Analysis of Distribution and Access Time to Transplant in Patients with Acute Lymphoblastic Leukemia and Acute Myeloid Leukemia in Brazil (2016-2022)

https://doi.org/10.32635/2176-9745.RBC.2024v70n4.4749

Análise da Distribuição e Tempo de Acesso ao Transplante em Pacientes com Leucemia Linfoblástica Aguda e Leucemia Mieloide Aguda no Brasil (2016-2022)

Análisis de la Distribución y el Tiempo de Acceso al Trasplante en Pacientes con Leucemia Linfoblástica Aguda y Leucemia Mieloide Aguda en el Brasil (2016-2022)

Wini de Moura Miguel[1]; Carlos Alberto Esteves Adão[2]; Janaína Santos Paulista[3]; Bright Amenu[4]

ABSTRACT

Introduction: Bone marrow transplantation is a crucial treatment for patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Analyzing demographic distribution and access time to transplantation provides insights into disparities in treating these conditions. **Objective:** To analyze the distribution of patients with ALL and AML and identify factors influencing the time to transplantation in Brazil between 2016 and 2022. **Method:** Data from 11,908 patient records from Redome-net were collected, with 1,129 transplanted patients included in the statistical analysis. Shapiro-Wilk test for normality, Levene's test for homogeneity, and Kruskal-Wallis and Mann-Whitney tests for median comparisons were used, with a 95% significance level. Variables such as sex, race/color, age group, type of service, and state were analyzed. **Results:** Most patients were male (57%) and adult (62%), with a predominance of White individuals (59%). Only 19% of the patients were transplanted. Older patients and those from the public system had longer median waiting times. Significant differences were observed between states, with Paraná showing the shortest waiting time. **Conclusion:** The study revealed regional and sociodemographic disparities in the time to bone marrow transplantation in Brazil. Older patients and those from the public system face longer waiting times, highlighting the need for improvements in healthcare infrastructure and equitable access to treatment. These findings emphasize the importance of health policies targeted to reduce inequalities and optimizing treatment for patients with acute leukemias.

Key words: Hematopoietic Stem Cell Transplantation/statistics & numerical data; Acute Myeloid Leukemia; Precursor Cell Lymphoblastic Leukemia-Lymphoma; Waiting Lists; Health Services Accessibility.

RESUMO

Introdução: O transplante de medula óssea é um tratamento essencial para pacientes com leucemia linfoblástica aguda (LLA) e leucemia mieloide aguda (LMA). A análise da distribuição demográfica e do tempo de acesso ao transplante fornece *insights* sobre as disparidades no tratamento dessas condições. **Objetivo:** Analisar a distribuição de pacientes com LLA e LMA e identificar fatores que influenciam o tempo de acesso ao transplante no Brasil entre 2016 e 2022. **Método:** Foram coletados 11.908 registros de pacientes do Redome-net, dos quais 1.129 pacientes transplantados foram incluídos na análise estatística. Foram utilizados o teste de Shapiro-Wilk para normalidade, Levene para homogeneidade, e os testes Kruskal-Wallis e Mann-Whitney para comparação de medianas, com um nível de significância de 95%. Foram analisadas variáveis como sexo, raça/cor, faixa etária, tipo de serviço e Estado. **Resultados:** A maioria dos pacientes era masculina (57%) e adulta (62%), com predominância de brancos (59%). Apenas 19% dos pacientes foram transplantados. Pacientes mais velhos e aqueles atendidos pelo sistema público apresentaram tempos medianos de espera mais longos. Diferenças significativas foram observadas entre os Estados, com o Paraná apresentando o menor tempo de espera. **Conclusão:** O estudo revelou disparidades regionais e sociodemográficas no tempo de acesso ao transplante de medula óssea no Brasil, destacando a necessidade de melhorias na infraestrutura de saúde e na equidade do acesso ao tratamento. Tais descobertas sublinham a importância de políticas de saúde para reduzir desigualdades e otimizar o tratamento para pacientes com leucemias agudas.

Palavras-chave: Transplante de Células-Tronco Hematopoiéticas/estatística & dados numéricos; Leucemia Mieloide Aguda; Leucemia-Linfoma Linfoblástico de Células Precursoras; Listas de Espera; Acessibilidade aos Serviços de Saúde.

RESUMEN

Introducción: El trasplante de médula ósea es un tratamiento crucial para pacientes con leucemia linfoblástica aguda (LLA) y leucemia mieloide aguda (LMA). Analizar la distribución demográfica y el tiempo de acceso al trasplante proporciona información sobre las disparidades en el tratamiento de estas condiciones. **Objetivo:** Analizar la distribución de pacientes con LLA y LMA e identificar los factores que influyen en el tiempo de acceso al trasplante en el Brasil entre 2016 y 2022. **Método:** Se recopilaron datos de 11 908 registros de pacientes del Redome-net, de los cuales 1129 pacientes trasplantados fueron incluidos en el análisis estadístico. Se utilizaron las pruebas de Shapiro-Wilk para normalidad, de Levene para homogeneidad y las de Kruskal-Wallis y Mann-Whitney para comparación de medianas, con un nivel de significación del 95%. Se analizaron variables como sexo/color, raza, grupo etario, tipo de servicio y estado. **Resultados:** La mayoría de los pacientes eran hombres (57%) y adultos (62%), con predominio de individuos blancos (59%). Solo el 19% de los pacientes fue trasplantado. Los pacientes mayores y aquellos del sistema público presentaron medianas de tiempo de espera más largas. Se observaron diferencias significativas entre los estados, siendo Paraná el que mostró el menor tiempo de espera. **Conclusión:** El estudio reveló disparidades regionales y sociodemográficas en el tiempo de acceso al trasplante de médula ósea en el Brasil. Los pacientes mayores y los del sistema público enfrentan tiempos de espera más largos, destacando la necesidad de mejoras en la infraestructura de salud y en el acceso equitativo al tratamiento. Estos hallazgos subrayan la importancia de políticas de salud enfocadas en reducir desigualdades y optimizar el tratamiento para pacientes con leucemias agudas.

Palabras clave: Trasplante de Células Madre Hematopoyéticas/estadística & datos numéricos; Leucemia Mieloide Aguda; Leucemia-Linfoma Linfoblástico de Células Precursoras; Listas de Espera; Accesibilidad a los Servicios de Salud.

[1,2]Instituto Nacional de Câncer (INCA). Rio de Janeiro (RJ), Brasil. E-mails: winimm17@gmail.com; carloseadao@gmail.com. Orcid iD: https://orcid.org/0000-0002-1336-3252; Orcid iD: https://orcid.org/0009-0003-6207-3096
[3]A. C. Camargo *Cancer Center*. São Paulo (SP), Brasil. E-mail: janainaonco@gmail.com. Orcid iD: https://orcid.org/0000-0002-2146-5259
[4]Universidade Federal do Rio de Janeiro (UFRJ). Rio de Janeiro (RJ), Brasil. E-mail: amenubright2@gmail.com. Orcid iD: https://orcid.org/0000-0003-0985-7820
Corresponding author: Wini de Moura Miguel. Rua Zamenhof, 62 – Estácio. Rio de Janeiro (RJ), Brasil. CEP 20250-070. E-mail: winimm17@gmail.com

INTRODUCTION

Bone marrow, a substance found in the cavities of the bones, especially axial and long bones, is responsible for the production of red cells, white cells and platelets, essential for oxygenation, defense and blood clotting[1]. Patients with blood disorders can be treated with medications, chemotherapy or transfusions; hematopoietic stem cells transplantation (HSCT), also known as bone marrow transplant (BMT) are options if treatment fails. HSCT aims to augment bone marrow function with stem-cells of a compatible donor for acute leukemias and lymphomas[2,4]. Despite the risks, it has been shown effective with remarkable results in survival and cure[5].

