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Patient-Reported Outcomes

The Association Between Physical Performance and Health-Related Quality of Life Based on the EQ-5D-3L Questionnaire in Patients With Chagas Disease

Wylisson Marcelo Almeida Lins, MS, Bernardo Rangel Tura, PhD, Daniel Arthur Kasal, PhD

ABSTRACT

Objectives: Chagas disease (CD) is a chronic disease to millions worldwide, and many patients develop heart disease. In addition, they are part of an aging population. These characteristics can be associated with a reduction in physical performance and health-related quality of life (HRQoL). This study evaluated HRQoL, and the relationship between physical performance and HRQoL in patients with chronic CD.

Methods: We used the 3-level version of EuroQol 5-dimensional questionnaire (EQ-5D-3L), with the visual analog scale (VAS). Physical performance was measured with 30-s chair-stand test (30sCST) and timed up and go test (TUGT).

Results: Sixty-three patients were evaluated. The majority were women (68.2%) aged 67.7 ± 9.7 years. Overall EQ-5D-3L utility index was 0.65 ± 0.28, and VAS score was 68.4 ± 25.1. Most patients with intermediate and high performance in 30sCST referred no problems in the domains "mobility," "usual activities," and "pain/feeling ill" ($P < .001$, $P = .01$, and $P = .025$, respectively). In a similar way, most patients with intermediate and high performance in TUGT referred no problems in "mobility" ($P < .0001$) and "usual activities" ($P = .001$). Higher performance in both tests was associated with higher overall EQ-5D-3L utility and VAS scores. HRQoL measured by EQ-5D-3L was associated with physical status in a cohort of patients with chronic CD. The results underscore the contribution of physical performance, measured by 2 inexpensive and safe physical tests, to HRQoL in these patients.

Conclusion: Strategies aiming the improvement of HRQoL in patients with CD may focus on mobility skills and force. Future studies evaluating interventions in physical performance should be a priority in these patients.

Keywords: 30-s chair-stand test, Chagas disease, health-related quality of life, timed up and go test.

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Introduction

Chagas disease (CD) is a chronic infectious condition caused by the protozoan *Trypanosoma cruzi*, which affects approximately 6 million individuals worldwide.[1] In the chronic stage, nearly 30% of patients with CD develop the cardiac form,[2] characterized by heart failure (HF), arrhythmias, and stroke. It is considered by the World Health Organization as a neglected disease,[3] with the majority of patients living in Latin America.[4]

CD represents a significant economic burden to Latin America, where the highest annual healthcare costs are in Brazil (with a mean cost of $129 211 209).[5] Studies of health economics aim to provide strategic data to policymakers, assisting in the incorporation of new technologies, with a financially sustainable approach. One method used for this purpose is cost-utility analysis. In this system, the incremental cost of an intervention is compared with incremental health improvements, expressed in the unit of quality-adjusted life years (QALYs).[6] The 3-level version of the EuroQol 5-dimensional questionnaire (EQ-5D-3L) is one of the most widely used generic measurements of health-related quality of life (HRQoL), for the assessment of benefits in economic evaluations. This questionnaire provides a utility factor between 1 and 0, which is used to calculate the QALY value for a given health intervention.[7]

Previous studies have evaluated HRQoL in patients with CD. However, most of them used generic measurements, including the Medical Outcomes Study 36-item Short Form (SF-36),[8,9] which do not translate directly into a utility index. In this context, an assessment of the EQ-5D-3L profile, which provides utility, enables improved economic analysis for resource utilization in the care of patients with chronic CD.

In a previous study with EQ-5D-3L valuation with general Brazilian population, mobility problems were associated with the highest decrements in utility values,[10] underscoring the importance of physical performance to HRQoL in the region. Interventions aiming to improve physical performance have previously proved cost-effective for society in heart disease, including ischemic heart disease[11] and after heart valve surgery.[12]

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Accordingly, it would be useful to describe the association between physical performance and utility in a cohort of patients with chronic CD.

Patient health status consists in a multidimensional assessment, comprising the evaluation of symptoms, functional limitation, and HRQoL.[13] An increased awareness of patient-centered outcomes has been observed in HF clinics, with progressive inclusion of these parameters in routine ambulatory care.[14] There are few studies evaluating simultaneously HRQoL and physical functional status in patients with CD.[15,16] Accordingly, the present study aimed to evaluate concurrently the main cardiovascular symptoms, HRQoL by a utility-generating score, and physical performance in a cohort of patients with chronic CD.

