DOI: 10.1111/tmi.13784

RESEARCH ARTICLE

Cost-effectiveness of an exercise-based cardiovascular rehabilitation program in patients with chronic Chagas cardiomyopathy in Brazil: An analysis from the PEACH study

Valeria Alencar Linhares Simões[1] | Fernanda de Souza Nogueira Sardinha Mendes[1] | Alexandre Monken Avellar[1] | Gilberto Marcelo Sperandio da Silva[1] | Fernanda Martins Carneiro[1] | Paula Simplício Silva[1] | Flavia Mazzoli-Rocha[1] | Rudson Santos Silva[1] | Marcelo Carvalho Vieira[1,2] | Celson Júnio do Nascimento Costa[3] | Andrea Silvestre de Sousa[1] | Claudia Maria Valete Rosalino[1] | Patrícia Fernandes da Silva Nobre[4] | Marcelo Teixeira de Holanda[1] | Henrique Silveira Costa[5] | Roberto Magalhães Saraiva[1] | Alejandro Marcel Hasslocher-Moreno[1] | Rodolfo Castro[6,7] | Mauro Felippe Felix Mediano[1,3]

[1]Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

[2]Centre for Cardiology and Exercise, Aloysio de Castro State Institute of Cardiology, Rio de Janeiro, Brazil

[3]Department of Research and Education, National Institute of Cardiology, Rio de Janeiro, Brazil

[4]National Institute Quality Control in Health, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

[5]Department of Physical Therapy, Faculty of Healthy and Biological Sciences, Federal University of Vales do Jequitinhonha e Mucuri (UFVJM), Diamantina, Brazil

[6]Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

[7]Institute of Collective Health, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil

Correspondence
Mauro Felippe Felix Mediano, Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil.
Email: mffmediano@gmail.com

Abstract

Objectives: The present study aimed to perform a cost-effectiveness analysis of an exercise-based cardiovascular rehabilitation (CR) program in patients with chronic Chagas cardiomyopathy (CCC).

Methods: Cost-effectiveness analysis alongside a randomised clinical trial evaluating the effects of a 6-month exercise-based CR program. The intervention group underwent 3 weekly exercise sessions. The variation of peak oxygen consumption (VO_{2peak}) was used as a measurement of clinical outcome. Cost information from all healthcare expenses (examinations, healthcare visits, medication and hospitalisation) were obtained from the medical records in Brazilian reais (R$) and transformed into dollars using the purchasing power parity ($PPP). The longitudinal costs variation was evaluated through linear mixed models, represented by β coefficient, adjusted for the baseline values of the dependent variable. The cost-effectiveness evaluation was determined through an incremental cost-effectiveness ratio using the HEABS package (Stata 15.0).

Results: The intervention group presented higher costs with healthcare visits ($\beta = +3317.3$; $p < 0.001$), hospitalisation ($\beta = +2810.4$; $p = 0.02$) and total cost ($\beta = +6407.9$; $p < 0.001$) after 3 months of follow-up. Costs related to healthcare visits ($\beta = +2455.8$; $p < 0.001$) and total cost ($\beta = +4711.4$; $p < 0.001$) remained higher in the intervention group after 6 months. The CR program showed an incremental cost-effectiveness ratio (ICER) of $PPP 1874.3 for each increase of 1.0 ml kg^{-1} min^{-1} of VO_{2peak}.

Conclusions: The CR program can be considered a cost-effective alternative and should be included as an intervention strategy in the care of patients with CCC.

KEYWORDS
cardiac rehabilitation program, Chagas disease, chronic Chagas cardiomyopathy, cost-effectiveness analysis

Sustainable Development Goal: Good Health and Wellbeing.

INTRODUCTION

Chagas disease (CD) is a neglected tropical disease associated with a high medical and socioeconomic burden that affects about 6 to 8 million individuals worldwide, most of them in Latin America. Recently, migratory movements have also led to an increased number of cases in other world regions, such as North America and Europe [1, 2].

Approximately 30% of the individuals with chronic CD develop the cardiac form, also known as chronic Chagas cardiomyopathy (CCC), which has a worse prognosis than other clinical forms of CD, accounting for high morbidity and mortality rates and high economic impact on the healthcare system [3–5].

Intervention strategies used to treat CCC are similar to those employed for other cardiomyopathies and may include pharmacological treatment, cardiac devices implantation and heart transplantation [5, 6]. Exercise-based cardiovascular rehabilitation (CR) is a low-cost strategy that has been widely advocated for secondary prevention in individuals with different cardiovascular diseases, aiming to reestablish functional capacity, improve health-related quality of life and reduce hospitalisation and mortality [7–9]. In CCC, CR programs seem to improve functional capacity, health-related quality of life and cardiac function in patients with a varied degree of cardiac commitments in comparison to usual care including pharmacological treatment and nutritional counselling [10–12].

