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Analysis

Increased Health Care Utilization and Costs during Allogeneic Hematopoietic Cell Transplantation for Acute Leukemia and Myelodysplastic Syndromes in Adolescents and Young Adults Compared with Children: A Multicenter Study

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A B S T R A C T

Allogeneic hematopoietic cell transplantation (HCT) is a curative option for patients with acute leukemia and myelodysplastic syndromes (MDS) but is associated with significant cost. Compared with children (age <15 years), adolescents and young adults (AYA; age 15 to 39 years) undergoing HCT have an increased risk for transplantation-related complications. However, whether such complications translate into increased resource utilization and costs during HCT remains unknown. Therefore, we conducted a multicenter database study using the Pediatric Health Information System database, an administrative database containing resource utilization data from 49 US tertiary children's hospitals to compare inpatient costs and resource utilization in children and AYA undergoing HCT for acute leukemia and MDS. The International Classification of Diseases, Ninth Revision, Clinical Modification codes were used to identify HCT recipients and transplantation-related complications occurring up to 1 year post-HCT. We identified 1693 HCT recipients at pediatric centers between January 2010 and September 2014. Eighty percent of the total costs (from admission for HCT up to 1 year post-HCT) occurred during the initial transplantation admission. During initial admission, although AYA and children had a similar median length of stay (LOS) of 43 days, AYA incurred significantly greater adjusted costs ($338,458 versus $275,723; $P < .001$) and costs per hospital day ($7122 versus $5838; $P < .001$). Median total costs and costs per day during subsequent time periods post-HCT were also significantly greater in the AYA group. In multivariable analysis, increasing age at HCT, LOS, use of cord blood or an unrelated donor, occurrence of any graft-versus-host disease, infection, and use of dialysis or mechanical ventilation were significant drivers of increased cost at initial admission. In conclusion, allogeneic HCT for acute leukemia and MDS is associated with higher costs in AYA recipients than in children. Therefore, directing efforts and resources aimed at reducing HCT-related costs may be advantageous in this high-risk group.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT), a curative option for patients with high-risk hematologic malignancies, such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), and myelodysplastic syndromes (MDS), is a highly specialized, resource-intensive, and costly medical procedure. A report from the Health Research and Quality Agency on hospital expenditures identified HCT as one of the top 10 procedures with the greatest cost increase, from $694 million in 2004 to $1.3 billion in 2007 [1]. Moreover, financial burden and subsequent bankruptcy ("financial toxicity"), a complication experienced by HCT recipients, can lead to noncompliance and hesitancy in accepting medical care [2,3]. Therefore, it is crucial to identify special populations at risk for incurring increased costs associated with allogeneic HCT to enable sensible resource allocation and cost containment.

Adolescent and young adult (AYA) patients (age 15 to 39 years) with cancer are recognized as a distinct population with historically poor outcomes compared with children (age <15 years) and older populations [4-11]. Factors such as differing biology of primary malignant disease, limited participation in clinical trials, noncompliance, lack of insurance, and unique psychosocial

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challenges have been implicated in contributing to worse outcomes in AYA with cancer [12-16]. This high-risk group is also hit hardest by financial toxicity due to disease coinciding with life transitions (eg, education, job, marriage, starting a family) and thus incur the greatest medical debt [17]. Recent studies have suggested that clinical outcomes are improved in AYA patients with acute leukemia who receive a pediatric treatment regimen at a National Cancer Institute- or Children's Oncology Group- designated cancer center [11,18,19]. Because AYAs with cancer are being increasingly treated at pediatric centers [18], whether they incur increased health care costs or utilization when treated at pediatric centers or whether being treated at a pediatric center reduces resource utilization remains unclear.

Large retrospective studies have shown that pediatric HCT recipients (age ≤20 years) incur greater HCT-related costs compared with adults (age >20 years) [20,21]. In contrast, a single-center study from Europe showed lower HCT-related costs in children compared with adults [22]. There are no published studies comparing HCT-related costs at pediatric hospitals between AYA and children. Thus, we performed this retrospective multicenter database study using the Pediatric Health Information System (PHIS) database to compare health care utilization and costs related to allogeneic HCT between children and AYA with acute leukemia and myelodysplasia.

METHODS

Data Source

The PHIS, a large administrative and billing database maintained by the Children's Hospital Association (CHA, Lenexa, KS), contains comprehensive clinical and resource utilization data on patient encounters from 49 US tertiary care children's hospitals. Billing information in PHIS is facilities-based and, accordingly, does not include professional fees. Before inclusion in the database, all patient data are deidentified and assigned an identification number, allowing individual patients to be followed over time [23]. Data content in the PHIS is continually subjected to reliability and validity checks to ensure data quality. This study was deemed exempt by the Institutional Review Board of Nationwide Children's Hospital in Columbus, Ohio.

