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Cost of hemophilia A in Brazil: a microcosting study

Ana Paula Beck da Silva Etges[1,2], Nayê Balzan Schneider[1,2], Erica Caetano Roos[1,7], Miriam Allein Zago Marcolino[1,2], Margareth Castro Ozelo[6], Mariana Midori Takahashi Hosokawa Nikkuni[6], Luany Elvira Mesquita Carvalho[4], Tatyane Oliveira Rebouças[4], Monica Hermida Cerqueira[5], Veronica Mata[3] and Carisi Anne Polanczyk[1,2*]

Abstract

Background Patients with Hemophilia are continually monitored at treatment centers to avoid and control bleeding episodes. This study estimated the direct and indirect costs per patient with hemophilia A in Brazil and evaluated the cost variability across different age groups.

Methods A prospective observational research was conducted with retrospective data collection of patients assisted at three referral blood centers in Brazil. Time-driven Activity-based Costing method was used to analyze direct costs, while indirect costs were estimated based on interviews with family and caregivers. Cost per patient was analyzed according to age categories, stratified into 3 groups (0–11;12–18 or older than 19 years old). The non-parametric Mann-Whitney test was used to confirm the differences in costs across groups.

Results Data from 140 hemophilia A patients were analyzed; 53 were 0–11 years, 29 were 12–18 years, and the remaining were older than 19 years. The median cost per patient per year was R$450,831 (IQR R$219,842; R$785,149; $174,566), being possible to confirm age as a cost driver: older patients had higher costs than younger's ($p = 0.001$; median cost: 0–11 yrs R$299,320; 12–18 yrs R$521,936; ≥19 yrs R$718,969).

Conclusion This study is innovative in providing cost information for hemophilia A using a microcosting technique. The variation in costs across patient age groups can sustain more accurate health policies driven to increase access to cutting-edge technologies and reduce the burden of the disease.

Highlights

- This study provides cost data, measured with microcosting methodology, for Hemophilia A patients in an LMIC, demonstrating how costs are sensible to the patient's age.
- The results showed the importance of considering patients' clinical and demographic characteristics to establish adequate reimbursement policies driven to reduce the health impact of the disease, due to the cost variability observed.
- Brazil has one of the biggest hemophilia A populations, and based on the cost measured, the financial burden associated with this condition is estimated to be R$ 5,19 billion yearly.

Keywords Hemophilia A, Health Care costs, Economic evaluation

*Correspondence:
Carisi Anne Polanczyk
cpolanczyk@hcpa.edu.br

Full list of author information is available at the end of the article

Background

Hemophilia is a rare inherited disease that affects approximately 13,000 individuals in Brazil, which places the country as the fourth largest population with the disease [1]. Severe hemophilia A cases are those with less than 1% of normal factor VIII activity, and moderate cases are those with activity from 1 to 5% of normal levels [2]. The standard treatment consists in replacing the deficient coagulation factor VIII and monitoring patients continuously in accredited hemophilia treatment centers. In Brazil, this treatment is offered exclusively through the publicly funded Unified Health System at several accredited blood centers, which account for the *Hemovida Web – Coagulopatias* system, developed by the Brazilian Ministry of Health, to unify the clinical records of all patients and to monitor the control of medication supplies.

Even with appropriate treatment, with indications provided for primary, secondary, and tertiary prophylaxis, 20–30% of patients with hemophilia develop polyclonal alloantibodies ("inhibitors") that neutralize factor VIII coagulant activity [3]. The development of an inhibitor is a major complication of hemophilia [3]. There are drugs that are indicated for this profile of patients, such as bypassing agents and emicizumab; the latter is a monoclonal antibody that mimics the cofactor function of factor VIII [4]. In 2019, after a recommendation from the Brazilian National Committee for Technology Incorporation in the Unified Health System (CONITEC), emicizumab was incorporated as a prophylactic treatment of persons with hemophilia A and factor VIII inhibitors who failed immune tolerance therapy [5].

Strongly influenced by the technologies mentioned to manage the disease over the life cycle, hemophilia is recognized as a high-cost, low-volume disease where most of the resources are spent on blood products [6, 7]. In addition, the overall cost of caring for these patients in Brazil is unknown, including direct medical costs incurred by both the system and the patients and indirect costs of disease.

