Abstract:

Background: Pediatric acute lymphoblastic leukemia (ALL) treatment regimens are lengthy, and there is limited data on the systemic and individual economic burden associated with treatment of ALL.

Objective: This study aims to examine healthcare resource utilization (HCRU) and costs accrued during the first year of therapy among pediatric ALL patients, and to compare costs among those who are Commercially and Medicaid insured.

Methods: Administrative claims data from 2011-16 were analyzed utilizing IBM MarketScan. Newly-diagnosed ALL patients with at least 12 months of enrollment were studied. Demographics and HCRU and costs were stratified by insurance type. The mean (standard deviation (SD) HCRU and reimbursed costs were measured during the first year post-diagnosis. Multivariable generalized linear models were run for total healthcare costs.

Results: 730 (528 Commercial) patients with median age of 6 years were studied. During the 12 months following diagnosis, the mean(SD) inpatient admissions and ER visits for Commercial and Medicaid patients was 6.2(3.7) vs. 6.0(4.6), p=0.6310 and 2.8(6.4) vs. 2.1(2.6),p=0.0380, respectively. Commercial patients experienced more outpatient visits (77.2(28.1) versus 57.4(33.3), p<0.0001) and less pharmacy claims (54.1(22.9) and 61.0(41.8), p<0.0001) versus Medicaid patients. Total healthcare costs were $535,135.89($547,506.23) versus $198,694.94($181,856.27), p<0.0001 for Commercial and Medicaid patients, respectively. When adjusted for age and gender, total healthcare costs in the year post-diagnosis for Commercial patients were 1.60 times the costs in patients with Medicaid.

Conclusion: Pediatric ALL patients have high HCRU and incur significant economic burden. The total cost of care for Commercially insured patients is more than double that of Medicaid insured patients.

Introduction

Pediatric cancer patients have complex healthcare needs,[1] and disease-related hospitalizations, on average, have been shown to cost five times as much as hospitalizations for other pediatric conditions in the United States.[2] Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, and with the advent of modern therapy this patient population maintains an overall survival rate of over 90%.[3] In a single-institution study, Kaul et al showed that first-year per-patient hospitalization costs of ALL increased at an annual average growth rate of 6% in 2012 alone.[2] However, due to the relatively low incidence of cancer in children, and proportion of total health care expenditures attributable to pediatric oncology, there is a paucity of data related to healthcare utilization and costs associated with childhood ALL.[1,2,4]

In the United States, children may be enrolled on Medicaid if their family's income meets the state determined poverty line. Additionally, in some states, children with cancer may qualify if they meet criteria for disability, or by loss of income/ resources associated with the financial burden of childhood cancer.[1] Literature suggests that mortality odds among children with ALL may be related to hospital payer mix.[5] Large data sets that contain payor claims data, which includes both community and tertiary care facility information, as well as inpatient, outpatient, and pharmacy data, allow for a comprehensive assessment of resource utilization and cost-of-care received by children and adolescents with cancer.

In the United States the financial burden associated with cancer is expected to increase faster than overall healthcare costs.[2] Utilizing the International Business Machines (IBM) MarketScan® Commercial Claims and Encounters (Commercial) Database and the IBM MarketScan Multi-State Medicaid (Medicaid) Database this study aims to elucidate the economic burden incurred during the first year of treatment among pediatric ALL patients, as well as to contrast healthcare resource utilization and examine outcome disparities between those with Commercial and Medicaid insurance.

Methods

Study Design and Data Source

This observational retrospective cohort study utilized de-identified administrative claims data from the IBM MarketScan® Commercial Claims and Encounters (Commercial) Database and the IBM MarketScan Multi-State Medicaid (Medicaid) Database.[6] The MarketScan databases provide cost, utilization and outcomes data for healthcare services performed in both inpatient and outpatient settings as well as linked outpatient prescription drug claims and person-level enrollment data. The Commercial Database contains inpatient, outpatient, and outpatient prescription drug claims of approximately 127.6 million employees and their dependents. The population includes patients from several fee-for-service and managed care health plans and is generalizable to the United States insured population. The Medicaid Database also includes inpatient, outpatient, and outpatient prescription drug claims for patients enrolled in Medicaid, who have insurance coverage through several fee-for-service and managed care plans. All study data were obtained using International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes, Current Procedural Terminology (CPT) 4th edition codes, Healthcare Common Procedure Coding System (HCPCS) codes, and National Drug Codes (NDC).

