Original Study

Volume–Outcome Relationships in Pediatric Acute Lymphoblastic Leukemia: Association Between Hospital Pediatric and Pediatric Oncology Volume With Mortality and Intensive Care Resources During Initial Therapy

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Abstract

A volume–outcome relationship has been shown in adult oncology. We investigated if an inverse association of volume and death exists in pediatric acute lymphoblastic leukemia (ALL) care. In assessing the association of volume and outcomes in a cohort of hospitalized pediatric ALL patients, we did not show an inverse relationship between volume and mortality or need for intensive care.

Background: There are few contemporary studies of volume–outcome relationships in pediatric oncology. Children with acute lymphoblastic leukemia (ALL) are treated at a wide variety of hospitals. We investigated if inpatient hospital volume influences outcomes. The objective of this study was to evaluate the relationship between inpatient pediatric and pediatric oncology volume and mortality and intensive care resources (ICU care). We hypothesized an inverse relationship between volume and these outcomes. **Patients and Methods:** This was a retrospective cohort study. Patients 0 to 18 years of age in the Pediatric Health Information System or Perspective Premier Database from 2009 to 2011 with ALL were included. Exposures were considered as the average inpatient pediatric and pediatric oncology volume. The primary outcome was inpatient mortality; secondary outcome was need for ICU care. **Results:** The included population comprised 3350 patients from 75 hospitals. The inpatient mortality rate was 0.86% (95% confidence interval, 0.58%-1.2%). In the unadjusted analysis, mortality increased as pediatric oncology volume increased from low (0%) to high volume (1.3%) ($P = .009$). The small number of deaths precluded multivariable analysis of this outcome. Pediatric and pediatric oncology volume was not associated with ICU care when we controlled for potential confounders. **Conclusion:** Induction mortality was low. We did not observe an inverse relationship between volume and mortality or ICU care. This suggests that in a modern treatment era, treatment at a low-volume center might not be associated with increased mortality or ICU care in the first portion of

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therapy. This relationship should be evaluated in other oncology populations with higher mortality rates and with longer-term outcomes.

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Introduction

Volume–outcome relationships associate the amount of care provided at a hospital level to the quality of care received by an individual patient.[1] These relationships have been studied extensively in procedural fields, and an inverse relationship between volume and patient mortality found.[2,3] Studies in adult oncology have suggested that higher-volume centers have better outcomes for surgical and nonsurgical management.[4-6] In pediatric oncology, a volume–outcome relationship has been less well examined. A systematic review undertaken to evaluate volume in pediatric oncology concluded that higher volumes are related to better survival.[7] However, the generalizability of this finding might be limited by the heterogeneity of the cancer populations included and of the definitions of the volume exposures.[7] More recent studies focused on specific pediatric tumors including Wilms tumor and neuroblastoma did not find a relationship between volume and outcome.[8,9] The potential effect of a volume–outcome association across different types of pediatric malignancy is needed because the findings might help either optimize the provision of care for these patients, or help to reinforce current practice.

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy and, therefore, represents an important group in which to investigate the volume–outcome paradigm. It is estimated that thirty-five hundred pediatric patients will be diagnosed with ALL in the United States in 2016.[10] Fortunately, remarkable improvements in survival have occurred in recent decades, resulting in a 90% survival rate.[11] The improvement in survival has been achieved via optimization of risk classification and intensification of chemotherapy. This has led to well established, but complex, treatment protocols that require comprehensive hospital services. Previous studies of the volume–outcome relationship among children with ALL did suggest an association, but this represented an earlier era of therapy.[12] Currently, there are a number of established protocols for the management of ALL that might reduce variation in outcomes. However, recent data suggest that mortality among children with ALL continues to vary according to insititution.[13] It is possible that this variation in mortality might be related to hospital volume. A better understanding of the volume–outcome association across different types of pediatric malignancy is needed. We hypothesized that mortality and need for intensive care resources (ICU care) during the period of ALL induction chemotherapy would be inversely related to a hospital's volume of inpatient pediatric and pediatric oncology patients.

