Five-year direct costs of acute lymphoblastic leukemia pediatric patients undergoing allogeneic stem cell transplant

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Practice points

- This study assesses the 5 years economic burden of allogeneic hematopoietic stem cell transplant (HSCT) in acute lymphoblastic leukemia pediatric patients.
- The economic burden was described by assessing healthcare costs and resource use using claims data.
- Healthcare resource use and costs were substantial following HSCT.
- The highest costs and most intensive resource use were observed in first year after HSCT (US\$683,099).
- Resource use and costs remained significant even 5 years after the HSCT.

Aim: To assess the 5-year healthcare resource utilization (HRU) and direct payer costs following allogeneic hematopoietic stem cell transplants (HSCTs) in acute lymphoblastic leukemia pediatric patients using data from two large US administrative databases.

Patients & methods: Among the 209 patients with acute lymphoblastic leukemia, HRU and costs were described over the up to 5 years after the HSCT. **Results:** HRU and costs following the HSCTs were substantial. The highest average costs and most intensive HRU were observed within the first year following the HSCTs (49 outpatient visits; 29 laboratory service visits; 68 inpatient days), with a first year cost of US\$683,099 and substantial costs over the following years. **Conclusion:** HRU and direct costs associated with allogeneic HSCTs are substantial.

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Hematopoietic stem cell transplantation (HSCT) consists of transplantation of multipotent hematopoietic stem cells from bone marrow, peripheral blood or umbilical cord blood generally administered after immune suppressive and myeloablative therapy [1]. HSCT draws its benefit from its capacity to restore stem cells following a conditioning regimen with high-dose chemotherapy or radiation therapy [2]. HSCT can be autologous (using patient's own cells), allogeneic (using stem cells from siblings, parents or unrelated donors) or syngeneic (using stem cells from identical twins) [3]. In allogeneic HSCT, donor T cells may recognize antigens present on the recipients' residual tumor cells which has the potential advantage of conferring additional immunologic benefits to recipients (the graft vs leukemia effect) [2]. In pediatric patients, the most common type of HSCT is allogeneic transplant, and bone

KEYWORDS

• acute lymphoblastic leukemia • allogeneic stem cell transplantation • direct costs • economic burden • healthcare resource utilization • pediatric patients

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marrow and umbilical cord blood are the main graft sources [3–5]. Acute lymphoblastic leukemia (ALL) has been reported to be one of the most common indications for allogeneic HSCT in pediatric patients in the USA, with approximately 350 procedures performed annually [3].

Many pediatric ALL patients can be cured by chemotherapy regimens. HSCT may be considered for high-risk patients after induction therapy or for refractory or relapsed patients [4–9]. However, HSCT is also recognized as a highly specialized, costly and resource intensive procedure requiring ongoing care over months to years. Within 3 years following HSCT, between 19 and 33% of ALL pediatric patients would relapse [10–14].

The current literature does not provide a thorough picture of the economic burden of allogeneic HSCT in pediatric ALL patients in the USA. Studies generally combined multiple conditions, age groups and types of HSCT, which all may impact the costs of HSCT. In addition, studies were generally conducted among a limited number of institutions (single-center studies), focused on early costs associated with HSCT (first 30–365 days after the HSCT procedure) and did not consider the economic impact of long-term care among survivors. To the best of our knowledge, two US studies have assessed the cost associated with HSCT in a sample of pediatric patients that include patients with ALL. In the first study, authors reported a median total healthcare inpatient and outpatient costs of US\$302,822 (interquartile range [IQR] US\$211,532–454,747) from the date of transplant hospitalization to day 100 post-transplant in pediatric patients ($n = 113$) with acute leukemia or myelodysplastic syndrome. Median hospital days were 43 and the majority of the medical costs were incurred during the initial hospitalization for the transplant [15]. The second study assessed healthcare costs among pediatric patients with acute leukemia and reported average total healthcare costs of US\$208,987 for the initial hospitalization of patients with bone marrow transplantation (BMT) and US\$282,577 for patients with peripheral blood stem cell transplantation (PBSCT). Depending on the risk level of the patients (number of prior relapses) the average total healthcare cost per patient over the first year post-transplant ranged between US\$352,885 and US\$457,078 in patients with BMT and between US\$377,316 and US\$512,294 in patients with PBSCT [16].

