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Overall survival in hematopoietic stem cell transplantation is correlated with the Number butnotwith the Age of Red Blood Cells Transfused

Fleur M Aung[1*], Roland L Bassett[2], Benjamin Lichtiger[1], Chitra Hosing[3], Emil J Freireich[4] and Issa Khouri[3]

*[*1]Departments of Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas*

[2]Departments ofBiostatistics,The University of Texas MD Anderson Cancer Center, Houston, Texas

[3]Departments ofStem Cell Transplantation,The University of Texas MD Anderson Cancer Center, Houston, Texas

[4]Departments of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas

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***Corresponding author:** Fleur M Aung, Department of Laboratory Medicine, Unit 0800, 1515 Holcombe Blvd, Houston, Texas 75088, USA, Tel: (713) 792-8630, Fax: (713) 792-2634; E-mail: fmaung@mdanderson.org*

Abstract

Red blood cells (RBC) undergo biochemical and morphologic changes during storage and the changes known as "storage lesion" have raised concerns that RBCs stored for lengthy periods could increase mortality risks in patients receiving transfusions.We sought to analyze the association between aged RBCs and intensive care unit admissions, short-term and long-term survivals of patients undergoing hematopoietic stem cell transplantation (HSCT) and the association between overall survival and the number of RBCs transfused up to 100 days after HSCT. We reviewed the data from the Blood Bank database files from November 2008 to December 2009 for 334HSCT patientswho were alive 100 days after HSCT at the University of Texas MD Anderson Cancer Center. The patients were categorized into ICU vs. non-ICU patients after HSCT. We compared the age of RBCs, units of RBCs transfused and patients admitted to the ICU vs. non-ICU patients after HSCT. We found that the number of RBCs transfused correlated with overall survival and not with the age of the red cells transfused before and after HSCT.For both categories of patients: ICU vs. non-ICU patients, our retrospective analysis noted that those who received the most RBC transfusions had the worst survival.

Introduction

Red blood cells (RBCs) undergo well-documented biochemical and morphologic changes during storage. These "storage lesions," 1-14and have raised concerns that stored older RBCs could increase mortality risk in patients receiving RBC transfusion. Donor RBCs contain a mixed population of cells ranging from newly formed reticulocytes to 120-day-old RBCs at the time of donation, and it has not been established with certainty whetherstorage lesions affect different stages of maturity equally.9Prolong storage of RBCs results in increased oxygen affinity after 14 days of storage due to progressive consumption of the high-energy phosphate (2,3-diphophoglycerate 2,3-DPG), decreased activity of most enzymes involved in energy metabolism (metabolic dysregulation), accumulation of reactive oxygen species (ROS), protein fragmentation and impairment of the band 3 transport metabolon, preferential loss of certain lipids and enrichment of others in the membrane fraction with exacerbation of membrane loss (vesiculation). There is uncertainty to the actual effectiveness and damage that allogeneic blood can cause to the transfused patient.13, 14Theprimary aim of blood storage in the United States has been to extend the storage life of a preciousand perishable product with the use of additive storage solutions (AS-1, AS-3, AS-5 or AS-7) to maximize its availability such as the using the oldest stored blood first to avoid wasting the blood. However, the clinical consequences of transfusion of aged RBCs remain unclear for patients undergoing hematopoietic stem cell transplantation (HSCT).

Objectives

The primary objective of the current study was to analyze the association between the age of RBCs transfused before and after HSCT and intensive care unit (ICU) admission as well as short-term (100 days after transplant) and long-term (>100 days after transplant) overall survival rates after HSCT. The secondary objective was to analyze the association between overallsurvival ratesand the number of RBC units transfused up to 100 days after HSCT.

Methods

Study Design

The retrospective study design was approved by The University of TexasMD Anderson Cancer Center Institutional Review Board. Data were collected from the Blood Bank and Stem Cell and Cellular Therapy data-basesof our institution as well as patients' electronic medical records.The 2008-2009 Blood Bank records were reviewed for adult and pediatric patients who had undergone HSCT. All data onRBCs transfused at MD AndersonCancer Center before (D-100 to D-1) and after (D0 to D+100) were included. Patients who had received a mixture of newer and agedRBCs were included in the study. For our analysis, the age of RBCs transfused was grouped using three cutoff points:

RBCs aged <14 days or > 14 days, RBCs aged <21 days or> 21 days and RBC aged <28 days or > 28 days.Patients were grouped by ICU admissions: those admitted to the ICU up to HSCT day+100 and those not admitted to the ICU during this period. Because many patients had acute myeloid leukemia, a subgroup analysis of these patients was also performed.

