

The Epidemiology and Clinical Associations of Stroke in Patients With Acute Myeloid Leukemia: A Review of 10,972 Admissions From the 2012 National Inpatient Sample

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Abstract

Acute leukemia predisposes patients toward the development of stroke. The latter, although devastating clinically, has been infrequently studied. Our study, using the 2012 National Inpatient Sample, found a 50-fold increase in the risk of stroke as compared with all inpatient admissions with a corresponding 5.5-fold increased risk of mortality. Significant risk factors for the development of stroke included urinary tract infection, hypernatremia, and acute renal failure.

Background: Acute leukemia is known to confer an elevated risk of both hemorrhagic and thrombotic complications, but the development of stroke in this population is poorly characterized. This study assesses clinical and epidemiologic factors in a population of inpatients with acute myeloid leukemia (AML) and stroke. **Methods:** Using the 2012 National Inpatient Sample, demographic and clinical data including age, gender, race, length of stay, in-hospital procedures, discharge diagnosis, disposition, and mortality incidence were extracted. **Results:** Of 7,296,968 admissions, 10,984 patients with active AML were analyzed. Of these, 65 patients had a concomitant cerebrovascular accident (CVA) (hemorrhagic or ischemic). There was a 50-fold increase in the risk of stroke in patients with active AML compared with all admissions. Patients with AML and CVAs were found to have significantly higher inpatient mortality than for all admitted patients with stroke (36.9% vs. 6.7%; odds ratio, 5.5; 95% confidence interval, 2.3-8.8; $P < .0001$). Multivariate logistic regression, after controlling for confounding variables, identified acute renal failure with tubular necrosis, hypernatremia, urinary tract infection, and secondary thrombocytopenia as significant predictors of stroke. **Conclusions:** Patients with AML have an elevated risk of CVA compared with all inpatients, and mortality in this population is high. Better characterization of risk factors of stroke in this vulnerable population is still needed.

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Introduction

Hematologic malignancies predispose patients to a wide variety of hemorrhagic and thrombotic complications. These complications

can present at diagnosis or during treatment and can be catastrophic, leading to increased length of stay and mortality. Patients with acute myeloid leukemia (AML) are known to be at increased risk of both hemorrhage and thrombosis, including in the central nervous system.^{1,2} Early recognition and identification of these patients is critical to improving outcomes; however, there are limited data on the incidence, clinical associations, and mortality associated with cerebrovascular accident (CVA) in hospitalized patients with active AML. A current literature search revealed only 1 publication that specifically analyzed CVA in this population.³ Using a large national database, the present study evaluates the epidemiology and mortality of hospitalized patients who suffered concurrent stroke while hospitalized with AML.

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Stroke in Patients With Acute Myeloid Leukemia

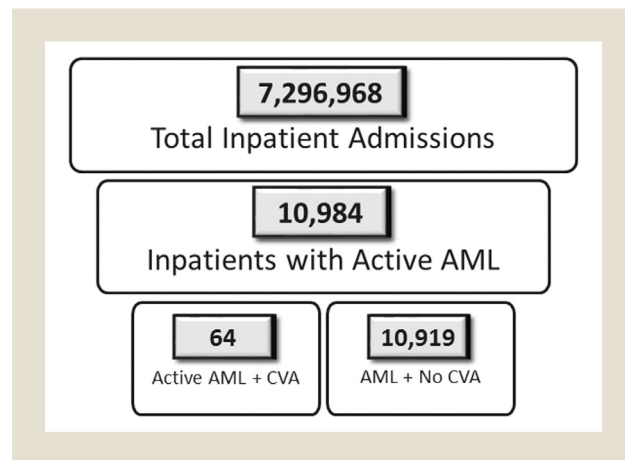
Methods

Using the 2012 National Inpatient Sample (NIS) dataset, admissions with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for AML without remission and AML in relapse (205.00 and 205.02, respectively) were extracted and correlated with age, gender, race, length of stay, in hospital procedures, discharge diagnosis, disposition, and mortality (Table 1). All CVA (ICD-9-CM 434.91) data were extracted as well for comparison of mortality and length of stay. Collected data were used to perform multivariate logistic regression analyses to show associations between CVA in patients with active AML with common discharge diagnoses and in-hospital procedures. Variables considered were limited to most commonly associated diagnoses and procedures in patients with active AML with CVA. Additionally, disseminated intravascular coagulation and leukocytosis were included in that analysis. Odds ratio (OR) calculators and a *t* test for inpatient outcomes were performed as appropriate along with confidence interval (CI) and *P*-value calculations to compare active AML patients with and without CVA (See Supplemental Table 1 in the online version).

