Original Article

Cost-Effectiveness of Heart Transplantation: Data from a Referral Center in the Central-West Region of Brazil

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Abstract

Background: **In Brazil, heart transplantation is fully funded by the Brazilian Unified Health System.**

Objectives: **The objective of this study is to explore, for the first time, the cost-effectiveness profile of heart transplantation in a convenience sample, in a referral center in the Central-West Region of Brazil.**

Methods: **Costs related to transplant hospitalization were evaluated, including those related to the surgical procedure, as well as hospitalization in the intensive care unit and in the inpatient ward, until patients were discharged. Costs associated with professional remuneration, fees, materials, and medications were computed. In order to assess effectiveness, post-transplant survival was used. For survivors, survival time was censored until the last contact recorded in the medical records of the transplant clinic. The cost-effectiveness ratio was expressed in Brazilian reals (BRL) per year of life saved.**

Results: **We observed that the cost-effectiveness ratio was 25,806 BRL/year of life saved. Considering the average survival projected by Kaplan-Meier analysis, the cost-effectiveness ratio was 6,842 BRL/year of life saved.**

Conclusion: **This result demonstrates a good cost-effectiveness ratio when compared to international studies that have evaluated this parameter. We did not, however, assess the micro-costing of the program and its feasibility for the institution. Given that this is a single-center study, the evaluation of other transplant centers is necessary in order to better elucidate this scenario.**

Keywords: **Heart Transplantation; Cost-Benefit Analysis; Capital Financing; Unified Health System.**

Introduction

Heart failure is considered an epidemic disease in the modern world. It affects approximately 1% to 2% of the adult population, and it is the leading cause of hospitalization in the South American population, with significant mortality.[1,2]

Heart transplantation is considered the gold standard therapy for heart failure that is refractory to medical treatment. It should be considered as a treatment for patients who remain in New York Heart Association functional classes III and IV, with recurrent hospitalizations and unfavorable prognostic markers notwithstanding full medical and surgical therapy.[3–5]

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Manuscript received February 04, 2022, revised manuscript May 02, 2022, accepted May 17, 2022

DOI: https://doi.org/10.36660/abchf.20220051

The first heart transplantation in Brazil took place in 1968, at Hospital das Clínicas in São Paulo. Currently, approximately 380 heart transplants are performed annually. This complex procedure is financed by the Brazilian Unified Health System (SUS) of the Ministry of Health, in accordance with Law 9.434, of 1997.

Health managers have sought to better understand the implementation of new health technologies by means of tools to assess their efficiency and their real benefit to the population. These analyses are important to decisions to incorporate new technologies, evaluate medications, and reflect on the costs of new or already incorporated procedures. Cost-effectiveness analysis is one of these tools to broaden debates on the topic.

Accordingly, the objective of this study is to explore, for the first time, the cost-effectiveness profile of heart transplantation in a convenience sample in Brazil. In order to do this, we consecutively analyzed the cohort of patients undergoing transplantation at our institution, computing the real costs and comparing them to absolute survival during follow-up and to actuarial survival.

Methods

Study design

This is a descriptive cost-effectiveness study, based on observational cost and survival data from a retrospective cohort of patients who consecutively underwent heart transplantation. Considering the single-center study design, this is an exploratory and hypothesis-generating study.

The research project received approval from the Institutional Research Ethics Committee, waiving the requirement to obtain an informed consent form, given that it comprises retrospective collection of coded secondary data, from the hospital's management system.

Sample selection and follow-up

All adults (≥ 18 years) who underwent heart transplantation at the Cardiology Institute of the Federal District (ICDF, acronym in Portuguese) were included in this analysis, from the beginning of the program (May 2009) until April 30, 2017, when follow-up analysis was performed for this study.

The ICDF is a private, non-profit institution that provides mixed care for patients in the public and supplementary systems. All transplants were financed by the SUS, of the Ministry of Health.

