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Schistosomiasis-associated pulmonary arterial hypertension: survival in endemic area in Brazil ☆

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ABSTRACT

Background: The survival of schistosomiasis-associated pulmonary arterial hypertension (Sch-PAH) patients in endemic areas is unknown, but can be estimated using predictive equations.
Methods: We retrospectively analyzed all consecutive patients diagnosed with Sch-PAH referred to the Pronto SocorroCardiologico de Pernambuco between 2004 and 2010 using specific therapy and measured laboratory, diagnostic imaging, and baseline hemodynamic parameters. Observed and predicted survivals according to the National Institutes of Health (NIH) and Pulmonary Hypertension Connection (PHC) registry equations were compared by the Kaplan–Meier method, log-rank test and Cox proportional hazards model.
Results: Sixty-eight patients (47 [69.1%] women) observed for a mean of 3.1 years (range, 7–72 months), median survival was 74 months, and 42 (61.7%) survived. The sex and age distributions were similar for functional class I/II and III/IV patients. Hemodynamic abnormalities were severe: mean right atrial pressure, 12.6 ± 6.2 mmHg; mean pulmonary artery pressure, 60.3 ± 13.69 mmHg; pulmonary vascular resistance, 14.62 ± 7.04 Wood units; and cardiac index, 2.3 ± 0.8 L/min/m^2. The usual idiopathic PAH predictors were not prognostic in Sch-PAH patients. The 1-, 3- and 5-year survival rates were 92.1%, 75.2%, and 50.8%, respectively, and those estimatedby the NIH and PHC registry equations were 68%, 45% and 32% ($p = 0.001$), and 93%, 79% and 68% ($p = 0.340$), respectively.
Conclusions: Sch-PAH patients in endemic areas have severe hemodynamic profiles and reduced long-term survivaldespite treatment. The PHC registry equation may be a useful tool to estimate survival in Sch-PAH.

1. Introduction

Pulmonary arterial hypertension (PAH) is a serious, fatal disease, characterized by an increase in progressive pulmonary vascular resistance (PVR) due to the proliferation and remodeling of small pulmonary arteries, resulting in a rise in pulmonary artery pressure, right-side heart failure and an increase in premature death [1]. Because of multiple factors, PAH can be idiopathic, inherited, or associated with other diseases or clinical conditions [2,3]. Treatment with prostanoids, endothelin receptor antagonists and phosphodiesterase-5 inhibitors has led to significant changes in the clinical and hemodynamic profile, with an impact on quality of life and an uncertain improvement in actual survival rates [4–6]. Predictive models have been developed and validated in idiopathic, hereditary, and anorexigen-associated PAH, but their usefulness in estimating the survival of patients with World Health Organization (WHO) group I PAH of all etiologies is unclear [7].

Schistosomiasis may be the most prevalent cause of PAH worldwide due to its global distribution and, until recently, its underestimated morbidity [8–10]. Recognized by WHO as a neglected

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disease, schistosomiasis is endemic in many developing countries, where poverty and poor basic sanitation result in the population coming in to contact with contaminated water during their daily activities. Such frequent and prolonged contact may be involved in the emergence of more severe disease. Present in 74 countries and concentrated in sub-SaharanAfrica, schistosomiasis may cause an annual loss of between 1.7 and 4.5 million disability-adjusted life years (DALYs). Around 207 million people are infected; over half of them have significant morbidity due to delays in diagnosis and treatment [11,12]. Disease prevalence in nonendemic regions has increased because of migration. These findings highlight the importance of schistosomiasis-associatedPAH (Sch-PAH) and foster studies on the subject [13–15]. In Brazil, data from referral centers in nonendemic regions indicate that up to 30% of PAH cases may be related to schistosomiasis, with a prevalence of Sch-PAH in 4.6% of hepatosplenic PAH patients [16]. Survival rates of inhabitants with Sch-PAH in endemic regions remain unclear. The development of tools for estimating survival may help in the development of guidelines for preventing and controlling the disease. The National Institutes of Health (NIH) registry described the natural history of primary pulmonary hypertensionand proposed an equation for predicting prognosis based on hemodynamic parameters [17]. Recently, however, data from contemporary registries worldwide have shown this equation tobe unsuitable for estimating survival in the modern therapy era [18–23]. In 2010, the Pulmonary Hypertension Connection (PHC) registry suggested an update of this equation based on similar hemodynamic parameters [mean right atrial pressure (mRAP), mean pulmonary arterialpressure (mPAP) and cardiac index (CI)] as being applicable to WHO category I PAH patients (idiopathic, familial, and anorexigen-associated PAH) whose disease fails to respond to calcium channel blockers. The registry reported 1-, 3-, and 5-year survival rates of 84%, 67% and 58%, respectively [24], which are significantly higher than those estimated by the NIH equation in the same population (65%, 43% and 32%, respectively; $p < 0.0001$). We set out to: 1)characterize the survival rate of Sch-PAH patients in endemic areas; 2)determine factors associated with survival; and 3)ascertain whether the PHC registryequation predicts the survival of Sch-PAH patients more accurately than the NIH equation.

