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Risk of Coronary Heart Disease in Blood of Marrow Transplant Survivors

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RISK OF CORONARY HEART DISEASE IN BLOOD OR MARROW TRANSPLANT SURVIVORS

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ABSTRACT

Background: Blood or marrow transplant (BMT) recipients are vulnerable to accelerated atherosclerosis due to prior exposure to chemotherapy and radiation, and consequent long-term cardiovascular morbidity, such as coronary heart disease (CHD). A comprehensive evaluation of the risk of late-occurring CHD in adult BMT survivors and the associated risk factors has not been performed.

Patients and Methods: Using the Blood or Marrow Transplant Survivor Study (BMTSS), we analyzed the incidence and risk factors for CHD in patients who underwent BMT between 1974 and 2014, and survived ≥2 years. The risk of CHD was examined in BMT survivors as compared to 1,131 siblings.

Results: The study included 3,479 BMT survivors; 50.3% had received an allogeneic BMT, and 71.4% were non-Hispanic whites. Median age at study participation was 59 years (interquartile range [IQR]: 48-66 years) for BMT survivors and 57 years (IQR: 46-64 years) for siblings. Conditional on surviving ≥2 years after BMT, the cumulative incidence of CHD was 6.5±0.7% at 20 years**.** Allogeneic BMT survivors were at a 7.2-fold higher risk of reporting CHD as compared to siblings (95%CI: 4.0-13.0, p<0.0001), and autologous BMT recipients were at a 11.7-fold higher risk (95%CI: 6.8-20.2, p<0.0001). Increasing age at BMT (HR=1.04/year, 95%CI: 1.01-1.07, p=0.003), male sex (HR=2.08, 95%CI: 1.12-3.88, p=0.021), and history of cardiovascular risk factors

including diabetes, hypertension or dyslipidemia (HR=3.55, 95%CI: 1.70-7.42, p=0.0008) were associated with increased CHD risk in allogeneic BMT survivors. In autologous BMT survivors, increasing age at BMT (HR=1.06/y, 95%CI: 1.03-1.09, p<0.0001), male sex (HR=2.43, 95%CI: 1.38-4.27, p=0.002), and history of pre-BMT chest radiation (HR=3.24, 95%CI: 1.48-7.11, p=0.003) were significantly associated with CHD.

Conclusion: BMT survivors are at an increased risk of developing CHD when compared to unaffected siblings. Our study also identified subgroups among BMT survivors at increased risk of CHD. These findings suggest a need for increased awareness of CHD as a late complication of BMT, such that aggressive management of cardiovascular risk factors can be instituted among those at highest risk.

Keywords: Coronary heart disease, Blood or marrow transplantation, Survivors, Cardiac risk factors, Chest radiation

DEDICATION

To Praveen, my husband and my family. This work would not have been possible without your unyielding support, constant encouragement, unconditional love and patience.

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ALL: Acute lymphoblastic leukemia

AML: Acute myeloid leukemia

BMT: Blood or marrow transplant

BMTSS: Blood or marrow transplant survivor study

BMI: Body mass index

CVD: Cardiovascular disease

CVRF: Cardiovascular risk factors

CI: Confidence interval

CHD: Coronary heart disease

GvHD. Graft versus host disease

HR: Hazard ratio

HL: Hodgkin lymphoma

IQR: Interquartile range

MDS: Myelodysplastic syndrome

NHL: Non-Hodgkin lymphoma

PBSC: Peripheral blood stem cells

SAA: Severe aplastic anemia

SD: Standard deviation

TBI: Total body irradiation

UAB: University of Alabama at Birmingham

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of morbidity and mortality in the United States (US).[1] The risk factors for CHD such as hypertension, diabetes, dyslipidemia, obesity and smoking are well established in the general population.[2,3] Blood or marrow transplant (BMT) recipients are uniquely vulnerable to new onset cardiovascular risk factors (CVRFs) such as hypertension, dyslipidemia and diabetes due to high intensity therapeutic exposures, both pre-BMT and as part of the conditioning regimens.[4,5] Exposure to total body irradiation (TBI) as well as chest radiation are associated with accelerated atherosclerosis. Previous studies have shown increased risk of metabolic syndrome in BMT recipients.[6-8] In allogeneic BMT recipients, endocrinopathies, inflammation due to chronic graft versus host disease (GvHD) and its treatment further increase the risk of developing these co-morbidities.[9,10] These factors, with or without additional health behaviors such as smoking and physical inactivity place BMT survivors at a high risk for cardiovascular disease (CVD) (Figure 1). However, the long-term risk of coronary heart disease (CHD) and the associated risk factors are not well characterized in adult BMT survivors.

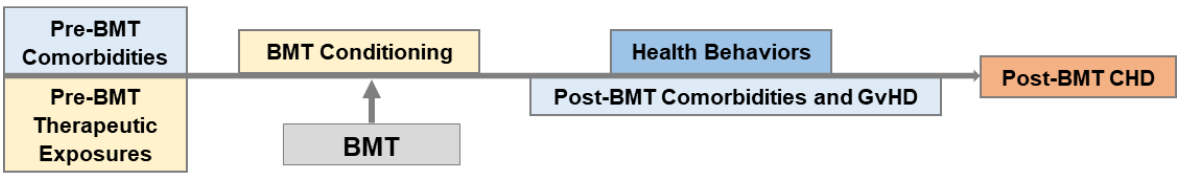


Figure 1. Risk factors associated with CHD in BMT survivors

Improvement in survival rates after BMT have resulted in recognition of late complications in BMT recipients, posing an ongoing challenge in the long-term care of these patients.[11] Previous studies that assessed the risk of CHD in BMT recipients are limited by being single center studies, with small sample sizes, short follow up and the lack of assessment of health behaviors and therapeutic exposures.[5,10,12-14] We addressed this gap using the resources offered by the BMT survivor study (BMTSS) which provides a unique opportunity to study the long-term complications and associated risk factors in a diverse and large, multi-institutional cohort of BMT survivors. In this study, we examined the incidence of CHD amongst adults who survived two or more years after BMT, and compared this risk to an unaffected sibling comparison group, representative of the general population. We also sought to identify sociodemographic characteristics, comorbidities, behavioral characteristics and therapeutic exposures associated with CHD development.