Statistical Analysis

The Fisher's exact test was used to compare the distribution of categorical variables between patients who did and did not receive aged RBCs (for each age distinction) and between patients admitted or not admitted to the ICU.The Kaplan-Meier methodwas used to estimate the distribution of overall survival rate from the date of HSCT, and distributions were compared using the log-rank test. Cox proportional hazards regression was also used to assess the relationship between overall survival and continuous variables. P-values of less than 0.05 were considered statistically significant. No adjustment was made for multiple testing. Analyses were performed for all patients, in the cohort and then repeated for the subset of patients with AML (R version 3.3.1).

Results

We identified a total of 397 patients who underwent HSCT during that time periodstudied and of those, 335 (84%) were alive at HSCT day+100. Among these 335 patients (199male, 136 female), six (0.6%) were under the age of 6 years.The median age was52 years (range,2-72 years).Most patients(74%) werewhite and received peripheral hematopoietic progenitor cells (n=212; 63%) and an ABO mismatched graft (n=215; 64%).All of the major ABO incompatible grafts were RBCs depleted. Nearly half of the patients had been diagnosed with AML. Other common diagnoses were lymphoma, chronic lymphocytic leukemia and acute lymphocytic leukemia (Table 1).There were no patientswith benign hematologic issues (e.g. sickle cell disease) in this study. Overall, patients had received a total of1869 RBC units (median, 3 units; range, 0-39 units) before HSCT and 3649 RBC units (median, 7 units; range, 0-112 units) after HSCT (Table 2). More specific ages of the units of RBCs transfused before and after HSCT are shown in (Table 3).

Table 1: Clinical Characteristics of HSCT patients (total vs. ICU vs.Non-ICU) alive at post-transplant D+100

	Total n=335(%)	**Admitted to ICU n=27(%)**	**Not Admitted to ICU n=308 (%)**	
Sex				
Male	199 (59)	16 (59)	183 (60)	1
Female	136 (41)	11 (41)	125 (40)	
Median Age (range)	52 (2-72)	51 (20-70)	52 (2-72)	0.66
Race/Ethnicity				0.28
White	249 (74)	20 (74)	9(74)	
Hispanic	58 (17)	3 (11)	55 (18)	
African American	14 (4)	3 (11)	11 (3.6)	
Asian	13 (3.8)	1 (8)	12 (4)	
Unknown	1 (0.2)	0	1 (0.3)	
Diagnosis				0.25
AML	162 (48)	11 (41)	151 (49)	
CML/MPD	24 (7)	2 (7)	22 (7)	
ALL	35 (10)	5 (18)	30 (10)	
CLL	40 (12)	4 (15)	36 (12)	
Lymphoma/Hodgkin's disease	61 (19)	3 (11)	58 (19)	
Myeloma	7 (2)	1 (4)	6 (2)	
Aplastic Anemia	4 (1)	0 ()	4 (1)	
Non-hematologic disorders	2 (1)	1 (4)	1 (0.3)	
Graft Source				0.43
Peripheral stem cell	227 (68)	16 (59)	211 (69)	
Marrow	67 (20)	8 (30)	59 (19)	
Cord blood	41 (12)	3 (11)	38 (12)	

Conditioning regimen				
HLA Match Grade (Peripheral stem cell & Marrow)				
8/8 (HLA-A, -B,-C, -DR)	274 (94)	20 (83)	253 (94)	0.18
7/8 (HLA-A, -B, -C, -DR)	12 (4)	2 (8)	10 (4)	
Haploidentical	9 (3)	2 (8)	7 (3)	
Cords				
>4/6 (HLA-A, -B, -DR)	41 (100)	3 (100)	38 (100)	
Myeloablative-Reduce intensity conditioning	270 (80)	22 (81)	248 (80)	0.48
Non-Myeloablative	65 (20)	5 (19)	60 (20)	
ABO-matched				0.4
ABO-matched	120 (36)	12 (44)	108 (35)	
ABO-mismatched	215 (64)	15 (56)	200 (65)	
Major mismatched	132 (61)	10 (67)	122 (61)	
Minor mismatched	83 (39)	5 (33)	78 (39)	
Engrafted	328 (98)	26 (96)	302 (98)	0.45
Absolute Neutrophil count (ANC)/uL	12 (0-43)	14 (7-24)	12 (0-43)	0.13
Median Platelet count (uL)	16 (0-203)	17 (0-63)	15 (0-203)	0.09
Alive @ last follow-up	137 (41)	2 (7)	135 (44)	0.0001
Median number of days since transplantation at last follow-up(range)	1567 (175-2203)	1819/1901	1556 (175-2203)	
p value calculated by Fisher's exact test				

