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BARRIERS TO ACCESS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION: AN INTEGRATIVE REVIEW

João Victor Piccolo Feliciano[1], MSc (ORCid 0000-0002-2034-7015)
José Carlos Lopes[1], PhD
José Alexandre Buso Weiller[2], PhD (ORCid 0009-0005-4330-5933)
Jaqueline Vilela Bulgareli[3], PhD (ORCid 0000-0001-7810-0595)

1Faculdade de Medicina de São José do Rio Preto - FAMERP
2 Administração Central da Ebserh – Ministério da Saúde – Brasil
3 Universidade Federal de Uberlândia – UFU

Corresponding author: João Victor Piccolo Feliciano (E-mail: joao.feliciano@edu.famerp.br)

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ABSTRACT

Introduction: Hematopoietic stem cell transplantation is a therapy for which even countries with universal health systems face challenges to ensure its access to the population. Barriers to access can be characterized as geographic, organizational, socioeconomic and of information.

Objective: To conduct an integrative review of barriers to access of hematopoietic stem cell transplantation. Methods: Databases chosen were BVS, PubMed and Scopus. Population and phenomenon were established, respectively as "hematopoietic stem cell transplantation" and "barriers to access" with descriptors in Portuguese and English. 22 articles, published between 2012 and 2022, were selected.

Results: Access was hampered by the distance to transplant center, in more populous regions, with high demand for services and transportation difficulties. There was better access in countries with higher GDP per capita, more installed transplant centers and for the population with higher income. Insurance coverage, support by public policies, assistance in academic centers, organized regulation and prioritization of emergencies facilitated access. The understanding of the diseases, the adherence to the treatments, the perception of survival by the patients and the skills of the professionals improved the access.

Conclusion: All categories of access barriers were addressed, with multifactorial and interrelated origins, with the vulnerable population being the most affected.

Keywords: Health services accessibility. Bone marrow transplantation. Hematopoietic stem cell transplantation.

INTRODUCTION

Bone marrow transplantation or hematopoietic stem cell transplantation (HSCT) is a form of cell therapy used to treat various hematological and onco-hematological diseases. When the patient happens to be his/her own donor, this transplant is characterized as autologous, with control or cure of the underlying disease being dependent on high doses of chemotherapy. To the contrary, when we have another compatible individual donating to the patient, whether a family member or not, this characterizes the allogeneic transplant - a process in which immunological modulation plays a role, and in which the cure is dependent on the graft versus tumor process or on the recovery of effective hematopoiesis[1].

Both HSCT modalities are successfully used worldwide, with the main indications for autologous transplantation being multiple myeloma and lymphomas, and the main indications for allogeneic transplantation being acute leukemias[2,3]. The number of transplants has progressively increased in recent decades, because of technological advances and better understanding of clinical management, thereby allowing better survival of this group of patients, despite the considerable morbidity and mortality still associated with the treatment. Furthermore, due to the increase in the incidence and prevalence of onco-hematological diseases in the elderly population, combined with improvements in the health conditions of this group, indications and procedures for transplantation are being performed with increasing frequency in patients of advanced age, guided by status adequate performance and geriatric clinical evaluation [4].

Access to health services is a complex multidimensional concept that involves several determinants. There is a better understanding when the concept is related to health planning in accordance with data on population needs, which help to shape the characteristics of the provision of services in that health system. The epidemiological profile and health conditions of the population are related to the social inequalities prevailing in that society, and the differences in access to health services are reflections of the characteristics of health systems and the value attributed to public policies by decision makers[5]. Even in populations whose health care is provided by universal systems there is no uniformity in access and each country has its own dilemmas regarding the barriers faced which can be subdivided into four main types of interrelated categories: geographic, financial/socioeconomic, organizational and information/cultural[5].

Geographical barriers are those imposed by space, which can hinder movement/ transportation of the population to health services [5]. These barriers mainly arise in the case of treatments that involve high complexity of health technologies with high costs and health systems must structure reference centers. Other factors, such as income, can minimize the impact of geographic barriers by mechanisms facilitating transport, by the private disbursement of transport costs, for example.

Even developed countries suffer the impact of rising health costs and some adopt the strategy of sharing the costs of these services with users[6]. The greatest impacts occur on the population with the lowest income, leading to further deepening of social inequalities, a fact that can be minimized with strategies enabling universal access [5].

The way health services are organized generates facilities or limitations for gaining access. This impact occurs not only on an initial attendance, but also has repercussions on the continuity of care. This may involve parameters such as collaborative models, methodological and cultural diversity of professionals, communication problems, differences in management models, issues related to socioeconomic diversity and the present legislation[7].

Cultural aspects and the level of information of the population can also affect access to transplantation since it is a procedure involving considerable morbidity and mortality. Religion, for example, can be an important barrier to access by Jehovah's Witnesses, with autologous HSCT being the only possible modality for selected cases[8]. Whereas well-informed patients can make more conscious decisions, such as undergoing transplantation in cases of those who perceive worsening of their clinical condition, even during the pandemic[9].