In rare diseases, the literature recommends measuring direct and indirect costs, as they often involve a high cost with lost productivity. In Brazil, patients with hemophilia A are eligible for the home treatment, offered by the Brazilian Unified Health System [2]. Therefore, it is essential to measure the family costs with disease management, which can be direct or indirect. Generating information on costs and their origin facilitates the implementation of actions aimed at efficient resource utilization in disease management, thus contributing to the efficiency of the system.

This study estimated the costs per patient with hemophilia A in Brazil and evaluated the cost variability between age ranges.

Methods

Research classification

This study was designed as prospective observational research with retrospective data collection in patients followed at referral blood centers of the Brazilian Unified Health System. The research protocol was submitted and approved by the Research Ethical Committee from Hospital de Clínicas de Porto Alegre (CAAE: 52727121.8.1001.5327) and by the committees of the participating institutions. Considering the current national context of the hemophilia technology incorporation processes and the concentration of the treatment within the public healthcare system in Brazil, evaluating costs with ahigh accuracy is crucial to guide policymakers on the establishment of national sustainable policy. Based on the that, the use of a microcosting approach on this study was identified as the best alternative.

The literature on economic analysis in health care shows microcosting studies as the gold standard method for measuring accurate costs in the field [8]. Microcosting studies can be performed using a top-down or bottom-up approach, the latter being the one that provides the most accurate cost information [9]. The method, Time-driven Activity-based Costing (TDABC) is a method with a bottom-up approach that has been commonly used in microcosting studies, as it allows us to investigate cost information over the entire patient care cycle [10, 11]. In addition, it allows us to demonstrate the cost composition, facilitating the use of cost information for the management of health resources and the redesign of health services [12, 13].

Sample of patients

Three reference blood centers from different federal States were selected to participate in the research. From the Northeast region of Brazil, a blood center in Ceará, with 454 hemophilia A patients registered; from the Southeast region, blood centers in Rio de Janeiro and São Paulo, with 1,022 and 347 hemophilia A patients registered, respectively.

For four months, from February 2022 to August 2022, all patients under treatment in the blood centers with moderate or severe A hemophilia, without other bleeding disorders, were invited to participate. Patients and/or guardians of pediatric patients, (under 18 years of age) who agreed to participate signed the Informed Consent Form.

Data collection

The application of TDABC followed the method established steps: mapping the patient care pathway; identifying resources consumed by patients along the care pathway; assessing the cost of each resource identified; estimating the capacity of each resource; calculating the

capacity cost rate (CCR) for each resource; structuring the cost equations per patient; creating a database for cost data analysis; and assessing unit costs and their composition along the care pathway [13].

- Mapping the care cycle with the main activities to which the patient is subjected.

The care cycle was mapped by a multidisciplinary team that includes health professionals from the participating blood centers and researchers in the field of health technology assessment (Supplementary Material).

- Identifying all resources and departments consumed by the patient.

Clinical records on the electronic medical records of a sample of patients were studied to identify activities routinely performed during the care cycle. Based on the text freely written by health professionals, it was possible to identify the blood center's departments, equipment and professionals involved in the activities to which patients have been subjected. For each activity, it was estimated the type of resource consumed, including the center's physical structure, health professionals, and/or equipment.

Based on this mapping, a structured form on Otus Platform (Porto Alegre, Brazil) was developed to assess the involvement of each resource required to perform care activities for patients with hemophilia A in blood centers.

- Estimating the total cost and capacity of each resource identified in the care cycle and calculating the CCR.

For the blood centers in the states of Ceará and São Paulo the financial and capacity data used throughout the application of the method are considered as a reference for the mean values for the year of 2020, being obtained from the institutions' finance departments. This analysis allowed the parameterization of the cost per procedure consumed by patients treated at each blood center. Financial data include fixed costs for operating the structure, such as electricity supply, depreciation, taxes, support materials, expenses with health professionals by professional category (wages and taxes), and expenses with the purchase of supplies and medications. For the latter, we used the average purchase cost calculated for the year 2020 without adding any profit margin. For the blood center in Rio de Janeiro, the mean costs of the two other centers were used due to financial data unavailability.

