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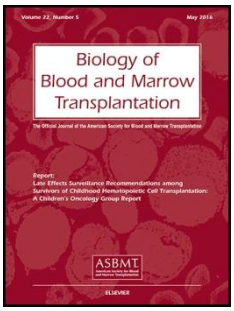

Title: Low Body Mass Index is Associated with Increased Risk of Acute GvHD after Umbilical Cord Blood Transplantation in Children and Young Adults with Acute Leukemia: a Study on Behalf of Eurocord and the EBMT Pediatric Disease Working Party

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Low body mass index is associated with increased risk of acute GvHD after umbilical cord blood transplantation in children and young adults with acute leukemia: a study on behalf of EUROCORD and the EBMT Pediatric Disease Working Party

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Highlights

- We analyzed 855 acute leukemia patients aged 2 to 20 years who underwent UCBT
- All patients were classified according to BMI
- A BMI <5th percentile at UCBT was associated with an increased risk of aGvHD

Abstract

Body mass index (BMI) might influence outcomes after allogeneic stem cell transplantation (HSCT). However, the impact of BMI on survival in children undergoing HSCT is not well defined, with conflicting results being reported on this issue. We analyzed 855 patients aged 2 to 20 years with diagnosis of acute leukemia who underwent umbilical cord blood transplantation (UCBT) from 1990 to 2015. Patients were classified according to BMI as normal (5th-85th percentile), underweight (<5th percentile), overweight (85th-95th percentile) and obese (>95th percentile) using growth charts for age and gender. All patients received single unit UCBT after a myeloablative conditioning regimen. Diagnosis was acute lymphoblastic leukemia in 68% of the patients. Sixty one percent of patients (n=523) were in the normal BMI category, 11% (n=96) were underweight, 16% (n=137) overweight and 12% (n=99) obese.

The cumulative incidence of grade II-IV acute GvHD (aGvHD) was 35% (32-38%). According to pre-transplantation BMI, aGvHD was 46% (33-59%) for underweight, 34% (31-42%) for normal, 36% (18-38%) for overweight and 27% (15-37%) for obese (p=0.04). ~~Among underweight patients who experienced grade II-IV aGvHD (n=43), 23 had grade III-IV, with gut involvement in 14 of them.~~ In multivariate analysis, a BMI <5th percentile was associated with higher incidence of acute grade II-IV GvHD compared to normal BMI patients (HR=1.61, CI 95 % 1.15-2.26, p=0.006). Our results show that being underweight at the time of

transplantation is associated with an increased risk ~~increases the risk~~ of aGvHD, highlighting the importance of nutritional status before UCBT.

Introduction

Body mass index (BMI) may have an impact on outcomes after allogeneic hematopoietic stem cell transplantation (HSCT)[1].

Obesity and undernourishment have been previously associated with complications and inferior outcomes after HSCT in adult patients[2 3 4]. The effect of BMI has also been analyzed in pediatric patients with hematologic diseases. Several studies have reported poor survival rates after induction chemotherapy in either obese and underweight children with acute leukemia[5 6 7]. A retrospective study described worse outcomes after HSCT in obese children with severe aplastic anemia[8]. In a more recent study, no association between poor outcomes and obesity or undernourishment was found in a cohort of 200 children undergoing umbilical cord blood transplantation (UCBT) [9]. Even though the impact of BMI has been thoroughly reported with other graft sources, ~~however~~ large studies investigating the effect of this factor in children with acute leukemia receiving UCBT are still needed.

Both underweight and obese individuals may have an altered drug pharmacokinetics due to a different distribution of adipose tissue from that of normal subjects, however, controversial results have been reported in pediatric patients [6 10].

Our aim is to analyze the effect of BMI on UCBT outcomes in children with acute leukemia.

