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ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ELDERLY PATIENTS IN BRAZIL: A COHORT

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ABSTRACT

The allogeneic hematopoietic stem cell transplant (allo-HCT) represents an important therapeutic strategy for acute leukemias, lymphomas and solid neoplasms, also used in benign diseases, such as aplastic anemia and inborn errors of immunity. This treatment requires myeloablative chemotherapy (conditioning regimen) followed by the infusion of donor-derived hematopoietic stem cells. However, this procedure carries some risks, such as infections, graft versus host disease (GVHD) and conditioning toxicity, which may result in transplant-related mortality. Over the decades, due to the increasing life expectancy and new advances in medicine, the cases of patients > 50 years with hematologic diseases that need allogeneic transplant have grown, requiring a comprehensive geriatric assessment as a mechanism for the best treatment option choice. Objective: To apply a clinical frailty score and Karnofsky score in allogeneic hematopoietic stem cell older than 50 years old for three years in Walter Cantídio University Hospital (Fortaleza/Ceará) and in Amaral Carvalho Hospital (Jaú/São Paulo), expecting to recognize the profile of this patients and to demonstrate the relation between the clinical frailty score and overall survived, besides to estimate the contribution of GVHD prophylaxis and relapse in overall survival. Methods: Multicentric, retrospective, descriptive, analytical and quantitative study, acquiring dates by means of exams and medical record from Walter Cantídio University Hospital in Fortaleza/Ceará and Amaral Carvalho Hospital in Jaú/São Paulo. Results: The study selected 252 patients, 147 males and 105 females, sort in gender, disease, HCTCI score, CFS and KPS. In three years, the overall survival in FIT score is 2,46 years, while in FRAILTY score is 1,82 years. About the prophylaxis, the combination of cyclosporine, mycophenolate mofetil, cyclophosphamide had worse results than others prophylaxis. As expected, in case of relapse, there is shorter survival. Conclusion: The elderly population require a geriatric score in order to evaluate the profile of this patients once the allogeneic transplant must happen, then FIT patients has longer survival than FRAILTY patients.

Keywords: Geriatric Health. Bone marrow transplantation. Rating Scales.

INTRODUCTION

The hematopoietic stem cell transplant (HSTH) emerged as a revolutionary strategy in acute leukemia, lymphoma and solid neoplasms treatment, in addiction benign diseases treatment, for example severe aplastic anemia[1]. This treatment requires myeloablative chemotherapy therapy followed by the infusion of hematopoietic stem cells from the own patient or from the donor, who is related or not[2].

The allogeneic hematopoietic stem cell transplant could be the cure for this patient, but it could show bad results in older ages because of the toxicided in the protocols, high relapse risk and difficulties in the access[3].

Because the oldest of the population, there are the identification of more cases of hematological diseases[4], whose has the transplant a way of treatment. Furthermore, it must be necessary the application of strategies to evaluate this patient oldest 50 years old, to stratify who has a real benefit in a hematopoietic stem cell transplant.

The clinical geriatric score analyzed the patient as social support, healthy system access, falls in the last year, medications use, functionality, cognition, self-evaluation, depressive symptoms, nutrition and speed step. According to these criterias, the patient was scored in the scale[5].

METHODOLOGY

It is a retrospective, analytical study and analysis of data proven through exams. The population aged 50 years or older were used as inclusion cells in allogeneic hematopoietic stem transplantation at the University Hospital Walter Cantídio and Hospital Amaral Carvalho from 2009 to 2021. Excluding the individuals whose age was less than 50 years, selected for autologous transplantation or technical conditions that analyzed medical records or for lack of essential records for the work.

They will be used as information contained in medical records and institutional information systems. The data will be sent and through record sheets released in a Microsoft Excel spreadsheet.

Analytical data is analytical using Master and AGHU programs. There will be variables inherent to the patient (age, sex, underlying disease, comorbidities, performance status, geriatric scales, comorbidity score), to the donor (type of donor, age, sex) and to the transplant (transplant date, type of transplantation, cell source, conditioning type, GVHD profile, outcome or sequence from the last day of follow-up). The contracts to be executed correspond dead or alive.

According to these dates, the patients were separated in three groups: fit, unfit and frailty. This classification was based on Critical Frail Scale (CFS), so the grade 1 and 2 are fit, grade 3 is unfit and grade 4 to 9 mean frailty.

RESULTS

The sample collected is composed of 252 patients, 147 of which are male, which corresponds to 58.33% of the total sample. These will be divided according to sex, type of disease, as well as their classifications on the HCTCI, CFS and KPS scales.

Regarding diseases, most patients have AML, namely 100 patients (39.68%), and MDS and CML, as there is a scarcity of therapy with Tyrosine Kinase Inhibitors and difficulty in carrying it out due to the nutritional deficiency of patients in this population, are the other two most prevalent, which are present in 20.24% and 12.70% of patients, respectively.

According to the frequency distribution of variables, such as type of conditioning, cell source and prophylaxis for GVHD (Table 2), a balance is analyzed regarding the type of conditioning used, since myeloablative therapy was used in 118 patients and in 115 of reduced intensity, which in percentage terms is equivalent to 46.83% and 45.63%, respectively.

Regarding prophylaxis, the most used was cyclosporine and methotrexate (CyA+MTX), which was performed in 112 patients, followed by cyclosporine, methotrexate and anti thymoglobulin (CyA+MTX-+ATG) and cyclosporine and mycophenolate mofetil (CyA+MMF) , both applied to 43 patients.