For capacity data, the number of beds and chairs available to serve the population and the operating hours of the patient care unit were used for estimating the capacity of the blood center structure. For data on professionals' capacity, the mean workload established per professional category was considered, and as recommended on cost management literature [14] an expected 20% inactive time within this workload was discounted. Once the information on expenses with resources involving physical structure and health professionals and their respective capacities has been obtained, CCRs were calculated using Eqs. 1 and 2, described in Supplementary Material.

- Analyzing the time consumed by each resource per patient and structuring the time and cost equations.

To collect and analyze the mean length of time spent by patients in each activity, the health professionals involved in the care pathway collected time data during their routines in the blood centers of São Paulo and Ceará. In the blood center of Rio de Janeiro state, mean times from the other two other centers were used due to data unavailability.

- Structuring the direct cost calculations per patient.

We reviewed the data from available clinical records to obtain the rate of procedures performed per patient at the blood center over the course of 12 months. With the identification of procedures consumed by patients based on the process mapping initially performed, we multiplied the rate of procedures, the resources used to perform the procedure, the time consumed by each resource, and the CCR for each resource (Eq. 4 described in Supplementary Material). Finally, we added the medications and supplies used by each patient throughout the year.

For medications and supplies, we considered the amount of each medication or supply consumed by patients. We obtained the purchase cost data from the Brazilian public healthcare system financial database and extracted the consumption data per patient from registers of Hemovida Web – Coagulopathies. For the total cost related to medications, the most recent individual cost per bottle was used. When the most recent purchase cost data had more than one year, the cost was updated using inflation rates for medications for 2022.

The sum of all costs for procedures performed per patient at the blood center and medications consumed resulted in the direct cost per patient in the last 12 months. In addition to the cost of procedures at the blood center, transportation costs per patient considering their address of origin and the need for a companion were estimated. It includes the costs of regional urban or intercity transportation for a round trip. In sequence, the household expenditure and costs on disease management,

including expenses with medications, private health insurance, and consultations, among others were estimated (out-of-pocket cost). These data were collected by applying a form to the patient or his family via phone call and registered on Otus Platform (Porto Alegre, Brazil). Once the data have been collected, the economic impact of productivity loss was estimated by applying Eqs. 5 and 6 described in Supplementary Material.

All costs are expressed in the Brazilian currency (Brazilian reais - R$). International dollars were calculated based on the purchasing power parity (PPP) value 2022 by conversion rate of 1 International Dollars is equivalent to 2.58 Brazilian Reais R$ [15].

Data analysis

The direct and indirect cost results were described by age (0–11;12–18 or older than 19) and stratum (disease severity, disease presentation, presence of the inhibitor, and age group) using mean costs, median costs, standard deviation, and interquartile range. Within each age group and stratum, direct costs include outpatient, expert care, out-of-pocket, and transportation costs. Indirect costs include lost productivity and absenteeism for the patient and/or for the family.

The Wilcoxon rank non-parametric test was applied to identify direct and indirect cost predictors. We estimated costs according to each stratum, and the strata defined for the descriptive cost analysis served as groups (disease severity, presence of inhibitors, bleedings, surgeries, and hospitalizations). We have considered a p-value <0.1 as significant.

Finally, a descriptive estimation of the burden of the disease for the National Healthcare System was made taking into account the number of patients with hemophilia A with and without the presence of inhibitors in Brazil according to the national report [1]. The median cost measured in the study and interquartile ranges (IQR) for both groups were used to estimate distinct burden scenarios from the perspective of the health care system.

Results

Data from 140 hemophilia A patients were analyzed, 52 from the blood center of Ceará state, 28 from Rio de Janeiro, and 60 from São Paulo. Table 1 shows the sample characteristics according to the age group and total sample.

For the total sample, 14% of the patients have the presence of inhibitors. Another aspect of the sample was the presence of patients with bone-joint conditions and bleeding episodes registered during the last year, which represents 43% and 44% of the total sample, respectively.

The CCR of professional and structural resources are described in Table 2.

The median cost per patient/year was R$ 450,831 (IQR R$ 219,842; R$ 785,149). Table 3 shows the analysis of cost drivers and estimating costs for each blood center and according to the patient's conditions. Significant differences were identified within the patient's age, and hemophilia severity. Other variables have shown no statistical difference, indicating that they were not cost drivers in this sample.

