


# Acute lymphocytic leukemia severity and mortality hospitalizations in the United States: A population-based study

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## ABSTRACT

**Objectives:** The objective of the study was to understand the relationship between social and economic indicators of health and its association with hospitalization severity and mortality risk among ALL patients.

**Methods:** In this retrospective study, hospitalizations with primary and secondary diagnosis were identified using International Classification of Diseases (ICD 10) codes (C91.00, C91.01, C91.02) of ALL in the National Inpatient Sample (NIS) between 2016 and 2018. Hospitalization outcomes such as LOS, mortality, severity and mortality risk, cost, diagnosis (NDX), number of procedures (NPR) were analyzed by race and ethnicity, household income, and patient location among patients with primary and secondary ALL diagnoses.

**Results:** A total of 158090 hospitalizations were identified as meeting the inclusion criteria without missing cases with a primary or secondary diagnosis of ALL using ICD-10 codes. Severity risk at presentation varied from one area to the next, with the highest rate (per 10K) presentations in the New England region for both extreme likelihood (778) and extreme loss of function (2198) at presentation. Mortality and severity among uninsured patients were the second highest (614, 2193) compared to other payers. Extreme mortality risk at presentation was higher among African American (711), Caucasian (648), and Native American (612) populations compared to other racial and ethnic groups.

**Conclusion:** The findings of this study suggest a relative decrease in presentation rate by year and higher mortality among specific groups-based demographics indicators. It also confirms the impact of advanced therapeutics and improved severity and mortality among younger populations with ALL compared to the older population.

**Keywords:** Acute lymphocytic leukemia, hospitalization, mortality, severity, United States population

## Introduction

Acute lymphocytic leukemia (ALL) is multiplying lymphoid progenitor cells in the bone marrow, blood, and extramedullary sites. It is the most prevalent type of cancer in the pediatric population, it is also prevalent as a devastating disease in the adult population.<sup>[1]</sup> Factors such as radiation, exposure to benzene, infection with EBV, HTLV-1, down syndrome, male, sex, and Caucasian or White are risk factors for ALL.<sup>[2,3]</sup> Survival rates and effectiveness of therapeutics have been found to vary by age.<sup>[4-7]</sup> It is therefore imperative to understand the dynamic of presentation at the population level. Such an understanding would aid in developing effective strategies to address the potential inequity in access to care that may exist. These advances in treatment

modalities often come at a cost and availability limited to large metropolitan-populated centers. The reason for these variations is multiprone including technical expertise and resource availability. Other important factors associated with better outcomes in these patient populations include age at diagnosis, prognosis, presence of the Philadelphia chromosome, and response to chemotherapy. Studies have shown improvement in health outcomes for these populations attributed to advancements in treatment modalities and targeted therapies,<sup>[6,7]</sup> but as with other medical conditions, factors influencing health-care access and equity directly or indirectly impact the care patients receive. This study explores the relationship between social and economic indicators of health and its association with hospitalization severity and mortality risk among ALL patients.

## Methods

In this retrospective study, hospitalizations with primary and secondary ALL diagnosis were identified using International Classification of Diseases (ICD 10) codes (C91.00, C91.01, and C91.02) in the National Inpatient Sample (NIS) between 2016 and 2018. All cases with any missing variables were excluded from any analysis. The NIS dataset is part of a family of all payers' inpatient datasets available through the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ). The population set covered in this dataset is estimated to cover about 97% of the US population (47 States). The dataset is de-identified to protect the privacy of patients, providers, and hospitals. The demographic information available in the dataset was analyzed for the patient population that meets the inclusion criteria. Outcomes of hospitalization such as LOS, mortality, severity and mortality risk at presentation, cost of care, Number of diagnosis (NDX), Number of procedures (NPR) were analyzed by race and ethnicity, household income, and patient location among patients with primary and secondary ALL diagnoses. The most common Major Diagnostic Category (MDC) procedures were also analyzed by race, household income, and patient location.

The study cohort consisted of 158090 patients, with ALL hospitalized between 2016 and 2017. A total of 84645 hospitalizations were identified as meeting the inclusion criteria without missing cases with a primary or secondary diagnosis of ALL using ICD-10 codes. Primary ALL diagnosis included ALL without remission (21855), ALL in remission (3080), ALL in relapse (5275) between 2016 and 2018. Of the 54435 (64%) secondary ALL diagnoses, the most common primary cause of hospitalizations included disease and disorders of blood (14%), infectious and parasitic infections (9%), diseases or disorders of the respiratory system (4%), circulatory (3%) and digestive system (3%), nervous system (3%), and hepatobiliary and pancreases (1%).