Patients and Methods

Overview and Study Design

A retrospective cohort study of patients with new-onset ALL was performed with 2009 to 2011 data from the Pediatric Health Information System (PHIS) and Perspective Data Warehouse (Premier Inc, Charlotte, NC). Forty-one hospitals from PHIS, and 34 hospitals from Premier were included. The institutional review board of the Children's Hospital of Philadelphia reviewed the study and determined exempt status.

Data Sources

The PHIS database has previously been described in detail.[14,15] Briefly, PHIS includes administrative and billing data from 46 freestanding, noncompeting, not for profit tertiary children's hospitals across the United States. PHIS data include demographic characteristics, dates of service, discharge disposition, International Classification of Diseases, Ninth Revision (ICD-9) discharge diagnosis and procedure codes, and detailed billed resource utilization information. Data are deidentified at the time of submission and subjected to reliability and validity checks. Data quality is assured through a combined effort between the Children's Hospital Association (Overland Park, KS), Truven Health Analytics, and participating hospitals.

Perspective Data Warehouse, maintained by Premier, Inc (Charlotte, NC) is a large administrative database representative of a distinct consortium of US not for profit hospitals. Hospitals contributing to the Premier database include academic and community hospitals. These institutions represent one-sixth of all hospitalizations in the United States. Importantly, although PHIS hospitals are dedicated children's hospitals, hospitals in Premier admit children and adults. Data elements in Premier are similar to those found in PHIS and include demographic and hospitalization data, ICD-9 discharge diagnoses and procedures codes, pharmacy billing data, and charges.[16]

Study Cohort

A previously established and validated inpatient cohort of pediatric ALL patients from PHIS was extended to include the years under study.[14] A parallel cohort was constructed from Premier using the same steps applied to assemble the PHIS cohort. In brief, all patients younger than 19 years of age with a discharge ICD-9 code for ALL (204.xx) were identified. Pharmacy billing records were reviewed for medications and timing consistent with known ALL induction chemotherapeutic regimens. We restricted the study population to 2009 to 2011 to use parallel years from each data source. Patients with an ICD-9 code for trisomy 21 (758.0) were excluded because of potential for differential morbidity, mortality, and clinical practice in this population. There were 2 hospitals that contribute to Premier and PHIS. Data for these hospitals from Premier were omitted to avoid duplicate patients (see Supplemental Figure 1 in the online version). Of note, only 1 patient had a discharge status that was unknown.

Outcome Measures

The a priori primary outcome of interest was inpatient mortality in the first 60 days after initial admission containing induction chemotherapy. The secondary outcome was receipt of ICU care at any time after the first 2 admission days and up to day 60. Both outcomes were dichotomous. ICU care was defined using resource utilization data, rather than location. These definitions included clinical resources used, medication bills, and ICD-9 procedure codes separated into the following categories: cardiovascular, respiratory, hemodialysis, leukapheresis, and neurologic. ICU care identification according to these definitions of resource allocation has been previously described by our research group.[17] Patients receiving ICU care resources in the first 2 days of admission were excluded from the ICU care outcome analysis because the need for ICU care after the first 2 days might reflect severity of illness at presentation rather than quality of care provided.

Primary Independent Variables (Exposures)

Hospital pediatric volume was calculated as the average number of pediatric hospitalizations (1-19 years of age) per year and categorized as low (<7000), medium (7000-11,000) and high (>11,000) on the basis of the distribution of volume. Pediatric oncology volume was calculated in a similar manner and categorized as low (<650), medium (650-1500), and high (>1500). Pediatric oncology admissions were identified using Complex Chronic Condition (CCC) codes for malignancy.[18]

Patient and Hospital-Level Covariates

Patient-level covariates included age, race, sex, requirement of ICU care during the first 2 days of admission (for mortality analysis only), and number of days hospitalized during the 60 days from the index admission date. Hospital-level factors included teaching status, defined as whether a hospital had any training programs, and census region. Data on proportion of public insurance was collected as a percentage of total admissions to a hospital for which a patient had an indication of public insurance. Hospital transfer rates were also recorded. Laboratory values were not available for analysis.