METHODS

Study Design and Population

BMTSS is a retrospective cohort that includes patients transplanted for hematologic malignancies and other life-threatening conditions between January 1, 1974 and December 31, 2014 at City of Hope, University of Minnesota and University of Alabama at Birmingham (UAB). BMTSS aims to examine the long-term outcomes in individuals who have survived two or more years after undergoing BMT at one of the three institutions. For the current study, patients who were alive and 18 years or older at survey participation were included. A cohort of 1,131 siblings of the BMTSS participants completed an identical BMTSS survey but without BMT-specific questions and served as a comparison group. UAB Institutional Review Board served as the single IRB of record and informed consent was provided according to the Declaration of Helsinki.

Covariate Measures from the BMTSS Survey

A BMTSS survey was administered to eligible patients, and asked participants to report chronic health conditions diagnosed by their healthcare provider (including CHD, diabetes, hypertension, dyslipidemia etc.), along with age at diagnosis, medication use, history of GvHD, relapse of primary cancer and development of subsequent neoplasms. The participants self-reported sociodemographics (sex, race/ethnicity, education, employment, household income and health insurance), health behaviors (history of smoking [age when they started smoking, number of cigarettes per day, years of

smoking], alcohol use and physical activity), along with height and weight at survey participation.[15] The reliability and validity of the BMTSS questionnaire have been previously tested against medical records, confirming that BMT survivors are able to accurately report the occurrence of adverse medical conditions.[16] Information regarding primary cancer diagnosis, therapeutic exposures, donor type, stem cell source (bone marrow, cord blood or peripheral blood stem cells [PBSC]), and history of chronic GvHD for allogeneic BMT recipients was abstracted from medical records. We categorized radiation exposure to the neck, chest, cranium, spine, abdomen, pelvis, extremities total body irradiation, as yes *vs.* no, and recorded total radiation dose for each field. A list of covariates included in analytic models is shown in Table 1.

Table 1.

Sociodemographic, clinical data and therapeutic exposures available in BMTSS

Variable	Source of Information	Details of analytic variables
Sociodemographics	BMTSS survey	Age at completion of survey, age at BMT, sex, race/ethnicity, income, education, health insurance
Health Behaviors	BMTSS survey	Smoking, alcohol, physical activity
Hematologic malignancy characteristics	Medical record abstraction	Diagnosis, relevant biologic characteristics
Pre-BMT exposures	Medical record abstraction	*Radiation therapy:* radiation dosimetry to calculate organ-specific radiation dose *Chemotherapy:* protocols/regimens, agents, routes of administration, cumulative dose for select agents (anthracyclines, alkylators, topoisomerase II inhibitors, platinum, bleomycin) *Other biologic agents (targeted therapy):* agents
BMT related variables	Medical record abstraction	*Donor type:* unrelated (degree of match), related (matched, mismatched) *Stem cell source:* bone marrow, peripheral blood stem cells, cord blood (single/ double) *Conditioning regimens:* agents, dose

		Conditioning Intensity: Reduced intensity/ non-myeloablative/ myeloablative
Comorbidities	BMTSS survey	*Pre-BMT and new onset comorbidities: CVRFs* (hypertension, diabetes, dyslipidemia, obesity), congestive heart failure, chronic kidney disease, venous thromboembolism, stroke, arrhythmia and medications *GvHD:* age of onset, organs involved

Outcome of interest

The diagnosis of CHD was based on positive responses to questions that asked if participants had been told by a health-care professional that they had hardening of the arteries or arteriosclerosis, coronary artery disease, or angina pectoris (chest pain due to lack of oxygen to heart requiring medication such as nitroglycerin). This was confirmed by a history of angioplasty or coronary artery bypass surgery in their surgical history.

Statistical Analysis

Descriptive statistics including mean, standard deviation (SD), median, range, interquartile range (IQR), and frequencies were summarized. We used two-sample *t* test or Wilcoxon rank-sum test (for continuous variables) and chi-square test (for categorical variables) to compare the difference between BMT survivors and siblings, and between allogeneic and autologous transplant recipients.

Risk of CHD in BMT survivors vs. siblings

We used Cox regression to examine the risk of CHD in BMT survivors compared to siblings; the magnitude of the association was expressed as a hazard ratio (HR), with its associated 95% confidence interval (95% CI). We adjusted the analysis for sex, race/ethnicity, education, annual household income, smoking and alcohol history, body

mass index (BMI), and comorbidities (hypertension, diabetes, dyslipidemia, chronic kidney disease, arrhythmias, and stroke).

Risk of CHD in BMT survivors

We calculated cumulative incidence of CHD in BMT survivors conditional on surviving two years or more after BMT, using Fine and Gray methods. We used multivariable Cox regression analysis with backward variable selection, keeping variables with $p<0.1$ in the model to identify factors associated with CHD risk in BMT survivors.[17] We stratified the analyses by BMT type (allogeneic, autologous), considering that the therapeutic exposures are different for these patients. Risk factors evaluated for association with CHD included age at BMT, sex, race/ethnicity, education, annual household income, history of smoking, BMI, comorbidities, primary cancer type, relapse of primary cancer or development of a subsequent malignancy, stem cell source, pre-transplant chemotherapy, conditioning regimens used for BMT, chronic GvHD, and radiation (pre-BMT radiation exposures and TBI). Age at BMT and BMI were treated as continuous variables and the remaining variables were considered as categorical. We treated comorbidities, relapse of primary cancer or development of subsequent neoplasms and chronic GvHD (in allogeneic BMT recipients) as time-varying variables. Patients who had a history of CHD prior to BMT were excluded from the association analysis.

Two-sided tests with $p<0.05$ were considered statistically significant. We performed all analyses with SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina, US).

RESULTS

Participant Characteristics

Of the 6,453 eligible BMT survivors, 489 were lost to follow up. Of the 5,964 patients approached, 698 (11.7%) refused, and 1,787 (30.0%) did not respond to the invitation to participate, yielding 3,479 (58.3%) participants. Figure 2 provides a consort diagram of eligible participants. Participants were older at BMT compared to non-participants (mean age, 44.4 years *vs.* 36.8 years, p<0.0001), and were more likely to be females (45.2 *vs.* 42.1%, p=0.02) and non-Hispanic whites (77.1% *vs.* 62.3%, p<0.0001).

