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Establishment of an 11-Year Cohort of 8733 Pediatric Patients Hospitalized at United States Free-standing Children's Hospitals with *de novo* Acute Lymphoblastic Leukemia from Healthcare Administrative Data

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Abstract

Background—Acute lymphoblastic leukemia (ALL) accounts for almost one quarter of pediatric cancer in the United States. Despite cooperative group therapeutic trials, there remains a paucity of large cohort data on which to conduct epidemiology and comparative effectiveness research studies.

Research Design—We designed a three-step process utilizing ICD-9 discharge diagnoses codes and chemotherapy exposure data contained in the Pediatric Health Information System administrative database to establish a cohort of children with *de novo* ALL. This process was validated by chart review at one of the pediatric centers.

Results—An ALL cohort of 8,733 patients was identified with a sensitivity of 88% (95% CI: 83–92%) and a positive predictive value of 93% (95% CI: 89–96%). The 30-day all cause inpatient case fatality rate using this three-step process was 0.80% (95% CI: 0.63–1.01%), which was significantly different than the case fatality rate of 1.40% (95% CI: 1.23–1.60%) when ICD-9 codes alone were used.

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Conclusions—This is the first report of assembly and validation of a cohort of *de novo* ALL patients from a database representative of free standing children's hospitals across the United States. Our data demonstrate that the use of ICD-9 codes alone to establish cohorts will lead to substantial patient misclassification and result in biased outcome estimates. Systematic methods beyond the use of just ICD-9 codes must be employed prior to analysis to establish accurate cohorts of patients with malignancy. A similar approach should be followed when establishing future cohorts from administrative data.

Keywords

leukemia; health administrative data; children

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children, accounting for almost one quarter of pediatric cancer cases and 77% of pediatric leukemia cases in the United States (1). Cooperative group trials have led to current therapies with event free-survival approaching 85%.(2) Depending on the trial, 1–2% of ALL patients die during their induction chemotherapy, which represents approximately one-tenth of all ALL-associated deaths(3–5). Although case fatality rates have improved over time, chemotherapy treatment advances are still needed to reduce treatment related morbidity.

To date, studies in pediatric ALL have been performed using either single institution trials or cooperative group therapeutic protocols. While these study populations have effectively tested chemotherapy efficacy hypotheses, they are not well suited to clinical epidemiology and comparative effectiveness research questions. In addition, cooperative group studies are limited strictly to patients participating in a trial. Clinical epidemiology and comparative effectiveness research studies require large sample sizes that include both on and off-protocol therapy patients, as well as daily medication and medical procedure utilization data. To our knowledge, such data sets have not been established either in the United States or European countries for the analysis of pediatric oncology clinical epidemiology questions.

In order to address this research gap, we sought to assemble and validate a large cohort of patients with newly diagnosed pediatric ALL receiving treatment at one of 43 free-standing pediatric institution throughout the United States that contribute to the Pediatric Health Information Systems (PHIS) administrative database. While PHIS data do not include outpatient data, the initial diagnosis and treatment of pediatric ALL is almost always performed in the inpatient setting. Therefore, the PHIS data set represents a unique opportunity to identify a cohort of children with this malignancy.

PHIS currently captures approximately 85% of the freestanding pediatric hospitals registered with the National Association of Children's Hospitals and Related Institutions. The hospitals that contribute data to this database serve a diverse population with most of the metropolitan areas in the United States represented. PHIS data includes International Classification of Diseases-9 Clinical Modification (ICD-9) discharge diagnoses and procedure codes, as well as day-by-day pharmacy billing data. Investigators have used PHIS data to study a wide range of important clinical epidemiology questions, such as the use of steroids in the treatment of meningitis and Henoch-Schonlein purpura, and medical therapy of appendicitis (6–8).