The International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) codes at initial admission were used to identify patients with AML, ALL, or MDS who underwent initial HCT (codes 41.xx) between January 2010 and September 2014 at the participating PHIS hospitals (**Supplementary Table S1**). ICD-9 CM codes were replaced by ICD-10-CM codes in September 2015 at all participating PHIS hospitals. Therefore, to maintain homogeneity of data collection, the period January 2010 to September 2014 was chosen. Recipients who had undergone more than 1 allogeneic HCT during the study period were excluded, because they are inherently at greater risk for HCT-related complications, which can increase costs.

Patient Cohorts and Transplantation Time Periods

Patients were stratified into 2 cohorts based on age at the time of HCT: children (age <15 years) and AYA (age 15 to 39 years). Four HCT time periods were defined: initial HCT admission (index admission; T1), discharge from index admission up to day (D) +100 post-HCT (T2), D+101 to D+180 post-HCT (T3), and D+181 to D+365 post-HCT (T4). All inpatient admissions up to 1 year post-HCT were included for the subsequent statistical analysis. Data for patients with a prolonged index admission that lasted longer than 100 days was included in the category of index admission (T1) only.

Transplantation-Related Complications

ICD-9-CM codes were used to identify relevant HCT-related complications during each patient admission up to 1 year post-HCT and compared between the 2 cohorts (AYA versus children). Post-HCT complications were categorized by relevant organ system as cardiovascular (CVS), pulmonary, renal/genitourinary, gastrointestinal, and nervous system (**Supplementary Table S2**). Prevalence of graft-versus-host disease (GVHD) and infections were also tracked in the study cohorts. Infections were further grouped into fungal, viral, bacterial and central venous line infections.

Resource Utilization and Cost Calculations and Validation

Inpatient clinical and financial data (hospital charges and source of payment) were collected from identified inpatient admissions up until one year following initial allogeneic HCT. Total hospital length of stay (LOS), frequency and duration of intensive care unit (ICU) admission, and use of invasive inpatient procedures, such as mechanical ventilation, dialysis, extracorporeal membrane oxygenation, photopheresis, and plasmapheresis were also extracted.

Charges (total $ amount that is charged to payers) were adjusted to standardize geographical differences using the Federal Register's wage index for each hospital and were organized into the following categories: clinical, imaging, laboratory, pharmacy, supply, and other. The latter category includes room and board, nursing, operating room, and emergency department charges. Costs (actual $ amount that hospital incurs while delivery services) were estimated from charges using 21 hospital-, year-, and department-specific ratios of cost-to-charge (RCC) by multiplying the charge by the appropriate RCC. Cost per hospital day during each admission was calculated by dividing the total cost by the number of inpatient days. Calculated costs were not adjusted for inflation because the study period did not exceed 5 years. Internal validation was performed by matching patients at our institution that are in the PHIS database for accuracy of diagnosis, date of HCT, number of inpatient admissions, all-cause in-hospital mortality, and internal charges associated with transplantation.

Statistical Analyses

Descriptive statistics were used to summarize all data. Bivariate analyses were performed between age cohorts. The chi-square or Fisher exact test was used to compare percentages between groups, and the Mann-Whitney test was used to compare continuous variables between age cohorts. Due to the significantly positive skewed nature of hospital cost data, the impact of clinical and demographic factors on total cost was performed with linear mixed models using log-transformed costs as the dependent variable. A hospital variable was added to the model as a random effect to account for the clustering of patients treated within the same hospital. Factors found to be significant on bivariate analysis or those deemed clinically relevant were considered for a multivariable regression model. Regression coefficients were presented with corresponding Wald 95% confidence intervals. All P values were 2-sided, and those <.05 were considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient and Transplantation Characteristics

Using the PHIS database, we identified a total of 1781 HCT recipients (514 AYA and 1179 children) during the study period. After excluding 88 recipients (27 AYA and 81 children) who underwent more than 1 allogenic HCT, a total of 1693 subjects met the inclusion criteria, including 848 with ALL, 642 with AML, and 142 with MDS (Table 1). The remaining 61 patients (4%) were coded as having either unspecified leukemia or both AML and ALL. There was a significantly higher proportion of males in the AYA cohort (65.8% versus 57.6%; P =.002), but there were no significant differences in racial or ethnic distribution between the 2 cohorts. The majority of AYA patients were e age 15 to 22 years (Figure 1). Payer source was predominantly commercial (49%) in the AYA cohort and largely via public sources in the children (49.7%) (P = .003).

Umbilical cord blood (UCB) (all from unrelated donors) was identified (ICD-9-CM code 41.06) as the graft source in 18.4% of patients (n = 311). However, due to the lack of a specific ICD-9-CM code, bone marrow (BM) and peripheral blood stem cells (PBSCs) as graft sources could not be separated. Within this group (PBSC+ BM), 591 matched unrelated donor (MURD) and 513 matched related donor (MRD) graft recipients were identified. The distribution of graft source differed between the 2 cohorts, with greater proportion of AYA receiving MURD BM/PBSCs (38.5% versus 33.3%; P = .001) and a greater proportion of children receiving UCB (20.8% versus 12.8%; P = .001).

