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Analysis of epidemiological and economic data of hemophilia A patients in Brazil

Análise de dados epidemiológicos e econômicos de pacientes com hemofilia A no Brasil

Túlio Tadeu Rocha Sarmento[1], Renato Mantelli Picoli[1], Marília Renni[2], Yukie Sato-Kuwabara[3], Verônica Elizabeth Mata[3]

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Keywords:
hemophilia A, epidemiology, cost of illness, healthcare resource utilization, patient journey

ABSTRACT

Objective: To describe the annual medical direct costs per hemophilia A (HA) patient in the Brazilian public healthcare system (SUS) and to understand and describe the patients' hospital journey, demographical characteristics, and the procedures in the. **Methods:** This retrospective analysis of DataSUS databases. Data from individuals with registries of HA treatment were gathered between January 1st, 2018, and June 30th, 2021. Besides the D66 ICD-10th code (HA), were also considered the occurrence of some procedures like factor VIII dosage and by-pass therapy dispensation or administration as inclusion criteria. Exclusion criteria were occurrence of factor IX dispensation and female patients were excluded, among others. A record linkage using sociodemographic characteristics was conducted to identify unique patients. **Results:** Were identified 2,298 individuals underwent ambulatory and 1,018 underwent hospital treatments. The results show that most patients are from the Southeast region of the country, white and middle-aged individuals. The median cost of HA treatment per patient-year was BRL 90.36 for ambulatory care and BRL 1,015.31 for hospital care procedures. The costs were significantly higher for more severe patients and for those between 12 and 18 years old (BRL 1,974.75 and BRL 1,049.09, respectively). **Conclusion:** The evidence demonstrated encourages the implementation of policies aiming to improve the quality of care provided to patients with HA. Providing referral centers for hemophiliac patients is primordial for the success of the treatment and can result in efficiency.

Palavras-chave:
hemofilia A, epidemiologia, custo da doença, utilização de recursos de saúde, jornada do paciente

RESUMO

Objetivo: Descrever os custos médicos diretos anuais por paciente com hemofilia A (HA) no sistema público de saúde brasileiro (SUS) e compreender e descrever a jornada do paciente em âmbito hospitalar, as características demográficas e os procedimentos realizados no SUS. **Métodos:** Análise retrospectiva das bases de dados do DataSUS. Foram coletados dados de indivíduos com registro de tratamento de HA entre 1º de janeiro de 2018 e 30 de junho de 2021. Além do código D66 CID-10 (HA), foi considerada a ocorrência de procedimentos como dosagem do fator VIII e dispensação ou administração de terapia de *by-pass* como critérios de inclusão. Dentre os critérios de exclusão, destacam-se a dispensação do fator IX e indivíduos do sexo feminino. Um pareamento de registros usando características sociodemográficas foi realizado para identificar pacientes únicos. **Resultados:** Foram identificados 2.298 indivíduos em tratamento ambulatorial e 1.018 em tratamento hospitalar. Os resultados mostraram que a maioria dos pacientes são da região Sudeste do país, brancos e de meia-idade. O custo médio do tratamento da HA por paciente-ano foi de R$ 90,36 para atendimento ambulatorial e de R$ 1.015,31 para atendimento hospitalar. Os custos foram significativamente maiores para pacientes mais graves e entre 12 e 18 anos (R$ 1.974,75 e R$ 1.049,09, respectivamente). **Conclusão:** As evidências demonstradas incentivam a implementação de políticas que visem melhorar a qualidade da assistência prestada aos pacientes com HA. A disponibilização de centros de referência para pacientes hemofílicos é primordial para o sucesso do tratamento e pode resultar em maior eficiência.

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1. Cerner Enviza, São Paulo, SP, Brazil.
2. Instituto Estadual de Hematologia Arthur de Siqueira Cavalcanti, Rio de Janeiro, RJ, Brazil.
3. F-Hoffmann La-Roche, São Paulo, SP, Brazil.
Funding: F-Hoffmann La-Roche, São Paulo, SP, Brazil.
Corresponding author: Túlio Sarmento Tadeu Rocha. Cerner Enviza Brasil. Avenida das Nações Unidas, 14.171, Torre Marble, 15º andar, Morumbi, São Paulo, SP, Brazil. CEP: 04794-000. E-mail: tulio.sarmento@cernerenviza.com

Introduction

Hemophilia A is an X-linked recessive genetic disorder that predominantly affects males and is characterized by trauma-related or even spontaneous bleeding episodes (Ferreira *et al.*, 2014; Bolton-Maggs & Pasi, 2003).