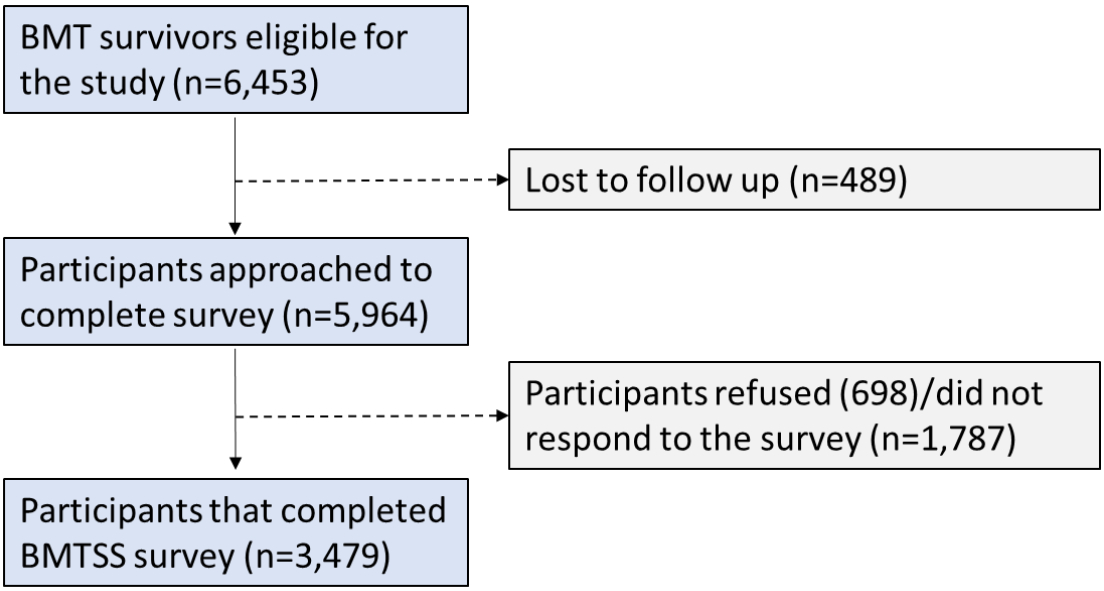


Figure 2. Consort diagram for participants included in the study.

BMT recipients compared with siblings

Table 2 provides details on sociodemographic characteristics of BMT survivors

and siblings. Of the 3,479 BMT survivors, 54.8% were males, and 71.4% were non-Hispanic whites. Median age at study participation was 59 years (IQR: 48-66 years) for BMT survivors and 57 years (IQR: 46-64 years) for siblings. Siblings were younger than BMT survivors, and there were more females and non-Hispanic White individuals in the siblings group compared to BMT survivors. BMT survivors reported lower education and had more comorbidities compared to siblings.

Table 2.

Demographic and clinical characteristics of BMT survivors and siblings

Variable	BMT survivors (N=3,479)	Siblings (N=1,131)	p-value
Coronary Heart Disease (n, %)			
Yes	179 (5.15%)	32 (3.10%)	**0.0064**
Age at survey in years			
Median (Interquartile range)	59 (48-66)	57 (46-64)	**<0.0001**
Gender (n, %)			
Male	1907 (54.81%)	410 (39.77%)	**<0.0001**
Race (n, %)			
White	2485 (71.43%)	889 (86.23%)	**<0.0001**
Hispanic	559 (16.07%)	77 (7.47%)	
Black	164 (4.71%)	23 (2.23%)	
Asian	173 (4.97%)	31 (3.01%)	
Other	98 (2.82%)	11 (1.07%)	
Education (n, %)			
≤High School	609 (17.51%)	133 (12.90%)	**<0.0001**
Some college	1267 (36.42%)	358 (34.72%)	
College Graduate	1531 (44.01%)	530 (51.41%)	
Missing	72 (2.07%)	10 (0.97%)	
Annual income (n, %)			
<50k	1043 (29.98%)	229 (22.21%)	**<0.0001**
50-100k	1009 (29.00%)	303 (29.39%)	
>100k	1351 (38.83%)	394 (38.22%)	
Missing	76 (2.18%)	105 (10.18%)	
Health Behaviors (n, %)			
Smoking	1137 (32.68%)	332 (32.20%)	**0.77**
Alcohol	1754 (50.42%)	598 (58.0%)	**<0.0001**
Body mass index			
Mean, SD	26.74 (6.31%)	27.66 (6.52)	**<0.0001**
Comorbidities (n, %)			
Diabetes	445 (13.28%)	42 (4.21%)	**<0.0001**
Hypertension	954 (31.58%)	207 (21.84%)	**<0.0001**
Dyslipidemia	888 (29.42%)	171 (17.85%)	**<0.0001**
Chronic kidney disease	154 (4.50%)	34 (3.30%)	0.094

Congestive heart failure	162 (4.69%)	14 (1.37%)	**<0.0001**
Stroke	109 (3.14%)	10 (0.97%)	**<0.0001**
Arrhythmia	339 (10.0%)	64 (6.28%)	**0.0003**
Venous thromboembolism	370 (10.72%)	29 (2.82%)	**<0.0001**
Acute GvHD	556 (16.78%)	-	
Chronic GvHD	627 (18.61%)	_-_	
Relapse of primary cancer/ SMN	525 (15.27%)	-	
Indication for BMT			
Non-Hodgkin lymphoma	880 (25.29%)		
Acute myeloid leukemia/ Myelodysplastic syndrome	803 (23.08%)		
Plasma cell dyscrasias	738 (21.21%)		
Chronic myelogenous leukemia	279 (8.02%)		
Hodgkin lymphoma	258 (7.42%)		
Acute lymphoblastic leukemia	246 (7.07%)		
Severe aplastic anemia	92 (2.64%)		
Other	146 (4.20%)		
Type of BMT			
Allogeneic BMT	1751 (50.33%)		
Autologous BMT	1728 (49.67%)		

SD, standard deviation; BMT, Blood or marrow transplant; GvHD, graft vs host disease; SMN, subsequent malignant neoplasm.

After adjusting for sociodemographics and comorbidities, allogeneic BMT survivors were at a 7.2 times higher risk (95%CI: 4.0-13.0, p<0.0001) and autologous BMT recipients at a 11.7 times the risk (95%CI: 6.8-20.2, p<0.0001) of reporting CHD as compared to siblings.