Our study had 2 research questions: (1) what is the EQ-5D-3L utility profile of a cohort of patients with chronic CD; (2) is physical performance level associated with EQ-5D-3L utility values?

Methods

Study Design and Patients

This was a cross-sectional study of 63 consecutive adult patients treated at the CD outpatient clinic, at the National Institute of Cardiology, Brazil. Eligibility criteria were age ≥18 years, with 2 serologies (with different methods) positive for CD.[17] The exclusion criteria were decompensated HF (New York Heart Association functional class IV or impairment in functional class during the previous month), and incapacity to communicate or to perform the physical performance tests. The study was approved by the Local Ethics Research Committee under protocol #CAAE 47563415.9.0000.5272, and informed consent was obtained from all participants.

Clinical data, including comorbidities and left ventricular ejection fraction (LVEF, measured with transthoracic echocardiogram using the Teicholz method), were obtained from medical records. Symptom severity was evaluated with the New York Heart Association functional class.[18] Demographic information was obtained through interview, at the day of the medical visit. All data were considered when collected in the previous 12 months before recruitment.

HRQoL

The evaluation of HRQoL was performed with the EQ-5D-3L questionnaire, using the visual analog scale (VAS). The EQ-5D-3L comprises 5 dimensions: "mobility," "self-care," "usual activities," "pain/discomfort," and "anxiety/depression." Each dimension is categorized as causing no problems, moderate problems, or severe problems. The scores on the 5 dimensions can be expressed as an overall utility index (range, 0-1). Scores based on the VAS can range from 0 (worse state) to 100 (best state).[19] The EQ-5D-3L is validated for the use in Portuguese for Brazilian individuals.[20] The questionnaire, social, and demographic data were obtained at the same occasion, by a trained member of the research team.

Physical Performance Evaluation

To evaluate patient dynamic stability and mobility, we used the timed up and go test (TUGT). The patient was asked to stand up from an armless chair, to walk a 3 meter distance, return, and sit down at the fastest pace possible, under supervision. Performance in this test was categorized in 3 levels, according to the time interval used to accomplish the task (high, <10.9 seconds; moderate, 11-20.9 seconds; and low, >21 seconds).[21] Lower extremity strength was evaluated by the 30-s chair-stand test (30sCST). The patient started seated up straight in an armless chair, with the feet flat on the floor and arms held across the chest. After the instruction, the patient was asked to stand up and sit down repeatedly, as quickly as possible, for 30 seconds. The number of completed stands was registered. Values were classified in low (<9 repetitions), moderate (9-17 repetitions), and high (>17 repetitions).[22]

Statistical Analysis

Variables were tested for normality using the Kolmogorov-Smirnov test. Comparison of numerical variables with normal distribution was analyzed by Student's t test, and variables with non-Gaussian distribution were analyzed by Mann-Whitney test. Categorical variables were analyzed by χ^2 or Fisher exact test. P values $< .05$ were considered significant. The results of normal distribution variables were presented as mean ± SD. Non-Gaussian variables were presented as median and percentiles. The statistical package used for the statistical analyses is Prism version 6.0 (GraphPad Software, La Jolla, CA).

Results

Patient Demographics, Clinical Characteristics, and Physical Evaluation

Between March 2018 and March 2019, 68 patients were assessed for the study eligibility. After use of the selection criteria, 63 patients were included in the evaluation (Fig. 1). Sociodemographic features are presented in Table 1. Most individuals were women (68.2%), >60 years old (82.5%) and originated from the northeast region of Brazil (60.3%). Most patients had a family income of 2 times or less the minimum wage (57.1%) and had ≤2 years of education (66.6%). The most frequent skin color was white (36.5%).

The clinical features and physical performance tests of patients with CD are presented in Table 2. The most frequent comorbidities were hypertension (76.2%), dyslipidemia (65.1%), and diabetes (33.4%). LVEF was preserved (60.1 ± 16.11), and most patients had a reported New York Heart Association functional class I (54%). Most individuals presented performed high (58.7%) in TUGT, and most patients displayed moderate performance in 30sCST (54%). There were no untoward events associated with any of the

Figure 1. Data collection flow chart.

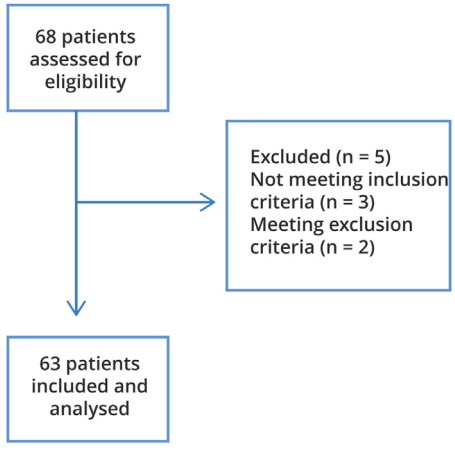

Table 1. Sociodemographic characteristics of patients with Chagas disease.