According to the Annual Global Survey 2020 of the World Federation of Hemophilia, Brazil has the world's third-largest population of people with hemophilia A (10,821 patients), after the United States and India – it is important to say that there is no data from China (Stonebraker *et al.*, 2020).

In 2019, among all hereditary coagulopathies and other bleeding disorders diagnosed, the prevalence of hemophilia A was 38.66% (n = 10,821) (with 98.5% of males) in Brazil. Most of all people diagnosed with hemophilia A were found in the Southeast region of Brazil (41.6%, n = 4,502). In that same year, 36.6% (n = 3,961) of people with hemophilia A presented the severe form of the disease, 19.2% (n = 2,081) of the moderate form, and 22.2% (n = 2,402) were diagnosed with the mild form of the disease.

The hemophilia A treatment aims to reestablish adequate concentrations of factor VIII (FVIII) to reduce bleeding episodes, prevent sequelae due to hemorrhagic events, and, consequently, the mortality risk (Soares *et al.*, 2020). The hemophilia A treatment can be managed in two different regimens: 1) on-demand modality (episodic replacement), in which the clinical management is done to treat a bleeding episode using factor reposition with Factor VIII concentrate or bypassing agents (Blatny *et al.*, 2008; Brasil, 2015b), and 2) prophylaxis modality, to improve hemostasis with a factor or nonfactor agents, thus preventing bleeding episodes with a focus on an articular bleeding episode that could lead to sequelae (Bolton-Maggs & Pasi, 2003). Nowadays, the unique nonfactor agent is emicizumab, a humanized bispecific antibody against activated factor IX (FIXa) and factor X (FX), which mimics the cofactor function of activated FVIII (FVIIIa) by spatially relocating FIXa and FX to the appropriate position in the tenase complex. This treatment is administered subcutaneously and has a long half-life (approximately 30 days) (Kitazawa *et al.*, 2012).

The treatment can often be a factor of complication in hemophilia A patients, affecting their quality of life, especially when there is a need to switch the type of regimen. In this case, switching from on-demand to prophylactic treatment is potentially a driver for the improvement of quality of life in patients with hemophilia A (Ozelo *et al.*, 2015; Santagostino *et al.*., 2014). However, patients with inhibitor-complicated hemophilia have their quality of life affected by bleeding episodes and preexisting arthropathy (mobility and pain), family circumstances, and loss of productivity (Neufeld *et al.*, 2012; Ozelo *et al.*, 2015; Recht *et al.*, 2014; Santagostino *et al.*, 2014).

Epidemiological Brazilian data of patients aged between 15 and 79 years old have shown that hemorrhages are responsible for 32.4% of all causes of death, of which more than half (54%) were due to intracranial bleeding (Jardim *et al.*, 2019). Other complications are joint bleeding that can cause arthropathy, pain, permanent impairment (sequelae), and treatment-related infections (i.e., hepatitis and others) (Ferreira *et al.*, 2014; Bolton-Maggs & Pasi, 2003).

In Brazil, the Unified Health System (SUS) guarantees the treatment of hemophilia A for patients registered in one of the Hemophilia Treatment Centers. The treatment can improve the quality of life of the patients, with better childhood education, physical activity without frequent or permanent joint problems, productive professional life, and increasing life expectancy. This could prevent a severe form of hemophilia A and hence disabilities, posing a possible economic burden to individuals and health systems (Berntorp & Shapiro, 2012; Chen, 2016; Schieve *et al.*, 2020).

With this in mind, we conducted a study under the SUS perspective and its main objective was to describe the annual medical direct costs per hemophilia A patient in SUS. Additionally, we aimed to understand and describe the patients' hospital journey, identifying their demographical characteristics and the most frequent procedures in the Brazilian public healthcare system.

Methods

Study design and population

This is a retrospective, observational study using secondary data from DataSUS, the Department of Informatics of the Brazilian national public health system (SUS) (Brasil, 2021). The DataSUS owns real-world claims databases containing information regarding the reimbursement of ambulatory and hospital procedures. The whole database is anonymized, and the data is publicly and freely available on the DataSUS web page (Brasil, 2021). Therefore, no ethical approval was required.

The data used in this study was obtained from two of the DataSUS information systems: ambulatory/high complexity procedures system (SIA/SUS); and hospital procedures system (SIH/SUS). A deterministic record linkage was performed to link each procedure to a specific individual. In SIA/SUS databases, the record linkage was performed using the CNS (national health register), a unique code for each SUS patient. Although a few individuals may have more than one CNS, this is not expected to be a common fact, so we assumed each CNS as a unique patient within SIA/SUS users. On the other hand, in SIH/SUS the CNS code is not available, which led to the need of performing a record linkage using non-unique values: Zip Code, sex, and birth date. These three data, when combined, frequently have the capacity of identifying unique individuals in a population (Sweeney, s.d.). To assure the quality of the matching algorithm within SIH, unlikely or implausible links were removed from the study population

(Doidge *et al*., 2020). The criteria for identifying unlikely or implausible links used sex (unique individuals with records of both sex) and ethnicity, when individuals presented records of both of the following pairs: (1) Asian and White; (2) Asian and Black; (3) Black and White; (4) Indian and White; (5) Indian and Asian; (6) Asian and Brown; (7) Black and Indian.