Table 1 Sample characteristics classified by age

	0–11 years (*n* = 53)	**12–18 years (*n* = 29)**	**19 + years (*n* = 58)**	**Total (*n* = 140)**
Age (years)[a]	6.07 ± 3.26	15.07 ± 2.20	33.62 ± 10.54	20.71 ± 15.64
Age at diagnosis (years)[a]	0.83 ± 1.49	1.79 ± 2.66	10.79 ± 11.49	5.16 ± 8.92
Severity of hemophilia A				
Moderate	4%	3%	5%	4%
Severe	96%	97%	95%	96%
Presence of inhibitors	23%	7%	10%	14%
Presence of bone-joint conditions	19%	34%	69%	43%
Number of target joints affected[b]				
One	60%	30%	5%	18%
Two	30%	30%	18%	22%
Three	10%	40%	31%	28%
More than three	0%	0%	49%	32%
Patients with bleeding registered during the last year	43%	34%	48%	44%
Type of prophylaxis[c]				
Primary continuous	45%	21%	0%	22%
Secondary continuous	21%	31%	12%	19%
Tertiary continuous	17%	31%	74%	44%
Intermittent	0%	7%	3%	3%
Consumption of FVIII (IU/kg/year/patient)[a]	3,702 (3,135)	3,182 (2,515)	4,274 (4,140)	3,819 (3,489)

[a]mean±SD.[b] Percentages referring to the total number of patients with bone-joint conditions. [c]Defined as Rayment et al., 2020 [16]

Table 2 Mean times and capacity cost rate (CCR) per resource

	Mean time[a] (h)	CCR (*R*$/h)
Structure	6.23	33.00
Professionals		
Psychologist	1.40	26.00
Social worker	0.50	28.75
Dentist	0.97	32.17
Physiotherapist	0.86	53.35
Nurse	0.19	56.02
Pharmacist	0.21	59.37
Hematologist	0.45	130.05
Orthopedist	0.37	139.44

[a]The mean time represents the mean total hours spent per patient at the blood center over the year

Table 3 Identification of cost drivers

Variable	Sub-groups	Cost per patient (*R*$)[a]	*n* (%)	*p*
Blood center	1	504,513 (326,200–853,159)	28 (20.0)	0.289
	2	364,922 (197,522–698,929)	60 (42.9)	
	3	500,084 (179,742–940,828)	52 (37.1)	
Age (years)	≤ 12	299,320 (157,536 – 503,463)	53 (37.9)	< 0.001
	12–18	521,936 (338,050–690,006)	29 (20.7)	
	≥ 19	718,969 (226,939- 1,007,211)	58 (41.4)	
Severity	Moderate	172,720 (96,264–278,445)	6 (4.3)	0.096
	Severe	488,947 (239,520–805,822)	134 (95.7)	
Inhibitors	No	440,752 (224,758 – 748,379)	120 (85.7)	0.175
	Yes	702,444 (202,677–1,055,373)	20 (14.3)	
Bleeding	No	446,173 (256,039–707,851)	79 (56.4)	0.764
	Yes	455,488 (204,485–974,735)	61 (43.6)	
Surgery	No	445,145 (217,936 – 773,504)	138 (98.6)	0.261
	Yes	1,053,913 (767,551–1,340,276)	2 (1.4)	
Hospitalization	No	446,173 (230,801 – 733,936)	131 (93.6)	0.625
	Yes	873,538 (93,474–1,206,184)	9 (6.4)	
ICU hospitalization	No	450,831 (222,116–773,504)	138 (98.6)	0.752
	Yes	475,584 (276,607–674,561)	2 (1.4)	

[a]Cost shown as median (IQR). n: number of patients; ICU: intensive care unit

Estimating costs according to age group considering disease characteristics are shown in Table 4. The median cost per patient per year is higher in severe patients than in moderate ones, and is higher in older groups with severe hemophilia. The composition of costs (costs at blood center, household and transportation) for every patient according to patient age is shown in Table 5. Unlike the total median cost and the blood center cost, which includes medication expense, the cost associated with household and transportation do not increase with older age groups.