Given the complexity of the spectrum of access due to the organizational variables of health systems and the socioeconomic and geographic aspects involved in the concept, this study becomes relevant. Its aim was to analyze the barriers that hinder access to HSCT, identify the types of barriers found into a discussion on determination of these barriers and the challenges for improving access to HSCT.

MATERIAL AND METHODS

This study was an integrative systematized review of the literature with the objective of searching the databases to identify knowledge about the barriers to access to HSCT. Descriptors were chosen and search strategies were defined to answer the research question: "What does the scientific literature present about the Barriers to access to hematopoietic stem cell transplantation?". The databases chosen for searches were BVS, PubMed and Scopus.

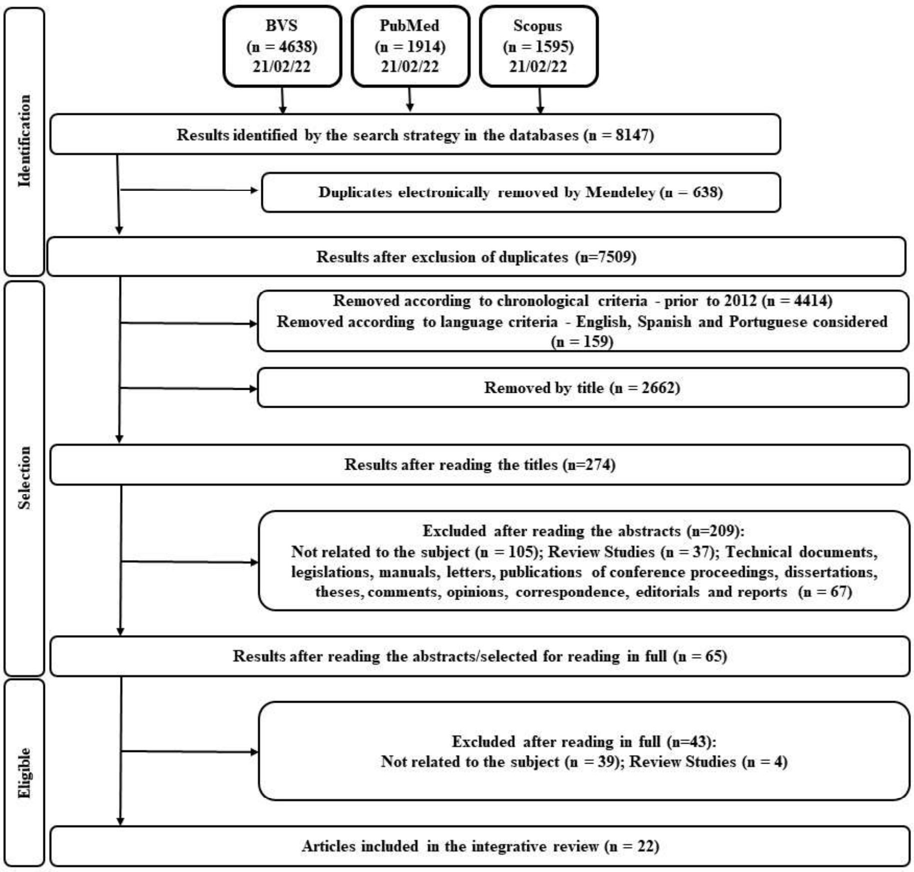
Based on the research question, the poles of population and phenomenon were established as being "hematopoietic stem cell transplantation" and "barriers to access", respectively. Descriptors in Portuguese were used, according to "DeCS - Descritores em Ciências da Saúde" for the search in the BVS and according to MeSH for PubMed and Scopus.

The inclusion and exclusion criteria adopted were scientific articles that discussed barriers to access to bone marrow transplantation; studies in Portuguese, English and Spanish and publications from January 2012 to February 2022. Scientific articles that were unrelated to the subject studied were excluded from the study, and so were technical documents, legislation, manuals, letters, publications of conference proceedings, dissertations, theses, comments, opinions, correspondence, editorials, reports, articles not available for reading and review studies.