Statistical Analysis

Descriptive statistics were calculated using frequencies and medians with interquartile ranges. Bivariate analyses using Fisher exact test, were performed to compare the distribution of the patient- and hospital-level covariates according to volume categories. Mortality rates are presented as number of events per 100 patients. Nonparametric trend testing was performed to evaluate mortality rates across volume categories. Generalized estimating equations accounting for clustering within institutions was performed to estimate the population-averaged association between patient volume and the probability of using ICU care.[19] Clustering was evaluated because of the potential for unmeasured characteristics at the institution level that might be associated with hospital volume and the outcome of interest.[20,21] For each model, adjusted coefficients were estimated by including all relevant patient- and hospital-level covariates. Manual selection of covariates for inclusion in the final models was on the basis of a significance level of $P < .2$. Marginal probabilities of each outcome at the different levels of volume were estimated from these models.[19]

Sensitivity analyses used trend analysis for proportions between volume categories. All analyses were performed using STATA 13 (StataCorp LP, College Station, TX).

Results

Patient and Hospital Characteristics

A cohort of 3350 pediatric patients with ALL from 75 hospitals was assembled from the PHIS and Premier data sources (see Supplemental Figure 1 in the online version). The distribution of hospital and patient characteristics according to pediatric volume and pediatric oncology volume categories is represented in Tables 1 and 2. Table 1 represents distribution of patients according to the hospital characteristics of teaching status and census region. The number of teaching hospitals varied according to pediatric oncology volume. Median public insurance rates at each hospital did not differ according to pediatric hospital volume but increased as pediatric oncology volume increased. Age and sex were similar across volume categories (Table 2). Race distributions differed according to overall pediatric volume, but not by pediatric oncology volume. The median number of inpatient days in the 60 days from presentation varied across pediatric volume categories but was similar across pediatric oncology volume categories.

Mortality Outcome

Twenty-nine patients died within 60 days of initial ALL diagnosis (0.86% of the cohort; 95% confidence interval [CI], 0.58%-1.2%). Most deaths occurred within 3 weeks of the index admission (see Supplemental Figure 2 in the online version). Although mortality rates appeared to be least in the lowest-volume category, the mortality rates were not statistically significantly different according to pediatric volume (0.30% for low, 1.01% for medium, and 0.99% for high; $P = .184$; Figure 1A). However, mortality rates increased in association with the increase in hospital pediatric oncology volume, from 0% in the low-volume, 1.02% in the medium-volume, and 1.30% in the high-volume ($P = .009$; Figure 1B). Because of the few deaths, we were unable to perform traditional adjusted analyses for potential confounders, at the patient level and at the hospital level. Similar to previous publications from our group, the raw number of deaths peaked during the third week of induction (see Supplemental Figure 2 in the online version).

Because multivariate modeling could not be performed because of the small number of deaths, additional sensitivity analyses were performed to further assess the association of volume and mortality. These sensitivity analyses sought to address the following issues: potential for differential loss of follow-up because of patient transfer out of a hospital, variation in patient complexity at time of diagnosis and outcome, and differential capture of exposure and outcome according to data source. In total, 15 of 3350 patients transferred during the 60-day follow-up period (0.45%; 95% CI, 0.22%-0.67%). Although this rate is low, significantly higher transfer rates occurred at the low-volume pediatric oncology hospitals (1.15%) versus the medium- and high-volume pediatric oncology hospitals

Table 1 Hospital Characteristics (75 Hospitals)

Characteristic	Value				*P*
	Total	Low (<7000; 33 Hospitals)	Medium (7000-11,000; 34 Hospitals)	High (>11,000; 8 Hospitals)	
Pediatric Volume					
Teaching hospital	65 (87)	28 (85)	30 (88)	7 (87.5)	.730
Census region					.110
West	16 (21)	5 (15)	11 (32)	0 (0)	
Midwest	16 (21)	6 (18)	8 (24)	2 (25)	
South	31 (41)	17 (51)	10 (29)	4 (50)	
Northeast	12 (16)	5 (15)	5 (15)	2 (25)	
Median proportion public insurance (IQR)	0.54 (0.46-0.62)	0.55 (0.45-0.62)	0.54 (0.46-0.63)	0.53 (0.46-0.59)	.74
Pediatric Oncology Volume	**Total**	**Low (<650; 40 Hospitals)**	**Medium (650-1500; 29 Hospitals)**	**High (>1500; 6 Hospitals)**	
Teaching hospital	65 (87)	31 (77.5)	28 (96.6)	6 (100)	.018
Census region					.020
West	16 (21)	6 (15)	9 (31)	1 (17)	
Midwest	16 (21)	7 (17.5)	9 (31)	0 (0)	
South	31 (41)	19 (47.5)	9 (31)	3 (50)	
Northeast	12 (16)	8 (20)	2 (7)	2 (33)	
Median proportion public insurance (IQR)	0.54 (0.46-0.62)	0.51 (0.43-0.55)	0.55 (0.46-0.63)	0.59 (0.53-0.73)	.001