Although CR has been postulated as an effective strategy to ameliorate the functional capacity of CCC patients [12], studies on the economic analysis of CR programs in CCC are still scarce. Economic evaluations of healthcare interventions are important to assist healthcare managers and policy-makers on the decision-making process and resources allocation [13]. Cost-effectiveness analysis is the most common economic approach used to compare the costs and the effects between two or more healthcare interventions, resulting in a ratio that expresses the additional cost necessary to achieve an extra unit of clinical benefit, known as incremental cost-effectiveness ratio (ICER). The ratio between the incremental cost and the incremental effect of the interventions is calculated by dividing the difference in the costs by the difference in the effects [14, 15].

Considering increased functional capacity is positively associated with quality of life and that CR programs may improve functional capacity and health-related quality of life of patients with CCC [16], whose treatment costs are usually high in the context of scarce resources, studies evaluating the cost-effectiveness of CR programs designed for CCC patients are required for better allocation of healthcare resources. Therefore, the present study aimed to perform an economic evaluation of a CR program designed for patients with CCC, considering the overall healthcare costs and the cost-effectiveness evaluation.

METHODS

Health economic analysis study design

The present study is a cost-effectiveness analysis alongside a randomised clinical trial protocol (piggyback) that assessed the effect of a CR program in CCC patients—the PEACH study. The detailed methodological description of the PEACH study can be found elsewhere [17]. The study demonstrated an important positive effect of physical exercise on improvement of peak functional capacity, through evaluation of peak oxygen consumption (VO_{2peak}) [12]. All 30 patients included in the PEACH study were included in this cost-effectiveness secondary analysis. The present manuscript followed the CHEERS 2022 recommendations.

Setting and location

The PEACH study included patients of both sexes with a diagnosis of CD confirmed by two serological tests (immunofluorescence and ELISA), regularly followed at the CD ambulatory of the Evandro Chagas National Institute of Infectious Disease from the Oswaldo Cruz Foundation (INI-Fiocruz), Rio de Janeiro, Brazil. The INI-Fiocruz is a referral institution in the diagnosis, treatment and research of infectious and tropical diseases in the Brazilian Unified Health System (SUS) that offers a comprehensive and multidisciplinary health service that includes exams, healthcare visits, dispense of medications and hospitalisation for CD patients and other infectious diseases.

Perspective

The perspective adopted for this cost-effective analysis was the Brazilian public health system (SUS) considered as the provider of healthcare.

Study population

Eligible patients had left ventricular ejection fraction (LVEF) below 45% without (stage B2) or with heart failure (stage C) [2], were clinically stable during the last 3 months (NYHA Functional Class I to III), used their prescribed medications and complied with ambulatory treatment, were not engaged in regular physical activity (≥1× week) in the 3 months prior to the study, and were available to participate in the CR sessions three times a week for a minimum period of 6 months. The study did not include patients with motor abnormalities and/or musculoskeletal injuries that could interfere with performance of the proposed exercises. Patients that presented non-CD cardiomyopathies, had absolute contraindication to physical activities, had cognitive impairment that precluded controlling the intensity of the prescribed exercise, had obstructive or restrictive pulmonary disease, were smokers or pregnant were also excluded.

All participants received explanations on the objectives of the study and agreed to participate, signing a free and informed consent form. The Local Ethics Committee approved this research project under number CAAE 20215519.3.0000.5262. The sample size calculation for the PEACH study was based on the primary outcome considering a VO_{2peak} modification of 2.9 ml kg^{-1} min^{-1} with a standard deviation of 2.0 ml kg^{-1} min^{-1} [18]. Using a power of 90%, a level of significance of 5%, and increasing the sample size by 20% to compensate for possible losses to follow-up or refusals, 30 individuals (15 per group) were deemed necessary to carry out the study.

Intervention

The patients included in the PEACH study were randomised in a 1:1 allocation ratio (intervention and control groups) and were followed during 6 months. The intervention group underwent 3 weekly sessions of physical exercises, including 30 min of aerobic activity comprised of 20 min of strength training for large muscle groups and 10 min of stretching and balance exercises. The intensity of the aerobic exercise was defined according to the heart rate obtained during the maximum progressive cardiopulmonary exercise test (CPET), corresponding to 90–110% of the anaerobic threshold. Blood pressure and heart rate were measured before, during (at 20 min) and at the end of each session, using an aneroid sphygmomanometer and a heart rate monitor (Polar FT1). Individuals with severe arrhythmia were also monitored by electrocardiogram (ECG) during the exercise sessions. All physical activity sessions took place in the morning and under medical supervision.

Comparator

Participants in both intervention and control groups were provided with the same monthly nutrition and pharmaceutical counselling during the study. The nutritional counselling consisted of general instructions on healthy eating habits, focused on reduction of saturated fatty acids and promotion of vitamins and high-fibre carbohydrates consumption. For patients with heart failure, the reduction of sodium and fluids ingestion was also stimulated. Pharmaceutical care comprised general information about the use of medicines, especially regarding dose and compliance. Patients received personalised packages according to the medical prescription, with pills organised by the time and days that should be taken. Patients in the control group were not given a formal physical exercise prescription. Therefore, the only difference between intervention and control groups was the physical exercise training in the intervention group.

