Clinical risks and healthcare utilization of hematopoietic cell transplantation for sickle cell disease in the USA using merged databases

Staci D. Arnold,[1] Ruta Brazauskas,[2,3] Naya He,[2] Yimei Li,[4] Richard Aplenc,[4] Zhezhen Jin,[41] Matt Hall,[5] Yoshiko Atsuta,[6,7] Jignesh Dalal,[8] Theresa Hahn,[9] Nandita Khera,[10] Carmem Bonfim,[11] Navneet S. Majhail,[12] Miguel Angel Diaz,[13] Cesar O. Freytes,[14] William A. Wood,[15] Bipin N. Savani,[16] Rammurti T. Kamble,[17] Susan Parsons,[18] Ibrahim Ahmed,[8] Keith Sullivan,[19] Sara Beattie,[20] Christopher Dandoy,[21] Reinhold Munker,[22] Susana Marino,[23] Menachem Bitan,[24] Hisham Abdel-Azim,[25] Mahmoud Aljurf,[26] Richard F. Olsson,[27,28] Sarita Joshi,[29] Dave Buchbinder,[30] Michael J. Eckrich,[31] Shahrukh Hashmi,[26,32] Hillard Lazarus,[33] David I. Marks,[34] Amir Steinberg,[35] Ayman Saad,[36] Usama Gergis,[37] Lakshmanan Krishnamurti,[1] Allistair Abraham,[38] Hemalatha G. Rangarajan,[29] Mark Walters,[39] Joseph Lipscomb,[40] Wael Saber[2,*] and Prakash Satwani[5,*]

Co-senior Authors

[1]Emory University Hospital, Atlanta, GA, USA; [2]CIBMTR (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; [3]Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI, USA; [4]University of Pennsylvania, Philadelphia, PA, USA; [5]Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, Department of Pediatrics, Columbia University Medical Center, New York, NY, USA; [6]Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan; [7]Nagoya University Graduate School of Medicine, Japan; [8]Rainbow Babies & Children's Hospital, Cleveland, OH, USA; [9]Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA; [10]Department of Hematology/Oncology, Mayo Clinic, Phoenix, AZ, USA; [11]Hospital de Clinicas-Federal University of Parana, Curitiba, Brazil; [12]Blood & Marrow Transplant Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [13]Department of Hematology/Oncology, Hospital Infantil Universitario Nino Jesus, Madrid, Spain; [14]Texas Transplant Institute, San Antonio, TX, USA; [15]Division of Hematology/Oncology, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA; [16]Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; [17]Divsion of Hematology and Oncology, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX, USA; [18]Tufts Medical Center, Boston, MA, USA; [19]Duke University Medical Center, Durham, NC, USA; [20]University of Ottawa, Canada; [21]Cincinnati Children's Hospital Medical Center, OH, USA; [22]Section of Hematology/Oncology, Department of Internal Medicine, Louisiana State University Health Shreveport, LA, USA; [23]University of Chicago Hospitals, Chicago, IL, USA; [24]Department of Pediatric Hematology/Oncology, Tel-Aviv Sourasky Medical Center, Israel; [25]Division of Hematology, Oncology and Blood & Marrow Transplantation, Children's Hospital of Los Angeles, University of Southern California Keck School of Medicine, CA, USA; [26]Department of Oncology, King Faisal Specialist Hospital Center & Research, Riydah, Saudi Arabia; [27]Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinksa Institutet, Stockholm, Sweden; [28]Centre for Clinical Research Sormland, Uppsala University, Sweden; [29]Pediatric Hematology, Oncology and BMT, Nationwide Children's Hospital and Ohio State University Wexner, Columbus, OH, USA; [30]Division of Pediatrics Hematology, Children's Hospital of Orange County, Orange, CA, USA; [31]Levine Children's Hospital, Charlotte, NC, USA; [32]Department of Internal Medicine, Mayo Clinic, Minneapolis, MN, USA; [33]Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, OH, USA; [34]Adult Bone Marrow Transplant, University Hospitals Bristol NHS Trust, Bristol, United Kingdom; [35]Department of Hematology-Oncology, Mount Saini Hospital, New York, NY, USA; [36]Division of Hematology/Oncology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; [37]Hematologic Malignancies & Bone Marrow Transplant, Department of Medical Oncology, New York Presbyterian Hospital/Weill Cornell Medical College, New York, NY, USA; [38]Division of Blood and Marrow Transplantation, Center for Cancer and Blood Disorders, Children's National Medical Center, Washington, DC, USA; [39]Children's Hospital & Research Center Oakland, Oakland, NY, USA; [40]Health Policy and Management, Rollins School of Public Health, Winship Cancer Institute, Emory University, Atlanta, GA, USA and [41]Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY, USA.