Internal validation performed on 38 patients from our institution showed 100% accuracy for diagnosis and HCT admission date. Two of 10 deaths occurred at home/hospice and thus were not captured in the database. Three patients who underwent a second HCT within 1 year were inadvertently included in our study cohort, which likely reflects undercoding. We captured 97% of all inpatient admissions of these patients during the study period. The charges extracted from the PHIS showed

Table 1
Patient and Transplantation Characteristics

Characteristic	All	AYA (15-39 yr)	Children (<15 yr)	*P* Value
Number of patients (%)	1693	514 (30.4)	1179 (69.6)	
Age at HCT, yr, median (IQR)		17.7 (15.0-32.7)	7.8 (.3-14.9)	<.0001
Male sex, n (%)	1017 (60.0)	338 (65.8)	679 (57.6)	.002*
Race, n (%)				.280
White	1118 (66.0)	357 (69.5)	761 (64.5)	
Black	152 (9.0)	37 (7.2)	115 (9.7)	
Asian	68 (4.0)	19 (3.7)	49 (4.2)	
American Indian	24 (1.4)	9 (1.8)	15 (1.3)	
Pacific Islander	7 (.4)	1 (.2)	6 (.5)	
Other†	324 (19.1)	91 (17.7)	233 (19.8)	
Ethnicity, n (%)				.700
Hispanic/Latino	433 (25.6)	130 (25.3)	303 (25.7)	
Non-Hispanic/Latino	1142 (67.5)	352 (68.5)	790 (67.0)	
Unknown	118 (7.0)	32 (6.2)	86 (7.3)	
Payer source, n (%)				.003*
Commercial	752 (44.4)	252 (49.0)	500 (42.4)	
Public	796 (47.0)	210 (40.9)	586 (49.7)	
Other/unknown‡	145 (8.6)	52 (10.1)	93 (7.9)	
Disease, n (%)				
ALL	848 (50.1)	258 (50.2)	590 (50.0)	
AML	642 (37.9)	198 (38.5)	444 (37.3)	
MDS	142 (8.4)	47 (9.1)	95 (8.1)	
Unspecified leukemia group	61 (3.6)	11 (2.1)	50 (4.2)	
Graft and donor source, n (%)				.001*
Matched related BM/PBSCs	513 (30.3)	163 (31.7)	350 (29.7)	
Matched unrelated BM/PBSCs	591 (34.9)	198 (38.5)	393 (33.3)	
UCB§	311 (18.4)	66 (12.8)	245 (20.8)	
Unknown graft or donor source	278 (16.4)	87 (16.9)	191 (16.2)	

* *P* significant at <.05.
† Other as defined by the US Census Bureau; not falling into any of the above defined categories based on self-report.
‡ Other/unknown: self-pay, charity, not billed by hospital, unknown.
§ All from a matched unrelated donor.

100% concordance with financial data obtained from our institutional records.

Hospital Charges and LOS

We identified 4585 unique hospital admissions for eligible patients (AYA, 1429; children, 3156) during the defined study period. Median total adjusted costs in each Transplantation period were significantly greater for AYA compared with children: T1, $338,458 versus $275,723 ($P < .001$); T2, $24,367 versus $18,184 ($P < .001$); T3, $22,569 versus $17,025 ($P < .05$); T4, $26,119 versus $17,556 ($P < .001$) (Table 2). Cost per hospital day was also greater in AYA patients than children during all time periods. Pharmacy and "other costs" (ie, room and board, nursing, operating room, and emergency department charges) were the major drivers of costs, contributing to 59% to 71% of total costs during in both groups. Notably, pharmacy-related costs were significantly higher in the AYA cohort throughout the study period. Median hospital and ICU LOS (not shown) were similar in the 2 cohorts across all time periods.

In both cohorts, 80% of total median adjusted costs throughout the study period occurred during T1, during which a significantly greater proportion of AYA than children incurred costs ≥$1,000,000 (8% versus 4%; $P < .001$) (Figure 2). Median hospital and ICU LOS were the longest during T1 and were similar in the 2 groups, at 43 and 14 days, respectively.

By graft source, during index admission, UCB HCT was associated with the longest median hospital LOS compared with MURD PBSC/BM and MRD PBSC/BM sources (52 days versus 43 days versus 39 days; $P < .001$) in both AYA and children. UCB HCTs were also the most expensive, followed by MURD BM/PBSC and then MRD BM/PBSC HCTs, as evidenced by total median costs ($418,910 versus $310,920 versus $212,532; $P < .001$) and cost per hospital day ($7014 versus $6720 versus $5175; $P < .001$). Costs across all categories (ie, imaging, lab, pharmacy, supply, and other costs) were significantly greater in UCB HCT recipients (data not shown). When stratified by graft/donor source, costs during index admission remained significantly higher in AYA compared with children (**Supplementary Table S3**).