Table 2: RBC units transfused to patients before and after hematopoietic stem cell transplantation (HSCT) who werealivealive 100 days after HSCT, stratified by whether or not they admitted to the intensive care unit (ICU)

RBC units transfused	**Total (n=335)**			**Admitted to ICU (n=27)**			**Not admitted to ICU (n=308)**			***P ****
	No.	Median	Range	No.	Median	Range	No.	Median	Range	
Before HSCT	1869	3	0-39	151	4	0-18	1718	3	0-39	*0.7*
After HSCT	3649	7	0-112	554	19	Feb-73	3095	7	0-112	*<0.0001*

Table 3: Units of red blood cells of various ages (0-7, 8-14, 15-21, 22-28, 29-35 and >or 35 days) transfused to patients before and after hematopoietic stem cell transplantation (HSCT) admitted to the intensive care unit (ICU) who were alive 100 days after HSCT

	Totaln=334(%)	**Admitted to ICU n=27(%)**	**Not admitted to ICU,n=307(%)**	***p ****
Before HSCT				
RBC units, total	1869	151 (8)	1718 (92)	0.7
0-7 days	599 (32)	45 (30)	554 (32)	0.63
8-14 days	589 (32)	54 (36)	535 (31)	0.53
15-21 days	409 (22)	25 (17)	384 (22)	0.74
22-28 days	252 (13)	25 (17)	227 (13)	0.37
29-35 days	20 (1)	2 (1)	18 (1)	0.86
36-42 days	0	0	0	NA
After HSCT				
RBC units, total	3649	554 (15)	3095 (85)	<0.0001
0-7 days	1169 (32)	175 (32)	994 (32)	0.0004

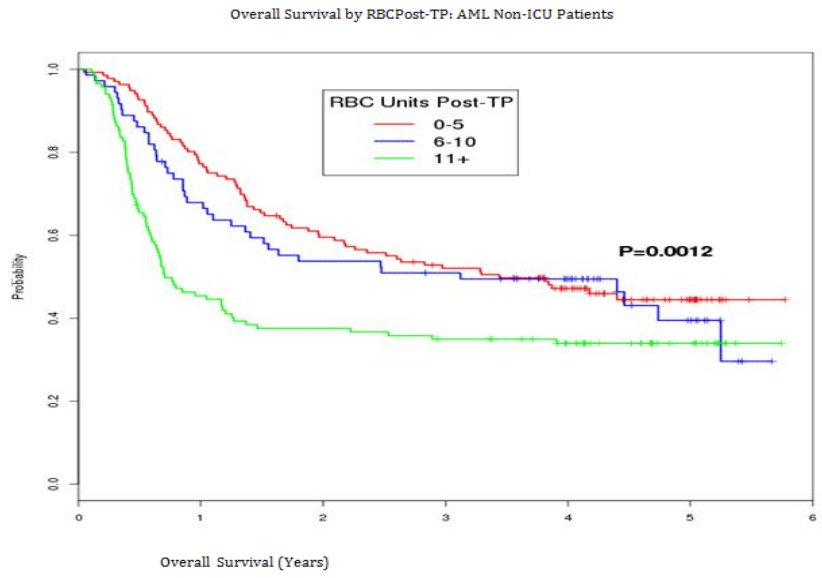
8-14 days	1191 (33)	193 (35)	998 (32)	0.0001
15-21 days	810 (22)	113 (20)	697 (23)	0.0002
22-28 days	434 (11.9)	67 (12)	367 (11.9)	0.02
29-35 days	41 (1)	6 (1)	35 (1)	0.02
36-42 days	4 (0.1)	0	4 (0.1)	0.61
p value calculated by Fisher's exact test				