 doi:10.3324/haematol.2017.169581

Received: March 23, 2017.

Accepted: August 10, 2017.

Pre-published: August 17, 2017.

Correspondence: wsaber@mcw.edu

Supplemental Data

eTable A.1 Characteristics of pediatric patients (age≤21) receiving first allogeneic hematopoietic cell transplant for sickle cell disease in USA reported to the CIBMTR between 2000 and 2013 (*CRF only*)

Variable	Related cord blood (N=22)	Unrelated cord blood (N=33)	HLA identical sibling (N=67)	Well-matched unrelated (N=27)	Other Unrelated (N=11)
Patient related					
Age, median, years	6 (2-11)	9 (1-19)	10 (<1-19)	13 (6-19)	13 (3-21)
Age at transplant, years					
<10	21 (95)	19 (58)	36 (54)	7 (26)	2 (18)
≥10	1 (5)	14 (42)	31 (46)	20 (74)	9 (82)
Gender					
Male	13 (59)	15 (45)	34 (51)	15 (56)	4 (36)
Female	9 (41)	18 (55)	33 (49)	12 (44)	7 (64)
Karnofsky/Lansky score prior to transplant, %					
>90	11 (50)	20 (61)	39 (58)	14 (52)	7 (64)
<=90	9 (41)	10 (30)	19 (28)	10 (37)	3 (27)
Missing	2 (9)	3 (9)	9 (13)	3 (11)	1 (9)
Disease related					
Transplant Indication					
Stroke	6 (27)	7 (21)	19 (28)	12 (44)	3 (27)
Acute chest syndrome	3 (14)	7 (21)	5 (7)	2 (7)	1 (9)
Recurrent vaso-occlusive pain	5 (23)	6 (18)	14 (21)	9 (33)	1 (9)
Other, specify*	6 (27)	11 (33)	19 (28)	3 (11)	5 (45)
Missing	2 (9)	2 (6)	10 (15)	1 (4)	1 (9)
Sickle Cell Genotype					
HbSS	21 (95)	25 (76)	58 (87)	22 (81)	10 (91)
HbS beta thalassemia	0	4 (12)	4 (6)	1 (4)	1 (9)
Other genotype**	1 (5)	3 (9)	3 (4)	3 (11)	0
Missing	0	1 (3)	2 (3)	1 (4)	0
Chronic transfusion					
No	11 (50)	7 (21)	26 (39)	5 (18)	3 (27)