2. Methods

2.1. Patient population

Adult men and women (>18 years) diagnosed with Sch-PAH between June 2004 and July 2010 were retrospectively followed. All were treated at the Pronto Socorro Cardiologico de Pernambuco (PROCAPE). All patients gave their informed consent; the study was approved by the Institutional Review Board and Ethics Committee of the PROCAPE-University of Pernambuco hospital (No. 01–2008) in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

PAH was defined as mPAP ≥25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg assessed by right heart catheterization (RHC). The inclusion criteria for Sch-PAH were PAH associated with sonographic findings highly suggestive of schistosomiasis (enlarged left hepatic lobe, periportal fibrosis, or both) and at least one of the two following characteristics: living in or being from a schistosomiasis-endemic region and presence of eggs of *Schistosoma mansoni* on parasitological examination of the stool. Patients were excluded if information on the stage of the disease or contemporary test results were not available, if they had PCWP >15 mmHg, chronic thromboembolic PH or PH associated with lung disease, congenital systemic-pulmonary shunts, portal hypertension, HIV infection, collagen diseases, exposure to or use of appetite suppressants, chronic kidney disease, chronic liver failure, thyroid disease, or left ventricular failure shown on the echocardiogram or RHC. The sources used for selecting cases and obtaining variables of interest were registry and hospital records. Fig. 1 shows the study flow chart.

2.2. Clinical and hemodynamic measures

Baseline evaluation included demographics; medical history; physical examination; biochemical analyses quantified from blood samples collected at enrollment; an echocardiogram to evaluate pulmonary arterial systolic pressure (PASP); a 6-minute walk distance (6MWD) test without encouragement or supplemental oxygen, with the severity of dyspnea stratified according to the Borg scale, as described by the American Thoracic Society [25]; WHO functional class (FC) assessment and RHC to evaluate mRAP; mPAP; pulmonary artery oxygen saturation (PA $SatO_2$); total pulmonary resistance (TPR); PVR; and CI. An acute test response to vasodilator using nitric oxide was performed during RHC. A positive response was defined as a ≥ 10 mmHg reduction in mPAP, with a final value of ≤40 mmHg and a sustained or increased cardiac output [2]. Serum NT-proBNP levels were measured 24 h before RHC. Patients were divided into FC I/II and III/IV groups; the clinical and hemodynamic outcomes were compared.

2.3. Survival

The date of RHC was considered as the beginning of the survival period, the cutoff being July 2010. Death attributed to PAH was considered as the "event". Data from all patients who were alive