Leukemia is a malignant disease affecting the bone marrow which suppress the production of normal blood cells and replace them by abnormal cells. There are more than 12 types of leukemia, the most important are: acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and chronic lymphoblastic leukemia (CLL). Incidence increases with age, ALL is predominant in children and AML and CLL in older adults. In 2020, 475 thousand new cases of leukemia worldwide have been estimated, 270 thousand in males and 205 thousand in females, with great incidence in North America, Australia and Western Europe. In Brazil, in the same year, 6,738 individuals died by leukemia[6].

AML is a malignant disease of hematopoietic stem-cells most common in adults with high mortality and more than 20 thousand cases annually in the United States of America (USA). The treatment has improved but is more effective in young adults, while older adults have worst prognosis and are treatment-resistance. Therapies include cytotoxic chemotherapy and HSCT with benefits and risks as relapses and transplantation-related mortality[7].

As soon as transplantation occurs, better is the overall survival for AML patients. Studies show that ten-year overall survival is 22.9% for these patients, however, the rate depends of the disease stage at transplantation – 56.3% for patients in first complete remission, 38% for patients in second remission and only 3.7% for patients with advanced disease. These results show a remarkable progress of treatment and survival for patients with AML, from 20% to more than 50% in the last 20 years post-HSCT[8,9].

ALL is a precursor B-cell malignant lymphoid neoplasm with excessive proliferation of blasts in the bone marrow, most common in children but with worst prognosis for older adults causing genetic mutations[10].

The standard-of-care for refractory or high risk ALL is allogeneic stem-cells transplant, better than chemotherapy, its effectiveness depends on Philadelphia chromosome (Ph+ALL) and other mutations and is less effective in older adults due to comorbidities. The graft-versus-host disease (GVHD) is a severe complication while autologous transplant, despite high relapse risk, can improve the quality-of-life. Allogeneic HSCT improves disease-free survival (DFS) from 30% to 65% in the first complete remission, but cure occurs in 5%-17% of the cases[10,11].

Cells are collected from the bone marrow, peripheral blood or placenta/umbilical cord. Transplant can be autologous (own patient), allogeneic (compatible donor) or syngeneic (identical twins). In autologous transplant, cells are harvested, frozen and reinfused after the treatment. In syngeneic, cells are harvested from identical twins and in allogeneic, from a related or unrelated[12] compatible donor. The type of cancer, general health condition, age and existing compatible donor will define the choice between autologous and allogeneic[13].

Genetic compatibility, especially in genes of the human major histocompatibility complex (MHC) plays a key role in successful HSCT, reducing the risks of graft rejection and GVHD[14]. A successful transplant hinges on a full compatibility analysis.

BMT requires 100% donor-receptor compatibility, but the odds of finding a related compatible donor is but 40%. In Brazil, the likelihood of finding an unrelated donor in donor database is one in 100 thousand[5].

Because of this obstacle, many patients seek alternative sources as haploidentical donors (more than 50% compatibility among individuals with partial haplotypes match, usually among first or second degree relatives), and umbilical cord and placental blood (UCPB). UCPB is harvested at birth, has advantages as prompt availability, few conditions for HLA match and low risk of GVHD, although grafting is slower with few clinical data than BMT[15].

If a related donor is not available, the search for unrelated donor requires the sign-in of the patient at the National Registry of Bone Marrow Recipients (Rereme). The staff of the Brazilian Registry of Volunteer Bone Marrow Donors (Redome) coordinates the search and shipping of cell products from unrelated donors[14]. Currently, Rereme counts with nearly 650 patients seeking for an unrelated donor[16].

The registries oversee the search for stem-cells unrelated donors, including umbilical cord blood for potential recipients[15]. In Brazil, Redome is the only certified registry to find and keep volunteer donors as part of the Ministry of Health Program, under the purview of the National Cancer Institute (INCA). With more than five million registers, Redome is the third major world

bank and annually, more than 300 thousand new donors are signed-in[16].

Redome-net is an information system developed by INCA to register bone marrow recipients and data from registered volunteer donors that allow the identification of compatible donors for patients/recipients. The Ministry of Health established the criteria for selection and identification of compatible donors for HSCT as Directive 931[17] of 2009 which created rules to improve the utilization of the available resources and updating the national donors registry, making INCA the institution in charge of providing technical support to the National Transplant System related to HSCT and develop computer-based system to manage Redome and Rereme[18].

The last years have witnessed a significant increase of the possibility of finding a compatible unrelated donor, due to the expansion of the number of volunteer donors registered in innumerous donor centers scattered worldwide[14]. According to data of the Hospital Admissions Information System of the National Health System (SIH/SUS), the number of unrelated BMT increased in the last ten years in Brazil with annual mean of 138.9. The lowest number was detected in 2020 (n = 86), and the highest in 2017 (n = 181)[13].

However, a study has addressed the issues related to the HSCT system in Brazil for an expressive portion of the patients, showing that there are insufficient hospital beds, decline of transplants and poor access to HSCT associated technology[19].

The most concerning ethical issue is the death of patients in the waiting list for transplantation or even before being included in the list due to obstacles to access basic health services and specific exams since health-related deaths are the clear expression of inequities and unfairness[19].

Possibly, socio-economic inequalities, especially in Latin America and social disparities are responsible for poor access to HSCT and its benefits[19]. Notwithstanding the utilization of alternative donors, age, race/color and socioeconomic conditions are obstacles to access HSCT with scarce studies so far[21].

The objective of the present study, considering BMT-related challenges, is to analyze the distribution of patients with ALL and AML registered at Redome-net between 2016 and 2022 and identify annual variations of the number of patients registered and transplanted with focus on potential significant changes to access transplant during the COVID-19 pandemic. The analysis of the data and barriers faced can contribute to optimize the access and improve survival and success rates for these patients.

METHOD

Descriptive cross-sectional study with data of recipients registered at Rereme, diagnosed with ALL and AML through Redome-net[16], with available clinical and socioeconomic data, whose transplantation centers have actively searched the registry from January 2016 and December 2022 (analysis of seven years). This time period was chosen to reduce the variability of registers to ensure data consistency due to missing data in earlier years. A longer period of 10 years could potentially present variations and affect the analysis, in addition, the period analyzed offered a robust and detailed sample allowing a more accurate analysis.

The variables age at registration, sex, race/color, type of service, current status, diagnosis and period of register in general or origin States of the recipients registered were analyzed.

Age range was simplified to facilitate the interpretation and analysis of the data, reflecting different characteristics of the range in relation to the process of HSCT: children (0-12 years), adolescents (12-19 years), adults (20-65 years) and older adults (65 years or older), following the Child and Adolescent Statute and WHO (World Health Organization) guidelines.

The methodology of "*Instituto Brasileiro de Geografia e Estatística (IBGE)*" to classify race and color based on the Brazilian Census race standard (Black, Brown, Yellow and Indigenous) was applied.