Similar findings were observed in a subgroup analysis of index costs in patients with ALL (n = 848) and AML (n = 642) (**Supplementary Tables S4 and S5**). Total median HCT costs for patients with ALL ($334,835 versus $263,835; $P < .001$) and AML ($352, 971 versus $286,756; $P < .001$) and cost per hospital day for patients with ALL ($6772 versus $5810; $P < .001$) and AML ($7264 versus $5850; $P < .001$) were significantly higher in the AYA cohort compared with children, but median hospital LOS was similar in the 2 cohorts (ALL, 44 versus 44 days; AML, 42 versus 42 days).

Transplantation-Related Complications, Mortality, and Resource Utilization

Organ complications, such as renal/ genitourinary, gastrointestinal, and neurologic complications, were seen more frequently in the AYA cohort (Table 3). Within the organ systems, specific diagnosis of hypertension, veno-occlusive disease (VOD), and posterior reversible encephalopathy syndrome did not differ significantly between the cohorts, whereas pain/neuropathy was more common in the AYA (30.7% versus 17.6%; $P < .001$).

The prevalence of any GVHD was similar in the 2 cohorts (55.1% in AYA versus 50.8% in children; $P = .11$). Bacterial infections, septic shock, and opportunistic fungal infections were more common in the AYA. Although the rate of viral infections was similar in the 2 cohorts, cytomegalovirus infections were

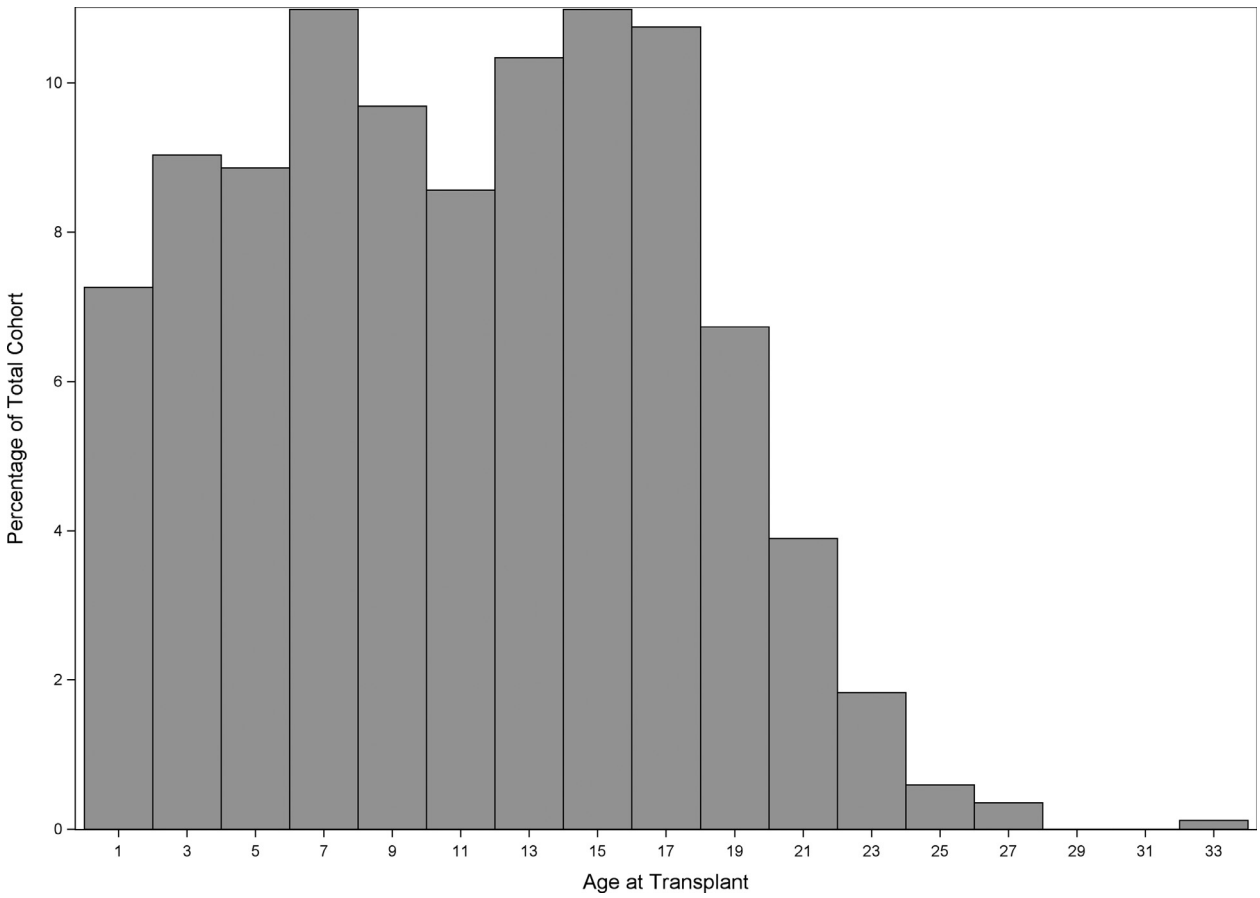

Figure 1. Age distribution at transplantation, total cohort (N = 1693).

more common in the AYA, and adenoviral infections were more frequent in children (Table 3). The use of invasive procedures during inpatient stay (ie, mechanical ventilation, extracorporeal membrane oxygenation, and plasmapheresis) did not differ significantly between the 2 cohorts; however, photopheresis (3.5% versus 1.9%; $P = .041$) and dialysis (11.9% versus 7.3%; $P < .05$) were used more frequently in the AYA. There were no significant differences between the AYA and children in the rate of ICU utilization (42% versus 43%; $P = .65$) or all-cause in-hospital mortality at D+100 (12.6% versus 1.2%; $P = .16$) or 1 year (19.5% versus 16.5%; $P = .15$).