Results

Of the 7,296,968 unweighted admissions in the 2012 NIS, 9384 involved patients with AML who had not yet achieved remission, and 1600 involved relapsed AML (prevalence of 0.12% and 0.021%, respectively). Of the combined group of admitted patients with active AML (*N* = 10,974), 65 (0.59%) patients had a concomitant CVA (either hemorrhagic or ischemic, of whom 56 [0.50%] had active disease and 9 [0.08%] had relapsed disease) (Figure 1). Compared with all other patients with active AML, those who developed stroke were older (median age, 68 years vs. 63 years; *P* = .003). Patients with active AML and who developed stroke had longer length of stay (20 days vs. 12 days; *P* = .006) and were predominantly female (55% vs. 45%; *P* = .078), but this was not statistically significant. Patients with active AML and who developed stroke had significantly higher inpatient mortality rates (36.9% vs. 10.5%; OR, 3.5; 95% CI, 2.2-5.5; *P* < .0001). Furthermore, patients with AML with CVA had significantly higher inpatient mortality than for all admitted patients with

Figure 1 Patient Flowchart



Abbreviations: AML = acute myeloid leukemia; CVA = cerebrovascular accident.

stroke (36.9% vs. 6.7%; OR, 5.5; 95% CI, 3.5-8.8; *P* < .0001) (Table 2).

Multivariate logistic regression attempting to find significant clinical associations in patients with AML who develop stroke, after controlling for confounding variables, found that acute renal failure with tubular necrosis (OR, 4.94; 95% CI, 1.97-12.4; *P* = .0006), urinary tract infection (UTI) (OR, 3.28; 95% CI, 1.8-6.1; *P* = .0002), and secondary thrombocytopenia (OR, 2.92; 95% CI, 1.5-5.7; *P* = .0018) were all significantly predictive, as were mechanical ventilation (OR, 2.45; 95% CI, 1.17-5.13; *P* = .018) and continuous positive airway pressure ventilation (OR, 2.8; 95% CI, 1.05-7.49; *P* = .04). Disseminated intravascular coagulation (OR, 2.55; 95% CI, 0.78-8.34; *P* = .12) and leukocytosis (OR, 0.71; 95% CI, 0.20-2.45; *P* = .58) were more prevalent in patients with AML with CVA compared with all patients with AML, but the difference did not reach statistical significance (Table 3).

Discussion

There are few studies that have analyzed the clinical correlations and incidence of stroke in acute leukemia and fewer still that have characterized its incidence in the subset of patients with AML.^{1,3} The present study investigated the incidence, risk factors, and outcomes associated with stroke in patients admitted with AML. We also compared the stroke rate in patients with AML to that of all admitted patients in the same cohort.

While the previous studies were single-center studies involving a Southeast Asian patient population over a 20-year period from the late 1980s, our study includes data collected from a diverse patient population admitted to centers throughout the United States in 2012, which may render it more generalizable. The identification of acute promyelocytic leukemia as a risk factor for intracranial hemorrhage (relative risk, 3.67³ and 4.05¹) and the evolution of acute promyelocytic leukemia treatment including the widespread use of all-trans retinoic acid since the mid-1990s renders our study more relevant for the present day.⁴

Although CVA was a rare event in our dataset, our analysis revealed a 50-fold increase in the incidence of stroke in patients with

Table 1 Comparison of Characteristics of Patients With Active AML With and Without Stroke

	Patient Characteristics, %		
	CVA	No CVA	<i>P</i> Value
No. patients	65	10,974	N/A
Median age, y	68	63	N/A
Female	55	45	.078
Race			
White	75	76	.49
Black	8.90	11	.5
Hispanic	13	9.30	.5
Asian	0	3.20	.34
Native American	3.60	0.50	.01

Abbreviations: AML = acute myeloid leukemia; CVA = cerebrovascular accident.

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