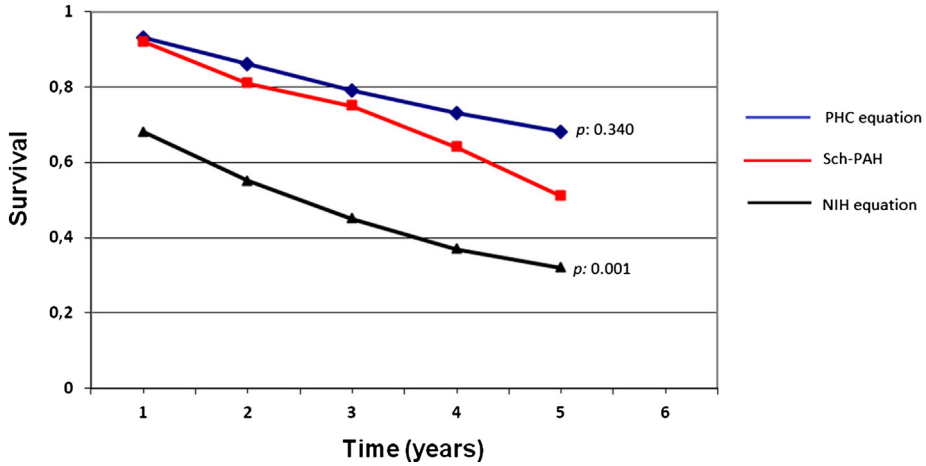

Fig. 1. Survival curves in Sch-PAH and estimated using NIH equation and PHC registry equation.

at the end of the study were finalized at the last date of medical records. For information on the outcome, such as the date and/or cause of death, records of medical files of place of death, usually another hospital belonging to the Single Health System, were also consulted. Clinical events that led to the hospitalization and/or death of the patient were determined. If a patient died from an unknown cause, but had been diagnosed with PAH or had received home care without any information on the existence of other underlying disease in medical records, the death was considered to have resulted from PAH. Patients who died from other causes or who were not submitted to the research protocol because of the severity of their condition were withdrawn from the study. A survival analysis of the overall cohort was performed; results were compared with those estimated by NIH[17] and PHC registry equations [24].

Estimated survival in the group was initially calculated by the NIH equation:

$$P(t) = [H(t)]^{A(xyz)}$$

where P (*t*) is the probability of survival

$$H(t) = 0.88 - 0.14\,t + 0.01\,t^2$$

t is time in years.

$$A(xyz) = e^{(0.007325x + 0.0526y - 0.3235z)}$$

$x = \text{mPAP}, y = \text{mRAP}, z = \text{CI}.$

A new overall survival was calculated using the PHC registry equation developed for nonresponders to calcium channel blockers, using the same hemodynamic variables in the equation above, but with constants readjusted based on exponential regression analysis:

$$P(t) = e^{-A(xyz)t}$$

where $A(x,y,z) = e^{(-1.270 - 0.0148x + 0.0402y - 0.0361z)}$.

Patients with arterial oxygen saturation < 90% were given supplemental oxygen nasally. FC III/IV group patients received digitalis and diuretics when required to treat symptoms of right-sid heart failure. For ethical reasons and in the absence of contraindication, FC II, III, and IV group patients were treated with conventional therapies and sildenafil.

2.4. Statistical analysis

Data were analyzed with Stata, ver.12.0 (StataCorp LP). Descriptive statistics were used to describe patient characteristics. Differences between groups were analyzed by the unpaired Student's *t*-test and summarized as mean ± SD for continuous data. Categorical data are presented as percentages and were analyzed by the χ^2 or Fisher's Exact tests where appropriate. The Kolmogorov–Smirnov test was used for verifying the hypothesis of normality. Univariate and multivariate statistical analysis with logistic regression were used for identifying and estimating risk factors. Kaplan–Meier estimates and Cox proportional hazards models were used for outcome analyses. Odds ratios and 95% confidence intervals were calculated. $P < 0.05$ indicated statistical significance.

3. Results

3.1. Study population

Sixty-eight patients in the registry (mean age, 46.6 ± 12.9 years; 69.1% female) were enrolled. Participants were from rural areas and treated in our tertiary center. During enrollment, 2 patients (2.9%) were classified as WHO FC I, 25 (36.8%) as FC II, 16 (23.5%) as FC III and 25 (36.8%) as FC IV. They were divided into an FC I/II group of 27 patients (39.7%) and an FC III/IV group of 41 patients (60.3%). The age distribution was similar in the two groups; most patients in both groups were women. Sixty percent of FC III/IV group patients were diagnosed in the fourth or fifth decade of life. Baseline clinical and hemodynamic data are shown in Table 1.