Assuming that hemophilia is a rare disease, estimates were for a small population. Also, since there is no unique key able to link and integrate both SIA and SIH systems, and due to recurring missing values in Zip Code in SIA databases, a record linkage process to integrate both SIA and SIH information systems would lead to patient loss. For this reason, we decided to not perform a record linkage between these information systems, preserving cohort size.

All individuals with registries of hemophilia type A treatment between January 1st, 2018, and 30th June 2021 were included in this study. The inclusion criteria (for identifying patients with hemophilia type A diagnosis) contemplated individuals with:

- at least one record of D66 ICD-10th code;
- at least one record of factor VIII administration or dispensation;
- at least one record of by-pass therapy administration or dispensation;
- at least two records of factor VIII dosing;
- at least two records of factor VIII inhibitor dosing.

Female individuals were removed from the analysis since they were not expected to be hemophiliac patients but carriers. Besides that, patients with at least two occurrences of factor IX dosing, at least one record of factor IX dispensation or administration or at least one record of D67 or D68.4 ICD-10th codes were excluded from the study population since this would indicate they are most likely individuals with hemophilia type B (hereditary factor IX deficiency and acquired coagulation factor deficiency, respectively) (WHO, 2021).

All data regarding public healthcare consumption for each identified patient in this period were extracted, including but not limited to: costs for each inpatient or outpatient treatment, registries with other diseases, drugs used, diagnosis tests performed, age, ethnicity, and sex.

Statistical analysis

A descriptive analysis of all important variables was conducted, revealing absolute and relative frequencies of categorical data (e.g. ethnicity, comorbidities, and top-ranked procedures). For continuous variables, the central tendency (median and IQR or mean and SD) was estimated, according to data distribution. The follow-up period for each patient was defined as the interval between the year of first and last occurrence in the database. No minimum follow-up time was applied.

Although women may inherit affected X chromosomes and even experience symptoms of hemophilia type A, the disease is expected to affect mostly and more intensely male patients. For this reason, all analyses presented here is regarding male patients with hemophilia type A.

The costs of inpatient and outpatient procedures for the identified individuals were analyzed for all the study periods. These results will be presented in different sections of this study regarding whether they are inpatient or outpatient costs to facilitate the understanding of the data. Since subjects had different follow-up periods, costs were projected for each patient year. All costs arising from the clinical management of hemophilia A in our population were considered – costs associated with medication and their administration, diagnostic tests, outpatient consultations, and other outpatient or hospital services.

To identify the factors with the greatest impact on the composition of costs, the study population was divided into subgroups, respecting the following criteria: age group; the patient's state or region of residence; the patient's gender; and severity of hemophilia. An examination of the frequency of the "hemophilia A treatment" procedure per patient was performed, with those with a frequency higher than the third quartile of the sample being considered the more severe ones. The stratification by age group, in turn, considered three groups: children under 12 years old; between 12 and 18 years old; and over 18 years old.

P-values were estimated through Mood's test when comparing median values and T-test when comparing mean values. The null hypothesis was rejected, that is, differences were considered statistically significant when a p-value of equal or less than 0.05 was observed. The statistical analyses were performed with the Python software, version 3.9.6 and R (R Foundation for Statistical Computing, software version 3.6.1, Vienna, Austria). For geographical visualization, we used the Leaflet tool within folium python library.

Results

After applying both inclusion and exclusion criteria, we were able to identify 2,298 individuals in the ambulatory information system (SIA) and 1,018 in the hospital information system (SIH). Figure 1 shows all the steps to get the final study population, including the removal of implausible or impossible links for each information system.

The mean age was considerably similar for both cohorts (25.89 *vs*. 24.12 in ambulatory and hospital, respectively). In both SIA and SIH populations, the most frequent age group was the one with individuals older than 18 years old, 61.14% and 51.96%, respectively. The geographical distribution of the population is similar for both SIA and SIH, with the southeast region being the most common in both cases: 75.68% and 55.39%, respectively.

