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Journal

Baylor University Medical Center Proceedings, 36(3)

ISSN

0899-8280

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Publication Date

2023-05-04

DOI

10.1080/08998280.2023.2187209

Peer reviewed

PROC (BAYL UNIV MED CENT)
2023;36(3):308–313

https://doi.org/10.1080/08998280.2023.2187209

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Comparison of trends and outcomes of infective endocarditis in patients with versus without leukemia, 2002 to 2017, from a nationwide inpatient sample

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ABSTRACT

Patients with leukemia are at an increased risk for infective endocarditis secondary to their immunocompromised state, chemotherapy, and specific risk factors such as the presence of indwelling central venous catheters. There is a paucity of data regarding temporal trends and clinical outcomes of infective endocarditis in leukemia patients. Previous studies have shown a high rate of complications related to surgical valve procedures for treatment of infective endocarditis in patients with hematological malignancies. In this study, we aimed to analyze the contemporary trends and clinical outcomes of treatment in infective endocarditis patients with and without leukemia based on data available from the Nationwide Inpatient Sample, which is a publicly accessible, large sample-sized national dataset of hospitalized patients across the US. We present key findings on baseline characteristics, microbiological profile, outcomes, rates of valve surgical procedures, and mortality in infective endocarditis patients with and without leukemia between 2002 and 2017 in the US.

KEYWORDS infective endocarditis; inpatient mortality; leukemia; valve surgery

Infective endocarditis (IE) is associated with significant morbidity and mortality.[1] Concurrent comorbidities such as cancer can increase the risk of mortality even further.[2] Patients with leukemia are at increased risk for IE due to an immunocompromised state from the malignancy itself and chemotherapy. Abnormal B or T lymphocyte function in patients with leukemia alters immune response, making them susceptible to infectious agents.[3] Mechanisms of entry of pathogens into the bloodstream can vary from mucositis to the presence of an indwelling central venous catheter.[4,5] The knowledge of IE in the setting of leukemia has been previously published, but is mainly limited to case reports;[6,7] large scale published data are lacking. To address this issue, we used a publicly available, contemporary dataset, representing a national sample of hospitalized patients in the US. We also sought to study various types of microorganisms involved in IE, along with outcomes of treatment provided to patients with leukemia compared to nonleukemia patients.

METHODS

The National Inpatient Sample (NIS) database for the years 2002 to 2017 was used for this study. NIS is part of Healthcare Cost and Utilization Project databases sponsored by the Agency for Healthcare Research and Quality. The NIS is derived from all states for national estimates of healthcare utilization, costs, and outcomes. Since the NIS is compiled annually, the data can be used for analysis of disease trends over time. Institutional review board approval and informed consent were not required for this study given the deidentified nature of the NIS database and public availability.

We analyzed NIS data from January 2002 to December 2017 using the International Classification of Diseases, 9th

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The authors report no funding or conflicts of interest.

Received March 30, 2022; Revised January 9, 2023; Accepted February 27, 2023.

Revision, Clinical Modification (ICD-9-CM) codes and ICD-10-CM codes. All patients of IE were identified using ICD-9-CM codes of 421.0, 421.1, and 421.9 and ICD-10-CM codes of I33.0 and I33.9. Patients with leukemia were identified with ICD-9-CM codes of 204 (01,11,21,31,81,91), 205 (01,11, 21,31,81,91), 206 (01,11,21,31,81,91), 207 (01,11,21,31,81, 91), and 208 (01,11,21,31,81,91) and ICD-10-CM codes of C91 (01,11,21,31,41,51,61,A1,Z1), 92 (01,11,21,31,41,51, 61,A1,Z1), C93 (01,11,21,31,41,51,61,A1,Z1), C94 (01,11,21, 31,41,51,61,A1,Z1), and 95 (01,11,21,31,41,51,61,A1,Z1) *(Figure 1)*. The patients in remission status were excluded to maintain a final cohort with active disease or in a relapse status.

