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Predictors of lost to follow-up among pediatric and adult hematopoietic cell transplant survivors: A report from the Center for International Blood and Marrow Transplant Research

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Abstract

Background—Follow-up is integral for hematopoietic cell transplant (HCT) care to ensure surveillance and intervention for complications. We characterized the incidence of, and predictors for, being lost to follow-up.

Methods—Two-year survivors of first allogeneic (10,367 adults and 3,865 children) or autologous (7,291 adults and 467 children) HCT for malignant/non-malignant disorders from 2002–2013 reported to the Center for International Blood and Marrow Transplant Research were selected. The cumulative incidence of being lost to follow-up (defined as having missed 2 consecutive follow-up reporting periods) was calculated. Marginal Cox models (adjusted for center effect) were fit to evaluate predictors.

Results—The 10-year cumulative incidence of being lost to follow-up among adult allogeneic and autologous HCT survivors was 13% (95% CI, 12–14) and 15% (95% CI, 14–16), respectively. Among pediatric HCT survivors, estimates were 25% (95% CI, 24–27) and 24% (95% CI, 20–29), respectively. In adult allogeneic HCT survivors, younger age, non-malignant disease, public/no insurance (reference: private), living farther from the HCT center, and being unmarried were associated with being lost to follow-up. For adult autologous HCT survivors, older age and testicular/germ cell tumor (reference: non-Hodgkin lymphoma) were associated with greater risk of being lost to follow-up. Among pediatric allogeneic HCT survivors, older age, public/no insurance (reference: private), and non-malignant disease were associated with being lost to follow-up. Among pediatric autologous HCT survivors, older age was associated with greater risk of being lost to follow-up.

Conclusion—Follow-up focusing on minimizing attrition in high-risk groups is needed to ensure surveillance for late effects.

Keywords

Bone marrow transplantation; stem cell transplantation; survivors; lost to follow-up

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Conflict of Interest Disclosure

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Introduction

By 2030, it is estimated that there will be 0.5 million hematopoietic cell transplant (HCT) survivors in the United States (US) [1]. Despite the increasing survival rates of HCT recipients, there is ongoing risk for early morbidity related to acute graft-versus-host disease (GVHD) and late morbidity related to late effects including cardiovascular, gastrointestinal, endocrinologic dysfunction, psychosocial distress, and risk of subsequent malignant neoplasms [2–4]. Follow-up is an integral part of HCT care which ensures surveillance and intervention for early and late complications [5]. Among populations with chronic health conditions [6–9] as well as non-HCT cancer survivors [10], studies have characterized the proportion of survivors that are lost to follow-up and risk factors for being lost to follow-up.

An overall assessment of the number of HCT survivors that are lost to follow-up is needed. Information is also needed to identify HCT survivors at greatest risk for being lost to follow-up. The Center for International Blood and Marrow Transplant Research (CIBMTR) Registry, the largest sample of HCT recipients, has the potential to be a vital resource in the characterization of lost to follow-up patterns among HCT survivors. These analyses provide the first characterization of, and predictors for being lost to follow-up among HCT survivors reported to the CIBMTR. The primary objective of this study was to estimate the cumulative incidence of being lost to follow-up among HCT survivors. A secondary aim was to identify patient, disease, and HCT-related factors that predict being lost to follow-up.

Methods

Study Design, Setting, and Data Source

CIBMTR represents a voluntary working group of more than 500 HCT centers worldwide that contribute detailed data on consecutive allogeneic and autologous HCT procedures to a Statistical Center at the Medical College of Wisconsin and the NMDP Coordinating Center. Centers that participate in CIBMTR report all transplants consecutively. Participants are followed longitudinally. Data quality is ensured by the completion of computerized checks for discrepancies, physicians' review of submitted data, and on-site audits. Studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of CIBMTR research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

The CIBMTR collects data which includes disease type, age, sex, pre-transplant disease stage and chemotherapy-responsiveness, diagnosis date, graft type, conditioning regimen, post-HCT disease progression and survival, development of a subsequent malignancy, and cause of death. More detailed disease and pre- and post-HCT clinical information is collected on a subset of CIBMTR patients sampled using a weighted randomization scheme. Data are collected at specific intervals including pre-HCT, 100 days post-HCT, six months post-HCT, and annually for the first 6 years post-HCT and biennially thereafter or until death.