It was observed that 52 patients had relapse, which corresponds to 20.63% of the total number of patients in the study, as seen in graph 1. We also found that 119 patients died, that is, 47.22% of the patients in the study, and among these deaths, the most recurrent cause of death was relapse and infection, where 33.61% and 32.77% of the patients who died had this cause of death, respectively (Graph 2).

The study highlights the relationship between the geriatric CFS score and survival time. We can see that the average lifetime recorded is slightly higher in cases where the score is of fit classification. Time is 2.81 years on average in those with this geriatric rating, down to 2.45 in the frailty category. Accord-

ing to the p-value of the significance test, there is evidence to state that the geriatric classification is related to survival time, so that those with a Fit classification have a longer survival time.

When performing the survival assessment, Fit patients have greater survival than patients with scores classified as Frailty. As for median and mean survival, those who fit into the Fit category have a median of 6.92 and a mean of 6.13 years, those in the Frailty category have a median of 2.95 years and a mean survival of 5.91 years.

However, based on the p-value of the log-rank test, we conclude that there is no statistical significance in the differences in survival probability, regardless of the CFS classification, the expected survival time will be the same. However, having observed that in the first years there is a greater difference in the survival curves, and assuming that after a certain period there are deaths from other reasons independent of our studied objective, it is important to analyze the events considering the events only up to a certain time limit. So, evaluating the 3-year case, we can observe that statistical significance was found, so that patients with a geriatric fit score have greater survival. The median survival time for these is 2.46 years, while for those classified as Frailty it is 1.82 years.

Regarding survival according to the KPS score, practically the same occurs as for the CFS score, with the KPS 60 and 70 categories being the ones that apparently have the highest survival, but with the application of the significance test we can prove that there is no association of these geriatric scores with patient survival.

In Graph 6, we have survival stratified by the variable DRI, noting that there is a certain tendency to decrease survival according to the highest DRI, despite these indications, it was not possible to prove an association between DRI and survival, as we found that there is no evidence enough for us to believe that patient survival changes according to the DRI classification.

Regarding the donor, in all groups the highest survival observed is that of unrelated and the lowest survival is that group whose donors were haploidentical. However, the significance test indicated that there are no significant differences between survival according to the type of donor.

Considering the donor's gender, the median survival of those whose donor was a man is 2.75 years, and the median survival time of these is 6.2 years. The median survival of those whose donor was a woman is 3.73 years, and the mean survival time of these patients is 5.61 years. Despite the differences, there is no significance in these differences, so we cannot say that the sex of the donor influences the survival of patients.

In Table 4, we can conclude that there is no significant association between CFS, KPS scores and donor age with patient survival.

It is possible to observe that up to 1.5 years after BMT there is a differentiation between the survival of HLA 8/8 patients and those of HLA ≤ 7/8, where the survival of patients with HLA 8/8 donors is higher. However, from that point onwards, a decrease in the survival gap appears to begin.

According to Graph 10, we can say that there are also not many differences in the survival of the groups of patients of each type of conditioning, myeloablative and of reduced intensity. In this case, no statistical significance was found about the relationship between survival and conditioning.

Regarding survival in the main cellular sources, we see that there is a small difference in survival up to 6 years after transplantation, after that period the survival is practically the same for these sources, and in this period up to 6 years, the survival of the group with PB source is larger than the BM group. Despite these observations, once again the significance test showed that there was no association between the cell source and the survival of patients undergoing HSCT.

In graph 12, we can quickly see that the group of patients whose prophylaxis was CyA+MMF+CyPT has a lower survival rate, because within approximately 1 year after transplantation, the survival of patients in this group reaches less than 25%, which is below of patients who used other prophylaxis. We observed that the CyA+MMF prophylaxis and other prophylaxis have very close and intermediate survival rates, whereas the CyA+MTX, CyA+MTX+ATG and CyA+MMF+ATG prophylaxis are the prophylaxis of patients who survived the most over time.

We can conclude that CyA+MMF prophylaxis differs from CyA+MTX, such that the survival of patients in the CyA+MTX group is higher and that CyA+MMF+-CyPT prophylaxis differs from CyA+MTX and CyA+MTX+ATG prophylaxis, so that the latter two cause greater survival for patients.

Finally, we analyzed patient survival according to the presence of relapse over time. As expected, we can clearly see in Graph 13 that the group of pa-

tients who had relapse had higher mortality. After one year of transplantation, patients who have not relapsed have an expected survival rate of approximately 68%, while those who have ever relapsed have approximately a 40% survival expectation.

With statistical relevance, the average life span of patients according to the presence of relapse, the average of those who did not relapse is 7.08 years, whereas for those who did, it is only 2.41 years, much lower.

For an even better interpretation of these results, which were significant, it was identified that patients who relapsed patients had 2.45 times higher risk of death than patients who did not, whereas patients whose prophylaxis is CyA+MMF have 2. 09 times more risk of death than patients in the CyA+MTX group, in addition to the fact that patients whose prophylaxis is CyA+MMF+CyPT have a 3.32 times greater risk of death than those in the CyA+MTX group. Such conclusions can be seen in table 5.

In order to summarize the information and tests given in the survival analyses, Table 6 shows the crossing of variables with death, in addition to the log-rank test that compares the survival curves, and the mean and median survival values.

As shown in Table 7, we found that the type of donor variable is significant, which means that an unrelated donor is a protective factor against death, and patients to whom the donor is not related have 0.29 times the risk of death of those whose donor was related.

DISCUSSION

In view of the analyzed data, the importance of applying geriatric scores in the population over 50 years old submitted to allogeneic hematopoietic stem cell transplantation is observed, aiming at the best therapeutic adequacy.

As the population was evaluated as Frailty, the 3-year survival was reduced in relation to the Fit population. The median survival time in Fit patients was 2.46 years, while in Frailty patients it was only 1.82 years.