Among other US studies conducted in combined samples of pediatric and adult patients or in adult patients only, median total healthcare costs ranged from US\$42,149 to US\$303,709 in the first 100 days after HSCT [15,17,18].

Post-transplant complications such as infections and graft-versus-host-disease (GVHD) have been shown to be very common after HSCT both in the short- and long-term follow-up. GVHD rates following unrelated HSCT have been estimated at up to 50–70%, with opportunistic infections commonly complicating GVHD due to the need for augmented immune suppression [19,20]. The short follow-up in the published literature on the cost of HSCT may not be sufficient to capture the overall costs related to post-transplant complications which can also significantly contribute to the economic burden of these malignancies and the HSCT [15,18,21].

With the refinement of methods to determine histocompatibility, the increased quantity of unrelated-donors and the improvements in supportive care for HSCT, there has been an increasing trend in the last decade in the number of HSCTs performed in the USA. With the increasing number of HSCT procedures performed, HSCT-associated costs and resource utilization are becoming a major consideration. In its 2014 report, the Milliman research group stated that the number of HSCT procedures has also steadily been increasing over the past years with an increase of approximately 20% from 2010 to 2014 [22]. Based on this report, the estimated total average amount charged in 2014 for allogeneic HSCT was US\$930,600 per patient – including all charges from the 30 days pre-transplant period to the 180 days post-transplant discharge [22]. However, the report does not include information on the proportion of the costs incurred by payers; therefore, the burden from a payer's perspective is still unknown.

The objective of this study was to assess the economic burden of HSCT from US private payers' perspective in a sample of pediatric patients with ALL followed up to 5 years after the HSCT.

Methods

• Data source & inclusion criteria

Two administrative claims databases, the IMS LifeLink PharMetrics Plus™ and the Truven Health MarketScan®, were used to identify commercially insured pediatric patients with ALL who underwent an allogeneic HSCT in the

USA between 2002 and 2013. PharMetrics and MarketScan are two of the largest claims databases in the USA, together including detailed claims information for more than 200 health plans and representing over 90 million covered lives annually, which is likely to provide a representative sample of commercially insured pediatric patients in the USA. These databases include detailed information on history of healthcare plan enrollment, demographics, diagnoses, claims for medical care received across all settings (including hospital stay, emergency department visits, physician outpatient office visits and other services such as home care services) and claims for pharmacy services for the covered employees and their dependents. The data were de-identified and comply with the confidentiality requirements of the Health Insurance Portability and Accountability Act (HIPAA).

Selected ALL pediatric patients had at least two diagnoses for ALL (International Classification of Diseases, Ninth Revision [ICD-9 CM] code 204.0x); at least one procedure code for an allogeneic HSCT (ICD-9 CM procedure codes 41.02, 41.03, 41.05, 41.06, 41.08) during an inpatient (IP) stay, and a diagnosis for ALL recorded on the date of the HSCT. The date where the HSCT was recorded was defined as the index date. Selected patients were less than 18 years old as of the index date and

continuously enrolled in their healthcare plan for at least 6 months before and at least 1 month after the index date.

In addition, to avoid selecting patients based on misdiagnoses, patients who did not have ALL as the most frequent diagnosis for a blood malignancy recorded between the index date and the date of the HSCT hospitalization discharge (index hospitalization) were excluded from the study. Patients with a documented history of HSCT (ICD-9 V42.81, V42.82), graft-versus-host disease (ICD-9 CM 279.5), post-transplant lymphoproliferative disorder (ICD-9 CM 238.77) or complications of transplanted organ (ICD-9 996.8) any time before the index date were excluded as their index date would be unlikely to correspond to the first HSCT. Finally, patients with a claim for the HSCT of US\$0 were excluded.