The final syntax for the database of BVS was (mh:(“acesso a medicamentos essenciais e tecnologias em saude” OR “acesso universal aos servicos de saude” OR “barreiras ao acesso aos cuidados de saude” OR “cobertura universal de saude” OR “equidade no acesso aos servicos de saude” OR “judicializacao da saude” OR “qualidade, acesso e avaliacao da assistencia a saude” OR “acesso aos servicos de saude” OR “acesso efetivo aos servicos de saude” OR “controle de acesso” OR “decisoes judiciais” OR “jurisprudencia” OR “custos de medicamentos” OR “imunossupressores” OR “uso de medicamentos”)) AND (mh:(“hematologia” OR “transplante de medula ossea” OR “transplante de celulas-tronco hematopoeticas” OR “transplante de celulas-tronco de sangue periferico”)). For Pubmed the following terms were used (((Hematology[MeSH Terms]) OR (Bone Marrow Transplantation[MeSH Terms])) OR (Hematopoietic Stem Cell Transplantation[MeSH Terms])) AND (((((Delivery of health care[MeSH Terms]) OR (Social Deprivation[MeSH Terms])) OR (Jurisprudence[MeSH Terms])) OR (Referral and consultation[MeSH Terms])) OR (Health care costs[MeSH Terms])), and for Scopus (KEY (“Hematology”) OR KEY (“Bone Marrow Transplantation”) OR KEY (“Hematopoietic Stem Cell Transplantation”)) AND (KEY (“Delivery of health care”) OR KEY (“Social Deprivation”) OR KEY (“Jurisprudence”) OR KEY (“Referral and consultation”) OR KEY (“Health care costs”)).

The syntaxes were used for database searches on February 21, 2022, with the result being 4638 documents obtained in BVS, 1914 documents in PubMed and 1595 documents in Scopus, totaling a survey of 8147 results. This dataset was imported into the Mendeley, and 638 items were electronically excluded because they were duplicates. After this, the list of documents was imported into the Rayyan application, then the chronological and language criteria were applied, resulting in the exclusion of 4414 and 159 documents, respectively. The next filter procedure involved reading the titles; this resulted in the exclusion of 2662 items. After applying these processes, 274 results remained for reading the abstracts. According to the exclusion criteria, after reading the abstracts, 65 articles were selected for reading in full with 22 articles being retained, as shown in the flowchart below based on PRISMA (Figure 1) [10].

FIGURE 1. Flowchart of the article selection process



RESULTS

The documents selected for the integrative review are listed below according to main author, year, title, and journal of publication (Table 1).

TABLE 1. Articles included in the integrative review, according to author, year of publication, title and periodical.

ID	Main Author	Year	Title	Journal
1	Gramajo, P	2012	Accesibilidad al trasplante de células progenitoras hematopoyéticas según entidades financiadoras de salud en Argentina, 2000-2010.	Rev Argent Salud Pública
2	Bierenbaum, J	2012	Racial differences in presentation, referral and treatment patterns and survival in adult patients with acute myeloid leukemia: a single-institution experience.	Leukemia Research
3	Urbano-Ispizua, A	2012	Hematopoietic stem cell transplantation in Europe. Differences between Eastern and Western countries.	Hematology
4	Omondi, N	2013	Barriers to hematopoietic cell transplantation clinical trial participation of african american and black youth with sickle cell disease and their parents.	J Pediatr Hematol Oncol
5	Moore, H	2013	Barriers to accessing health care for hematopoietic cell transplantation recipients living in rural areas: perspectives from healthcare providers.	Clin J Oncol Nurs
6	Pidala, J	2013	Practice variation in physician referral for allogeneic hematopoietic cell transplantation.	Bone Marrow Transplantation
7	Thompson, A	2013	An educational symposium for patients with sickle cell disease and their families: results from surveys of knowledge and factors influencing decisions about hematopoietic stem cell transplant.	Pediatr Blood Cancer
8	Maeda, T	2014	Regional differences in performance of bone marrow transplantation, care-resource use and outcome for adult T-cell leukaemia in Japan.	BMC Health Services Research
9	Mikles, B	2014	Pediatric hematology providers on referral for transplant evaluation for sickle cell disease: a regional perspective.	J Pediatr Hematol Oncol
10	Besse, KL	2015	Estimating demand and unmet need for allogeneic hematopoietic cell transplantation in the United States using geographic information systems.	Health Care Delivery
11	Mitchell, J	2015	Factors affecting receipt of expensive cancer treatments and mortality: evidence from stem cell transplantation for leukemia and lymphoma.	Health Services Research
12	Patel, MI	2015	How do differences in treatment impact racial and ethnic disparities in acute myeloid leukemia?	Cancer Epidemiol Biomarkers Prev
13	Alsultan, A	2016	Demands and challenges for patients with sickle-cell disease requiring hematopoietic stem cell transplantation in Saudi Arabia.	Pediatr Transplantation
14	Delamater, P	2016	Geographic access to hematopoietic cell transplantation services in the United States.	Bone Marrow Transplantation
15	Schriber, JR	2017	Hispanics have the lowest stem cell transplant utilization rate for autologous hematopoietic cell transplantation for multiple myeloma in the United States: a CIBMTR report.	Cancer
16	Umakanthan, JM	2018	Factors associated with receipt of hematopoietic cell transplantation for acute lymphoblastic leukemia.	Future Oncology