The primary endpoints studied were mortality, discharge disposition, and resource utilization in IE patients with and without leukemia. Baseline characteristics of IE patients with and without leukemia were compared using a Pearson chi-square test and Fisher's exact test for categorical variables and independent samples *t* test for continuous variables. The Kruskal-Wallis test was used for testing medians. Due to significant heterogeneity in the baseline characteristics of patients, a propensity score-matching model was used with logistic regression. Two matched groups (IE with and without leukemia) were derived. A nearest neighbor 1:2 variable ratio, parallel, balanced propensity-matching model was made using a caliper width of SD 0.2. Multivariable analysis was done using a logistic regression model to estimate odds ratios with 95% confidence intervals to determine variability in mortality. A type I error rate of <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Science version 26 (IBM Corp) and R Project for Statistical Computing V3.5.

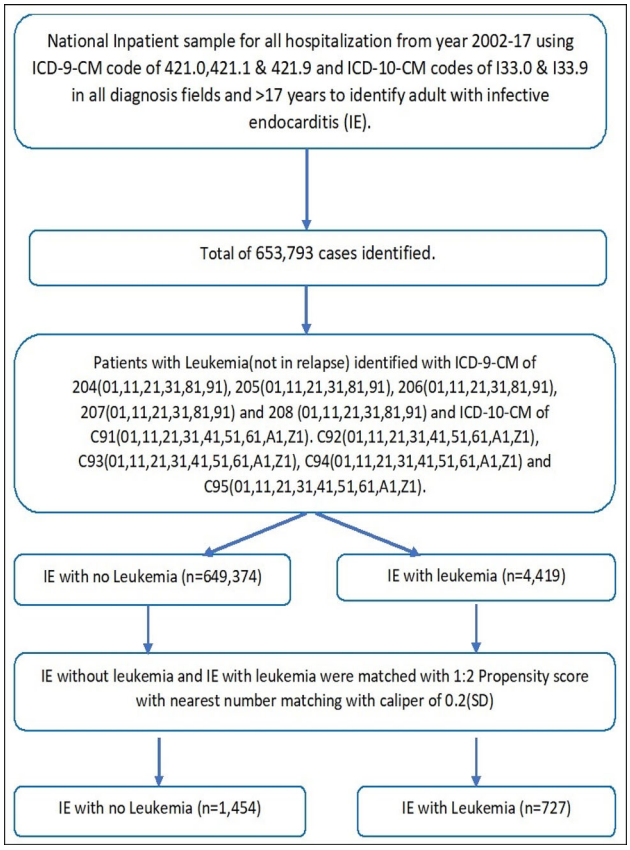

Figure 1. Flow chart.

RESULTS

There were 653,788 patients with IE; 4414 cases were in leukemia patients (0.7%) and 649,374 were in patients without leukemia. Patients with leukemia were older (median age of 72 years vs 60 years in the group without leukemia), were more likely to be male and white, and had a lesser overall burden of comorbidities *(Table 1)*. There was significant heterogeneity in regional median household income, insurance status, geographic region, and hospital size and location between the two groups. After 1:2 propensity score matching, 1454 patients without leukemia were matched with 727 patients with leukemia. There was no statistical difference between the two groups in baseline characteristics *(Table 1)*. Before matching, the mortality (18.0% vs. 11.6%) in the leukemia group was higher compared to the nonleukemia group. After propensity score matching, there was no difference in mortality between the two groups (17.7% in the leukemia group vs. 15.5% in the nonleukemia group, $P = 0.19$).

IE patients with leukemia were less likely to undergo valve procedures. Before propensity score matching, about 9.2% of patients without leukemia underwent a single valve procedure, while only 3.6% with leukemia underwent a single valve procedure ($P < 0.01$). Similarly, 2.3% of patients without leukemia and 1.1% of patients with leukemia underwent multiple valve procedure ($P < 0.01$). Even after the matching, 9.2% and 2.6% of patients without leukemia underwent single and multiple valve procedures, respectively ($P < 0.01$), while only 3.7% and 0.8% of patients with leukemia underwent single and multiple valve procedures, respectively ($P < 0.01$).