Measurement of outcomes

Variation of VO_{2peak} during the follow-up period was used as a measure of effect (clinical outcome) due to its significant prognostic value, whose increase of 1 ml kg^{-1} min^{-1} is associated with an approximate 10% reduction in the risk of death [19]. Moreover, VO_{2peak} is also associated with patient-reported outcomes, including health-related quality of life [16]. VO_{2peak} was measured by CPET on a treadmill (Inbramed, Brazil), using a ramp protocol, being considered the maximum value achieved 60 s before or after the peak workload. All patients performed the CPET at the baseline, after 3 and 6 months of follow-up. The study used the VO2000 gas analyser (MedGraphics, St. Paul, MS) connected to a computerised Ergo PC Elite System (Micromed, Brazil) with sample collection every 10 s. VO_{2peak} was measured at baseline, after 3 and 6 months of follow-up.

Covariates

Demographic characteristics (sex, race and income) were self-reported. At baseline, the body mass index was calculated using the ratio between weight (kg) and squared height (m^2), and the LVEF was calculated using the Simpson method through a bi-dimensional transthoracic echocardiogram.

Measurement and valuation of resources and costs

The study collected information related to healthcare expenses paid for each participant on the 9-month period, considering the 3 months prior to the participation of each patient in the study as the baseline measure, and the information on the 6 subsequent months decomposed into two periods (3 and 6 months), as the follow-up of effect measure during the CR program.

Time horizon and discount rate

The study time horizon was 6 months that is an appropriate time to achieve improvements on VO_{2peak} (REF). Due to the time horizon being <12 months, no discount rate was applied.

Measurement and valuation of resources and costs

A micro-costing approach (activity-based costing method) was used to estimate all direct costs. Data of all healthcare expenses actually paid for each participant were obtained in Brazilian Reais (R$), including exams (laboratory and imaging examinations), healthcare visits (CR sessions, ambulatory and emergency visits), medications and hospitalisation (nonintensive or intensive care unit). Data were extracted from the patients' electronic medical records (Clinical Surveys Information System—SIPEC/INI-Fiocruz), an information system that considers usual care assistance costs in this referral unit (INI-Fiocruz) of the Brazilian public health system. More detailed information of costs can be found in Tables S1–S4.

Currency and conversion

The costs were obtained at 2017 prices and deflated using the IPCA index (that stands for "Broad Consumer Price Index" in Portuguese, the official federal inflation index in Brazil) in national currency. All costs were converted from Brazilian Reais (R$) into dollar currency using purchasing power parity ($PPP) of 2017 ($PPP 1.00 = R$ 2.18) for better comparison with findings of international studies.

Cost-effectiveness analysis

Cost-effectiveness analysis was conducted alongside clinical trial with an intention-to-treat analysis. The analysis used ICER calculated as the ratio between the difference in costs and the difference in effects of the alternatives under evaluation (ICER = Intervention Cost − Control Cost/ Intervention Effect − Control Effect). ICER represents the additional cost for each increased unit of effect under consideration, which was VO_{2peak} in the present study.

The study considered the thresholds of willingness to pay recommended by WHO, whose interventions costing less than the gross domestic product (GDP) per capita are very cost-effective; interventions that cost up to three GDPs per capita are cost-effective; and those exceeding this value are not cost-effective [20]. The study used Brazil's per capita GDP for 2017, that is, R$ 31833.50, equivalent to $PPP 14602.40. The cost-effectiveness analysis was implemented using Stata's HEABS and HEAPBS commands. Cost-effectiveness scatter plot was developed for a bootstrapped dataset with 1000 replications implemented using the primary PEACH study data [21]. Sensitivity analysis was employed to study the effect of individual parameters uncertainty on the Incremental Net Monetary Benefits (INMB).

The statistical analysis was performed using the Stata 15.0. The descriptive analysis consisted of the estimate of medians and interquartile intervals (25–75%). The longitudinal modification of healthcare costs (exams, visits, medications, hospital stays and overall costs) during the period of the study was analysed through a linear mixed model that estimates the rate of change of the dependent variable between the groups over time (intervention vs. control), represented by coefficient β, adjusted for the baseline values of the dependent variable. All measures were considered in the data analysis, regardless of losses of follow-up or participation in CR program sessions, characterising an intention-to-treat analysis. A level of statistical significance of $p \leq 0.05$ was adopted for all analyses.

Approach to engagement with patients

The Fiocruz was the setting of the first discovery of Chagas disease, where patients and the population are involved in scientific dissemination strategies and advocacy, including the clinical trial recruiting and reporting results/discussion with the patients' audience.