• Study design

A retrospective cross-sectional cohort design was used (Figure 1). The baseline period was defined as the 6-month period preceding the index date. As we aimed to assess the economic burden of HSCT over the short- and long-term horizon following the HSCT, the follow-up period after the index date was divided into seven periods; between the index date (day 0) and index hospitalization discharge date during the first 100 days

Figure 1. Study design. A retrospective cross-sectional cohort design was used to examine outcomes in the up to 5 years following HSCT. HSCT: Hematopoietic stem cell transplantation.

following the index date (including the index hospitalization; from day 0 to 100), during the first year following the index date (including the index hospitalization; from day 0 to 364), during the second year following the index date (from day 365 to 729), during the third year following the index date (from day 730 to 1094), during the fourth year following the index date (from day 1095 to 1459) and during the fifth year following the index date (from day 1460 to 1824). For each time period, the analyses were conducted among patients with continuous healthcare plan enrollment for the entire period.

• Outcomes

Healthcare resource utilization and costs were descriptively reported for each study period. Healthcare resource utilization components included number of inpatient (IP) admissions,

total number of IP days and number of days with at least one outpatient (OP) visit, number of days with an emergency room (ER) visit, number of days with at least one laboratory test (multiple laboratory tests may have been conducted on the same day) and number of days with other medical services (e.g., medical services that patients received at home). For each study period, the average number of events was reported for each component.

Healthcare costs were measured from private payers' perspective and therefore reflected the claims reimbursed by the private payers. Costs were adjusted for inflation using the consumer price index for medical components and reported in 2014 US dollars (USD). The total healthcare costs for each time period was broken down by types of medical services, including IP, OP, ER, laboratory service, other medical service costs

Figure 2. Sample selection flowchart. Description of inclusion and exclusion criteria. ALL: Acute lymphoblastic leukemia; HSCT: Hematopoietic stem cell transplant.

and pharmacy costs. For each study period, the average and median costs were reported for each cost component and for the total healthcare cost.

Results

A total of 209 pediatric ALL patients met the study inclusion criteria (**Figure 2**). Although the databases covered the period from 2002 to 2013, most of the patients had their HSCT in the most recent 6 years covered by the data – 76.6% of the patients had undergone an HSCT between 2008 and 2013. As of the index date, mean age was 9.8 years and 56.9% of patients were male. About two thirds (66.5%) of patients were covered by a preferred provider organization (PPO) insurance plan (**Table 1**). For 98.6% of the patients, the HSCT procedure was recorded on the date of the hospital admission. Cord blood transplant was performed in 21.5% of patients

(**Table 2**). The median follow-up period after the index date was 1.3 years, 61.2% of patients had at least one year of follow-up data (continuous healthcare plan enrollment), 34.9% had at least two years of follow-up and 7.2% had at least five years of follow-up. During the 6 months prior to the index date, patients incurred average total healthcare costs of US\$287,001 (**Table 1**).

Overall, results show intensive resource utilization following the index date mainly driven by IP days, OP visits and laboratory services (**Figure 3 & Table 3**). The median duration of the index hospitalization was 42 days (IQR 32–55) (**Table 3**). During the first 100 days from the day the HSCT procedure was recorded, patients had an average of 13.8 days with OP visits, 9.4 days with laboratory services visits and an average of 1.7 IP admissions (including the index hospitalization). During the first year following the HSCT

Table 1. Description of study sample characteristics.