In a separate analysis (data not shown) comparing the prevalence of HCT-related complications in the UCB, MURD BM/PBSC, and MRD BM/PBSC HCT subgroups, the rates of GVHD, opportunistic fungal infections, mechanical ventilation, and dialysis were similar in the UCB and MURD BM/PBSC groups but were significantly lower in the MRD BM/PBSC group (data not shown). On the other hand, renal complications, bacterial and viral infections, and the need for ICU care were significantly more prevalent in the UCB group.

Influence of Transplantation-Related Complications and Variables on Total Costs

On multivariable analysis, the use of a URD graft, UCB as graft source, older age, LOS, occurrence of GVHD, any infection, use of dialysis, and mechanical ventilation were identified as independent factors significantly increasing the total cost of the transplantation admission (Table 4). Although the presence of VOD did not significantly impact cost, it was included in the final model. While controlling for other factors, total cost was found to increase by an average of 1% for each day spent in the hospital and by 1% for every 1-year increase in age at the time of transplantation. Compared with HCT with a matched related graft and donor source, the total cost was 42% (95% CI, 36% to 49%) greater for HCT with UCB and 37% (95% CI, 32% to 42%) greater for HCT with MURD. The impacts of other factors are summarized in Table 4.

DISCUSSION

Costs incurred due to HCT are often difficult to compute because the care of HCT recipients requires a multidisciplinary approach involving several teams, such as the ICU, apheresis outpatient clinic, and different laboratories [24,25]. This complexity, along with frequent admissions in the first year post-HCT, can complicate cost analysis. AYAs treated with pediatric-based regimens have been shown to have better survival than AYAs treated with adult regimens [18,19]. A review of 1473 AYA patients from the California Cancer registry revealed that the proportion of AYAs treated in a pediatric setting has increased significantly, from 27.3% in 2004 to 2007 to 34.9% in 2012 to 2014 [18]. However, in the United States, pediatric HCT is more expensive than adult (>20 years) HCT [20,21]. Differences in physician practices, such as choice of graft sources, GVHD treatment strategies, and supportive care practices [26,27], all of which can increase LOS, have been postulated to contribute to this discrepancy [20,28,29]. The AYA group was not analyzed separately in those previous reports, however. In contrast, in the present study, costs of HCTs performed at pediatric centers were higher for AYAs compared with children, despite a similar median hospital LOS in the 2 cohorts. This was true even in

Table 2
Median Costs by Transplantation Period in AYA (Age 15 to 39 Years) and Children (Age <15 Years)

Time Period	Median Costs, US$, Median (IQR)		*P* Value
	AYA (N = 514)	Children (N = 1179)	
Index admission (T1)			
Total cost	338,458 (206,554-566,252)	275,723 (186,945-452,868)	<.0001*
Costs per day	7122 (5221-10,463)	5838 (4309-7910)	<.0001*
Clinical costs	61,707 (16,464-116,479)	56,128 (18,825-101,230)	.14
Imaging costs	1405 (364-4152)	1175 (368-3624)	.12
Laboratory costs	24,964 (13,853- 50,333)	20,311 (12,378- 37,961)	.0002*
Other costs†	104,184 (68,097-153,441)	106,497 (73,991-148,401)	.30
Pharmacy costs	91,699 (46,629-196,955)	55,373 (32,345-118,423)	<.0001*
Supply costs	1283 (145-7163)	1494 (229-7298)	.38
Discharge to D+100 (T2)			
Total cost	24,367 (11,335-62,773)	18,184 (9237-42,397)	.0006*
Cost per day	4087 (3047-5465)	3816 (2746-5357)	.0142*
Clinical costs	838 (182-2546)	648 (69-1540)	.0097*
Imaging costs	184 (0-969)	110 (0-678)	.0101*
Laboratory costs	2707 (1193-7320)	2197 (1035-4990)	.0032*
Other costs†	11,328 (5684-31,048)	9410 (4876-22,341)	.0159*
Pharmacy costs	6203 (1777-17,325)	3347 (1302-10,511)	<.0001*
Supply costs	90 (0-754)	56 (0-501)	.22
D+100 to D+180 (T3)			
Total cost	22,569 (11,553-45,701)	17,025 (9140-48,796)	.0233*
Cost per day	4542 (3319-6527)	4061 (2930-5609)	.0003*
Clinical costs	1011 (227-2590)	870 (202-2526)	.40
Imaging costs	246 (0-931)	125 (0-878)	.08
Laboratory costs	2770 (1253-6006)	2292 (981-5971)	.0537
Other costs†	9278 (4859-21,892)	8329 (4376-22,816)	.27
Pharmacy costs	5733 (1848-13,691)	3234 (1121-14,021)	.0037*
Supply costs	144 (0-1008)	141 (0-832)	.90
D+180 to D+365 (T4)			
Total cost	26,119 (10,743-58, 935)	17,556 (8582-44,934)	.0005*
Cost per day	4743 (3380-6706)	4047 (2905-5525)	<.0001*
Clinical costs	979 (285-2663)	915 (173-2475)	.18
Imaging costs	305 (0-1267)	172 (0-830)	.0110*
Laboratory costs	2869 (1201-6984)	2058 (852-5359)	.0004*
Other costs†	10,448 (4795-25,549)	8142 (4251-19,874)	.0319
Pharmacy costs	6500 (1952-21,312)	3362 (1046-11,650)	<.0001*
Supply costs	155 (0 -1001)	150 (0-861)	.62