Logistic regression was performed to estimate the predictors of mortality in the patient population. The independent variables include number of diagnoses (NDX), number of procedures (NPRs), region, sex, patient location, payer, household income (quartiles), and length of stay (LOS). The mortality rate for each patient's demographics was calculated over time (2016–2018).

Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp., Armonk, NY) was utilized to analyze data in this study. Descriptive statistics of the variables of interest were conducted, and records with missing data were not included in any further analysis. A Chi-squared test was utilized to evaluate the relationship between variables of interest and the study sample. All analyses were conducted based on recommended HCUP guidelines; discharge weight was

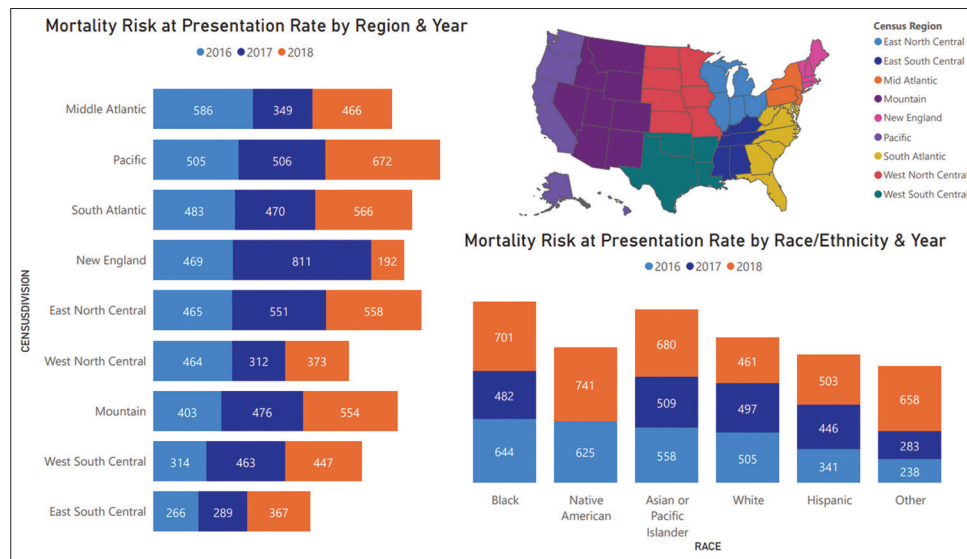
applied to obtain a nationally representative sample. Power B.I. (2019, Microsoft Corporation, Redmond, WA) was used to graph and calculate the rate of presentation among the population of interest.

## Results

A total of 158,090 hospitalizations were identified as meeting the inclusion criteria without missing cases with a primary or secondary diagnosis of ALL using ICD-10 codes. Primary ALL diagnosis included ALL without remission (21855), ALL in remission (3080), and ALL in relapse (5275) between 2016 and 2018. Of the 54435 (64%) secondary ALL diagnoses, the most common primary cause of hospitalizations included Disease and Disorders of blood (14%), infectious and parasitic infections (9%), diseases or disorders of the respiratory system (4%), circulatory (3%) and digestive system (3%), nervous system (3%), and hepatobiliary and pancreases (1%). The rate of the extreme likelihood of dying at presentation increased between 2016 and 2018 in all regions across the country, as shown in Figure 1 ( $P < 0.001$ ). Severity risk at presentation varied from one area to the next, with the highest rate (per 10K) presentations in the New England region for both extreme likelihood (778) and extreme loss of function (2198) at presentation. The severe severity of disease at presentation was highest in large metropolitan (2112). The extreme likelihood of dying was highest in non-metropolitan or micropolitan (702) per 10000 hospitalizations, as shown in Table 1.

Evaluation of mortality and severity risk by payer shows a consistent rate by year with a higher rate among Medicare (1394, 3142) and others (484, 1817). Mortality and severity among uninsured patients were the second highest (614, 2193) compared to other payers. Extreme mortality risk at presentation was higher among Black (711), White (648), and Native American (612) populations compared to other racial and ethnic groups, as shown in Table 1. The highest extreme severity risk at presentation was observed among Asian and Pacific islanders (2297), Native Americans (2143), White (2057), and Black (2040). The highest mortality rate among ALL presentations by household income was observed in the middle two quartiles. The highest severity rate was observed among household income of <71K (1713) and <54 (1495) between 2016 and 2017 ( $P < 0.001$ ).