Data are presented as n (%) except where otherwise mentioned.
Abbreviation: IQR = interquartile range.

(0.25% and 0.29%, respectively; $P = .016$; Figure 1B). No statistically significant difference in transfer was seen in ordered groups according to general pediatric volume, with rates of transfer at low-volume institutions of 0.61%, 0.40% for medium-volume, and 0.28% for high-volume institutions (Figure 1A). With this variation in transfer rate according to pediatric oncology volume levels, we further explored the potential effect of transfers on the volume–outcome association. If half of the patients transferred were assumed to die, an increasing mortality trend over categories of pediatric oncology volume was apparent but not statistically significant (0.46% for low-volume, 1.10% for medium-volume, and 1.30% for high-volume institutions; $P = .140$). Alternatively, we assumed pessimistically that all patients who required ICU care at the time of transfer died. With this assumption, the population averaged mortality rates for low, medium, and high pediatric oncology volume hospitals were 0.4%, 1.10%, and 1.45%, respectively ($P = .059$ for nonparametric trend).

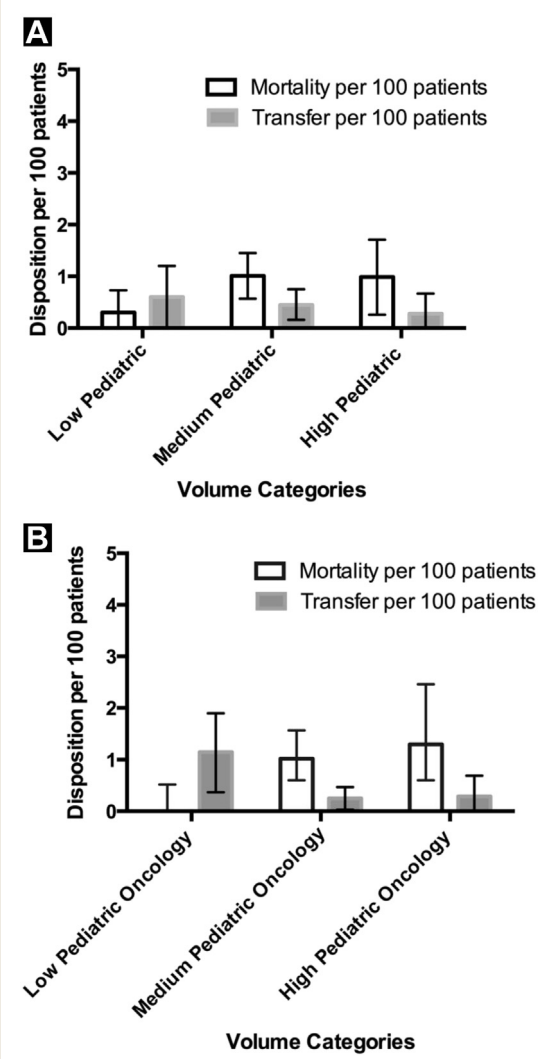
The second sensitivity analysis was conducted to assess whether potential variation across hospitals of patient complexity occurred at the time of diagnosis. Our hypothesis was that patients

Table 2 Patient Characteristics (n = 3350; 75 Hospitals)