Study Population

Two-year survivors were selected if they had received a first HCT for malignant and non-malignant disorders performed in the US from 2002–2013 and reported to the CIBMTR. Adult (≥18 years of age at the time of HCT) and pediatric (<18 years of age at the time of HCT) recipients of autologous and allogeneic HCT were included in these analyses. Overall, 14,232 (10,367 adults and 3,865 pediatric) allogeneic HCT recipients and 7,758 (7,291 adult and 467 pediatric) autologous HCT recipients met the study eligibility criteria.

Study Endpoint

The primary outcome was lost to follow-up status which was defined as a patient having missed 2 consecutive follow-up reporting periods (using the date of last contact).

Independent Variables

Sociodemographic variables considered included: patient's age at the time of HCT, sex, Karnofsky/Lansky performance status pre-HCT, race, median income of the ZIP code where the HCT recipient resides (obtained from US census data) [11], health insurance status, marital status, and distance from HCT survivor's home to their HCT center (estimated as the geodetic distance in miles between the two ZIP code locations – that of the patient and the transplant center). The centroid of each ZIP code is used in the calculation [12]. Disease and HCT-related variables included disease type as well as year of transplant.

Statistical Analyses

Descriptive statistics were calculated for sociodemographic, disease, and HCT-related variables. Cumulative incidence of being lost to follow-up for HCT recipients was estimated treating death as a competing event. Cumulative incidence estimates accompanied by 95% confidence intervals are provided. For the multivariable analyses, marginal Cox models were constructed to adjust for center effect. Individual models were constructed for four distinct populations: 1) adult allogeneic HCT survivors, 2) adult autologous HCT survivors, 3) pediatric allogeneic HCT survivors, and 4) pediatric autologous HCT survivors. Backward model selection procedures with an $\alpha < 0.05$ was used to identify significant independent variables to be included in the final models. SAS version 9.4 (Cary, NC) was used for all analyses.

Results

Patient, disease, and transplant characteristics

Patient, disease, and HCT-related characteristics of the study population are summarized in Table 1A, B. Among 2-year adult HCT survivors, the median age at the time of HCT was 49 years (range, 18–81) and 58 years (range, 18–82) for allogeneic and autologous patients, respectively. Corresponding median follow-up was 80 months (range, 24–174) and 85 months (range, 24–175). For adults, the majority of allogeneic HCT procedures were completed for acute myelogenous leukemia (35%). For adult survivors the majority of autologous HCT procedures were completed for multiple myeloma (65%). The majority of

adult allogeneic and autologous HCT survivors were covered by private health insurance (64% and 57%, respectively).

For 2-year pediatric HCT survivors, the median age at the time of HCT was 7 years (range, <1–18) and 5 years (range, <1–18) for the allogeneic and autologous survivors, respectively. Corresponding median follow-up was 77 months (range, 24–175) and 76 months (range, 24–173). For pediatric HCT survivors the majority of allogeneic HCT procedures were completed for acute lymphoblastic leukemia (22%). For pediatric survivors the majority of autologous HCT procedures were completed for central nervous system tumors (78%) which included neuroblastoma. Slightly less than half (43%) of pediatric allogeneic HCT survivors were covered by private health insurance while nearly half of the pediatric autologous HCT survivors had public insurance (48%).

The Cumulative Incidence of Lost to Follow-up

Figure 1 depicts the cumulative incidence of being lost to follow-up since HCT by age at the time of HCT (adult versus pediatric) and by type of HCT (allogeneic versus autologous) among 2-year survivors.

The 3-year, 5-year, and 10-year cumulative incidence of being lost to follow-up post-HCT among adult allogeneic HCT survivors was 2% (95% confidence interval [CI], 1–2), 5% (95% CI, 5–6), and 13% (95% CI, 12–14). Among adult autologous HCT survivors, the 3-year, 5-year, and 10-year cumulative incidence of being lost to follow-up post-HCT was 2% (95% CI, 2–3), 7% (95% CI, 7–8), and 15% (95% CI, 14–16).

For pediatric allogeneic HCT survivors the 3-year, 5-year, and 10-year cumulative incidence of being lost to follow-up post-HCT was 3% (95% CI, 2–3), 11% (95% CI, 10–12), and 25% (95% CI, 24–27). For pediatric autologous HCT survivors the 3-year, 5-year, and 10-year cumulative incidence of being lost to follow-up post-HCT was 4% (95% CI, 2–6), 12% (95% CI, 9–15), and 24% (95% CI, 20–29).

Risks factors for Lost to Follow-up

Risk factors for lost to follow-up among adult allogeneic and autologous HCT survivors as well as pediatric allogeneic and autologous HCT survivors are depicted in Tables 2–5.