In the logistic regression, females (OR: 1.27,  $P < 0.001$ ), East South Central (OR: 1.62,  $P < 0.001$ ), West South Central (OR: 1.28,  $P < 0.001$ ), Black (OR: 1.82,  $P < 0.001$ ), Hispanic (OR: 1.32,  $P < 0.002$ ), Asian/Pacific Islander (OR: 1.44,  $P < 0.003$ ), and median income quartile (OR: 1.32,  $P < 0.001$ ) predicted mortality among patients with ALL, as shown in Table 2. The rate of patients with the emergency department (E.D.) as a point of admission continuously increased between 2016 and 2018. The severity and mortality risk among patients with E.D as the end of admission continued to increase.



**Figure 1:** Rate (per 10,000) of mortality risk by region, race/ethnicity, and year among patients with ALL in the United States

**Table 1:** Descriptive statistics(weighted) of ALL hospitalizations by socioeconomic and demographic characteristics

Demographics	N (2016–2018)	Mortality and Severity Risk at Presentation (2016–2018)	
		Extreme likelihood of dying	Extreme loss of function
	158,090 (%)	9640	30960
		Rate per 10,000 hospitalizations	
Sex			
Male	85,800 (57)	602	2013
Female	64,600 (43)	615	1978
ED indicator			
The record does not meet any HCUP Emergency Department criteria	99,600 (66)	456	1757
Emergency department revenue code on record	34,495 (23)	880	2418
Positive Emergency Department charge(when revenue center codes are not available)	13,505 (9)	1014	2700
Condition code P7 indication of E.D. admission, point of origin of E.D., or admission source of ED	2880 (2)	761	2180
Disposition			
Routine	128,980 (82)	278	1503
Transfer to Short-term Hospital	3830 (2)	1188	2963
Transfer other: includes skilled nursing facility	4265 (3)	2743	5381
Home Health Care(HHC)		971	3274
Against Medical Advice(AMA)	16,845 (11)	462	2154
Died	3425 (2)	7942	9124
Census division			
New England	5635 (4)	778	2198
Middle Atlantic	18,760 (12)	572	1964
East North Central	19,610 (13)	613	1962
West North Central	8595 (7)	580	2061
South Atlantic	25,495 (18)	613	1915
East South Central	9775 (6)	556	1659
West South Central	23,495 (15)	530	1939
Mountain	9540 (7)	621	2134
Pacific	29,575 (19)	672	2175

(Contd...)

**Table 1:** (Continued)

Demographics	N (2016–2018)	Mortality and Severity Risk at Presentation (2016–2018)	
		158,090 (%)	Extreme likelihood of dying
		9640	30960
Location by Population			
“Central” counties of metro areas of $\geq 1$ million population	50545 (33)	642	2112
“Fringe” counties of metro areas of $\geq 1$ million population	35,580 (24)	582	1945
Counties in metro areas of 250,000-999,999 population	31,835 (21)	586	1911
Counties in metro areas of 50,000-249,999 population	11745 (8)	549	2091
Metropolitan counties	11580 (8)	587	1889
Not metropolitan or micropolitan counties	7905 (5)	702	1817
Payer			
Medicare	19,010 (12)	1394	3142
Medicaid	52,405 (35)	475	1768
Private insurance	67,050 (15)	511	1888
Self-pay	4645 (3)	549	1845
No charge	570 (0.4)	614	2193
Other	6600 (4)	484	1817
Race/Ethnicity)			
White	79,560(50)	648	2057
Black	11,805 (7.5)	711	2040
Hispanic	41,410 (26)	548	1911
Asian or Pacific Islander	6530 (4)	597	2297
Native American	1470 (1)	612	2143
Other	9640 (6)	534	1872
Median household income national quartile for patient ZIP Code			
<43K	39,615 (26)	569	1940
<54K	36,390 (24)	630	1977
<71K	37,450 (25)	607	2127
71K +	34,335 (23)	617	1933
Age Group			
<18	72,310 (49)	201	1051
18–24	14,030 (9)	554	1495
25–34	13,285 (9)	595	1855
35–44	10,885 (7)	573	1757
45–54	12,000 (8)	601	2085
55–64	13,275 (9)	743	2185
65–74	10,035 (7)	1004	2218
75+	4660 (3)	1624	2622

The highest mortality rate was observed among individuals aged 75 + (672) and 65–74 (358) per 10,000 patient presentations. The lowest mean mortality rate was observed among patients <18 (57), 18–24(173), as shown in Figure 2 ( $P < 0.001$ ). The highest likelihood of dying and loss of function at presentation was also observed among the older population compared to younger ones. Moreover, the highest rate of presentation was observed among household income less than \$71,000 annually, as shown in Figure 2.