Table 1
Baseline clinical and hemodynamic data.

Variable	Functional class		*p*-Value*
	I/II	III/IV	
Population (*n*)	27	41	
Age (yr)	44.0 ± 14.7	48.2 ± 11,4	0.186
Female (%)	16 (59.3)	31 (75.6)	0.153
6MWD (m)	355.5 ± 71.3	168.8 ± 106.3	< 0.001
NT-proBNP (UI)	505 ± 544.1	1684.4 ± 2506.3	0.093
Echocardiogram			
PASP (mmHg)	85.3 ± 26.6	99.0 ± 24.8	0.041
Hemodynamics			
mRAP (mmHg)	12.6 ± 6.4	12.6 ± 6.2	0.992
mPAP (mmHg)	59.2 ± 15.7	60.3 ± 13.9	0.762
TPR (Wood units)	14.71 ± 6.78	18.9 ± 8.0	0.031
PVR (Wood units)	11.1 ± 6.3	14.6 ± 7.0	0.047
CI (L/min/m^2)	2.9 ± 1.0	2.3 ± 0.8	0.025
PA $SatO_2$ (%)	63.7 ± 12.1	58.4 ± 10.5	0.108

CI: cardiac index; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; 6MWD: 6-minute walk distance; PA $SatO_2$: pulmonary artery oxygen saturation; PASP: pulmonary arterial systolic pressure; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance.
* $p < 0.05$ was considered a statistically significant difference.

3.2. Clinical and hemodynamic measures

6MWD and PASP were significantly different in the FC I/II and III/IV groups. However, the NT-proBNP plasma level measured in 43 patients (63.2%) did not significantly differ from one group to the other despite great variability ($p = 0.093$). A baseline echocardiogram was performed in all patients and was available for 62 patients (91.2%). These findings disappeared after diagnosis in five cases; one patient showed no significant tricuspid regurgitation.

RHC was performed in all patients; baseline data revealed severe PAH in both groups. Three patients (4.4%) were lost during follow-up; in five cases (7.3%), patients or the patients' relatives reported the date of RHC and/or the date of death, when needed. FC III/IV patients had significantly higher TPR, PVR and CI values than FC I/II patients. No patient showed a response to the acute vasodilator test.

3.3. Survival analysis

Mean follow-up was 37.2 months (range, 7 months to 7.1 years). The median survival was 74 (interquartile range, 38–85.2) months. The incidence-density was 9.7 deaths per 1000 patients/month. At the end of the study, 42/65 patients who were not lost to observation (61.7%) were alive and 23 (33.8%) had died. Survival rates in FC I/II and III/IV groups were not significantly different (Table 2). The survival rate was significantly higher in patients with higher mPAP (>60 mmHg); no other variable was significantly associated with survival. Mean survival was longer for women than men (60.6 vs. 43.3 months), but the difference was not significant. Similarly, the univariate analysis showed that reduced mPAP increased the risk of death ($p = 0.025$) (Table 3).

For the multivariate analysis, three models were constructed. Model 1 included the variables mRAP, mPAP and CI that were used in the NIH equation; model 2 used two variables from the first model and included age as a variable; and model 3 considered variables that were significant in the univariate analysis.

Table 2
Average survival for each variable evaluated in Sch-PAH patients.