17	Ailawadhi, S	2019	Racial disparities in treatment patterns and outcomes among patients with multiple myeloma: a SEER-Medicare analysis.	Blood Advances
18	Mupfudze, TG	2020	A qualitative analysis of state Medicaid coverage benefits for allogeneic hematopoietic cell transplantation (alloHCT) for patients with sickle cell disease (SCD).	Transplantation and Cellular Therapy
19	Truong, T	2020	Regional differences in access to hematopoietic stem cell transplantation among pediatric patients with acute myeloid leukemia.	Pediatr Blood Cancer
20	Leuthold, N	2021	Patient preferences for allogeneic hematopoietic stem cell transplantation: how much benefit is worthwhile from the patient´s perspective?	Supportive Care in Cancer
21	Worel, N	2021	Changes in hematopoietic cell transplantation practices in response to COVID-19: A survey from the Worldwide Network for Blood & Marrow Transplantation.	Transplantation and Cellular Therapy
22	Pan, D	2021	Evaluating race and time to transplantation in multiple myeloma: The Mount Sinai Hospital Experience.	Clinical lymphoma, myeloma & leukemia

Data were summarized in a summary spreadsheet with the following parameters: main author, study design, study participants, type of transplant involved, type of access barrier discussed, main results and conclusions (Table 2).

TABLE 2. Summary of articles selected for the integrative review

Main Author	Study Design	Study Participants	Type of Transplant involved	Barriers to Access	Main Results	Conclusion of Study
Gramajo (2012)	Retrospective	Population submitted to transplant with procedure financed by different entities, in Argentina, between 2000 and 2010.	Not discriminated	Organizational and Geographic	Patients with health insurance had higher rates of transplantation compared with patients without insurance, considering all insurance entities in the country. There were differences in access among the insured population depending on geographic localization. Better access in the province of Buenos Aires for patients without health insurance because it has its own financing entity.	There was vertical inequality in access to transplants in Argentina, which should motivate further studies on the issue of financing these procedures and, in the analysis of only the group with health insurance, there was horizontal inequality that needs organizational discussion.
Bierenbaum (2012)	Retrospective	Patients with acute myeloid leukemia, white versus black, treated from 2000 to 2009 at a tertiary university hospital in Baltimore (United States).	Allogeneic	Socioeconomic and cultural	Fewer black patients had access to transplants compared with whites, especially males, and these findings may also reflect lower access to clinical studies. The income of the black families assisted was lower than that of the white patients.	The authors were unable to explain the disparities, but it was speculated that there were socioeconomic and cultural factors involved.

Urbano-Ispizua(2012)	Retrospective	Transplant candidate population in Western and Eastern Europe based on registry data since 1990.	Autologous and allogeneic	Financial	Countries with higher GDP per capita and higher density of transplant teams had higher transplant rates.	Macroeconomic factors influenced access to transplantation, with higher rates in countries in Western Europe compared with Eastern Europe, since the number of teams also depended on the economic and financial power of the country
Omondi (2013)	Cross-sectional	Parents of young patients (<16 years) and young Black patients with sickle cell disease in the United States.	Allogenic	Information	The lack of information about the disease and understanding of the treatment, mainly by the parents responsible for the patients, suggested difficulties in gaining access to transplantation by clinical trials.	Identifying barriers to information could help healthcare professionals and managers to perform interventions to improve access to transplantation for patients with sickle cell disease in the United States.
Moore (2013)	Cross-sectional	In 2009, Health professionals questioned about access to post-transplant care for patients living in rural areas far from a transplant center (over two hours of traveling by car) in the United States.	Not discriminated	Geographic	Limitations of transport to the transplant center, lack of expertise in assistance at the place of residence and the distance from the transplant center restricted access to post-transplant care.	There was a need for education of health providers in locations close to the patients' homes to ensure continuity of care and these objectives must be worked on at an organizational level.
Pidala (2013)	Cross-sectional	Medical specialists questioned about referring onco-hematological patients for transplantation in the United States in 2011.	Allogeneic	Information and organizational	Lack of transplant coverage by insurers, lack of social support, non-adherence to treatment and lack of understanding of treatment by the patients were factors associated with lack of referral to transplant centers.	Improvements in coverage, investment in education and social support for patients were necessary to enable decision-making that would allow better access to transplantation.
Thompson (2013)	Cross-sectional	Patients with sickle cell disease and their caregivers were questioned about factors that influenced their decision on whether or not to undergo a transplant, in Washington (United States) in the years 2011 and 2012.	Allogeneic	Information	The factors with the greatest impact on the decision were the risk of death from the procedure, complications of the underlying disease, risk of transplant complications, trust in the medical team, risk of transplant failure and the emotional impact caused by the transplant.	It was not possible to generalize the findings to a larger population of patients with sickle cell disease and their families, however, the expectation was that the dissemination of information would increase the search for transplantation to cure this disease and improve the quality of life of patients.