CHD Risk in BMT survivors

This analysis included 3,422 participants after excluding those with pre-BMT CHD (n=57). Median age at BMT was 41 years (IQR: 25-54 years) for allogeneic and 53 years (IQR: 42-61 years) for autologous BMT recipients. BMT survivors were followed for a median of 9 years (range: 2-41 years) from BMT. CHD was diagnosed after BMT in 122 BMT survivors (52 allogeneic, 70 autologous). Conditional on surviving ≥2 years

after BMT, the cumulative incidence of CHD was 3.2±0.4% at 10 years and 6.5±0.7% at 20 years after BMT (Figure 3).

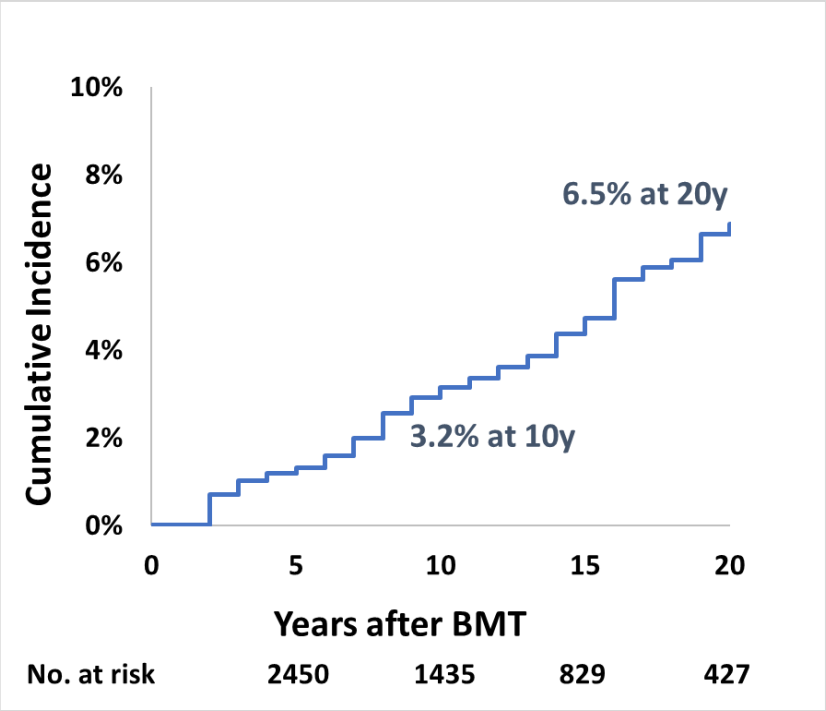
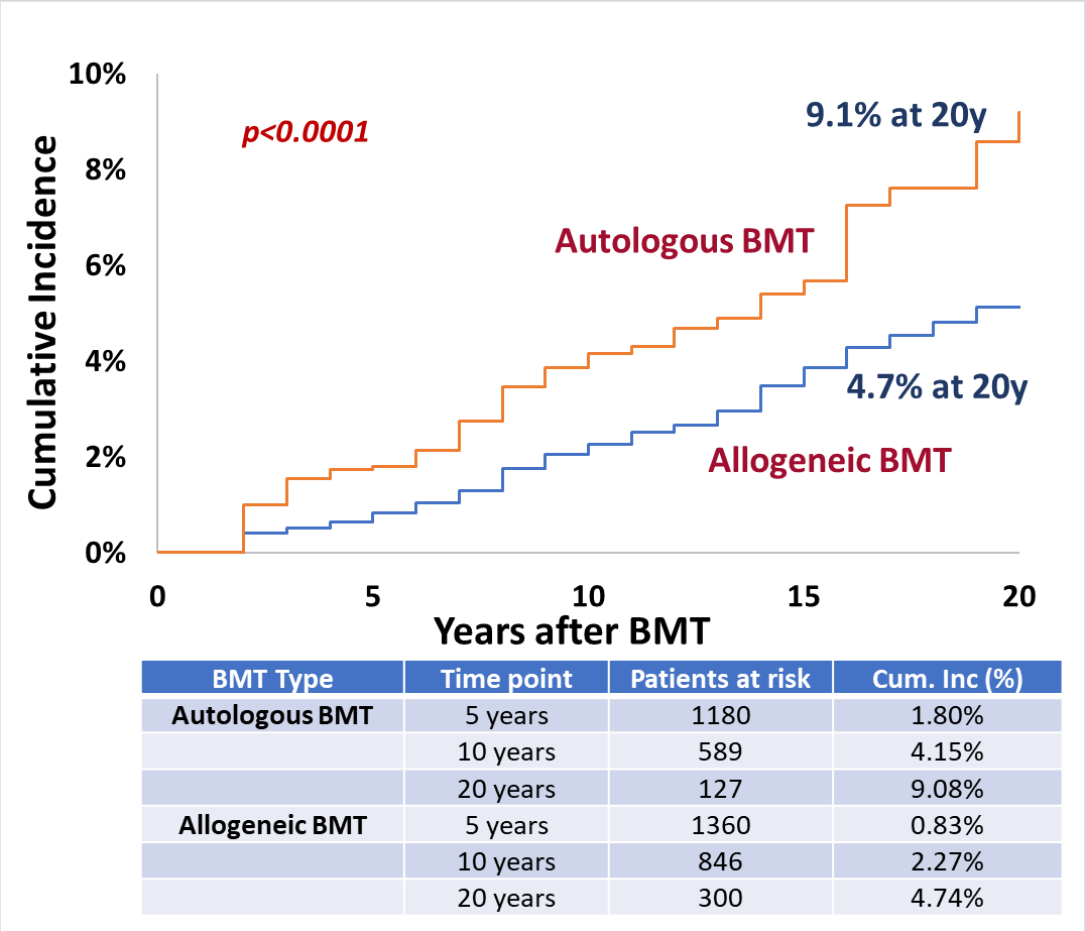


Figure 3. Cumulative incidence of CHD in the entire BMT population

Median age at CHD diagnosis was 55 years (range: 27 to 71 years) in allogeneic BMT survivors and 62 years (range: 34 to 84 years) in autologous BMT survivors. The cumulative incidence was 2.3±0.4% for allogeneic BMT survivors and 4.2±0.6% for autologous BMT survivors at 10 years, and 4.7±0.8% and 9.1±1.4% respectively at 20 years ($p<0.0001$) (Figure 4).