RESULTS

Thirty CCC patients were included in the PEACH study. At baseline, the median age was 61 years, with most patients being men (67%), mixed race (46.7%) and incomes below three minimum wages (93.3%). Most were at stage C of CCC (73.0%), with medians of LVEF of 33.5% (IQR 25%–75% 29.0–40.0) and VO_{2peak} of 15.7 ml kg^{-1} min^{-1} (IQR 25%–75% 13.0–19.4). The median of expenses with healthcare visits ($PPP 554.4; IQR 25%–75% 369.6–947.7) represented most of the overall costs ($PPP 1060.9; IQR 25%–75% 606.1–1591.7), followed by expenses with exams ($PPP 264.9; IQR 25%–75% 153.2–421.7) and medications ($PPP 31.1; IQR 25%–75% 15.6–94.3). Two hospitalizations occurred in the 3 months prior to the beginning of the study (a period that was considered as baseline measurement), both involving patients of the control group, representing costs of $PPP 11022.3 and $PPP 8637.4. Table 1 describes the main clinical and demographic characteristics and the healthcare costs of participants at the baseline, stratified according to randomization (intervention and control). In general, no significant differences were observed between the groups for any of the variables investigated, except for a higher value of VO_{2peak} in the intervention group compared to the control group.

During the follow-up period, one patient of the control group died in the period between the 3- and the 6-month visits after a femur fracture and decompensated HF, not performing the last CPET evaluation. Two participants of the exercise group did not attend the exercise training sessions between 3 and 6 months. The attendance of exercise sessions was 80% during the first 3 months and 74% during the entire 6 months of follow-up.

The healthcare costs during the follow-up period are depicted in Table 2. The intervention group presented higher expenses for healthcare visits ($\beta = +3317.3$; $p < 0.001$), hospitalisation ($\beta = +2810.4$; $p = 0.02$) and overall cost ($\beta = +6407.9$; $p < 0.001$) after 3 months of follow-up. Costs of healthcare visits ($\beta = +2455.8$; $p < 0.001$) and overall cost ($\beta = +4711.4$; $p < 0.001$) also remained higher in the intervention group after 6 months of follow-up, without significant differences for the other types of costs. Cost-effectiveness analysis at 6 months of follow-up had an ICER of R$ 4085.9, corresponding to $PPP 1874.30 (Table 3), representing the value spent to increase VO_{2peak} by 1.0 ml kg^{-1} min^{-1}. The cost-effectiveness plot shows that the intervention was more expensive and effective in all bootstrap runs (bootstrapped dataset implemented with

TABLE 1 Baseline clinical and demographic characteristics and healthcare costs ($PPP) of participants in the PEACH clinical trial ($n = 30$)

	Control	Intervention
Variables	**(n = 15)**	**(n = 15)**
Percentage (absolute frequency)		
CCC stage		
B2	27% (4)	27% (4)
C	73% (11)	73% (11)
Sex		
Women	40% (6)	27% (4)
Men	60% (9)	73% (11)
Race		
White	27% (4)	53% (8)
Mixed	53% (8)	40% (6)
Black	13% (2)	7% (1)
Indigenous	7% (1)	0% (0)
Monthly income		
<2 minimum wages	23.3% (8)	60% (9)
2–3 minimum wages	33.3% (5)	40% (6)
>3 minimum wages	13.3% (2)	0% (0)
Median (IQR 25%–75%)		
BMI (kg/m^2)	25.5 (22.8–29.6)	24.8 (20.8–28.5)
LVEF	34 (32–39)	32 (28–41)
VO_{2peak} (ml kg^{-1} min^{-1})	13.3 (12.0–17.7)	17.2 (14.2–22.7)
Age (years)	64 (51–67)	58 (51–63)
Healthcare expenses		
Healthcare visits ($PPP)	669.4 (369.6–985.5)	538.8 (369.6–947.7)
Exams ($PPP)	230.5 (113.3–547.8)	299.4 (153.2–403.0)
Medications ($PPP)	25.6 (7.7–94.3)	34.3 (23.7–105.8)
Hospitalisation ($PPP)	0.0 (0.0–0.0)[a]	0.0 (0.0–0.0)
Overall cost ($PPP)	1145.7 (606.1–1589.8)	976.1 (574.5–1589.4)

Abbreviations: BMI, body mass index; CCC, chronic Chagas cardiomyopathy; IQR, interquartile interval; LVEF, left ventricular ejection fraction; VO_{2peak}, peak oxygen consumption.

[a]Two patients were hospitalised at the baseline of the control group, with costs of $PPP 11022.29 and $PPP 8637.43.

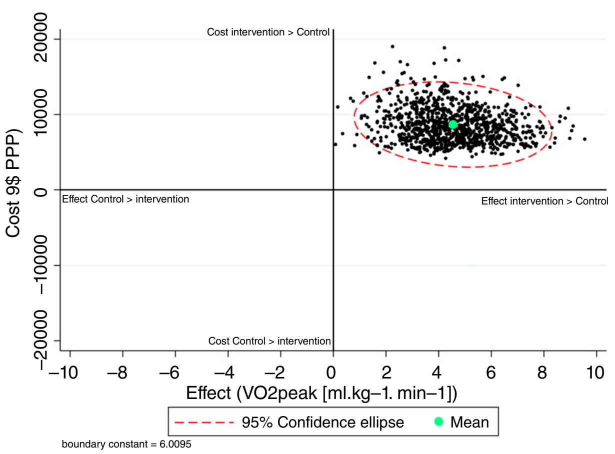

FIGURE 1 The plot of cost-effectiveness bootstrapped dataset (1000 replications) with 95% confidence ellipse and mean.