The male/female binary classification of sex according to the WHO Guidelines was adopted. The patients were classified according to the type of service (public or private) and State of residence: Ceará (CE), Distrito Federal (DF), Minas Gerais (MG), Pernambuco (PE), Paraná (PR), Rio de Janeiro (RJ), Rio Grande do Sul (RS), Santa Catarina (SC) and São Paulo (SP).

The current status was divided in three groups: awaiting transplantation, transplanted or not transplanted. The category "not transplanted" includes patients who, for several reasons, as death or other forms of treatment did not submit to HSCT. Due to poor accuracy of the number of deaths registered at Redome-net[16], this parameter was not calculated in the present study to avoid biases.

Longest and shortest waiting time for HSCT were considered for the two types of diseases in nine Brazilian states.

The State population was not considered to analyze the waiting time of patients registered at Redome-net[16], because the focus was to analyze the waiting time for the patients registered, its inclusion could tamper the results as in more populous States and failing to reflect the actual issues of the transplantation system. However, this

variable is important in future studies of public health for better understanding.

11,908 patients registered at Redome-net[16] have been collected for 2016-2022. Of these, 474 registers were excluded due to nonupdated information and 6,161 were selected for analysis of ALL (3,708) and AML (2,908) from the 11,434 remaining registers to perform a descriptive analysis of the distribution of these diseases. For statistical studies, only 1,276 patients transplanted were included. This result was adjusted to 1,129, 619 ALL and 510 AML to establish a consistent sample for each group.

1,129 cases of patients transplanted for ALL (619) and AML (510) were analyzed. The variables investigated were: sex, race/color, age at the register and State. The Shapiro-Wilk[22] normality and Levene[23] homogeneity tests were applied. Medians were compared with the test Kruskal-Wallis[24] for groups with more than two categorical variables and the Mann-Whitney[25] for groups with two variables. Both tests adopted the confidence interval of 95% and $p < 0.05$ was considered significant .

Biserial Mann-Whitney test[25] was utilized for effect size and omega for Kruskal-Wallis[24]. Adjustment of p values followed the Bonferroni[26] method. Statistical charts were created with the package ggbetweenstats[27] and tables were created with the package gtsummary[28]. All the statistical and descriptive analyzes were performed with the software R[29].

INCA's Institutional Review Board (IRB) approved the study, report number 6128694 (CAAE (submission for ethical review: 69971023.5.0000.5274) in compliance with Directive 466[30], December 12, 2012 of the National Health Council.

RESULTS

As shown in Table 1, the study encompassed 6,161 patients from different States with mean age of 30.04 years of age with slight predominance of males (57%) over females (43%). Most of the patients (62%) were adults, followed by children (21%) and adolescents (11%), while older adults were the smallest portion of the sample (5.5%). Most of the patients claimed they were White (59%) followed by Browns (33%) and Blacks (5.4%).

A significant portion of the patients (65%) utilized private health institutions and 35%, public services. The diagnoses were evenly distributed among ALL (56%) and AML (44%).

Only 19% of the patients were submitted to transplantation, 71% were not transplanted and 9.5% were still awaiting transplantation when the study was conducted.

Graph 1 shows the trends of increase of patients registered and of access to treatment (awaiting transplantation, not transplanted and transplanted) analyzed from 2016 to 2022. From 2016 to 2018, the number of patients registered increased, stabilized from 2018 to 2020 and resumed growth after 2020.

The quantity of patients not submitted to transplantation followed a similar trajectory of patients registered with slight decline after 2020. Patients in the waiting list increased constantly through this period, but accentuated since 2018, while those who submitted to transplantation kept relative stable from 2016 to 2018 with slight increase in the following years.

The statistical study on the influence of the variables of the patients on the access to transplantation encompassed 1,129 patients. Of these, 619 were transplanted for ALL and 510, for AML. The analysis was divided by sex, race/color, age-range, type of health service (private or public) and State of origin. The variation of the median time of access to transplantation for ALL and AML is shown in Table 2.

The median time of access for female patients is 6.20 months, slightly higher than males, whose median is 4.6 months. There is an even distribution of ALL and AML, with higher proportion of women diagnosed with AML (52%) and men with ALL (63%).

Black patients waited more to access the treatment with median of 7.15 months, followed by Brown patients with 6.70 months and White with 6.30 months. White patients predominated for both types of leukemia with 71% of the cases.

Adolescents waited more to access the treatment with median of 6.90 months, 15% of which with ALL. Adult patients, the majority of cases of AML (71%) had median time of access of 6.60 months and children, mostly with ALL, had the lowest time of access with median of 5.80 months.

Patients of the public system had more time of access to treatment with median of 7.00 months than patients of private institutions, whose median is 6.20 months. AML and ALL cases were distributed evenly for both types of service.

The State of Paraná presented the lowest median time of access to HSCT with 5.10 months of waiting time, while Minas Gerais had the highest median with 7.70 months of waiting time.

The differences among the variables of the patients diagnosed with ALL and AML were analyzed in relation to the time to access the transplant, including statistical tests which evaluated the effect size and corresponding adjusted p values (Table 3, Graph 2).

Comparison between ALL and AML presented a biserial effect size of 0.08 with 0.01-0.15 confidence

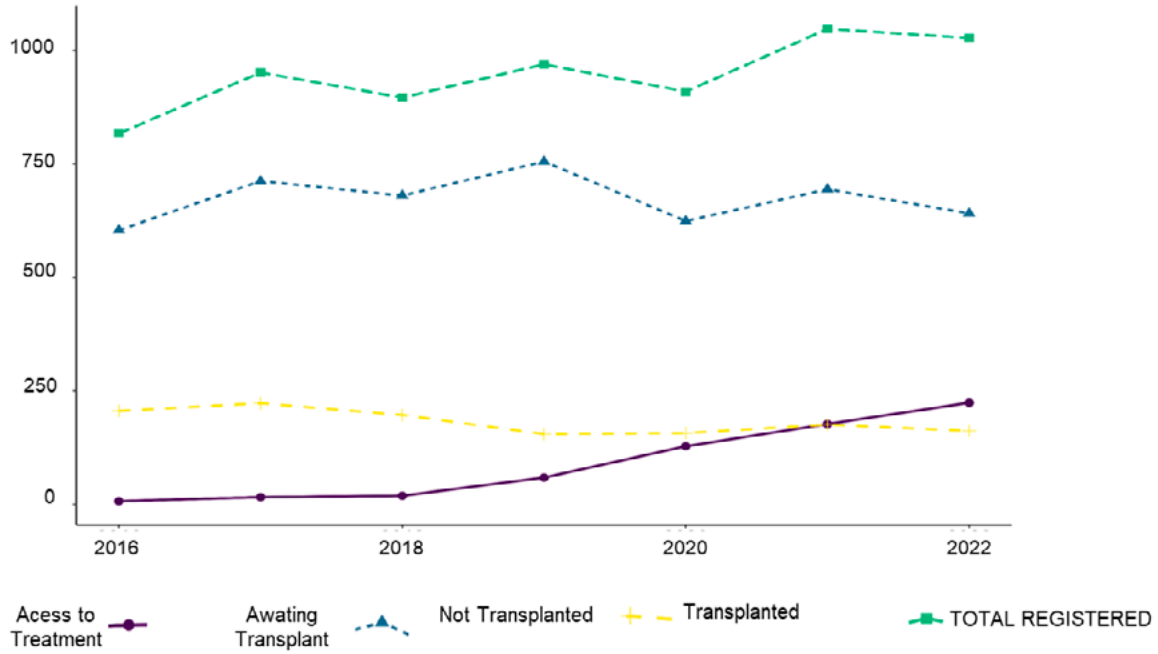
Table 1. General distribution of patients with ALL and AML registered at Redome-net, 2016-2022