Table 2 shows that the predictors of mortality were significant ( $P < 0.05$ ) in most regions, except for East North Central, West North Central, and South Atlantic regions. Mortality by patient location was also significant in large populated areas compared to less populated areas. Mortality was more likely among patients with Medicaid, Medicare, and self-pay than other payer groups. Higher odds of mortality were observed among the White, Black, and lower-income quartiles population.

**Table 2:** Weighted multivariable logistic regression

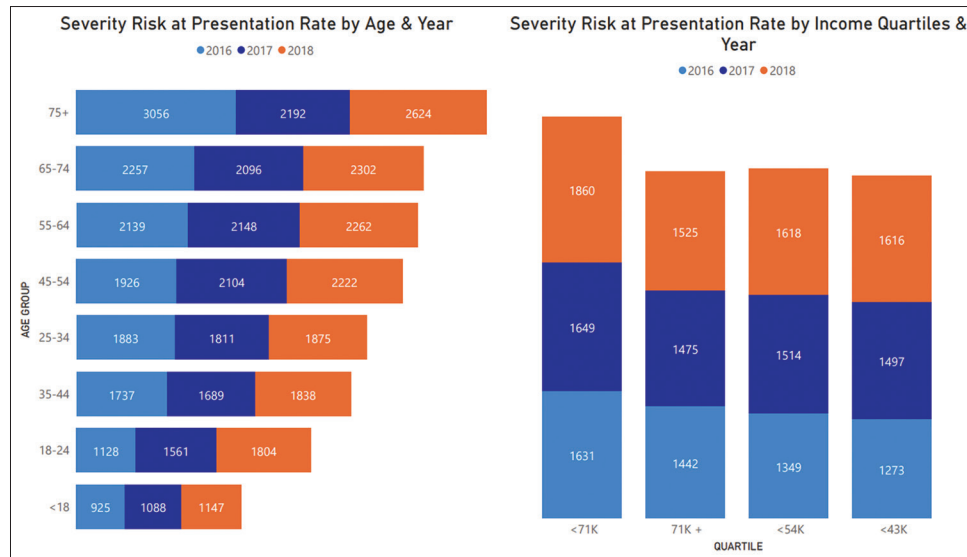
Characteristics	P-value	OR Mortality	95% C.I	
			Lower	Upper
Male	0.000	1.257	1.163	1.357
Female	0.000	0.824	0.763	0.889
Pacific	0.000	Reference		
New England	0.034	0.790	0.635	0.982
Middle Atlantic	0.213	1.094	0.950	1.259
East North Central	0.000	0.725	0.628	0.837
West North Central	0.001	0.704	0.574	0.864
South Atlantic	0.000	0.720	0.628	0.825
East South Central	0.000	1.628	1.362	1.946
West South Central	0.000	1.283	1.121	1.467
Mountain	0.032	1.206	1.016	1.431
Other	0.000			
Medicare	0.000	0.663	0.537	0.819
Medicaid	0	0.695	0.570	0.847
Private insurance	0.001	0.714	0.590	0.865
Self-pay	0.916	0.985	0.742	1.307
No charge	0.092	1.658	0.920	2.986
Not Metropolitan or Micropolitan Counties	0.045			
“Central” counties of metro areas of >=1 million population	0.927	0.991	0.825	1.192
“Fringe” counties of metro areas of >=1 million population	0.108	0.854	0.705	1.035
Counties in metro areas of 250,000-999,999 population	0.193	0.884	0.733	1.065
Counties in metro areas of 50,000-249,999 population	0.594	0.944	0.764	1.167
Micropolitan counties	0.814	1.025	0.833	1.263
Other	0.000			
White	0.004	1.287	1.084	1.527
Black	0.000	1.821	1.487	2.228
Hispanic	0.002	1.324	1.106	1.585
Asian/Pacific Islander	0.003	1.446	1.130	1.851
Native American	0.583	1.146	0.704	1.867
Quartile 4(highest)	0.000			
Quartile 1(lowest)	0.860	1.011	0.891	1.148
Quartile 2	0.000	1.320	1.174	1.484
Quartile 3	0.089	1.103	0.985	1.235
Number of diagnosis(NDX)	0.000	1.166	1.159	1.174
Number of procedure(NPR)	0.000	1.137	1.128	1.146
75+	0.000			
<18	0.000	0.151	0.124	0.184
18–24	0.000	0.306	0.248	0.377
25–34	0.000	0.391	0.323	0.475
35–44	0.000	0.442	0.365	0.536
45–55	0.000	0.400	0.332	0.483
56–64	0.000	0.477	0.400	0.569
65–74	0.000	0.534	0.457	0.624