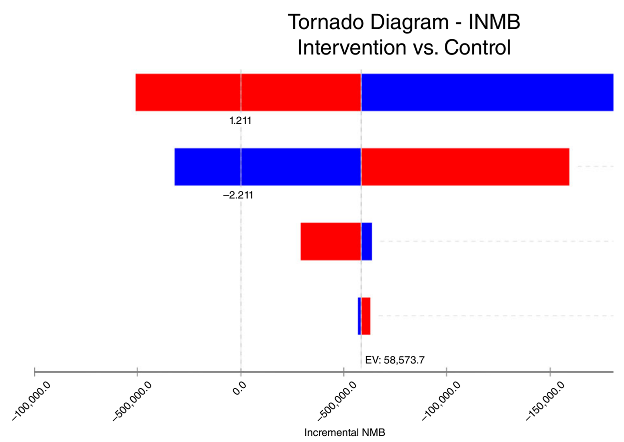

FIGURE 2 Tornado diagram presenting the impact of parameters on the incremental net monetary benefits (INMB).

TABLE 2 Median (interquartile range) and rate of change over time (beta coefficient) for the variables related to healthcare costs ($PPP) during the follow-up period of the PEACH study

Variables	3rd month Median (IQR 25%–75%)	3rd month β	3rd month p value	6th month Median (IQR 25%–75%)	6th month β	6th month p value
Healthcare visits						
Control ($n = 15$)	739.2 (646.7–989.5)	+3317.3	<0.001	958.7 (462.0–1238.2)	+2455.8	<0.001
Intervention ($n = 15$)	4446.7 (3800.2–5014.0)			3140.3 (2045.6–5278.3)		
Exams						
Control ($n = 15$)	578.8 (262.7–896.2)	+225.0	0.14	529.3 (328.4–746.9)	+119.4	0.43
Intervention ($n = 15$)	711.2 (410.9–1037.2)			405.1 (263.6–847.1)		
Medications						
Control ($n = 15$)	4.3 (0.2–109.5)	+55.3	0.62	13.1 (0–64.5)	+44.7	0.69
Intervention ($n = 15$)	18.6 (8.9–144.5)			27.2 (8.3–38.2)		
Hospitalisation						
Control ($n = 15$)	0.0 (0.0–0.0)	+2810.4	0.02	0.0 (0.0–0.0)	+2091.5	0.08
Intervention ($n = 15$)	0.0 (0.0–0.0)[a]			0.0 (0.0–0.0)[b]		
Overall cost						
Control ($n = 15$)	1305.3 (853.1–1918.7)	+6407.9	<0.001	1558.8 (997.1–1991.7)	+4711.4	<0.001
Intervention ($n = 15$)	5367.5 (4848.5–6347.1)			3511.5 (–6319.0)		

Abbreviations: β, mixed linear model coefficient (time vs. group) adjusted for the baseline values (intervention vs. control); IQR, interquartile range.
[a]One patient was hospitalised at time 3 in the intervention group, at a cost of $PPP 22496.33.
[b]One patient was hospitalised at time 6 in the intervention group, at a cost of $PPP 11713.07.

TABLE 3 Cost-effectiveness evaluation at 6 months of follow-up in the PEACH study

	Overall cost (PPP$) Minimum	Overall cost (PPP$) Maximum	Overall cost (PPP$) Average	Total effect (ml kg^{-1} min^{-1}) Minimum	Total effect (ml kg^{-1} min^{-1}) Maximum	Total effect (ml kg^{-1} min^{-1}) Average	Incremental cost (PPP$)	Incremental effectiveness (ml kg^{-1} min^{-1})	ICER (PPP$)
Control ($n = 15$)	1333.4	7556.9	3031.3	−12.4	+4.7	−2.8	+8597.3	+4.6	1874.3
Intervention[a] ($n = 14$)	6366.9	41176.7	11628.6	−4.4	+8.7	+1.8			

[a]One patient was excluded for not having VO_{2peak} at 6 months of follow-up.

1000 replications of the PEACH study data). The estimated probability of cost-effectiveness was 99.5%. A 95% confidence ellipse and mean were also indicated in the scatter plot (Figure 1). The Tornado diagram presents a set of one-way sensitivity analyses. The parameters with higher impact on the INMB were the effectiveness of the control group or the standard of care (SoC), followed by the effectiveness of the CR intervention (Figure 2).

DISCUSSION

CR programs have been widely recommended as an adjuvant in the treatment of numerous cardiovascular diseases, including CCC [22–24]. In a pioneer study, Lima et al. [10] conducted a randomised clinical trial aiming to evaluate the effects of a physical exercise program in 40 patients with CCC. After 3 months of follow-up, patients who performed physical exercise improved their functional capacity, clinical symptoms and health-related quality of life when compared with those who only received usual care. These results were confirmed by later studies performed by our group that showed that a CR program with physical exercises can bring benefits for different health parameters in patients with CCC, including improvement of cardiorespiratory capacity, microcirculatory function and health-related quality of life, with stabilisation of inflammatory markers [12, 25, 26].

