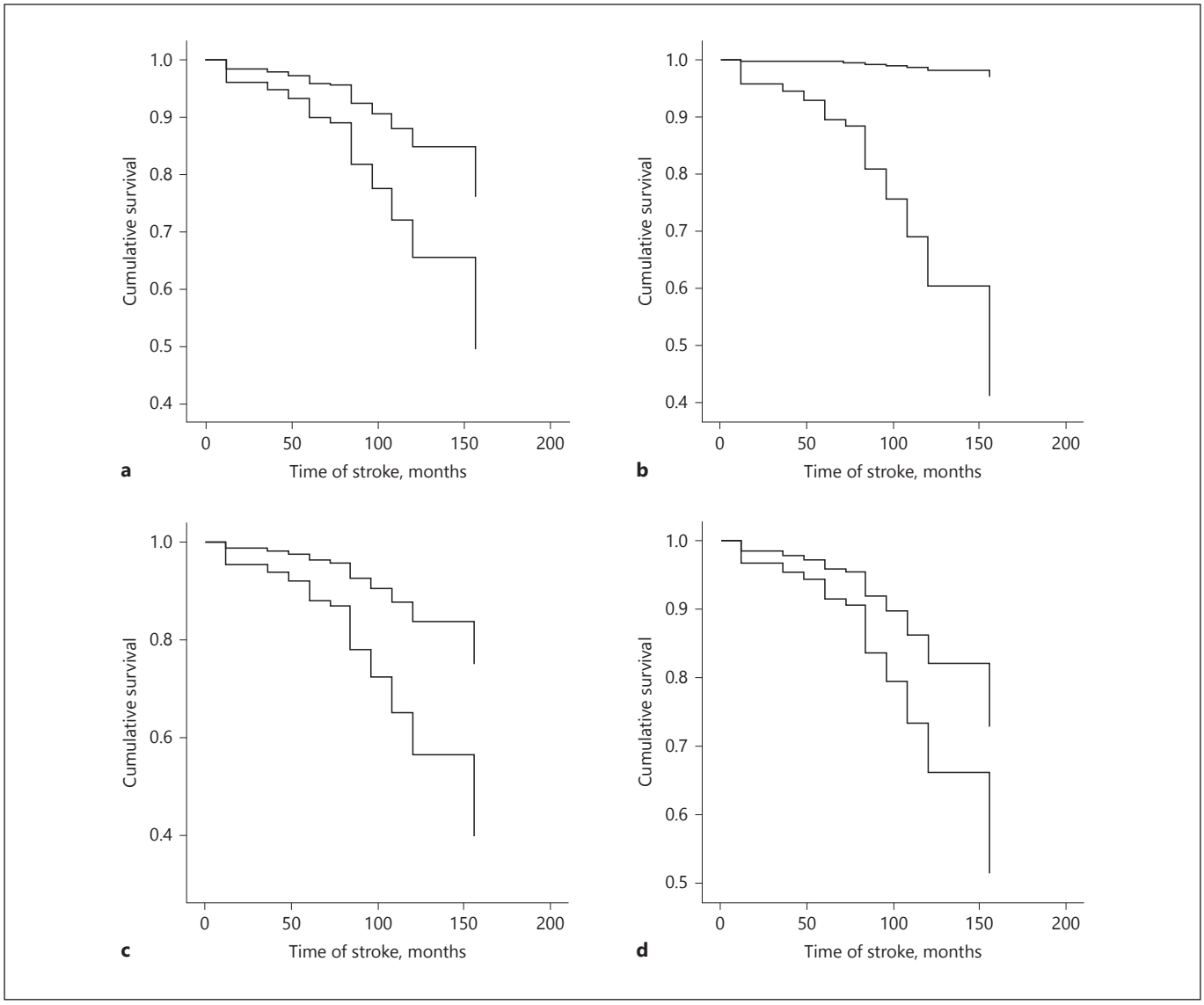

Fig. 2. Cumulative survival curves. **a** Bladder dysfunction curve, the upper curve represents those without this condition with a better survival on follow-up. **b** The initial mRS appears to be a determinant of mortality outcome. Those with scores ≤3 (upper curve) show a better survival rate. **c** Diabetes mellitus (DM), the absence (upper curve) of DM indicates a higher survival rate on follow-up. **d** Presence of alcoholism (lower curve) tends to reduce the survival rate assessed during follow-up.

