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Original Article

Days Alive Outside Hospital and Readmissions in Patients Undergoing Allogeneic Transplants from Identical Siblings or Alternative Donors

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Abstract. We have studied the number of days alive outside the Hospital (DAOH) and the number of readmissions within the first 100 days after transplant in 185 patients who received an allogeneic hemopoietic stem cell transplant (HSCT). The donors were matched siblings (SIB; n=61), or alternative donors (ALT; n=124). The median number of DAOH for SIB transplants (78 days, range 21-84) was significantly greater than DAOH for ALT donor grafts (73 days, range 2-87) (p=0.0003). Other positive predictors of DAOH were the use of reduced-intensity regimens (p=0.01), grade 0-I acute graft versus host disease (GvHD) (p=0.0006), and a comorbidity index equal or less than two (p=0.04). Fifty-one patients required readmission (22%), which was predicted by grade II-IV acute GvHD (p=0.009), higher comorbidity index (p=0.06), and ALT donors as compared to SIBS (p=0.08). The CI of readmission was 18% (95%CI 10-31) for SIB and 30% (95%CI 23-39) for ALT donor grafts. The non relapse mortality (NRM) for patients re-admitted was 25% (95%CI 15-43%), compared to 5% (95%CI 2-12%) for patients not readmitted (p=0.0001). In a multivariate analysis, readmission was the strongest predictor of non-relapse mortality (NRM) (HR 2.0) (p=0.0006) and survival (HR 3.4) (p<0.0001).
In conclusion: ALT donor transplants have lower numbers of DAOH, as compared to SIB grafts, which implies longer stay in hospital and higher costs. Readmission to hospital within 100 days, is predicted by acute GvHD, comorbidity index, donor type, and has a significant strong impact on non-relapse mortality and survival.

Keywords: Allogeneic hemopoietic stem stell transplantation; Readmission; Length of stay; Healthcare and personalized medical care.

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Introduction. Allogeneic hemopoietic stem cell transplantation (HSCT) can be performed using different donor types, including HLA identical siblings (SIB), unrelated donors (UD), matched unrelated donors (MUD), mismatched unrelated donors (mmUD), cord blood units (CB), or family HLA haploidentical donors (HAPLO). Many retrospective studies have compared the outcome of transplants from different donor types,

with endpoints such as acute and chronic graft versus host disease (GvHD), non-relapse mortality (NRM), relapse, relapse related death, survival, and disease-free survival.[1-7] Another less common outcome is the length of stay in hospitals and the number of readmissions in the first 100 days. Length of stay in Hospital (LOS) within 100 days from transplant is a significant component of early post-transplant costs and is estimated to represents between 75% and 95% of the total transplant cost;[8-11] it also provides a surrogate marker of early complications. The bias due to early deaths, leading to a short Hospital stay, can be overcome by calculating the number of days alive out of Hospital (DAOH), within the first 100 days,[12] therefore excluding patients who were never discharged. This parameter gives a rapid evaluation of tolerance of a given procedure and toxicity, beyond crude NRM, including readmissions due to cytopenia or GvHD. In a recent paper,[2] patients receiving CB grafts had a significantly lower number of days alive outside the hospital, as compared to matched and mismatched UD grafts.

The primary objective of our present study was to compare days alive and outside the Hospital (DAOH) in recipients of HSCT, together with the rate of readmission to the transplant ward, in the first 100 days after HSCT, in patients receiving grafts from SIB donors, UD and HLA family HAPLO identical donors.

Material and Methods.

Patients. We retrospectively analyzed medical records of 185 patients who received an allogeneic transplant for hematological malignancies between February 2012 and January 2018 in our Department and had been discharged after transplantation within 100 days. The study was approved by our Institutional Review Board. Included were consecutive transplants from different donor types, excluding one unrelated cord blood graft. Medical records were retrospectively reviewed for demographic data, diagnosis and disease phase, GVHD prophylaxis, stem cell source and donor type, CD34+ cell dose in the graft, duration of hospital stay, time of engraftment, and acute GvHD. When a potential transplant candidate lacked a suitable HLA-identical sibling donor (SIB), the search for a matched unrelated donor (UD) was started. A haploidentical related donor (HAPLO) was chosen as a donor, when suitable HLA matched sibling or volunteer UD, were either temporarily or definitively unavailable; when 8/8 HLA matched unrelated donor clinical characteristics of 185 patients are outlined in **Table 1**. GvHD prophylaxis consisted of cyclosporine A and short-course methotrexate (CsA+MTX) for SIB grafts, with the addition of rabbit anti-thymocyte globulin (ATG) (Thymoglobulin, Genzyme, Boston USA), 5 mg/kg for UD transplants. Patients receiving bone marrow grafts from HAPLO related donors received GvHD prophylaxis with CsA, mycophenolate mofetil, and high dose post-transplant cyclophosphamide on days +3+5 (PT-CY).[14-19]

Table 1. Clinical characteristics of 185 patients.