Variable	No. (%)	Mean ± SD
Sex		
Female	43 (68.2)	
Age (y)		
≥60	52 (82.5)	67.8 ± 9.7
Skin color		
White	23 (36.5)	
Brown	18 (28.6)	
Black	22 (34.9)	
Marital status		
Single	10 (15.8)	
Married	32 (50.8)	
Divorced	5 (8.0)	
Widow	16 (25.4)	
Education level		
None	9 (14.3)	
≤2 y	42 (66.6)	
Elementary school	5 (8.0)	
Secondary school or more	6 (11.1)	
Country region of birth		
Northeast	38 (60.3)	
Southeast	16 (25.4)	
Center east	1 (1.6)	
South	2 (3.2)	
North	5 (7.9)	
Foreign	1 (1.6)	
Family income (MW)		
1-2	36 (57.1)	
3-5	25 (39.6)	
>5	2 (3.3)	

MW indicates minimum wage; SD, standard deviation.

Table 2. Clinical features and physical evaluation of patients with Chagas disease.

Variable	No. (%)	Mean ± SD
Clinical features		
Hypertension	48 (76.2)	
Diabetes	21 (33.4)	
Dyslipidemia	41 (65.1)	
LVEF (%)		60.1 ± 16.1
Left ventricular systolic dysfunction		
<50% LVEF	17 (27.0)	
≥50% LVEF	46 (73.0)	
NYHA		
I	34 (54.0)	
II	26 (41.3)	
III	3 (4.7)	
Physical performance tests		
30sCST (no. of repetitions)		
≤8	18 (28.6)	
9-17	34 (54.0)	
≥18	11 (17.4)	
TUGT (seconds)		11.6 ± 7.6
≤ 10.9	37 (58.7)	
11-20.9	17 (27.0)	
≥21	9 (14.3)	

30sCST indicates30-s chair-stand test; LVEF, left ventricular ejection fraction measured by Teicholz; NYHA, New York Heart Association; SD, standard deviation; TUGT, timed up and go test.

performance tests used (ie, no symptoms requiring emergency evaluation).

HRQoL

The evaluation of HRQoL according to EQ-5D-3L is presented in Tables 3 to 5. The domains with more frequent report of problems were "pain/discomfort" and "anxiety/depression," both with 31.7%. The results of the reports from all domains are presented in Table 3.

The association between physical performance and HRQoL is shown in Tables 4 and 5. Table 4 presents the association between 30sCST and HRQoL. Most patients with moderate and high performance in this test reported no problems in the domains "mobility," "usual activities," and "pain/discomfort." Both the EQ-5D-3L utility index and VAS score improved according to higher performance level (P = .001 and .023, respectively).

Table 5 presents the association between TUGT and HRQoL. Most individuals with moderate and high performance in this test reported no problems in the domains "mobility" and "usual activities" ($P < .001$ for both). Both the EQ-5D-3L utility index and VAS score improved according to the performance level (P = .001 and .032, respectively).

Discussion

Despite improvements in transmission control, 70 million individuals in South and Central America are at risk of CD infection.[23] Estimates of CD global economic burden are US$627.46 million per year, with 806 170 disability-adjusted life years.[5] Most patients have reduced access to adequate treatment and information.

Demographic and Clinical Data From Patients With CD

Most patients of the present study were >60 years old, with preserved LVEF, and mild dyspnea symptoms. Similar clinical characteristics are found in other studies with urban Brazilian CD cohorts,[24,25] whereas surveys performed in rural regions with higher CD prevalence present younger patients with more advanced disease.[15] The analysis of cohorts with long-term diseases is prone to survival-related biases.[26] A previous study of the temporal evolution of CD mortality in Brazil has shown that prior cohorts exhibited higher mortality compared with current cohorts of patients with CD.[27] This generational effect is hypothesized as related to improvements in the access to healthcare over time.[28] Accordingly, the elderly patients treated at our institution exhibited less severe cardiac manifestations of CD, possibly representing the survivors of previous generations which endured both disease burden and the historical barriers in access to healthcare systems.