Table 3. Univariate and multivariate analyses of factors associated with recurrence

	Univariate analysis		Multiple analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Stroke, age, years	0.982 (0.978–0.987)	0.000	0.966 (0.955–0.978)	0.000
Cognitive deficit	0.476 (0.308–0.706)	0.200	0.442 (0.249–0.785)	0.005
Cardioaortic embolic etiology	0.194 (0.122–0.310	0.000	2.473 (1.374–4.451)	0.003
Initial mRS >3	1.885 (0.988–2.888)	0.122	1.846 (1.043–3.265)	0.035
Gender, female	1.546 (0.888–2.555)	0.107	2.732 (1.433–5.205)	0.002
Anticoagulant use	0.345 (0.27–0.464)	0.000		

ing the study leading to a selection bias. In addition to its association with mortality, the initial mRS showed a correlation with recurrence. Patients with greater disability could potentially show a greater degree of medical complications, which could affect the administration of adequate therapy, interfere with physical activities, and therefore, raise the risk of vascular events.

Cardioaortic embolic etiology is a strong risk factor associated with recurrence, showing a 2.4-fold increase in risk. Interestingly, female sex was most significantly associated with the risk of recurrence (OR 2.71). Although the reason for this finding remains unclear, it could possibly relate to a higher vascular risk observed in women [33]. Most patients in our study who theoretically needed anticoagulation did not receive it, which might explain why multivariate analysis did not show this to be a statistically significant protective factor.

Although cognitive deficit was shown to be a protective factor for recurrence, our population did show a lower prevalence of cognitive deficit compared to other cohorts, which could be characterized of a selection bias [34]. Another explanation is that cognitive deficit was associated with mortality when assessed using univariate analysis; therefore, a higher mortality rate in these patients could explain lower recurrence rates.

We observed that a normal TTE exam was common in patients with Chagas disease and IS, which could be a confounding factor in accurately determining the etiology and administering correct secondary prophylaxis. Given the fact that cardioaortic embolic etiology showed a significant association with stroke recurrence, efforts directed toward identifying factors linked to this etiology must be considered, such as greater use of cardiac magnetic resonance and insertable cardiac monitors [35–36]. Interestingly, systolic dysfunction did not correlate with either recurrence or mortality, as would be expected in patients without IS, based on other data [32]. These results also show a lack of correlation between the IPEC\FIOCRUZ embolic score and recurrence rates [17].

Additionally, many strokes may have not been of cardioembolic nature, as there is evidence that chronic infection by CD causes generalized vasculitis, which could be the cause of stroke in many patients [37].

The following are the strengths of our study: (1) Our study was performed in a quaternary multicentric rehabilitation network setting ensuring reasonable etiological investigation and follow-up of patients. Thus, a significant number of patients could be enrolled. (2) Routine use of scales such as the Mini-Mental State Examination and mRS increased the accuracy of these variables. (3) Vector-linked transmission of *Trypanosoma cruzi* is considered eradicated from Brazil since 2006 [38], and prospective studies will be increasingly difficult to perform.

The following are the limitations of our study: (1) Ours was a retrospective study. (2) There was a prolonged time lapse between ictus and hospitalization; therefore, some patients may have shown recurrence or died before enrollment in our study. (3) Data were obtained from medical records, which had not been compiled as research data. (4) Patients presenting with minor or fatal strokes, and therefore not needing or looking for a rehabilitation center were not studied because they did not attend our service, which might have led to a selection bias.

Conclusions

The association between Chagas disease and IS remains poorly understood, especially in an endemic area such as ours, so the correlation could even be incidental. Individual factors such as initial mRS, age at ictus, alcoholism, diabetes, and bladder dysfunction show a significant correlation with increased mortality. At least 3 of these variables are known to respond/are responsive to medical interventions after stroke and could change the natural history of these patients.

We found that female sex, initial mRS, and cardioaortic embolic etiology did correlate with a higher risk of recurrence. Therefore, there is scope to decrease the risk of stroke recurrence in patients with Chagas disease if these variables can be effectively targeted.

