DOI: 10.46765/2675-374X.2021v2n2p99

CURRENT USE AND OUTCOMES OF HEMATOPOIETIC STEM CELL TRANSPLANTATION: THE FIRST BRAZILIAN SUMMARY SLIDES

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Runing title: CURRENT USE AND OUTCOMES OF HSCT

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ABSTRACT

Understanding the HSCT scenario in Brazil is challenging due to the lack of a national registry that allows the analysis of results. The partnership between the Brazilian Cellular Therapy and Bone Marrow Transplant Society (SBTMO) and the Center for International Blood and Marrow Research (CIBMTR) allowed the return of Brazilian data registered in the CIBMTR, through the Data Back to Center (DBtC), in a standardized and organized way. With this database it was possible to know the demographic data and the outcomes of transplants performed in Brazil. The spreadsheet was imported into the Power BI desktop, and functions and charts were created. Between 2008 and 2019, 7,264 transplants were reported to the CIBMTR from 24 Brazilian transplant centers. The partnership between SBTMO and CIBMTR, made the Brazilian registry possible and allowed the development of the first Brazilian Summary slides. Despite the difference in the number of cases and of follow-up time, the results in this study were similar to those presented in the US Summary Slides.

Keywords: Data Management. Hematopoietic Stem Cell Transplantation. CIBMTR. SBTMO. DBtC. Brazilian Summary Slides.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a therapy that can be the only option for curing many malignant and non-malignant hematological diseases, as well as extending the survival of many patients[1]. Brazil has a large HSCT program, with 126 teams in 86 transplant centers recognized by the Brazilian Ministry of Health. The results of these transplants are not organized and available for public awareness.

The only current source of information is the Brazilian Association of Organ Transplants (ABTO), which discloses the number of procedures performed each year. According to ABTO, in 2019, 3,805 transplants were performed: 1,428 allogeneic and 2,377 autologous[2]. According to the Center for International Blood and Marrow Transplant Research (CIBMTR), a total of 269,203 autologous and 280,299 related and unrelated allogeneic transplants were reported around the world between 1970 and 2020.[3]

Understanding the HSCT scenario in Brazil is challenging due to the lack of a national registry that allows the analysis of results and provides greater scientific production and national benchmarking. Therefore, over the years, through a working group composed of physicians and data managers (DM) and with the collaboration of the CIBMTR and the Brazilian Society of Cellular Therapy and Bone Marrow Transplantation (SBTMO), strategies such as continuing education in data management and communication channels were developed. These actions increased the number of registered and active Brazilian centers in the CIBMTR.[4]

The partnership between SBTMO and CIBMTR allowed access through the tools available in the registry, such as the Data Back to Center (DBtC), which allows the return of the data sent to the transplant center. Part of the data inserted can return to the centers registered in a standardized and codified way, allowing the analysis of the outcomes of transplants performed in the country. Accessibility to these data is fundamental for health and public administration.

OBJECTIVE

Our objective is to understand the demographic data and the outcomes of transplants performed in Brazil using the DBtC tool to retrieve the data registered in the CIBMTR in a standardized and organized way.

METHODS

Make the data available to HSCT centers and maintain a routine to update the results.

Data from transplants performed between 2008 and 2019 were extracted from the CIBMTR portal using the DBtC, with information from transplanted patients in 24 Brazilian centers that sent their data to the CIBMTR. The records that had completed HSCT data were selected for analysis, totalizing 7,264 transplants. The spreadsheet was imported into Power BI Desktop (PBI). Functions were created to count the number of transplants performed and the number of participating centers, to translate some columns into Portuguese, to categorize disease classification, to group variables, and for calculating global survival analyses, and sheet relationships.

Patients were classified in pediatric (0-17 years of age) and adults (≥ 18 years of age). Allogeneic transplants were categorized as matched related donor, mismatch related donor, and unrelated donor. Grafts were classified as Bone Marrow (BM), Peripheral Blood Stem Cells (PBSC) and umbilical cord blood (CB). The disease stage for acute leukemias was classified as early disease for patients transplanted in 1st remission, intermediate disease for patients in 2nd or further remission and advanced for patients who underwent HSCT with active disease.

Patients with Myelodysplastic Syndrome (MDS) were divided into Early Stage, which is subdivided into refractory anemia (RA); refractory anemia with ring sideroblasts (RARS); refractory cytopenia with multilineage dysplasia (RCMD); and with MDS with del(5q) alone, or Advanced Stage, including refractory anemia with excess blasts (RAEB) and Chronic Myelomonocytic Leukemia (CMML). Patients with Lymphoma were categorized as chemosensitive and chemoresistant disease by the response to treatment prior to HSCT.

The classification of conditioning was based on the agents and doses used, Myeloablative Conditioning (MAC) for patients who received total body irradiation (TBI) ≥500 cGy in a single dose or ≥800 cGy in fractionated doses; busulfan >9 mg/kg oral or ≥7.2 mg/kg IV or melphalan >150 mg/m2 as a single agent or in combination with other drugs. The other conditionings that did not fill the criteria for MAC were classified as Reduced Intensity/Non-Myeloablative (RIC/NMA).[5-6] The causes of death were classified using the standard classification from DBtC. The main causes of death between 2015-2019 were

separated between deaths 0-100 days and deaths >100 days up to 3 years after HSCT. For the analysis of overall survival (OS), patients who underwent 1st HSCT were selected, and those who were without follow-up update after transplantation or had error in survival time were excluded (table 1).

The charts were generated in the PBI and exported to PowerPoint for publication. Global survival analyses were performed by the Kaplan Meier method (Comparison between groups by long-rank test) using the R program (Version 4.0.3).

RESULTS

Between 2008 and 2019, 7,264 transplants were reported from 24 transplant centers in Brazil (table 2), 14 (58%) located in the state of São Paulo; 2 in Rio de Janeiro; 2 in Rio Grande do Sul; and 1 center in each state: Ceará, Distrito Federal, Minas Gerais, Paraná, Rio Grande do Norte, and Santa Catarina.

An increase in the number of active centers was observed in recent years, reaching 23 active centers in 2019 (figure 1). This increase in the number of participating and active centers contributed to the increase in the total number of transplants registered in the CIBMTR since 2016, reaching 1,073 transplants in 2019 (figure 2). The increase in registered cases was observed both in allogeneic and autologous transplants.

Half of the allogeneic transplants performed in Brazil used a matched related donor (49.7%), followed by an unrelated donor (BM/PBSC) (28.9%), and a mismatch related donor (15.8%).

Regarding the graft source for allogeneic transplants, BM was used in most pediatric transplants and in adults, the main source was PBSC from 2018 on (table 3).