BMT Type	Time point	Patients at risk	Cum. Inc (%)
Autologous BMT	5 years	1180	1.80%
	10 years	589	4.15%
	20 years	127	9.08%
Allogeneic BMT	5 years	1360	0.83%
	10 years	846	2.27%
	20 years	300	4.74%

Figure 4. Cumulative incidence of CHD by BMT type

Risk factors for CHD in BMT survivors

Table 3 summarizes the sociodemographic and clinical characteristics of the BMT survivors by BMT type. Primary cancer diagnoses included non-Hodgkin lymphoma (NHL: 25.2%), acute myeloid leukemia/ myelodysplastic syndrome (AML/MDS: 23.0%), plasma cell dyscrasias (PCD: 21.1%), chronic myelogenous leukemia (CML: 8.1%), Hodgkin lymphoma (HL: 7.5%), acute lymphoblastic leukemia (ALL: 7.1%), and severe aplastic anemia (SAA: 2.7%), and other miscellaneous diagnoses (5.3%). The majority of BMT survivors (n=2484, 72.6%) were transplanted with PBSCs (94.7% of autologous; 51.0% of allogeneic BMT recipients). Chemotherapy was used as part of

conditioning in all the patients and any radiation in 44.4% (25.5% in autologous and 62.8% in allogeneic BMT recipients, p<0.0001). The most commonly used chemotherapeutic agents for conditioning were cyclophosphamide (53.7%), melphalan (40.4%), etoposide (36.4%), fludarabine (21.6%), carmustine (16.5%) and busulfan (12.1%). Total body irradiation was used in conditioning regimens for 42.1% of patients, 24.2% of autologous and 59.5% allogeneic recipients. The most common pre-BMT chemotherapeutic agents included anthracyclines (66.7%), corticosteroids (64.4%), alkylators (47.6%), plant alkaloids (46.9%), antimetabolites (44.4%), targeted therapies (30.7%), topoisomerase inhibitors (26.4%), monoclonal antibodies (21.6%), platinum agents (19.7%) and thalidomide (14.5%). Radiation was used prior to BMT for treatment of primary cancer in 21.6% of autologous and 8.7% of allogeneic BMT recipients, and 4.98% participants received pre-BMT chest radiation (8.1% autologous and 1.9% allogeneic BMT recipients). We assessed the risk factors for CHD by BMT type (allogeneic, autologous), considering that the therapeutic exposures are different for these patients.

Table 3.

Demographic and clinical characteristics of BMT survivors based on the type of BMT.

Variable	Autologous (1690)		Allogeneic (1732)	
Coronary Heart Disease (n, %)	70	4.14	52	3.00
Age at BMT (Mean, SD)	49.99	14.34	38.45	18.21
Sex (n, %)				
Male	935	55.33	923	53.29
Race/Ethnicity (n, %)				
Non-Hispanic white	1171	69.29	1269	73.27
Hispanic	292	17.28	262	15.13
Black	121	7.16	40	2.31
Asian	60	3.55	110	6.35
Other	46	2.72	51	2.94
Education (n, %)				

Variable	Autologous (1690)		Allogeneic (1732)	
≤High School	311	18.40	285	16.45
Some college	615	36.39	636	36.72
College Graduate	742	43.91	763	44.05
Missing	22	1.30	48	2.77
Annual Income (n, %)				
≤50k	515	30.47	515	29.73
50-100k	507	30.00	481	27.77
>100k	625	36.98	706	40.76
Missing	43	2.54	30	1.73
Stem cell source (n, %)				
Cord Blood	1	0.06	184	10.62
Peripheral Blood Stem Cells	1600	94.67	884	51.04
Bone Marrow	89	5.27	663	38.28
Medications (n, %)				
Oral contraceptive pills	476	28.17	507	29.27
Female Hormone replacement	533	31.54	590	34.06
Testosterone replacement	193	11.42	272	15.70
Immunosuppressants	367	21.72	1093	63.11
Comorbidities (n, %)				
Acute Graft vs Host Disease	-	-	547	34.71
Chronic Graft vs Host Disease	-	-	597	36.56
Diabetes	174	10.65	266	16.00
Body mass index, mean, SD	27.78	6.82	25.73	5.60
Hypertension	421	28.68	513	33.97
Dyslipidemia	405	27.68	453	29.94
Stroke	46	2.74	60	3.47
Kidney Disorder	73	4.41	81	4.73
Relapse of cancer/ second neoplasm	267	16.00	258	15.06
Congestive heart failure	76	4.53	77	4.47
Venous thromboembolism	170	10.15	199	11.57
Health Behaviors (n, %)				
Alcohol	931	55.09	839	48.44
Smoking	619	36.63	526	30.37
Any Exercise	1142	67.57	1234	71.25
Vigorous Exercise	649	38.40	691	39.90
Moderate Exercise	568	33.61	528	30.48
Primary Cancer Diagnosis (n, %)				
Acute myeloid leukemia/Myelodysplasia	110	6.51	677	39.09
Acute lymphoblastic leukemia	8	0.47	236	13.63
Chronic myelogenous leukemia	9	0.53	269	15.53
Non Hodgkin lymphoma	628	37.16	233	13.45
Hodgkin lymphoma	222	13.14	35	2.02

Variable	Autologous (1690)		Allogeneic (1732)	
Plasma cell dyscrasias	658	38.93	63	3.64
Other	55	3.20	218	12.5
Therapeutic exposures (n, %)				
Pre-BMT any Chemotherapy	1590	93.36	1435	85.01
Any radiation before BMT	365	21.6	151	8.72
Chest Radiation	115	8.1	27	1.89
Total body Irradiation	408	24.21	1027	59.54

Risk factors for CHD in Allogeneic BMT survivors

In Table 4, we summarize the association between allogeneic BMT recipient characteristics and risk of CHD. Increasing age at BMT (HR=1.04/year, 95%CI: 1.01-1.07, p=0.003), male sex (HR=2.08, 95%CI: 1.12-3.88, p=0.021), and history of CVRFs including diabetes, hypertension or dyslipidemia (HR=3.55, 95%CI: 1.70-7.42, p=0.0008) were associated with increased CHD risk in allogeneic BMT recipients. The association between pre-BMT exposure to bleomycin and CHD (HR=3.93, 95%CI: 0.96-16.08, p=0.057) approached statistical significance. Higher education with some college education was associated with a lower CHD risk compared to less than high school (HR=0.35, 95%CI: 0.16-0.77, p=0.009).

Table 4.