This demonstration shows the importance of applying geriatric scores to ensure the best therapeutic choice for this patient population.

It is still observed that survival in the CyA+MTX group is higher than the others, with prophylaxis CyA+MTX and CyA+MTX+ATG causing greater survival in patients than CyA+MMF+CyPT. This observation reinforces the better suitability of GVHD (graft versus host disease) prophylaxis in the population over 50 years of age.

It is possible to conclude that those who relapse will have a higher mortality in relation to those who do not relapse, since survival in this group is 7.08 years, while in that group it is 2.41 years.

REFERENCES

1. Flowers MED, Kansu E. Late complications of hematopoietic stem cell transplantation. Medicina (Ribeirão Preto) 2000;33:415-32.

2. Rodrigues M, de Souza PM, Koch LO, Hamerschlak N. The use of comprehensive geriatric assessment in older patients before allologeneic hematopoietic stem cell transplantation: A cross-sectional study. J Geriatr Oncol. 2020;11(1):100-6.

3. Lin RJ, Elko TA, Devlin SM, et al. Impact of geriatric vulnerabilities on allogeneic hematopoietic cell transplantation outcomes in older patients with hematologic malignancies. Bone Marrow Transplant. 2020;55(1):157-164.

4. Al-Mansour Z, Ramanathan M, Cerny J. Hematopoietic Cell Transplant (HCT) in the Elderly: Myths, Controversies and Unknowns. Drugs Aging. 2018;35(12):1055-64.

5. Muffly LS, Boulukos M, Swanson K, et al. Pilot study of comprehensive geriatric assessment (CGA) in allogeneic transplant: CGA captures a high prevalence of vulnerabilities in older transplant recipients. Biol Blood Marrow Transplant. 2013;19(3):429-34.

TABLE 1 – Frequency distribution of variables: sex, HCTCI, CFS, KPS and disease.

Variables	Frequency	Percentual
Sex		
Male	147	58,33%
Feminine	105	41,67%
Total	252	100%
HCTCI		
0	137	54,37%
1	49	19,44%
2	26	10,32%
3	27	10,71%
4	8	3,17%
5	1	0,40%
6	2	0,79%
7	2	0,79%
Total	252	100%
CFS		
Very fit	6	2,38%
Fit	25	9,92%
Managing well	170	67,46%
Very mild frailty	47	18,65%
Mild frailty	3	1,19%
Moderate frailty	1	0,40%
Total	252	100%
KPS		
60	5	1,98%
70	5	1,98%
80	32	12,70%
90	74	29,37%
100	136	53,97%
Total	252	100%
Disease		
AML	100	39,68%
MDS	51	20,24%
CML	32	12,70%
Ph+ ALL	16	6,35%
Myelofibrosis	14	5,56%
B/T ALL	13	5,16%
CLL	8	3,17%
NHL B	6	2,38%
Aplastic anemia	5	1,98%
MDS/MPN	4	1,59%
Other	2	0,79%
Dendritic cell Leukemia	1	0,40%
Total	252	100%

TABLE 2 - Distribution of frequencies of variables according to type of conditioning, cell source and prophylaxis

Variables	Frequency	Percentual
Conditioning		
Myeloablative	118	46,83%
Reduced intensity	115	45,63%
Sem resposta	19	7,54%
Total	252	100%
Source		
PB	111	44,05%
BM	120	47,62%
CB	1	0,40%
PB+BM	1	0,40%
Sem resposta	19	7,54%
Total	252	100%
GVHD_proph		
CyA+MTX	112	44,44%
CyA+MTX+ATG	43	17,06%
CyA+MMF+ATG	7	2,78%
CyA+MMF	43	17,06%
Other	10	3,97%
CyA+MMF+CyPT	17	6,75%
Sem resposta	20	7,94%
Total	252	100%