Maeda (2014)	Cross-sectional	Patients with adult T-cell leukemia treated in different regions of Japan in 2010.	Allogeneic	Organizational	Although there were no apparent differences in per capita health expenditure between regions, Kanto and Kansai had higher transplant rates.	There were regional differences in access to transplantation related to local factors, with better efficiency in the use of resources.
Mikles (2014)	Cross-sectional	Healthcare Providers for Pediatric Patients with Sickle Cell Disease on the Perspective of Transplant Referral in the Northeastern United States in 2011.	Allogeneic	Information, geographic and organizational	Professionals who received training less than 20 years ago and those who worked in centers that performed transplants tended to refer a larger number of patients for the procedure. The phenotype of the disease had an impact on the rate of referrals. There were variations in the rates of transplants by teams. The degree of risk of death perceived relative to the procedure also affected referral rates.	There was a need to develop national guidelines to achieve greater uniformity of professional conduct in relation to the indication and referral of patients with sickle cell disease for transplantation.
Besse (2015)	Cross-sectional	Population that underwent transplantation in the United States in 2012.	Allogeneic	Geographic and organizational	There was difficulty with meeting the demand in areas with a larger population, with New York and California being the regions with the highest demand and the fewest needs of the adult and pediatric population being met, respectively.	The study revealed the need to build and expand transplant centers to cover unmet needs based on the perspective of analyzing geographic information.
Mitchell (2015)	Retrospective	Patients with leukemia and lymphoma treated in California (United States) in 2002 and 2003.	Not discriminated	Organizational, Socioeconomic and Geographic	The population of patients with private insurance and white men were more likely to undergo a transplant, and so were patients who lived closer to treatment centers and had higher incomes.	There were multiple variables involved in gaining access to transplantation, seen as a high-cost therapy for the health system, and the financing model could affect both access and clinical outcomes.
Patel (2015)	Cross-sectional	Population with acute myeloid leukemia diagnosed in California (United States) in the period between 2008 and 2018.	Not discriminated	Socioeconomic	In the population analyzed, Black patients were less likely to receive chemotherapy and transplantation than white patients. Patients of Latin origin had less access to transplants than white patients.	Further studies are needed, which correlate the differences in access to treatments among different ethnic groups with socioeconomic differences.

Alsultan (2016)	Cross-sectional	Patients with sickle cell anemia under follow-up in Saudi Arabia in the period from 2009 to 2014.	Allogeneic	Geographic and financial	The number of centers and teams that perform transplants was insufficient to meet the local demand, and some patients left the country to undergo the procedure.	The article recommended that greater funding (should be provided) for transplant programs, which would allow new centers to be opened and more teams to be trained.
Delamater (2016)	Cross-sectional	Total adult and pediatric population based on the number of transplant centers in the United States in 2015.	Not discriminated	Geographic	The adult population had better geographic access than the pediatric population. The white population had worse geographical access than ethnic minorities, and this data could reflect the predominance of the white population in rural areas.	Despite variations in terms of distance from transplant centers, approximately 94% of the population had geographic access to these centers, within 3 hours. Further studies were needed to assess clinical outcomes in relation to patients' distance from transplant centers.
Schriber (2017)	Cross-sectional	Patients with multiple myeloma (of Latino, Black, and white origin) undergoing autologous transplantation in the United States in the period between 2008 and 2014.	Autologous	Socioeconomic	Although the rate of using transplantation increased in the three groups from 2008 to 2013, fewer Latino and black patients over 60 years of ag underwent transplantation compared with whites. The white population had faster access to transplantation, from the time of diagnosis through to the procedure,	There are differences in access to transplantation for multiple myeloma among ethnic groups and new strategies are needed to minimize this disparity. Moreover, further studies are needed to better elucidate the factors that determine these differences.
Umakanthan (2018)	Retrospective	Patients with acute lymphoblastic leukemia, adults diagnosed in the United States in the period between 2003 and 2012.	Allogeneic	Socioeconomic and organizational	The factors related to a lower chance of undergoing a transplant were treatment at a non-academic center, low educational level, being a Medicare/ Medicaid user or one without health insurance coverage, and male gender.	The data found suggested that socioeconomic differences and differences in coverage of the procedure by the health system can affect access to transplantation. The reason why female patients had more access in this study, was not clear.