Mismatched related donors were used to treat non-malignant diseases (30.1%), followed by acute myelogenous leukemia (AML; 29.4%) and acute lymphoblastic leukemia (ALL; 21.1%); half of them used MAC (50.5%) and 49.5% used RIC/NMA.

The number of autologous and allogeneic transplants have increased in recent years in recipients over 60 years of age.

The main indications for HSCT in Brazil between 2017-2019 were Multiple Myeloma (25%), followed by AML (16%), ALL (13%), non Hodgkin lymphoma (NHL; 12%) and Hodgkin disease (HD; 9%) (figure 3). In pediatric allogeneic HSCT, the main diseases were ALL (32%), other Non-Malignant (25%) and AML (18%). In adults, the main indications for allogeneic transplants were AML (33%), ALL (19%) and MDS (14%).

Acute leukemias continue to be the main indication for allogeneic transplantation, but from 2016 on, there was an increase in indications for MDS/MPN and Lymphomas. The main indications for autologous HSCT remain Multiple Myeloma and Lymphomas.

In patients with acute leukemias, half of the patients with AML were in the early phase of the disease (50.4%), but for ALL 45.9% were in the intermediate phase. Most HSCT were from matched related donor in both AML (55.1%), as well as in ALL (44.9%) (table 4).

Adults and children having an allogeneic HSCT in early phase of the disease had a higher OS ($p<0.001$ and $p=0.008$, respectively; table 5).

Infections were the leading cause of death in the first 100 days after all transplants: autologous (60%), matched related donor (38%), unrelated donor (40%), and mismatch related donor (54%). The most common cause of death more than 100 days after HSCT was the primary disease: autologous (76%), matched related donor (39%), unrelated donor (44%) and mismatch related donor (48%).

For the analysis of OS, the median follow-up was 25 months in allogeneic and 23 months in autologous HSCT. Patients who underwent transplantation with advanced stage had lower survival rates compared to the other stages.

Adults had a significantly better survival after HSCT from matched sibling donors when having HSCT for AML ($p=0.047$; figure 4) and ALL ($p=0.027$; figure 5), but donor source had no impact in pediatric patients with acute leukemias.

The 2-year survival for MDS was similar despite disease risk and donor source (figure 6). Patients with CML a 2-year OS of 60.1% with a matched related donor and 55.0% with an unrelated donor ($p=0.314$) (figure 7). Patients with Myelofibrosis had a survival of 59.0% in 2 years (figure 8). Donor source had no impact in adults and children with Aplastic Anemia (figure 9).

Patients undergoing autologous HSCT to treat chemosensitive Lymphomas had a significantly better 2-year OS than chemoresistant disease: 89.2% versus 64.9% in HD ($p=0.005$) and 79.7% versus 58.6%

in NHL (p=0.019) (figure 10). In Multiple Myeloma, the 2-year OS was 83.4% (figure 11).

DISCUSSION

Our study, using DBtC data, demonstrated a greater number of allogeneic than autologous transplants reported to the CIBMTR, but according to ABTO there is a greater number of autologous transplants in the country. The explanation for this difference is due to the larger number of affiliated centers in the CIBMTR that perform allogeneic transplants.

We observed an increase in the number of transplants with mismatch related donor since 2012, and a decrease in unrelated CB transplants in the same period, probably due to the use haploidentical donors with cyclophosphamide after transplantation.

Comparing our data with the American summary slides published in the CIBMTR website,[7] the matched related donor is the main type of transplants performed in Brazil, while in the United States (USA), it is unrelated BM/PBSC.

In pediatric patients, the main source was BM in Brazil, following the same trend in the USA; in adult, while in Brazil the use of PBSC has been increased over the years and has become the main source used since 2018, in the three modalities of allogeneic donors, in the USA the main source was PBSC since 2000.

In Brazil, in recent years, the main indications for HSCT were MM, AML, ALL, NHL, and HD, while in the USA in 2019 were MM, NHL, AML, MDS/MPN and ALL.

Another important comparison was the cause of early death, 0 to 100 days after transplantation: in Brazil, the main cause of early mortality was infection for autologous and matched related donor transplants, while in the USA, it was the primary disease; in transplants with mismatch related and unrelated donors, in Brazil the main cause of death was infections, while in the USA, organ failure was classified as the leading cause.

Comparing the 2-year OS in our study with the 3-year OS in the US Summary Slides, the Brazilian data is similar to the survival reported by American centers (table 6) despite the socioeconomical differences.

CONCLUSION

The partnership between SBTMO and CIBMTR made the Brazilian registry possible through the DBtC. The analysis of the data from Brazil, allowing us to develop Brazilian Summary slides to know the outcomes of transplants, making them available to centers as a national and international benchmarking. The Brazilian Summary slide will be updated twice a year and published at the SBTMO website. Despite the difference in the number of cases and follow-up time, the results in this study were similar to those presented in the US Summary Slides.

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TABLE 1. Exclusion criteria for overall survival

Exclusion criteria	n
Patients without follow-up update	1,014
Error in survival time	4
2nd HSCT or more	626

TABLE 2. HSCT centers

Participants Centers
Associação Hospitalar Moinhos de Vento
Bio Sana's São Camilo
Centro de Pesquisas Oncológicas Dr. Alfredo Daura Jorge (CEPON)
Complexo Hospitalar de Niterói
Fundação Pio XII - Hospital de Amor
Hospital Amaral Carvalho
Hospital das Clínicas da Faculdade de Medicina da USP
Hospital de Clínicas da Universidade Federal do Paraná
Hospital de Clínicas de Porto Alegre
Hospital Israelita Albert Einstein
Hospital Leforte Liberdade
Hospital Samaritano
Hospital Sírio Libanês
Hospital Universitário Walter Cantídio da Universidade Federal do Ceará / HUWC-UFC
IBCC - Instituto Brasileiro de Controle do Câncer
Instituto da Criança - Hospital de Clínicas da Faculdade de Medicina da Universidade de São Paulo (ITACI)
Instituto de Cardiologia do Distrito Federal - Unidade de TMO Pietro Albuquerque
Instituto de Oncologia Pediátrica - GRAACC
Instituto Nacional de Cancêr - INCA
Natal Hospital Center
Real e Benemérita Sociedade de Beneficência Portuguesa de São Paulo
Universidade Estatual de Campinas (UNICAMP)
Hospital das Clínicas da Universidade Federal de Minas Gerais
Universidade Federal de São Paulo - Hospital São Paulo