Recent literature has highlighted the importance of validating the mechanism in which patient cohorts representing a specific disease are assembled from health administrative data (9). To our knowledge no investigators have assembled and validated a cohort of patients

with *de novo* ALL from PHIS. We hypothesized that such a cohort could be established within PHIS by utilizing a multi-step process that employed a combination of ICD-9 discharge diagnosis and procedure codes as well as billing data for various chemotherapy agents typically utilized in induction therapy for ALL. We hypothesized that this multi-step process would result in a higher positive predictive value than, and comparable sensitivity to, using ALL ICD-9 discharge diagnosis codes alone to determine subjects eligible for inclusion into the final cohort. As a measure of external validity, we compared select demographic characteristics of our final cohort to those reported by the Surveillance Epidemiology and End Results (SEER) Program.

Materials and Methods

Data Source

PHIS is a comparative pediatric administrative database including inpatient data from 43 not-for-profit, tertiary children's hospitals affiliated with the Child Health Corporation of America (Overland Park, KS). PHIS data are derived from two primary data sources within the participating hospitals. The hospital's medical record system provides patient identification, demographics, dates of service, discharge disposition, and up to 40 ICD-9 discharge diagnosis and procedure codes. Since PHIS member hospitals do not yet contribute ICD-10 codes, only ICD-9 codes were used when applicable. Additionally, the hospital's billing system provides billed resource utilization data for each patient for every hospital day of service. This resource utilization data include all billed pharmaceuticals, laboratory tests (without results), imaging procedures (without results), and supplies. Each patient's vital status at the time of the hospital discharge is also recorded. Patients are assigned a unique identifier in the PHIS database that is preserved for all admissions. Therefore, patients can be followed from one inpatient admission to the next.

Oversight of the methods to maintain PHIS data quality is a joint effort between Child Health Corporation of America, Thomson Reuters Healthcare (data processing partner), and participating hospitals. Each hospital uses a uniform file layout created specifically for PHIS with each data element having a detailed definition. After file submission to Thomson Reuters, data quality audits are performed. These audits primarily check for valid entries (e.g., valid ICD-9 diagnosis codes) and reasonable patient information (e.g., birth weight). Reports are generated that identify errors needing correction. Error rates above predefined threshold values require hospitals to perform a data review and resubmission until error rates fall below the threshold values. Known data quality issues are transparently communicated to all PHIS data users. These data quality reports allow the data users to exclude data for data quality reasons.

Study Cohort Assembly

The source population for this cohort was patients aged 0 to 21 years admitted to a PHIS contributing hospital between the dates of January 1, 1999 and December 31, 2009. A three-step process was performed to assemble a cohort of patients with presumed *de novo* ALL. Step 1 included screening the PHIS database to identify a patient's first hospital admission during which an ICD-9 discharge diagnosis code within the 204.xx subset was assigned. The 204.xx code is not exclusive to patients with newly diagnosed ALL and can refer to patients with *de novo* relapsed, or secondary ALL. Patients were excluded if the PHIS data for the hospitalization containing the 204.xx ICD-9 discharge diagnosis code was not complete, for instance if the child was admitted to a PHIS contributing hospital during periods where that hospital's data were not complete or the patient specific hospital data were missing (i.e. unavailable pharmaceutical billing data). In step 2, patients were excluded if data suggested the presence of an alternative malignancy or receipt of a bone marrow transplant during the

index hospital admission. The presence of the former was based on the assignment of an ICD-9 discharge diagnosis code consistent with an additional or alternative malignancy diagnosis (140.xx – 239.xx, excluding 204.xx). The latter was based on the presence of an ICD-9 discharge diagnosis (v42.81, v42.82, 279.50, or 996.85) or procedure code (41.0x) consistent with a bone marrow transplant or the billing for a medication (e.g. busulfan, melphalan, and thiotepe) consistent with the same. Patients with evidence of hematopoietic stem cell transplantation in their index admission were excluded because this intervention is nearly exclusively used for therapy of relapsed or secondary ALL. In the rare case of a child with primary refractory or very high-risk disease who would require an early transplant for ALL, it is extremely unlikely for the child to receive the transplant in the first admission. Patients who received a stem cell transplant in a subsequent hospital admission were not excluded from the final cohort, as it is plausible that they had *de novo* ALL during their index hospitalization but had a subsequent medical need for transplantation. Step 3 involved a comprehensive review of the chemotherapy agents billed for during each patient's first identified ALL admission to determine whether such chemotherapy was consistent with induction therapy for *de novo* ALL.