Ailawadhi (2019)	Retrospective	Black, white, and Latino patients with multiple myeloma covered by Medicare in the United States in the period from 2007 to 2014.	Autologous	Socioeconomic	Black and Latino patients experienced more delay in gaining access to new treatments and Latino patients were less likely to undergo transplantation within a year of diagnosis compared with white and Black patients.	Disparities in access to more modern treatments and transplantation between different ethnic groups involved socioeconomic variables that needed to be overcome to achieve equity of health in the group studied.
Mupfudze (2020)	Cross-sectional	Population with sickle cell disease covered by Medicaid in eight states in the United States.	Allogeneic	Organizational	All states reported that children with a fully matched related donor were covered, however, in clinical trials, only two states reported policies covering costs. Accommodation and travel expenses were not covered in most states. Funding did not cover the costs of the procedures, and the transplant center paid the difference. The different Medicaid plans led to differences in the process of obtaining authorization for the transplant.	The study pointed out the need for discussions concerning the legislation so that there could be greater uniformity in patients' access to transplantation for sickle cell disease. This referred especially to the issue of financing clinical studies for transplants with alternative donors, and to public policies that made it feasible for patients and caregivers to obtain accommodation and transport.
Truong (2020)	Retrospective	Pediatric population with acute myeloid leukemia diagnosed in different regions of Canada in the period between 2001 and 2015.	Allogeneic	Geographic	Patients with an indication for transplantation before the first relapse had better access when diagnosed in the East of the country compared with the Center and West. Patients with indication for transplantation after the first relapse had faster access if the leukemia treatment was carried out at a center that performed transplantation.	Although other variables such as distance from home to the hospital, income and ethnicity did not have an impact on access to transplantation in this study, the data found may help in the formulation of public policies and guide other studies that clarify the geographic and socioeconomic impact on the treatment of the condition in this population.

Leuthold (2021)	Cross-sectional	Adult patients submitted to bone marrow transplantation up to October 2018, were asked about the benefits in terms of survival and cure they considered receiving when accepting the procedure in a university hospital in Switzerland.	Allogeneic	Information	Approximately 95% of the patients considered a gain in survival of one-year as being acceptable to undergo the procedure, and 85% of the study population considered a minimum of 5 years justifiable. Most patients considered at least a 50% cure rate as being acceptable.	Further studies were needed to understand the gains in survival and cure from the perspective of patients, since there may have been selection bias and the younger population tended to accept more risks with fewer benefits.
Worel (2021)	Cross-sectional	Members of several international transplant societies asked online about changes in the handling of allogeneic and autologous donor products during the COVID-19 pandemic in 2020.	Allogeneic and autologous	Organizational	Most centers changed the criteria for cell collection and mobilization during the pandemic, in accordance with the recommendations of international societies. Some centers only performed urgent transplants and some even completely stopped performing autologous collections.	The pandemic imposed changes in conduct on transplant centers, with the need to postpone transplants considered non-urgent due to the risk of SARS-CoV-2 infection of donors, patients, and health professionals.
Pan (2021)	Retrospective	Both white and Black multiple myeloma patients, transplanted at a center in New York (United States) in the period from 2011 to 2016.	Autologous	Socioeconomic	No difference in time between diagnosis and collection of cells was demonstrated between white and black patients, but socioeconomic status based on difference in income had an impact on access to transplantation.	Although there was no statistical significance, the transplant center recognized the elapse of a longer time from diagnosis to collection of cells for black people, which may have been related to the socioeconomic situation of this population, which must be improved for then to gain faster access to cell therapy.

Eight retrospective studies and 14 cross-sectional studies with an approach to transplantation modalities were identified. There were 12 studies on allogeneic transplantation, 3 on autologous transplantation, 2 discussed both modalities and 5 studies did not discriminate the type of HSCT. Most of the studies found were conducted in the United States, with 15 of these corresponding to 68% of the total articles analyzed. The other articles found, one for each location, were carried out in Argentina, Saudi Arabia, Canada, Japan, Switzerland, in addition to one involving European countries and one with a global perspective. Six studies addressed the context of barriers to access in cases of leukemia, 5 in sickle cell disease and 3 in multiple myeloma.

Some of them involved the entire population residing in the country, with an indication for undergoing the procedure, when the issues discussed involved financing modalities or geographic distance. The studies with health professionals raised questions about geographic difficulties, regulation of access and changes in behavior in the COVID-19 pandemic. All categories of barriers to access were discussed. For geographic, organizational and culture/information barriers there were 3 articles to discuss each of the topics and 5 studies relative to financial/ socioeconomic barriers. Eight articles discussed more than one barrier.

DISCUSSION

Access to health care is a complex concept that involves factors that are intermediaries between demand, access to health services, possible therapeutic interventions, and clinical follow-up. Following the proposal of the flow of events proposed by Frenk cited by Travassos & Castro, for the discussion and planning of access to health care, it is necessary to start from a population health need[5]. Through this flow, health systems should be based on reaching the broad domain of access, which involves everything from educational and cultural aspects that pertain to the way in which the population wants to obtain health care, through to the continuity of health care, whether preventive or curative. Even in universal health systems, planning and guaranteeing access to the broad domain are constant challenges. If only the aspects of seeking and entering health services were to be considered, this would generate public policies that would not consider aspects of prevention and would not guarantee continuity of care[5].

There are many factors involved in determining access that will help characterize the population's ability to use services within health systems. According to Rocha et al., the factors associated with access to allogeneic HSCT are availability donor, socioeconomic factors, aspects of health systems, actions related to health care providers and geographic determinants[11]. Adequate knowledge of these factors will help plan the type of access that health systems will offer, with the possibility of eliminating or reducing barriers, thereby promoting health of the population. This study was designed by grouping barriers to access into four categories that will be discussed: geographic, financial/socioeconomic, organizational, and information/cultural types.