Characteristics	n = 209
Age on the index date (years), mean $\pm$ SD (median)	9.8 $\pm$ 4.8 (10.0)
Age categories (years), n (%):	
– 0–5	43 (20.6)
– 6–11	79 (37.8)
– 12–17	87 (41.6)
Male, n (%)	119 (56.9)
Type of insurance plan, n (%):	
– Comprehensive/indemnity plan	7 (3.3)
– Consumer directed healthcare/high-deductible health plan	12 (5.7)
– Point of service (POS)/exclusive provider organization (EPO)	12 (5.7)
– Health maintenance organization (HMO)/POS with capitation	33 (15.8)
– Preferred provider organization (PPO)	139 (66.5)
– Unknown	6 (2.9)
Time from the index date to the end of patient's eligibility (days), mean $\pm$ SD (median):	1.96 $\pm$ 1.80 (1.33)
– ≥ 30 days, n (%)	209 (100.0)
– ≥ 100 days, n (%)	196 (93.8)
– ≥ 1 year, n (%)	128 (61.2)
– ≥ 2 years, n (%)	73 (34.9)
– ≥ 3 years, n (%)	46 (22.0)
– ≥ 4 years, n (%)	30 (14.4)
– ≥ 5 years, n (%)	15 (7.2)
Total healthcare costs during the 6 months prior to the index date, mean $\pm$ SD (median):	287,001 $\pm$ 187,222 (239,311)
– Total medical costs	282,666 $\pm$ 186,610 (232,774)
• Inpatient	206,723 $\pm$ 178,725 (170,418)
• Outpatient	64,635 $\pm$ 51,071 (52,259)
• Emergency room	1083 $\pm$ 6006 (0)
• Laboratory services	9672 $\pm$ 15,735 (3237)
• Other medical services	553 $\pm$ 2508 (0)
– Prescription drug costs	4335 $\pm$ 6813 (1415)

SD: Standard deviation.

Table 2. Description of the type of hematopoietic stem cell transplant and duration of index hospitalization.

Index HSCT characteristics	n = 209
Type of HSCT, n (%):	
– Cord blood	45 (21.5)
– Other allogeneic HSCT	164 (78.5)
Index hospitalization duration (days), mean ± SD (median) [†] :	48.8 ± 28.8 (42)
– <14 days, n (%)	3 (1.4)
– ≥14 and <28 days, n (%)	27 (12.9)
– ≥28 and <56 days, n (%)	126 (60.3)
– ≥56 days, n (%)	53 (25.4)

[†]The duration of the hospitalization was based on the number of days between the index date and the discharge date.
HSCT: Hematopoietic stem cell transplant; SD: Standard deviation.

procedure, patients had an average of 48.8 days with OP visits, 28.9 days with laboratory services and an average of 3.1 IP admissions (including the index HSCT hospitalization; 30.5% of patients had only one IP admission, 35.9% had four or more IP admissions). Although a decreasing trend was observed over time, healthcare resource utilization remained relatively high; 28.8% of patients had at least one IP admission at year 2, 19.6% at year 3, 20.0% at year 4 and the proportion decreased to 6.7% at year 5. The number of days with OP visits and the number of days with laboratory services visits also remained

very high over time: 26, 20, 27 and 13 days with at least one outpatient visit and 12, 6, 11, 8 days with at least one laboratory service visit at year 2, 3, 4 and 5, respectively.

Consistent with healthcare resource utilization, patients incurred substantial healthcare costs following the index date (Figure 4). During the first 100 days and the first year following the HSCT procedure, patients incurred an average total healthcare cost of US\$509,520 ± 406,114 (median of US\$374,715) and US\$683,099 ± 550,283 (median of US\$511,021), respectively (Table 4). The index hospitalization costs represented 62.4% (US\$426,128) of the total healthcare cost incurred during the first year following the HSCT procedure. Total healthcare costs were mainly driven by medical service costs (98.4% in the first year following the index date), with IP and OP costs making up 83.1% (US\$558,670) and 13.0% (US\$87,317) of the medical service costs in the first year following the index date, respectively. Although a decreasing trend was observed over time, healthcare costs remained high; average total healthcare costs was US\$104,584 (median of US\$21,877) at year 2, US\$79,092 (median of US\$11,000) at year 3, US\$106,334 (median of US\$10,426) at year 4 and, over the fifth year following the

Figure 3. Healthcare resource utilization. Description of healthcare resource utilization following the index date.
[†]IP admissions and IP days for the first 100 days and for year 1 include index hospitalization. OP visits and laboratory service visits are mutually exclusive categories.
ER: Emergency room; IP: Inpatient; OP: Outpatient.
Please see [23] for a synopsis of these data.