Data collection

Data were collected from a clinical-epidemiological source from the heart transplantation program. Before acquisition, data were duly coded, so that it was not possible to identify patients. The following were collected: demographic and clinical characteristics, cause of the cardiomyopathy that led to transplantation, and death with respective cause. The program Business Intelligence (QlickView®, QlikTech, Pennsylvania, EUA, 2007) was used to obtain cost data.

Definitions of survival and mortality

Survivors' survival time was censored until the last contact registered in the medical records of the transplant clinic. During follow-up, the maximum life span after transplantation was recorded in individuals who died. The evolution of medical records was analyzed to define the causes of death, classified as follows: death related to the transplant procedure; death not related to the transplant procedure, which was subdivided into heart disease-related and non-heart disease-related. Surgery-related deaths were defined as those due to complications from the transplant procedure, such as primary graft dysfunction (cardiogenic shock), bleeding, nosocomial infection, or perioperative stroke. Cardiac death unrelated to surgery was defined as due to rejection (defined by evidence of rejection on endomyocardial biopsy), allograft vascular disease (coronary atherosclerosis), or immunosuppression-related infection. Finally, non-heart disease-related death was defined as death due to pathologies not associated with transplantation, for example, external causes or neoplasms unrelated to the transplant.

Definitions of cost

Costs were defined as the absolute amount spent by the hospital to perform each procedure, regardless of the amount transferred through the SUS. Therefore, this information reflects the real cost of the procedure and not the cost to the health system.

The overall cost of transplantation was generated during the entire hospital stay, subdivided into surgery costs (material, medications, procedures, room fees, and professional remuneration) and hospitalization costs (material, medications, procedures, hospital stay fees, and professional remuneration). The amounts spent on organ harvesting surgery and staff mobilization were not considered, because these results were not available in the hospital system.

Cost-effectiveness analysis

Time was described as median and interquartile range due to non-normal distribution. Normality was assessed using the Kolmogorov-Smirnov test. Survival time was defined by the time elapsed between transplantation and death or by the time censored in the maximum follow-up of survivors in the other individuals. It was described as median and interquartile range. The cost of transplantation was described as mean ± standard deviation. Kaplan-Meier analysis was used to project total life span after transplantation and calculate cumulative probability of survival. Clinical outcomes were described as an overall percentage considering all procedures and were expressed as proportions, with their respective 95% confidence intervals. We reported p values to 3 decimal places with p values less than 0.001 reported as $p < 0.001$. For all tests, we used the two-tailed alpha significance level = 0.05. Residual examination provided an assessment of model assumptions for the regression analyses.

The cost-effectiveness ratio was expressed in Brazilian reals (BRL) per year of life saved and calculated as a fraction whose numerator was the sum of each patient's hospital cost, and the denominator was the sum of years of life after transplantation for each patient. This analysis did not consider cost after hospital discharge, seeing that it would consist of a combination of factors related to the procedure and factors inherent to remaining alive, whose discrimination could be inaccurate. Therefore, the decision was made to focus the analysis on the "investment" related to the surgery. Years of life saved were defined as the entire life span after transplantation, under the hypothetical premise that the patients would have received the new organ on their last day of life in the absence of the transplant.

Given that the overall survival time is underestimated due to the study's short follow-up, the cost-effectiveness ratio was secondarily calculated using the projected survival time in Kaplan-Meier analysis.

Statistical analyses were performed using the program SPSS, version 25 (SPSS Inc, Chicago, Illinois, USA).

Results

Sample characteristics

Between May 2009 and April 2017, 154 patients received transplantations. Patients' age ranged from 49 ± 12 years,

and 59% were men. Donors were 29 ± 12 years old, and 79% were male. Among the causes that led to transplantation, Chagas cardiomyopathy was predominant, accounting for 69% of the cases, followed by the other causes illustrated in Figure 1. The immunosuppressive regimen was tacrolimus in 60% of the patients and mycophenolate in combination with a calcineurin inhibitor in the others.