Among the 73 patients who had been admitted to the ICU, 27 (37%) were alive at HSCT day+100 and59% were male. The median age was 52 years (range,20-70years) with a median ICU stay of 3 days (range, 1-69 days). A total of 151units of RBCs (median, 4 units; range, 0-18 units) were transfused before HSCT and 554 units (median, 19 units; range, 2-73 units) were transfused after HSCT (Table 2).Of the 324 patients not admitted to the ICU, 308 (95%) were alive at HSCT day +100 which was significantly more (*p= 0.0001*) than among those admitted to the ICU and 60% were male. The median age was 52 years (range, 2-72 years). Atotal of 1718units of RBCs (median, 3 units; range, 0-39 units) were transfused before HSCT and 3095units (median, 7 units; range, 0-112 units) were transfused after HSCT which was significantly different (*p=<0.0001*) than among patients admitted to the ICU. Three of the patients not admitted to the ICU received four 4 units (two units for one patient, one unit each for the others) of RBCs> 35 days of age. None of the patients admitted to the ICU received RBCs that were in their last week of storage (35-42 days).

When the RBCs transfused were categorizedas <28 days or >28 days old, 99% regardless of ICU admittances had received RBCs that were <28 days old. When the RBCs transfused were categorized as <21 or >21 days old, 83% of the patients admitted to the ICU and 85% of the patients not admitted to the ICU had received RBCs that were <21 days old. When the RBCs transfused were categorized as <14 or > 14 days old, 66% of the patients admitted to the ICU and 63% of the patients not admitted to the ICU had received RBCs that were <14 days old after HSCT. RBC ages <14 or >14 days old, <21 days or >21 days or <28 days or >28 days did not significantly differ in pre-HSCT transfusions between patients admitted to the ICU and those not admitted to the ICU. However, RBC ages did significantly differ for post-HSCT transfusions between patients admitted to the ICU and patients notadmitted to the ICU for all three categories of RBC ages: <14 or >14 days (*p=0.001*); <21 days or >21 days (*p=0.001*) and < 28 or > 28 days (*p=0.02*).

However, for post-HSCT transfusion, patients admitted to the ICU received significantly fresher RBCs than did patients not admitted to the ICU for all three categories of RBC ages (<14 days or >14 days,<21 days or >21 days and <28days and >28 days).

Overall survival did not correlate with age of RBCs transfused in patients admitted to the ICU as well as patients not admitted to the ICU. Patients who were not admitted to the ICU who were alive at HSCT day+100 and had received the most RBCS units had the poorest overall survival rates (*p=<0.0012*;Figure 1). Similarly, for the 160 patientswith AML who were not admitted to the ICU, those who had received the most RBC units had the poorer survival rate (p=0.0019; Figure 2).



	0-5 RBC	6-10 RBC	>10RBC	p value
Total n=160(%)	57 (36)	40(25)	63 (30)	0.0012
live n=59 (%)	24(41)	18(30)	17 (29)	

Figure 1: Kaplan-Meier estimates of overall survival according to the number of red blood cells (RBC) units transfused after hematopoietic stem cell transplantation in patients not admitted to the intensive care unit

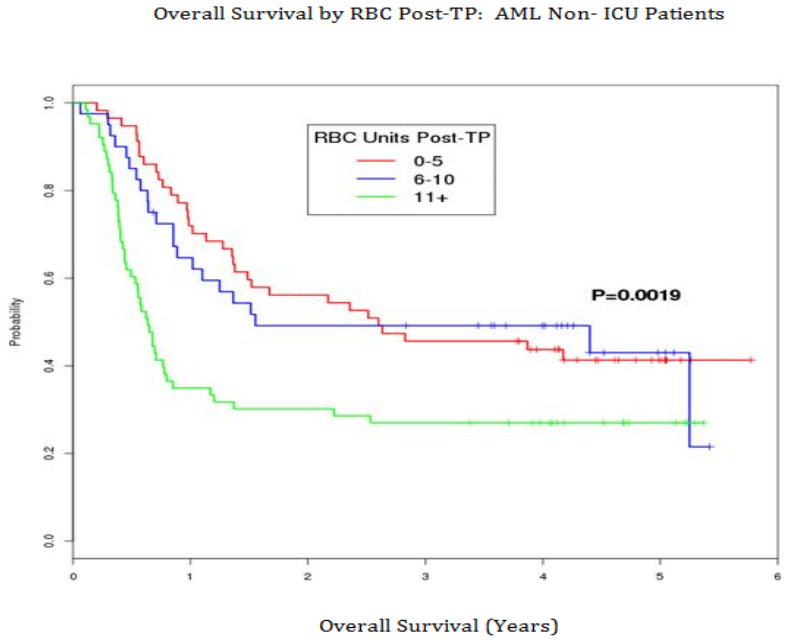


Figure 2: Kaplan-Meier estimates of overall survival according to the number of red blood cells (RBC) units transfused after hematopoietic stem cell transplantation in patients with acute myeloid leukemia who were not admitted to the intensive care unit