Methods

We retrospectively analyzed 855 patients aged 2 to 20 years, with a diagnosis of acute myeloid (AML) or lymphoblastic leukemia (ALL), who underwent single UCBT with myeloablative conditioning regimen in European Society for Blood and Marrow Transplantation (EBMT) centers from 1990 to 2015. Myeloablative conditioning regimen was defined as a regimen containing total body irradiation (TBI) > 6 Gy, a dose of busulfan >8 mg/Kg oral or 6.4 mg/Kg i.v. (for patients with body weight above 34 kg) or age body-weight adapted dose for children weighting less (0.8 to 1.2 mg/Kg) , or a dose of thiotepa >10 mg/Kg. Patients were classified according to BMI as normal (5th-85th percentile), underweight (<5th percentile), overweight (85th-95th percentile) or obese (>95th percentile) using the Centers of Disease Control and Prevention growth charts for age and gender [11]. The patient groups' characteristics were compared using the Kruskal-Wallis test for continuous variables and the Pearson chi-squared test for categorical values.

Primary endpoint was overall survival (OS) defined as time from UCBT to death of any cause or last follow-up, whichever comes first; patients alive at last follow up were censored. Secondary endpoints were leukemia free survival (LFS), non-relapse mortality (NRM), relapse incidence (RI), incidence of acute and chronic graft-versus-host disease (GvHD) and neutrophil engraftment. LFS was defined as time from transplantation to relapse, death of any cause or last follow-up, whichever comes first; patients alive without disease at last follow-up were censored. NRM was defined as time to death from any cause not related to relapse and RI was defined as time from UCBT to relapse. Acute and chronic GvHD were defined according to standard criteria[12] [13]. Variables with a p value<0.20 in univariate analyses were included in the multivariate models to evaluate the possible association with BMI. Cumulative incidence curves were used in a competing risk setting to calculate

probabilities of acute and chronic GvHD, neutrophil recovery, NRM and relapse. Probabilities of survival were calculated using the Kaplan-Meier estimate. P-values were two sided and type I error was settled at 0.05. Confidence intervals (CI) were estimated at 95%. Analyses were performed with SPSS 19 (IBM SPSS Statistics for Windows, Version 19.0. IBM Corp, Armonk, NY) and R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) software packages.

Results

A total of 855 patients were included in the study. Table I and table II show patient and transplant characteristics, respectively. Diagnosis was ALL in 68% of cases; 61% of patients were male. Median follow-up for survivors was 59 (2-218) months. According to BMI, 96 (11%) patients were underweight, 523 (61%) had normal BMI, 137 (16%) were overweight and 99 (12%) were obese. Year of UCBT, recipient's gender, cytomegalovirus (CMV) serology, performance status at UCBT and number of HLA disparities in the donor-recipient pair did not vary significantly among the four groups. Also, conditioning regimen and type of GvHD prophylaxis had similar distributions among the groups. Median age at UCBT was lower for obese patients compared to the other groups (p=0.004). ALL was the most common diagnosis. Patients were more frequently in second CR in all groups, but the frequency of patients in advanced disease status at UCBT was higher in the underweight group.

Engraftment

The cumulative incidence of neutrophil engraftment at 60 days was 87% (95% CI 85-90%) at a median time of 23 (range 5-73) days. The cumulative incidence of engraftment did not differ among the four BMI groups (87% in underweight, 88% in normal BMI, 88% in overweight and 85% in obese, p=0.99) (TABLE III).

In multivariate analysis (MVA), UCBT performed after 2009 (HR 1.22, 95% CI 1.05-1.43, p=0.01) and TNC >4.5 $x10^7$/Kg at infusion (HR 1.4, 95% CI 1.14-1.60, p=0.001) were independently associated with a better engraftment (TABLE IV).

Acute GvHD

Two hundred ninety six patients experienced aGvHD in a median time of 24 (range 3-139) days. The cumulative incidence of 100-day grade II-IV acute GvHD was 35% (32-38%).

According to BMI, CI of grade II-IV aGvHD was 46% in underweight, 34% in normal BMI, 36% in overweight and 27% in obese patients (p=0.04) (figure 1). The effect of BMI on this outcome was confirmed in MVA, which showed that being underweight, compared with normal BMI, was associated with a higher risk of aGvHD (HR 1.67, 95% CI 1.19-2.35, p=0.003). The use of ATG reduced the risk for aGvHD (HR 0.51, 95% CI 0.39-0.67, p<0.001).