Variable	Related cord blood (N=22)	Unrelated cord blood (N=33)	HLA identical sibling (N=67)	Well-matched unrelated (N=27)	Other Unrelated (N=11)
Yes	10 (45)	26 (79)	38 (57)	21 (78)	8 (73)
Missing	1 (5)	0	3 (4)	1 (4)	0
Hydroxyurea					
No	16 (73)	14 (42)	40 (60)	7 (26)	5 (45)
Yes	5 (23)	18 (55)	24 (36)	19 (70)	5 (45)
Missing	1 (5)	1 (3)	3 (4)	1 (4)	1 (9)
Sickle cell related complications					
ACS $\pm$ vaso-occlusive pain	8 (36)	15 (45)	25 (37)	9 (33)	4 (36)
Stroke $\pm$ ACS $\pm$ vaso-occlusive pain	6 (27)	14 (42)	23 (33)	11 (41)	4 (36)
Vaso-occlusive pain only	3 (14)	1 (3)	10 (15)	3 (11)	1 (9)
None	3 (14)	3 (9)	6 (9)	1 (4)	1 (9)
Missing	2 (9)	0	3 (4)	3 (11)	1 (9)
Transplant related					
Time from diagnosis to transplant (months)	71 (21-115)	106 (7-223)	116 (10-229)	156 (20-232)	144 (15-242)
Conditioning					
Myeloablative (Bu/Cy, Bu/Flu, or Mel-based)	17 (77)	16 (49)	54 (81)	4 (15)	4 (36)
Reduced Intensity (Flu/Mel or Bu/Flu-based)	5 (23)	15 (45)	7 (10)	21 (78)	6 (55)
Non-myeloablative (Flu-based)	0	2 (6)	6 (9)	2 (7)	1 (9)
Graft Source					
Bone Marrow	0	0	62 (93)	27	7 (64)
Peripheral Blood	0	0	5 (7)	0	4 (36)
Cord Blood	22	33	0	0	0
Donor/Recipient CMV match					
-/-	5 (23)	7 (21)	26 (39)	7 (26)	2 (18)
-/+	2 (9)	7 (21)	9 (13)	4 (15)	2 (18)
+/-	2 (9)	7 (21)	13 (19)	7 (26)	2 (18)
+/+	9 (41)	6 (18)	18 (27)	5 (18)	3 (27)
Missing	4 (18)	6 (18)	1 (1)	4 (15)	2 (18)
Year of transplant					
2000-2006	5 (24)	4 (12)	31 (44)	1 (4)	1 (9)

Variable	Related cord blood (N=22)	Unrelated cord blood (N=33)	HLA identical sibling (N=67)	Well-matched unrelated (N=27)	Other Unrelated (N=11)
2007-2013	17 (79)	29 (87)	36 (53)	26 (96)	10 (90)
ATG / CAMPATH					
ATG alone	18 (82)	12 (36)	48 (72)	2 (7)	2 (18)
CAMPATH alone	4 (18)	18 (55)	15 (22)	22 (81)	9 (82)
No ATG or CAMPATH	0	3 (9)	4 (6)	3 (11)	0
GVHD Prophylaxis					
Ex-vivo T cell depletion	0	0	2 (3)	0	0
CD34 selection	0	0	2 (3)	0	2 (18)
Cyclophosphamide	0	0	1 (1)	0	0
FK506 $\pm$ MMF $\pm$ others	3 (14)	16 (48)	18 (27)	14 (52)	6 (54)
CSA $\pm$ MMF $\pm$ others	17 (77)	17 (51)	40 (60)	11 (41)	3 (27)
Others	1 (5)	0	1 (1)	0	0
Missing	1 (5)	0	3 (4)	2 (7)	0
Median follow-up of survivors (range), months	47 (12-103)	48 (6-138)	60 (3-138)	25 (6-73)	36 (5-61)

Footnote: 1 patient with donor type information missing is excluded from this table.