	0-5RBC	6-10 RBC	>10 RBC	p value
Total n=160(%)	57 (36)	40 (25)	63 (39)	0.0019
Alive n=59 (%)	24 (41)	18 (30)	17 (29)	

As expected, patients admitted to the ICU had significantly poorer overall survival than those not admitted to the ICU (*p=<0.0001*). At last follow-up, 135 of the 324 patients not admitted to the ICU were alive (median overall survival 1556 days after HSCT; range, 175-2203 days after HSCT) compared with only 2 of the 73 patients admitted to the ICU (1819 and 1901 days after HSCT) (*p=0.0001*).

Discussion

Our retrospective analysis revealed that the number of RBCs transfused to HSCT patientshad a correlation with overall survival rather than the age of the red cells.

The age of the RBCs stored at our institution is largely dependent on the demand for transfusion, the frequent episodic inability to purchase RBC units, and the unforeseen emergency needs of our patients. The focus of our RBC inventorymanagement is not on minimizing the number of expired products but on maintaining an adequate supply for the needs of ourpatients. We do not usually practice the first-in and first-out RBC inventory optimization common at many hospitals. Forty percent of RBCs transfused in our institution are from local blood donors collected by our blood donor center; the rest are purchased from Blood Centers around the country. The age of the purchased RBCs is calculated on the basis of the expiration date and shelf-life duration of 42 days. Some purchased RBCs are irradiated, likely leading to an overestimation of the RBC age for these irradiated units, which have a shelf life of 28 days. The value of inventory reserve is different for different ABO groups. We maintain a higher inventory of Group O RBCs, due to the fact that only group O RBCs can be transfused to group O recipients and this also helps meet our needs of ourmajor ABO mismatched hematopoietic stem cell transplants.None of the RBCs transfused were volume reduced or washed.Dzik et al. 11provided a general approach for estimating the minimum mean age of RBCs at the time of issue to the patient based on considerations of demand for RBCs in patients admitted to the hospital. Studies that have shown an association between the age of RBCs and an increase in the risk of patient death have been conducted mostly at single centers and limited to specific patient groups (e.g., patients with acute cardiovascular disease or trauma)14, 15. A recent meta-analysis by Wang et al. 5 concluded that on the basis of published clinical experience, the use of older stored blood is associated with a significantly increased risk of death. We were unable to confirm that finding in our small cohort of patients who underwent HSCT. Variables such as race (*p=0.28*), age (<50 years or >50 years) (p=0.66), diagnosis (p=0.25), graft source (p=0.43), HLA match grade (p=0.18),pre-conditioning therapy (p=0.48) and ABO matching (p=0.4) was not associated with overall survival (Figures 3-8). However, we did not adjust for possible independent confounding variables such as other co-morbidities, illness-severity scores, prior transplantation history orreceipt of certain lipophilic drugs on RBCs and did not compare patients with identical risk factors for the outcome that would allow for correction.Aged RBCs that were stored for 35 to 42 days was not one of the confounding variables in our studymainly due to the high volume of transfusions that take place daily at our institution.Thus, the findings in our retrospective analysis arelimited by potential confounding by indication. 17Studies of the effects of RBC age on outcomes have yielded conflicting results.