IQR indicates interquartile range.
* *P* significant, <.05.
† Other costs include room, board, nursing, operating room, and emergency department costs.

subgroup analyses of costs when stratified by donor/graft source and disease type (ALL and AML).

In line with numerous previous adult and pediatric studies [20,22,28-32], in the present study, the HCT costs were concentrated mostly in the initial HCT admission. The median cost of HCT at the index admission was $338,458 (interquartile range, $206,554 to $566,252) in the AYA and $275,723 (interquartile range, $186,945 to $452,868) in the children, similar to recent reports [20,32,33]. The average cost of HCT in children with AML undergoing HCT on the Children's Oncology Group AML0531 trial was $260,000 [33]. Another study using a private insurance claims database found a median cost of HCT in patients with MDS/leukemia of $302,822 in those age ≤20 years versus $191,142 in those age >20 years [20]. In that report of allogenic HCT, 6% of subjects age ≤20 years and 1% of those age >20 years incurred costs of >$500,000, compared with 29% of the AYA and 22% of the children in our series (Figure 2). Therefore, our study not only confirms the previous findings that HCT is more expensive in children than in adults, but also, and more importantly, shows that HCT in AYA is more expensive when performed at pediatric centers.

Room and board charges, major contributors to HCT costs [22,28,29,33], are influenced by hospital LOS. In a report from Health Research and Quality Agency, 25.6% of the increase in costs of HCT from 2004 to 2007 was due to an increase in the mean cost of hospital stay, with 59.3% due to an increase in LOS [1]. Despite a similar incidence of post-HCT complications in pediatric and adult HCT recipients, in a single-center study, Majhail et al [29] found a longer median LOS in pediatric patients compared with adults during the first 100 days post-HCT (51 versus 44 days; $P < .01$), which contributed to increased costs. In contrast, we observed a similar median LOS in both the AYA and the children but higher median adjusted cost per hospital day in the AYA. A study comparing health care spending in the United States and other high-income countries identified pharmaceutical costs as one of the major driving forces for higher health care expenditures in the US [34]. Interestingly, in our study, pharmacy-related costs were significantly greater in the AYA group during all time periods (Table 2). Although we were unable to completely explain this finding owing to the nature of our study, we hypothesize that this could be due to the older patients receiving a greater volume of medications due to increased body weight dosing as well as a greater use of age-related chronic medications. A study comparing pediatric (age <18 years) and adult (age >18 years) HCT recipients showed that although total costs of HCT were higher in the pediatric age group, 100-day pharmacy-related costs were considerably higher in adults [21]. Varying biology of the disease with age (eg, greater incidence of Philadelphia chromosome-positive ALL in older age groups) and need for maintenance therapies (eg, use of tyrosine kinase inhibitors) in such instances also could explain the higher pharmacy costs noted in periods