	Not readmitted	Readmitted	p
N=	134	51	
Age	49 (14-71)	48 (19-63)	0.7
Proportion patients >60%	28%	23%	0.6
Gender	69/65	33/18	0.1
Diagnosis			
Acute lymphoblastic leukemia	13	7	0.2
Acute myeloid leukemia	78	25	
Myelodysplasia	12	10	
Myelofibrosis	9	3	
Chronic Lymphoprolifer. Disease	22	6	
Phase of the disease: early /advanced	79/55	20/31	0.01
Sorror Comorbidity In dex 0-2 / >2	90/43	28/23	0.1
Donor type: Sibling / Alternative	49/85	12/39	0.09
CD34 cells infused x10^6/kg	5.3 (0.45-21)	5.0 (0.41-21)	0.6
Conditioning regimen: MA / RIC	115/19	44/7	0.8

Abbreviations: Sibling= HLA identical sibling; MA= myeloablative conditioning ; RIC= reduced intensity conditioning.

The comorbidity index was calculated as described by Sorror and coworkers.[20] The number of CD34+ cells infused with the graft was significantly higher in patients receiving PB cells. In the UD group, 36 patients received an 8/8 HLA allele matched donor graft, whereas 26 patients received a graft from a donor mismatched for 1 HLA alleles/antigens.

Endpoints. The primary endpoint of this study was days alive and out of the Hospital (DAOH), as previously reported.[12] The secondary endpoint was the probability of readmission. Other endpoints were: time to neutrophil engraftment; time to first discharge; time and causes of readmission; overall survival; non-relapse mortality; graft versus host and relapse-free survival (GRFS).[13] Patients were readmitted either because of fever, diarrhea, suspected GvHD, respiratory insufficiency, hemorrhagic cystitis. The attending physicians have not changed in the study period. First, second and third readmissions were recorded.

Statistical analysis. The NCSS19 software was used for statistical analysis. Contingency table analysis and the Chi-square test were used for categorical variables. Median, mean, and the T-test were used for numerical variables. The cumulative incidence (CI) of readmission to the hospital was calculated using death as a competing event, and Gray's test was used to assess differences

between groups. The CI of non-relapse mortality (NRM) was calculated with relapse as a competing event. A Cox multivariate analysis was run on the probability of being readmitted to the hospital, with the following variables: donor and recipients age and gender, donor type, the intensity of the conditioning regimen myeloablative (MA) vs. reduced-intensity (RIC), disease phase (remission vs. non-remission), Comorbidity Index (<=/> 2), diagnosis (acute vs. chronic disorders), the presence of GvHD grade 0-I vs. grade II-IV. A second Cox model was run for NRM, which included the same variables, with the addition of readmission (no vs. yes). Survival curves were drawn according to Kaplan Meier, and the log-rank test was used for differences between groups.

Results.

DAOH. The median number of DAOH was 73 days (range 0-88); it was 59 days (2-82), and 77 (21-87) for patients readmitted or not (p<0.00001) **(Table 2)**. Patients receiving SIB grafts had significantly more DAOH as compared to ALT donor grafts: median 78 days (21-78) compared to 73 days (2-78), p=0.0003. This difference was also seen for SIB vs. MUD grafts (78 vs. 63 days, p=0.00002), vs. HAPLO grafts (78 vs. 72 days, p=0.0008), or vs. mmUD grafts (78 vs. 73 days, p=0.008). There was no significant difference in DAOH between HAPLO and UD grafts.

Other variables predictive of DAOH were the intensity of the conditioning regimen (79 days, range 24-87, for RIC vs. 74 days, range 2-78, for MA regimens)(p=0.01), the presence of GvHD grade II-IV (72 days, range 3-87) compared with GvHD grade 0-I (76 days, range 2-78) (p=0.006), and a comorbidity index of 0-2 (76 days, range 9-87) vs. an index >2 (72 days, range 2-78) (p=0.04). By adding together the positive predictors (SIB transplant, comorbidity index <=2, RIC regimen and GvHD grade 0-I), the median DAOH ranged from 79 days for patients with all four positive predictors, with a minimum of 64 DAOH, to 59 DAOH for patients with none of them, with a minimum of 2 DAOH (p=0.00001); their combination for DAOH also predicted the probability of readmission.