Prior to reviewing the PHIS chemotherapy billing data, guidelines were established to guide the execution of step 3. These guidelines included 14 distinct chemotherapy regimens frequently used for induction ALL chemotherapy (available from author R.A.). Recognizing that some patients may not receive one of these specific regimens, we also considered two additional *de novo* ALL chemotherapy patterns. Patients who were billed for at least three of four standard ALL induction chemotherapy agents (vincristine, asparaginase, an anthracycline (daunorubicin or doxorubicin) and a steroid (prednisone, methylprednisone, or dexamethasone)) within a 14-day window during their first ALL admission were identified. Patients started on a regimen consistent with ALL induction therapy but discharged prior to completion of induction therapy, presumably to complete the regimen in the outpatient setting, were also identified.

Once these *priori* chemotherapy guidelines were established, each patient's hospital chemotherapy billing data for up to 60 inpatient days were manually reviewed by study personnel to determine if the patient met criteria for *de novo* ALL induction therapy. If a patient was billed for chemotherapy consistent with one of the 14 defined regimens then they were considered to have received this regimen. Those patients not receiving one of the 14 regimens but still meeting criteria for receipt of ALL induction chemotherapy were classified as "ALL Chemotherapy Not Otherwise Specified (NOS)". Patients not satisfying any of these chemotherapy regimen criteria were classified as not having *de novo* ALL and thus were not included in the final cohort. Finally, the first review of a minority of patients resulted in the designation of an 'uncertain' regimen. These 'uncertain' regimens were subsequently reviewed by a study committee comprised of four study authors (B.T.F., A.E.S., S.R.R. and R.A.). If an 'uncertain' regimen was deemed to be consistent with induction chemotherapy by this committee then the patient was included in the cohort as "ALL Chemotherapy Not Otherwise Specified (NOS)", otherwise they were excluded from the final cohort.

The primary chemotherapy review was performed equally by two study authors (T.H. and K.T.). In order to assess the inter-rater reliability of the two reviewers, a 15% sample of the cohort was reviewed by both. The correlation of the two reviews for this 15% sample was assessed using the prevalence-adjusted bias-adjusted Kappa statistic to measure the level of consistency (10).

Study Cohort Validation

Both the positive predictive value and the sensitivity of the cohort assembly at each of the three steps above were determined via hospital chart review for all patients admitted to the Children's Hospital of Philadelphia (CHOP) from 2004 through 2009 (CHOP began PHIS data contribution in 2004). A systematic chart review was performed for each patient in PHIS that was admitted to CHOP to establish whether the patient was truly a *de novo* ALL case. Members of the study team (B.T.F. and A.S.) reviewed the bone marrow aspirate/ biopsy pathology results and the attending oncology clinician's progress notes to determine the actual malignancy diagnosis. Additionally, the past medical history was reviewed from the admission history and physical to identify any prior malignancies. The chart abstractionists were blinded to the PHIS data at the time of chart review. An internal CHOP ALL registry, which catalogues all new ALL diagnoses at CHOP, was used as the gold standard for patients with *de novo* ALL at CHOP. The patients from this registry were compared with those patients identified in PHIS and validated by chart review as having *de novo* ALL to calculate the sensitivity of our cohort assembly mechanism.

The negative predictive value was not calculated as the PHIS database contains millions of non-ALL admissions, which would translate into numerous true negative patients, and therefore the negative predictive value would be predictably high. Likewise the number of patients admitted to CHOP without ALL during the period of interest would be numerous enough that the specificity would also be predictably high.