## Discussion

This study’s utilization of primary and secondary diagnosis of inpatient ALL presentations allows for a better understanding of presentations for a more comprehensive population range. It aids in understanding the prevalence of the disease by age group and other demographics characteristics, which could help tailor therapeutics aimed at outcome improvement. Evidence from multiple studies shows advances in treatment modalities for the younger population and better outcomes.<sup>[4,5,8,9]</sup> Other publications have also recommended improved focus on sex differences and rural–urban and adherence to up to date guidelines to improve care and preventive strategies.<sup>[10,11]</sup> It is therefore imperative to understand the indicators that impact outcome improvement among diverse populations with ALL. Even though the presentation rate decreased in 2018 for some age groups, older adults had poorer outcomes and severity at presentation than the younger population.<sup>[12-14]</sup> These findings further support other publications on the effectiveness of treatment modalities for older populations with ALL.<sup>[12,14]</sup>

As shown in this study, a high severity and mortality risk among these populations may be associated with other comorbidities, given the higher number of potential comorbidities that may complicate treatment approaches. Mortality and severity rate variance by population demographics shows a changing trend with higher rates observed in 2018 in micropolitan or less populated areas. These presentations may be associated with variance in access to cancer treatment in these areas. The difficulties associated with reaching large urban centers for care have been found in other studies focusing on the socioeconomic impact of other malignancies.<sup>[15,16]</sup> The observed higher mortality for the Black population is similar to other studies that have found high mortality for Blacks for other cancer diagnoses.<sup>[17,18]</sup> Further analysis shows higher severity and loss of function rate at a presentation by race for the lowest income quartiles among all racial groups – a finding supported by other studies outside the U.S on cancer care for poor and minority communities.<sup>[14,19,20]</sup> A study conducted in Sudan by Muddathir *et al.*<sup>[21]</sup> on acute myeloid leukemia (AML) found the mean age of presentation to be 32 compared to this ALL study with the mean age of 18. A multinational study conducted by Bond *et al.*<sup>[22]</sup> on adult ALL found varied treatment outcome based on specific implicated gene and therapeutic intervention. The findings of these studies further support the argument of more efforts by providers to develop strategies to provide tailored care to these populations, given the diversity of factors that impacts presentation or severity. Understanding presentation dynamics and the impact of modifiable factors that impact inpatient presentation, severity, and mortality risk for these patient populations could promote the development of practical population-based treatment approaches to improve health outcomes.





**Figure 2:** Rate (per 10,000) of severity risk by age, income quartiles and year among patients with ALL in the United States

### Limitations

The use of only inpatient or hospitalization data does not provide a comprehensive overview of all the potential interactions between ALL patients and health-care providers or resource utilization. A combination of both inpatient and outpatient data may provide a better understanding of resource utilization among all population groups.

### Conclusion

This study shows the trends associated with severity and mortality rate associated with inpatient ALL presentations. The findings of this study suggest a relative decrease in presentation rate by year and higher mortality among specific group-based demographics indicators. This study confirms the impact of advanced therapeutics and improved severity and mortality among younger populations with ALL compared to the older population.

In addition, the findings of this study could aid in the development of population-based risk stratification of patients based on these socioeconomic and demographic indicators. Our observation highlights the need to access and develop treatment modalities to improve health outcomes among the more aging population with ALL. It also highlights the need to evaluate care approaches to ensure patients in less populated areas and micropolitan locations have an equitable distribution of care resources.

### Authors' Declaration Statements

#### Ethics approval and consent to participate

This study only involved secondary data analysis and consent was not required. All identifiers (patient and hospital) were not available in the dataset utilized for conducting this research.

### Consent for publication

Not applicable.

### Data availability statement

The data that support the findings of this study are available from the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ). Researchers could access the National Inpatient Sample after completing the HCUP data use agreement training.

### Competing interests

All authors declare no competing interests.

### Funding statement

Authors declare no external funding for this research.

### Authors' Contributions

Saanie Sulley: Conceptualization, data analysis, data visualization, methodology, writing, review, and editing. Abimbola Saka: Review, Editing, data validation, methodology and review. Memory Ndanga: Review, Editing, data validation, methodology and review.

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