Readmissions. One hundred and seventy-nine patients were discharged within 100 days. Fifty-one patients had to be readmitted to the Unit, within 100 days, because of complications, and the overall cumulative incidence (CI) was 22% (95%CI 18-29%) **(Figure 1)**: Forty patients had one readmission, eight patients were readmitted twice, and three patients were admitted three times. The CI of readmission was 18% (95%CI 10-31%) for SIB grafts and 30% (95%CI 23-39%) for ALT donor grafts (p=0.09): it was 20% for HAPLO, 47% for MUD 30% for mmUD. A higher risk of readmission was seen in patients with acute GvHD grade II-IV (35%) compared to patients with acute GvHD grade 0-I (21%) (p=0.01), and in patients with advanced disease compared to patients with early disease (35% vs. 20%) (p=0.02). Age did not impact readmission: in patients aged 14-48, the CI of readmission was 28%; for the age >48 years, it was 24% (p=0.6).

Other non-predictive variables were the intensity of the conditioning regimen and the number of CD34+ cells infused.

Fever with or without documented infections was the leading cause of the first readmission to Hospital after HSCT: 20 for ALT donor grafts and 9 for SIB grafts. Acute GvHD was the cause of readmission in 5 ALT donor grafts and 1 SIB graft. Other reasons for readmission to the hospital, were hemorrhagic cystitis, thoracic, or abdominal pain **(Table 3)**.

A second readmission was recorded in 10/124 ALT donor grafts and 2/61 SIB grafts (p=0.2). Reasons for readmission were GvHD (n=6) and fever (n=6). A third readmission was recorded in 6 patients receiving ALT donor grafts and 0 in SIB grafts (p=0.1): reasons for a third readmission were GvHD in 2 patients, fever in 2 patients, dyspnea in 1 patient and pancytopenia in 1 patient.

In multivariate Cox analysis, GvHD grade II-IV was

Table 2. Main clinical outcome of 185 patients.

	Not readmitted	Readmitted	p
N=	134	51	
Days to PMN 0.5x10^9/L	17 (8-54)	17 (12-88)	0.5
Duration of 1st admission			
In days: median (range)	22 (13-76)	25 (15-71)	0.06
Days in hospital	22 (13-64)	41 (24-95)	<0.00001
DAOH(days)	77 (21-87)	59 (2-82)	<0.00001
Acute GvHD 0-I / II-IV	99/35	27/34	0.006
Non relapse mortality (NRM)	129/5	40/11	0.0001
Patients surviving (yes/no)	105/29	23/28	0.00001
Follow up in days: median (range)	405 (60-1800)	270 (60-1710)	0.006

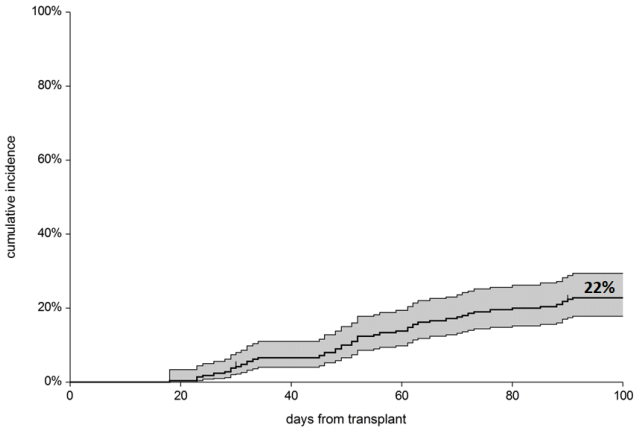

Figure 1. Cumulative incidence of re-admission after allogeneic HSCT.

Table 3. Causes for first re-admission to the Unit.

	SIB	Alternative donors
Patients	n=61	n=190
GvHD	1	5
PRCA	0	1
Abdominal pain	0	1
Cellulitis	1	0
Chemotherapy	0	1
Cytopenia	0	2
Diarrhoea	0	3
Thoracic pain	0	1
Cystitis	0	4
Fever	9	20
Heart failure	0	2
Respiratory failure	0	1
Relapse	2	0
Loss of consciousness	0	1
Total	13	42

Note: some patients were re-admitted for more than one complication.
Abbreviations: GvHD= graft versus host disease; PRCA= pure red cell aplasia; SIB= sibling graft; Alternative donors include haploidentical family donors and unrelated donors

the strongest predictor of readmission (RR 2.2, p=0.009), with a trend for a Sorror risk score of greater than 2 (RR 1.8, p=0.06) and ALT donors compared to SIB grafts (RR 2.0, p=0.08) **(Table 4)**. Other variables, including stem cell source, were not significant predictors.