For adult allogeneic HCT survivors, younger age at the time of HCT was significantly associated with greater risk of being lost to follow-up (41–50 years versus 51+ years: HR 1.38; 95% CI 1.14–1.67, and 18–40 years versus 51+ years: HR 2.19; 95% CI 1.80–2.66). Diagnosis of non-malignant disease was associated with greater risk of lost to follow-up when compared to malignant diseases excluding chronic lymphocytic leukemia (HR 1.52; 95% CI 1.18–1.94). Compared to adult allogeneic HCT survivors with private health insurance, public (HR 1.29; 95% CI 1.13–1.48) or no insurance (HR 2.33; 95% CI 1.30–4.17) was significantly associated with higher risk of lost to follow-up. Living from the HCT center 100+ miles away (HR 1.39; 95% CI 1.11–1.72) compared to living 0–99 miles away from the HCT center was associated with greater risk of lost to follow-up. Unmarried (single/divorced/widowed) HCT survivors were significantly more likely to be lost to follow-up (HR 1.26; 95% CI 1.09–1.46).

For adult autologous HCT survivors, older age at the time of HCT was significantly associated with risk of being lost to follow-up. Specifically, patients 21–30 years of age had significantly greater risk of being lost to follow-up as compared to those transplanted at 18–20 years of age (Hazard Ratio [HR] 2.26; 95% CI 1.17–4.34). As compared to NHL patients, a diagnosis of a testicular or germ cell tumor was associated with greater risk of lost to follow-up (HR 1.95; 95% CI 1.32–2.87) whereas a diagnosis of multiple myeloma (reference: NHL) was associated with decreased risk of lost to follow-up (HR 0.72; 95% CI 0.56–0.92).

Among pediatric allogeneic HCT survivors, age 10–17 years at the time of HCT (reference: <10 years) was significantly associated with higher risk of being lost to follow-up (HR 1.97; 95% CI 1.65–2.36). Compared to those pediatric allogeneic HCT survivors with private health insurance, publicly insured (HR 1.34; 95% CI 1.09–1.63) or uninsured (HR 3.53; 95% CI 2.11–5.92) were significantly more likely to be lost to follow-up. Non-malignant disease was associated with greater risk of becoming lost to follow-up compared to patients diagnosed with malignant diseases (HR 1.25; 95% CI 1.05–1.49).

Among pediatric autologous HCT survivors age 11–17 years at the time of HCT (reference: < 11 years) was associated with greater risk of lost to follow-up (HR 1.72; 95% CI 1.01–2.93). Male gender was associated with greater risk of being lost to follow-up (HR 1.57; 95% CI 0.99–2.49) although this achieved only marginal statistical significance. A diagnosis of a central nervous system tumor (reference: lymphoma) was associated with decreased risk of being lost to follow-up (HR 0.55; 95% CI 0.34–0.90).

Discussion

We demonstrate that the cumulative incidence of lost to follow-up in the US is high at 10-years (e.g., ~25% among pediatric HCT survivors). Among pediatric HCT survivors follow-up may be even more important given the longer life expectancy. Adolescent and young adult age appeared to be associated with lost to follow-up among pediatric and adult autologous and allogeneic HCT survivors. Public health insurance or a lack of health insurance was associated with increased risk of lost to follow-up among both pediatric and adult allogeneic HCT survivors, whereas being unmarried and living at a greater distance from the HCT center was associated with greater lost to follow-up risk among only adult allogeneic HCT survivors. Non-malignant disorders were associated with greater risk of lost to follow-up among pediatric and adult allogeneic HCT survivors.

Over time survivors may perceive that their susceptibility to late effects is diminished [13]. Many late effects have a long latency period prior to manifestation [3–4] underscoring the importance of regular surveillance for late effects for an extended period following HCT [5,14]. Becoming lost to follow-up can diminish opportunities to prevent late effects or to limit the progression of late effects. Efforts are needed to ensure the retention of all HCT survivors in follow-up HCT care. Examples include the use of dedicated resources (e.g., specialized staff) to identify at-risk survivors or outreach efforts focused on those that are lost to follow-up or their referring providers [15]. Efforts to educate survivors about the importance of surveillance for late effects may also be beneficial [16]. Few HCT centers

have long-term follow-up programs; however, these may also provide an important structure to minimize lost to follow-up [14,17–18].