~~Forty-three patients with a BMI<5th percentile experienced grade II-IV aGvHD (20 grade II, 17 grade III and 6 grade IV). Among patients with grade II aGvHD the most common involved organ was skin, with stage 3 in only 4 cases. Gut involvement higher or equal to stage 3 was reported in 14 of the 23 patients with grade III-IV aGvHD~~. Among patients with grade III-IV aGvHD gut involvement higher or equal to stage 3 was reported in 61% of patients underweight, 42% of patients with normal BMI, 40% of patients overweight and 50% of patients with a BMI >95th percentile.

Chronic GVHD

The cumulative incidence of cGvHD was 17% (14-20%) at 1 year and 18% (16-21%) at 5 years. One hundred twenty nine patients experienced cGvHD in a median time of 134 (range 41-2429) days; 60 of them had extensive grade cGvHD. There was no difference according to BMI percentile in cGvHD incidence in univariate and multivariate analyses (TABLE III and IV).

Non-relapse mortality and relapse incidence

The cumulative incidence of relapse was 23% (21-26%) at 1 year and 29% (26-33%) at 5 years. The cumulative incidence of NRM was 23% (20-26%) at 1 year and 26% (23-29%) at 5 years. There was no difference neither in RI nor in NRM according to BMI percentile group (Table III).

In MVA, a positive CMV serology was associated with higher NRM (HR 1.71, 95% CI 1.28-2.29, p<0.001). Patients transplanted after 2009 had lower risk of relapse (HR 0.70, 95% CI 0.53-0.91, p=0.008) and NRM (HR 0.58, 95% CI 0.43-0.78, p<0.001). More advanced diseases were associated with higher relapse (HR 1.77, 95% CI 1.02-3.09, p=0.04 for >2nd CR and HR 5.83, 95% CI 3.68-9.20, p<0.001 for advanced disease) and NRM (HR 2.58, 95% CI 1.59-4.17, p<0.001 for >2nd CR and HR 2.22, 95% CI 1.29-3.82, p=0.004 for advanced disease). A total of 426 patients died (198 died of relapse, 215 of transplant related causes, and 13 of other causes). The most common causes of NRM were infections (39%), GvHD (20%), and ARDS (7%).

Overall survival and leukemia free survival

The 5-year OS and LFS were 47±2% and 45±2%, respectively. OS was 45±6%, 48±2%, 45±5% and 45±5% for underweight, normal BMI, overweight and obese patients at 5 years,

respectively (p=0.97). The four groups had similar LFS (44±5% in underweight, 46±2% in normal BMI, 42±4% in overweight and 42±5% in obese patients, p=0.80). In MVA, there were no differences according to BMI in survival rates. Patients with positive CMV serology before UCBT had a lower OS (HR 1.41, 95% CI 1.15-1.72, p=0.001) and LFS (HR 1.34, 95% CI 1.10-1.63, p=0.004) than those with negative CMV serology. Transplantation after 2009 was associated with higher LFS (HR 0.61, 95% CI 0.50-0.75, p<0.001) and OS (HR 0.65, 95% CI 0.52-0.81, p<0.001). Patients in second or higher CR at UCBT or in advanced disease experienced worse OS (HR 2.84, 95% CI 1.94-4.17, p<0.001 and HR 3.9, 95%CI 2.71-5.62, p<0.001, respectively) and LFS (HR 2.56, 95% CI 1.76-3.71, p<0.001 and HR 3.88, 95% CI 2.71-5.55, p<0.001, respectively).

Discussion

Our data demonstrate that a BMI<5th percentile is associated with a higher risk of grade II-IV aGvHD in patients aged 2 to 20 years with acute leukemia receiving UCBT.