Variables	Total n = 6,616[1]	CE n = 154[1]	DF n = 94[1]	MG n = 374[1]	PE n = 419[1]	PR n = 632[1]	RJ n = 777[1]	RS n = 516[1]	SC n = 54[1]	SP n = 3,596[1]
*Age	30.04 (84;1)	36.88 (69;18)	38.24 (77;9)	32.32 (75;2)	27.78 (69;2)	26.83 (75;1)	31.2 (76;2)	28.76 (75;1)	39.41 (66;17)	29.91 (84;1)
Sex										
Female	2.851 (43%)	82 (53%)	43 (46%)	146 (39%)	170 (41%)	254 (40%)	331 (43%)	211 (41%)	23 (43%)	1,591 (44%)
Male	3.765 (57%)	72 (47%)	51 (54%)	228 (61%)	249 (59%)	378 (60%)	446 (57%)	305 (59%)	31 (57%)	2,005 (56%)
Age range										
Child	1.399 (21%)	0 (0%)	4 (4.3%)	63 (17%)	84 (20%)	190 (30%)	163 (21%)	110 (21%)	0 (0%)	785 (22%)
Adolescent	755 (11%)	0 (0%)	5 (5.3%)	41 (11%)	44 (11%)	84 (13%)	82 (11%)	59 (11%)	1 (1.9%)	439 (12%)
Adult	4,099 (62%)	152 (99%)	77 (82%)	238 (64%)	285 (68%)	332 (53%)	485 (62%)	328 (64%)	51 (94%)	2,151 (60%)
Older adult	363 (5.5%)	2 (1.3%)	8 (8.5%)	32 (8.6%)	6 (1.4%)	26 (4.1%)	47 (6.0%)	19 (3.7%)	2 (3.7%)	221 (6.1%)
Race/color										
Yellow	83 (1.3%)	0 (0%)	0 (0%)	6 (1.6%)	18 (4.3%)	4 (0.6%)	1 (0.1%)	1 (0.2%)	0 (0%)	53 (1.5%)
White	3,932 (59%)	36 (23%)	54 (57%)	186 (50%)	143 (34%)	521 (82%)	417 (54%)	382 (74%)	39 (72%)	2,154 (60%)
Indigenous	22 (0.3%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)	5 (0.6%)	1 (0.2%)	0 (0%)	15 (0.4%)
Not informed	22 (0.3%)	0 (0%)	1 (1.1%)	2 (0.5%)	0 (0%)	2 (0.3%)	0 (0%)	2 (0.4%)	0 (0%)	15 (0.4%)
Brown	2,202 (33%)	110 (71%)	36 (38%)	141 (38%)	234 (56%)	96 (15%)	286 (37%)	104 (20%)	12 (22%)	1,183 (33%)
Black	355 (5.4%)	8 (5.2%)	3 (3.2%)	39 (10%)	23 (5.5%)	9 (1.4%)	68 (8.8%)	26 (5.0%)	3 (5.6%)	176 (4.9%)
Type of service										
Private	4,297 (65%)	9 (5.8%)	6 (6.4%)	262 (70%)	415 (99%)	441 (70%)	111 (14%)	264 (51%)	0 (0%)	2,789 (78%)
Public	2,319 (35%)	145 (94%)	88 (94%)	112 (30%)	4 (1.0%)	191 (30%)	666 (86%)	252 (49%)	54 (100%)	807 (22%)
Diagnosis										
ALL	3,708 (56%)	90 (58%)	52 (55%)	204 (55%)	263 (63%)	363 (57%)	459 (59%)	280 (54%)	23 (43%)	1,974 (55%)
AML	2,908 (44%)	64 (42%)	42 (45%)	170 (45%)	156 (37%)	269 (43%)	318 (41%)	236 (46%)	31 (57%)	1,622 (45%)
Access to treatment										
Awaiting transplantation	630 (9.5%)	10 (6.5%)	5 (5.3%)	29 (7.8%)	36 (8.6%)	80 (13%)	93 (12%)	54 (10%)	7 (13%)	316 (8.8%)
Not transplanted	4,710 (71%)	115 (75%)	70 (74%)	265 (71%)	316 (75%)	338 (53%)	561 (72%)	387 (75%)	40 (74%)	2,618 (73%)
Transplanted	1,276 (19%)	29 (19%)	19 (20%)	80 (21%)	67 (16%)	214 (34%)	123 (16%)	75 (15%)	7 (13%)	662 (18%)

Source: The Authors, based on Redome-net[16].

Captions: AML = Acute myeloid leukemia; ALL = Acute lymphoblastic leukemia; CE = Ceará; DF = Distrito Federal; MG = Minas Gerais; PE = Pernambuco; PR = Paraná; RJ = Rio de Janeiro; RS = Rio Grande do Sul; SC = Santa Catarina; SP = São Paulo.

*Mean (maximum age: minimum age); [1]n = Total number of patients (%).



Graph 1. Access of patients with AML and ALL to treatment registered at Redome-net, 2016-2022
Source: The Authors, based on Redome-net[16].

Table 2. Distribution of patients and variables chosen for statistical studies of time to access the transplantation for ALL and AML

Variable	Time of access (months)[1]	Total n = 1,129[2]	ALL n = 619[2]	AML n = 510[2]
Sex				
Female	6.20 (5.25)	497(44%)	231 (37%)	266 (52%)
Male	4.6 (4.60)	632(56%)	388 (63%)	244 (48%)
Race/color				
White	6.30 (4.90)	804 (71%)	442 (71%)	362 (71%)
Brown	6.70 (4.80)	279 (25%)	150 (24%)	129 (25%)
Black	7.15 (5.65)	46 (4.1%)	27 (4.4%)	19 (3.7%)
Age range				
Child	5.80 (3.90)	214 (19%)	155 (25%)	59 (12%)
Adolescent	6.90 (7.15)	115 (10%)	90 (15%)	25 (4.9%)
Adult	6.60 (5.07)	733 (65%)	369 (60%)	364 (71%)
Older adult	6.30 (5.60)	67 (5.9%)	5 (0.8%)	62 (12%)
Type of service				
Private	6.20 (4.90)	828 (73%)	454 (73%)	374 (73%)
Public	7.00 (5.10)	301 (27%)	165 (27%)	136 (27%)
State				
MG	7.70 (5.50)	79 (7.0%)	48 (7.8%)	31 (6.1%)
PE	6.70 (6.05)	63 (5.6%)	36 (5.8%)	27 (5.3%)
PR	5.10 (3.62)	212 (19%)	123 (20%)	89 (17%)
RJ	7.60 (4.25)	123 (11%)	61 (9.9%)	62 (12%)
SP	6.50 (5.00)	652 (58%)	351 (57%)	301 (59%)

Source: The Authors, based on Redome-net[16].
Captions: AML = Acute myeloid leukemia; ALL = Acute lymphoblastic leukemia; MG = Minas Gerais; PE = Pernambuco; PR = Paraná; RJ = Rio de Janeiro; SP = São Paulo.
[1]Median (interquartile range); Number of patients (n) (%); [2]n = Total number of patients