Variable	Average survival (months)	Standard error	95% Confidence interval	*p*-Value*
Sex				
Male	43.3	4.7	34.1–52.6	0.376
Female	60.6	5.0	50.8–70.3	
Age (yr)				
≤ 40	61.6	7.8	46.3–77.0	0.598
41–49	59.7	7.2	45.7–73.8	
≥ 50	45.5	4.3	37.2–53.8	
Functional class				
I/II	49.9	4.2	41.8–58.1	0.836
III/IV	57.8	5.5	47.1–68.5	
NT-proBNP (UI)				
≤ 150	63.3	8.2	47.2–79.5	0.851
>150	51.3	3.5	44.5–58.0	
6MWD (m)				
≤ 332	59.6	5.0	49.8–69.4	0.818
>332	48.7	5.4	38.0–59.3	
PASP (mmHg)				
≤ 90	53.6	8.3	37.4–69.8	0.863
>90	58.8	5.5	48.1–69.5	
mRAP (mmHg)				
≤ 11	60.9	6.1	49.0–72.9	0.800
>11	57.3	6.8	43.9–70.6	
mPAP (mmHg)				
≤ 60	50.3	6.6	37.3–63.3	0.036
>60	68.3	5.2	58.2–78.5	
PA $SatO_2$ (%)				
≤ 60	43.4	4.8	34.0–52.8	0.552
>60	49.7	3.6	42.7–56.8	
PVR (Wood units)				
≤ 12.5	59.8	6.1	47.9–71.7	0.879
>12.5	47.0	4.1	39.0–55.1	
CI ($L/min/m^2$)				
≤ 2.2	42.9	4.6	33.8–52.0	0.197
>2.2	63.6	5.7	52.4–74.8	

CI: cardiac index; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; 6MWD: 6-minute walk distance; PA $SatO_2$: pulmonary artery oxygen saturation; PASP: pulmonary arterial systolic pressure; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance.
* $p < 0.05$ was considered a statistically significant difference.

In model 1, an increase in the risk of death was observed with mPAP reduction ($p = 0.012$). This relationship does not change with increased age (model 2) and emerges as an independent prognostic factor (model 3). Overall Sch-PAH patient survival rates at 1, 3 and 5 years were 92.1%, 75.2% and 50.8%, respectively (Fig. 1). These rates are not significantly different from those predicted by the PHC registry equation (93%, 79% and 68%. respectively; $p = 0.340$). The NIH equation significantly underestimates survival in the present cohort (68%, 45% and 32%, respectively; $p = 0.001$) (Fig. 1).

Table 3
Univariate Cox regression and prognostic variables for the risk of death.

Variable	Hazard ratio	*p*-Value*
Age at diagnosis (increase in risk per decade)	1.20 (0.79–1.80)	0.380
Sex: male	1.51 (0.60–3.80)	0.382
Functional class		
I/II	Reference	
III/IV	1.10 (0.44–2.75)	0.837
6MWD (addition of 50 m)	0.99 (0.84–1.18)	0.987
mRAP (5 mmHg increase)	1.02 (0.71–1.48)	0.901
Mpap (decrease of 1 mmHg)	1.03 (1.005–1.066)	0.025
CI (1 $L/min/m^2$ increase)	0.75 (0.45–1.27)	0.284
PVR (6.25 Wood unit increase)	0.91 (0.624–1.344)	0.654
PA $SatO_2$ (5% reduction)	1.08 (0.898–1.298)	0.412

CI: cardiac index; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; 6MWD: 6-minute walk distance; PA $SatO_2$: pulmonary artery oxygen saturation; PVR: pulmonary vascular resistance.
* $p < 0.05$ was considered a statistically significant difference.

4. Discussion

The PHC registry equation predicted survival in Sch-PAH patients. None of our patients had a positive vasodilatory response. Fernandes et al. reported similar findings [14], although another study suggests vasoreactivity in a highly restricted number of cases [26]. The variables evaluated showed no significant prognostic association in our sample. In agreement with previous studies, the female-to-male ratio was 2.2:1. Registries from France [19], United States [20], and China [21] reported ratios of 1.9:1; 3.3:1 and 2.4:1, respectively. The REVEAL registry reported a ratio of 4.1:1 in idiopathic and associated PAH [27]. We did not observe any statistically significant association between the patient's sex and disease prognosis [18]; women and men did not differ regarding hemodynamic findings. However, female predominance and the higher survival rate in women, albeit not statistically significant, suggest an increased vulnerability to the disease and a worse prognosis in men, even in regions where exposure to the parasite is presumably similar for both sexes. This difference can be highlighted in a larger sample. Women in rural areas could be more exposed to the parasite because they have more contact with contaminated water while performing traditional daily household activities, but they may have decreased susceptibility to the parasite due to some hormonal influence [28]. Estrogen may have a protective effect by improving myocardial contractility or attenuating pulmonary arterial vasoconstriction. However, whether estrogen can prolong the life of women with PAH is still unknown [29,30].