Relative to the donor, with technological advances in the understanding of immunogenetics and advanced mechanisms for unrelated search, in addition to the advent of the use of high doses of cyclophosphamide as prophylaxis for graft-versus-host disease, most patients who need transplantation have donors. Therefore, despite the donor being a determining factor for HSCT to occur, this parameter was not considered in the searches of this study because of the wide donor availability in the current technical-scientific context.

CONCERNING THE SOCIOECONOMIC AND FINANCIAL BARRIERS

Socioeconomic and financial factors impact all levels of health care and characterize the barrier to access to HSCT found in this review [13–21]. Income is a parameter known to be an important factor in determining the health condition of populations whereas ethnic and socioeconomic issues are complex and require careful analysis of other factors, including clinical outcomes, which may influence them[22]. Furthermore, in recent decades, rising costs have had a significant impact on health systems around the world and pose, especially in underdeveloped countries, challenges for innovation in care models so that they are sustainable [23]. Human freedom to generate health is dependent on choices in the economic sphere and formulations of public policies for social well-being, mediated by the interests of the government around the world [24].

The results of this study reveal both micro and macroeconomic data that refer to differences in wealth among certain ethnic groups and even groups of countries. There was a significant finding of lower access to HSCT in groups of black people with lower income than white people[15,17,18]. Although other studies did not directly report results resulting from income discrepancies, there was a finding of difference in access between different racial and ethnic groups, with blacks and latinos also arriving later at HSCT centers [13,19,20] and in some situations had less access to chemotherapy for treatment prior to transplantation [19].

The GDP of countries affects health systems, and consequently access, however there are countries that, despite having a GDP per capita lower than developed countries, manage to organize themselves in a way that their population has a high life expectancy, which suggests that it is more important to know what to do with the resources available to be allocated than just their quantity[24]. Urbano-Ispizua et al. demonstrated that on the European continent, patients residing in countries with a higher GDP per capita, located predominantly in Western Europe had better access to HSCT[21]. In this same study, there was a positive impact in places with a higher density of health teams. There probably were more centers due to the availability of financial resources that allowed sustainability of a larger number of programs, and the findings of the study were interrelated. Alsultan et al. pointed out that there were cases such as Saudi Arabia, in which the offer of HSCT services for sickle cell disease was insufficient to meet the demand to the extent that people left the country to receive treatment elsewhere [14].

In this review, not all countries found had universal health systems, which would have helped to minimize financial barriers by the group of individuals who did not have health insurance, which was a significant factor reported in some studies to achieve improvements in access [16,17,25]. Some countries can include patients in clinical studies, which allows them to use technological innovations in their treatment, especially when treated in academic centers [15,16].

CONCERNING THE GEOGRAPHIC BARRIERS

Geographical barriers involve the spatial challenges imposed, from transportation difficulties to the lack of specialized teams for the procedure. Gramajo et al. reported that in Argentina there is better access to HSCT in the province of Buenos Aires, even for those who do not have health insurance, as this region has its own financing entity that minimizes the lack of coverage by insurance companies [25]. This same study also reports that even among the insured population, there is a difference in access depending on the region of residence in the country.

Moore et al. point out that, in addition to issues related to difficulty in transportation, there is no adequate support in rural areas further away from HSCT centers in the United States due to the lack of training of local teams, making post-transplant follow-up difficult [26]. In contrast, Besse et al. argue that in urban centers with large populations there is a lack of infrastructure to meet demand and population needs are not met [27]. In the first case, the organization of care networks with education and qualification programs for professionals could minimize possible clinical harm to patients due to the lack of specialized care. Telehealth systems could be of great benefit in minimizing distances. As for locations with high demographic density, management depends on financial and organizational factors for the solution, with an increase in the installed capacity of HSCT beds or logistical agreements for referral to other regions.

Many of the solutions to geographic barriers are at the organizational level: if there is no way to change the geography, there is a need to increase the number of transplant centers, with the need for better financing or improving the logistics of transporting the poorest patients, as income also affects the geographic mobility of people[14,28].

Delamater et al., when studying the impact that geography had on transplants in the United States, found that the adult population would have more access than the pediatric population due to the presence of more centers that perform transplants in adults [29]. This finding is compatible with the epidemiology of the main indications for HSCT, with a higher prevalence in adults [30]. However, this same study raises the curious question that the white population residing in rural areas, generally with a more favorable economic situation than ethnic minorities in large centers, would have worse geographic access to transplantation. Even with the variable distance within the country, most of the population has access to some service within a few hours of travel, which suggests that other factors are interrelated determinants [29].