The most common 10th ICD groups differed between SIA and SIH groups: Persons encountering health services

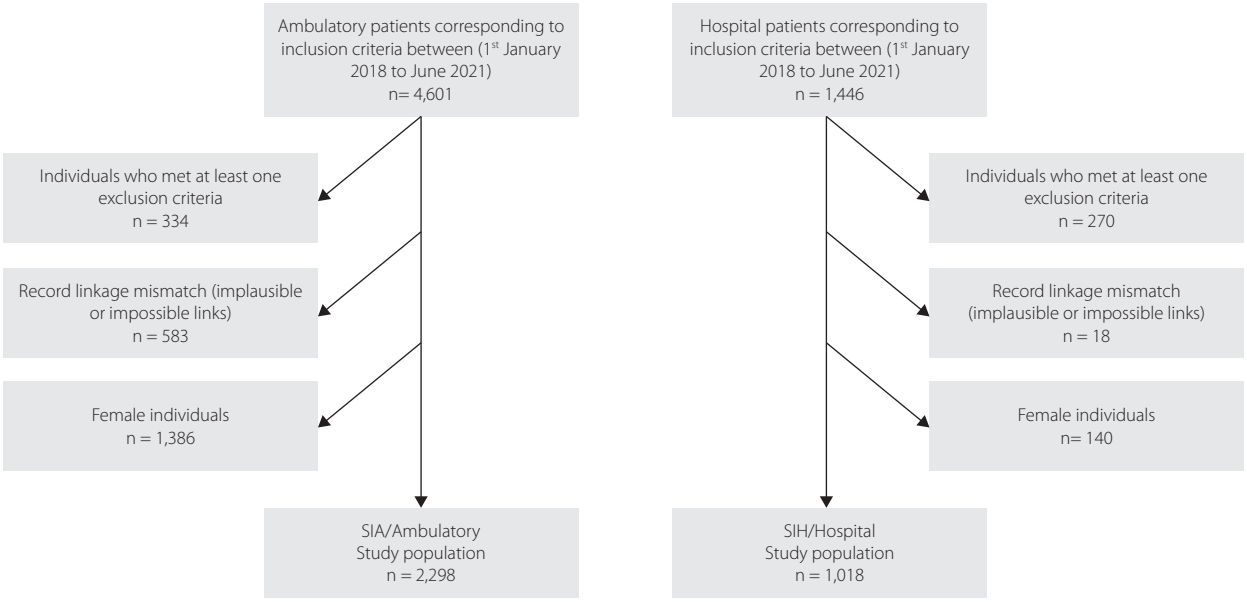

Figure 1. Study's population flow.

for examination – typical procedures in patient's follow-up – were the most prevalent ICD groups in the population identified in ambulatory datasets (24.85%); while cranial traumatisms and bacterial diseases were the most frequent 10th ICD disease groups in hospital population (3.14% and 2.85%, respectively) – more acute events that may require hospital care. A highlight must be made for the frequency of hepatitis in the ambulatory population: Affecting 5.66% of individuals, making it the third most frequent comorbidity. Table 1 shows the study's population characteristics.

When performing a subgroup analysis according to the age of the patients, we were able to identify the most common comorbidities within groups: among individuals younger than 12 years old, the most frequent comorbidities were Injuries to the head (5.84%), influenza and pneumonia (3.71%), and other bacterial diseases (2.92%); for patients between 12 and 18 years old, other diseases of blood and blood-forming (2.29%), injuries to the head (1.53%) and episodic and paroxysmal disorder (1.53%) were the most common comorbidities; for patients older than 18 years old, other bacterial diseases, other diseases of the digestive system and influenza and pneumonia, 3.77%, 3.59%, and 2.64% respectively.

We re-assessed the SIH population in terms of hemophilia A severity, defined as the 25% of individuals with the highest frequency of hemophilia treatments per year. These individuals are distributed throughout Brazilian territory similarly as "normal-risk" SIH patients, with the Southeast region containing most of them (63.72%). Table 2 shows other characteristics of this population.

Ambulatory procedures and costs

The most frequent ambulatorial procedure among patients who underwent ambulatory care was medical appointments at specialized healthcare facilities, accounting for 21.20% of all procedures during the analysis period and being performed in 65.07% of hemophilia A patients. Four of the five most frequent procedures correspond to the patient's follow-up and monitoring: physician (or other health professionals) visits and procedures regarding hemostasis monitoring (e.g., factor VIII dosage and hemogram). Urgency visits are only the fifth most frequent procedure, performed in only 14.54% of patients, indicating a more stable tendency in the clinical condition of the ambulatory population. Table 3 shows the most frequent ambulatory procedures with the number of times and patients in which each procedure was performed.