Our findings suggest that adolescent and young adult-aged HCT survivors may be at risk for lost to follow-up. Data document similar findings across other chronic disease populations [19–20] including non-HCT cancer survivors [21–23]. Among non-HCT cancer survivors, barriers to the provision of follow-up care for adolescent and young adult-aged survivors are numerous such as cost and a lack of health insurance, transition of care away from a parental locus of control, competing responsibilities, diminished perceived vulnerability to late effects, and lack of providers that are comfortable providing care to aging pediatric HCT survivors. For adolescent and young adult-aged HCT survivors there is a need to develop age appropriate approaches to HCT survivor care [24–26]. Strategies aimed at engaging survivors through the delivery of text messages, emails, and app notifications are examples [27–28]. Transitioning programs may also provide an important structure to minimize the lost to follow-up among this population [29].

Those children and adults with public or a lack of health insurance who were survivors of allogeneic HCT experienced greater risk for lost to follow-up. In general, children and adults with public insurance experience notable delays in obtaining necessary care [30–31]. Pediatric and adult allogeneic HCT survivors with public or a lack of health insurance may continue to face financial hardships or other challenges related to a lack of socioeconomic resources when compared to children and adult HCT survivors with private insurance [32]. Further research is needed to evaluate potential strategies that can be used to improve access to care and ensure health care delivery to these underserved populations of HCT survivors [33].

Given the complexity of the HCT process many patients that require post-HCT care are unable to receive care locally and may have to travel to specialized centers to receive care. HCT survivors face a variety of physical, psychological, and social barriers (e.g., getting time off work, lack of transportation) that influence the ability to travel a long distance to seek care at their respective HCT center [34]. Improving clinic efficiency to engage survivors [35], the provision of affordable transportation alternatives for HCT survivors, greater use of telemedicine, or the establishment of satellite clinics [36] may be valuable approaches to mitigate the burden of distance and its impact on lost to follow-up. Facilitating long-term follow-up care at a center near the HCT survivor may also be a valuable approach using survivorship care plans and the education of non-HCT providers [37–38].

Across many chronic disease populations, it has been documented that married or partnered persons tend to experience better physical, mental, and social health outcomes [39]. For example, married individuals with chronic health conditions may experience greater social support. A recent study from the CIBMTR found that marital status was not associated with overall survival and graft-versus-host disease risk among HCT survivors [40]. Despite these findings, given the resource intensive nature of the allogeneic HCT process, caregivers such as spouses or partners remain critical to supporting the retention of survivors in long-term follow-up.

Pediatric and adult allogeneic HCT survivors with non-malignant disease may perceive that they are cured and that their susceptibility to late effects is minimal. Moreover, adult autologous HCT recipients with a diagnosis of testicular or germ cell tumors are often exposed to limited outpatient therapy and may perceive that they are cured without susceptibility to late effects. On the other hand, pediatric patients with central nervous system tumors and adult patients with indolent diseases such as chronic lymphocytic leukemia and multiple myeloma may not be lost to follow-up due to the nature of their diseases (e.g., need for ongoing maintenance therapy and likelihood of relapse). Greater efforts are needed to educate survivors and their families about the importance of adequate surveillance for complications which may occur following HCT.

Limitations

We were unable to evaluate potentially important factors (e.g., educational attainment, current health status, and the presence of a long-term follow-up program) that may be associated with being lost to follow-up. The possibility of under-reporting or over-reporting of lost to follow-up remains. There may be a failure to update contact information, HCT survivors may be deceased or may be receiving follow-up care elsewhere. Alternatively, if a patient had missed two follow-up reporting periods, but later resumed their care at their respective HCT center they would still be classified as lost to follow-up. In the latter instance, the proportion in which this was felt to be the case was very small and unlikely to have impacted the results of our analyses. Some of these results (e.g., the association between insurance status and lost to follow-up status) may lack generalizability when considering other systems of health care delivery or health insurance coverage.

Conclusions

A national, comprehensive, risk-based approach to long-term follow-up focusing on minimizing the attrition in high-risk groups is needed. Patient reported outcomes may help describe reasons for lack of long-term follow-up. Collection of accurate epidemiologic and clinical data from all survivors can help refine strategies to improve the retention of HCT survivors which will support surveillance and intervention for potential complications.