FIGURE 1 - Frequency distribution of the occurrence of relapse

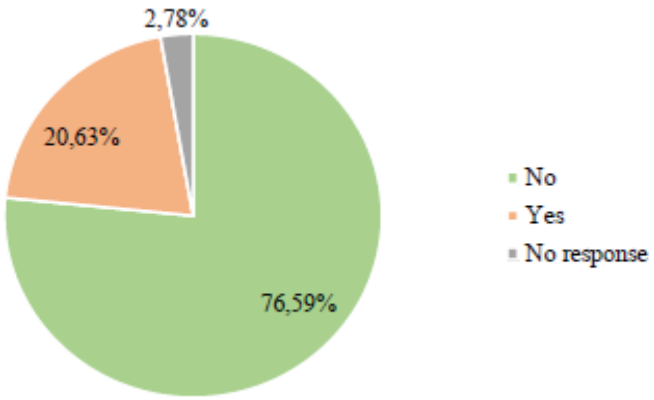

FIGURE 2 - Distribution of frequencies of death and cause of death

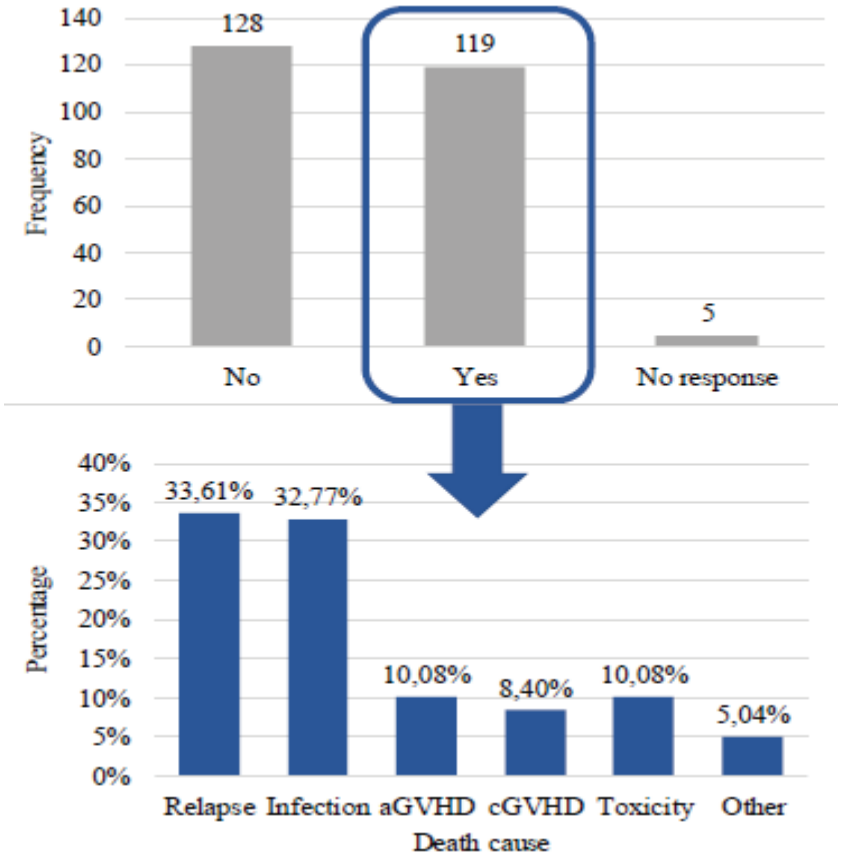

TABLE 3 - Relationship between CFS and survival time (in years)

Survival time (in years)	CFS			P Value
	Fit	Frailty	Total	
Mean	2,81	2,45	2,48	0,019
Standard deviation	2,50	2,88	2,85	
Minimal	0,06	0	0	
Maximum	10,02	12,05	12,05	