Abbreviations: CIBMTR= CRF= comprehensive research form, ACS= Acute Chest Syndrome, BU=Busulfan, CY=Cyclophosphamide, FLU=Fludarabine, MEL=Melphalan, CMV=Cytomegalovirus, ATG=Antithymocyte globulin, GVHD - graft versus host disease, CSA=Cyclosporine, MMF=Mycophenolate mofetil, FK506=Tacrolimus, MTX= Methotrexate

*__Related cord blood__: abnormal transcranial Doppler(n=1); excessive transfusion requirements (n=3); fever, ileus and mild chest syndrome or pneumonia(n=1); parents wanted a cure for their child's sickle cell disease(n=1);

__Unrelated cord blood:__ excessive transfusion requirements (n=6); cerebral vasculopathy(n=1); combination of acute chest and pain crisis (chronically ill) (n=1); extensive complications from sickle cell(n=1); rare disease type(n=1); best long-term, lifelong option for patient (n=1);

__HLA identical sibling:__ recurrent priapism (n=1); abnormal tcd- mri/mra with narrowing of supraclinoid portions of the internal carotid arteries bilat(n=1); excessive transfusion requirements (n=5); acute chest syndrome; pain; transfusions(n=1); cardiomyopathy/pulmonary stenosis(n=1); cranial vasculopathy therefore stroke prevention(n=1); develop allo antibodies, increasing hgb, decreased response to hydroxyurea (n=1); elevated transcranial Doppler(n=1); family wanted to move back to nigeria where there is not modern care nor safe transfusion(n=1); increased frequency of pain crisis, at significant risk end organ damage and dysfunction in adulthood(n=1); matched sib and hx pain crisis(n=1); pain; avn; mri changes; to correct sickle cell disease(n=1); presence of silent infarcts on mri(n=1); sickle cell disease(n=1);

__Well-matched unrelated:__ excessive transfusion requirements (n=1); both acute chest and pain crisis(n=1); improved quality of life(n=1);

__Other unrelated:__ excessive transfusion requirements (n=2); cure sickle cell (n=1); liver transplant (n=1); osteonecrosis/requiring hip replacement neuropathy-vision loss (n=1)

** __Related cord blood:__ HbSC (n=1);

__Unrelated cord blood:__ HbS beta+ thalassemia (n=1); HbSC (n=1); HbSHakkari (BETA 31 LEU -> ARG) (n=1);

__HLA identical sibling:__ HbSbarts (n=1); HbSC (n=1)

__Well-matched unrelated:__ HbSC (n=1); HbSDPunjabi (n=1); HbSOArab (n=1)

eTable A.2 Characteristics of pediatric patients (age≤ 21) receiving first allogeneic hematopoietic cell transplant for sickle cell disease in USA registered with CIBMTR between 2000 and 2011 (*TED/PHIS*)

Variable	Related cord blood (N=15)	Unrelated cord blood (N=20)	HLA identical sibling (N=126)	Well-matched unrelated (N=10)	Other Unrelated (N=7)
Patient related					
Age, median, years	6 (2-11)	10 (2-19)	9 (<1-20)	12 (6-19)	11 (4-17)
Age at transplant, years					
<10	14 (93)	12 (60)	69 (55)	3 (30)	2 (29)
≥10	1 (7)	8 (40)	57 (45)	7 (70)	5 (71)
Gender					
Male	9 (60)	13 (65)	69 (55)	6 (60)	1 (14)
Female	6 (40)	7 (35)	57 (45)	4 (40)	6 (86)
Karnofsky/Lansky score prior to transplant, %					
≥80	14 (93)	15 (75)	114 (90)	10	6 (86)
<80	0	2 (10)	0	0	0
Missing	1 (7)	3 (15)	12 (10)	0	1 (14)
Transplant related					
Time from diagnosis to transplant	68 (21-130)	116 (29-195)	112 (10-227)	137 (72-224)	157 (136-178)
Conditioning					
Myeloablative (Bu/Cy, Bu/Flu, Mel, or Flu±TBI-based)	12 (80)	9 (45)	97 (77)	2 (20)	1 (14)
Reduced Intensity (Bu/Flu, Mel, or Flu/TBI-based)	3 (20)	11 (55)	26 (21)	7 (70)	6 (86)
Non-myeloablative (Flu-based)	0	0	1 (1)	1 (10)	0
Missing	0	0	1 (1)	0	0
Donor/Recipient CMV match					
-/-	2 (13)	4 (20)	44 (35)	3 (30)	1 (14)
-/+	1 (7)	2 (10)	12 (10)	2 (20)	2 (29)
+/-	2 (13)	4 (20)	11 (9)	3 (30)	1 (14)
+/+	7 (47)	4 (20)	37 (29)	1 (10)	1 (14)
Missing	3 (20)	6 (30)	22 (17)	1 (10)	2 (29)