Post-transplant evolution

The majority of deaths occurred during the same hospitalization period as the transplant (63%), divided into 17 deaths due to primary graft dysfunction (28%), 12 deaths due to infection (20%), and 6 deaths due to stroke (10%). After discharge, there were 25 deaths, distributed as follows: 6 due to rejection, 11 due to infection, and 8 unrelated to heart disease. The causes of death are displayed in Figure 2.

Median time between transplantation and the date of this analysis was 2.2 years (interquartile range = 0.90 to 3.9), at which point 66% of patients were alive. Post-transplant survival time (until death or total follow-up time in survivors) showed a median of 1.27 years (interquartile range = 0.32 to 3.2), with a total gain of 196 person-years during this period. According to the Kaplan-Meier analysis, the estimated survival time after transplantation was 4.8 years (95% confidence interval = 4.1 to 5.5), with a cumulative survival probability of 52% (Figure 3).

Cost-effectiveness

With respect to cost, it ranged from a minimum of 11,909 BRL to a maximum of 137,596 BRL, with an average of 32,844 ± 21,768 BRL. The total cost of the 154 transplants was 5,058,013 BRL. Of this amount, about 40% came from the surgical procedure and the rest from hospitalization. The amplitude in costs is due to increased expenses in cases of extracorporeal membrane oxygenation or renal replacement therapy in some patients, in addition to costs with antibiotic therapy.

Using the absolute lifetime observed in this period during which 65% of patients were censored, the cost-effectiveness ratio was 25,806 BRL/year of life saved. Considering the average survival of 4.8 years projected by the Kaplan-Meier analysis, the cost-effectiveness ratio is reduced to 6,842 BRL/year of life saved.

Discussion

This study explores the potential cost-effectiveness ratio of heart transplantation in Brazil. A favorable ratio was demonstrated between investment and clinical benefit in only 2.2 years of follow-up.

The World Health Organization recommends, as a reference, 3 times the gross domestic product per capita per year of life saved in order to consider an intervention advantageous from the economic point of view, which, in 2017, was equivalent to the value of 29,463 dollars. Considering the short follow-up time, our crude analysis underestimates the years of life saved due to the large number of patients censored (still alive when follow-up was interrupted). Even so, the cost-effectiveness value obtained

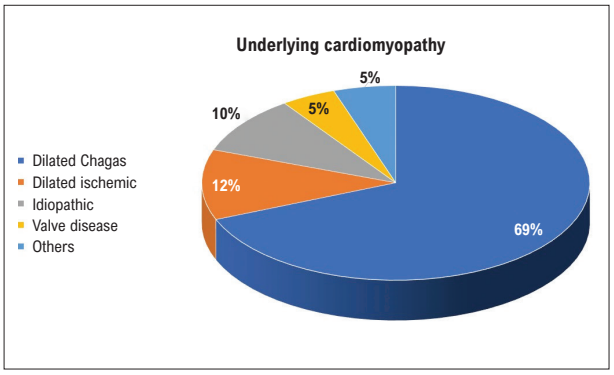

Figure 1 – *Distribution of the causes of heart failure that led to transplantation*

is about 25% of the limit proposed by the World Health Organization. The outlook becomes more favorable when we apply the mean survival estimated by the survival function, which suggests a cost-effectiveness ratio of 6,842 BRL/year of life saved.