It is estimated that 11,141 patients have hemophilia A in Brazil, and 1,096 of these have inhibitors. Considering the median costs that were calculated previously (R$ 702,444 for patients with inhibitors and R$ 440,752 for patients without inhibitors), the total expected financial burden is R$ 5,19 billion per year, mostly justified by the volume of patients treated without inhibitors. Table 6 demonstrates the total financial burden estimates.

Discussion

Rare diseases, including hemophilia A, account for an important proportion of the health care budget [6, 17, 18], and providing cost estimates per patient bearer of these illnesses represents a piece of important information to manage financial resources at a national level. Most economic analyses on hemophilia evaluate its burden in the healthcare system perspective focusing mainly on the high prices of the medications, such as the management of inhibitors [19]. However, studies of the complete care cycle for hemophilia and the relationship among patients' characteristics and cost items were still lacking. In this context, by applying a microcosting method, in this study we innovated and are turning public the median cost information per patient per year of R$ 450,831($ 174,566) considering the Brazilian public system perspective and demonstrated its sensibility to patient's age and disease severity. Reporting this result is an important step to subside policymakers on defining

Table 4 Median cost per hemophilia A patient according to patient age and clinical characteristics

	0–11 years (*n* = 53)	12–18 years (*n* = 29)	19 + years (*n* = 58)	Total (*n* = 140)
Type of hemophilia				
Moderate	256,970 (236,395 – 277,545)	35,546 (35,546 – 35,546)	129,622 (107,383–663,537)	172,721 (96,264–277,545)
Severe	303,601 (15,099–514,529)	540,633 (354,270–698,929)	726,561 (359,276–996,386)	488,948 (239,520–805,822)
Presence of inhibitors				
Yes	505,898 (200,403–774,557)	946,540 (836,118–1,056,961)	864,048 (297,335–1,428,737)	702,445 (202,677–1,055,373)
No	274,822 (157,536 – 365,392)	513,056 (329,957 – 679,370)	673,381 (286,092–967,392)	440,753 (224,758 – 748,379)
Bleeding				
Yes	267,015 (151,975 – 418,560)	540,633 (310,776 – 673,856)	782,214 (175,251–1,212,384)	455,489 (204,485–974,735)
No	307,721 (162,310–522,012)	513,056 (348,863 – 707,851)	571,247 (406,028–918,320)	446,174 (256,039–707,851)
Target joints affected				
Yes	514,529 (342,690 – 603,776)	479,615 (436,219–1,161,385)	742,436 (152,225–1,084,012)	545,036 (296,662–1,096,067)
No	235,524 (121,928 – 362,918)	559,329 (329,957 – 679,370)	673,381 (448,337–914,674)	355,981 (200,883 – 664,758)

Cost expressed in R$ (IQR).

Table 5 Median cost per hemophilia A patient according to category of cost

	0–11 years (*n* = 53)	12–18 years (*n* = 29)	19 + years (*n* = 58)	Total (*n* = 140)
Blood center	288,814 (156,112; 465,598)	521,131 (249,466; 616,766)	717,778 (213,191; 1,005,837)	450,113 (211,414; 778,896)
Household	2,413 (0; 4,286)	4,080 (0; 6,813)	1,680 (0; 5,427)	2,094 (0; 5,123)
Transportation	471 (308; 1,413)	1,015 (382; 1,512)	609 (371; 1,287)	592 (310; 1,497)

Cost expressed in R$ (IQR).

Table 6 Hemophilia A financial burden in Brazil

	Percentile 25	Median	Percentile 75
With inhibitor (*n* = 1.096)	222,134,825	769,879,648	1,156,689,126
Without inhibitor (*n* = 10.045)	2,257,703,151	4,427,359,724	7,517,468,763
Total impact (*n* = 11.141)	2,479,837,975	5,197,239,372	8,674,157,888

Cost expressed in R$

policies at a national perspective such as it is required in the universal healthcare system implemented in Brazil.