Truong et al. found better access to HSCT, in first remission, for children with acute leukemia in Canada who lived in the east of the country [31]. As should happen anywhere in the world, in patients with more urgent conditions, access is faster and more agile if the treatment takes place in an academic center that performs transplants [16,31].

CONCERNING THE ORGANIZATIONAL BARRIERS

The various health systems are organized to balance policies taking into account the interests of the State, the population and the market. Organizational issues affect equity in similar population groups with comparable per capita health expenditure [32], as well as in the case of patients with health insurance living in the same country, but who have differences in access to HSCT [25].

There is no uniformity in the coverage of HSCT procedures in the world [16,17,25,33,34], which interferes with decision-making by professionals [33], with the possibility of generating unfavorable outcomes. Furthermore, the lack of therapeutic guidelines makes regulating access and referral an additional challenge for the teams [35]. Locations with better efficiency in the use of resources have better access to HSCT [32], including covering the need to increase the number of centers and trained teams for some areas [27].

The COVID-19 pandemic led to an additional challenge with the need to change clinical protocols so that patients with an indication for transplantation could be treated according to their risk of exposure to SARS-CoV-2 and the risk of death from the underlying disease [36]. Most centers postponed HSCT for patients with chronic diseases, such as multiple myeloma, and there could have been an unmeasurable harm to the survival of those who did not have access to new pharmacological technologies for their treatment, deepening previously reported inequities [36,37].

CONCERNING THE CULTURAL AND INFORMATION BARRIERS

HSCT procedures bring with them the hope of curing diseases, but the therapeutic process imposes biopsychosocial challenges on patients, which includes a very considerable risk of death due to complications in some cases [38,39]. Transplant candidates and their families, in addition to the information provided by professionals, consider cultural and religious aspects and the emotional impact [40]. These parameters must be adequately understood and worked on by health teams, so that they are not barriers to access, but become tools that help in autonomous decision-making by the people involved.

Due to the multifactorial aspects involved in access to HSCT, it can be quite complex to infer the weight of cultural issues in decision-making. Bierenbaum et al. discussed the issue of access between white and black people with acute myeloid leukemia from the perspective of a single center in the United States, concluding that there was a difference in access between the groups, but without a significant explanation, suggesting that cultural factors may be involved [15].

Both for patients with chronic conditions, such as sickle cell disease, and for candidates for HSCT due to indications of onco-hematological diseases, adequate education and provision of information has an impact on the decision-making autonomy of patients and their families. Thompson et al. reported that the decision to undergo HSCT weighs not only on the perception of the complications of the underlying disease itself and of the HSCT, but also on trust in the medical team [40]. This is a complex decision for this group of patients, because they generally have no perception of the severity of their disease and lack technical-scientific alignment for uniform conduct in relation to indication and referral [35]. On the other hand, the onco-hematological patient with an indication for HSCT desires the transplant but needs information that brings security to their choice in terms of survival gains, as many would not accept the risks inherent to the transplant without the perception of a potential gain in survival [41].

Guiding patients and families about the entire HSCT process, its benefits, and complications, can even make a difference in access to clinical studies for this population, enabling the use of innovative therapeutic technologies[42]. It is important, therefore, to highlight that not only the level of information of the target population, but also the level of technical knowledge, the ability to disseminate guidance and the health teams' own perception of the HSCT process, its outcomes and the adherence to treatment may influence the regulation of access to transplantation [33,35].

FINAL CONSIDERATIONS

It is noteworthy that most of the studies found in this review were carried out in the United States, the country with the largest increase in health spending, but with questionable gains in survival and quality of life for the population[43]. As one of the highest-cost procedures, economic studies on HSCT should be of interest to society, especially for chronic diseases such as sickle cell anemia, which can be cured and generate social benefits for patients' families and gains in efficiency in health spending, avoiding treating late complications. Hong and Majhail proposed a model for studies that can better elucidate racial, socioeconomic, and geographic barriers, with factors that interfere in the patient's line of care, from social policies and interventions, through regulation of access and education of health professionals[44]. The factors that act in determining access to treatment are as complex as transplantation.

This study has some limitations. The fact that it is an integrative review refers to a methodology that covers part of the knowledge and that may fail to find and discuss all aspects involved in barriers to access to HSCT and be limited to the perspectives of the studies found.

CONCLUSION

The issues surrounding access to HSCT are complex and interrelated, considering that geographic, financial, socioeconomic, cultural, organizational and information factors form an even more diverse network of variables when we think about multiple care models and systems of health in the world. The greatest negative impacts occur on the health of the most socially vulnerable populations. It is challenging to study and characterize these determining factors, as many of the articles found in this review bring local perspectives that cannot be applied in all countries. Despite this, gathering knowledge of these barriers can guide new studies to formulate public policies that can guarantee better access to the procedure, especially in underdeveloped countries, with efficient use of resources to improve equity in access to healthcare.

DISCLOSURES

The authors have states that they have no conflict of interest.

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