Table 3. Results of the statistical analysis of factors associated with the time of access to transplantation for patients diagnosed with AML and ALL

Groups (*n = 1,129)	[1]Biserial	[2]Ômega	95% CI	[3]p
Diagnosis	0.08		(0.01 - 0.15)	
AML-ALL			(-0.12 - 0.02)	0.019 *
Sex	-0.05		(-0.12 - 0.02)	
Female - male				0.15
Type of service	-0.10		(-0.18 - 0.03)	
Private - public				0.009*
Age range	-	0.0091	(-0.003 1.0)	
Adolescent - adult				1.00
Adolescent - older adult				0.62
Adolescent - child				0.05
Adult - older adult				1.00
Adult - child				0.04*
Older adult - child				1.00
Race/color	-	0.0061	(0.001 - 1.0)	
White - Brown				0.09
White - Black				0.23
Brown - Black				1.00
State	-	0.050	(0.04 - 1.00)	
MG - PE				1.00
MG - PR				<0.0001***
MG - RJ				1.00
MG - SP				0.25
PE - PR				0.0001***
PE - RJ				1.00
PE - SP				1.00
PR - RJ				<0.0001***
PR - SP				<0.0001***
RJ - SP				0.03

Source: The Authors, based on Redome-net[16].

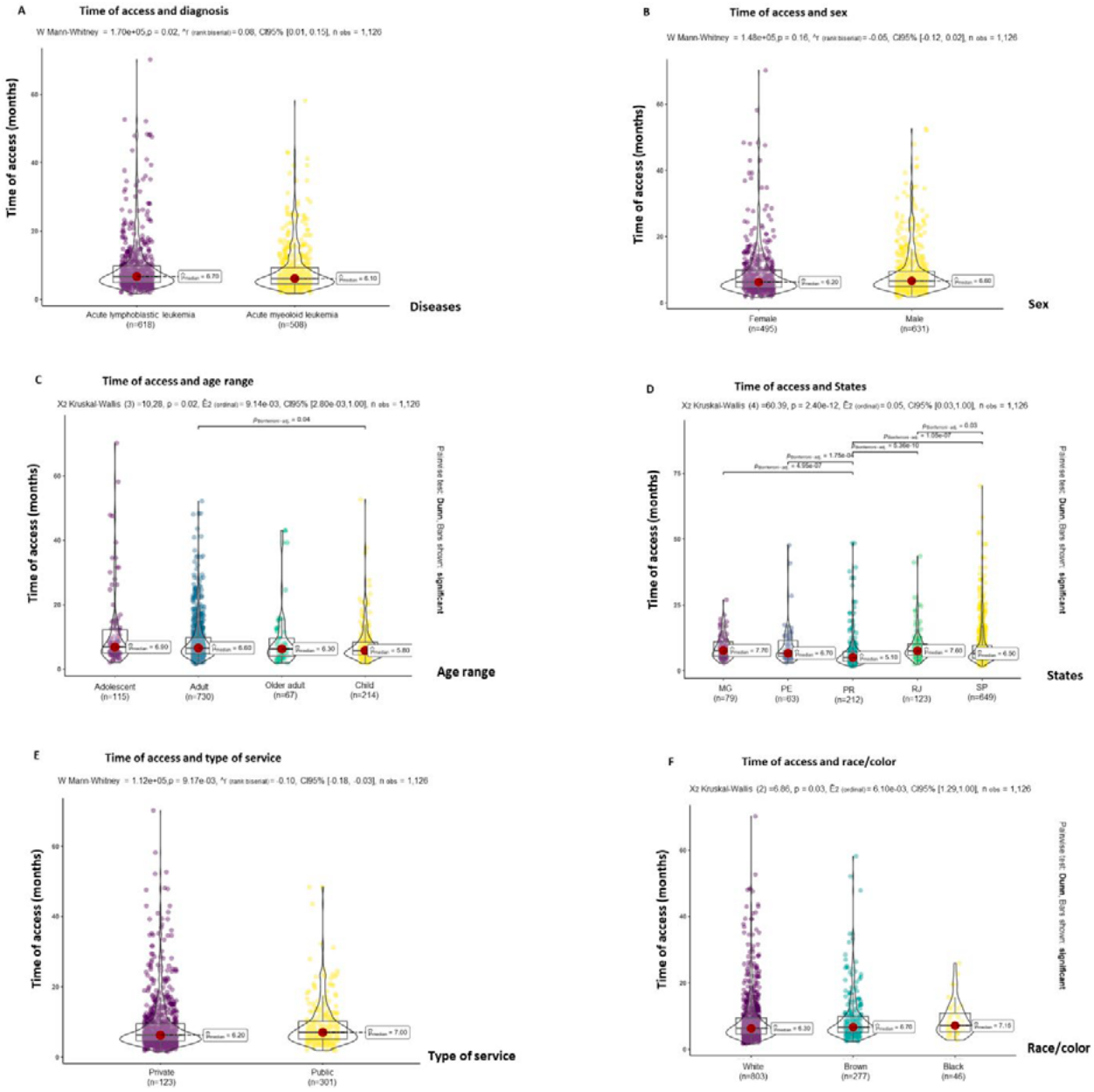
Captions: AML = Acute myeloid leukemia; ALL = Acute lymphoblastic leukemia; CI= Confidence interval; MG = Minas Gerais; PE = Pernambuco; PR = Paraná; RJ = Rio de Janeiro; SP = São Paulo.

[1]Biserial = Effect size (Mann-Whitney); [2]Omega = Effect size (Kruskal-Wallis); *n = Total patients; [3]*p* = ***Very significant, **significant, *Least significant.

interval, a statistically significant difference with $p = 0.019$. The biserial effect size related to sex was -0.05, with -0.12-0.02 confidence interval without statistical significance ($p = 0.15$). For the type of service – public *versus* private – the biserial effect size was -0.10, with -0.18-0.03 confidence interval, a significant difference of the time to access transplant ($p = 0.009$).

Age-range comparisons showed that no statistical significance among adolescents and adults ($p = 1.00$), adolescents and older adults ($p = 0.62$) or among older adults and children ($p = 1.00$) has been found. However, marginally significant difference among adolescents and children ($p = 0.05$) and significant difference among adults and children ($p = 0.04$) has been detected. Comparison among adults and older adults was not significant ($p = 1.00$).

Comparison among Whites and Browns ($p = 0.09$) and among Whites and Blacks ($p = 0.23$) was not statistically significant. Similarly, the comparison among Browns and Blacks did not show significant difference ($p = 1.00$).



Graph 2. Results of the statistical analysis of the factors associated with time of access to transplantation for patients diagnosed with AML and ALL

Source: The Authors, based on Redome-net[16].

Captions: A. Disease; B. Sex; C. Age-range; D. States; E. Type of services; F. Race/color; CI = Confidence interval.

The analysis between Minas Gerais and Pernambuco did not reveal significant difference (p = 1.00), similar to Minas Gerais and Rio de Janeiro (p = 1.00) and Minas Gerais and São Paulo (p = 0.25). However, the comparison between Minas Gerais and Paraná was highly significant (p < 0.0001). Comparisons between Pernambuco and Paraná (p = 0.0001) and between Paraná and Rio de Janeiro (p < 0.0001), and between Paraná and São Paulo (p < 0.0001) presented the same profile. The comparison between Rio de Janeiro and São Paulo was moderately significant with p = 0.03.