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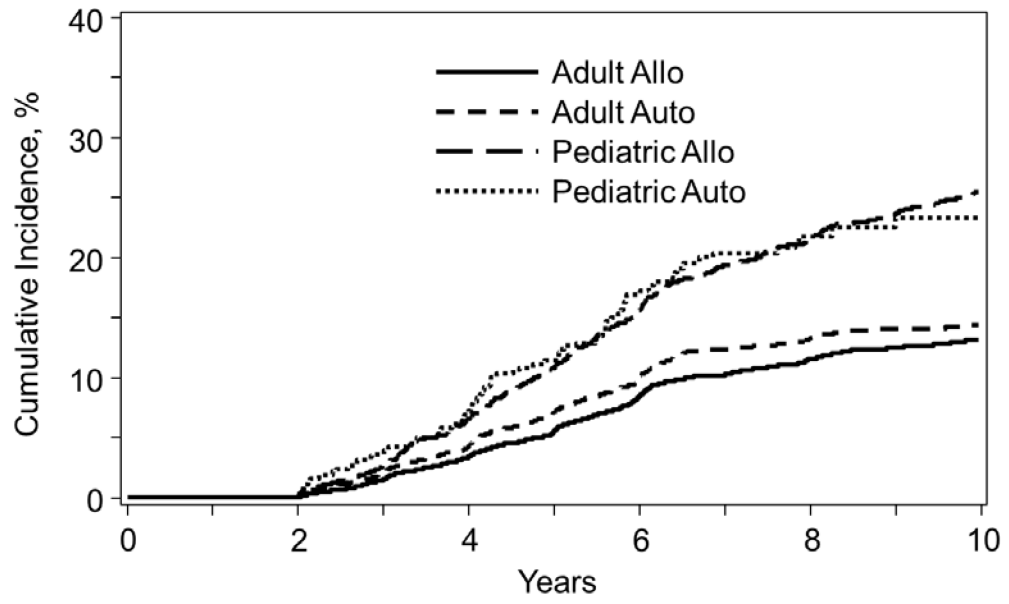


Figure 1: Among 2-year survivors, the cumulative incidence of becoming lost to follow-up by age at the time of transplantation (adult versus pediatric) and by type of transplant (allogeneic versus autologous).

Table 1A:

Sociodemographic characteristics of the study population

	Adult		Pediatric	
	Allogeneic (10,367)	Autologous (n=7,291)	Allogeneic (n=3,865)	Autologous (n=468)
	%	%	%	%
Age at HCT (years)				
Median (range)	49 (18–81)	58 (18–82)	7 (<1–18)	5 (<1–18)
Sex				
Male	57	60	60	59
Female	43	40	40	41
Race				
Caucasian	89	83	76	74
African American	5	14	11	15
Other	4	2	8	4
Missing	2	1	5	7
Marital Status				
Married	64	68	NA	NA
Single/Separated/Divorced/ Widowed	29	24	NA	NA
Missing	7	8	NA	NA
Health Insurance Status				
None	<1	<1	1	<1
Public	23	28	40	48
Private	64	57	43	38
Other/Unspecified	4	9	5	4
Missing	8	6	10	8
Income				
\$0–39,000	10	9	14	6
\$40–59,000	30	23	31	20
\$60–79,000	21	14	18	12
\$80–99,000	11	6	9	6
\$100,000+	8	4	6	2
Missing	19	44	21	53
Distance to Center (miles)				
0–100 miles	58	44	53	39
100+ miles	24	13	27	9
Missing	18	43	20	52

Table 1B:

Disease and transplant-related characteristics of the study population

	Adult		Pediatric	
	Allogeneic (10,367)	Autologous (n=7,291)	Allogeneic (n=3,865)	Autologous (n=468)
	%	%	%	%
Karnofsky Score at HCT				
<90	27	34	12	17
90	67	60	83	78
Missing	6	6	6	6
Disease				
AML	35	0	18	0
CLL	5	0	<1	
NHL	13	26	2	2
HL	3	8	<1	8
Mutiple Myeloma	4	65	<1	<1
Testicular/Germ Cell Tumor	0	1	0	2
CNS Tumor	0	<1	0	78
Other Solid Tumor	0	<1	0	10
Other Malignant	36	0	34	0
Other Non-Malignant	4	0	46	0
Year of HCT				
2002–2005	30	29	33	31
2006–2009	42	47	44	53
2010–2013	28	25	23	17

Abbreviation: AML=acute myelogenous leukemia; CLL=chronic lymphocytic leukemia; HL=Hodgkin lymphoma; NHL=Non-Hodgkin lymphoma

Table 2:

Multivariate analysis results of predictors for being lost to follow-up among adult 2-year survivors of allogeneic hematopoietic cell transplantation (n=10,367)