Patient Selection

This study utilized claims from January 1, 2011 through June 30, 2016 for ALL patients meeting select inclusion and exclusion criteria. Patients were required to have at least two diagnoses for ALL (ICD-9-CM 204.0x or ICD-10-CM C91.0x) between January 1, 2011 and June 30, 2015. Index date was defined as the date of the first diagnosis claim for ALL. Patients were also required to be continuously enrolled in medical and pharmacy benefits for a minimum of 3 months pre-index date (baseline) and to be newly diagnosed ALL patients. Newly diagnosed ALL was defined by no evidence of diagnosis codes for ALL or Acute Myeloid Leukemia (AML) anytime pre-index, no relapse or remission codes pre-index (e.g. the first diagnosis code for ALL is ICD-9 204.00/ICD-10 C91.00), and no evidence of chemotherapy or bone marrow transplant pre-index. Patients were also required to be treated with "induction therapy" defined as a steroid (dexamethasone, prednisone, prednisolone, or methylprednisolone) and any of the following drugs (doxorubicin, daunorubicin, vincristine, l-asparaginase) post-index as these are typically the first treatment regimens administered to pediatric ALL patients. Requiring patients to have this treatment post-index not only ensured that the study was considering an ALL

population during the treatment phase of disease, but also, when coupled with the exclusion criteria of no chemotherapy pre-index, provides additional confirmation that the population studied is newly diagnosed. Since the objective of this particular study was to examine healthcare resource utilization and costs in pediatric ALL patients during the first year following diagnosis, patients under 21, and those with evidence of capitated claims were excluded. Patients were also required to have a minimum of 1 year of continuous enrollment with medical and pharmacy benefits following initial ALL diagnosis in order to more fairly compare 12-month utilization and costs between Commercial and Medicaid patients. The study period comprised a 3-month baseline-period in addition to a variable-length follow-up (a minimum of 1 year) from index date to the end of follow-up [the earliest of inpatient death, end of continuous enrollment or end of study period (June 30, 2016)].

Demographic Characteristics and Treatment

Demographic variables of interest were measured on the index date and included age (in years as well as categorized into 0-9.99 years versus 10-20.99 years), gender (male or female), race (White, Black, Hispanic, Other; available for Medicaid only), United States Census Bureau geographic region of residence (northeast, north central, south, west, or unknown; available for Commercial only), health plan type (comprehensive/indemnity, Exclusive Provider Organization (EPO)/preferred provider organization (PPO), Health Maintenance Organization (HMO), Point of Service (POS)/POS with capitation, Consumer-Directed Health Plan (CDHP)/ High-Deductible Health Plan (HDHP), and index year (year of first ALL diagnosis claim during the study period). NCCN guideline-recommended treatments for pediatric ALL were flagged during the follow-up period, and included the following treatments (l-asparaginase, vincristine, doxorubicin/daunorubicin, methotrexate, 6-mercaptopurine (6-MP), cytarabine, etoposide, 6-thioguanine, cyclophosphamide, prednisone/methylprednisolone, prednisolone, dexamethasone). The number and proportion of patients with evidence of any of the above listed treatments at any time post-diagnosis was reported to provide a basic understanding of the treatments used by patients in Commercial and Medicaid populations as treatment can play a major role in healthcare resource utilization and costs. However, since this study was not aimed at understanding switching and discontinuation of treatments among a pediatric ALL population,

line of therapy logic was not applied and therefore treatment regimens and whether patients were administered therapies in combination or switching between treatments were not examined.

Healthcare Utilization and Costs

All-cause healthcare utilization and healthcare costs were reported separately for Commercial and Medicaid patients by type of service (inpatient, emergency room (ER), non-ER outpatient, pharmacy, and total) and measured during the first year following initial ALL diagnosis (index date). For all service types, the proportion of patients with the service type, the number of services, and the related healthcare costs were reported. Additionally, for inpatient admissions, the average length of stay [6] per admission was examined. Non-ER outpatient visits included any office visit outside of ER visits as well as additional outpatient services including chemotherapy administration, laboratory or imaging encounters. Healthcare costs were defined as the paid amount of fully-adjudicated claims including the plan reimbursement amount as well as the patient-paid portions (copay, coinsurance, deductible). Costs were adjusted for inflation to 2016 US dollars using the medical care component of the Consumer Price Index.[7]

Statistical Analysis

Results are reported stratified by Commercial and Medicaid patients. Continuous variables are presented with means, standard deviations, and medians while categorical variables are presented with counts and percentages. Demographic characteristics, treatments received and healthcare utilization and cost outcomes were compared between patients in the Commercial and Medicaid cohorts using t-tests for continuous variables and Chi-squared tests for categorical variables. Multivariable generalized linear models (GLM) with a log link and gamma error distribution were run to compare total healthcare costs in the year post-diagnosis between Commercial and Medicaid patients adjusting for age (age 10 to 20 versus age 0-9) and gender (male versus female). =For all statistical tests, a p-value < 0.05 was considered statistically significant. All analyses were conducted using Statistical Analysis Software (SAS®) 9.4 (SAS Institute Inc., Cary, NC).