TABLE 3. Source of cells used by donor type, age and year of HSCT

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Patients <18 Years												
Matched Related Donor												
PBSC	2.9%	1.8%	5.1%	1.8%	2.0%	5.0%	2.5%	3.4%	11.1%	5.6%	6.9%	9.1%
BM	94.1%	92.7%	94.9%	92.7%	96.0%	95.0%	97.5%	93.1%	88.9%	91.7%	89.7%	88.6%
CB	2.9%	5.5%	0.0%	5.5%	2.0%	0.0%	0.0%	3.4%	0.0%	2.8%	3.4%	2.3%
Unrelated Donor												
PBSC	0.0%	7.7%	7.7%	8.2%	5.3%	3.5%	14.5%	13.3%	8.1%	8.3%	14.0%	4.6%
BM	43.2%	42.3%	56.9%	58.9%	56.0%	75.4%	79.0%	73.4%	83.8%	85.0%	79.0%	90.8%
CB	56.8%	50.0%	35.4%	32.9%	38.7%	21.1%	6.5%	13.3%	8.1%	6.7%	7.0%	4.6%
Mismatch Related Donor												
PBSC	0.0%	0.0%	0.0%	25.0%	26.1%	10.3%	28.0%	10.7%	27.3%	21.3%	33.3%	31.0%
BM	100.0%	100.0%	100.0%	75.0%	73.9%	89.7%	72.0%	89.3%	72.7%	78.7%	66.7%	69.0%
Patients ≥18 Years												
Matched Related Donor												
PBSC	49.0%	50.9%	55.2%	49.4%	48.3%	47.4%	43.1%	52.5%	43.5%	53.9%	53.6%	60.7%
BM	51,0%	49.1%	44.8%	50.6%	51.7%	52.6%	56.9%	47.5%	56.5%	46.1%	46.4%	39.3%
CB	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Unrelated Donor												
PBSC	8.3%	17.6%	20.0%	24.5%	39.4%	29.1%	36.1%	54.2%	52.1%	48.2%	64.1%	57.3%
BM	75.0%	70.6%	53.3%	54.7%	43.9%	63.6%	63.9%	44.1%	47.9%	51.8%	35.9%	41.7%
CB	16.7%	11.8%	26.7%	20.8%	16.7%	7.3%	0.0%	1.7%	0.0%	0.0%	0.0%	1.0%
Mismatch Related Donor												
PBSC	0.0%	0.0%	50.0%	0.0%	13.3%	29.4%	36.8%	34.5%	41.9%	42.3%	60.5%	67.7%
BM	100.0%	100.0%	50.0%	100.0%	86.7%	70.6%	63.2%	65.5%	58.1%	57.7%	39.5%	32.3%

TABLE 4. Acute Leukemia by disease stage, donor type and HSCT year

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
AML												
Disease Stage												
Early	55.6%	53.7%	45.8%	44.4%	42.6%	53.3%	47.8%	45.3%	59.8%	50.0%	53.3%	53.9%
Intermediate	14.8%	26.8%	31.3%	30.9%	31.5%	22.7%	37.7%	41.9%	30.9%	29.8%	27.4%	25.1%
Advanced	29.6%	19.4%	22.9%	24.7%	25.9%	24.0%	14.5%	12.8%	9.3%	20.2%	19.3%	21.0%
Donor Type												
Matched Related Donor	77.8%	78.5%	74.0%	62.5%	52.8%	58.7%	68.1%	47.1%	49.5%	48.7%	46.7%	41.3%
Mismatch Related Donor	0.0%	1.5%	2.1%	2.5%	13.9%	6.7%	7.2%	18.4%	22.7%	25.6%	30.4%	32.3%
Unrelated Donor (BM/PBSC)	3.7%	10.8%	17.7%	22.5%	28.7%	25.3%	20.3%	33.3%	27.8%	25.6%	22.2%	26.3%
Unrelated Donor (CB)	18.5%	9.2%	6.3%	12.5%	4.6%	9.3%	4.3%	1.1%	0.0%	0.0%	0.7%	0.0%
ALL												
Disease Stage												
Early	26.5%	38.3%	34.6%	47.0%	44.8%	43.3%	55.4%	58.9%	50.6%	42.6%	52.2%	37.4%
Intermediate	64.7%	55.0%	52.6%	45.5%	51.0%	50.0%	36.5%	40.0%	39.1%	48.5%	34.8%	49.6%
Advanced	8.8%	6.7%	12.8%	7.6%	4.2%	6.7%	8.1%	1.1%	10.3%	8.9%	13.0%	13.0%
Donor Type												
Matched Related Donor	52.9%	63.3%	61.0%	50.0%	43.8%	56.7%	51.4%	44.2%	38.8%	37.0%	40.0%	29.0%
Mismatch Related Donor	0.0%	1.7%	3.9%	1.5%	6.3%	1.7%	2.7%	8.4%	18.8%	28.0%	27.0%	31.3%
Unrelated Donor (BM/PBSC)	23.5%	23.3%	20.8%	31.8%	32.3%	35.0%	44.6%	42.1%	41.2%	34.0%	32.2%	36.6%
Unrelated Donor (CB)	23.5%	11.7%	14.3%	16.7%	17.7%	6.7%	1.4%	5.3%	1.2%	1.0%	0.9%	3.1%

TABLE 5. Overall survival of AML/ALL patients

	N	OS in 2 years (%)	p
AML			
Patients Age 0-17 Years			
Donor Type			
Matched Related Donor	77	57.2%	
Unrelated Donor	87	54.9%	0.874
Mismatch Related Donor	40	62.5%	
Patients Age ≥18 Years			
Donor Type			
Matched Related Donor	462	56.3%	
Unrelated Donor	176	52.0%	0.047
Mismatch Related Donor	104	47.6%	
Matched Related Donor			
Patients Age 0-17 Years			
Disease Stage			
Early	40	58.6%	
Intermediate	24	65.3%	0.011
Advanced	13	38.5%	
Patients Age ≥18 Years			
Disease Stage			
Early	312	65.0%	
Intermediate	79	43.0%	<0.001
Advanced	71	30.6%	
Unrelated Donor			
Patients Age 0-17 Years			
Disease Stage			
Early	34	61.2%	
Intermediate	37	62.4%	0.013
Advanced	16	26.4%	
Patients Age ≥18 Years			
Disease Stage			
Early	64	69.7%	
Intermediate	74	52.5%	<0.001
Advanced	38	22.3%	