However, despite the acknowledged benefits, CR is still an underused intervention strategy worldwide, with a participation rate of around 30% for eligible patients in developed countries and around 15% in Brazil [27]. The low percentage of participation in CR programs can be explained by low rates of medical referral and by the unavailability of places that offer this type of treatment, especially in public health services [28, 29]. The low availability of specialised CR services, especially in Brazil, is associated with a scarcity of health resources; therefore, cost-effectiveness studies aiming to determine the feasibility of implementation of CR programs in the public health system are necessary [30].

The cost-effectiveness of CR programs with physical exercises has been the subject of some studies in the literature. Shierlds et al. [31] conducted a systematic review including 19 works, in which most of them showed that CR programs were more cost-effective when compared with intervention strategies without CR, presenting ICERs ranging from US$ 1065 to US$ 71755 per quality-adjusted life year (QALY). In another study, Driscoll [32] made a cost-effectiveness evaluation of CR programs in Australia, using their national database of health system information. The study observed an excellent cost-effectiveness ratio for CR programs (ICER US$ 6096 by QALY), reinforcing the need for more investments in the implementation of new CR centres with the goal of increasing participation rates, which are usually low. In this way, a Chilean study evaluating the cost-effectiveness of three different models of CR programs compared with the conventional treatment observed that regardless of the model of CR employed, all models of CR program were highly cost-effective when compared with conventional treatment. Therefore, the inclusion of CR programs should be recommended as an important secondary prevention strategy for cardiovascular diseases [33].

However, most cost-effectiveness studies were conducted in countries with high per capita income, making it harder to extrapolate results for other realities where health resources are scarce. In Brazil, the incorporation of CR programs into the conventional treatment of patients with heart failure has proven to be cost-effective, resulting in a cost-effectiveness ratio of $PPP 26,462 by QALY [34]. Therefore, government actions to implement such CR programs on a large scale are imperative [35]. In the case of CCC, a neglected disease that affects mostly individuals belonging to low social classes whose scarcity of health resources is even more pronounced, no previous studies were identified evaluating the cost-effectiveness of CR programs as a treatment strategy for CCC. In this context, the identification of cost-effective strategies can provide health managers with important information regarding the determination of priorities for the application of public resources [36].

In the present study, we observed an increase in the overall costs during the follow-up period, influenced mainly by higher costs with healthcare visits (throughout the follow-up period) and hospitalisation (in the first 3 months only). The increase in costs with healthcare visits was expected, as the CR program sessions demanded specialised care with physicians, physical therapists, physical education instructors and nursing professionals three times a week. The increase in hospitalisation costs can be explained by a closer clinical follow-up to patients during the CR sessions, facilitating the identification of eventual clinical decompensations of CCC.

The CR program with physical exercise generated an incremental cost of approximately $PPP 1800 for each increase of one unit of VO_{2peak}, showing an excellent cost-effectiveness ratio taking into account the threshold of willingness to pay considered in Brazil, in which interventions that cost up to one GDP per capita ($PPP 14602.5) are considered very cost-effective [20].

The willingness-to-pay (WTP) threshold is important for the evaluation of a new intervention or technology, representing the value needed to pay for an additional health gain. In the absence of a consisted threshold, countries that do not have an explicit definition usually use the WHO recommendation of 1 to 3 times the GDP per capita of the country [15]. Considering that Brazil still does not have an explicit WTP we have decided to follow the WHO recommendation, even considering that this approach would be more appropriate for analyses using disability-adjusted life years (DALY). We acknowledge that this approach results in limitations, which must be considered in the interpretation of findings.

In the present study, the lack of information on measures traditionally used in cost-effectiveness analysis studies (QALY or DALY) to calculate the ICER [37] can be considered a limitation. On the other hand, the use of VO_{2peak} as a measure of effect is clinically relevant due to its important association to mortality in different populations, including patients with CCC [19, 38]. Another potential limitation is that the results obtained reflect the context of a clinical trial with controlled conditions, limiting the generalisation of the results (external validity). Sensitivity analysis showed that the effectiveness of the control group standard of care intervention, followed by the effectiveness of the CR intervention were the parameters with higher impact on the INMB results. Therefore, the uncertainty of these parameters can modify the study results. Moreover, costs information was limited to that incurred at INI-Fiocruz. However, as INI-Fiocruz offers a comprehensive healthcare service, patients followed in its cohort have at their disposal all health services necessary for their clinical follow-up, except for surgical procedures. Therefore, we believe that the cost estimates are valid for services with similar characteristics. Finally, another important issue was that sample size was calculated only for the main clinical outcome (VO_{2peak} modification), with no guarantee of a sufficient sample size to cost-effectiveness analysis. Thus, future studies considering sample size calculations for cost-effectiveness analysis are necessary to confirm the results obtained in the present study.