DISCUSSION

Between 2016 and 2022, 6,161 patients with AML and ALL found in Redome-net[16] have been analyzed, most of them males, White who utilized private health services. Only 19% were transplanted, 71% were not transplanted yet and 9.5% were awaiting for the transplant. The number of patients registered increased until 2018, stabilized in 2020 and resumed hereinafter.

Older, Black women assisted by public institutions waited more. The State of Paraná presented the lowest

median waiting time and Minas Gerais, the longest. COVID-19 pandemic affected the number of patients registered and transplanted. The analyzes revealed significant differences of access time to transplant between public and private services and among States.

A great demand disparity for transplantation by States was noticed, with São Paulo reaching 3,596 requests and Santa Catarina, only 54. In addition, only eight States and *Distrito Federal* kept active registers at Redome-net, while 18 presented no registers. This difference reflects the access to transplantation specialized services in the country calling for in-depth investigation.

Currently, there are 55 unrelated transplantation centers in Brazil distributed as follows: four in the Midwest (only in Brasilia), four in the Northeast (two in Ceará, one in Pernambuco and one in Rio Grande do Norte), 39 in the Southeast (25 in São Paulo, eight in Minas Gerais and six in Rio de Janeiro) and eight in the South Region (four in Rio Grande do Sul, three in Paraná and one in Santa Catarina)[16]. The concentration in the Southeast region, especially in São Paulo, shows regional disparity that can limit the access to treatment. More inclusive health policies are required further to expanding the number of HSCT centers in underserved regions to promote a more even distribution of the services.

Although Paraná has only three transplantation centers, it has the second highest quantity of recipients registered and the second highest transplants performed between 2016 and 2022, behind São Paulo only. In addition, the State presented the lowest mean time to perform transplants than other Brazilian States, attributable to the State's Transplantation Central which, since its inauguration in 1995, has been managing and regulating the procedures and contributing for an equitable access and continuous improvement of the quality of care[31].

A portion of the total number of donors registered – 5,667,115 – is concentrated in the South and Southeast regions accounting for more than 60% of all the available donors in the country, the same profile of the recipients registered[16].

The existing literature has already highlighted a significant geographic discrepancy in accessing HSCT in other countries. A hospital-data based study identified disparities of access to HSCT in four North American states – California, Massachusetts, Maryland and New York – for 1988 and 1991 associated with health insurance and racial issues[21].

A study emphasized age as an essential factor of access to HSCT, younger individuals are more likely to be transplanted than older adults. Studies show that at every additional ten years in age, the likelihood of submitting to HSCT for leukemia or lymphoma drops between 10% and 18%, depending on the Region[21]. These data corroborate the current results that age is a significant factor of wait, and children have access to compatible donors faster than other age ranges.

Several studies evaluated the impact of sex on the access to transplantation for leukemia and lymphoma and some of them did not identify differences among men and women, while others showed that older males have more odds of being submitted to transplants but this does not apply to the youngest. Recent studies concluded that men are more likely to autologous transplant for lymphoma or myeloma but not allogeneic without conclusive justifications[21]. The current results did not identify significant differences in accessing transplants between both sexes.

The analysis of the impact of race/color on the access to HSCT requires a thorough approach, considering the complex nature of this concept influenced by social, cultural and political aspects. Studies indicate low likelihood of Black individuals to submitting to HSCT to treat leukemia or lymphoma, even in situations involving siblings or unrelated donors[21]. Matching odds are: 0.93 for Whites, 0.82 for Latins, 0.77 for Asian-Americans and 0.58 for Blacks. Recipients tend to find donors of the same race/ethnicity[32]. This inequality can aggravate, making the search for donors of ethnic minorities difficult[20].

The registers of unrelated donors consist mainly of European-origin donors, resulting in high likelihood of Caucasian patients to find a compatible HLA donor[19]. Recent data of Redome[16] show that most of the donors claim they are White followed by Browns, in contrast with the Continuous National Household Sample Survey (PNAD) of IBGE (2022), which indicates that Browns and Blacks represent 56% of the population[33]. Despite the Black majority, there are significant barriers to health access. It is crucial to implement affirmative actions to expand the diversity of registers of donors and encourage educational campaigns about bone marrow donation in underrepresented communities.

The results of the present study suggest that, despite the existing disparities in health access, racial disparities impact on waiting time to HSCT are not significant according to Redome registers, emphasizing the importance of this program to promote health access equity.

USA studies showed that the likelihood of Medicaid and uninsured patients or patients with low private coverage to submitting to transplantation for leukemia or lymphoma is lower than private insured patients[21]. These findings indicate that financial factors affect therapeutic decisions, especially referral for transplantations[34]. Similarly, the current study revealed that patients assisted by private

services wait less for HSCT than patients assisted by public services in Brazil.

The predominance of recipients of transplants assisted by private services in Redome emphasizes the influence of these services on referral to HSCT, whose cost can reach R$200 thousand in private hospitals. Although SUS assists a large part of the population, this disparity raises issues about equity of access to complex procedures as transplants for SUS exclusive patients, drawing attention to the necessity of public-private collaboration to ensure equitable access to these treatments[35].

The time the patient is waiting is an independent factor affecting survival and overall rate of mortality post-HSCT, a relevant aspect to determine the necessity and feasibility of the transplant since the overall survival rate diminished to 30% after 12 months in the waiting list[36]. A longer period between the diagnosis and HSCT is also associated with increased likelihood of relapse and accumulated toxicity because of the necessity of additional treatments while the patient awaits transplantation[36].

Quite often, the formal search for an unrelated donor takes nearly two months, however, the demands for urgent searches at the registers increase, with transplant centers attempting to analyze donors in weeks, no more in months[15]. However, the complexity of this process and preparations for harvesting and transportation can cause a delay of until six months to perform the HSCT[37].

A study conducted in Brazil showed that the mean time between diagnosis and allogeneic HSCT is ten months for primary myelodysplastic syndrome and from nine to 24 months for advanced lymphoproliferative disorders compared with mean of 26.8 months in early studies. In well developed countries, this timeline is usually shorter[36]. The mean time to find an AML and ALL donor at Redome as that study concluded varies from five to seven months, depending on the State, longer than three or four months reported in other studies, highlighting regional differences and challenges to identify compatible donors[36].

The majority of physicians and coordinators believe that urgent cases should be infused with hematopoietic stem-cells within no more than six weeks, however, this is not the reality for many Brazilian patients. Health professionals adopt strategies to reduce the waiting time as searching for multiple donors simultaneously, prioritize the analysis of donors and run additional tests. The search for unrelated donors is limited to two weeks after the initial search due to the low likelihood of finding compatible 8/8 HLA donor, which encouraged the pursue of alternative donors[38].

Even with compatible donor, some patients were unable to be transplanted because of clinical, social or bureaucratic issues[39]. Develop protocols addressing clinical and social issues to reduce delays and withdrawals is critical to overcome these challenges, in addition to speeding up paperwork processes and offer patients support while awaiting which will help to optimize the transplantation and improve the odds of success and recovery.

More than half of the patients (71%) with AML and ALL were classified as "non-transplanted", revealing that, in certain cases, HSCT was not performed because these patients died or the indication for transplant was removed because of disease progression while waiting in the list.