Characteristic	Value				*P* Value for Differences
	Total	Low (<7000; 33 Hospitals; n = 658)	Medium (7000-11,000; 34 Hospitals; n = 1982)	High (>11,000; 8 Hospitals; n = 710)	
Pediatric Volume					
Median age (IQR), years	5 (3-9.9)	4.7 (3-9.9)	5 (3-9.9)	4.9 (3.1-9.8)	.528
Male sex	1873 (56)	383 (58)	1091 (55)	399 (56)	.472
White race	2292 (68)	487 (74)	1282 (65)	523 (74)	<.01[a]
Median days in hospital (IQR)	14 (10-24)	15 (10-25)	13 (9-22)	16.5 (10-31)	<.01[a]
Pediatric Oncology Volume		**Low (<650; 40 Hospitals; n = 695)**	**Medium (650-1500; 29 Hospitals; n = 1922)**	**High (>1500; 6 Hospitals; n = 690)**	
Median age (IQR), years		4.7 (3-9.8)	4.9 (3-9.6)	5.2 (3-10.5)	.406
Male sex		399 (57)	1095 (56)	379 (55)	.781
White race		472 (68)	1367 (70)	453 (66)	.299
Median days in hospital (IQR)		14 (10-24)	14(10-24)	15 (9-28)	.282

Data are presented as n (%) except where otherwise noted.
Abbreviation: IQR = interquartile range.
[a]$P < .05$.

Figure 1 (A) Unadjusted Mortality and Transfer According to Pediatric Volume With 95% CIs. (B) Unadjusted Mortality and Transfer According to Pediatric Oncology Volume With 95% CIs



at higher-volume centers might be more medically complex at baseline, and this complexity could increase induction mortality. We used previously established CCC codes defined according to ICD-9 diagnosis codes to identify underlying chronic conditions other than malignancy.[18] There were 2657 patients from 74 hospitals who had no chronic care condition other than malignancy identified. In patients without an underlying chronic care condition, mortality rates according to group ranged from 0% (97.5% CI, 0%-0.5%) in the low pediatric oncology volume group, 1% (95% CI, 0.5%-1.5%) in the medium pediatric oncology volume group, and 1.12% (95% CI, 0.2%-2%) in the high pediatric oncology volume group ($P = .039$). There was still no trend across the groups of pediatric volume and mortality, with mortality of 0.3% (95% CI, 0%-0.9%) in the low-, 1% (95% CI, 0.5%-1.5%) in the medium-, and 0.7% (95% CI, 0.02%-1.4%) in the high-volume pediatric institutions.

Because of the potential for unobserved heterogeneity between PHIS and Premier data, a third sensitivity analysis was conducted using each data source alone. The relationship of increasing mortality with increasing pediatric oncology volume was statistically nonsignificant, with mortality rates of 0% in low-, 1.00% in medium-, and 1.45% in high-volume pediatric oncology centers ($P = .083$). In PHIS pediatric centers, mortality also did not statistically significantly differ according to pediatric volume category with 0.40% at low-, 1.10% at medium-, and 1.20% at high-volume pediatric centers ($P = .254$). In an analysis limited to Premier, of 535 patients, only 1 patient died during the 60-day follow-up period. Despite this low mortality, 6 patients were transferred from low-volume pediatric oncology institutions.

Intensive Care Unit Resources

As a secondary outcome we investigated whether volume category was associated with the receipt of ICU care after the first 2 hospital days. There were 24 patients who received ICU care at the time of or within 2 days of the initial admission. To distinguish between potential severity of illness at presentation and worsening clinical status after admission, we excluded the 24 patients who required ICU care in the first 2 days. In the remaining cohort, there were 279 of 3326 (8.4%; 95% CI, 7.4%-9.3%) patients who progressed to need at least 1 day of ICU care. In unadjusted analysis, there was a higher rate of ICU care utilization as pediatric oncology volume increased (Table 3). After adjustment for number of days in hospital, age, resident teaching status, hospital public insurance proportion, and data source, there was no difference between pediatric and pediatric oncology volume categories in the need for at least 1 day of ICU care in the first 60 days of the index admission. The marginal probability estimates for need of ICU care was similar across pediatric volume categories and ranged from 0.04 to 0.063 in low-volume pediatric oncology hospitals to high-volume pediatric oncology hospitals (Figure 2). There was also no difference among the volume categories if patients who had required ICU care at admission were included.