FIGURE 3 – **Kaplan Meier survival probability stratified by CFS.**

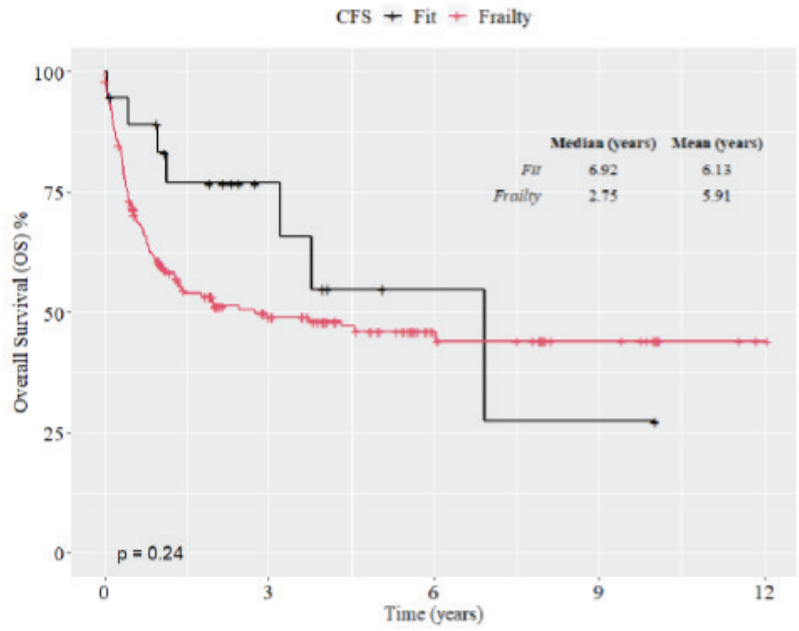

FIGURE 4 – **Kaplan Meier survival probability stratified by CFS (3 years)**

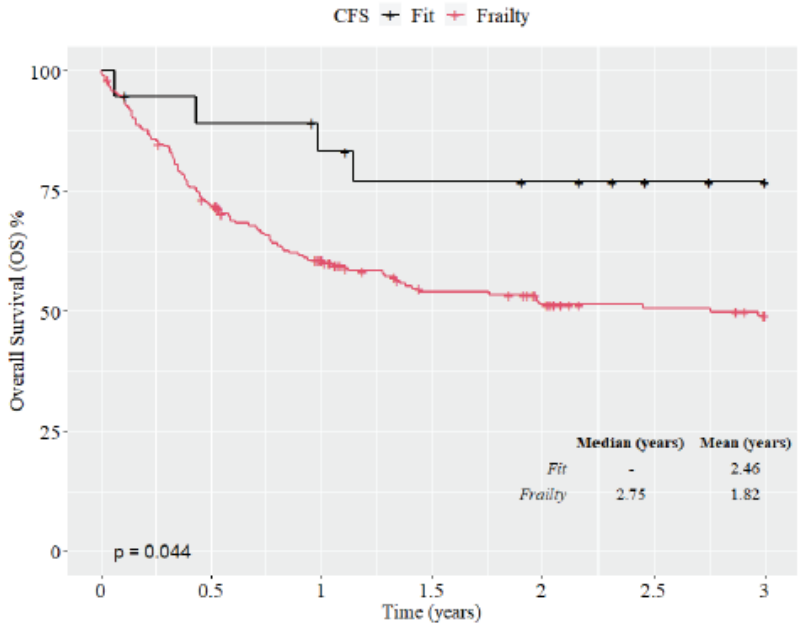

FIGURE 5 - Kaplan Meier probability of survival stratified by KPS

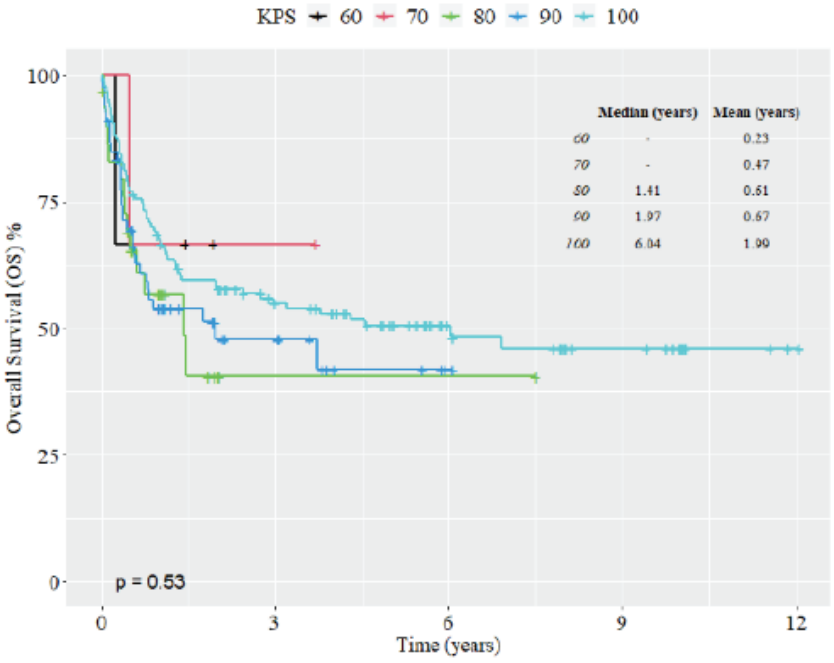

FIGURE 6 - Kaplan Meier probability of survival stratified by DRI

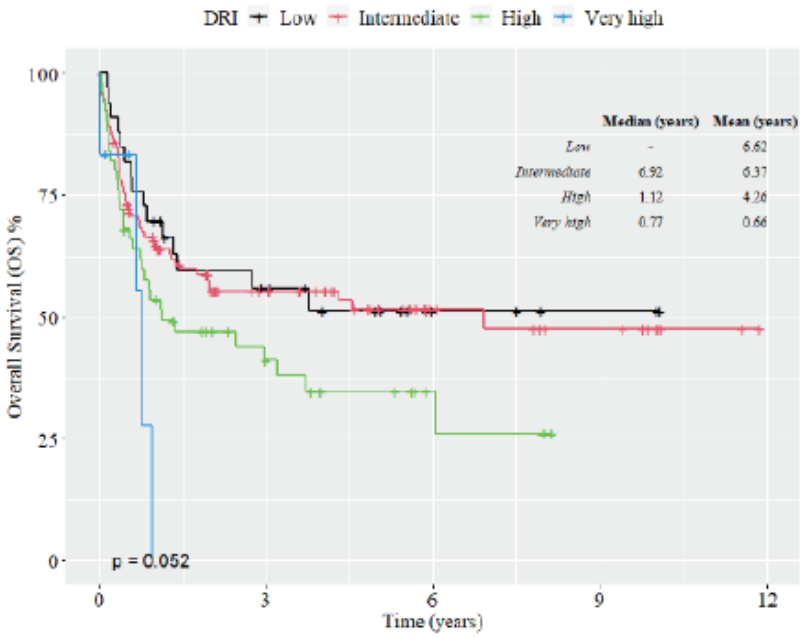

FIGURE 7 – Kaplan Meier survival stratified by type of donor

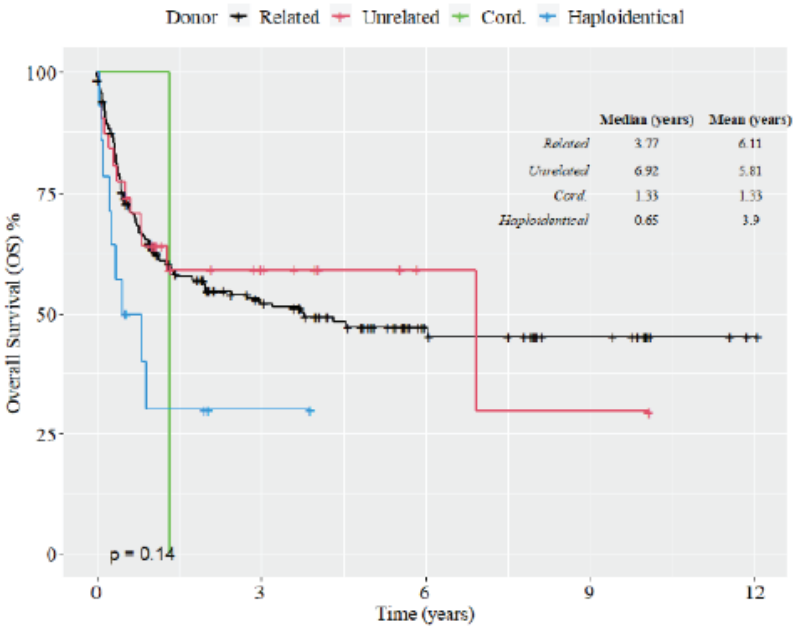

TABLE 4 - Relative risk and confidence interval for CFS, KPS and Age of donors scores

Variables	RR	CI (95%)	P-value
CFS	1,122	(0,83 - 1,51)	0,447
KPS	0,9883	(0,97 - 1,01)	0,28
Donor age	0,9924	(0,97 - 1,01)	0,415