The length of stay and cost of hospitalization was significantly higher in the leukemia group before and after propensity score matching *(Table 2)*. The trend of in-hospital mortality from 2002 to 2017 was reduced in both the nonleukemia and leukemia cohorts (14.6% to 10.4% and 20.3% to 14.9% respectively, P trend <0.01 for both). Overall, the mortality in patients with leukemia remained consistently higher throughout the study period *(Figure 2)*.

Nearly two-thirds of patients in both groups had microbial data available. *Staphylococcus aureus* remained the most common microbe in both groups (35.3% in patients without leukemia vs. 27.3% in patients with leukemia, $P < 0.001$) before matching. After matching, 31.8% of patients without leukemia and 27.1% of patients with leukemia had *S. aureus* infection ($P = 0.02$). Also, there was no statistical difference between the groups for other microbes including fungal IE *(Table 3)*.

Table 1. Baseline characteristics of patients with infective endocarditis, 2002 to 2017

Variable	Unadjusted cohort			Adjusted cohort		
	Without leukemia ($n = 649,374$)	With leukemia ($n = 4414$)	*P* value	Without leukemia ($n = 1454$)	With leukemia ($n = 727$)	*P* value
Age (years): Median (IQR)	60 (46–74)	72 (61–80)	<0.01	71 (58–81)	72 (61–80)	0.80
Female	266,540 (41.1%)	1471 (33.3%)	<0.01	480 (33.0%)	237 (32.6%)	0.85
Race						
White	402,271 (71.0%)	3178 (80.1%)	<0.01	1151 (79.2%)	581 (79.9%)	0.79
Black	88,381 (15.6%)	375 (9.4%)		154 (10.6%)	70 (9.6%)	
Hispanic	46,266 (8.2%)	262 (6.6%)		94 (6.5%)	49 (6.7%)	
Asian or Pacific Islander	10,880 (1.9%)	66 (1.7%)		30 (2.1%)	11 (1.5%)	
Native American	4040 (0.7%)	15 (0.4%)		7 (0.5%)	3 (0.4%)	
Other	14,712 (2.6%)	74 (1.9%)		18 (1.2%)	13 (1.8%)	
Medical comorbidities						
AIDS	2585 (0.4%)	4 (0.1%)	<0.01	<11	<11	–
Alcohol abuse	32,112 (5.1%)	71 (1.7%)	<0.01	28 (1.9%)	13 (1.8%)	0.82
Anemia	216,632 (34.2%)	1097 (25.6%)	<0.01	366 (25.2%)	195 (26.8%)	0.41
Congestive heart failure	237,700 (36.6%)	1577 (35.7%)	0.21	634 (43.6%)	264 (36.3%)	
Coagulopathy	117,062 (18.5%)	1236 (28.8%)	<0.01	429 (29.5%)	223 (30.7%)	0.57
Diabetes (with complications)	65,376 (10.3%)	239 (5.6%)	<0.01	95 (6.5%)	46 (6.3%)	0.85
Drug abuse	96,942 (15.3%)	108 (2.5%)	<0.01	45 (3.1%)	21 (2.9%)	0.79
Hypertension	306,408 (48.4%)	1888 (44.0%)	<0.01	668 (45.9%)	334 (45.9%)	1
Liver disease	55,490 (8.8%)	191 (4.5%)	<0.01	93 (6.4%)	38 (5.2%)	0.28
Obesity	55,468 (8.8%)	193 (4.5%)	<0.01	71 (4.9%)	33 (4.5%)	0.72
Peripheral vascular disorders	81,520 (12.9%)	385 (9.0%)	<0.01	79 (5.4%)	41 (5.6%)	0.84
Renal failure	179,497 (28.3%)	874 (20.4%)	<0.01	299 (20.6%)	156 (21.5%)	0.63
End-stage renal disease	83,139 (12.8%)	176 (4.0%)	<0.01	49 (3.4%)	28 (3.9%)	0.57
Prior prosthetic valve	40,286 (6.2%)	156 (3.5%)	<0.01	43 (3.0%)	26 (3.6%)	0.44
Prior device				77 (5.3%)	35 (4.8%)	0.63
Median household income percentile						
0–25th	185,215 (29.3%)	985 (22.7%)	<0.01	299 (20.6%)	167 (23.0%)	0.54
26–50th	157,956 (25.0%)	989 (22.8%)		353 (24.3%)	164 (22.6%)	
51–75th	146,294 (23.1%)	1107 (25.5%)		360 (24.8%)	183 (25.2%)	
76–100th	143,080 (22.6%)	1261 (29.0%)		442 (30.4)	213 (29.3%)	
Primary expected payer						
Medicare	336,863 (52.0%)	2986 (67.6%)	<0.01	1021 (70.2%)	509 (70.0%)	0.98
Medicaid	111,889 (17.3%)	332 (7.5%)		104 (7.2%)	54 (7.4%)	
Private insurance	137,953 (21.3%)	935 (21.1%)		274 (18.8%)	140 (19.3%)	
Self-pay	38,982 (6.0%)	72 (1.6%)		21 (1.4%)	9 (1.2%)	
Others	22,355 (3.5%)	95 (2.1%)		34 (2.3%)	15 (2.1%)	