Engraftment and first discharge. The median time to a neutrophil count of 0.5x10^9/L was 17 days (12-88). It was similar (17 days) in patients who would subsequently be readmitted or not **(Table 2)**. The median time to discharge was 23 days (13-76): it was 25 vs. 22 days for patients who would subsequently be readmitted or not (p=0.06) **(Table 2)**. Patients receiving ALT donor grafts were discharged at a median interval of 25 days (range 13-76) compared to 21 days (range 15-60) for SIB grafts (p=0.0007). The median day of discharge was 25.5 days (range 9-100) for MUD, 26 days (range 13-56) for mmUD, 25 days (range 7-100) for HAPLO grafts: there was no significant difference in time to first discharge, between HAPLO and MUD (p=0.7) and mmUD (p=0.8). Time to first discharge was significantly delayed in patients grafted with a MA regimen (24, range 15-71) compared to RIC regimens (20, range 13-76) (p=0.006). Age (<=48/ vs >48 years) had no effect on the duration of first admission (p=0.5). Similarly there was no difference in time to first discharge for patients receiving <=/> 5.3 x10^6/kg CD34 cells in the transplant: 23 days (15-76) vs 23.5 days (13-64) (p=0.2).

Table 4. Multivariate Cox analyses.

Variable	baseline	compared	RR (95% CI)	P
Cox analysis on the risk of readmission				
GvHD	0-I	II-IV	2.2 (1.2-4.1)	0.009
Sorror index	0-2	>2	1.8 (0.9-3.3)	0.06
Donor type	SIB	alternative	2.0 (0.9-4.3)	0.08
Cox analysis on non relapse mortality				
Readmission	no	yes	8.5 (2.5-28.9)	0.0006
Cox analysis on overall survival				
Readmission	no	yes	3.4 (1.8-6.2)	0.0001
Disease phase	remission	relapse	1.8 (1.3-4.4)	0.004

Non-relapse mortality (NRM). After discharge, patients who required readmission had a higher risk of non-relapse mortality (NRM), as shown in **Figure 2** (5% vs. 25%, p=0.0001). In a Cox model, readmission was the only predictor of NRM (RR 8.5, p=0.0006) and the strongest predictor of survival (RR 3.3 p=0.0001) **(Table 4)**.

Survival. The actuarial survival of patients who required readmission or not is shown in **Figure 3**, with a significant advantage for patients nor readmitted after transplantation. GRFS for the two groups at five years was 53% (95%CI 44-62) and 33% (95%CI 19-46), respectively (p=0.03).

Discussion. The number of days alive and outside the hospital, which we referred to as DAOH, can be regarded as a critical surrogate of transplant outcome: it gives an immediate perception of the clinical course of the patient, the number and severity of infections, the rate of acute GvHD and the severity of organ toxicity. When calculating DAOH together with the number of readmissions, one can analyze an outcome that includes many of the early transplant complications and also roughly evaluates the cost of the transplant. In a recent study, DAOH was 65 days for single cord blood transplants, 63 for double CB transplants, 79 for unrelated donor transplant, with a significant difference in favor of the latter.[12] This was true both for pediatric as well as adult patients, primarily driven by the fact that CB grafts have delayed engraftment when compared to UD peripheral blood transplants; the difference was less pronounced when comparing CB vs. mismatched UD marrow grafts.[12] In the present study, we focus on DAOH as well as on-time of first discharge and readmissions in patients grafted from different donor types, including unmanipulated HAPLO transplants.

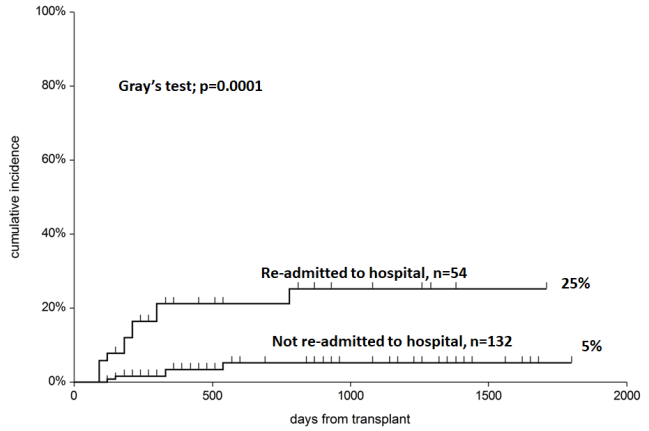

Figure 2. NRM: impact of re-admission to Hospital within 100 days from transplant.