Risk Factors Associated with Coronary Heart Disease in Allogeneic BMT survivors

Category	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age at BMT						
Per year increase in age	**1.06**	**1.04,1.09**	**<0.0001**	**1.04**	**1.02,1.07**	**0.003**
Gender (ref: Female)						
Male	**2.12**	**1.16,3.86**	**0.014**	**2.08**	**1.12,3.88**	**0.021**
Race (ref: non-Hispanic whites; non-Hispanic whites vs All Others for multivariable model)						
Hispanic	0.53	0.19,1.46	0.219	2.03	0.93,4.44	0.077
Black	1.45	0.35,5.99	0.607			
Asian	0.36	0.05,2.59	0.307			

Category	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p value	HR	95% CI	p value
Other	0.62	0.09,4.50	0.636			
Education (ref: ≤High School)						
Some college	**0.44**	**0.20,0.95**	0.037	**0.35**	**0.16,0.77**	**0.009**
College Graduate	0.81	0.42,1.55	0.519	0.55	0.28,1.1	0.099
Income (ref: <$50k)						
$50k-$100k	0.98	0.47,2.06	0.955			
>$100k	1.43	0.75,2.72	0.284			
Smoking						
Yes vs No	**1.85**	**1.06,3.24**	**0.032**	1.00	0.55,1.83	0.994
Comorbidities						
Diabetes/ Hypertension/ Dyslipidemia	**6.10**	**3.05,12.20**	**<0.0001**	**3.55**	**1.70,7.42**	**0.0008**
Obesity (Body mass index)	**1.05**	**1.00,1.09**	**0.034**	1.01	0.96,1.06	0.727
Chronic kidney disease	**3.00**	**1.19,7.55**	**0.020**	1.81	0.70,4.70	0.220
Arrhythmia	1.51	0.64,3.53	0.344			
Venous thromboembolism	1.32	0.47,3.66	0.601			
Stroke	NA	NA	NA			
Chronic graft vs host disease	1.42	0.80,2.51	0.226			
Relapse/ secondary malignancy	1.67	0.81,3.46	0.165	1.29	0.61,2.73	0.508
Primary Diagnosis (ref: Acute lymphoblastic leukemia)						
AML/Myelodysplasia	2.84	0.84,9.60	0.094	1.34	0.38,4.78	0.648
Chronic myelogenous leukemia	2.91	0.83,10.16	0.095	1.45	0.39,5.37	0.581
Non-Hodgkin lymphoma	2.40	0.57,10.10	0.232	0.74	0.17,3.26	0.689
Severe aplastic anemia	1.05	0.17,6.30	0.959	1.36	0.19,9.58	0.756
Other	3.04	0.82,11.30	0.096	1.57	0.37,6.67	0.541
Stem Cell Source (ref: bone marrow)						
Peripheral blood stem cells	**4.06**	**2.02,8.14**	**<0.0001**	1.38	0.58,3.29	0.472
Cord Blood	1.65	0.47,5.85	0.436	0.80	0.20,3.22	0.758
Conditioning regimen (ref: fludarabine + melphalan-based)						
Anti-thymocyte globulin based	0.47	0.15,1.43	0.183			
Busulfan + Cyclophosphamide	0.57	0.21,1.55	0.271			
Cyclophosphamide	0.14	0.02,1.12	0.064			
Cyclophosphamide + TBI	**0.39**	**0.18,0.84**	0.017			
Etoposide + TBI	**0.27**	**0.08,0.91**	0.035			
Other	0.46	0.15,1.40	0.169			
Total body irradiation						
Yes vs No	0.65	0.37,1.16	0.146			
Pre-BMT chemotherapy						
Alkylators	1.00	0.53,1.86	0.994			
Anthracyclines	0.72	0.41,1.27	0.259			
Antimetabolite	0.77	0.44,1.35	0.363			

Category	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p value	HR	95% CI	p value
Asparaginase	0.26	0.06,1.06	0.060			
Bleomycin	**3.86**	**1.38,10.77**	**0.010**	**3.93**	**0.96,16.08**	**0.057**
Hydroxyurea	1.19	0.64,2.19	0.587			
Hypomethylating agents	2.25	0.68,7.42	0.182			
Immunosuppression	0.67	0.09,4.83	0.687			
Platinum agents	1.17	0.42,3.3	0.764			
Purine Nucleoside Analogs	1.52	0.6,3.86	0.380			
Plant Alkaloid	0.82	0.45,1.51	0.531			
Corticosteroids	0.68	0.38,1.23	0.201			
Targeted therapies^	1.45	0.63,3.32	0.384	1.46	0.58, 3.66	0.419
Thalidomide	3.42	0.81,14.45	0.095	1.70	0.35,8.31	0.515
Topoisomerase inhibitors	0.91	0.42,1.95	0.804			
Monoclonal Antibodies	0.69	0.21,2.25	0.535			
Interferon	1.85	0.78,4.38	0.165			
Pre-BMT radiation						
Any radiation	0.32	0.08,1.31	0.112			
Chest radiation (Yes vs No)	2.21	0.54,9.11	0.272			

^Targeted therapies included tyrosine kinase inhibitors, proteasome inhibitors etc.

Abbreviations: BMT, blood or marrow transplant; HR, Hazard ratio; CI, Confidence interval; AML, Acute myeloid leukemia; TBI, total body irradiation.

Risk factors for CHD in Autologous BMT survivors

The risk factors for CHD in autologous BMT survivors included: increasing age at BMT (HR=1.06/y, 95%CI: 1.03-1.09, p<0.0001), male sex (HR=2.43, 95%CI: 1.38-4.27, p=0.002), and history of pre-BMT chest radiation (HR=3.24, 95%CI: 1.48-7.11, p=0.003). For every 100 centiGray increase in the dose of chest radiation, there was a 4% increase in the risk of CHD (p=0.0002). History of CVRFs including diabetes, hypertension or dyslipidemia (HR=1.68, 95%CI: 0.98-2.08, p=0.06), history of smoking (HR=1.63, 95%CI: 0.99-2.66, p=0.053), and arrhythmia (HR=1.83, 95%CI: 0.98-3.42, p=0.056) approached statistical significance (Table 5).

Table 5.