Table 3. Healthcare resource utilization.

	Index hospitalization [†] n = 209	First 100 days [‡] n = 196	Year 1 [†] n = 128	Year 2 n = 73	Year 3 n = 46	Year 4 n = 30	Year 5 n = 15
Inpatient admissions:							
Proportion of patients with ≥1 visit, n (%)	209 (100.0)	196 (100.0)	128 (100.0)	21 (28.8)	9 (19.6)	6 (20.0)	1 (6.7)
Number of inpatient days, mean ± SD (median)	48.83 ± 28.81 (42.0)	53.47 ± 21.36 (50.0)	68.02 ± 37.41 (56.0)	8.85 ± 22.15 (0.0)	8.48 ± 34.73 (0.0)	8.00 ± 23.57 (0.0)	1.20 ± 4.65 (0.0)
Number of inpatient visits, mean ± SD (median)	1.00 ± 0.00 (1.0)	1.72 ± 0.95 (1.0)	3.10 ± 2.24 (2.0)	0.78 ± 1.57 (0.0)	0.50 ± 1.11 (0.0)	0.80 ± 2.22 (0.0)	0.13 ± 0.52 (0.0)
Number of inpatient visits, n (%):							
– 1	209 (100.0)	101 (51.5)	39 (30.5)	7 (9.6)	2 (4.3)	1 (3.3)	0 (0.0)
– 2	–	63 (32.1)	27 (21.1)	6 (8.2)	1 (2.2)	3 (10.0)	1 (6.7)
– 3	–	22 (11.2)	16 (12.5)	0 (0.0)	5 (10.9)	0 (0.0)	0 (0.0)
– ≥4	–	10 (5.1)	46 (35.9)	8 (11.0)	1 (2.2)	2 (6.7)	0 (0.0)
Outpatient visits[§]:							
– Proportion of patients with ≥1 visit, n (%)	–	173 (88.3)	121 (94.5)	61 (83.6)	41 (89.1)	27 (90.0)	13 (86.7)
– Number of outpatient visits, mean ± SD (median)	–	13.84 ± 9.95 (13.5)	48.83 ± 32.08 (45.0)	26.33 ± 31.50 (18.0)	20.02 ± 17.23 (15.5)	26.63 ± 30.92 (13.5)	12.93 ± 9.20 (12.0)
Emergency room visits:							
– Proportion of patients with ≥1 visit, n (%)	–	23 (11.7)	52 (40.6)	21 (28.8)	11 (23.9)	5 (16.7)	7 (46.7)
– Number of emergency room visits, mean ± SD (median)	–	0.31 ± 1.57 (0.0)	1.39 ± 5.10 (0.0)	0.42 ± 0.76 (0.0)	0.41 ± 0.86 (0.0)	0.27 ± 0.69 (0.0)	0.67 ± 1.05 (0.0)
Laboratory services visits:							
– Proportion of patients with ≥1 visit, n (%)	–	148 (75.5)	108 (84.4)	39 (53.4)	27 (58.7)	20 (66.7)	9 (60.0)
– Number of laboratory services, mean ± SD (median)	–	9.41 ± 11.14 (5.5)	28.92 ± 35.77 (16.0)	11.75 ± 30.71 (2.0)	6.28 ± 9.53 (1.5)	10.93 ± 18.40 (2.5)	8.27 ± 18.28 (1.0)
Other medical services[¶]:							
– Proportion of patients with ≥1 visit, n (%)	–	31 (15.8)	38 (29.7)	9 (12.3)	7 (15.2)	5 (16.7)	1 (6.7)
– Number of other medical services, mean ± SD (median)	–	0.83 ± 3.00 (0.0)	2.95 ± 7.77 (0.0)	0.56 ± 1.82 (0.0)	0.98 ± 4.90 (0.0)	2.43 ± 8.61 (0.0)	1.60 ± 6.20 (0.0)