(*Continued on next page*)

Table 1. Continued

Variable	Unadjusted cohort			Adjusted cohort		
	Without leukemia ($n = 649,374$)	With leukemia ($n = 4414$)	*P* value	Without leukemia ($n = 1454$)	With leukemia ($n = 727$)	*P* value
Region						
Northeast	149,471 (23.0%)	1094 (24.7%)	<0.01	381 (26.2%)	190 (26.1%)	0.94
Midwest	134,534 (20.7%)	990 (22.4%)		292 (20.1%)	140 (19.3%)	
South	238,251 (36.7%)	1481 (33.5%)		519 (35.7%)	259 (35.6%)	
West	127,118 (19.6%)	855 (19.4%)		262 (18.0%)	138 (19.0%)	
Hospital location						
Rural	45,913 (7.1%)	271 (6.1%)	<0.01	80 (5.5%)	42 (5.8%)	0.88
Urban nonteaching	206,279 (31.8%)	1272 (28.8%)		438 (30.1%)	212 (29.2%)	
Urban teaching	397,183 (61.2%)	2876 (65.1%)		936 (64.4%)	473 (65.1%)	
Hospital size						
Small	72,627 (11.2%)	500 (11.3%)	<0.01	178 (12.2%)	83 (11.4%)	0.29
Medium	156,959 (24.2%)	936 (21.2%)		339 (23.3%)	151 (20.8%)	
Large	419,787 (64.6%)	2983 (67.5%)		937 (64.4%)	493 (67.8%)	

Table 2. In-hospital outcomes of patients with infective endocarditis, 2002 to 2017