FIGURE 8 - Kaplan Meier survival stratified by gender of donor

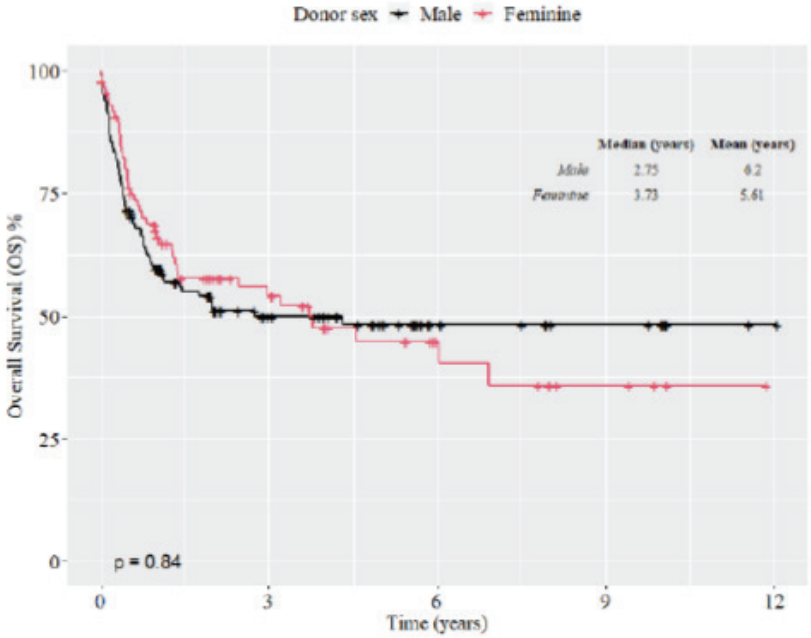

FIGURE 9 - Kaplan Meier survival stratified by HLA donor

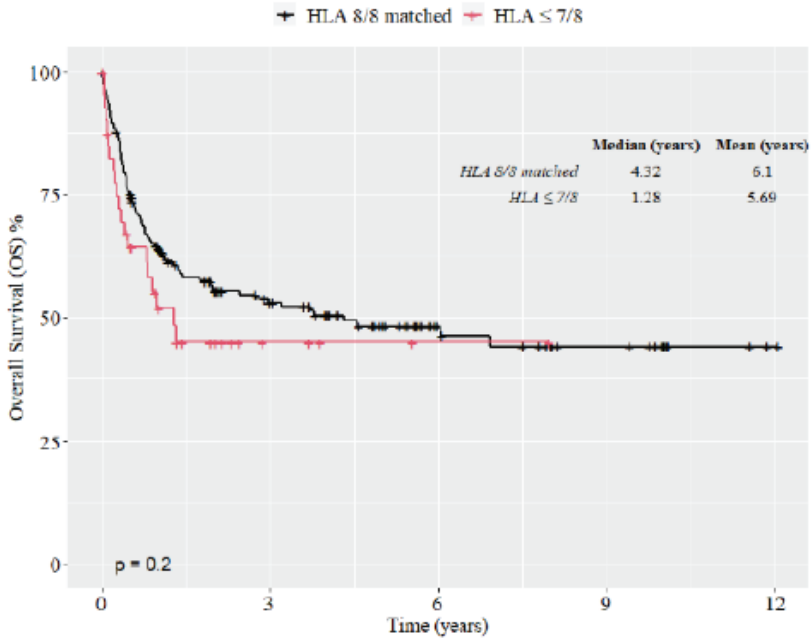

FIGURE 10 - Kaplan Meier survival stratified by conditioning

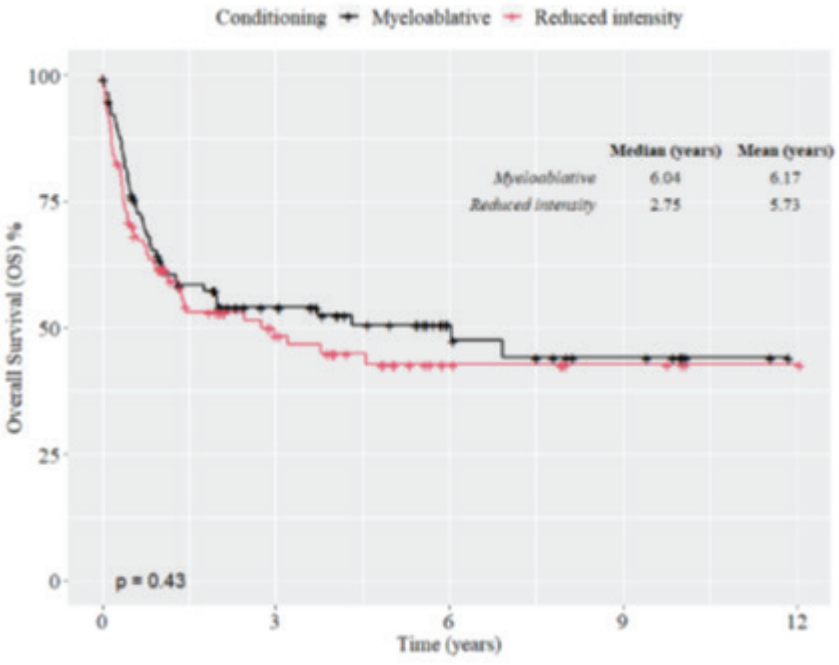

FIGURE 11– Kaplan Meier survival stratified by gender of cell source.