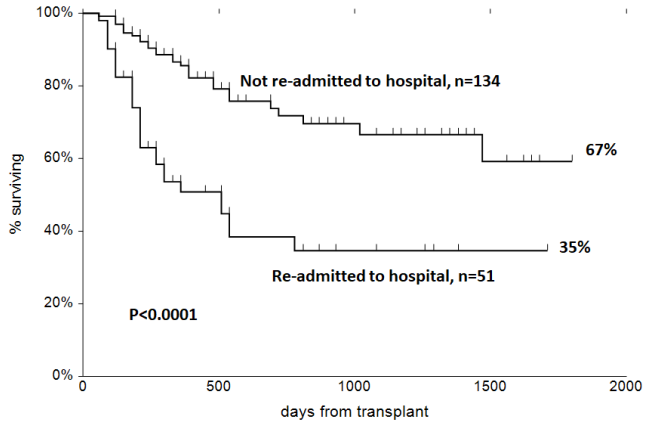

Figure 3. Survival: impact of re-admission to Hospital within 100 days from transplant.

Time to first discharge was shorter in SIB transplants as compared to ALT donor transplants by four days; interestingly there was no difference between matched UD, mismatched UD, and HAPLO donors, despite the fact that the latter were grafted with marrow stem cells; alternative donor transplants were discharged 4-5 days later than SIB grafts, suggesting a role of alloreactivity in ALT donor transplants on top of cell dose of inoculum. In keeping with this observation, there was no effect of the dose of CD34 cells on the duration of the first admission. We would instead have expected a more prolonged first admission in older patients, but this was not the case, which contradicts what we think to be shared in our daily practice. Myeloablative conditioning delayed the time to first discharge, by four days, when compared to RIC regimens, and this was statistically significant.

After the patients had been discharged a first time, we asked what was the cumulative incidence of readmission within 100 days: this turned out to be 22% (18-29%), suggesting that 1 in 5 patients, at least in our experience will be readmitted to the hospital after an allogeneic transplant, the leading cause being fever (29 patients). Other causes for readmission were acute GvHD (n=6), diarrhea with or without cytopenia (n=6), and cystitis (n=4). Then we looked at predictive factor for readmission: these turned out to be acute GvHD II-IV (p=0.006), advanced disease at transplant (p=0.02), a graft from an ALT donor (p=0.09) and a Sorror score greater than 2 (p=0.09. In a multivariate Cox analysis, factors predicting readmission were acute GvHD, followed by donor type and comorbidity index greater than 2. Again older age was not a negative predictor of readmission.

We then looked at DAOH: the median number of days alive and outside the hospital was 75 days with a wide range from a minimum of 2 days to a maximum of 78 days. A higher number of DAOH was predicted by a SIB transplant, acute GvHD grade 0-I, a Sorror score of <=2, and a RIC regimen. There was no significant difference in DAOH when comparing different alternative donor sources, UD, mismatched UD, and HAPLO donors. When we considered the positive predictors jointly, the patients with at least one of them has a median of 79 days of DAOH, with a minimum of 64 DAOH, compared to 59 DAOH for patients with no positive predictor, and a minimum of 2 DAOH (p=0.00001), with a median difference of 20 days. This suggests that SIB donor results in more days outside the hospital; however, the intensity of the conditioning regimen and the occurrence of acute GvHD also play a major role in determining the early outcome of the transplant.

How did these events impact NRM and survival? Patients requiring readmission had a significantly increased risk of NRM, and, in a multivariate Cox analysis, re-entry was the strongest predictor of NRM. This may be useful information for transplant programs: a patient being readmitted within 100 days is at higher risk of NRM, whatever the cause of readmission, and should, therefore, be considered at high risk of death. In patients being readmitted, one may tentatively reduce the risk of death, by the intensification of infection surveillance and treatment, or possibly prophylaxis. The relevance of readmission on the outcome is confirmed by the 30% difference in five-year survival, which can be seen when looking at patients readmitted or not.

There are limitations to this study, which include the retrospective nature, the fact that we analyzed patients from one Center, and that the analysis was limited to the first 100 days post-transplant.

Conclusions. we see more days alive outside Hospital (DAOH) and fewer readmissions in SIB grafts, as compared to alternative donor grafts, suggesting a more favorable transplant course; acute GvHD, and the intensity of the conditioning regimen also play a role in DAOH. After a first discharge, readmission to the Transplant Unit is more frequent if the patient develops acute GvHD and in donors other than HLA identical siblings. Readmission is a significant predictor of non-relapse mortality and should call for dedicated

procedures.

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