Risk Factors Associated with Coronary Heart Disease in Autologous BMT survivors

Category	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age at BMT						
Per year increase in age	**1.06**	**1.04,1.09**	**<0.0001**	**1.06**	**1.03,1.09**	**<0.0001**
Sex (ref: Female)						
Male	**2.76**	**1.60,4.77**	**0.0003**	**2.43**	**1.38,4.27**	**0.002**
Race (ref: non-Hispanic whites; non-Hispanic whites vs All Others for multivariable model)						
Hispanic	1.22	0.66,2.25	0.523	0.99	0.58,1.69	0.963
Black	0.59	0.14,2.44	0.468			
Asian	**2.97**	**1.27,6.94**	0.012			
Education (ref: ≤High School)						
Some college	0.82	0.44,1.53	0.527	**0.74**	**0.39,1.41**	**0.363**
College Graduate	0.75	0.41,1.38	0.356	0.71	0.37,1.33	0.280
Income (ref: <$50k)						
$50k-$100k	1.02	0.55,1.89	0.941			
>$100k	1.09	0.61,1.95	0.769			
Missing	1.22	0.28,5.22	0.790			
Smoking						
Yes vs No	**2.23**	**1.35,3.68**	**0.002**	**1.63**	**0.99,2.66**	**0.053**
Comorbidities						
Diabetes/ Hypertension/ Dyslipidemia	**3.05**	**1.84,5.06**	**<0.0001**	**1.68**	**0.98,2.89**	**0.060**
Obesity (Body mass index)	1.00	0.97,1.03	0.985			
Chronic kidney disease	1.35	0.49,3.71	0.561			
Arrhythmia	**2.47**	**1.35,4.52**	**0.003**	**1.83**	**0.98,3.42**	**0.056**
Venous thromboembolism	1.26	0.58,2.75	0.564			
Stroke	**2.80**	**1.02,7.73**	**0.046**	2.07	0.73,5.92	0.173
Relapse/ secondary malignancy	1.00	0.43,2.31	1.00			
Primary Diagnosis (ref: Acute myelogenous leukemia/myelodysplastic syndrome)						
Hodgkin lymphoma	1.68	0.59,4.79	0.329	0.80	0.22,2.89	0.729
Non-Hodgkin lymphoma	1.59	0.61,4.17	0.346	0.53	0.18,1.62	0.268
Plasma cell dyscrasias	2.22	0.81,6.03	0.120	0.41	0.11,1.47	0.171
Other	1.05	0.28,3.92	0.942	0.75	0.17,3.35	0.707
Conditioning (ref: Melphalan)						
Cyclophosphamide + Etoposide + TBI	0.47	0.21,1.03	0.058			
Carmustine + Cyclophosphamide + Etoposide	0.88	0.42,1.85	0.736			
Carmustine + Cytarabine	1.48	0.67,3.28	0.332			
Cyclophosphamide + TBI	0.34	0.11,1.07	0.064			
Cyclophosphamide + Etoposide	0.71	0.24,2.13	0.542			
Other	0.67	0.29,1.54	0.344			
Total body irradiation						
Yes vs No	**0.53**	**0.31,0.92**	**0.030**	0.93	0.48,1.8	0.825
Pre-BMT chemotherapy						

Category	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p value	HR	95% CI	p value
Alkylators	1.03	0.62,1.71	0.901			
Anthracyclines	0.72	0.41,1.26	0.245			
Asparaginase	0.71	0.10,5.21	0.739			
Antimetabolites	**0.47**	**0.27,0.81**	**0.007**	0.56	0.28,1.11	0.096
Antimitotic agents	3.03	0.74,12.39	0.123			
Bleomycin	0.66	0.34,1.26	0.204			
Monoclonal Antibodies	1.51	0.87,2.62	0.143			
Platinum agents	0.92	0.53,1.57	0.746			
Pyrimidine antagonists	1.54	0.37,6.35	0.548			
Plant Alkaloid	0.86	0.53,1.40	0.542			
Corticosteroids	1.37	0.73,2.56	0.326			
Targeted therapies^	**1.84**	**1.08,3.15**	**0.026**	1.28	0.72,2.30	0.403
Thalidomide	1.50	0.80,2.79	0.205			
Topoisomerase inhibitors	0.82	0.49,1.38	0.461			
Purine Nucleoside Analogs	0.76	0.11,5.47	0.786			
Anti-Estrogen	4.15	0.57,30.1	0.159			
Pre-BMT radiation						
Any radiation	1.60	0.97,2.64	0.065			
Chest radiation, Yes vs No	**2.01**	**1.01,3.99**	**0.046**	**3.24**	**1.48,7.11**	**0.003**

^Targeted therapies included tyrosine kinase inhibitors, proteasome inhibitors etc.

Abbreviations: BMT, blood or marrow transplant; HR, Hazard ratio; CI, Confidence interval; TBI, total body irradiation.

DISCUSSION

In a large cohort of two or more year BMT survivors, we found that the cumulative incidence of CHD was 3.2% at 10 years after BMT. Allogeneic BMT survivors were at a 7.2-times and autologous BMT survivors were at 11.7-times the risk of reporting CHD compared to siblings without a history of cancer. Older age at BMT, male sex, CVRFs such as diabetes, hypertension and dyslipidemia in allogeneic BMT survivors, and older age, male sex, pre-BMT exposure to chest radiation in autologous BMT recipients were associated with increased CHD risk.

Cardiac toxicity is a well-known complication after BMT occurring in 0.9% to 8.9% of the patients, and is associated with patient-specific and treatment-related factors such as cardiotoxic therapeutic exposures.[18,19] The most commonly reported adverse events during acute period of BMT include arrhythmias, congestive heart failure and pericardial effusion; these complications are leading causes of early mortality after BMT.[18,20,21] Prior exposure to radiation and/or chemotherapy, and ongoing inflammation due to chronic GvHD in allogeneic BMT recipients predisposes to atherosclerosis.[22] In addition to accelerated atherosclerosis, consequent long-term cardiovascular morbidities such as hypertension, dyslipidemia and diabetes increase their risk of CVD.[5,12,23-26] However, these events commonly occur several years after BMT due to the long time interval needed for these clinical manifestations to occur. Indeed, CVD would be expected decades after transplantation. In a retrospective multi-center European Group of Blood and Marrow Transplantation analysis including 548 one-year BMT survivors,

Tichelli et. al., reported that 3.6% of study patients had an arterial event including CHD, stroke or peripheral vascular disease. The cumulative incidence of CVD was 6% at 15 years after BMT, and was significantly higher in patients who were older at the time of BMT and had CVRFs. However, there were only 20 patients with arterial events in this study and only 12 had CHD.[27] In a previous report from BMTSS in allogeneic BMT survivors, although the prevalence of CVRFs was high, prevalence of arterial events or myocardial infarction was reported to be less than 2%. This is likely due to younger patient population, short follow up time and the long latency required to develop CHD.[12] The current study included 122 post-BMT CHD events, and is the largest report analyzing CHD risk in long-term BMT survivors.