Nutritional status at time of transplantation is an indirect index of patient global well-being[14]. The current literature focuses, mostly, on obesity and the associate risk of morbidity and mortality after HSCT, while little has been reported on the impact of undernourishment. Some studies have demonstrated that adult patients undergoing HSCT with low BMI have poorer outcomes[3 15], longer hospitalization[16] and delayed engraftment[17]. However, results are scarce and controversial in the pediatric setting. Excessive treatment-related mortality rates have been reported after induction chemotherapy for underweight and obese children and young adults with acute leukemia[18 19]. Also, some retrospectives studies reported inferior survival and higher NRM after HSCT in children with malignant and non-malignant disease[20] and children with aplastic anemia transplanted from sibling or unrelated donor [8]

having a BMI>95th percentile. Differently, other authors have reported no significant impact of BMI in post-transplant outcomes in the same setting[21 9].

In our study, being in an either extreme BMI category (underweight or obese) was not statistically associated with survival, NRM, RI and cGvHD. However, we observed that underweight patients had an increased risk of aGvHD. Similar findings have been reported by Huan et al. in adult patients in the setting of haploidentical HSCT[22]. A low BMI has also been associated with greater incidence of transplant related microangiopathy in 45 patients (age 7-54 years) transplanted for lymphoid malignancies with TBI-based conditioning regimen. This finding suggests that adipose tissue (less vascularized) may lower the distribution of TBI dose[23] and, consequently, endothelial damage caused by a TBI-based conditioning regimen might be higher in low BMI recipients, leading to higher incidence of aGvHD.

Interestingly, a study on nutritional risk in 51 adults undergoing HSCT reported that aGvHD was more severe and occurred more frequently in patients with more than 7.5% of body weight loss after transplant[24]. Moreover, in another analysis, a poor oral intake was associated with higher incidence of aGvHD grade III-IV after HSCT [25]. Although both of these studies refer to weight loss after HSCT and not to BMI at time of transplant, it is biologically plausible that the mechanism disturbed during the process of weight loss may be similar to the current environment seen in undernourished patients (mucosal atrophy, inflammatory stimuli, local cytokines production). In our study, the majority of underweight patients who experienced aGvHD had grade III-IV gut involvement. It is possible that a poor nutritional status at the time of transplant influences inflammatory cytokine production that, together with the conditioning regimen, could worsen gastrointestinal tract damage, favoring the development of aGvHD. An increasing number of studies demonstrate that intestinal microbiota derived metabolites play an important role in aGvHD with gut involvement[26].

Moreover, a recent study performed in children undergoing HSCT found elevated permeability of gastrointestinal mucosa after 30 days from transplantation and demonstrated that lower levels of vitamin A are associated with higher incidence of gut aGvHD and bloodstream infections supporting the hypothesis that low vitamin A levels actively promote development of gut aGvHD[27]. Although vitamin deficiency may occur in any patient regardless of BMI, it is more likely that undernourished patients will experience this deficit more often.

A previous study[9] investigating the impact of obesity on outcomes after UCBT did not find significant differences across BMI groups. The study included 200 children with hematological malignant diseases, however only 9 were underweight. In our study, underweight and obese patients were 11% (n=96) and 12% (n=99) respectively, this finding conferring comparable statistical power to both groups.

Although several nutritional assessment tools already exist, nutritional risk assessment needs standardization in the pediatric HSCT setting to improve accuracy for the evaluation of undernutrition[28 29 30 31 32]. The existing HSCT comorbidity index (HCT-CI) has also been applied to children, but it considers only obesity (BMI>95th percentile) as one of the comorbidity factors[33]. White et al. suggested that body cell mass (the mass of metabolically active cells in the body) is more sensitive than BMI for assessing pre-HSCT nutritional status in children, but unfortunately, this information is usually not available in the clinical setting[34].

Nevertheless, we cannot exclude the possibility that undernourishment could be a proxy measure of disease severity. In fact, in our study the relative percentage of older patients and patients with advanced disease was higher in the underweight category than in the other BMI groups. However, to control for these possible confounders we adjusted our MVA

models for ~~age and disease status among other significant variables~~ these factors when indicated.