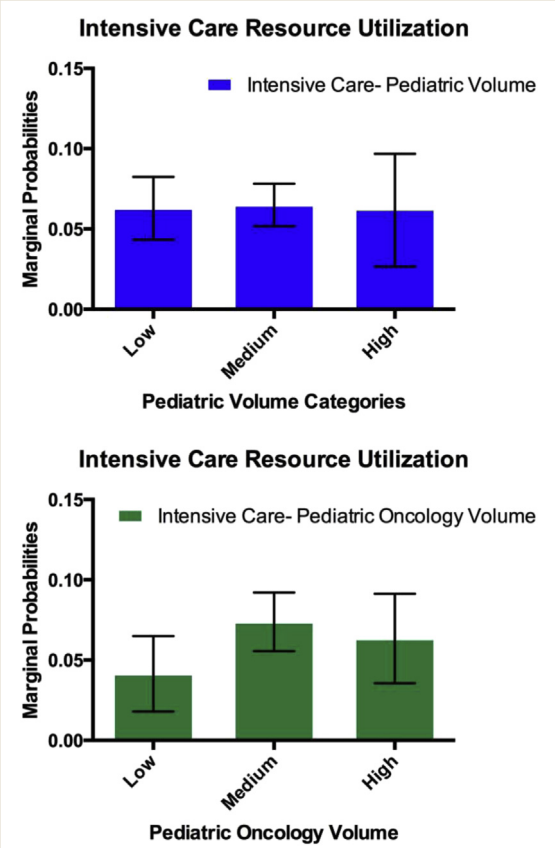
Discussion

In this large, nationally representative sample of US hospitals, we analyzed the relationship between hospital volume and mortality

Table 3 Unadjusted and Adjusted Odds Ratios of ICU Utilization According to Volume Category Adjusted for Age, Length of Stay, Data Source, and Teaching Status

Volume Category	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Pediatric Volume		
Low	Reference	Reference
Medium	1.00 (0.72-1.38)	1 (0.70-1.45)
High	1.51 (1.00-2.28)	1.00 (0.53-1.87)
Pediatric Oncology Volume		
Low	Reference	Reference
Medium	1.63 (1.10-2.41)	1.61 (0.81-3.21)
High	1.93 (1.29-2.91)	1.44 (0.65-3.21)

Figure 2 Marginal Probability of Intensive Care Resources According to Volume Category Adjusted for Age, Length of Stay, Data Source, and Teaching Status



during the induction period for pediatric ALL. The overall induction mortality rate of 0.86% in this cohort is consistent with recent literature.[11,13] We hypothesized that a hospital's volume of pediatric patients and pediatric oncology patients would be inversely associated with mortality. However, in unadjusted analyses of trend according to ordered group, mortality rates did not significantly vary across the 3 pediatric volume categories, whereas mortality increased as pediatric oncology volume increased. Similar to previous publications from our group, the raw number of deaths peaked during the third week of induction (see Supplemental Figure 2 in the online version), a finding which likely coincides with the period of neutropenia.

These unadjusted findings might be confounded by the fact that hospitals with higher pediatric oncology volume are more likely to care for patients who are acutely ill at presentation and might be more likely to have an underlying complex chronic condition at the time of presentation of their ALL. Alternatively, lower-volume hospitals might be more likely to transfer critically ill ALL patients before death. Because of the few deaths, we were unable to perform traditional adjusted multivariate analysis of the mortality outcome. Therefore, sensitivity analyses were performed to address patient transfers, presence of a chronic condition, and data source. Each of these sensitivity analyses reduced the trend between mortality and pediatric oncology volume category but mortality was not found to be inversely associated with volume as we hypothesized and in certain circumstances increased volume remained associated with increased mortality. Likewise, a hospital's pediatric volume and pediatric oncology volume was not inversely associated with the need for ICU care even after adjustments used in multivariate analysis. It is possible that residual confounding persisted to explain the lack of an inverse association. Alternatively, it remains possible that mortality is associated with increasing pediatric oncology volume. For instance, hospitals that have higher volumes might be overly taxed and not able to focus on the important details for each patient.