Studies involving cost-effectiveness in patients undergoing heart transplantation are scarce. Evans demonstrated that the overall cost-effectiveness ratio of heart transplantation in the United States was estimated at 44,300 dollars/year of life saved.[6] Our results are advantageous in relation to those that have been described in developed countries, whose costs related to transplantation are much more significant than in Brazil.[7]

The survival rate of heart transplant recipients from 2009 (when this analysis began) to 2017 was 66%. According to survival function, we estimated that 50% of patients would be alive at 4.8 years. Accordingly, for this follow-up period, the magnitude of the death reduction is 50% in relative terms and 50% in absolute terms, with a number needed to treat of 2. This explains why, even though it is a high-cost procedure, it is economically efficient, even when circulatory support is required in the context of primary graft failure.[8]

It is necessary to recognize that our survival numbers are below international references.[9] This may be due to the severity with which our patients are operated, the low accessibility to the system (selection of more severe patients), and the congested waiting line for transplantation; other factors such as socioeconomic level, comorbidities (the majority of patients had Chagas disease), and limited volume of transplants per center can also contribute negatively. Accordingly, this makes it more difficult in our environment to obtain ideal results. This gives greater relevance to our data, which suggest that, in less favorable scenarios, the magnitude of the benefit may be sufficient to generate cost-effectiveness.

Cost-effectiveness thresholds are arbitrary, and they serve only to guide analysis. The decision to implement an intervention is more complex. For example, more important than categorizing an intervention as cost-effective is the comparison of the efficiency profile with other interventions that compete to be subsidized by the same health system. In this sense, cost-effectiveness is not the same as low cost, and we must remember that we are dealing with a high-cost therapy.

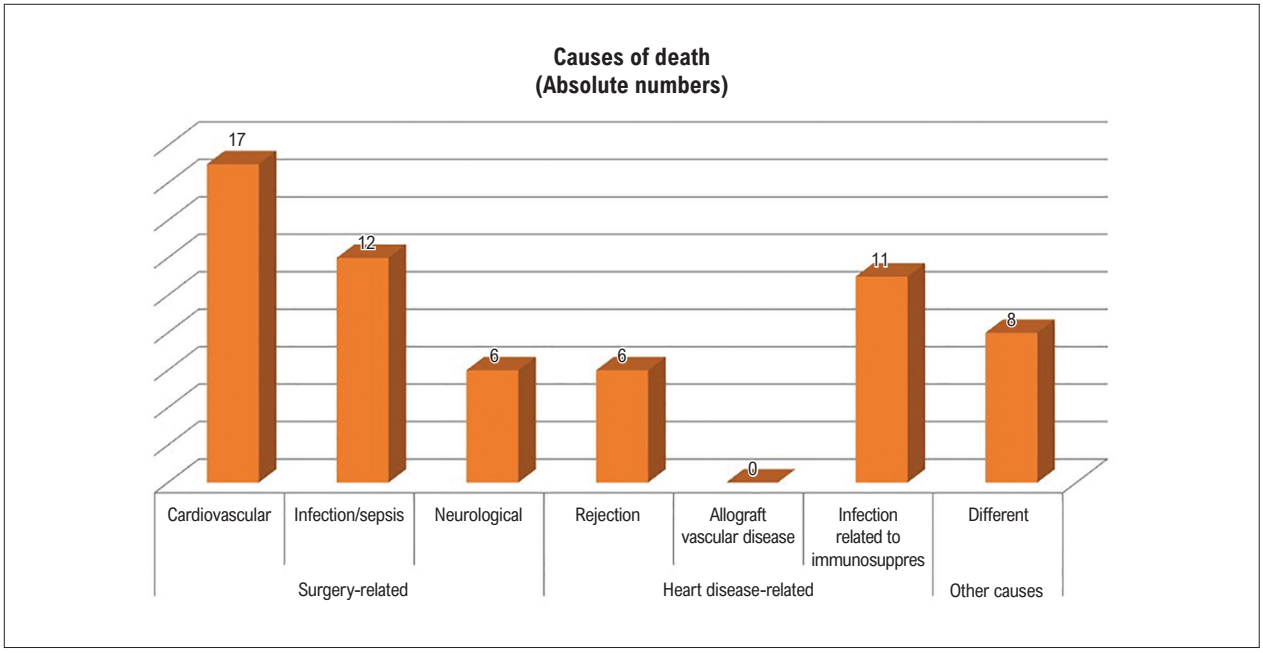

Figure 2 – *Causes of death: related versus not related to transplant surgery. Other causes represent causes not related to heart disease.*