To conclude, the CR program can be considered a cost-effective alternative in the care of patients with CCC. Studies evaluating the cost-effectiveness over a longer period, as well as those evaluating the budget impact for the incorporation of this intervention strategy in other scenarios are necessary. Due to their clinical benefits and excellent cost-effectiveness ratio, CR programs should be included as part of healthcare provided to patients with CCC in secondary prevention.

ACKNOWLEDGEMENT

The authors thank the Evandro Chagas National Institute of Infectious Diseases and the National Institute of Cardiology for their clinical and logistic support.

REFERENCES

1. PAHO. PAHO issues new guide for diagnosis and treatment of Chagas disease. Anguilla: Organization PAH; 2019.
2. Dias JC, Ramos AN Jr, Gontijo ED, Luquetti A, Shikanai-Yasuda MA, Coura JR, et al. Towards control of Chagas disease: the contribution of the new Brazilian consensus. Rev Soc Bras Med Trop. 2016;49-(Suppl 1):3–60.
3. Lee BY, Bacon KM, Bottazzi ME, Hotez PJ. Global economic burden of Chagas disease: a computational simulation model. Lancet Infect Dis. 2013;13(4):342–8.
4. da Nobrega AA, de Araujo WN, Vasconcelos AMN. Mortality due to Chagas disease in Brazil according to a specific cause. Am J Trop Med Hyg. 2014;91(3):528–33.
5. Perez-Molina JA, Molina I. Chagas disease. Lancet. 2018;391(10115): 82–94.
6. Nunes MCP, Beaton A, Acquatella H, Bern C, Bolger AF, Echeverría LE, et al. Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American Heart Association. Circulation. 2018;138(12): e169–209.
7. Ambrosetti M, Abreu A, Corra U, Davos CH, Hansen D, Frederix I, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the secondary prevention and rehabilitation section of the European Association of Preventive Cardiology. Eur J Prev Cardiol. 2020;28:460–95.
8. Carvalho T, Milani M, Ferraz AS, Silveira ADD, Herdy AH, Hossri CAC, et al. Brazilian Cardiovascular Rehabilitation Guideline: 2020. Arq Bras Cardiol. 2020;114(5):943–87.
9. Eijsvogels TMH, Maessen MFH, Bakker EA, Meindersma EP, van Gorp N, Pijnenburg N, et al. Association of cardiac rehabilitation with all-cause mortality among patients with cardiovascular disease in The Netherlands. JAMA Netw Open. 2020;3(7):e2011686.
10. Lima MMO, Rocha MOC, Nunes MCP, Sousa L, Costa HS, Alencar MCN, et al. A randomized trial of the effects of exercise training in Chagas cardiomyopathy. Eur J Heart Fail. 2010;12(8): 866–73.
11. Mediano MFF, Mendes FSNS, Pinto VLM, Silva GMS, Silva PS, Carneiro FM, et al. Cardiac rehabilitation program in patients with Chagas heart failure: a single-arm pilot study. Rev Soc Bras Med Trop. 2016;49(3):319–28.
12. de Souza Nogueira Sardinha Mendes F, MFF M, de Castro e SFC, da Silva PS, Carneiro FM, de Holanda MT, et al. Effect of physical exercise training in patients with Chagas heart disease (from the PEACH STUDY). Am J Cardiol. 2020;125(9):1413–20.
13. Rabarison KM, Bish CL, Massoudi MS, Giles WH. Economic evaluation enhances public health decision making. Front Public Health. 2015;3:164.
14. Bambha K, Kim WR. Cost-effectiveness analysis and incremental cost-effectiveness ratios: uses and pitfalls. Eur J Gastroenterol Hepatol. 2004;16(6):519–26.
15. Vanni T, Luz PM, Ribeiro RA, Novaes HM, Polanczyk CA. Economic evaluation in health: applications in infectious diseases. Cad Saude Publica. 2009;25(12):2543–52.
16. Almeida ILGI, Oliveira LFL, Figueiredo PHS, Oliveira RDB, Damasceno TR, Silva WT, et al. The health-related quality of life in patients with Chagas disease: the state of the art. Rev Soc Bras Med Trop. 2022;55:e0657.
17. Mendes FSNS, Sousa AS, Souza FCCC, Pinto VLM, Silva PS, Saraiva RM, et al. Effect of physical exercise training in patients with Chagas heart disease: study protocol for a randomized controlled trial (PEACH study). Trials. 2016;17(1):433.
18. Freyssin C, Verkindt C, Prieur F, Benaich P, Maunier S, Blanc P. Cardiac rehabilitation in chronic heart failure: effect of an 8-week, high-intensity interval training versus continuous training. Arch Phys Med Rehabil. 2012;93(8):1359–64.
19. Laukkanen JA, Zaccardi F, Khan H, Kurl S, Jae SY, Rauramaa R. Long-term change in cardiorespiratory fitness and all-cause mortality. Mayo Clin Proc. 2016;91(9):1183–8.