The study results can explain the COVID-19 impact on HSCT, which reduced the transplants due to infection risks and resources restraints. In addition, studies concluded that register of new donors dropped which diminished the availability of compatible donors, explaining the stabilization and mild decline of patients registered and transplanted between 2018 and 2020.

Advanced HLA techniques and resources together with customized clinical guidelines can accelerate the identification of treatment plans and speeding up the patients' journey while seeking care[29]. Clear guidelines should be created to prioritize urgent cases and encourage the collaboration among transplant centers to expedite the search for unrelated donors in critical situations.

The analysis encountered limitation of the data found at Redome-net processed in the software R[29]. Non-updated and insufficient data caused the exclusion of patients and regions with impacts on representativeness. The generalization of the data and sample size were also impacted because only two diseases were investigated and patients excluded due to missing data. Thorough analyzes were conducted to circumvent these limitations to ensure best possible utilization of the data available. The study focused key-variables and adjusted the sample to reflect the diversity of the cases registered to minimize the burden of the exclusions in the final analysis.

In addition, the analysis may not fully reflect all the transplantation centers, especially those off the database or with incomplete data. The quantity of transplantation centers in each region were included to mitigate this problem and offer a broader view of the distribution of the services.

Important restrictions are the period selected (2016-2022) and lack of longitudinal data about the evolution of techniques and practices. Future studies addressing the efficacy of transplant centers should be conducted to overcome these barriers. Longitudinal studies and thorough analyzes of clinical variables, comparison of practices and evaluation of the impact of novel technologies are essential to provide a comprehensive and updated perspective for improved transplantation techniques and formulation of effective public policies.

CONCLUSION

The distribution and time of access to HSCT of patients with ALL and AML in Brazil was investigated, utilizing Redome-net data between 2016 and 2022, revealing that most of the patients are adults, but only a small portion was transplanted, highlighting the challenges to access the treatment.

Differences of time to access the transplant associated with clinical and socioeconomic variables have been identified for older, Black, female patients assisted by public institutions with longer waiting time, reflecting access disparities.

Significant variations of time to access HSCT were also found in the States, the lowest time in Paraná and the longest time in Minas Gerais. COVID-19 pandemic has also impacted HSCT, reducing the number of transplants due to the risk of infection and reduction of new donors, which accounted for the stabilization and decline of patients registered and transplanted between 2018 and 2020.

The results indicate the necessity to improve the efficacy of the transplant system and access to the treatment to shorten the waiting time and ensure the required health equity. Continuous improvement of coordination and effectiveness of transplantation systems are essential to optimize treatment in Brazil.

CONTRIBUTIONS

Wini de Moura Miguel contributed to the study design, acquisition, analysis and interpretation of the data, wording and critical review. Carlos Alberto Esteves Adão and Janaína Santos Paulista contributed to the study design, wording and critical review. Bright Amenu contributed to the acquisition, analysis and interpretation of the data. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

FUNDING SOURCES

None.

REFERENCES

1. Assunção F. Doação de medula óssea no Brasil: compatibilidade HLA e métodos de coleta. [Monografia] [Internet]. Caxias do Sul: Universidade de Caxias do Sul; 2022. [acesso 2024 set 10]. Disponível em: https://repositorio.ucs.br/xmlui/bitstream/handle/11338/12036/TCC%20Fernanda%20de%20Assuncao.pdf?sequence=1&isAllowed=y.
2. Khaddour K, Hana CK, Mewawalla P. Hematopoietic stem cell transplantation. Em: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2023. [acesso 2023 maio 10, atualizado em 2023 maio 6]. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK536951/.
3. Jo T, Arai Y, Kondo T, et al. Advantages of peripheral blood stem cells from unrelated donors versus bone marrow transplants in outcomes of adult acute myeloid leukemia patients. Cytotherapy. 2022;24(10):1013-25. doi: https://doi.org/10.1016/j.jcyt.2022.05.009
4. Santos IJ, Gonçalves JFF, Brandão LFS. Transplante de medula óssea: importância do sistema HLA [monografia] [Internet]. Pouso Alegre: Centro Universitário UNA; 2022. [acesso 2024 set 10]. Disponível em: https://repositorio.animaeducacao.com.br/items/56f7c8b4-2a5f-4210-9a56-b768e57e1e79
5. Santis JO. Frequência dos antígenos HLA classe I e II em pacientes indicados para transplante de medula óssea na região de Ribeirão Preto - SP. [Monografia] [Internet]. Ribeirão Preto: Universidade de São Paulo; 2018. [acesso 2024 set 10]. Disponível em: https://docs.bvsalud.org/biblioref/2019/05/996719/pap_santisjo_2018.pdf
6. Instituto Nacional de Câncer. Estimativa 2023: incidência de câncer no Brasil [Internet]. Rio de Janeiro: Instituto Nacional de Câncer; 2022. [acesso 2024 set 10]. Disponível em: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-2023.pdf.
7. He P, Liang J, Zhang W, et al. Hematopoietic stem cell transplantation for acute myeloid leukemia: an overview of systematic reviews. Int J Clin Pract. 2022;2022:1828223. doi: https://doi.org/10.1155/2022/1828223
8. Lamego RM, Clementino NCD, Costa ÂLB, et al. Transplante alogênico de células-tronco hematopoéticas em leucemias agudas: a experiência de dez anos do Hospital das Clínicas da UFMG. Rev Bras Hematol Hemoter. 2010;32(2):108-15. doi: https://doi.org/10.1590/S1516-84842010005000040.
9. Fleischhauer K, Tran TH, Meisel R, et al. Donor selection for allogeneic hematopoietic cell transplantation. Dtsch Arztebl Int. 2023;120(15):261-8. doi: https://doi.org/10.3238/arztebl.m2023.0031
10. Matias NMA. Leucemia linfoblástica aguda: fisiopatologia, diagnóstico e abordagens terapêuticas. [monografia]. Lisboa: Universidade de Lisboa, Faculdade de Farmácia; 2019. [acesso 2024 set 10]. Disponível em: https://repositorio.ul.pt/bitstream/10451/43361/1/MICF_Nidia_Matias.pdf.
11. Ministério da Saúde (BR). Ministério da Saúde. Portaria Conjunta nº 21, de 10 de dezembro de 2021. Aprova

as Diretrizes Diagnósticas e Terapêuticas – Mesilato de Imatinibe no Tratamento da Leucemia Linfoblástica Aguda Cromossoma Philadelphia Positivo do Adulto. Diário Oficial da União, Brasília, DF. 10 dez 2021; Edição 234; Seção 1:111.