In a previous study, the risk of CVD was reported to be higher after allogeneic BMT with a 15-year cumulative incidence of 7.5% as compared with 2.3% after autologous BMT.[10] In our study, the risk of CHD was higher in autologous BMT survivors, and is likely because autologous BMT survivors were older than allogeneic BMT survivors, and older age was associated with CHD risk in both groups. Age is an independent risk factor for CHD,[28] and is incorporated in the widely used Framingham risk score for CVD risk assessment.[29] Aging is also associated with acquisition of major modifiable risk factors that contribute to development of CVD. Further, presence of CVRFs accentuate the age associated CVD risk, and it has been shown that absence of these risk factors results in reduction of CVD risk.[3] The incidence of CHD is higher in men compared to women at age <50 years. Median age at study participation was 59 years for BMT survivors which explains the elevated risk of CHD in men who underwent BMT in our study.[30]

A previous study comparing the risk of CVD in one-year BMT survivors to the general population showed a high risk of CVRFs; hypertension, dyslipidemia, diabetes and smoking were independent risk factors for ischemic heart disease.[13,14] Our study confirms these findings supporting intensive preventive therapy for CVRF reduction. Healthy lifestyle characteristics attenuated the CVD risk associated with BMT,[14] stressing the importance of diet and physical activity interventions.

Similar to other cancer survivors, chest radiation is associated with an elevated risk of CHD, with a dose response relationship identified in autologous BMT survivors.[31,32] In testicular cancer survivors, cisplatin, vinblastine and bleomycin chemotherapy was associated with an increased risk of myocardial infarction.[33] Pre-BMT treatment with bleomycin was associated with increased CHD risk in allogeneic BMT survivors in our cohort. However, p value was marginally significant and only 2.6% of allogeneic BMT recipients were treated with bleomycin in our study. Education is an indicator of socioeconomic status and low education has been associated with increased CHD risk and as a predictor of adverse outcomes in patients with CHD, affirming our results.[34,35]

The Center for International Blood and Marrow Transplant Research and the European Group for Blood and Marrow Transplantation Late Effects Working Groups guidelines provide consensus recommendations for screening and prevention of metabolic syndrome and CVD in BMT recipients.[36] These guidelines recommend that screening should be made on a case-by-case basis after careful discussion with the patient about the risks and benefits, and recommends routine clinical assessment and CVRF evaluation for all BMT recipients at 1 year and annually thereafter. They acknowledge that given the low incidence of CHD in BMT survivors, likely due to under-reporting

because of attrition in long-term survivors, and due to the limitations in evidence about specific interventions in the BMT population, they recommend a similar approach for CHD assessment as in the general population. Given the high risk of CHD and associated morbidity, clinical trials evaluating the role of frequent screening for CVRFs, aggressive management of modifiable CHD risk factors (e.g., diabetes, hyperlipidemia and hypertension, smoking), screening stress tests among those who received chest radiation, and the role of antiplatelet therapies and statins for primary CHD prevention are of utmost importance in this population.

STRENGTHS

The current study used a large population of BMT survivors with long-term follow up. A comparison group of siblings, representative of the general population enabled assessing CHD risk in populations with presumably similar genetic and environmental risks. We were also able to assess the impact of pre-BMT and BMT-related therapeutic exposures, in addition to sociodemographics, chronic health conditions and health behaviors as risk factors for CHD, which is a major strength of the study.

LIMITATIONS

The study relied on self-report for identifying patients with CHD. However, the validity of the BMTSS questionnaire examined previously showed that BMT survivors were able to report the occurrence of adverse medical conditions with accuracy.[16] Since our study was based on patient surveys, we could not capture complete details regarding clinical presentation and laboratory abnormalities at the time of CHD development. Further, recall bias is also a limitation since the survey was administered several years after BMT. However, since the sibling comparison group also provided self-reported data, there should not have been any systematic differences in bias by case or control status. The survey included information regarding surgical history, physical activity, use of corticosteroids and immunosuppressants by the time of survey completion, but we did not have this information at the time of CHD development. Other known risk factors for CHD such as family history and markers of inflammation were not assessed. The risk of CHD in BMT recipients was conditional on surviving the first 2 years after BMT. Our intention was to determine the risk of CHD in long-term BMT survivors, and BMT recipients who died within the first 2 years were not included in the analysis, likely resulting in an underestimation of CHD risk after BMT, if some events occurred during the first two years.

CONCLUSION

BMT survivors are at a 7 to 12 times the risk of CHD compared with a sibling comparison group suggesting a need for increased awareness of CHD as a late complication of BMT. Older age at BMT, male sex, and CVRFs are independent risk factors for CHD. Pre-BMT chest radiation further increases this risk in autologous BMT recipients. It is particularly important to understand this risk in long-term BMT survivors because of the long latency for development of CVD and proven efficacy of early intervention through life style modifications and strict control of CVRFs.

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APPENDIX A

IRB Approval Letter

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

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APPROVAL LETTER

TO: Bhatia, Smita

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 09-Feb-2021

RE: IRB-160322005
UAB SIRB - Blood or Marrow Transplant Long-Term Follow-up Study - 2

The IRB reviewed and approved the Continuing Review submitted on 26-Jan-2021 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Expedited
Expedited Categories:	3, 5, 7,
Determination:	Approved
Approval Date:	28-Jan-2021
Approval Period:	One Year
Expiration Date:	27-Jan-2022

The following populations are approved for inclusion in this project:

- Children – CRL 1

The following apply to this project related to informed consent and/or assent:

- Waiver of Consent Documentation
- Waiver of HIPAA
- Waiver of Informed Consent

Documents Included in Review:

- CONTINUING REVIEW EFORM

To access stamped consent/assent forms (full and expedited protocols only) and/or other approved documents:
1. Open your protocol in IRAP.
2. On the Submissions page, open the submission corresponding to this approval letter. NOTE: The Determination for the submission will be "Approved."
3. In the list of documents, select and download the desired approved documents. The stamped consent/assent form(s) will be listed with a category of Consent/Assent Document (CF, AF, Info Sheet, Phone Script, etc.)