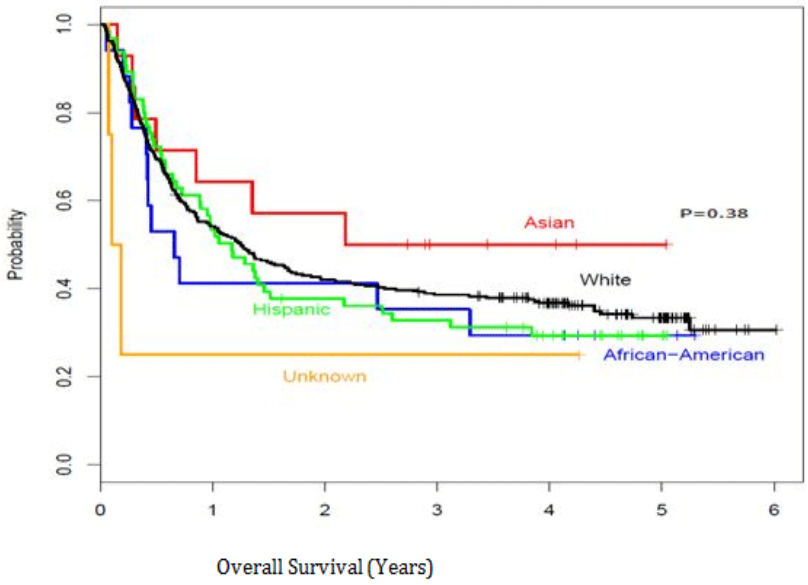


Figure 3: Kaplan-Meier estimates of overall survival by race/ethnicity

	Caucasian	African American	Hispanic	Asian	Unknownp value
Total n=397(%)	397 (75)	17 (4) 65 (16)	14(4)	4(1)	0.38
Alive n=137(%)	104 (76)	5(4)	20 (14)	7(5)	1(1)

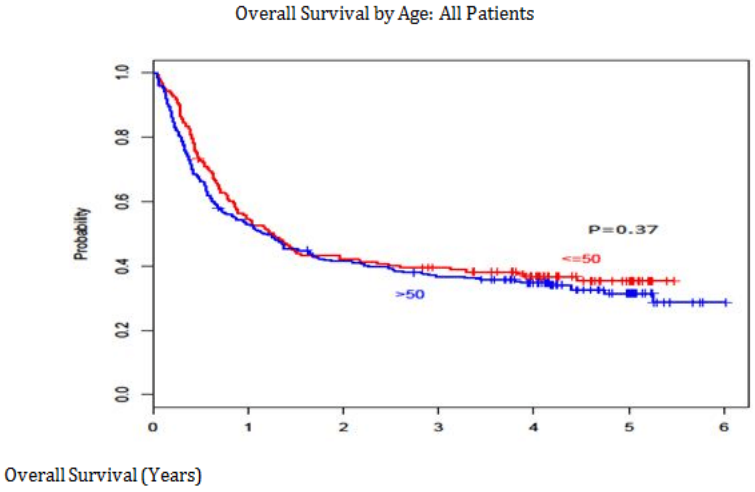


Figure 4: Kaplan-Meier estimates of overall survival by age (< 50 years or > 50 years)

	Age <50	Age >50	*p value*
Total n=397 (%)	143 (36)	254 (64)	0.37
Alive n=437 (%)	62 (45)	74 (54)	

In a large-scale retrospective population study, Edgrenet al.16 found a 5% excess mortality in both short- and long-term analyses when blood stored for more than 30 days was transfused. In contrast,Yap et al.18 concluded that the age of transfused RBCs was not associated with early mortality and morbidity in their review of 6370 consecutive patients who underwent non emergent cardiac surgery and had received at least two units of 2 RBCs. In their recent study of 8416 patients admitted to the ICU who had received a median of four units of RBCs, Aubronet al.19 found that RBC age was not independently associated with mortality. Kekre et al.20 in their analysis of 640 patients who underwent HSCT, reported that RBC storage time did not appear to influence clinical outcome and patients with increased RBC transfusion requirements had greater toxicity after HSCT. In the RECESS13 clinical trials, transfusion of RBCs stored for 10 days or lesswas not superior to the transfusion of RBCs stored for 21 days or more among patients aged 12 years or older whounderwent cardiac surgery. Similar findings were noted by the ABLE investigators and the Canadian Critical Care Trials group as well as in the ARIPI Randomized Trail. 21-22 in a most recent randomized controlled trial of 20858 patients, Heddle et al.23 concluded that among patients in a general hospital population