Variable	Related cord blood (N=15)	Unrelated cord blood (N=20)	HLA identical sibling (N=126)	Well-matched unrelated (N=10)	Other Unrelated (N=7)
Graft Source					
Bone Marrow	0	0	126	10	4 (57)
Peripheral Blood	0	0	0	0	3 (43)
Cord Blood	15	20	0	0	0
Year of transplant					
2000-2006	2 (14)	5 (25)	43 (34)	1 (10)	3 (43)
2007-2011	13 (86)	2 (75)	83 (66)	9 (90)	4 (57)
Ex vivo T-cell depletion					
No	15	20	125 (99)	10	6 (86)
Yes	0	0	1 (<1)	0	1 (14)
GVHD Prophylaxis					
FK506 based	1 (7)	7 (35)	26 (21)	3 (30)	0
CSA based	14 (93)	12 (60)	94 (75)	5 (50)	7
Others	0	0	2 (2)	0	0
Missing	0	1 (5)	4 (3)	2 (20)	0
Median follow-up of survivors (range), months	47 (17-94)	55 (24-105)	49 (11-137)	53 (24-73)	59 (47-145)

Footnote: 5 patients with donor type information missing are excluded from this table.

Abbreviations: CIBMTR= TED= transplant essential data, PHIS= pediatric health information system, ATG=Antithymocyte globulin, BU=Busulfan, CY=Cyclophosphamide, FLU=Fludarabine, MEL=Melphalan, CMV=Cytomegalovirus, GVHD - graft versus host disease, CSA=Cyclosporine, FK506=Tacrolimus

eTable B. Incidence of transplant related outcomes

	Study population (N = 161)	
Outcomes	N Eval	Prob (95% CI)
Neutrophil engraftment	161	
28-day		85 (79-90)%
100-day		100%
Platelet recovery	158	
100-day		94 (90-98)%
Grade 2-4 acute GVHD	159	
100-day		19 (13-26)%
Grade 3-4 acute GVHD	160	
100-day		14 (9-20)%
Chronic GVHD	156	
1-year		26 (19-33)%
2-year		31 (23-38)%
3-year		31 (23-38)%[1]
GREFS	158	
1-year		68 (61-75)%
2-year		64 (56-71)%
3-year		63 (55-70)%
Overall survival	161	
1-year		94 (89-97)%
2-year		90 (85-95)%
3-year		89 (83-93)%

[1] Actual last event occurred in 22 months.

GVHD - graft versus host disease, GREFS - the survival free of graft failure, chronic GVHD, or death

eTable C. Characteristic of patients who died after transplant

	CRF N(%)	TED/PHIS N(%)
Number of patients	16	14
Age, median, years	16 (5-19)	15 (4-19)
Time of death, median, days	9 (<1-30)	
Time of death,		
within 3 months	3 (19)	
3-6 months	2 (13)	
6-12 months	5 (31)	
12-24 months	4 (25)	
24-36 months	2 (13)	
Causes of death		
GVHD	1 (6)	
Infection	4 (25)	
Organ failure	6 (38)	
Other cause	4 (25)	
Unknown	1 (6)	
Gender		
Male	4 (25)	4 (29)
Female	12 (75)	10 (71)
Donor type		
Cord blood (unrelated)	3 (19)	4 (29)
HLA identical sibling	4 (25)	5 (36)
Well-matched unrelated	7 (44)	2 (14)
Mismatched unrelated	1 (6)	2 (14)
Unrelated (matching cannot be determined)	1 (6)	-
Missing		1 (7)
Graft Source		
Bone Marrow	11 (69)	9 (64)
Peripheral Blood	2 (13)	1 (7)
Cord Blood (unrelated)	3 (19)	4 (29)
Year of transplant		
2001-2006	2 (13)	5 (36)
2007-2013	14 (87)	9 (64)
Sickle cell related complications		
Acute Chest Syndrome	1 (6)	-
Stroke	4 (25)	-
Vaso-occlusive pain	1 (6)	9 (64)
Acute Chest Syndrome+Vaso-occlusive pain	4 (25)	4 (29)
Stroke+Vaso-occlusive pain	2 (13)	4 (29)
Acute Chest Syndrome+Stroke+Vaso-occlusive pain	2 (13)	-
Missing	2 (13)	