Although schistosomiasis is a globally distributed disease, some epidemiological, pathogenic, physiopathological and clinical features of the disease remain unclear. Approximately 779 million people worldwide are at risk for contamination, of whom 106 million (13.6%) live in areas that are waterlogged or in close proximity to water reservoirs, especially in developing countries, where the disease is endemic. This represents a 10.9% increase compared with the previous estimate [31]. Schistosomiasis is a major public health problem in Brazil, where it is associated with low social development and is spread by frequent contact with contaminated water (an average of 3.2 contacts/person/day) during household chores, leisure activities, and work [32]. Schistosomiasis is the cause of between 7.5% and 25% PAH cases in Brazil. Growing recognition of the problem is emerging in other countries [16,33]. Adequate knowledge of disease development in these patients has medical and social implications when attempting to estimate the impact of the disease on the affected populations.

Schistosomiasis diagnosis in the present study was based on parasitological findings but, as in other series, the absence of parasite eggs does not rule out the diagnosis. Since the study comprised inhabitants of endemic areas, it is probable that periportal fibrosis was a frequent finding compared with other signs of liver and spleen damage. Approximately 4%–8% of schistosomiasis carriers develop the hepatosplenic form of PAH; PH incidence in this population varies from 6.3% to 13.5% [13]. The estimates depend on the diagnostic criteria, populations studied and methods used [16,34–37], in association with the combined effect of the parasite in the host and the latter's immune response to the parasite. The pathogenic mechanism remains unknown.

The determinants of cardiopulmonary involvement in schistosomiasis remain unclear. Initially, the accumulation of eggs, with consequent vascular obstruction and focal arteritis, was emphasized as the most important mechanism [34]. Subsequently, inflammation, vascular remodeling, and plexiform lesions occurring in locations unrelated to angiomatoid injuries were identified as characteristic of schistosomiasis [38,39]. These findings liken schistosomiasis to other etiologies of WHO category 1 PAH, although, in a group of diverse disorders, it is reasonable to assume that prognosis determinants are etiology-specific. A recent meta-analysis pointed to 107 prognostic predictors in PAH patients, but few reflect the prognosis in most etiologies of WHO category 1 PAH; there is no consensus on the best method or combination of methods of assessment [4,6]. Data evaluating these markers specifically in Sch-PAH are scarce [14]. It is well established that building predictive models for rare diseases involves numerous difficulties [40]. An attempt to replace the influence of variables by only three hemodynamic parameters may limit the ability to assess the impact of the disease in the population, with a possible negative effect on the reliability of the prediction.

Studies to assess 6MWD as a surrogate prognostic factor are difficult to compare because of the variability of the analyses used. A meta-analysis [6] reported that one study used a cutoff point of 332 m, another 250 m, yet another 358 m; two used increments of 50 m, and the other three failed to define the unit of analysis. Some authors used univariate analysis, while others reported results only of multivariate analysis. These approaches may be of particular importance in the evaluation of Sch-PAH because inclusion in a specific FC depends on information provided by the patient. Patients in our cohort were from rural areas, relied on their physical capacity to work, and tended not to take account of mild respiratory symptoms or reductions in effort capacity until they became significantly limiting, thereby increasing the time between symptom onset and diagnosis.

Some baseline parameters in Sch-PAH are more severe than those in PAH of other etiologies. Patients in other series walked a mean distance of 231 m [41], whereas in our study the mean distance was 168 m for FC III/IV patients. In our study, the mean PVR was 11.1 and 14.6 Wood units in FC I/II and III/IV patients, respectively; these values are worse than those in Hachulla's scleroderma cohort: 5.3 Wood units in FC II patients and 11.5 Wood units in FC IV patients, a high-risk condition for poorer outcomes between WHO group I PAH etiologies. The mean 6MWD and PVR were 355.8 m and 11.5 Wood units, respectively, in 25 FC II Sch-PAH patients, of whom 22 (88%) had mPAP >35 mmHg and 7 (30%) had CI < 2.0 L/min/m^2. One patient, who died within the first year of follow-up, walked 297 m with a PVR of 24.6 Wood units and a CI of 1.53 L/min/m^2. Thus, as observed in systemic sclerosis-associated PAH, Sch-PAH patients may show a discrepancy between physical performance (assessed by 6MWD and FC) and hemodynamic profile (assessed by RHC) [42]. As noted in cardiopulmonary disease, peripheral changes may favorably affect exercise tolerance and diminish resting hemodynamic abnormalities [43].