A few previous studies including pediatric ALL patients have investigated the volume–outcome association. Contrary to our findings, Stiller and Draper concluded that the reduction in mortality seen in their study occurred in parallel with increased numbers of patients treated with standardized protocols.[12] It is notable that the ALL patients from the previous study were cared for during an earlier decade of pediatric ALL treatment, a period in which chemotherapy regimens differed from current regimens.[7,12] In a more recent ALL cohort, increases in pediatric ALL volume were not associated with improved survival.[13] Similarly, in another common pediatric tumor with a low mortality rate, Wilm tumor, investigation of pediatric patients found that survival was not associated with volume.[8,9]

A major strength of the current study was the use of multiple data sources to examine patients cared for at a broad range of institutions treating children with cancer. It is the first study in ALL to evaluate hospital pediatric and oncology volume and outcomes in the current era of treatment. However, our study needs to be interpreted in the context of its limitations. First, there is the possibility of "selective referral" in which more complicated patients are treated at higher-volume centers or sicker patients at lower-volume hospitals are transferred out of an institution. In either situation, the results would be biased toward a finding of worse outcomes at higher volume centers. We attempted to address these concerns in various sensitivity analyses, but this bias might have persisted. Identifying reasons for transfer was not possible from these source data but would be a topic for further study. Second, the lack of laboratory results precluded our ability to determine certain biologic-level risk factors (eg, initial white count, cytogenetics, and minimal residual disease evaluation) known to influence mortality. Therefore, we were unable to adjust for variation in laboratories including presenting white blood cell counts across patients at each volume level. Third, the study hospitals might over-represent the south census region, and therefore, limit generalizability of our findings. Finally, and likely most importantly, the induction mortality events in this cohort were rare. Although beneficial for patients and their families, this precluded the use of multivariable adjustment. When an adjusted analysis was performed with our secondary outcome, ICU care, the relationship between volume and outcome seen in unadjusted rates did not persist. Although the very low inpatient mortality rate limits the ability to adjust for covariates, the low mortality rate itself across each grouping despite a large cohort argues that this malignancy can be managed appropriately across these volumes in induction. However, this result cannot be extrapolated to other pediatric malignancies.

Conclusion

In a large sample of US hospitals with different volumes that care for children with ALL, we did not see higher induction mortality or utilization of ICU care at lower-volume institutions, as we hypothesized. There was a suggestion of worse outcomes among higher pediatric oncology volumes for mortality, but not for need for use of ICU care. Further investigation is needed to confirm our findings and to identify factors distinct from hospital volume that might explain variation in outcomes across institutions. Our findings are not generalizable beyond ALL induction or to other pediatric oncology diseases. For example, hospital volume might be more important in higher-risk conditions for which care is provided more frequently in the inpatient setting such as patients treated for acute myeloid leukemia or relapsed leukemia. Specifically assessing for a volume outcome association in these other patient populations is warranted.

Clinical Practice Points

- Patients with pediatric ALL are treated at many different institutions with varying pediatric and pediatric oncology volumes.
- Unlike in adult oncology cohorts, an inverse relationship between volume and mortality or volume and need for intensive care does not appear to exist for children with ALL during the initiation of treatment.
- These data do not support preferential management of children with ALL in induction at high-volume centers. Evaluation of the volume–outcome association for other pediatric malignancies is needed.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figures accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clml.2016.04.016.

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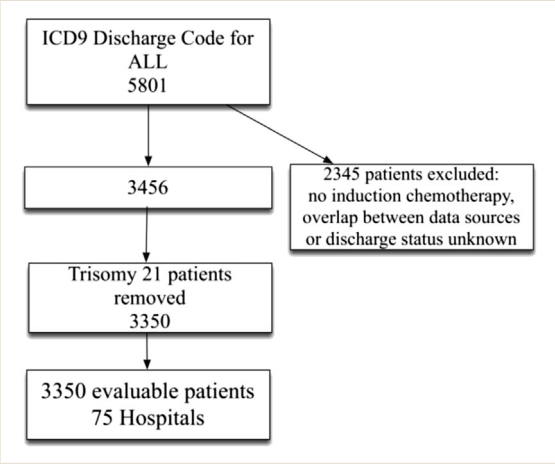
Supplemental Figure 1 Cohort diagram of patient included and excluded



Abbreviations: ALL = acute lymphoblastic leukemia; ICD9 = International Classification of Diseases, Ninth Revision.

Supplemental Figure 2 By volume category, Raw Numbers of Deaths by Day of Induction