	N	OS in 2 years (%)	p
ALL			
Patients Age 0-17 Years			
Donor Type			
Matched Related Donor	131	56.5%	
Unrelated Donor	221	59.9%	0.232
Mismatch Related Donor	55	37.2%	
Patients Age ≥18 Years			
Donor Type			
Matched Related Donor	266	51.6%	
Unrelated Donor	139	45.4%	0.027
Mismatch Related Donor	57	46.6%	
Matched Related Donor			
Patients Age 0-17 Years			
Disease Stage			
Early	36	71.1%	
Intermediate	81	47.6%	0.131
Advanced	14	67.5%	
Patients Age ≥18 Years			
Disease Stage			
Early	195	61.5%	
Intermediate	57	24.1%	<0.001
Advanced	14	15.3%	
Unrelated Donor			
Patients Age 0-17 Years			
Disease Stage			
Early	61	73.7%	
Intermediate	145	56.8%	0.008
Advanced	15	38.1%	
Patients Age ≥18 Years			
Disease Stage			
Early	80	57.1%	
Intermediate	45	33.4%	<0.001
Advanced	14	14.3%	

TABLE 6. Comparison overall survival – Brazil and USA

	Brazilian Registry		US Summary Slides 2020	
	N	OS in 2 years (%)	N	OS in 3 years (%)
AML				
Matched Related Donor				
Patients Age 0-17 Years				
Disease Stage				
Early	40	58.6%	406	70.0%
Intermediate	24	65.3%	136	67.0%
Advanced	13	38.5%	84	33.0%
Patients Age ≥18 Years				
Disease Stage				
Early	312	65.0%	5,228	57.0%
Intermediate	79	43.0%	1,275	53.0%
Advanced	71	30.6%	1,838	31.0%
Unrelated Donor				
Patients Age 0-17 Years				
Disease Stage				
Early	34	61.2%	509	61.0%
Intermediate	37	62.4%	302	61.0%
Advanced	16	26.4%	166	34.0%
Patients Age ≥18 Years				
Disease Stage				
Early	64	69.7%	8,101	55.0%
Intermediate	74	52.5%	2,467	50.0%
Advanced	38	22.3%	3,091	30.0%
ALL				
Matched Related Donor				
Patients Age 0-17 Years				
Disease Stage				
Early	36	71.1%	332	81.0%
Intermediate	81	47.6%	472	68.0%
Advanced	14	67.5%	42	52.0%
Patients Age ≥18 Years				
Disease Stage				
Early	195	61.5%	2,258	62.0%
Intermediate	57	24.1%	621	43.0%
Advanced	14	15.3%	279	34.0%
Unrelated Donor				
Patients Age 0-17 Years				
Disease Stage				
Early	61	73.7%	450	74.0%
Intermediate	145	56.8%	611	62.0%
Advanced	15	38.1%	64	58.0%
Patients Age ≥18 Years				
Disease Stage				
Early	80	57.1%	2,707	61.0%
Intermediate	45	33.4%	1,006	42.0%
Advanced	14	14.3%	350	32.0%
MDS				
Matched Related Donor				
Disease Stage				
Early	99	63.2%	704	51.0%
Advanced	99	56.8%	1,645	46.0%
Unrelated Donor				
Disease Stage				
Early	68	59.3%	1,265	44.0%
Advanced	43	59.2%	3,166	43.0%
Aplastic Anemia				
Patients Age 0-17 Years				
Donor type				
Matched Related Donor	95	86.7%	503	97.0%
Unrelated Donor	85	85.4%	450	85.0%
Patients Age ≥18 Years				
Donor type				
Matched Related Donor	162	79.2%	653	81.0%
Unrelated Donor	69	64.2%	711	74.0%