The median cost for outpatient treatment during the follow-up period was BRL 80.36 per patient-year, a value considerably lower when compared to inpatient costs (to be shown in the next section). Median costs were decreasing at the same pace as individuals got older, but the difference found was not statistically significant (Table 4).

Hospital procedures and costs

When assessing the hospitalization events in the study's population, we were able to detect that the most frequent procedure within the analysis period was the treatment of hemophilia A, corresponding to 61.99% of all procedures and being performed on 85.88% of the identified patients (Table 5). Table 5 presents information regarding the most frequent procedures, health facilities, and length of each hospitalization event. The mean length in Intensive Care Unit (ICU) stay was extremely close to the mean length of the normal inpatient stay: 6.00 *vs.* 6.19, respectively.

Three of the five health facilities with the most patients who underwent hospitalization are from the southeast region, notably the most frequent Brazilian geographical

Table 1. Study's population characteristics

Variables	SIA/Ambulatory population n (%)	SIH/Hospital population n (%)
Age		
Under 12 years old	556 (24.20)	369 (36.25)
From 12 to 18 years old	337 (14.66)	120 (11.79)
More than 18 years old	1,405 (61.14)	529 (51.96)
Mean (SD)	25.89 (19.37) years	24.12 (20.38) years
Race/Ethnicity		
White	951 (41.38)	391 (38.41)
Brown	472 (20.54)	439 (43.12)
Black	70 (3.05)	47 (4.62)
Other or not reported	805 (35.03)	141 (13.85)
Region		
Southeast	1,738 (75.63)	565 (55.50)
Northeast	117 (5.09)	229 (22.50)
South	283 (12.32)	109 (10.70)
North	35 (1.52)	75 (7.37)
Midwest	125 (5.44)	40 (3.93)
Most frequent comorbidities/ICD-10th groups*		
#1	Persons encountering health services for examination: 571 (24.85)	Other bacterial diseases: 32 (3.14)
#2	Systemic connective tissue disorders: 173 (7.53)	Injuries to the head: 29 (2.85)
#3	Viral hepatitis: 130 (5.66)	Other diseases of the blood and blood-forming organs: 17 (1.67)

region among the identified patients, as discussed before. Figure 2 shows the distribution of hospitalized population through Brazilian territory on a heatmap, with each icon representing a health facility/blood center. The five health facilities with the most patients are represented by a blue icon star on Figure 2: *Instituto Estadual de Hematologia Arthur de Siqueira Cavalcanti* (16.57%); *Hospital de Transplantes Euryclides de J. Zerbini* (8.63%); *Fundação Hemope* (7.94%); *Hospital das Clínicas da Faculdade de Medicina da USP* (4.12 %); and *Hospital Regional de Bom Jesus* (PI) (3.14%). As presented previously in Table 1, patients are mainly from the Southeast (55.39%) and Northeast (22.55%) regions.

We estimated a median cost of BRL 1,015.31 per patient-year during the study period. When performing a subgroup analysis, it was possible to observe that individuals with a more severe clinical condition presented higher median costs (BRL 1,974.75 per patient-year). This was an expected result, because more severe patients may go through hospitalization more frequently or even with more complicated clinical conditions, requiring longer hospital stays or intensive care settings. Besides that, the estimated median cost for patients from 12 to 18 years old was greater than the other age groups (BRL 1,049.09) (Table 6).

When assessing each age group, more severe patients had higher median costs: in all scenarios, the median cost for more severe patients was higher than the third quartile of less severe patients (Figure 3): 39.29%, 54.70%, and 51.36% for under 12 years old, from 12 to 18 years old, and for older than 18 years old, respectively (comparing more severe patients with "normal severity" ones). Higher variations were identified in costs for individuals older than 18 years old.

Discussion

The study highlighted the epidemiological and economic aspects of hemophilia A in Brazil using the data systems of DataSUS. The population of hemophiliacs analyzed was mostly male with an average age of adults. It is important to notice that, according to the standard deviation, this population comprehends children and middle-life people. Furthermore, most of them were from the Southeast regions of Brazil.