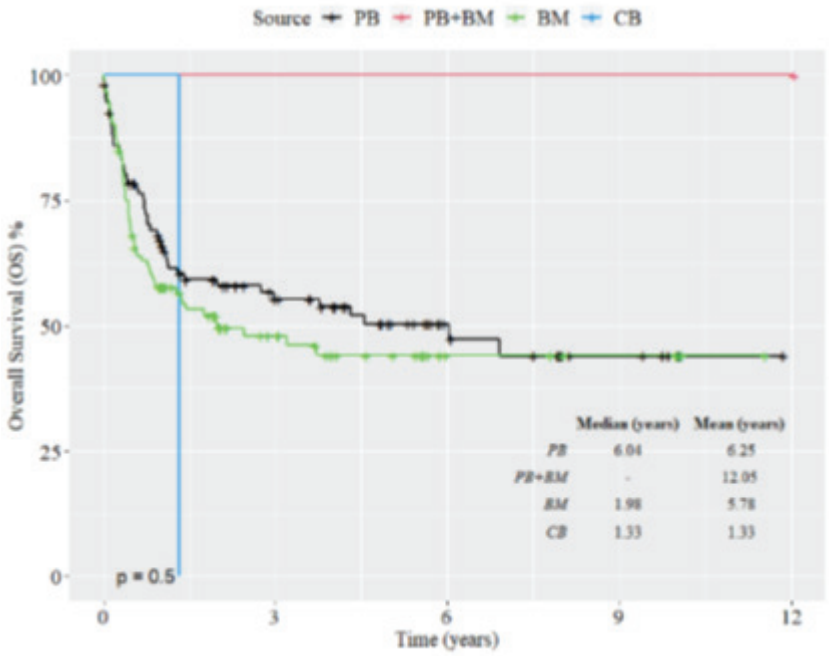

FIGURE 12 - Kaplan Meier survival stratified by GVHD prophylaxis

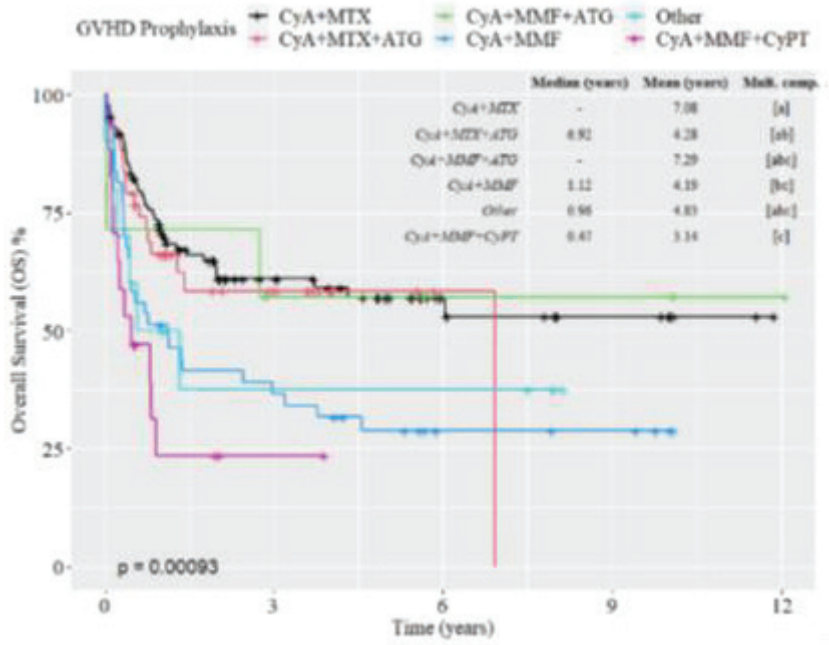

FIGURE 13 – Kaplan Meier probability of survival stratified by relapse.

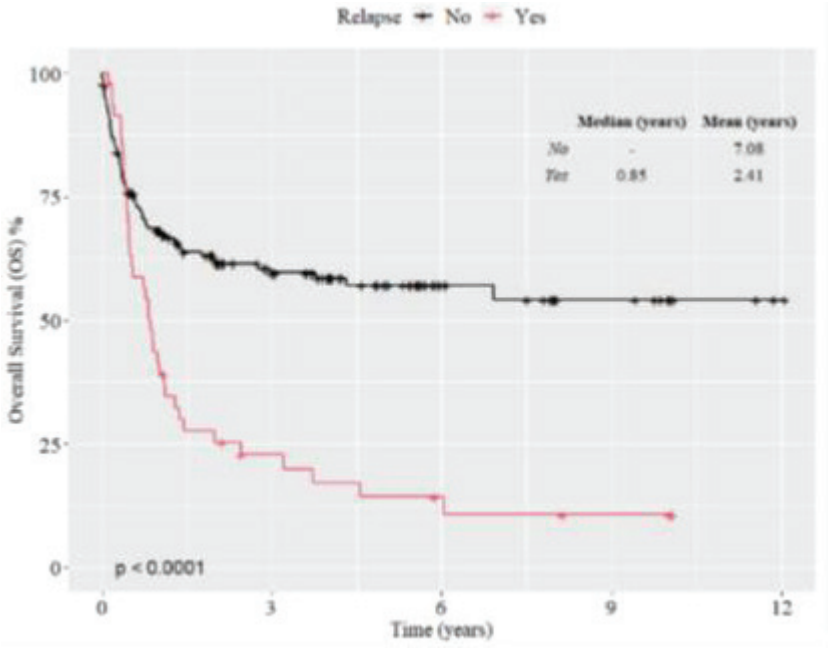

TABLE 5 - Relative risk and confidence interval for relapse and GVHD prophylaxis

Variables	RR	CI (95%)	P-value
Relapse	2,452	(1,66 - 3,63)	**<0,001**
GVHD prophilaxis			
CyA+MTX+ATG	1,174	(0,67 - 2,06)	0,578
CyA+MMF+ATG	1,078	(0,33 - 3,48)	0,901
CyA+MMF	2,094	(1,31 - 3,35)	**0,002**
Other	1,862	(0,79 - 4,39)	0,155
CyA+MMF+CyPT	3,321	(1,74 - 6,35)	**<0,001**

TABLE 6 - Crosses with death, p-value of the log rank test and median and mean survival time.