The literature shows that direct and indirect costs increase according to disease severity, with concentrated coagulation factors accounting, on average, for 54% of disease costs in mild hemophilia, reaching 92% in critically ill patients receiving prophylactic treatment [6]. In a similar path, our study measured the incremental cost associated with the disease's severity and was able to demonstrate the influence of patient age by demonstrating that adults register the highest costs. These results can help define payment policies in healthcare systems in terms of the budget distribution between the blood centers due to the profile of the patients they are assisting. Nevertheless, the large difference in median cost identified between children and adult patients suggests that defining a unique standard fee for all patients, as it is seen in Brazil, in which the reimbursement is only modified by the serviced delivered and technology used, will lead to unbalanced reimbursement policy. Understanding the value of providing information about the disease's financial burden, this study can support the establishment of more sustainable health policies according to the population characteristics, especially in low and middle-income countries (LMICs) that deal with more challenges and budgetary restrictions than high-income countries [20–22].

Although it was not identified as a significant cost variable, complications such as bleeding deserve our attention. An analysis of real-life data after the implementation of inhibitor therapies pointed to a medium- and long-term cost reduction due to a reduction in complications. Bleeding episodes interfere in planned activities of patients and caregivers and were associated with worse quality-of-life (QoL) compared to days with no bleeding. The impacts occur on patients' mobility, pain, anxiety, and others [23, 24]. Additionally, it is important to note that hemophilia patients treated on-demand had a worse QoL index and were more likely to report bleeds compared to patients on long-term prophylaxis [25].

Even though the results presented contribute to the hemophilia cost information already available, its interpretation needs to consider a few limitations. The real-world data of the study are limited to the sample of patients treated at the participating reference blood centers, so that they do not cover all patients from Brazil.

Future use of our results must always consider this aspect and the interpretation of the total burden estimated may consider this limitation. This study did not evaluate the effects of therapeutic strategies on the patient's health status or factors related to adherence to guidelines and availability of services in the network, as the analyses focused mainly on costs. This study did not explore potential challenges and gaps in diagnosis access, which can be explored in future analyses driven to evaluate the impact of earlier diagnosis on costs and disease management. Aiming to use the results to guide health policies redesign, future studies exploring the interaction among the cost drivers are needed, as also applying similar methods to those applied in this study to measure the cost of hospitalizations for complications in patients with hemophilia A in Brazil.

Conclusion

To our knowledge, this is the first study to provide cost information for hemophilia A using a microcosting technique and real-world data from a LMIC. The results identified patient's age as an important predictor of overall cost for the management of this disease. These findings can motivate future studies designed to evaluate health policies driven to increase access to cutting-edge technologies and reduce the burden of the disease.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13561-024-00539-x.

Supplementary Material 1

Acknowledgements
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Author contributions
ALPS and CAP participated in study design and coordination, analyzed and interpreted data, and contributed to manuscript writing and reviewing. NBS and ECR collected, analyzed and interpreted data, contributed to manuscript writing and reviewing. MAZM analyzed and interpreted data, and contributed to manuscript writing, MCO, MMTHN, LEMC, TOR, MHC collected data and contributed to manuscript writing. VM participated in study design and contributed to manuscript reviewing.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Only patients who agreed with the General Personal Data Protection Law [*Lei Geral de Proteção de Dados* (LGPD)] were invited to participate in the study. All patients included have signed the Informed Consent Form. This study was submitted to and approved by the Ethical Committee of Hospital de Clínicas de Porto Alegre (CAAE: 52727121.8.1001.5327).

Consent for publication
Not applicable.

Competing interests
The study was an initiative of the company Produtos Roche Químicos e Farmacêuticos S/A do Brasil. The researchers involved in the study had full autonomy in conducting the study and are responsible for the data presented here.

Author details
[1]National Institute of Science and Technology for Health Technology Assessment (IATS) - CNPq/Brazil (project: 465518/2014-1), Ramiro Barcelos, 2350, Building 21- 507, Porto Alegre 90035-903, Brazil
[2]Graduate Program in Epidemiology, Universidade Federal do Rio Grande do Sul School of Medicine, Porto Alegre, RS, Brazil
[3]Roche Produtos Farmacêuticos, São Paulo, Brazil
[4]Ceará Hematology and Hemotherapy Center-HEMOCE, Ceará, Brazil
[5]Instituto Estadual de Hematologia Arthur de Siqueira Cavalcanti-HEMORIO, Rio de Janeiro, Brazil
[6]Hemocentro UNICAMP, Department of Internal Medicine, School of Medical Sciences, University of Campinas, Campinas, SP, Brazil
[7]Graduate Program in Industrial Engineering, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

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