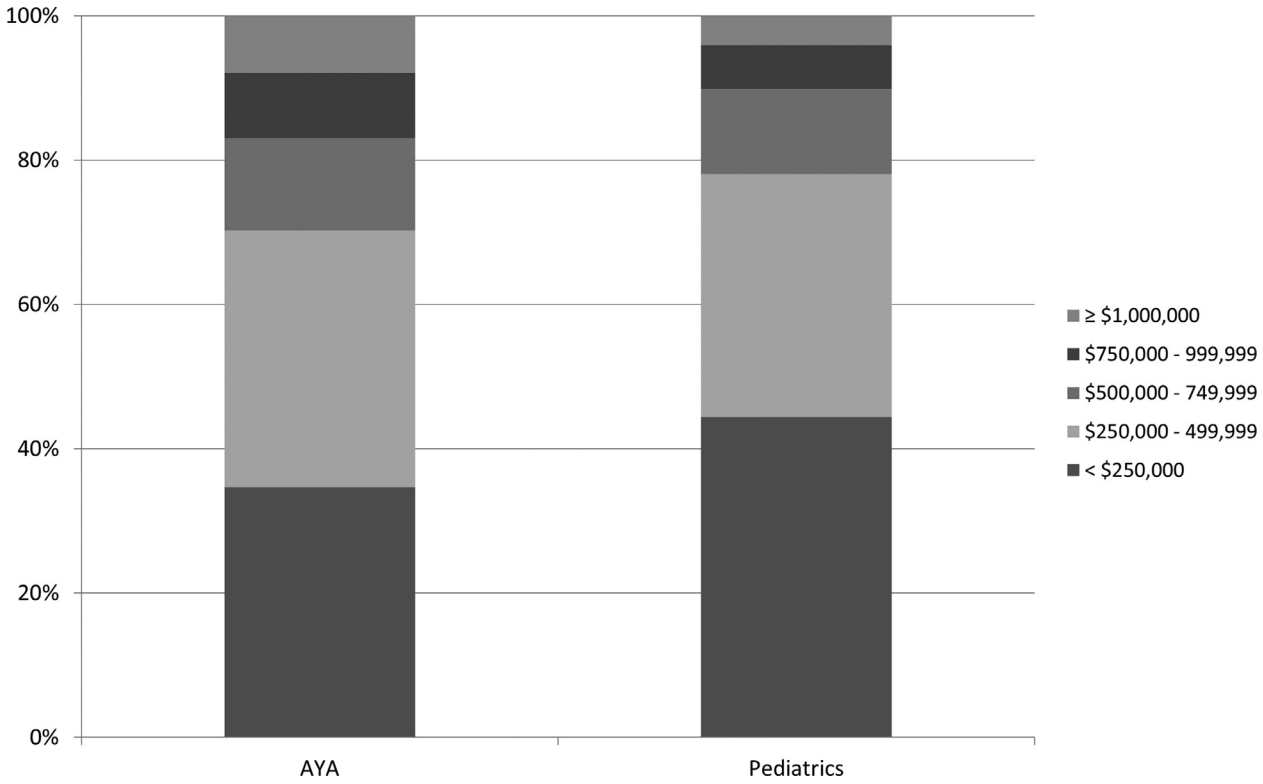

Figure 2. Costs during the index admission in AYA and children.

Table 3
Post-Transplantation Complications in AYA (Age 15 to 39 Years) and Children (Age <15 Years)

Complication	AYA (N = 514), n (%)	Children (N = 1179), n (%)	*P* Value
Organ toxicities			
Cardiovascular complications	158 (30.7)	313 (26.6)	.0768
Pulmonary complications	257 (50.0)	556 (47.2)	.28
Gastrointestinal complications	440 (85.6)	948 (80.4)	.0105*
VOD	44 (8.6)	95 (8.1)	.73
Renal complications	392 (76.3)	811 (68.8)	.0018*
Hypertension	315 (61.3)	691 (58.6)	.30
CNS complications	209 (40.7)	325 (27.6)	<.0001*
Pain/neuropathy	158 (30.7)	208 (17.6)	<.0001*
PRES	18 (3.5)	48 (4.1)	.58
GVHD and infections			
GVHD (any)	283 (55.1)	599 (50.8)	.11
Acute	144 (28.0)	330 (28.0)	.99
Chronic	65 (12.6)	111 (0.09)	.045*
Acute or chronic	25 (0.05)	28 (0.02)	.0007*
Unspecified	177 (34.4)	352 (30)	.06
Septic shock	169 (32.9)	271 (23.0)	<.0001*
Bacterial infection	351 (68.3)	693 (58.8)	.0002*
Viral infection	282 (54.9)	653 (55.4)	.84
CMV	126 (24.5)	209 (17.7)	.0013*
EBV	17 (3.3)	48 (4.1)	.45
HHV6	47 (9.1)	123 (10.4)	.42
Adenovirus	40 (7.8)	147 (12.5)	.0047*
Fungal infection	175 (34.1)	287 (24.3)	<.0001*
Central line infection	111 (21.6)	257 (21.8)	.93
Invasive procedures during inpatient admission and ICU care			
ICU admission	221 (43.0)	493 (41.8)	.65
Mechanical ventilation	114 (22.2)	238 (20.2)	.35
ECMO use	2 (0.4)	5 (0.4)	.99
Dialysis	61 (11.9)	86 (7.3)	.002*
Plasmapheresis	13 (2.5)	23 (2.0)	.45
Photopheresis	18 (3.5)	22 (1.9)	.041*

CNS indicates central nervous system; PRES, posterior reversible encephalopathy syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV6, human herpesvirus 6; ECMO, extracorporeal membrane oxygenation.
* *P* significant at <.05.