FIGURE 1. Brazilian active centers in the CIBMTR by year

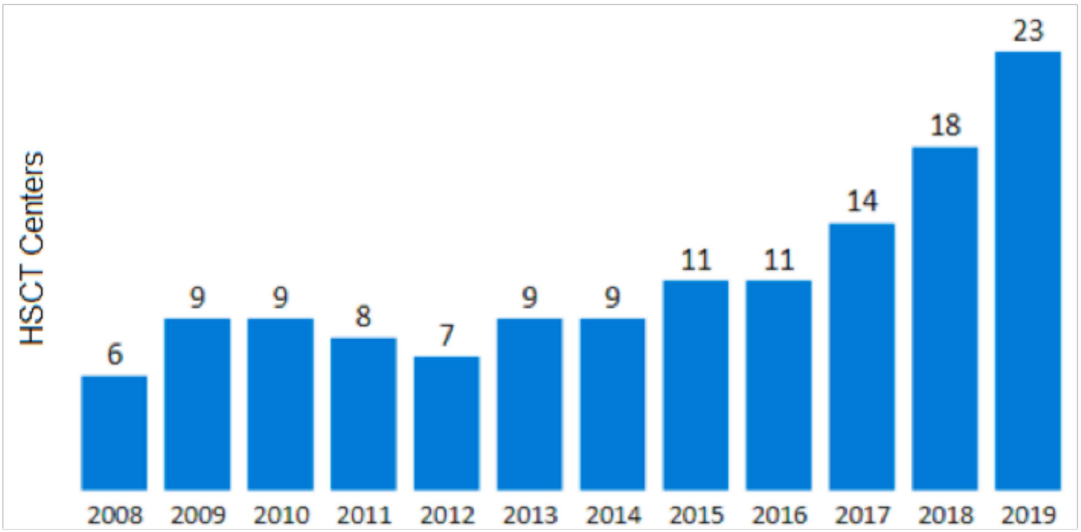

FIGURE 2. Tranplants performed in Brazil and reported in the CIBMTR

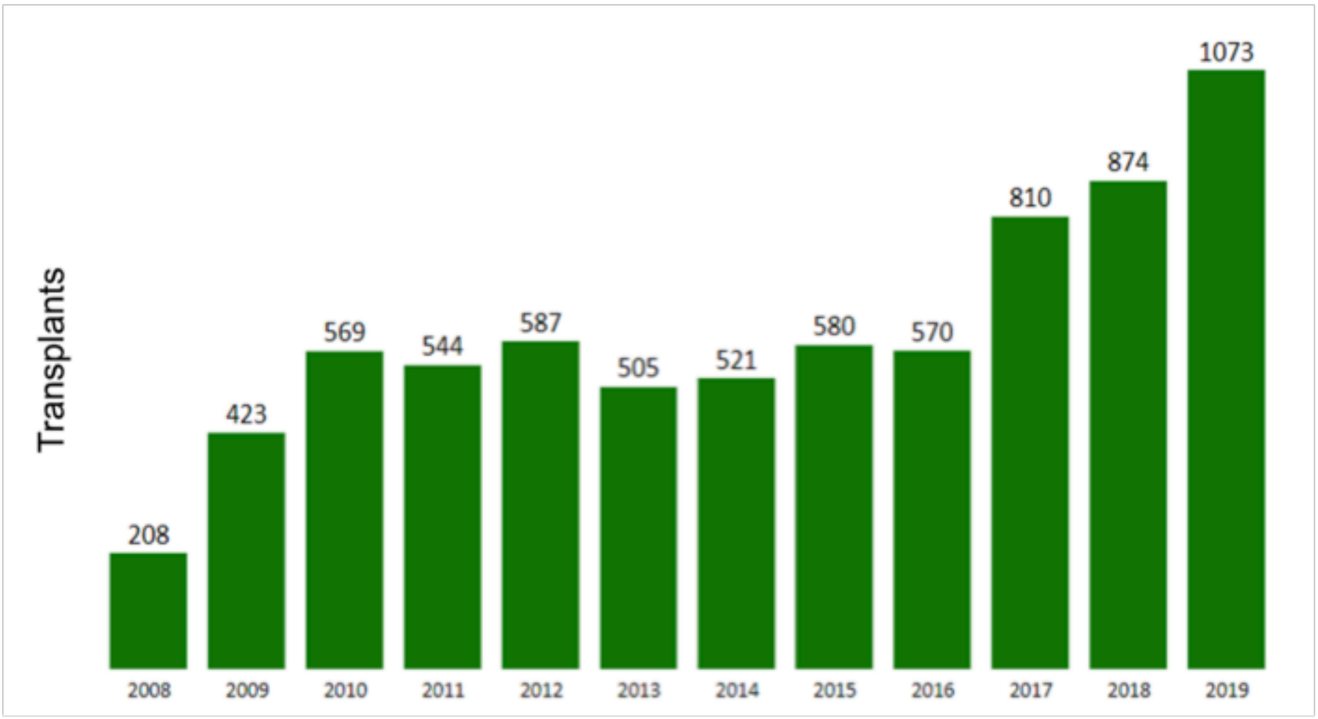

FIGURE 3. Indications for HSCT in Brazil, 2017-2019

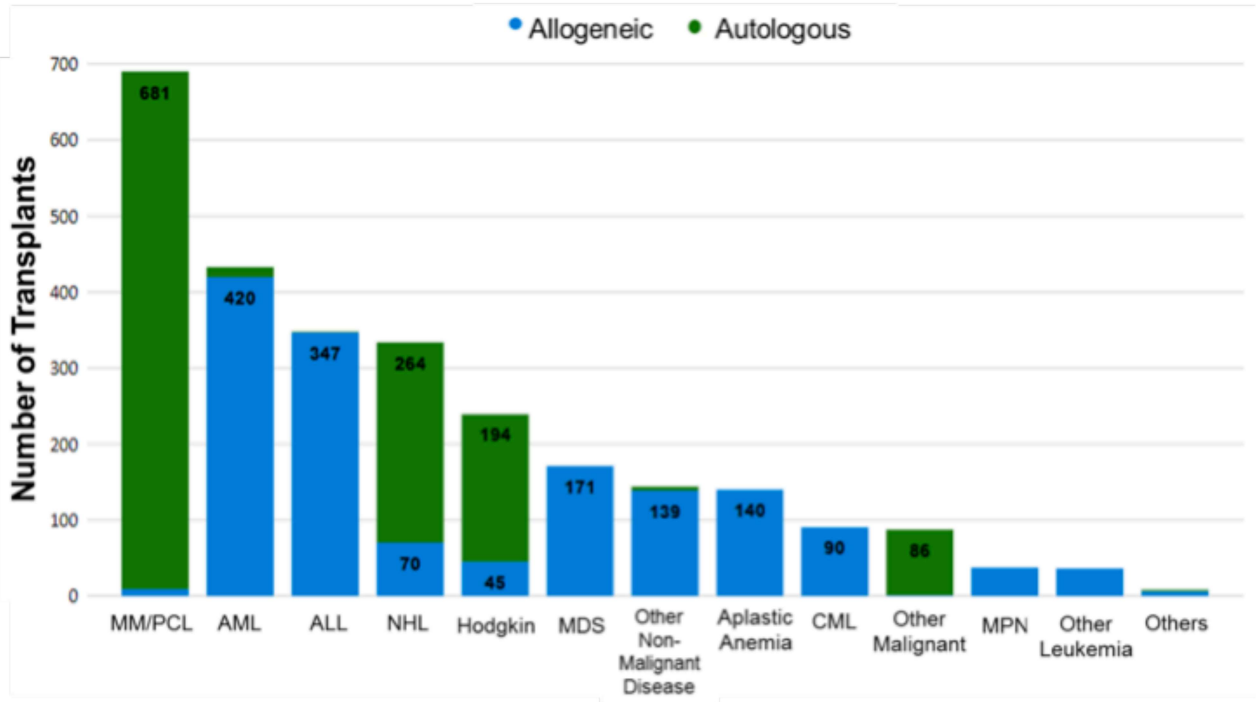