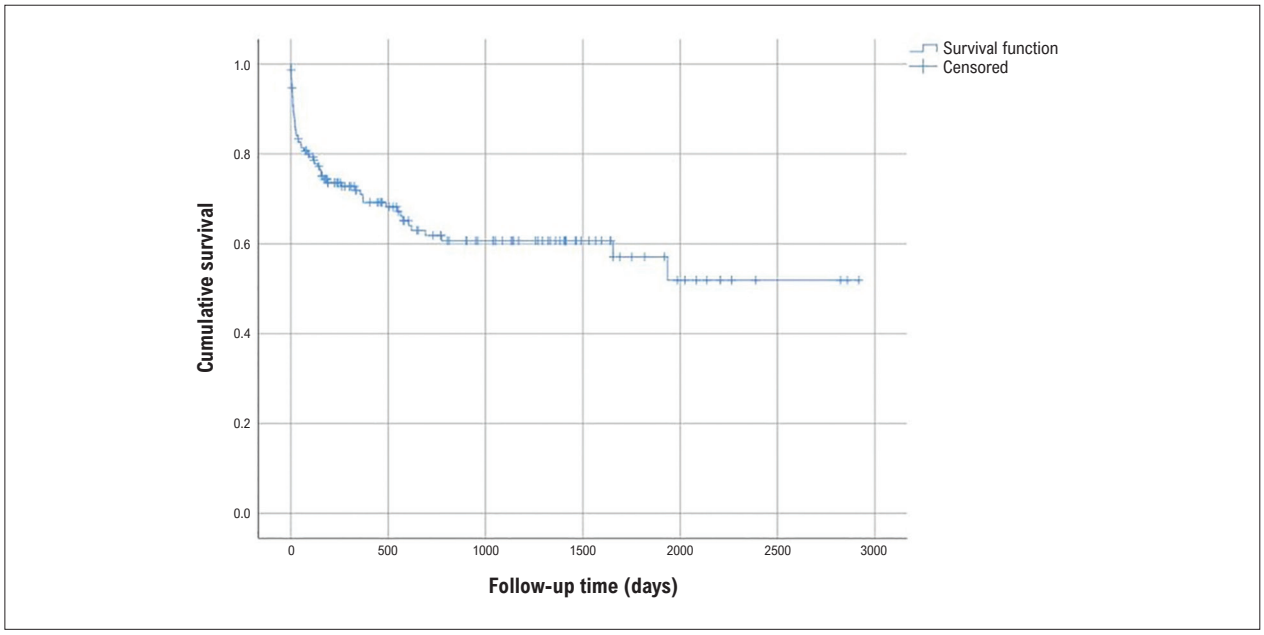

Figure 3 – *Cumulative survival.*

It is important to emphasize that cost-effectiveness analysis does not take into consideration the financial viability of a transplantation program. The analysis under consideration refers to the impact of heart transplantation on society. Based on the data presented, there is benefit in a program with these characteristics for a health system such as Brazil's. On the other hand, programs are recognized to be underfunded, when analyzing the micro-costing of heart transplants in Brazil.[10,11]

It is necessary to recognize limitations to our analysis, which make our study insufficient to be considered definitive. First, this is a single-center study, with a convenience sample of the real situation in Brazil. Second, certain costs inherent to the transplantation process were not considered, such as pre-transplant evaluation and management, logistics and transport for organ harvesting, hospitalizations, and post-transplant follow-up. The impacts in relation to returning to work and social security, with financial and psychosocial influence on

the patient and on society, were also not analyzed. Another important point to be evaluated is the quality of life after transplantation, which was not evaluated in this study. Finally, our follow-up was short, and this study should be reproduced with a longer follow-up period.