Variables	Death			Survival time		P-value
	No	Yes	Total	Median	Mean	
Sex						
Male	68 (51,13%)	65 (48,87%)	133 (100%)	3,21	5,76	0,290
Feminine	52 (53,61%)	45 (46,39%)	97 (100%)	4,56	6,17	
Total	120 (52,17%)	110 (47,83%)	230 (100%)			
CFS						
Very fit	4 (80%)	1 (20%)	5 (100%)	-	9,11	0,520
Fit	8 (57,14%)	6 (42,86%)	14 (100%)	6,92	5,71	
Managing well	83 (50,61%)	81 (49,39%)	164 (100%)	2,97	5,86	
Very mild frailty	23 (51,11%)	22 (48,89%)	45 (100%)	2,75	5,96	
Mild frailty	2 (100%)	0 (0%)	2 (100%)	-	12,05	
Total	120 (52,17%)	110 (47,83%)	230 (100%)			
KPS						
60	2 (66,67%)	1 (33,33%)	3 (100%)	-	0,23	0,530
70	2 (66,67%)	1 (33,33%)	3 (100%)	-	0,47	
80	16 (53,33%)	14 (46,67%)	30 (100%)	1,41	0,61	
90	35 (52,24%)	32 (47,76%)	67 (100%)	1,97	0,67	
100	65 (51,18%)	62 (48,82%)	127 (100%)	6,04	1,99	
Total	120 (52,17%)	110 (47,83%)	230 (100%)			
DRI						
Low	18 (54,55%)	15 (45,45%)	33 (100%)	-	6,62	0,052
Intermediate	76 (56,72%)	58 (43,28%)	134 (100%)	6,92	6,37	
High	19 (38%)	31 (62%)	50 (100%)	1,12	4,26	
Very high	2 (33,33%)	4 (66,67%)	6 (100%)	0,77	0,66	
Total	115 (51,57%)	108 (48,43%)	223 (100%)			
Donor						
Related	97 (52,72%)	87 (47,28%)	184 (100%)	3,77	6,11	0,140
Unrelated	18 (58,06%)	13 (41,94%)	31 (100%)	6,92	5,81	
Cord	0 (0%)	1 (100%)	1 (100%)	1,33	1,33	
Haplo	5 (35,71%)	9 (64,29%)	14 (100%)	0,65	3,9	
Total	120 (52,17%)	110 (47,83%)	230 (100%)			
Donor sex						
Male	76 (52,78%)	68 (47,22%)	144 (100%)	2,75	6,2	0,840
Feminine	44 (51,16%)	42 (48,84%)	86 (100%)	3,73	5,61	
Total	120 (52,17%)	110 (47,83%)	230 (100%)			
Donor HLA8						
HLA 8/8 matched	99 (52,38%)	90 (47,62%)	189 (100%)	4,32	6,1	0,200
HLA <=7/8	21 (51,22%)	20 (48,78%)	41 (100%)	1,28	5,69	
Total	120 (52,17%)	110 (47,83%)	230 (100%)			
Conditioning						
Myeloablative	62 (53,45%)	54 (46,55%)	116 (100%)	6,04	6,17	0,430
Reduced intensity	58 (50,88%)	56 (49,12%)	114 (100%)	2,75	5,73	

TABLE 7 - Relative Risk Indices and Confidence Interval for the Cox Multivariate Regression Model

Variables	RR	CI (95%)	P-value
CFS	0,992	(0,71 - 1,39)	0,961
KPS	0,984	(0,96 - 1,01)	0,228
Sex Feminine	0,838	(0,56 - 1,26)	0,394
Donor Unrelated	0,291	(0,1 - 0,81)	**0,018**
Donor Haploidentical	2,076	(0,58 - 7,47)	0,263
Donor Age	0,975	(0,95 - 1)	0,081
Donor HLA <= 7/8	0,543	(0,21 - 1,41)	0,210
Conditioning Reduced intensity	1,008	(0,67 - 1,51)	0,971
Source BM	1,056	(0,69 - 1,62)	0,803

REFERENCES

1. Flowers MED, Kansu E. Late complications of hematopoietic stem cell transplantation. Medicina (Ribeirão Preto) 2000;33:415-32.
2. Rodrigues M, de Souza PM, Koch LO, Hamerschlak N. The use of comprehensive geriatric assessment in older patients before allologeneic hematopoietic stem cell transplantation: A cross-sectional study. J Geriatr Oncol. 2020;11(1):100-6.
3. Lin RJ, Elko TA, Devlin SM, et al. Impact of geriatric vulnerabilities on allogeneic hematopoietic cell transplantation outcomes in older patients with hematologic malignancies. Bone Marrow Transplant. 2020;55(1):157-164.
4. Al-Mansour Z, Ramanathan M, Cerny J. Hematopoietic Cell Transplant (HCT) in the Elderly: Myths, Controversies and Unknowns. Drugs Aging. 2018;35(12):1055-64.
5. Muffly LS, Boulukos M, Swanson K, et al. Pilot study of comprehensive geriatric assessment (CGA) in allogeneic transplant: CGA captures a high prevalence of vulnerabilities in older transplant recipients. Biol Blood Marrow Transplant. 2013;19(3):429-34.