Our study demonstrates that a BMI<5th percentile at UCBT is associated with an increased risk of aGvHD ~~underweight children are more at risk of aGvHD~~. However, prospective studies are needed to confirm our findings and to better explain the pathophysiological mechanism. BMI can be an important tool to identify early in the disease course who are the children in need of preemptive nutritional support with the aim of indirectly improving outcomes. Future studies might help also determining the appropriate threshold of BMI percentile for starting nutritional support, when needed, and prevent undernourishment or malnourishment in pediatric patients undergoing HSCT.

Author contributions

AP designed the study, AP, AR, FV, and EG wrote the manuscript, AP performed the statistical analysis, JHD, MA, JJB, API, MPS, MAD, GM, FL, CJ, IYA, HB, YB, PB, provided cases for the study. All authors edited and approved the final version of the manuscript.

Conflict of interest

The authors have no conflict of interest to disclose

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Figure 1. Cumulative incidence of 100-day acute GvHD according to BMI percentile of underweight (black continuous line), normal BMI (dotted line), overweight (dashed line) and obese patients (dashed and dotted line).

Table I. Patient characteristics

		UNDERWEIGHT (n=96)	NORMAL (n=523)	OVERWEIGHT (n=137)	OBESE (n=99)	*p value*
Age at UCBT in years, median, (range)		6.95 (2.1-19.3)	7.6 (2-19.6)	6.3 (2-19.4)	6.2 (2-17.5)	*0.004*
Age group at UCBT*						
	<= 4~~,.60~~ years	28 (29%)	118 (23%)	39 (28%)	31 (31%)	*0.002*
	4~~,.61~~ - 7~~,.20~~ years	24 (25%)	123 (23%)	35 (26%)	33 (34%)	
	7~~,.21~~ - 11~~,.60~~ years	12 (13%)	143 (27%)	38 (28%)	21 (21%)	
	>11~~,.60~~ years	32 (33%)	139 (27%)	25 (18%)	14 (14%)	
Gender						
	Male	61 (64%)	303 (58%)	94 (69%)	60 (61%)	*0.13*
	Female	35 (36%)	220 (42%)	43 (31%)	39 (39%)	
Diagnosis						
	ALL	59 (61%)	335 (64%)	109 (80%)	74 (75%)	*0.001*
	AML	37 (39%)	188 (36%)	28 (20%)	25 (25%)	
Patient CMV serology						
	negative	44 (47%)	253 (48%)	63 (46%)	48 (50%)	*0.92*
	positive	50 (53%)	269 (52%)	74 (54%)	48 (50%)	
Performance status at UCBT						
	<90%	10 (20%)	58 (17%)	17 (19%)	13 (19%)	*0.95*
	≥90%	41 (80%)	267 (83%)	72 (81%)	54 (81%)	
Disease status at UCBT						
	1st CR	38 (40%)	186 (36%)	42 (31%)	21 (22%)	*0.01*
	2nd CR	40 (42%)	258 (50%)	74 (54%)	60 (62%)	
	>2nd CR	7 (7%)	35 (7%)	16 (12%)	11 (11%)	
	advanced disease	11 (11%)	36 (7%)	4 (3%)	5 (5%)	

Abbreviations*:* UCBT, unrelated cord blood transplantation; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CMV, cytomegalovirus; CR, complete remission.

*Groups divided by age quartiles.