[†]The index hospitalization includes the period from the index date to the discharge date.
[‡]The first 100 days and year 1 include the index hospitalization.
[§]Outpatient visits and laboratory service visits are mutually exclusive categories.
[¶]Other medical services included all medical claims that were not inpatient, outpatient, emergency room visits or laboratory services (e.g., medical services that patients received at home).
SD: Standard deviation.

index date, patients had an average total healthcare cost of US\$38,291 (median of US\$10,082). IP costs remained the main driver of total medical services costs for year 2 and 3, while OP and laboratory costs were the main drivers in the fourth and fifth years following the index date.

Our results also showed high variation in healthcare costs across patients following the index date (**Figures 5 & 6**). In the first year 29.4% of

the total costs (over the entire sample of patients) were incurred by the 10% patients with the highest costs. Starting from the second year, the 10% of patients with the highest costs accounted for 61.3–76.6% of the total costs for each year.

Discussion

Using US claims data, this study evaluated the healthcare resource utilization and direct

Figure 4. Average total healthcare costs. Description of the average total healthcare costs following the index date.

†Costs for the first 100 days and year 1 include the index hospitalization costs.

Please see [23] for a synopsis of these data.

healthcare costs following HSCT that are reimbursed by private payers in a sample of commercially insured pediatric ALL patients. This study provides the first comprehensive estimate of the economic burden of HSCT in pediatric patients with ALL over 5 year time frame.

Findings from our study showed intensive healthcare resource utilization and substantial costs associated with the HSCT procedure over 5 years. The highest healthcare costs and most intensive healthcare resource utilization were observed within the first year following the HSCT; patients incurred an average total healthcare cost of US\$683,099 (median of US\$511,021) and had an average of 48.8 days with OP visits, 28.9 days with laboratory service visits and 3.1 IP admissions. The majority of costs were incurred during the first 100 days; they were mainly driven by the costs of the hospitalization during which the HSCT was performed. Although a decreasing trend was observed over time, healthcare resource utilization and costs remained substantial with an average total healthcare cost of US\$38,291 (median of US\$10,082) during the fifth year after the HSCT procedure. Findings also suggest a high variation in healthcare costs across pediatric patients following the HSCT; 29.4% of

the total costs (over the entire sample of patients) in the first year were incurred by the 10% of patients with the highest costs. Starting from the second year following the HSCT the 10% of patients with the highest costs accounted for 61.3–76.6% of the total healthcare costs for each year, suggesting that a small proportion of patients still incur very high costs several years after the HSCT, potentially related to some complications or relapse. However, the database did not include clinical information to verify this hypothesis. Further research would be warranted to assess the cost trajectory for a specific population of patients who relapse following the HSCT. Additional studies, using different data sources that provide detailed clinical information such as disease state at the time of the transplantation, type of donor and response would also be warranted to provide a thorough picture of the factors associated with increased cost. Nevertheless, the costs reported in the current study should be representative of the average costs across a privately insured population of pediatric patients with ALL who underwent an HSCT. As an attempt to better describe the cost profile of ALL patients who undergo an HSCT, additional analyses were conducted to assess the total healthcare costs during the

first year after the HSCT stratified by type of transplant (i.e., cord blood vs other HSCT). Findings showed that during the first year after the HSCT, the costs of patients who received a cord blood transplant versus other types of allogeneic HSCT were very similar (cord blood: US\$674,646 vs. other HSCT: US\$686,035). It should, however, be noted that, as there is no incentive for clinicians to use the specific ICD-9 code for a cord blood transplant, it is indeed possible that clinicians only used the general ICD-9 for an allogeneic transplant for some patients who actually received a cord blood transplant.