CRF – comprehensive research form, TED – transplant essential data, PHIS – pediatric health information system, GVHD - graft versus host disease

eTable D. Severity determinations

Severity	Age <10yrs	Age>10yrs
Low (N=36)	36	-
Moderate (N=68)	48	20
ACS	2	-
VOC (3)	30	-
ACS and VOC	16	-
No disease sequelae	-	20
High (N=79)	17	62
ACS	-	-
VOC (3)	-	32
ACS and VOC	-	18
Stroke	5	2
Stroke and ACS or VOC	12	10

ACS – acute chest syndrome, VOC – vaso-occlusive crises

eTable E. Comparison of available pre- and post-allogeneic hematopoietic cell transplant inpatient healthcare utilization per 30 days among high severity patients based on PHIS reporting

	Cases (per 30d)		
	Pre- AlloHCT (N=30, mean(SD) median[IQR])	Post- AlloHCT (N=30, mean(SD) median[IQR])	Wilcoxon Signed rank test p-value
Inpatient visit	0.86(0.61) 0.73 [0.33, 1.50]	0.17(0.19) 0.11 [0.07,0.17]	<0.001
Length of stay	2.75 (2.70) 1.97 [1.05, 3.42]	0.90(1.21) 0.40 [0.20, 1.15]	<0.001
Inpatient total adjusted cost ($)	22,646.73 (26,936.30) 10,870.25 [5,773.39; 31,858.02]	9,064.19 (14,311.61) 1,971.93 [794.59; 17,277.86]	<0.001
Clinical	1,259.47 (1,625.38) 563.25 [63.07; 2,115.17]	969.34(1,883.29) 108.70 [45.93, 343.97]	0.440
Pharmacy	6,991.84 (13,758.01) 1,977.16 [553.79; 5,205.95]	3,013.03 (6,078.37) 306.44 [80.50; 3,653.89]	0.014
Imaging	1,322.05 (1,683.49) 639.09 [227.18; 1,465.76]	453.34 (793.90) 78.78 [4.53, 494.81]	0.006
Lab	4,443.67 (6,380.53) 1,792.14 [718.44; 5,635.39]	1,453.58 (2,505.04) 319.16 [107.39; 2,142.88]	0.002
Supply	1,300.34 (1,696.71) 634.03 [185.30; 1,677.37]	167.89 (300.39) 68.65 [23.92, 214.52]	<0.001
Other	7,319.00 (6,780.53) 4,303.05 [2,349.22; 9,005.71]	2,996.82 (4,196.97) 1,033.90 [317.72; 4,331.30]	<0.001

PHIS – pediatric health information system, AlloHCT – hematopoietic cell transplant, SD – standard deviation, IQR – interquartile range