Table 2. Characteristics of more severe patients

Variables	Number of patients (%)
Age	
Under 12 years old	75 (33.19)
From 12 to 18 years old	17 (7.52)
More than 18 years old	134 (59.29)
Mean (SD)	26.37 (19.07) years
Race/Ethnicity	
White	102 (45.13)
Brown	90 (39.82)
Black	17 (7.52)
Other or not reported	17 (7.52)
Region	
Southeast	144 (63.72)
Northeast	44 (19.47)
South	20 (8.85)
North	15 (6.64)
Midwest	3 (1.33)
Most frequent comorbidities/ICD-10th codes*	
#1	Other bacterial diseases: 9 (3.98)
#2	Injuries to the head: 8 (3.54)
#3	Other diseases of the digestive system: 7 (3.09)
Number of procedures	
Hospitalizations per patient-year (SD)	1.14 (1.22)

Table 3. Most frequent ambulatory procedures

Variables	Number of procedures (%)	Number of patients (%)
Procedures		
Medical appointments at specialized healthcare facilities	18,938 (21.29)	1,457 (63.40)
Higher education professionals consultation in specialized care (except physician)	5,104 (5.74)	696 (30.29)
Factor VIII dosage (inhibitor)	3,650 (4.10)	1,100 (47.87)
Complete hemogram	3,381 (3.80)	1,157 (50.35)
Urgency visits at specialized healthcare facilities	2,998 (3.37)	356 (15.49)

Table 4. Ambulatory costs per patient-year according to patient's age group

Variables	Median (p-value) BRL	1st-3rd quartile BRL
Entire population	80.36	36.95-145.77
Age groups		
Under 12 years old	85.58 (ref)	36.92-154.81
From 12 to 18 years old	76.74 (0.12)	34.59-136.47
More than 18 years old	78.40 (0.10)	37.64.63-145.47

Table 5. Procedures and health facilities regarding hospitalization events

Variables	Number of procedures (%)	Number of patients (%)
Procedures		
Hemophilia treatment	1,428 (61.95)	874 (85.85)
Diagnosis or urgency treatment in the pediatric clinic	100 (4.34)	80 (7.86)
Treatment of purpura coagulation defects or other hemorrhagic problems	90 (3.90)	52 (5.10)
Hospitalization events		
Mean length of hospital stay (SD)	6.19	6.81
Mean ICU days (SD)	6.07	5.78
Number of ICU events (%)	140 (6.06)	94 (9.22)
Number of hospitalizations per year (SD)	577.50 (165.46)	348.50 (111.04)*

*Hospitalizations per patient-year. ICU: intensive care unit.

Table 6. Costs of hospitalization in hemophilia A patients

Variables	Median (p-value) BRL	1st-3rd quartile BRL
Entire population	1015.31	929.05-1890.70
Is a more severe Hemophilia A clinical condition?		
Yes	1,974.55 (ref)	1,130.52-3,268.75
No	**971.52 (<0.001)**	929.05-1,230.31
Age groups		
Under 12 years old	981.10 (ref)	937.05-1,471.51
From 12 to 18 years old	**1,049.09 (0.004)**	951.05-1,455.36
More than 18 years old	**1,044.96 (0.001)**	929.05-2,297.66

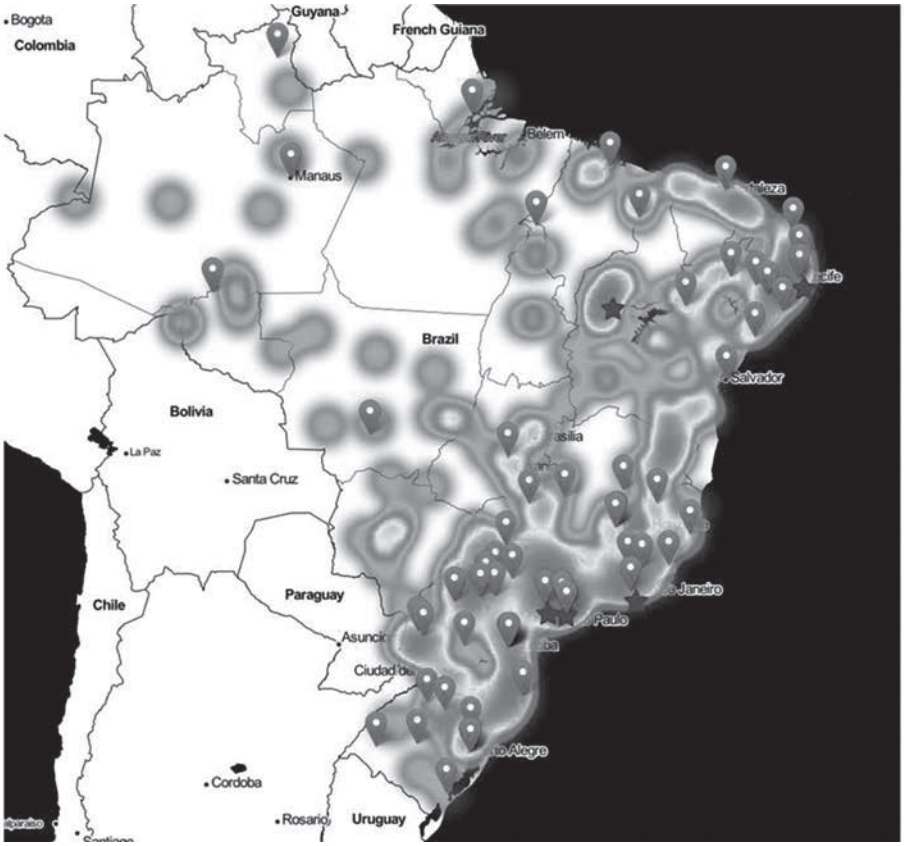

Figure 2. Heatmap of patients and health facilities and blood centers.