When comparing our results to the estimates of studies investigating the total healthcare cost of pediatric patients with other chronic conditions (spina bifida and attention-deficit/hyperactivity disorder [ADHD]) and spina bifida-free and ADHD-free cohorts from the same data source, the total healthcare cost observed in our study for the fifth year after HSCT was twice as high as the average annual cost reported in patients with spina bifida, 20-times higher than the cost of patients with ADHD and over 30-times higher than the annual average cost of the spina bifida-free and ADHD-free patients reported in these studies [24,25]. These observations confirm that even 5 years after HSCT, the economic burden among HSCT survivors is substantial.

To the best of our knowledge, no study has assessed the economic burden of HSCT in a US-based population of pediatric patients with ALL over a time frame longer than 1 year after the HSCT procedure. One study investigating the costs associated with allogeneic HSCT in pediatric patients with acute myeloid leukemia, ALL, or myelodysplastic syndrome in the USA reported a median total cost of US\$302,822 over the first 100 days following HSCT [15]. In another study, the average total healthcare costs for the initial hospitalization of pediatric patients with acute leukemia who received allogeneic transplant was US\$208,987 in patients with BMT and US\$282,577 in patients with PBSCT. The average total healthcare cost per patient over the first year post-transplant ranged between US\$352,885 and US\$457,078 in patients with BMT and between US\$377,316 and US\$512,294 in patients with PBSCT, depending on the risk level of the patients (number of prior relapses) [16].

The total healthcare costs reported in combined samples of pediatric and adult patients or

Table 4. Description of the healthcare costs following the index date.

Healthcare costs	Index hospitalization [†] n = 209	First 100 days [‡] n = 196	Year 1 [§] n = 128	Year 2 n = 73	Year 3 n = 46	Year 4 n = 30	Year 5 n = 15
All-cause costs, mean ± SD (median):							
Total healthcare costs	426,128 ± 395,071 (304,341)	509,520 ± 406,114 (374,715)	683,099 ± 550,283 (511,021)	104,584 ± 224,819 (21,877)	79,092 ± 235,116 (11,000)	106,334 ± 196,826 (10,426)	38,291 ± 85,579 (10,082)
Total medical costs	424,964 ± 395,148 (301,723)	506,164 ± 406,330 (370,479)	672,376 ± 547,874 (489,809)	99,064 ± 216,330 (18,546)	76,117 ± 231,185 (9,523)	101,612 ± 188,812 (8,895)	35,591 ± 84,723 (6,899)
Inpatient	424,964 ± 395,148 (301,723)	474,094 ± 408,132 (340,325)	558,670 ± 499,739 (389,544)	57,559 ± 169,715 (0)	54,065 ± 221,380 (0)	41,547 ± 119,964 (0)	37,556 ± 14,548 (0)
Outpatient	–	23,668 ± 31,529 (16,772)	87,317 ± 102,967 (59,096)	33,056 ± 56,221 (10,258)	17,745 ± 27,506 (8,088)	49,584 ± 92,606 (7,703)	11,508 ± 18,027 (4,262)
Emergency room	–	179 ± 819 (0)	793 ± 2374 (0)	199 ± 402 (0)	254 ± 584 (0)	201 ± 740 (0)	545 ± 1234 (0)
Laboratory services	–	7668 ± 11,765 (2595)	23,507 ± 40,133 (8229)	7345 ± 16,367 (268)	3784 ± 6402 (161)	9339 ± 24,212 (372)	19,530 ± 67,626 (0)
Other medical services [§]	–	555 ± 4067 (0)	2088 ± 7071 (0)	905 ± 4139 (0)	267 ± 1086 (0)	941 ± 2963 (0)	252 ± 974 (0)
Prescription drug costs	1163 ± 1683 (590)	3355 ± 4415 (1771)	10,723 ± 13,705 (5412)	5520 ± 16,530 (263)	2975 ± 5635 (299)	4721 ± 9,348 (641)	2700 ± 6041 (127)

[†]The index hospitalization was the period from the index date to the discharge date.