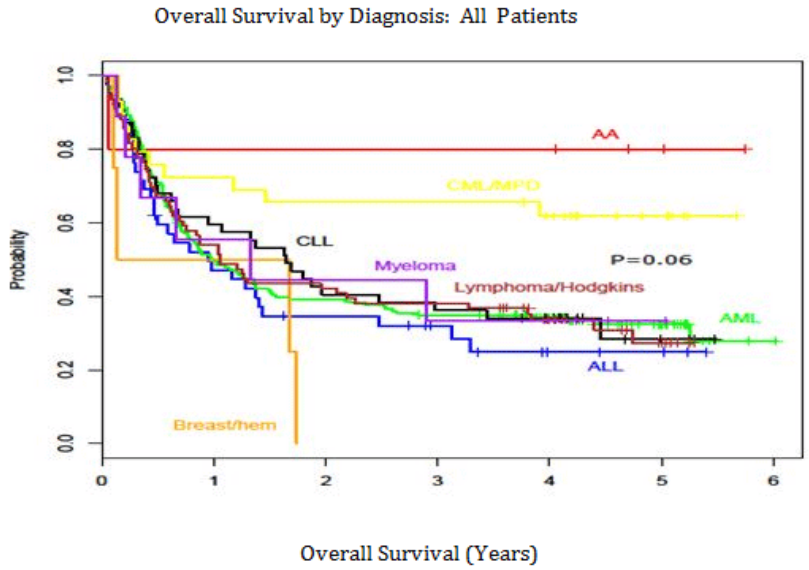


Figure 5: Kaplan-Meier estimates of overall survival by diagnosis

AML	CML/MPD	ALL	CLL	Lymph/Hodgkin's	Myeloma	AA	Non-hematologic			*p value*
Total n=397(%)	185 (47)		29 (7)	42 (11)	47 (12)	76 (19)	9 (2)	5 (1)	4 (1)	*0.06*
Aliven=137 (%)	61 (45)		18 (13)	12 (9)	15 (11)	24 (18)	3 (2)	4 (3)	0 ()	

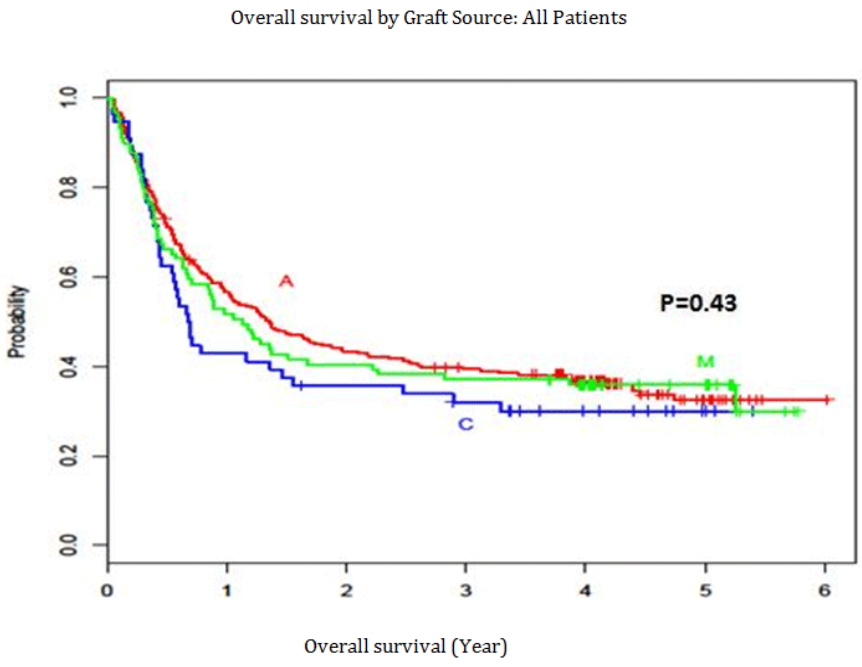


Figure 6: Kaplan-Meier estimates of overall survival by graft source

	Peripheral stem cell	Marrow	cords	*p value*
Total n=397 (%)	227 (68)	67 (20)	41(12)	*0.43*
Alive n=137 (%)	89 (65)	31 (23)	17 (12)	