Table II. Transplant characteristics

	UNDERWEIGHT (n=96)	NORMAL (n=523)	OVERWEIGHT (n=137)	OBESE (n=99)	*p value*
Year of UCBT					
≤2004	26 (27%)	129 (24%)	37 (27%)	33 (33%)	*0.87*
2005 - 2008	22 (23%)	134 (26%)	36 (26%)	19 (19%)	
2009 - 2012	29 (30%)	150 (29%)	38 (28%)	27 (27%)	
2013-2015	19 (20%)	110 (21%)	26 (19%)	20 (20%)	
Time from diagnosis to UCBT					
< 6months	26 (27%)	98 (19%)	22 (16%)	4 (4%)	*<0.001*
≥6 months	70 (73%)	422 (81%)	115 (84%)	95 (96%)	
Number of HLA MM					
0-1	55 (63%)	285 (64%)	83 (72%)	57 (73%)	*0.23*
2 or more	32 (37%)	159 (36%)	33 (28%)	21 (27%)	
UCBT type					
related	6 (6%)	19 (4%)	14 (10%)	15 (15%)	*<0.001*
unrelated	90 (94%)	504 (96%)	123 (90%)	84 (85%)	
Conditioning regimen					
Cy + TBI	15 (16%)	104 (20%)	20 (15%)	12 (12%)	*0.11*
Cy+Bu	14 (15%)	85 (16%)	21 (15%)	10 (10%)	
VP16+TBI	11 (12%)	38 (7%)	10 (7%)	6 (6%)	
Cy+Flu+TBI	7 (7%)	60 (12%)	13 (10%)	13 (13%)	
Bu+Flu+Thio	7 (7%)	40 (8%)	11 (8%)	12 (12%)	
TBI+other chemotherapy agents	16 (17%)	108 (21%)	33 (24%)	32 (32%)	
Other chemotherapy regimen	26 (27%)	87 (17%)	28 (21%)	14 (14%)	
GvHD prophylaxis					
CsA only	21 (22%)	76 (15%)	21 (15%)	13 (13%)	*0.58*
CsA+MMF	16 (17%)	98 (19%)	22 (16%)	21 (21%)	
CsA+PDN	45 (47%)	272 (52%)	67 (49%)	46 (47%)	
others	14 (15%)	77 (15%)	27 (20%)	19 (19%)	
TNC at cryopreservation x10^7/Kg, median, range	7.13 (1.37-22.3)	5.9 (1.43-27.4)	5.68 (1.26-19.1)	4.90 (0.5-18.1)	*0.001*
TNC at infusion x10^7/Kg, median, range	4.97 (1.3-15.9)	4.5 (0.3-17.8)	4.55 (1-15.9)	4 (0.6-18.3)	*0.17*
CD34 at cryopreservation x10^5/Kg, median, range	2.18 (0.1-12.7)	2.1 (0.1-20.4)	2.3 (0.1-15)	1.7 (0.1-15.5)	*0.32*
CD34 at infusion x10^5/Kg, median, range	1.62 (0.1-10.1)	1.6 (0.01-11.1)	1.9 (0.08-12)	1.5 (0.04-15.2)	*0.83*

Abbreviations: UCBT, unrelated cord blood transplantation; HLA MM, human leukocyte antigen mismatch; TBI, total body irradiation; Cy, cyclophosphamide; Bu, busulfan; VP16, etoposide; Fludarabine; Thio, thiotepa; GvHD, graft versus host disease; CsA, cyclosporine A; MMF, mycophenolate mofetil; PDN, prednisone; TNC, total nucleated cell.

Tab. III Multivariate analysis

PMN engraftment			
	HR	**95% CI**	**p-value**
TNC at infusion >4.5x10^7/Kg versus≤4.5x10^7/Kg	1.4	1.14-1.60	*0.001*
positive versus negative CMV serology	0.88	0.76-1.03	*0.12*
normal BMI	Ref.		
underweight	1.05	0.82-1.35	*0.67*
overweight	0.96	0.77-1.19	*0.7*
obese	1.04	0.81-1.35	*0.74*
Year of UCBT≥2009 versus <2009	1.22	1.05-1.43	*0.01*
Median age at UCBT ≤7.2 versus >7.2 years	1.02	0.86-1.22	*0.78*
ATG use versus no use	0.82	0.38-0.99	*0.04*
1st CR	Ref.		
2nd CR	1.06	0.90-1.25	*0.5*
> 2nd CR	0.82	0.60-1.13	*0.23*
advanced disease	1.09	0.77-1.53	*0.63*
acute GvHD			
	HR	**95%CI**	**p-value**
ATG use versus no use	0.51	0.39-0.67	*<0.001*
TBI use	1.14	0.85-1.52	*0.37*
1st CR	Ref.		
2nd CR	1	0.77-1.31	*0.98*
> 2nd CR	1.32	0.84-2.06	*0.22*
advanced disease	1.18	0.74-1.89	*0.48*
TNC at infusion >4.5x10^7/Kg versus ≤4.5x10^7/Kg	1.27	1-1.61	*0.05*
AML versus ALL	0.95	0.70-1.29	*0.75*
normal BMI	Ref.		
underweight	1.67	1.19-2.35	*0.003*
overweight	1.01	0.72-1.40	*0.97*
obese	0.84	0.55-1.28	*0.41*
chronic GvHD			
	HR	**95%CI**	**p-value**
Median age at UCBT ≤7.2 versus >7.2 years	1.1	0.77-1.58	*0.6*
positive versus negative CMV serology	0.84	0.59-1.19	*0.32*
1st CR	Ref.		
2nd CR	0.95	0.65-1.40	*0.81*
> 2nd CR	1.48	0.75-2.90	*0.26*
advanced disease	1.01	0.40-2.56	*0.98*
normal BMI	Ref.		
underweight	0.7	0.36-1.36	*0.29*
overweight	1.38	0.89-2.14	*0.15*