[‡]The first 100 days and year 1 include the index hospitalization costs.

[§]Other medical services included all medical claims that were not inpatient, outpatient, emergency room or laboratory visits. It included medical services that patients received at home.

SD: Standard deviation.

Figure 5. Distribution of total healthcare costs following the index date.

in adult patients only vary significantly across US studies; during the first 100 days after the HSCT procedure, studies reported total healthcare costs ranging from US\$42,149 to US\$303,709 [15,17–18]. In its 2014 report, the Milliman research group reported an estimated total average charged amount of US\$503,00 per patient for the hospitalization associated with the HSCT (including facilities and physicians charges) for patients who received allogeneic HSCT and US\$930,600 per patient for all charges incurred from the 30 days pretransplant period to the 180 days post-transplant discharge [22]. The variations in costs reported across studies reflect the heterogeneity of the study samples, including patients with different underlying diseases, types of transplant (allogeneic, autologous or cord blood), donor source, intensity of the conditioning regimen and different age groups. In addition to these differences in study populations, the short follow-up period

over which costs were measured and the primary focus on inpatient costs within the transplant center limit comparisons between our study and these prior studies [15,26,27].

This analysis was subject to some limitations. Firstly, retrospective databases are subject to potential coding errors or data omissions. Secondly, the total healthcare costs reported in this study reflect costs reimbursed under contractual agreements from private payers. Accordingly, the generalizability of these findings is limited to the population of ALL patients insured by a private insurer and may not be representative of the costs reimbursed by governmental payers such as the Centers for Medicare and Medicaid Services. Although the sample size is relatively small, our findings are likely to be representative of the economic burden of allogeneic HSCT in pediatric ALL patients covered by private insurers given the low number of allogeneic HSCT performed annually in pediatric ALL patients; in its 2013

report, the Center for International Blood and Marrow Transplant Research estimated that approximately 350 patients received an allogeneic HSCT in the USA in 2011 [3]. Thirdly, costs reported in our study are likely to be an underestimation of the overall economic burden of HSCT as they do not include nonmedical and nonpharmacy costs incurred by patients or caregivers such as temporary housing, transportation or indirect costs such as salary loss due to absenteeism, which could be substantial especially for caregivers or expenses to institutions for uncovered costs payment of denied claims, or for uncovered costs. Fourthly, the database did not include sufficient information to confirm that our identification of the HSCT costs

also included the costs for conditioning therapy. However, based on current standards of terminology, we can assume that the conditioning therapy is included as part of the costs reported for HSCT [28]. Finally, information on patient survival was not available in the PharMetrics or MarketScan databases. For each study period over which outcomes were assessed, only patients continuously enrolled in their healthcare plan during the entire period were included. Therefore, our estimates for each time period only reflect the costs incurred by patients who survived and were continuously enrolled in their healthcare plan over the entire period.

Notwithstanding these limitations, our study is the first to assess the economic burden

Figure 6. Proportion of total healthcare costs accounted by patients with the highest costs – following the index date.

†Costs for the first 100 days and year 1 include the index hospitalization costs.

associated with allogeneic HSCT among a US nationally representative sample of pediatric ALL patients with a focus on early costs of HSCT as well as costs of long-term care among survivors. With the increasing number of HSCTs performed, the economic burden of HSCT will become a major consideration for payers. Our study provides a benchmark of the economic burden of allogeneic HSCT in pediatric ALL patients. However, further research would be warranted to assess the nonmedical and nonpharmacy costs incurred by patients or caregivers, as well as other indirect costs. Other studies dissecting the costs associated with sibling, unrelated or alternative donor transplantation in ALL pediatric patients would also be necessary to fully understand the economic burden of transplant based on different donor types.

Conclusion

Findings showed that, among pediatric patients with ALL, healthcare resource utilization and direct costs associated with allogeneic HSCT are substantial with the first year direct costs alone of US\$683,099 and with substantial costs over the following years.

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