Results:

A total of 790 Commercial patients and 550 Medicaid patients met the study inclusion and exclusion criteria. A further restriction to patients with no evidence of capitated claims reduced

the analytic sample size for cost analyses to 758 for Commercial and 231 for Medicaid. Requiring a minimum of 1 year of continuous enrollment post-index resulted in a final cohort of 528 and 202 patients with Commercial and Medicaid insurance, respectively. (Figure 1, Figure 2)

Demographic Characteristics and Treatments

The mean (SD) age of patients with Commercial and Medicaid insurance was 7.9(5.4) and 7.0(5.2), respectively and 56.4% of Commercial and 59.4% of Medicaid patients were male (Table 1). A greater proportion of patients with Medicaid insurance were indexed (first ALL diagnosis) in 2014/2015 compared to those with Commercial insurance. Medicaid patients in our study cohort also had significantly longer average follow-up compared to Commercial patients (1036 days versus 948 days, respectively). The majority of patients in the Medicaid database (94%) were covered under a comprehensive/indemnity payer plan while the majority of patients in the Commercial database were covered under an EPO/PPO payer plan. Region was reported for Commercial patients only and the largest proportion of patients were from the South (39.2%) and North Central (25.6%) regions. Race information was available for Medicaid patients only and the largest proportion of patients were White, followed by a fairly even split among the remaining reported races (Black, Hispanic, and Other). (Table 1)

Since patients in this study were required to have evidence of treatment with vincristine, l-asparaginase, daunorubicin, doxorubicin, methotrexate, cyclophosphamide or etoposide along with steroid use anytime post-index, there were no untreated patients included in this analysis. Almost 100% of patients had evidence of either vincristine or methotrexate post-index. Prednisone use was slightly more common than dexamethasone use, though both treatments were used in more than 97% of the study population at some point following diagnosis. Overall, treatment use was similar between patients with Commercial versus Medicaid insurance, though cytarabine was more commonly used among Commercial patients (89.0% versus 80.7% for Medicaid). (Table 2)

Healthcare Utilization and Costs

Utilization and costs were computed for the first year following ALL diagnosis. (Table 3, Table 4). A greater proportion of patients with Commercial insurance had at least 1 inpatient admission (98% versus 89% for Medicaid) and at least 1 ER visit (75% versus 67% for Commercial versus Medicaid, respectively). (Table 3) The average length of stay per admission for patients with an admission was approximately 6 days for patients regardless of insurance type. The mean (SD) number of inpatient admissions and ER visits for Commercial and Medicaid patients was 6.2(3.7) vs. 6.0(4.6), p=0.6310 and 2.8(6.4) vs. 2.1(2.6), p=0.0380, respectively. Commercial patients experienced significantly more outpatient visits (77.2[28.1] versus 57.4[33.3], p<0.0001) and significantly less pharmacy claims (54.1[22.9] and 61.0[41.8], p=0.0268) versus Medicaid patients.

The average total healthcare costs during the first year following diagnosis were more than double for patients with Commercial insurance compared to patients with Medicaid ($535,135.89[$547,506.23] versus $198,694.94[$181,856.27], p<0.0001). Costs were mainly driven by inpatient costs ($304,024.86 for Commercial versus $120,743.26 for Medicaid) and non-ER outpatient costs ($221,333.37 versus $63,876.76 for Commercial versus Medicaid, respectively). Pharmacy-related costs were significantly greater for Medicaid patients ($13,244.76) versus Commercial patients ($6,707.19). (Table 4)

Adjusting for age and gender, patients with Commercial insurance had 1.60 times the costs of patients with Medicaid insurance during the year following initial ALL diagnosis (Table 5). Additionally, older pediatric patients (aged 10 to 21) cost on average 1.89 times the cost of patients less than 10 years of age and male patients cost on average 1.08 times the cost of female patients. Models were also run for inpatient costs, ER costs, non-ER outpatient costs, and pharmacy costs in the first year following initial ALL diagnosis, and confirmed the unadjusted results presented in Table 4. Specifically, adjusting for age and gender, patients with Commercial insurance had 1.48 times the inpatient costs, 1.83 times the ER costs, 1.83 times the non-ER outpatient costs, and 0.68 times the pharmacy costs compared to patients with Commercial insurance.