Variables	Unadjusted outcomes			Adjusted outcomes after 1:1 propensity matching		
	Without leukemia ($n = 649,374$)	With leukemia ($n = 5226$)	*P* value	Without leukemia ($n = 1454$)	With leukemia ($n = 727$)	*P* value
Discharge disposition of surviving patients						
Inpatient mortality	75,121 (11.6%)	792 (18.0%)	<0.01	226 (15.5%)	129 (17.7%)	0.19
Routine discharge	143,705 (25.1%)	920 (20.9%)		259 (17.8%)	155 (21.3%)	<0.01
Short-term hospital	69,799 (12.2%)	312 (7.1%)		142 (9.8%)	54 (7.4%)	
Long-term care facility	211,684 (36.9%)	1272 (28.8%)		515 (35.4%)	208 (28.6%)	
Home with home health	128,412 (22.4%)	1104 (25.0%)		303 (20.8%)	179 (24.6%)	
Against medical advice	19,010 (3.3%)	<11		<11	<11	
Resource utilization						
PEG	16,074 (2.5%)	87 (2.0%)	0.03	48 (3.3%)	17 (2.3%)	0.21
Tracheostomy	12,791 (2.0%)	78 (1.8%)	0.33	33 (2.3%)	14 (1.9%)	0.60
Vasopressors	12,277 (1.9%)	80 (1.8%)	0.69	37 (2.5%)	14 (1.9%)	0.37
Prolonged ventilator (<96 h)	55,386 (8.5%)	330 (7.5%)	0.01	137 (9.4%)	53 (7.3%)	0.09
Valve surgery						
Single valve surgery	59,884 (9.2%)	157 (3.6%)	<0.01	134 (9.2%)	27 (3.7%)	<0.01
Multiple valve surgery	14,969 (2.3%)	50 (1.1%)		38 (2.6%)	6 (0.8%)	
Length of stay, median (IQR), days (unadjusted)	10 (6–18)	11 (6–21)	<0.01	10 (6–17)	11 (6–20)	<0.01
Cost of hospitalization median (IQR), $ (unadjusted)	21,224 (11,053–45,087)	24,253 (13,194–56,693)	<0.01	21,645 (12,146–46,559)	23,860 (13,124–56,693)	0.02

DISCUSSION

We report several important findings in our study. First, IE patients with leukemia were less likely to undergo valve surgery procedures when compared to IE patients without leukemia. Second, *S. aureus* was the most common microorganism reported in IE patients with or without leukemia. However, there was no statistically significant difference in the microbiological profile, including the frequency of fungal endocarditis, between the two groups. Third, the average length of stay, cost of hospitalization, and in-hospital mortality among IE patients with leukemia were higher compared to patients without leukemia. In-hospital mortality in IE patients with leukemia remained consistently higher throughout the study period, although the overall trend of in-hospital mortality in IE patients with or without leukemia has significantly decreased over the last two decades *(Figure 3)*.

Leukemia is a relatively common hematological malignancy with serious consequences. With improvement in the available therapeutic options, the 5-year relative survival rate for leukemia has more than quadrupled between the 1960s and the 2010s (from 14% to 65.8%).[8] Chemotherapy for leukemia is often administered through a central venous catheter, and development of systemic infection and IE in such a vulnerable population group can worsen their prognosis.

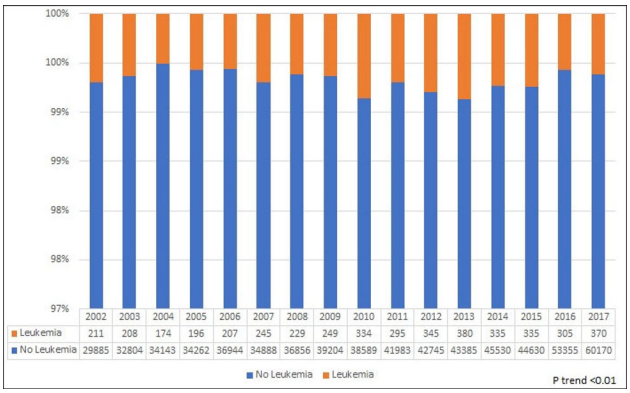

Figure 2. Proportion of infective endocarditis with and without leukemia.

To the best of our knowledge, the present study is the only analysis done on a large dataset to look for rates of surgical valve procedures performed for IE in patients with leukemia. Our finding of lower rates of valve surgical procedures being performed for IE in patients with leukemia can be secondary to cautious patient selection given their malignancy-related poor prognosis, besides their high-risk surgical candidacy.