Demographic characteristics (age, race, sex and ethnicity) were compared to those reported by the National Cancer Institutes' SEER Program from 1992–2004 using Pearson's Chi-Square test. The SEER Program maintains the preeminent national, population based cancer registry available in the United States. It compiles demographic data on various malignancies and thus is the best available standard for evaluating the demographic characteristics of the PHIS based cohort.

All cause mortality

All cause inpatient case fatality rates within 30 days from the admission date of each patient's first hospitalization were calculated at each step of the cohort assembly process. The case fatality rates for those patients included at each step were compared to the case fatality rates for patients excluded at the same step using Pearson's Chi-Square test.

The above described data compilation, management and analyses were performed using Microsoft Excel, SAS version 9.2(Cary, NC) and STATA statistical software version 10.0 (College Station, TX).

Results

The initial query of the PHIS database from January 1999 to December 2009 identified 15,970 unique patient hospital admissions containing the ICD-9 code of 204.xx. The three-step process narrowed this cohort to 8,733 patients with presumed *de novo* ALL from 39 different freestanding pediatric institutions across the United States (Figure 1).

Characteristics of the cohort are shown in Table 1 and are compared to those reported from the National Institute of Cancer's SEER Program for 1992–2004 (1). The PHIS and SEER cohorts shared similar sex distribution. Comparison of age and race composition also appeared to be similar, although formal statistical comparison of the two patient populations did reveal statistically significant differences.

The sensitivity and positive predictive value for each of the three steps of the cohort assembly process are shown in Table 2. The sensitivity of the ICD-9 discharge diagnosis

code for ALL alone was quite high, but the positive predictive value was only 69%. By excluding patients with evidence of another malignancy or receipt of a bone marrow transplant during the first hospitalization and then subsequently employing the manual chemotherapy review, the positive predictive value was optimized to 93%. Despite the addition of these more stringent inclusion and exclusion criteria there was only a modest loss of sensitivity to 88%.

Table 3 displays the 30-day inpatient mortality rate calculated at each of the three steps of the cohort assembly. By including all patients with an ICD-9 code of 204.xx the case fatality rate within 30 days of hospital admission was 1.4% (95% CI: 1.23–1.60%). After excluding patients with evidence of an alternative malignancy or receipt of a bone marrow transplant during the first identified hospitalization and excluding patients that did not receive an induction chemotherapy regimen during that same first hospitalization, the inpatient case fatality rate within 30 days of hospitalization was recalculated as 0.8% (95% CI: 0.63–1.01%). The case fatality rates for those patients excluded at each step were significantly higher than the case fatality rates for patients included at the same step ($P < 0.0001$).

The comparison of the chemotherapy regimen assignments between the two reviewers for the 15% sample resulted in a proportion of agreement of 0.98 and a prevalence-adjusted bias-adjusted Kappa statistic of 0.97.

Discussion

To our knowledge, this is not only the first report of successful assembly and validation of a cohort of pediatric *de novo* ALL patients from a large healthcare administrative database but also the first cohort of pediatric or adult hematologic malignancy patients defined with a combined ICD-9 diagnosis code/induction chemotherapy definition. This approach established a cohort that is demographically consistent with the SEER data from 1992–2004. Specifically, the cohort characteristics from our data set appear very similar to the SEER data relative to age, sex, and race. Although formal statistical comparisons demonstrated statistically significant differences for age and race, the actual proportions were very similar, and the statistically significant differences were due to the large sample sizes, rather than clinically meaningful differences. The data element representing ethnicity in the PHIS database is not reliable as it is often coded as missing and thus a comparison of ethnicity rates between the two data sources was not possible.