Figure legend

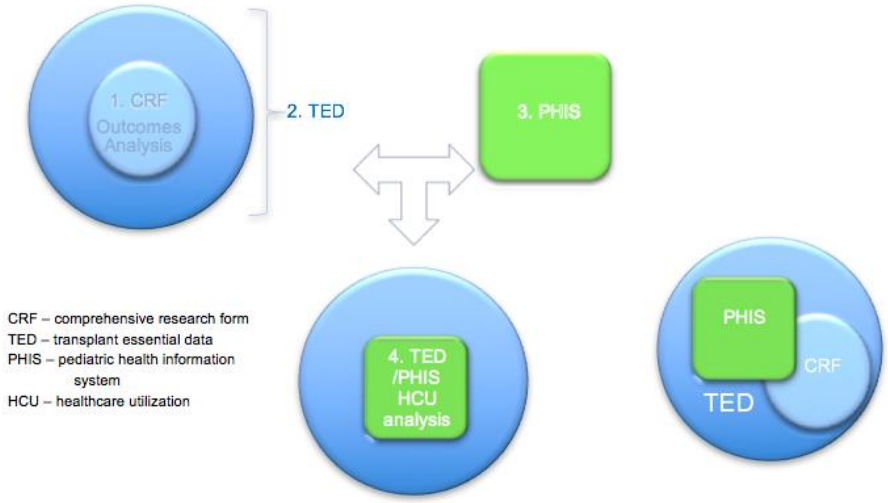
A. Provides a flow diagram of the various data sources used for study analysis. Outcomes data for analysis was provided by information in CRFs from CIBMTR; while healthcare utilization analysis included combined data from PHIS and TED forms from CIBMTR. This dual analysis was largely due to the minimal overlap between PHIS and CRF data.

B. Within the TED/PHIS healthcare utilization data, specific data sources were used in each transplant period. All data for descriptive analysis of healthcare utilization was provided by PHIS. PHIS was also used to make disease severity determinations; while, TED was used to compare transplant related variables (i.e., donor type, conditioning, etc.).

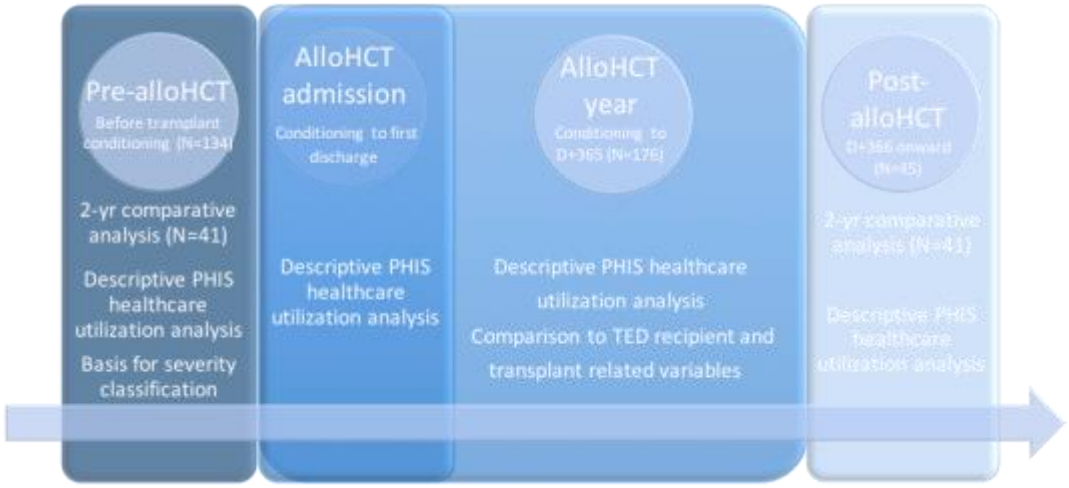
C. Depicts the statistically significant difference in overall survival between all transplant recipients and recipients by donor type with HLA identical sibling and cord blood showing the highest survival.