FIGURE 4. AML, overall survival after 1st allogeneic HSCT by donor type

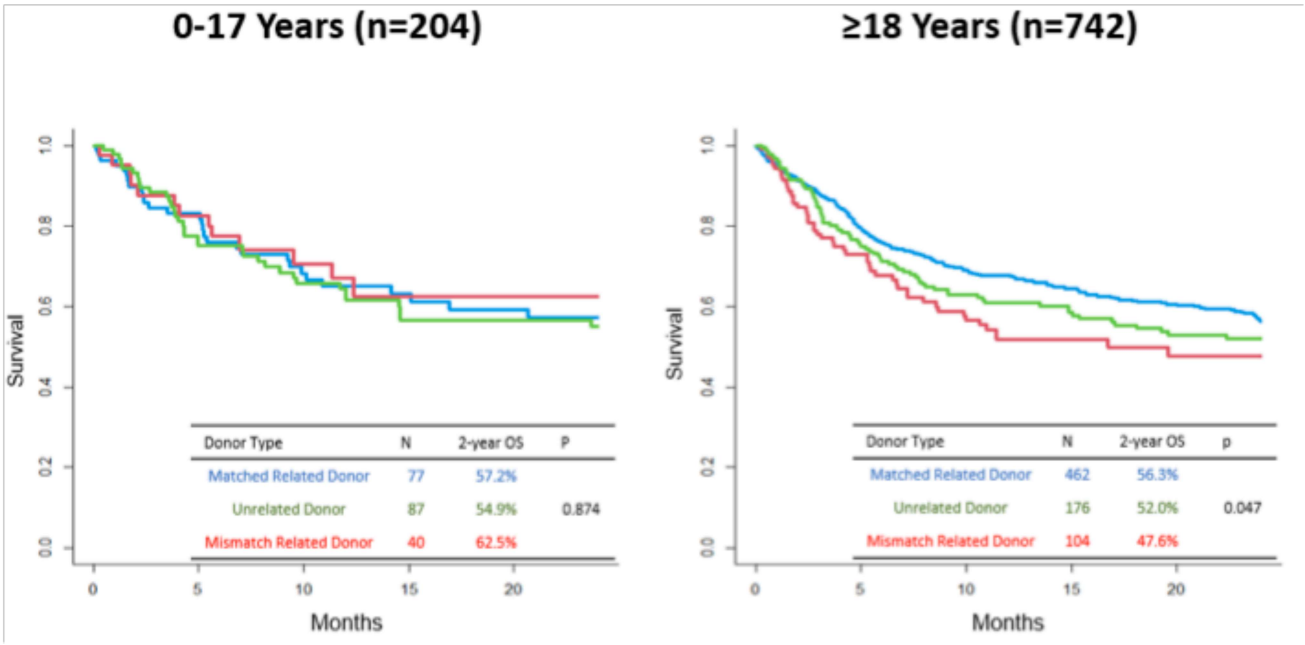

FIGURE 5. ALL, overall survival after 1st allogeneic HSCT by donor type

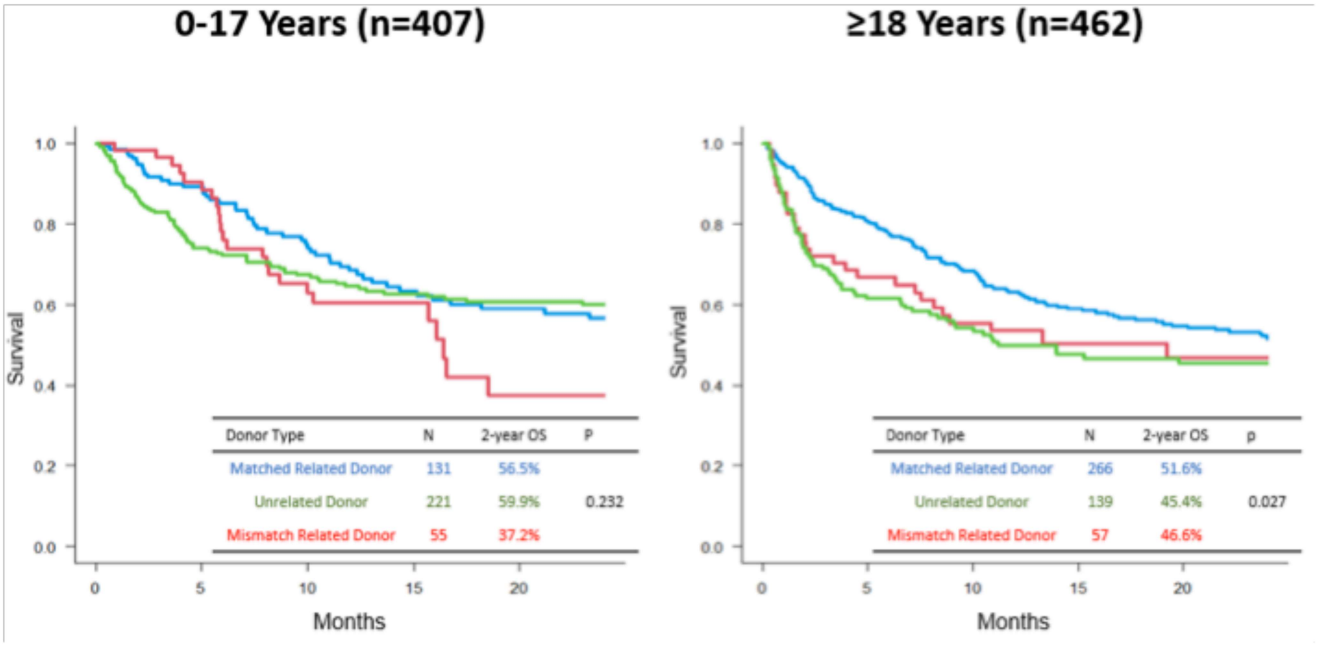

FIGURE 6. MDS, overall survival after 1st allogeneic HSCT by disease stage

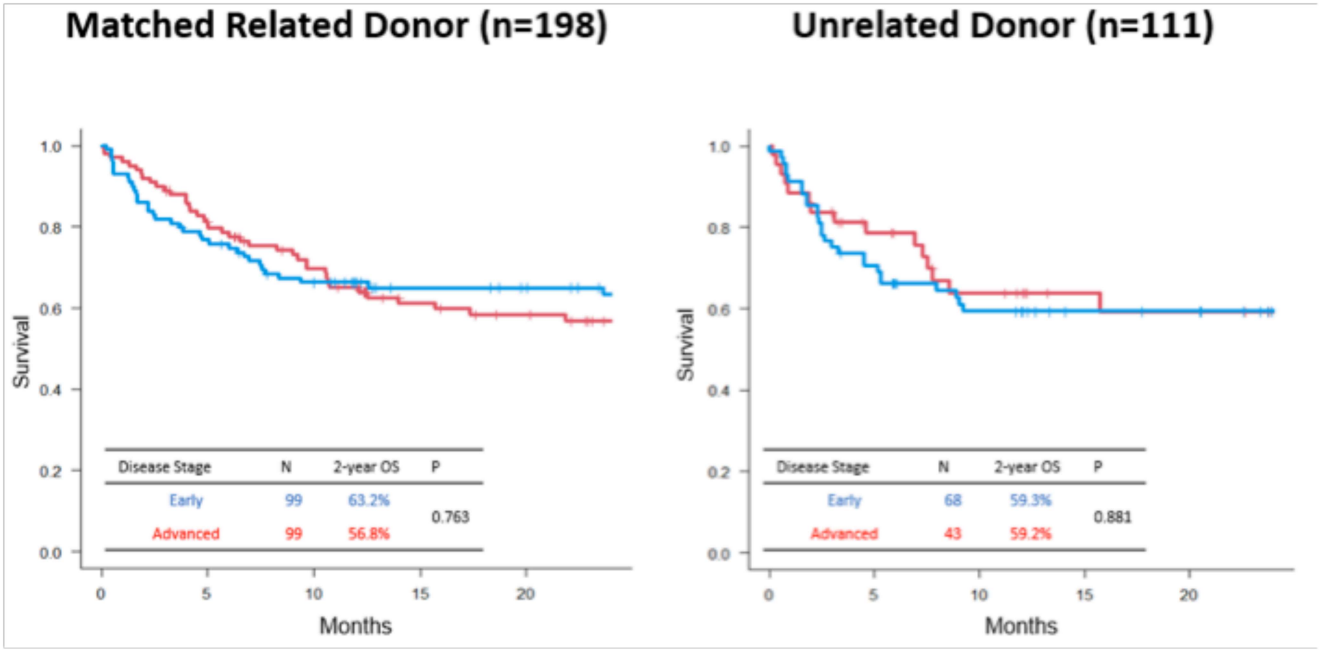