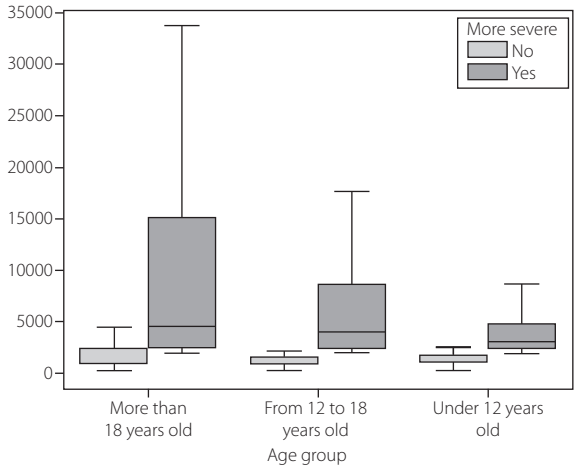

Figure 3. Boxplot of costs per patient-year according to age group and severity level.

The treatment of hemophilia was the most frequent procedure followed by the procedures related to the main diagnosis (hemophilia A), such as diagnosis and/or urgency treatment in pediatrician clinic and treatment of purpura coagulation defects or other hemorrhagic problems. The median annual direct costs per patient during the period of follow-up was BRL 1,307.81, being higher in individuals with greater severity.

As demonstrated by our study and according to the data from the Ministry of Health, almost all patients with hemophilia A (more than 90%) are males, aged between 15 and 59 years. Data from the Annual Global Survey corroborates with this, showing that, worldwide, there are 87% of males with the condition (Stonebraker *et al.*, 2020).

The treatment of hemophilia, both in ambulatory and hospital, is expensive and needs to be maintained throughout life. Even when treated, a significant number of patients still experience bleeding and need hospitalization, reflecting in their quality of life (Ozelo *et al.*, 2015; Santagostino *et al.*, 2014). In the past few years, significant therapeutic advances and unmet needs have been achieved with very high investments that hemophilia remains one of the most costly and challenging diseases to national health services and insurance providers in the long term. Still, one of the most unmet needs of patients with hemophilia was to reduce their treatment burden in terms of availability and manageability of treatments with a convenient route of administration and less frequent intravenous injections. A proposed solution for these unmet needs is the use of a monoclonal antibody targeting hemophilia A patients both with and without inhibitors (GlobalData Healthcare, 2021; von Mackensen *et al.*, 2017).

There are several studies analyzing economic burden and costs per patient. It is important to highlight that those studies vary in the treatment to the patients and the more severe the condition, the more are the costs. Most these studies come from developed countries. A recent American study showed that the mean annual direct cost for the treatment of an individual with hemophilia exceeds $150,000, of which 86%-92% are costs for clotting factor concentrates. As demonstrated by our study, direct costs are higher for patients with greater severity such as prophylaxis, presence of arthropathy, acquired immunodeficiency syndrome (AIDS), Hepatitis C Virus (HCV) infection, or coagulation factor inhibitors development (Ferreira *et al.*, 2020). Another study from the United States compared different treatments to understand the most cost-effective one, once the severe cause in the country represents 56,6% of the population with hemophilia A. The study found that recombinant FVIII with an extended half-life might offer a cost-effective option for severe cases (Bullement *et al.*, 2021).

Data from 2018 showed that in Australia its direct costs with the treatment represent 76.1% of the total hemophilia costs, while the indirect costs represent 12.9% of the total costs (Brown *et al.*, 2020b). Data from the 2015 Australian Burden of Disease Study showed that there was a total of 227 disability-adjusted life years (DALY), 138 years lived with disability (YLD) and 89 years of life lost (YLL) in males from hemophilia (Brown *et al.*, 2020b). This financial burden of the disease may be explained by the number of healthcare professionals involved in the care of patients with hemophilia A: hematologists, hemophilia nurses, social workers, physiotherapies, psychologists, psychotherapists, general practitioners, and a variety of complementary therapists (i.e., acupuncture or massage therapists) (Brown *et al.*, 2020a).