obese	0.62	0.31-1.24	*0.18*
Relapse			
	HR	**95%CI**	**p-value**
Median age at UCBT ≤7.2 versus >7.2 years	0.77	0.58-1.00	*0.05*
positive versus negative CMV serology	1.08	0.83-1.41	*0.55*
Year of UCBT≥2009 versus <2009	0.7	0.53-0.91	*0.008*
AML versus ALL	0.77	0.57-1.05	*0.1*
normal BMI	Ref.		
underweight	1.18	0.77-1.78	*0.46*
overweight	1.39	0.98-1.98	*0.06*
obese	1.29	0.86-1.93	*0.23*
1st CR	Ref.		
2nd CR	1.32	0.97-1.80	*0.08*
> 2nd CR	1.77	1.02-3.09	*0.04*
advanced disease	5.83	3.68-9.20	*<0.001*
NRM			
	HR	**95%CI**	**p-value**
1st CR	Ref.		
2nd CR	0.92	0.63-1.34	*0.66*
> 2nd CR	2.58	1.59-4.17	*<0.001*
advanced disease	2.22	1.29-3.82	*0.004*
Median age at UCBT ≤7.2 versus >7.2 years	0.99	0.72-1.35	*0.95*
positive versus negative CMV serology	1.71	1.28-2.29	*<0.001*
Year of UCBT≥2009 versus <2009	0.58	0.43-0.78	*<0.001*
AML versus ALL	1.09	0.82-1.45	*0.57*
TNC at infusion >4.5x10^7/Kg versus ≤4.5x10^7/Kg	0.74	0.54-1.01	*0.06*
ATG use versus no use	1.19	0.82-1.73	*0.36*
Median time from diagnosis to UCBT (>6 months versus <6 months)	1.37	0.84-2.24	*0.21*
normal BMI	Ref.		
underweight	0.85	0.53-1.36	*0.5*
overweight	0.74	0.49-1.12	*0.16*
obese	0.78	0.48-1.25	*0.3*
OS			
	HR	**95%CI**	**p-value**
ATG use versus no use	1.19	0.92-1.55	*0.18*
positive versus negative CMV serology	1.41	1.15-1.72	*0.001*
normal BMI	Ref.		
underweight	1.01	0.73-1.40	*0.94*
overweight	1.01	0.77-1.34	*0.93*
obese	0.98	0.71-1.36	*0.91*