Discussion

With the cost of pediatric cancer hospitalizations averaging nearly five times higher than hospitalizations for any other pediatric condition,[2,8] healthcare utilization and financial toxicity have rapidly emerged as areas of interest in pediatric oncology. To the best of our knowledge this is the first dedicated pediatric ALL investigation to utilize claims data to examine disparities in inpatient and outpatient healthcare utilization, as well as health outcomes, between those with Commercial and Medicaid insurance. Our findings indicate that in the first year of therapy the total reimbursement of care for Commercially insured patients is over two and a half times that of Medicaid insured patients. Patients with Commercial insurance did have a significantly higher average number of outpatient and ER visits, which may, in part, account for this reimbursement differential. However, reimbursement for hospital admissions among those with commercial insurance was also about two and a half times that of those with Medicaid insurance, despite a similar number of inpatient admissions and average length of stay between the two groups.

Children with cancer have high healthcare resource use and spending, and the notion that healthcare utilization differs for pediatric cancer related admissions paid for by Medicaid compared with Commercial insurance is not novel. Yet, in contrast to our findings, previous studies suggest that length of stay is substantially longer for Medicaid patients, with roughly equivalent total cost of admission for the two groups.[9] This discrepancy may stem from the fact that our analysis was limited to the first year of therapy. While the initiation of chemotherapy for ALL is conducted in the hospital, the bulk of the two to three-year treatment regimen for this condition occurs in the outpatient setting. Hospitalizations after the first several months are typically unplanned, and occur due to treatment-related toxicities including fever and neutropenia, infection, neurotoxicity, cardiotoxicity, thrombosis, and osteonecrosis.[2] Whittle et al showed that among pediatric cancer patients, Medicaid admissions were more commonly associated with younger patients, racial minorities, leukemia, as well as infections and toxicity, as compared to admissions in those with Commercial insurance. The authors cited post-procedure infections, which were significantly higher in Medicaid admissions, as one reason for this discrepancy.[9] Moreover, in this study, Medicaid patients also had a higher rate of chemotherapy administration during the same hospitalization as the procedure for which they were admitted, making hospital length of stay longer.[9] This trend may be accounted for by

medical provider biases and social determinants of health. Results from our study are limited in that they do not account for race, ethnicity, socioeconomic status, health literacy, location of care, and access to healthcare resources, all of which play a role in the complex process of healthcare resource utilization and cost analysis. Further studies incorporating these factors are needed to further understand the financial impact of ALL care, and to elucidate value-based interventions that will alleviate economic burden for healthcare systems and individual families.

Publications focusing on insurance status and health outcomes in pediatric oncology are limited, and show mixed results. In a study utilizing Surveillance, Epidemiology, and End Results (SEER) data, Lee and colleagues found that cancer survival is largely similar for children with Medicaid and those with private insurance at diagnosis.[10] Conversely, utilizing information from the Pediatric Health Information Systems administrative database, Fitzgerald and colleagues found that higher overall proportion of patients hospital-wide with public insurance is associated with higher center-level mortality for pediatric leukemia patients treated in the intensive care unit. These findings are in line with prior studies which point to a relationship between hospital payer mix and ALL induction mortality.[5,7] The etiology underlying the suggested discrepancy in outcomes based on insurance status is likely multifactorial, and related to hospital resources, location, financial strain, and adequate provider capacity. Moreover, disease risk stratification, adherence to protocols, and enrollment in research studies are all critical factors, which may play a role. The MarketScan database does not reflect such granular data, and thereby limits our ability to fully assess the impact of insurance on patient health outcomes. Future, prospective studies are needed to further evaluate this important area of pediatric cancer care.

The economic burden of cancer care is not isolated to healthcare systems. Families of pediatric cancer patients are at high risk for long-term financial hardship and stress during cancer treatment, with resultant negative effects on quality of life and parental emotional health.[8-11] Within our findings the only financial metric that was significantly higher among Medicaid patients is both average number, and cost of pharmacy claims. This suggests that commercially insured patients may be carrying a higher burden of out-of-pocket medication costs. Thus, medical providers caring for this patient population should be cognizant of the financial

adversity associated with this, and other factors, such as work disruption and cost of travel, which may make families vulnerable. When feasible, this should be considered when developing treatment and monitoring plans and prescribing brand versus generic medications.[9] Moreover, patients should be provided with adequate social support and resources to navigate these challenging circumstances.