Table 4
Influence of Transplantation-Related Variables and Complications on Total Costs

Variable	Multiplier	95% CI		*P* Value
		Lower	Upper	
Age at transplantation	1.01	1.01	1.02	<.001*
Insurance type (ref: commercial insurer)				
Public insurance	.99	.96	1.03	.62
Other†	1.05	.99	1.12	.09
Graft and donor source (ref: matched related)				
Matched unrelated	1.37	1.32	1.42	<.001*
UCB	1.42	1.36	1.49	<.001*
Post-transplantation complications				
LOS	1.01	1.01	1.01	<.001*
VOD	1.06	1.00	1.13	.12
Dialysis	1.19	1.10	1.29	<.001*
Mechanical ventilation	1.18	1.12	1.25	<.001*
Any GVHD	1.08	1.04	1.11	<.0001
Acute GVHD	1.07	1.02	1.11	.003*
Chronic GVHD	1.09	1.04	1.13	<.001*
Any Infection	1.14	1.10	1.19	<.001*

* *P* value significant at <.05.

beyond the initial HCT admission. In addition, the higher prevalence of some HCT-related complications (Table 3) seen in AYA compared with children may have necessitated additional workup that could have contributed to increased costs in other categories (eg, laboratory costs, imaging costs) during different time periods post-HCT.

The use of cord blood grafts, unrelated donors, older age, use of mechanical ventilation or dialysis, and the incidence of graft failure (GF), GVHD, VOD, or bacteremia have been shown to be associated with increased HCT-related costs [22,28,29]. Lee et al [35] found that infection, VOD, acute GVHD, and mortality each added $15,300 to $28,100 to HCT costs. In our multivariable analysis, all the foregoing variables excluding VOD were predictive of increased costs. In our study, UCB HCT was associated not only with increased median hospital LOS, but also with an increased prevalence of many post-HCT complications, which may have contributed to the higher costs associated with this graft source.

Compared with single-center studies, multicenter database studies allow costs to be captured from different institutions and provide a better understanding of HCT-related costs [20,33]. Owing to the heterogeneity of HCT, we studied a uniform contemporary population of patients with leukemias or MDS undergoing HCT at pediatric centers to better understand the economic impact of age on medical costs. Because these patients are often readmitted following HCT, we analyzed costs and complications incurred up to 1 year post-HCT. Unlike previous multicenter database studies, which only included patients with private insurance and thus reflected payments made by insurers [20,21], we included patients with different payer sources (ie, private, public, and self-pay) which is more representative of the typical patient population burden in pediatric centers.

Our study has several limitations inherent to the retrospective nature of the PHIS database. First, the nonspecific nature of ICD-9 codes and probable inaccuracy of coding may contribute to under or over-reporting of various diagnoses. As observed in our validation cohort, a proportion of patients who had more than 1 HCT might have been inadvertently included due to coding errors. We could not study the effect of intensity of conditioning regimen on costs due to a lack of details on drug dosing and frequency. In an analysis of 1562 patients using the Truven Health MarketScan insurance claims database, Broder et al [21] found the highest median total health care cost at 100 days in patients who received a myeloablative conditioning regimen compared with those who received a reduced-intensity conditioning or and non-myeloablative regimen ($289,283 versus $253,467). We were also unable to ascertain the influence of pre-HCT comorbidities on costs and resource utilization, as shown in previous in single-center studies. Decook et al [36] reported that adult HCT recipients with a higher pre-HCT comorbidity index had greater resource utilization, as defined by hospital LOS and readmission rate.

Disease remission status, risk status (cytogenetics, molecular abnormalities), severity of GVHD and GF, factors previously found to be associated with increased costs [22,25,32,37], could not be evaluated in our study. In our validation cohort and in previous PHIS-based studies conducted at our center [38], we have found the ICD-9-CM code for GF to be unreliable, and thus we did not use it in our analysis. In a single-center study of 131 pediatric HCT recipients, the median cost of HCT was considerably higher in those with GF compared with unaffected recipients ($628,179 versus $376,195) [25]. Although we found that the use of UCB as a graft source increased costs by 50%, similar to other reports [20,39], we could not estimate the cost differences between PBSC and BM recipients. Lin et al [32] reported decreased LOS and lower total median costs in pediatric PBSC recipients versus BM recipients. Similar to previous studies [20,28-30,35], we did not include costs associated with outpatient care, home infusions, donor search, graft procurement, physician charges, and patient evaluation for eligibility for transplantation in our analysis; the inclusion of these charges would increase estimated costs [2]. Despite these limitations, in our large cohort of patients, we observed significantly greater health care utilization and higher costs during HCT for acute leukemia/MDS in AYA compared with children.

CONCLUSION

In summary, HCT-related costs were greater in AYA compared with children when treated at pediatric hospitals. We observed significantly increased pharmacy charges in AYA and greater prevalence of many post-HCT complications in AYA, which may have contributed to observed cost differences between the 2 groups. Based on our present findings, cost containment strategies should be initially focused on AYA patients and during index admission, both of which are associated with increased risk for higher costs. Ideally, a cost comparison between AYA recipients treated at pediatric versus adult HCT centers may help determine the impact of center-related differences in HCT practices on costs incurred. Larger studies that merge PHIS with HCT-specific clinical databases may shed light on more definitive variables contributing to the higher costs seen in AYA.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.01.004.

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