Our findings regarding the microbiological profile in IE patients were similar in patients with and without leukemia. The overall microbiological profiles were in line with a prior study by Khan et al using NIS data from 2002 to 2017 in overall IE patients.[9] Furthermore, we found a significant decrease in the overall trend of in-hospital mortality over the study period in IE patients with or without leukemia. The reported downtrend in in-hospital mortality is in parallel with the findings of a prior NIS study of native valve IE that reported a decline in risk-adjusted mortality from 16.7% in 2002 to 9.7% in 2016.[10]

A few limitations in our study should be highlighted. First, although administrative datasets are being increasingly used for clinical outcomes-based research, as an administrative claim-based public database NIS is vulnerable to diagnostic coding inaccuracies based on reported ICD-9-CM and ICD-10-CM codes. However, data on major clinical endpoints such as major surgeries, inpatient mortality, and discharge disposition are less likely to be exposed to such diagnostic errors. Second, since individual hospitalization records are not followed longitudinally in the NIS dataset, it is not feasible to report long-term clinical outcomes and in an outpatient setting among the groups studied based on the

Table 3. Microbiological profile of patients with infective endocarditis, 2002 to 2017

Variables	Without leukemia ($n = 649,374$)	With leukemia ($n = 4414$)	*p* value	Without leukemia ($n = 1454$)	With leukemia ($n = 727$)	*p* value
Microbiology reported	418,620 (64.5%)	2763 (62.5%)	0.001	966 (66.4%)	462 (63%)	0.31
Type of microorganism						
Staphylococcus aureus	229097 (35.3%)	1205 (27.3%)	<0.0001	463 (31.8%)	197 (27.1%)	0.02
Streptococcus	117707 (18.1%)	954 (21.6%)	<0.0001	314 (21.6%)	160 (22.0%)	0.83
Enterococcus	45953 (7.1%)	405 (9.2%)	<0.0001	121 (8.3%)	68 (9.4%)	0.42
Gram-negative bacteria	39099 (6.0%)	286 (6.5%)	0.21	98 (6.7%)	48 (6.6%)	0.90
Anaerobic bacteria	2256 (0.3%)	5 (0.1%)	0.01	5 (0.3%)	1 (0.1%)	0.39
Other unspecified bacteria	18587 (2.9%)	194 (4.4%)	<0.0001	40 (2.8%)	32 (4.4%)	0.04
Fungal endocarditis	1495 (0.2%)	10 (0.2%)	0.96	1 (0.1%)	2 (0.3%)	0.22
Polymicrobial	33190 (5.1%)	256 (5.8%)	0.001	73 (5.0%)	40 (5.5%)	0.31

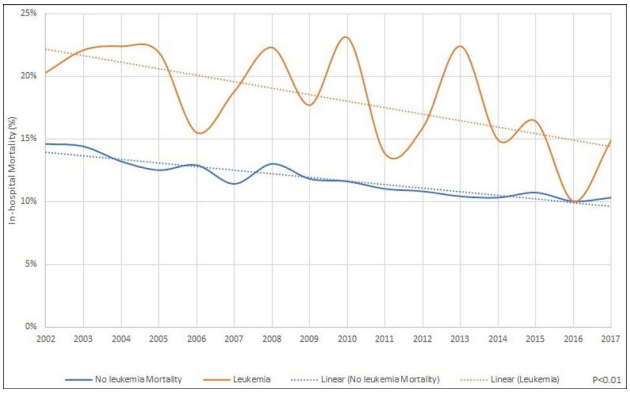

Figure 3. Inpatient mortality in infective endocarditis with and without leukemia.

available data. Nonetheless, given the predisposition to IE being an inpatient diagnosis, this dataset allowed us to study several key outcomes of interest in such hospitalized patients. Third, it is not possible to separate an index hospitalization from readmissions since NIS considers each hospitalization as an individual entry. As such, the estimated incidence of such readmissions would be low and is unlikely to cause significant change in the major findings of the study. Despite the above limitations, there are several principal strengths of the database, which provides a real-world large sample size analysis of inpatient hospitalizations and clinical outcomes.

In conclusion, we report an analysis of the largest available inpatient database over 2002 to 2017 in which IE patients with leukemia were noted to have consistently higher inpatient mortality, a longer hospital stay, a higher cost of hospitalization, and lower rates of valve surgical procedures while having a similar microbiological profile compared with IE patients without leukemia.

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