FIGURE 7. CML, overall survival after 1st allogeneic HSCT by donor type

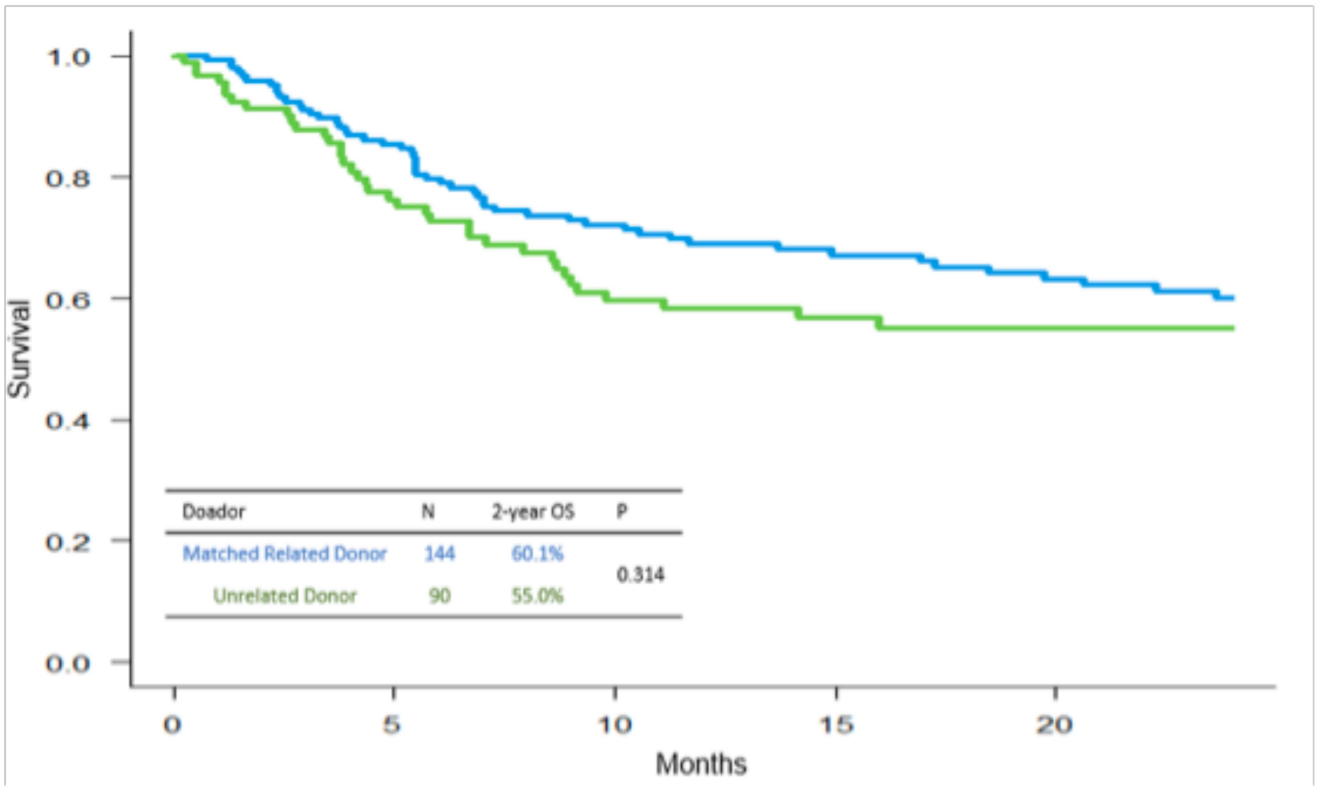

FIGURE 8. Myelofibrosis, overall survival after 1st allogeneic HSCT

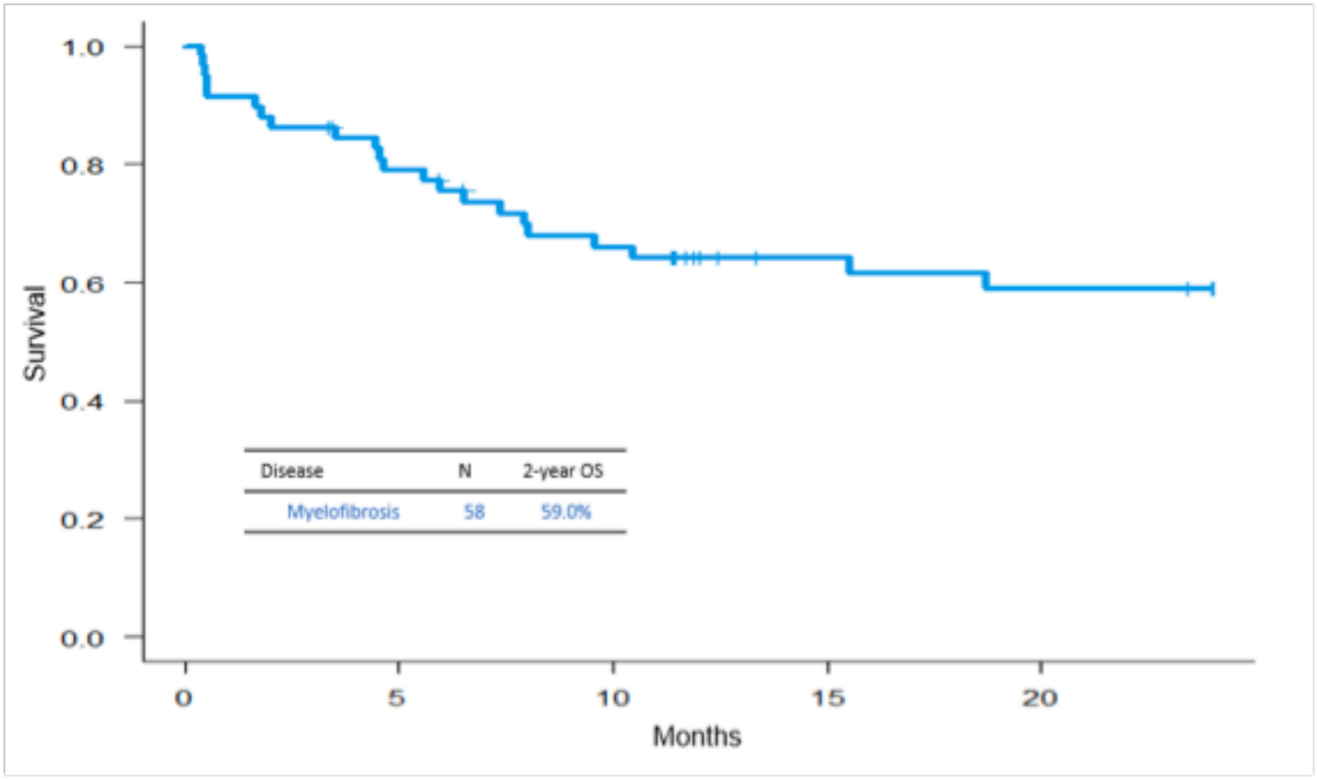

FIGURE 9. Aplastic Anemia, overall survival after 1st allogeneic HSCT by donor type