Year of UCBT≥2009 versus <2009	0.65	0.52-0.81	*<0.001*
1st CR	Ref.		
2nd CR	1.26	0.94-1.67	*0.16*
> 2nd CR	2.84	1.94-4.17	*<0.001*
advanced disease	3.9	2.71-5.62	*<0.001*
Median time from diagnosis to UCBT (>6 months versus <6 months)	0.91	0.65-1.28	*0.6*
TNC at infusion >4.5x10^7/Kg versus ≤4.5x10^7/Kg	0.87	0.71-1.06	*0.16*
LFS			
	HR	**95%CI**	**p-value**
ATG use versus no use	1.15	0.90-1.48	*0.27*
positive versus negative CMV serology	1.34	1.10-1.63	*0.004*
Year of UCBT≥2009 versus <2009	0.61	0.50-0.75	*<0.001*
AML versus ALL	0.87	0.70-1.09	*0.23*
Median time from diagnosis to UCBT (>6 months versus <6 months)	0.9	0.65-1.25	*0.54*
1st CR	Ref		
2nd CR	1.25	0.95-1.65	*0.11*
> 2nd CR	2.56	1.76-3.71	*<0.001*
advanced disease	3.88	2.71-5.55	*<0.001*
normal BMI	Ref.		
underweight	1.01	0.73-1.39	*0.94*
overweight	1.1	0.84-1.44	*0.49*
obese	1.07	0.78-1.46	*0.69*
TNC at infusion >4.5x10^7/Kg versus ≤4.5x10^7/Kg	0.89	0.73-1.08	*0.23*

Abbreviations: PMN, polymorphonuclear; HLA MM, human leucocyte antigen mismatch; TNC, total nucleated cells; aGvHD, acute versus graft disease; cG~~V~~vHD, chronic G~~V~~vHD; NRM, non-relapse mortality; OS, overall survival; LFS, leukemia free survival; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; UCBT, unrelated cord blood transplantation; TBI, total body irradiation; ATG, anti-thymocyte globulin; CR, complete remission; CMV, cytomegalovirus; BMI, body mass index; UCBT, umbilical cord blood transplantation.

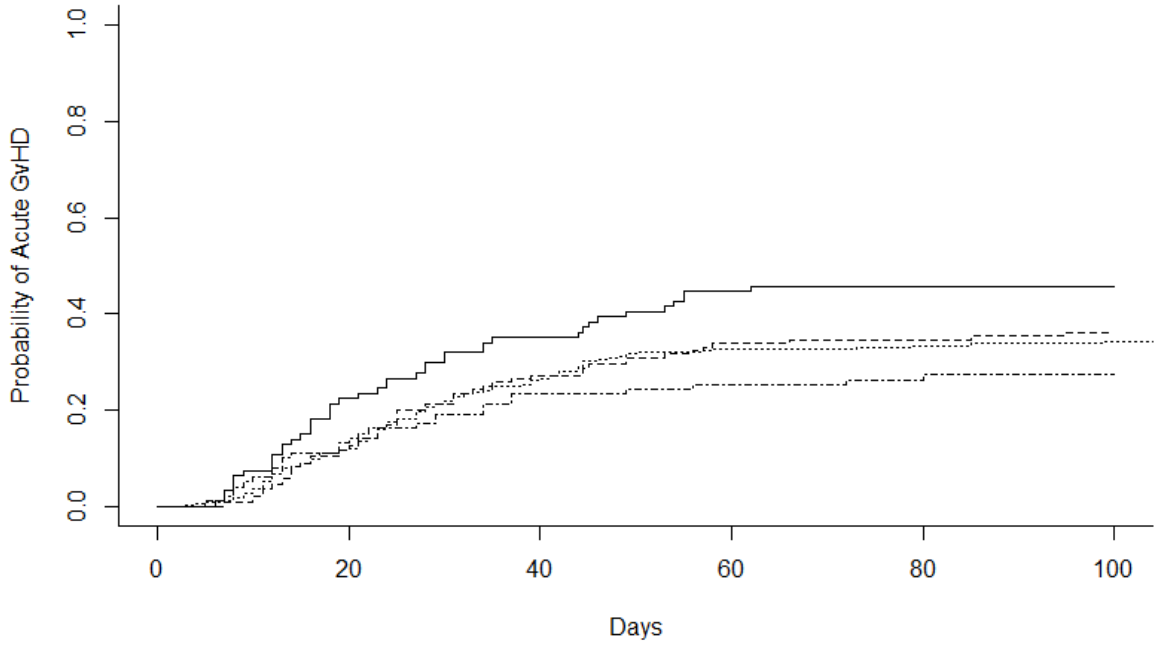

Figure 1.png