Limitations

There are several limitations to consider when interpreting results from this study. In general, administrative claims data are subject to coding limitations and data entry errors. Costs included in the MarketScan database reflect the paid amounts of adjudicated claims and therefore out of pocket care or care received as part of clinical trial participation may not be fully captured. Results from this study are not generalizable to patients who do not have Commercial or Medicaid health insurance.

Capitated services are often associated with lower per-patient costs than non-capitated services, and capitation was more common in Medicaid so this analysis was limited to patients with no evidence of capitated services during the study period. However, regardless of capitation, Medicaid tends to reimburse healthcare services at a lower rate than Commercial patients, and to fully compare burden of disease in these populations, it was important to examine both healthcare resource utilization and healthcare costs.

Lastly, an important limitation of the MarketScan database is that it does not account for clinical patient-level details such as disease risk-stratification and immunophenotype and has limited capture of clinical trial participation. These factors are critical in determining plan of care, length of treatment, risk of complication, and highly affect resource utilization and cost. Moreover, MarketScan does not fully account for race, ethnicity and socioeconomic status, all of which may be integral to disparities in patient care and outcomes. Thus, further studies utilizing more granular information in conjunction with claims data are needed to expand upon the findings of this investigation.

Conclusion

Pediatric ALL leads to significant financial burden in the first year of therapy, with a striking disparity in cost and healthcare resource utilization between Commercial and Medicaid insured patients. Further research is needed to better understand healthcare system and patient-related factors driving these differences, as well as short- and long-term systemic and personal economic implications, and impact on health outcomes for this population.

Funding

Support for data acquisition was provided by the Herbert Irving Comprehensive Cancer Center (P30CA013696).

Disclosures

Study authors are students or employed by Columbia University or Columbia University Irving Cancer Center. EM is a student at Columbia University and also employed by IBM Watson Health. Work on this study and manuscript was completed separately from her employment at IBM. LJ, ZJ, DH, and PS are employed by Columbia University. Additionally, PS is consultant for Mesoblast, Takeda and Sobi Pharmaceuticals.

Acknowledgments

The study authors would like to acknowledge Donna Buono at Columbia University for her early data management support.

REFERENCES

1. Mueller EL, Hall M, Berry JG, Carroll AE, Macy ML. Healthcare utilization and spending by children with cancer on Medicaid. *Pediatric blood & cancer.* 2017;64(11).
2. Kaul S, Korgenski EK, Ying J, et al. A retrospective analysis of treatment-related hospitalization costs of pediatric, adolescent, and young adult acute lymphoblastic leukemia. *Cancer medicine.* 2016;5(2):221-229.
3. Teachey DT, Pui CH. Comparative features and outcomes between paediatric T-cell and B-cell acute lymphoblastic leukaemia. *The Lancet Oncology.* 2019;20(3):e142-e154.
4. Parsons SK, Castellino SM, Yabroff KR. Cost, Value, and Financial Hardship in Cancer Care: Implications for Pediatric Oncology. *Am Soc Clin Oncol Educ Book.* 2018;38:850-860.
5. Fitzgerald JC, Li Y, Fisher BT, et al. Hospital Variation in Intensive Care Resource Utilization and Mortality in Newly Diagnosed Pediatric Leukemia. *Pediatr Crit Care Med.* 2018;19(6):e312-e320.
6. Lee RH, Pulin AA, Seo MJ, et al. Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6. *Cell Stem Cell.* 2009;5(1):54-63.
7. Seif AE, Fisher BT, Li Y, et al. Patient and hospital factors associated with induction mortality in acute lymphoblastic leukemia. *Pediatric blood & cancer.* 2014;61(5):846-852.
8. Pelletier W, Bona K. Assessment of Financial Burden as a Standard of Care in Pediatric Oncology. *Pediatric blood & cancer.* 2015;62 Suppl 5:S619-631.
9. Santacroce SJ, Kneipp SM. Influence of pediatric cancer-related financial burden on parent distress and other stress-related symptoms. *Pediatric blood & cancer.* 2020;67(3):e28093.
10. Kaul S, Barbeau B, Wright J, Fluchel M, Kirchhoff AC, Nelson RE. Statewide Longitudinal Hospital Use and Charges for Pediatric and Adolescent Patients With Cancer. *J Oncol Pract.* 2015;11(4):e468-475.
11. Warner EL, Kirchhoff AC, Nam GE, Fluchel M. Financial Burden of Pediatric Cancer for Patients and Their Families. *J Oncol Pract.* 2015;11(1):12-18.