HRQoL of Patients With CD

Previous studies have evaluated HRQoL in chronic CD patients. Oliveira et al found patients with CD to display lower scores in physical functioning and role emotional, using the SF-36 questionnaire compared with healthy controls.[29] In another study, Pelegrino et al found that patients with CD and cardiomyopathy had lower HRQoL also measured by SF-36 compared with non-Chagas cardiomyopathy, in physical functioning domains.[25] A systematic review of the literature associating CD and HRQoL

Table 3. Answers for each domain of the EQ-5D-3L questionnaire from patients with chronic Chagas disease.

Domain	Problem severity, no. (%)		
	None	Moderate	Severe/extreme
Mobility	38 (60.3)	15 (23.8)	10 (15.9)
Self-care	55 (87.3)	6 (9.5)	2 (3.2)
Usual activities	42 (66.7)	14 (22.2)	7 (11.1)
Pain/discomfort	28 (44.5)	20 (31.7)	15 (23.8)
Anxiety/depression	32 (50.8)	20 (31.7)	11 (17.5)

found 12 studies, most of them using the generic SF-36 or other instruments, not designed to directly measure utility.[30]

In our study, the domains with more frequent reports of problems were "pain/discomfort" and "anxiety/depression." Although the association between mental health and heart disease is well documented,[31] there are particular aspects regarding the emotional status of patients with CD. Chronic *T. cruzi* infection may have direct effects over neuronal and behavioral function, according to both animal and cohort studies.[32] In addition, disease stigmatization, associated with social and economic deprivation characteristic of patients with CD, contribute to adverse mental health outcomes.[33] In accordance with our findings, hopelessness and emotional difficulties were previously reported in more than half of patients with chronic CD, independently of cardiovascular symptoms.[34]

In the present study, we have chosen to use the generic questionnaire EQ-5D-3L, instead of a heart failure-specific instrument, such as the Minnesota Living with Heart Failure Questionnaire (MLHFQ), also previously validated in a Brazilian study.[35] Generic questionnaires are valuable for health policy evidence-guided decisions because they enable comparisons of HRQoL between different diseases, and populations with diverse diseases. Another important issue was the choice of generic instrument to use in the present study. The 5-level EQ-5D (EQ-5D-5L) questionnaire adds the levels "slight" and "severe" problems to each dimension. Indeed, this instrument has been evaluated as superior to EQ-5D-3L, displaying higher sensitivity in health status measurement.[36] However, until present, there is not a Brazilian value set using EQ-5D-5L with utility weights available. Therefore we used EQ-5D-3L because its health states were previously valuated in a multicentric study conducted in 4 Brazilian areas, interviewing 3362 individuals.[20]

Physical Performance and HRQoL in Patients With Chronic CD

The simultaneous evaluation of HRQoL and physical performance has been previously evaluated in CD, using different methods. Using cardiopulmonary exercise training, Mediano et al found reduced VO_2 in patients with CD, which also displayed reduced scores in MLHFQ,[37] while Lima et al used the SF-36 questionnaire.[38] Using an interventional approach, both studies found improvements in cardiopulmonary capacity after physical training. Although the second study found improvements in domains of the SF-36 questionnaire, the first study did not find changes in the MLHFQ after training.

The physical performance tests selected in the present study were the 30sCST and TUGT. The rationale was to choose inexpensive evaluations, quick and safe to execute in a setting of reduced space availability, and therefore suitable to the outpatient clinic. The combination of both tests assesses a range of functional components required to daily activities. Lower limb force is evaluated in 30sCST, whereas motor control, stability, and coordination are evaluated in TUGT.[39] In addition, these tests are widely used in the assessment of independent life skills of elderly

Table 4. Association between the 30-s chair-stand and health-related quality of life in patients with chronic Chagas disease.

Domain	Problem severity	30sCST performance (n, %)			*P* value
		Low	Moderate	High	
Mobility	None	4 (22.2)	33 (75.0)	1 (100.0)	<.001
	Moderate	5 (27.8)	10 (22.7)	0	
	Severe/extreme	9 (5.0)	1 (2.3)	0	
Self-care	None	14 (77.8)	40 (9.9)	1 (100.0)	.247
	Moderate	2 (11.1)	4 (9.1)	0	
	Severe/extreme	2 (11.1)	0	0	
Usual activities	None	8 (44.4)	33 (75.0)	1 (100.0)	.01
	Moderate	4 (22.3)	10 (22.7)	0	
	Severe/extreme	6 (33.3)	1 (2.3)	0	
Pain/discomfort	None	4 (22.2)	23 (52.3)	1 (100.0)	.025
	Moderate	5 (27.8)	15 (34.1)	0	
	Severe/extreme	9 (50.0)	6 (13.6)	0	
Anxiety/ depression	None	12 (66.7)	19 (43.2)	1 (100.0)	.182
	Moderate	2 (11.1)	18 (40.9)	0	
	Severe/extreme	4 (22.2)	7 (15.9)	0	
Overall index		.37 [.16-.55]	.74 [.63-1.00]	1.00 [1.00-1.00]	.001
VAS		50.0 [22.5-80.0]	80.0 [67.5-82.5]	70.0 [70.0-70.0]	.023

30sCST indicates 30-s chair-stand test; VAS, visual analog scale.