Our data demonstrate that the use of ICD-9 codes alone do not accurately identify pediatric patients with *de novo* ALL. The commonly used 204.xx series of codes does not differentiate in any way between newly diagnosed, relapsed, and secondary ALL. Therefore the use of ICD-9 code based cohort establishment method will lead to substantial patient misclassification (i.e. inclusion of patients without *de novo* ALL) and thus result in biased outcome estimates. To assess the impact of patient misclassification, we calculated the 30-day all cause inpatient case fatality rate at each of the three steps of our cohort assembly. Although 30-day all cause case fatality rates may underestimate induction case fatality rates (as the induction period for some patients may extend beyond 30-days from admission, and a small percentage of patients die before receiving any chemotherapy) they serve as a reasonable approximation. As noted in our results, the inpatient case fatality rate changed significantly from the first to third steps.

A primary reason for this decrease in death was the exclusion of patients with evidence of an alternative malignancy or receipt of a bone marrow transplant often used for therapy of relapsed and secondary ALL. This variation in mortality rates highlights the importance of performing the additional, time-intensive steps to establish a cohort of patients that is more

representative of the intended population. After an index admission, a patient could have been readmitted to a non-PHIS institution, and thus it is possible that our data would not capture a mortal outcome at that institution. However, we would anticipate that most non-PHIS centers would immediately transfer a sick pediatric oncology patient to the institution at which the patient's ALL treatment was initiated and thus the likelihood of missing an inpatient death at a non-PHIS center is assumed to be minimal.

The relatively poor performance of ICD-9 codes alone to define a cohort of patients with *de novo* ALL is not surprising, given the well-described limitations of ICD-9 codes. The inclusion of manual induction chemotherapy review significantly improved the validity of the study cohort. The manual review of chemotherapy was labor intensive, as the reviewer training, data evaluation, and validation required approximately 450 hours of reviewer time. The high reviewer correlation coefficient provides strong evidence that the review process was systematic and accurate. Our data argue that future pediatric or adult research using administrative data sets, such as PHIS, Medicare, or Medicaid, will need to perform a similar process to ensure the establishment of a homogeneous study population. In the future, chemotherapy review efficiency may be improved by using programmable review algorithms. Our group is currently evaluating such algorithms in the ALL data set.

Benchimol et al., recently proposed a set of criteria to guide researchers performing validation studies involving health administrative data and also to guide the reader in assessing the quality of such work (9). They emphasize the pitfalls of relying solely on ICD-9 codes to identify patient cohorts with a certain disease from health administrative data. They specifically state: "the dissemination of validation studies is vital to advance the field of research using health administrative data and should therefore be reported in peer-reviewed publications". While we performed our validation prior to the publication of these guidelines, we are confident that our approach is consistent with the general concepts presented. For instance we provided a complete description of the validation cohort, detailed how the reference standard was applied, provided statistics to assess inter-rater reliability and reported the diagnostic accuracy with 95% confidence intervals of such statistics as sensitivity and positive predictive value.

The primary limitation to our study is that validation occurred at only one of the PHIS contributing pediatric centers due to the limited resources available for this labor intensive approach to cohort definition. PHIS data completeness may vary by center, and thus a similar validation process at other institutions may result in variation in sensitivity estimates. For example if a hospital's billing data were not accurate for chemotherapy medications, some patients with *de novo* ALL may have been eliminated in the chemotherapy review stage (step 3), reducing the overall sensitivity of this approach. Additionally, our method would not detect a patient who was critically ill at the time of presentation with *de novo* ALL and died before receiving chemotherapy. Similarly these patients would be eliminated in the chemotherapy review stage (step 3) reducing the sensitivity. This latter circumstance is extremely rare (approximately 0.3% of all ALL patients)(11) and thus the impact on overall sensitivity is expected to be negligible. This potential reduction in sensitivity, however, does not obviate the need for inclusion of induction treatment data in the establishment of a cohort of *de novo* ALL patients. The absence of chemotherapy data at certain hospitals would not have altered the positive predictive value of our approach, and thus the patients retained in the final cohort are still likely to have *de novo* ALL making this a viable cohort for future analysis.