Aligned to our data, a study conducted at the Regional Blood Center of Juiz de Fora, in the state of Minas Gerais (the Southeastern region of Brazil), found that costs were higher when comparing severe to moderate hemophilia (respectively R$ 89,467.77 and R$ 53,486.50 per patient and per year, $p = 0.013$), and moderate to mild (R$ 53,486.50 *versus* R$ 2,962.10 per patient and per year, $p < 0.001$) respectively. The mean annual cost of the patient with an inhibitor, treated with an ITI, was R$ 170,706.48, that is, almost three times the total mean of R$ 57,416.43 (Ferreira *et al.*, 2020).

In Iran, a developing country, the annual cost with hemophilia A is USD 37661, with most of the budget from direct medical costs (Keshavarz *et al.*, 2020). The authors suggested using a domestic provision for medicines and more specialized services and care in towns. As shown on the map, in Brazil we also have a concentration in some regions of the country.

A higher prevalence of hemophilia A patient was found in the South, followed by the Southeast region of Brazil. Currently, in Brazil, 120 hemotherapy services linked to the public health network provide outpatient care for patients with hemophilia. Of this total, more than half is distributed in the South and Southeast regions. However, an accurate diagnosis and management of primary or emergency care represent the burden of disease to the public health service.

This can also be illustrated by the fact that, in the Rio Grande do Sul, more than 60% of patients are qualified to receive the FVIII, while in Bahia the rate of patients is 11.5% and, in Rondônia, only 4.7 % (2).

Another important aspect that is worth mentioning is the age, especially regarding under 12 years old. They represent a large number of patients, and the costs are high to maintain in the long term. The socioeconomic profile of hemophiliac patients and daily lifestyles should be considered, as they influence the severity of the consequences of the disease. Children without qualified parental care for self-care education, without specialized school monitoring, or who live in places and/or households with a higher risk of accidents will have earlier and more severe repeated bleeding and, consequently, more disabling complications and early mortality (Sayago & Lorenzo, 2020). For those children with severe hemophilia, the economic burden is even higher than those with mild, because they need to receive routine care while mild hemophilic patients have to attend to the clinic less often (Price *et al*., 2015). This factor may impose indirect costs to the family of children with hemophilia, once it affects the income of their caregivers in terms of absenteeism from work and loss of productivity (Chen, 2016).

Fortunately, the Brazilian public healthcare system provides economic benefits to hemophilia patients and their families (still, with important limitations). However, this factor, in addition to the costs with overall treatment, imposes a significant direct costs to the SUS. To reduce this economic burden in the early days of life and potentially for adults with the condition, a prophylaxis regimen is advantageous due to the higher effectiveness and utility when compared with an on-demand regimen (Zahedi *et al*., 2021).

It is desirable that the treatment of coagulopathies is increasingly decentralized, which humanizes the approach to affected patients (Brasil, 2015a). The follow-up (ambulatory or hospital) of the patient must be monitored by the multidisciplinary team. The provision of care by centers specializing in the treatment of hemophilia A with a complete multidisciplinary team is a desirable solution to reduce the overall costs of treating the disease, once it has been shown to decrease hemophilia-related morbidity and mortality (Price *et al*., 2015). However, it is estimated that most people with hemophilia are low-income, which interferes with the assurance of transport, specialized services, and high rates of school dropout and unemployment (Sayago & Lorenzo, 2020), added to one of the important limitations of the economic benefits provided by SUS – the inconsistent specialized center's distribution to the municipalities. This unmeasured cost of hemophilia treatment (e.g. travel expenses to attend a specialist hemophilia clinic or hemophilia treatment centers) represent an economic burden to families of children and adults with hemophilia (Price *et al*., 2015). Additionally, most of the Brazilian centers for specialized treatment for hemophilia lack an inpatient service, which often means that the bleeding event is treated on an outpatient basis when perhaps the most recommended is hospitalization (Sayago & Lorenzo, 2020). With all this in mind, ensuring this care and encouraging the implementation of policies aimed to improve the quality of care provided to patients is primordial for the success of the treatment and to reduce costs with complications.

Conclusion

It is extremely important to know and understand the hemophilic patient's treatment journey in the Brazilian public system. These individuals demand long-term treatment that can impose significant costs on both the health system and family members. The evidence demonstrated in this study encourages the implementation of policies aiming to improve the quality of care provided to patients, especially for children and middle-aged people who are affected by the disease. Furthermore, this study highlighted the obstacle of the inconsistent specialized center distribution in the municipalities. Providing referral centers for hemophiliac patients is primordial for the success of the treatment and results in better disease control, quality of life, a reduction in the economic and social burden of the disease.

Disclosure

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