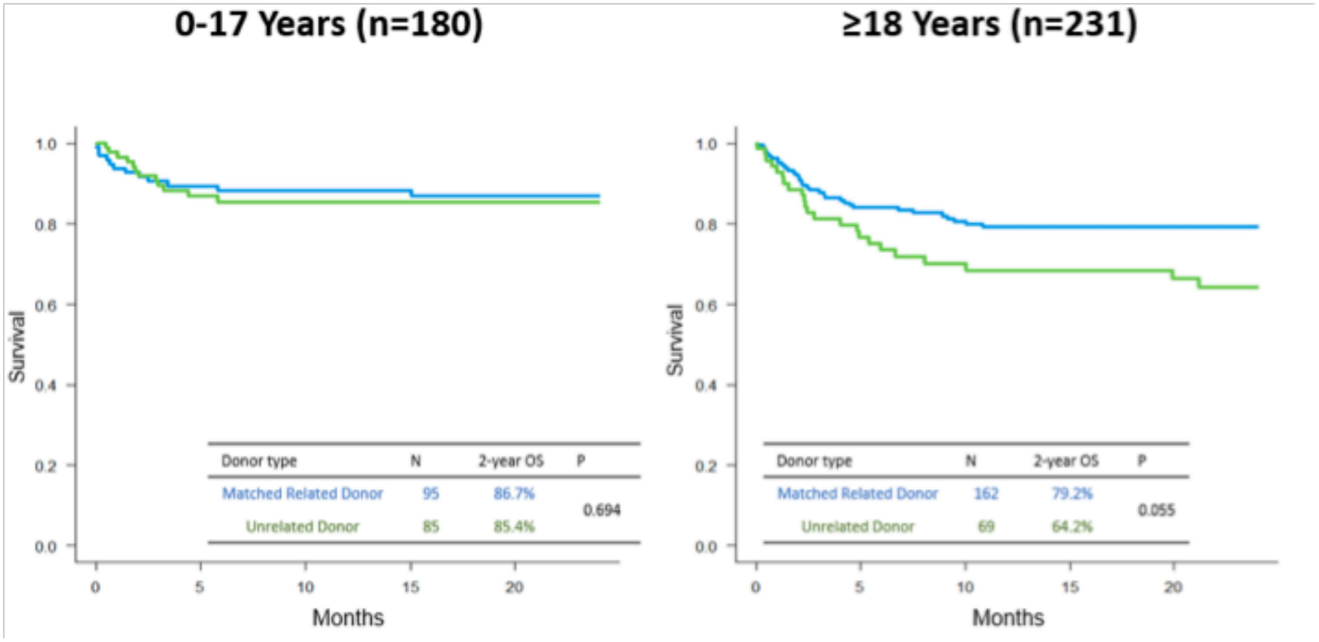

FIGURE 10. Lymphomas, overall survival after 1st autologous HSCT

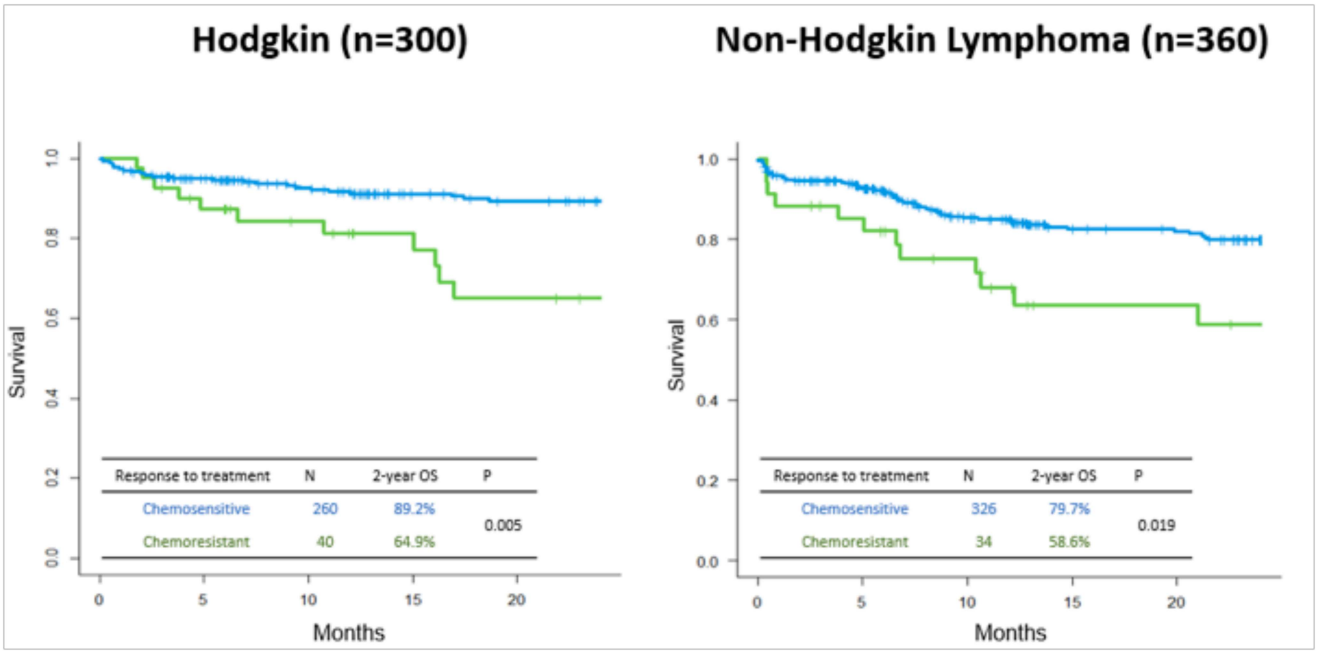

FIGURE 11. Multiple Myeloma/ Plasma Cell Leukemia, overall survival after 1st autologous HSCT