Additionally, while it is nationally representative in many respects, this cohort was established from large freestanding children's hospitals in the United States, and any subsequent analyses will only be representative of children treated at such institutions across

the country. Finally, ALL is most often diagnosed in the inpatient setting but subsequently managed outpatient. Although this dataset will not allow for the investigations specific to outpatient care, it will still provide valuable insight into the provision of inpatient medical resources and outcomes. Specifically, we predict that we will be able to study significant morbid and mortal events following induction, as these events are most likely to result in or occur during hospitalizations.

In summary, this validated cohort provides a novel opportunity to leverage the PHIS database to efficiently conduct clinical epidemiology and comparative effectiveness studies. Importantly, the size and multi-center nature of the cohort will also allow for the evaluation of practice variation across institutions, the comparison of outcomes for patients treated on or off cooperative group trials, and for the investigation of less common but severe co-morbid conditions that were previously limited by single center or smaller cohorts. It is clear that the combination of ICD-9 diagnosis codes with data on induction chemotherapy substantially reduced the risk of misclassification in establishing a cohort of *de novo* ALL. Such methods should be employed when utilizing administrative data to study pediatric and adult hematologic malignancies. In the future we aim to further validate our approach for other patient cohorts such as children with acute myeloid leukemia and those receiving bone marrow transplants.

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Figure 1. Flow chart depicting cohort assembly across the study's three-step process. PHIS: Pediatric Health Information Systems; ALL: Acute Lymphoblastic Leukemia

Table 1

Demographic characteristics from the PHIS assembled ALL cohort and the National Cancer Institute's SEER Program

	PHIS Assembled Cohort 1999–2009 No. (%)	National Cancer Institute's SEER Program 1992–2004 No. (%)	P value ³
Age Group ¹			
<1 Year	252 (2.9)	139 (3.0)	0.002
1–4 Years	3823 (44.1)	2169 (46.2)	
5–9 Years	2256 (26.0)	1176 (25.0)	
10–14 Years	1480 (17.0)	695 (14.8)	
15–19 Years	867 (10.0)	518 (11.0)	
Sex			
Male	4908 (56.2)	2678 (57.0)	0.364
Female	3825 (43.8)	2019 (43.0)	
Race ²			
White	6550 (80.9)	3890 (82.8)	0.001
Black	643 (7.9)	292 (6.2)	
Other	901 (11.1)	515 (10.9)	
Total	8733 (100)	4697 (100)	

¹ 55 subjects who are age 20–21 in PHIS data are excluded in the comparison, as NCI SEER program does not include this age group.

² 639 subjects with race missing in PHIS data are excluded in the comparison.

³ P value is based on the chi-squared test for difference of the proportions in PHIS and SEER data.

Positive predictive value and sensitivity of the three methods used to identify patients admitted to CHOP between 2004 and 2009 with *de novo* ALL from the PHIS database

Table 2

	True positives	False positives	False negatives	Positive Predictive Value (95% CI)	Sensitivity (95% CI)
STEP 1: Presence of ALL ICD-9 code and complete PHIS data	237	108	17	69% (64–74%)	93% (90–96%)
STEP 2: Criteria inclusive of step 1 AND lack of an ICD-9 diagnosis or procedure code consistent with an alternative malignancy or bone marrow transplant	230	45	24	84% (79%–88%)	91% (86–94%)
STEP 3: Criteria inclusive of step 1 and 2 AND manual review of induction chemotherapy	223	17	31	93% (89–96%)	88% (83–92%)

Table 3

Inpatient case fatality rates within 30-days from hospital admission at each step of the *de novo* ALL cohort assembly

	N	Death	Case Fatality Rate (%)	Exact 95% CI
STEP 1: Presence of ALL ICD-9 code and complete PHIS data	15733	221	1.40	(1.23–1.60%)
STEP 2: Criteria inclusive of step 1 AND lack of an ICD-9 diagnosis or procedure code consistent with an alternative malignancy or bone marrow transplant	13642	154	1.13	(0.96–1.32%)
STEP 3: Criteria inclusive of step 1 and 2 AND manual review of induction chemotherapy	8733	70	0.80	(0.63–1.01%)