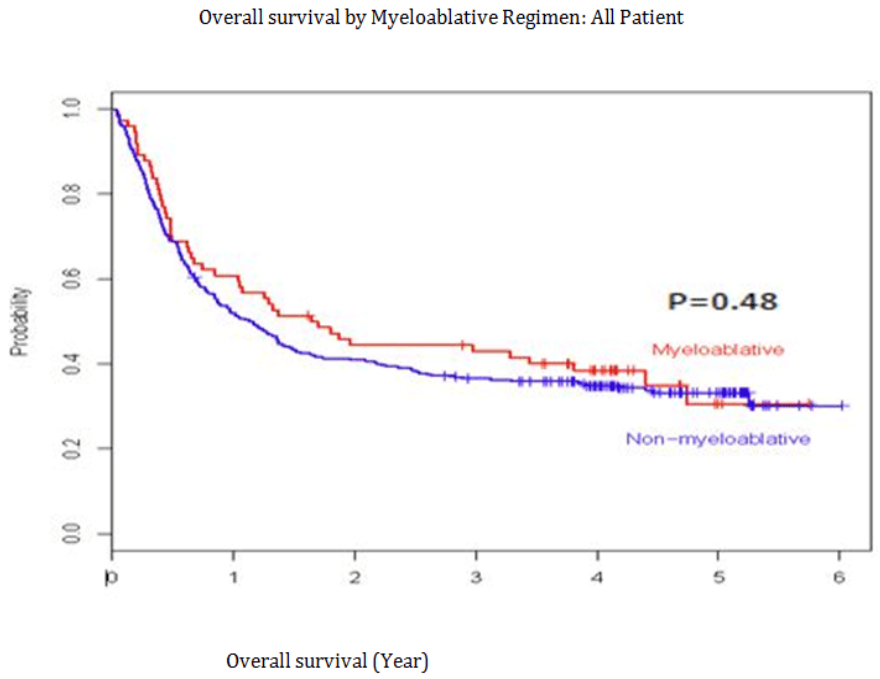


Figure 7: Kaplan-Meier estimates of overall survival by pre-conditioning therapy (myeloablative-Reduced intensity conditioning/non-myeloablative therapy)

	Myeloablative	Non-Myeloablative	*p value*
Total n=397 (%)	323 (81)	74 (19)	*0.48*
Alive n=137 (%)	110 (80)	27 (20)	

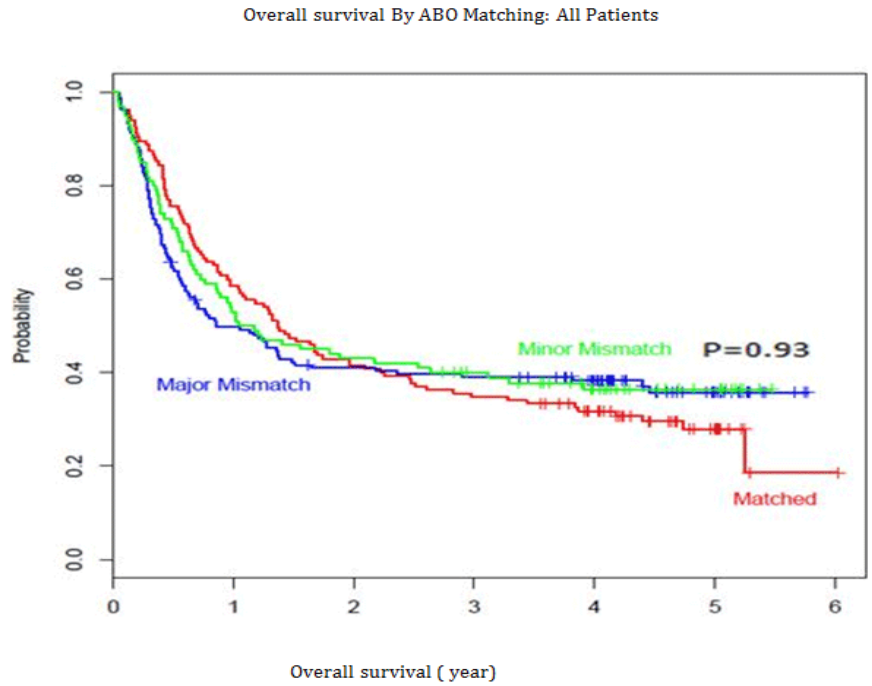


Figure 8: Kaplan-Meier estimates of overall survival by ABO matching

	ABO Matched	Major ABO Mismatch	Minor ABO Mismatch	p value
Total n=397 (%)	135 (34)	63 (41)	99 (25)	0.93
Alive n=135 (%)	38 (28)	61 (45)	36 (27)	

there was no significant difference in rate ofdeath among those who received freshest available blood transfusions than those who received transfusions of the oldest available blood.

We conclude by saying that overall survival did not correlate with age of RBCs transfused in patients admitted to the ICU as well as in patients not admitted to the ICU before and after HSCT. In addition, our study evaluated the age of RBCs transfused not only post-transplant but also pre-transplant in our HSCT patients which was not performed in previous studies. Our findingsare consistent with recent findings by various investigators studying the association of RBC age with patient mortality in critically ill patients, patients undergoing cardiac surgery or HSCT and in premature infants receiving RBC transfusions that RBC age is not correlated with an increase in short term mortality.

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Contributions

FMA designed the research, collected, analyzed, interpreted the data and wrote the paper. RB performed the statistical analysis. BL collaborated on the analysis and the interpretation. CH performed part of the research. CH, EJF and IK analyzed and reviewed the data.

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