There is lack of access of anticoagulant drugs in many areas in Brazil, as well as access to specialized rehabilitation programs, due to social and economic difficulties. Public access should be pursued. Finally, better identification of those patients with a high risk of recurrence and death would be useful for instituting adequate preventive strategies.

Acknowledgments

The authors would like to thank the SARAH Network of Rehabilitation Hospitals for providing the means and time for the realization of this research paper. No financial benefits were acquired by any of the authors.

Disclosure Statement

Authors declare that they have no conflicts of interest to disclose.

References

1 World Health Organization: Making Health Research Work for Poor People. Seventeenth Programme Report UNDP/TDR 2005, vol 17, pp 30–34.
2 Carod-Artal FJ: Policy implications of the changing epidemiology of Chagas disease and stroke. Stroke 2013;44:2356–2360.
3 Bern C, Kjos S, Yabsley MJ, Montgomery SP: Trypanosoma cruzi and Chagas' disease in the United States. Clin Microbiol Rev 2011; 24:655–681.
4 Chagas C: New human tripanozomiase: studies in the morphology and the evolutionary cycle of the Schizotrypanum cruzi n. Gen., n. SP Etiologic Agent of new morbid entity in man. Mem Inst Oswaldo Cruz 1909;1:159–218.
5 Mandell GL, Bennett JE, Dolin R: Principles and Practice of Infectious Disease, ed 7. 2010, vol 277, pp 3481–3487.
6 Pitella JE: Ischemic cerebral changes in the chronic chagasic cardiopathy. Arq Neuropsiquiatr 1984;42:105–115.
7 Oliveira-Filho J, Viana LC, Vieira-de-Melo RM, Faiçal F, Torreão JA, Villar FA, et al: Chagas disease is an independent risk factor for stroke: baseline characteristics of a Chagas disease cohort. Stroke 2005;36:2015–2017.
8 Paixão LC, Ribeiro AL, Valacio RA, Teixeira AL: Chagas disease: independent risk factor for stroke. Stroke 2009;40:3691–3694.
9 Cardoso EN, Macedo FYB, Garcia MN, Garcia DC, Benjo AM, Aguilar D, et al: Chagas cardiomyopathy is associated with higher incidence of stroke: a meta-analysis of observational studies. J Card Fail 2014;20:931–938.
10 Lima-Costa MF, Matos DL, Ribeiro AL: Chagas disease predicts 10-year stroke mortality in community-dwelling elderly: the Bambui cohort study of ageing. Stroke 2010;41:2477–2482.
11 Carod-Artal FJ, Gascon J: Chagas disease and stroke. Lancet Neurol 2010;9:533–542.
12 Andrade JP, Neto JAM, Paola AAV, Vilas-Boas F, Oliveira GMM, Bacal F, et al: Latin American guidelines for the diagnosis and treatment of chagas' heart disease: executive summary. Arq Bras Cardiol 2011;96:434–442.
13 Brucki SM, Nitrini R, Caramelli P, Bertolucci PHF, Okamoto IH: Suggestions for utilization of the mini-mental state examination in Brazil. Arq Neuropsiquiatr 2003;61:777–781.
14 Bonini M, Radanovic M: Cognitive deficits in post stroke aphasia. Arq Neuropsiquiatr 2015;73:840–847.
15 Ay H, Benner T, Arsava EM, Furie KL, Singhaal AB, Jensen MB, et al: A computerized algorithm for etiologic classification of ischemic stroke: the causative classification of stroke system. Stroke 2007;38:2979–2984.
16 Ay H: Causative Classification System for Ischemic Stroke. https://ccs.mgh.harvard.edu/ccs_title.php (accessed from January 15 to May 10, 2016.
17 Montanaro VV, da Silva CM, de Viana Santos CV, Lima MI, Negrão EM, de Freitas GR: Ischemic stroke classification and risk of embolism in patients with Chagas disease. J Neurol 2016;263:2411–2415.
18 Sousa AS, Xavier SS, Freitas GR, Hasslocher-Moreno A: Prevention strategies of cardioembolic ischemic stroke in Chagas' disease. Arq Bras Cardiol 2008;91:280–284.