Conclusion

In conclusion, this exploratory, single-center study suggests a favorable cost-effectiveness ratio for heart transplantation, and it should serve as a springboard for a multicenter study to reassess this issue with greater external validity, including generalization at the level of Brazil. Considering that this procedure is publically funded, this knowledge is of paramount importance to making decisions and adapting health policies in this area.

Author Contributions

Conception and design of the research: Biondi RS, Correia LC, Vieira NW, Barzilai VS, Chaves RB, Monte GU, Atik FA; Acquisition of data: Biondi RS, Vieira NW, Rocha Júnior EF, Araújo MCCL, Faria LR, Lucas PFS, Araujo JS, Araújo APC, Barbosa AA, Monte GU; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Biondi RS, Correia LC, Vieira NW, Barzilai VS, Chaves RB, Rocha Júnior EF, Araújo MCCL, Faria LR, Lucas PFS, Araujo JS, Araújo APC, Barbosa AA, Monte GU, Atik FA; Statistical analysis: Biondi RS, Correia LC, Monte GU, Atik FA; Writing of the manuscript: Biondi RS, Correia LC, Barzilai VS, Chaves RB, Monte GU, Atik FA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

References

1. Tanai E, Frantz S. Pathophysiology of Heart Failure. Compr Physiol. 2015;6(1):187-214. doi: 10.1002/cphy.c140055.
2. Bocchi EA. Heart Failure in South America. Curr Cardiol Rev. 2013;9(2):147-56. doi: 10.2174/1573403x11309020007.
3. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539. doi: 10.5935/abc.20180190.
4. Mangini S, Alves BR, Silvestre OM, Pires PV, Pires LJ, Curiati MN, et al. Heart Transplantation: Review. Einstein. 2015;13(2):310-8. doi: 10.1590/S1679-45082015RW3154.
5. Bacal F, Marcondes-Braga FG, Rohde LEP, Xavier JL Jr, Brito FS, Moura LAZ, et al. 3ª Diretriz Brasileira de Transplante Cardíaco. Arq Bras Cardiol. 2018;111(2):230-289. doi: 10.5935/abc.20180153.
6. Evans RW. Cost-effectiveness Analysis of Transplantation. Surg Clin North Am. 1986;66(3):603-16. doi: 10.1016/s0039-6109(16)43943-5.
7. Weintraub WS, Cole J, Tooley JF. Cost and Cost-effectiveness Studies in Heart Failure Research. Am Heart J. 2002;143(4):565-76. doi: 10.1067/mhj.2002.120965.
8. Lima EB, Cunha CR, Barzilai VS, Ulhoa MB, Barros MR, Moraes CS, et al. Experience of ECMO in Primary Graft Dysfunction After Orthotopic Heart Transplantation. Arq Bras Cardiol. 2015;105(3):285-91. doi: 10.5935/abc.20150082.
9. Lund LH, Khush KK, Cherikh WS, Goldfarb S, Kucheryavaya AY, Levvey BJ, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Heart Transplantation Report-2017; Focus Theme: Allograft ischemic time. J Heart Lung Transplant. 2017;36(10):1037-46. doi: 10.1016/j.healun.2017.07.019.
10. Goldraich LA, Neyeloff JL, Silva APBE, Zeilmann LG, Hastenteufel LT, Ghisleni EC, et al. Heart Transplantation Cost Composition in Brazil: A Patient-Level Microcosting Analysis and Comparison With International Data. J Card Fail. 2018;24(12):860-3. doi: 10.1016/j.cardfail.2018.10.011.
11. Barreto MFC, Dellaroza MSG, Fernandes KBP, Pissinati PSC, Galdino MJQ, Haddad MDCFL. Cost and Factors Associated With the Hospitalization of Patients Undergoing Heart Transplantation. Transplant Proc. 2019;51(10):3412-7. doi: 10.1016/j.transproceed.2019.08.038.