In the univariate model, only reduced mPAP remained associated with increased risk; the association persisted even after multivariate analysis, regardless of age, FC, and 6MWD. This paradoxical result has been observed by other authors and has been attributed to a function of the random analysis of variables in which mPAP can achieve a level of significance that is not in fact justified. The utility of mPAP as a prognostic variable is controversial [6], because it reflects only one aspect of pulmonary dynamics. Pulmonary resistance (mPAP/CI) has been suggested as a prognostic variable instead of mPAP alone [44]. Another hypothesis is that mPAP reduction is caused by the decrease in RV systolic function, with a resulting increase in mortality [21].

Our sample included Schistosomiasis patients with established PAH in whom the time of parasitic infection cannot be determined. We believe that it occurs early in the life considering the evolution of liver and lung changes. Frequent contacts with contaminated water favor reinfestations and often the patient does not recognize the evolution of disease that may remain stationary, tolerated or even ignored. The prognosis becomes particularly difficult to determine in Sch-PAH because there are no data on the effects of antiparasite therapy on pulmonary hemodynamics or clinical response. WHO recommended treatment with praziquantel in a single dose, if this drug modifies the severity, symptoms, or survival of Sch-HAP is unknown. Data on the response of Sch-PAH to PAH-specific therapy are also limited [15]. At the time of the study Sildenafil it was the only authorized specific therapy for PAH and, even currently, those drugs don't have uniform distribution in Brazil. Treatment with endothelin receptor antagonists and combined therapy appears promising [45]; the effects of "modern therapy" have not been studied in a specific long-term cohort in this patient population. As in other developing countries, the cost of drugs and the lack of appropriate treatment strategies limit the access of patients to first-line therapies [21].

In our patient cohort, 1-, 2- and 3-year survival rates were 92.1%, 81% and 75.2%, respectively. On the other hand, Fernandes et al. reported survival rates of 95.1%, 95.1% and 85.9%, respectively, for the same intervals in 54 untreated Sch-PAH patients living in a nonendemic region [14]. This difference suggests that, despite specific treatment, Sch-PAH patients in endemic regions have lower survival rates that may be related to prolonged and continuous exposure to the parasite, and prognostic factors related to the environment, parasites, and/or host that have not yet been elucidated [46]. Another possible explanation for this outcome could be an increased susceptibility to infection by *S. mansoni* in some families residing in endemic areas, suggesting that human resistance to the parasite is heterogeneous and related to a single gene [47]. Whether this affects the incidence or severity of Sch-PAH remains unknown.

5. Study limitations

The most important limitations of our study are its observational, uncontrolled nature and the fact that data were collected retrospectively, so that some gaps were unavoidable. The cases in our study can be considered "incident," because inclusion was based on the initial diagnosis of RHC. However, as observed in previous analyses, it is likely that "prevalent" cases influence general survival, resulting in a survival bias in our study. Our data may be conservative estimates of the true prevalence, as they include only patients diagnosed at a single PH reference center.

6. Conclusions

The PHC registry equation accurately predicted survival in Sch-PAH patients, particularly during the first 3 years of follow-up and may be a useful tool to identify patients at increased risk in endemic areas. Factors validated as predictive in WHO group I PAH patients included in this study were not associated with Sch-PAH prognosis. Further studies with larger numbers of patients are needed for comparison with our results and to characterize the prognosis of a chronic, life-threatening disease with a wide geographic distribution in Brazil, especially among disadvantaged inhabitants of endemic areas.

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Declaration of Competing Interest

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