D. Describes the different sources of inpatient cost in each transplant period with similar distributions of cost with the exception of larger inpatient pharmacy cost in the alloHCT year.

eFigure A. Depiction of data sources and analysis

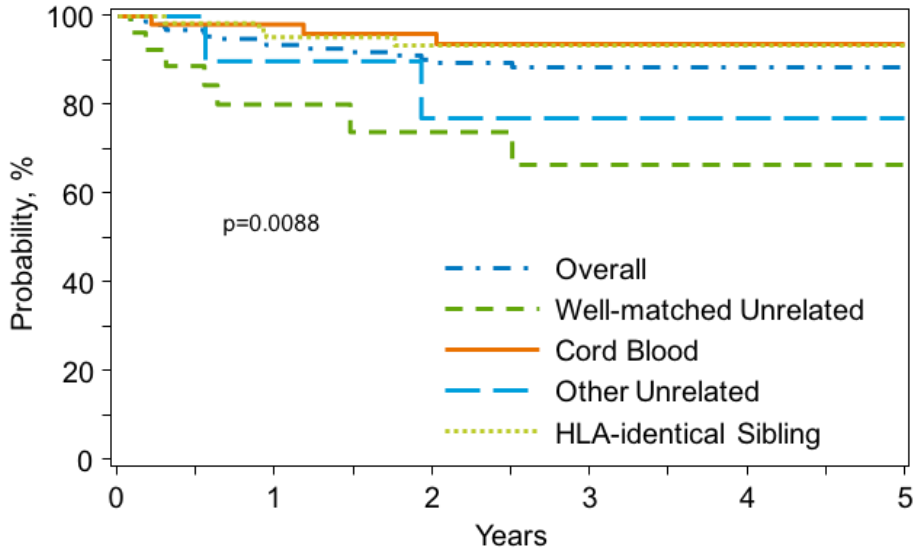


eFigure B. Phases of TED/PHIS Healthcare Utilization Analysis



TED – transplant essential data, PHIS – pediatric health information system, AlloHCT – hematopoietic cell transplant

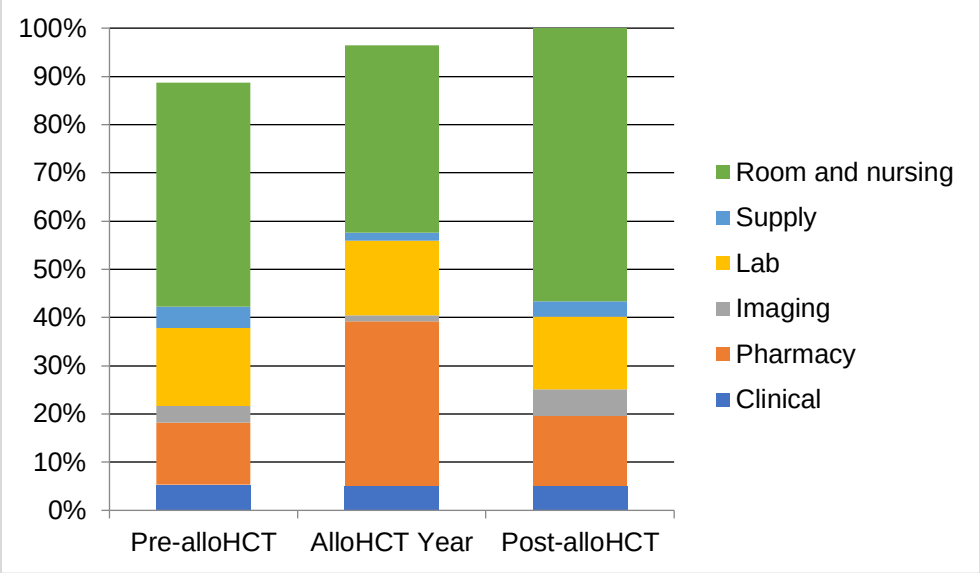
**eFigure C. ***Overall survival by donor group (CRF)



CRF – comprehensive research form

*Overall survival was calculated using the Kaplan-Meier product limit estimate.

eFigure D. Distribution of costs during study periods



AlloHCT – hematopoietic cell transplant