12. Archanjo LVF. Características e desfechos dos pacientes submetidos ao transplante de medula óssea admitidos na Unidade de Terapia Intensiva [dissertação]. São Paulo: Fundação Antônio Prudente; 2021. [acesso 2024 set 10]. Disponível em: https://docs.bvsalud.org/biblioref/2021/12/1348899/leticia-vicentin-finencio-archanjo.pdf.
13. Kiong LA, Hanna FSA, Souza GL, et al. Preditores de óbito em pacientes transplantados de medula óssea de um centro de referência na Amazônia brasileira. Rev HUGV. 2022;21:10780. doi: https://doi.org/10.60104/revhugv10780
14. Hoff PMG, editor. Tratado de oncologia. São Paulo: Atheneu; 2013. 2829 p.
15. Evseeva I, Foeken L, Madrigal A. The role of unrelated donor registries in HSCT. In: Carreras E, Dufour C, Mohty M, et al., editores. The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies [Internet]. 7 ed. Cham: Springer International Publishing; 2019. p. 19-25. [acesso 2023 dez 20]. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK553967/
16. REDOME [Internet]. Rio de Janeiro: INCA; [sem data]. Registro Brasileiro de Doadores Voluntários de Medula Óssea. [acesso 2023 dez 20]. Disponível em: https://redome.inca.gov.br/.
17. Ministério da Saúde (BR). Portaria n.º 931, de 29 de outubro de 2009. Estabelece regras para aprimorar a aplicação dos recursos disponíveis e a atualização do cadastro nacional de doadores, tornando o INCA. Diário Oficial da União, Brasília, DF, 30 out. 2009; Seção 1.
18. Ministério da Saúde (BR), Instituto Nacional de Câncer José Alencar Gomes da Silva. Tópicos em transplante de células-tronco hematopoéticas. Rio de Janeiro: INCA; 2012. [acesso 2024 ago 3]. 192 p. Disponível em: https://bvsms.saude.gov.br/bvs/publicacoes/topicos_transplante_celtronco_hematopoeticas.pdf.
19. Batistiolle JV. Acesso aos transplantes de medula óssea no Brasil: uma questão de justiça. [dissertação]. Rio de Janeiro: Universidade Federal do Rio de Janeiro; 2014.[Acesso 2023 maio 10]. Disponível em: https://www.arca.fiocruz.br/bitstream/handle/icict/13140/195.pdf?sequence=1&isAllowed=y.
20. Hong S, Majhail NS. Aumento do acesso a aloenxertos nos Estados Unidos: o impacto de raça, geografia e fatores socioeconômicos. Hematology Am Soc Hematol Educ Program. 2021;2021(1):275-280. doi : https://doi.org/10.1182/hematology.2021000259
21. Majhail NS, Omondi NA, Denzen E, et al. Access to hematopoietic cell transplantation in the United States. Biol Blood Marrow Transplant. 2010;16(8):1070-75. doi: https://doi.org/10.1016/j.bbmt.2009.12.529
22. Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). Biometrika. 1965;52(3-4):591-611.
23. Levene H. Robust test for equality of variances. In: Olkin I, editor. Contributions to probability and statistics: essays in honor of Harold Hotelling. Stanford: Stanford University Press; 1960. p. 278-92.
24. Kruskal WH, Wallis WA. Use of ranks in one-criterion variance analysis. J Am Stat Assoc. 1952;47(260):583-621. doi: https://doi.org/10.1080/01621459.1952.10483441
25. Hart A. Mann-Whitney test is not just a test of medians: differences in spread can be important. BMJ. 2001;323(7309):391-3.
26. Bonferroni CE. Teoria statistica delle classi e calcolo delle probabilità. Pubblicazioni del R Istituto Superiore di Scienze Economiche e Commerciali di Firenze. 1936;8:1-62.
27. Center for Humans and Machines, Max Planck Institute for Human Development, Berlin, Germany. Visualizations with statistical details: The 'ggstatsplot' approach.J Open Source Softw. 2021;6(61):3167. doi: https://doi.org/10.21105/joss.03167
28. Sjoberg DD, Whiting K, Curry M. Reproducible summary tables with the gtsummary Package. R J. 2021;13(1):570-80. doi: https://doi.org/10.32614/RJ-2021-053
29. R: The R Project for Statistical Computing [Internet]. Version 4.1.2 [place unknown]: The R foundation. 2021 Nov 2 - [acesso 2022 ago 6]. Disponível em: https://www.r-project.org/
30. Conselho Nacional de Saúde (BR). Resolução nº 466, de 12 de dezembro de 2012. Aprova as diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos. Diário Oficial da União, Brasília, DF. 2013 jun 13; Seção I:59.
31. Secretaria Estadual de Transplantes (PR) [Internet]. Curitiba: Secretaria de Saúde; [sem data]. [acesso 2023 dez 20]. Disponível em: https://www.paranatransplantes.pr.gov.br/
32. Majhail NS, Nayyar S, Santibañez ME, et al. Racial disparities in hematopoietic cell transplantation in the United States. Bone Marrow Transplant. 2012;47(11):1385-90. doi: https://doi.org/10.1038/bmt.2011.214
33. Instituto Brasileiro de Geografia e Estatística. PNAD Contínua - pesquisa nacional por amostra de domicílios contínua: características gerais dos domicílios e dos moradores, 2022. Rio de Janeiro: IBGE; 2022.
34. Flannelly C, Tan BE, Tan JL, et al. Barriers to hematopoietic cell transplantation for adults in the United States: a systematic review with a focus on age. Biol Blood Marrow Transplant. 2020;26(12):2335-45. doi: https://doi.org/10.1016/j.bbmt.2020.09.013
35. Zioldo RR, Gimenes RO, Júnior CC. A importância da saúde suplementar na demanda da prestação dos serviços assistenciais no Brasil. Mundo saúde [Internet]. 2013 [acesso

2024 jun 25];37(2):216-21. Disponível em: https://bvsms.saude.gov.br/bvs/artigos/mundo_saude/importancia_saude_suplementar_demanda_prestacao.pdf
36. Silva TS, Horvath JDC, Pereira MP, et al. Impacto do tempo na lista de espera na sobrevida pós-TCTH: um estudo de coorte em um hospital do sul do Brasil. Hematol Transfus Cell Ther. 2023;46(3):242-9. doi: https://doi.org/10.1016/j.htct.2023.03.021
37. Zago MA, Falcão RP, Pasquini R. Tratado de hematologia. 1. ed. São Paulo: Editora Atheneu; 2013.
38. Pidala JA, Hamilton BK, Martin PJ, et al. The chronic graft-versus-host disease failure-free survival (cGVHD-FFS) index. Biol Blood Marrow Transplant. 2019;25(12):2468-73. doi: https://www.doi.org/10.1016/j.bbmt.2019.07.040
39. Dehn J, Chitphakdithai P, Show BE, et al. Likelihood of proceeding to allogeneic hematopoietic cell transplantation in the United States after search activation in the National Registry: impact of patient age, disease, and search prognosis. Transplant Cell Ther. 2021;27(2):184.e1-13. doi: https://doi.org/10.1016/j.bbmt.2020.10.004
40. Farhadfar N, Weaver MT, Al-Mansour Z, et al. Self-efficacy for symptom management in long-term adult hematopoietic stem cell survivors. Transplant Cell Ther. 2022;28(9):606.e1-8. doi: https://doi.org/10.1016%2Fj.jtct.2022.05.035
41. Almeida GG, Cardoso LF, Paiva CRC, et al. Transplante de medula óssea no Brasil: distribuição e perfil de doadores cadastrados entre 2015 e 2022. Hematol Transfus Cell Ther. 2022;44(Supl 2). doi: https://doi.org/10.1016/j.htct.2022.09.555

Recebido em 17/6/2024
Aprovado em 23/9/2024

Associate-editor: Jeane Tomazelli. Orcid iD: https://orcid.org/0000-0002-2472-3444
Scientific-editor: Anke Bergmann. Orcid iD: https://orcid.org/0000-0002-1972-8777