20. Soarez PC, Novaes HMD. Cost-effectiveness thresholds and the Brazilian unified National Health System. Cad Saude Publica. 2017; 33(4):e00040717.
21. Gallacher D, Achana F. Assessing the health economic agreement of different data sources. Stata J. 2018;18(1):223–33.
22. Bozkurt B, Fonarow GC, Goldberg LR, Guglin M, Josephson RA, Forman DE, et al. Cardiac rehabilitation for patients with heart failure: JACC expert panel. J Am Coll Cardiol. 2021;77(11): 1454–69.
23. Mamataz T, Uddin J, Ibn Alam S, Taylor RS, Pakosh M, Grace SL, et al. Effects of cardiac rehabilitation in low-and middle-income countries: a systematic review and meta-analysis of randomised controlled trials. Prog Cardiovasc Dis. 2021;70:119–74.
24. PAHO. Chronic care for neglected infectious diseases: leprosy/Hansen's disease, lymphatic Filariasis, trachoma, and Chagas disease. Washington, D.C.: PAHO; 2021.
25. Mediano MFF, Mendes FSNS, Pinto VLM, Silva PS, Hasslocher-Moreno AM, Sousa AS. Reassessment of quality of life domains in patients with compensated Chagas heart failure after participating in a cardiac rehabilitation program. Rev Soc Bras Med Trop. 2017;50(3): 404–7.
26. Rodrigues Junior LF, Mendes F, Pinto VLM, da Silva PS, da Silva GM, Pinheiro RO, et al. A cardiac rehabilitation exercise program potentially inhibits progressive inflammation in patients with severe Chagas cardiomyopathy: A pilot single-arm clinical trial. J Res Med Sci. 2020; 25:18.
27. de Melo Ghisi GL, Oh P, Benetti M, Grace SL. Barriers to cardiac rehabilitation use in Canada versus Brazil. J Cardiopulm Rehabil Prev. 2013;33(3):173–9.
28. Cortes-Bergoderi M, Lopez-Jimenez F, Herdy AH, Zeballos C, Anchique C, Santibanez C, et al. Availability and characteristics of cardiovascular rehabilitation programs in South America. J Cardiopulm Rehabil Prev. 2013;33(1):33–41.
29. Britto RR, Supervia M, Turk-Adawi K, Chaves G, Pesah E, Lopez-Jimenez F, et al. Cardiac rehabilitation availability and delivery in Brazil: a comparison to other upper middle-income countries. Braz J Phys Ther. 2020;24(2):167–76.
30. Servio TC, Britto RR, de Melo Ghisi GL, da Silva LP, Silva LDN, Lima MMO, et al. Barriers to cardiac rehabilitation delivery in a low-resource setting from the perspective of healthcare administrators, rehabilitation providers, and cardiac patients. BMC Health Serv Res. 2019;19(1):615.
31. Shields GE, Wells A, Doherty P, Heagerty A, Buck D, Davies LM. Cost-effectiveness of cardiac rehabilitation: a systematic review. Heart. 2018;104(17):1403–10.
32. Driscoll A, Hinde S, Harrison A, Bojke L, Doherty P. Estimating the health loss due to poor engagement with cardiac rehabilitation in Australia. Int J Cardiol. 2020;317:7–12.
33. Seron P, Gaete M, Oliveros MJ, Roman C, Lanas F, Velasquez M, et al. Cost-effectiveness of exercise-based cardiac rehabilitation in Chilean patients surviving acute coronary syndrome. J Cardiopulm Rehabil Prev. 2019;39(3):168–74.
34. Kuhr EM, Ribeiro RA, Rohde LE, Polanczyk CA. Cost-effectiveness of supervised exercise therapy in heart failure patients. Value Health. 2011;14(5 Suppl 1):S100–7.
35. Borghi-Silva A, Mendes RG, Trimer R, Cipriano G. Current trends in reducing cardiovascular disease risk factors from around the world: focus on cardiac rehabilitation in Brazil. Prog Cardiovasc Dis. 2014; 56(5):536–42.
36. Alonso-Padilla J, Cortes-Serra N, Pinazo MJ, Bottazzi ME, Abril M, Barreira F, et al. Strategies to enhance access to diagnosis and

treatment for Chagas disease patients in Latin America. Expert Rev Anti Infect Ther. 2019;17(3):145–57.
37. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull. 2010;96:5–21.
38. Costa HS, Lima MMO, Figueiredo PHS, Martinelli PM, Camargos ER, Chaves AT, et al. Prognostic value of serum brain-derived neurotrophic factor levels in patients with Chagas cardiomyopathy. Mem Inst Oswaldo Cruz. 2018;113(10):e180224.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Simões VAL, Mendes FdSNS, Avellar AM, da Silva GMS, Carneiro FM, Silva PS, et al. Cost-effectiveness of an exercise-based cardiovascular rehabilitation program in patients with chronic Chagas cardiomyopathy in Brazil: An analysis from the PEACH study. Trop Med Int Health. 2022. https://doi.org/10.1111/tmi.13784