19 Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnel MJ, et al: Embolic stroke of undetermined source: the case for a new clinical construct. Lancet Neurol 2014; 13:429–438.
20 Baggio JA, Santos-Pontelli TE, Cougo-Pinto PT, Camilo M, Silva NF, Antunes P, Machado L, et al: Validation of a structured interview for telephone assessment of the modified Rankin scale in Brazilian stroke patients. Cerebovasc Dis 2014;38:297–331.
21 Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ: Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263–272.
22 Gy L: The CHA2DS2-VASc score for stroke risk stratification in patients with atrial fibrillation: a brief history. Eur Heart J 2015;36: 2880–2885.
23 Yuan Z, Voss EA, DeFalco FJ, Pan G, Ryan PB, Yannicelli D, et al: Risk prediction for ischemic stroke and transient ischemic attack in patients without atrial fibrillation: a retrospective cohort study. J Stroke Cerebrovasc Dis 2017;26:1721–1731.
24 Carod-Artal FJ, Vargas AP, Melo M, Horan TA: American trypanosomiasis (Chagas' disease): an unrecognised cause of stroke. J Neurol Neurosurg Psychiatry 2003;74:516–518.
25 Carod-Artal FJ, Vargas AP, Horan TA, Nunes LG: Chagasic cardiomyopathy is independently associated with ischemic stroke in Chagas disease. Stroke 2005;36:965–970.
26 Boden-Albala B, Cammack S, Chong J, Wang C, Wright C, Rundek T, et al: Diabetes, fasting glucose levels, and risk of ischemic stroke and vascular events: findings from the Northern Manhattan Study (NOMAS). Diabetes Care 2008;31:1132–1137.
27 Briasoulis A, Agarwal V, Messerli FH: Alcohol consumption and the risk of hypertension in men and women: a systematic review and meta-analysis. J Clin Hypertens (Greenwich) 2012;14:792–798.
28 Kodama S, Saito K, Tanaka S, Horikawa C, Saito A, Heianza Y, et al: Alcohol consumption and risk of atrial fibrillation: a meta-analysis. J Am Coll Cardiol 2011;57:427–436.
29 Zhang C, Qin YY, Chen Q, Jiang H, Chen XZ, Xu CL, et al: Alcohol intake and risk of stroke: a dose-response meta-analysis of prospective studies. Int J Cardiol 2014;174:669–677.
30 Borrie MJ, Campbell AJ, Caradoc-Davies TH, Spears GF: Urinary incontinence after stroke: a prospective study. Age Ageing 1986;15:177–181.
31 Ersoz M, Ulusoy H, Oktar MA, Akyuz M: Urinary tract infection and bacteriurua in stroke patients: frequencies, pathogen microorganisms, and risk factors. Am J Phys Med Rehabil 2007;86:734–741.
32 Martins-Melo FR, Ramos Júnior AN, Alencar CH, Heukelbach J: Multiple causes of death related to Chagas' disease in Brazil, 1999 to 2007. Rev Soc Bras Med Trop 2012;45:591–596.
33 Katsiki N, Mikhailidis DP: Emerging vascular risk factors in women: any differences from men? Curr Med Chem 2015;22:3565–3579.
34 Lima-Costa MF, Castro-Costa E, Uchoa E, Firmo J, Ribeiro AL, Ferri CP, et al: A population-based study of the association between Trypanosoma cruzi infection and cognitive impairment in old age (the Bambuí Study). Neuroepidemiology 2009;32:122–128.
35 Moreira HT, Volpe GJ, Marin-Neto JA, Ambale-Venkatesh B, Nwabuo CC, Trad HS, et al: Evaluation of right ventricular systolic function in chagas disease using cardiac magnetic resonance imaging. Circ Cardiovasc Imaging 2017;10:pii:e005571.
36 Uellendahl M, Siqueira ME, Calado EB, Kalil-Filho R, Sobral D, Ribeiro C, et al: Cardiac magnetic resonance-verified myocardial fibrosis in chagas disease: clinical correlates and risk stratification. Arq Bras Cardiol 2016; 107:460–466.
37 Petkova SB, Huang H, Factor SM, Pestell RG, Bouzahzah B, Jelicks LA, et al: The role of endothelin in the pathogenis of Chagas' disease. Int J Parasitol 2001;31:499.
38 Dias JC: Chagas disease: successes and challenges. Cad Saude Publica 2006;10:2020–2021.