Characteristics	N	HR (95% CI)	P-Value
Age at transplant (years)			<0.0001
51+	4665	Reference	
41–50	2307	1.38 (1.14–1.67)	0.0009
18–40	3395	2.19 (1.80–2.66)	<0.0001
Insurance			<0.0001
Private	6584	Reference	
None	70	2.33 (1.30–4.17)	0.004
Public	2394	1.29 (1.13–1.48)	0.0002
Other/Unspecified	449	1.41 (1.04–1.92)	0.03
Missing	870	1.22 (0.85–1.74)	0.29
Distance to center (miles)			0.0008
0–99	6056	Reference	
100+	2438	1.39 (1.11–1.72)	0.004
Unknown	1873	1.23 (1.00–1.53)	0.05
Marital status			0.008
Married	6644	Reference	
Single/Divorced/Widowed	3034	1.26 (1.09–1.46)	0.002
Missing	689	0.99 (0.75–1.31)	0.93
Disease			0.0008
Malignant/except CLL	9389	Reference	
CLL	525	0.61 (0.43–0.88)	0.007
Non-malignant	453	1.52 (1.18–1.94)	0.001

Abbreviations: CLL=chronic lymphocytic leukemia

Table 3:

Multivariate analysis results of predictors for being lost to follow-up among adult 2-year survivors of autologous hematopoietic cell transplantation (n=7,291)

Characteristics	N	HR (95% CI)	P-Value
Age at transplant (years)			0.0002
18–20	71	Reference	
21–30	268	2.26 (1.17–4.34)	0.01
31–40	473	1.82 (0.95–3.46)	0.07
41+	6479	1.21 (0.63–2.34)	0.57
Disease			0.0002
NHL	1877	Reference	
HL	552	1.14 (0.85–1.54)	0.38
Multiple myeloma	4738	0.72 (0.56–0.92)	0.008
Testicular/Germ cell	91	1.95 (1.32–2.87)	0.0008
CNS tumor	16	1.03 (0.17–6.27)	0.98
Other solid tumor	17	2.14 (0.79–5.81)	0.13
Year of transplant			0.04
2010–2013	1802	Reference	
2006–2009	3395	1.22 (0.75–1.98)	0.43
2002–2005	2094	1.70 (0.95–3.02)	0.07

Abbreviations: CNS=central nervous system; HL=Hodgkin lymphoma; NHL=Non-Hodgkin lymphoma

Table 4:

Multivariate analysis results of predictors for being lost to follow-up among pediatric 2-year survivors of allogeneic hematopoietic cell transplantation (n=3,865)

Characteristics	N	HR (95% CI)	P-Value
Age at transplant (year)			<0.0001
<10	2738	Reference	
10–17	1127	1.97 (1.65–2.36)	<0.0001
Race			0.0009
Caucasian	2938	Reference	
African American	439	1.18 (0.86–1.63)	0.31
Other	304	1.48 (1.20–1.84)	0.0003
Unknown	184	1.42 (0.85–2.36)	0.18
Insurance			<0.0001
Private	1676	Reference	
None	54	3.53 (2.11–5.92)	<0.0001
Public	1543	1.34 (1.09–1.63)	0.005
Other/Unspecified	197	1.23 (0.87–1.75)	0.24
Missing	395	1.24 (0.85–1.83)	0.26
Disease			0.01
Malignant	2076	Reference	
Non-malignant	1789	1.25 (1.05–1.49)	0.01
Year of transplant			0.004
2010–2013	901	Reference	
2006–2009	1694	1.46 (1.13–1.89)	0.0037
2002–2005	1270	1.75 (1.24–2.45)	0.0012

Table 5:

Multivariate analysis results of predictors for being lost to follow-up among pediatric 2-year survivors of autologous hematopoietic cell transplantation (n=467)

Characteristics	N	HR (95% CI)	P-Value
Age at transplant (year)			0.04
<11	370	Reference	
11–17	97	1.72 (1.01–2.93)	0.04
Gender			0.05
Female	192	Reference	
Male	275	1.57 (0.99–2.49)	0.05
Disease			0.01
Lymphoma (HL/NHL)	43	Reference	
Testicular/Germ cell	8	1.43 (0.33–5.26)	0.59
CNS tumor	366	0.55 (0.34–0.90)	0.02
Other solid tumor	45	0.50 (0.24–1.05)	0.07

Abbreviations: CNS=central nervous system; HL=Hodgkin lymphoma; NHL=Non-Hodgkin lymphoma