Table 5. Association between the timed up and go test and health-related quality of life in patients with chronic Chagas disease.

Domain	Problem severity	TUGT performance, no. (%)			*P* value
		High	Moderate	Low	
Mobility	None	29 (72.5)	9 (52.9)	0	<.001
	Moderate	8 (20.0)	6 (35.3)	1 (16.7)	
	Severe/extreme	3 (7.5)	2 (11.8)	5 (83.3)	
Self-care	None	37 (92.5)	14 (82.4)	4 (66.6)	.059
	Moderate	2 (5.0)	3 (17.6)	1 (16.7)	
	Severe/extreme	1 (2.5)	0	1 (16.7)	
Usual activities	None	31 (77.5)	10 (58.8)	1 (16.7)	<.001
	Moderate	8 (20.0)	5 (29.4)	1 (16.7)	
	Severe/extreme	1 (2.5)	2 (11.8)	4 (66.6)	
Pain/discomfort	None	18 (45.0)	10 (58.8)	0	.143
	Moderate	14 (35.0)	4 (23.6)	2 (33.3)	
	Severe/extreme	8 (20.0)	3 (17.6)	4 (66.7)	
Anxiety/ depression	None	19 (47.5)	10 (58.8)	3 (50.0)	.642
	Moderate	15 (37.5)	4 (23.6)	1 (16.7)	
	Severe/extreme	6 (15.0)	3 (17.6)	2 (33.3)	
Overall index		0.73 [0.59-0.85]	0.74 [0.36-1.00]	0.14 [0.09-0.21]	0,001
VAS		80.0 [67.5-90.0]	70.0 [50.0-80.0]	30.0 [2.5-72.5]	.032

TUGT indicates timed up and go test; VAS, visual analog scale.

individuals.[40] In our study, higher performance in 30sCST and TUGT was associated with higher EQ-5D-3L utility and VAS scores, while linked to lower rates of problem report in the domains "mobility" and "usual activities." Our results are in agreement with 2 previous observational studies evaluating HRQoL and physical performance in patients with CD.[15,16] Both studies used the 6-minute walk test (6MWT) and the MLHFQ, finding that longer distance walked in 6 minutes was associated with higher HRQoL. In addition, another study comparing TUGT with 6MWT in cardiac rehabilitation patients, found a significant correlation between the two methods.[41] Accordingly, our results suggest TUGT and 30sCST can evaluate properly the functional status and the association with HRQoL in patients with chronic CD, with less space requirement compared with 6MWT.

Limitations

The present study was performed on a selected clinical sample from a single healthcare center, and therefore may not be representative of a large population of patients with CD. In addition, the advanced age and mild left ventricular impairment of patients in our study preclude generalization of the results to larger groups.

Conclusion

To the best of our knowledge, this is the first report of HRQoL based on EQ-5D-3L in patients with chronic CD. In addition, we propose the use of 2 inexpensive and safe tests for the evaluation of physical performance in CD, which are associated with HRQoL. Strategies aiming the improvement of HRQoL in patients with chronic CD may focus on mobility skills and force. Additional studies evaluating interventions in physical functional status should be a priority in these patients.

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Author Affiliations: Research Division, National Institute of Cardiology, Ministry of Health, Rio de Janeiro, Brazil (Lins, Tura, Kasal); Internal Medicine Department, State University of Rio de Janeiro, Rio de Janeiro, Brazil (Kasal).

Correspondence: Daniel Arthur Kasal, PhD, Rua das Laranjeiras 374, 22240-006, Rio de Janeiro, Brazil. Email: dabkasal@gmail.com

Author Contributions: *Concept and design:* Tura, Kasal
Acquisition of data: Lins, Kasal
Analysis and interpretation of data: Lins, Tura, Kasal
Drafting of the manuscript: Tura, Kasal
Critical revision of the paper for important intellectual content: Lins, Tura, Kasal
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