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Original Article

A nationwide analysis of outcomes of stroke in hospitalized patients with essential thrombocythemia: 2006 to 2014

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Abstract: Background: Essential thrombocythemia (ET) is a subtype of myeloproliferative neoplasm associated with an increased risk of thrombohemorrhagic complications such as stroke. However, studies of prevalence and outcomes of stroke in hospitalized patients with ET have been limited to case series. Methods: Data from the National Inpatient Sample was utilized to identify outcomes in hospitalized patient with ET who were admitted for stroke. Utilizing the current procedural terminology code (CPT) for ET, outcomes of patients with ET who were hospitalized with stroke were studied for the years 2006 to 2014. Patient demographics of age, gender and race were collected and hospital characteristics of location and size were correlated to outcomes. Chi square test was used to determine odds ratios and multiple logistic regression was used to determine independent predictors of mortality. Results: Between the years of 2006 to 2014, a total of 552422 hospitalizations involved patients with a diagnosis of ET, 20650 of which were due to stroke. The percentage of stroke in these hospitalizations varied between 3.64 to 4.29 over 9 years and mortality in these patients did not significantly change during this time period. The prevalence of stroke was highest amongst Asians and Caucasians (4.7% and 3.86%) with a statistically significant difference (P=0.0000). A majority of ET patients with stroke were discharged to skilled nursing facilities. Multiple regression showed that female gender, atrial fibrillation, stroke, higher Charlson's comorbidity score and 80+ age were independent predictors of mortality (OR: 0.75, 1.35, 1.8, 2 to 5.7, 13.9 respectively). Conclusions: This study demonstrated that Female gender, atrial fibrillation, stroke, higher Charlson's comorbidity score and 80+ age group were found to be statistically significant independent predictors of mortality (OR: 0.75, 1.35, 1.8, 2 to 5.7, 13.9 respectively) in patients with ET and stroke. Inclusion of these factors in the risk stratification of patients with ET may decrease the morbidity and mortality associated with the disease.

Keywords: Essential thrombocythemia, stroke, outcomes

Introduction

Essential thrombocythemia (ET) is a myeloproliferative neoplasm characterized by hyperproliferation of hematopoietic tissue predominantly involving megakaryocytes that results in marked thrombocytosis. The incidence of ET is estimated at 1.2 to 3.0 per 100,000 population per year with a majority of individuals having a normal life expectancy on average [1]. While typically discovered incidentally on routine blood workups in asymptomatic patients, mortality rates in patients with Philadelphia chromosome-negative myeloproliferative disorders like ET are noted by some studies to be 1.5 times higher than in the general population [2-4]. ET has the potential to progress to acute myeloid leukemia and myelofibrosis. Yet, one of the major causes of morbidity and mortality in patients with ET are rare yet significant thrombo-hemorrhagic complications, the incidence of which range between 11 and 25% [5, 6]. In particular, patients with ET are at elevated risks for ischemic cerebrovascular events such as strokes that greatly alter patient quality of life [7]. A recent case series that investigated 148 patients found that cerebral ischemia was noted to be the most common manifestation in ET patients [8]. The major risk factors associated with clinical thrombosis among ET pati-

ents include age >60 years, the presence of Janus kinase 2 (JAK2) mutation, previous history of thrombosis, and cardiovascular risk factors in the form of tobacco use, hypertension, or diabetes mellitus [9, 10]. Pathogenesis of ET-associated thrombotic and microvascular complications are still not well understood [11].

Despite the severity and impact of these associated complications, only a few studies have evaluated the epidemiology of stroke in patients with ET. Previous estimates, clinical manifestations and outcomes regarding strokes in this patient population have been limited to case series [6, 12, 13]. The primary goal of this study was to assess the prevalence of strokes in ET patients across the United States as well as identify any statistically significant associations between stroke and/or in-hospital mortality with respect to patients' gender, age group, race, and comorbidities like hypertension, diabetes, atrial fibrillation and chronic kidney disease. Recognition and awareness of such contributing risk factors may help us more appropriately risk stratify stroke patients with ET and provide suitable prompt personalized treatment care.

Methods

Data from the years 2006-2014 were obtained from the National Inpatient Sample (NIS) database. NIS is a database maintained by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project [14]. This database represents the largest publicly available collection of longitudinal inpatient hospital care data in the United States. The NIS consists of data from approximately a 20% sampling of inpatient admissions to acute care hospitals in the United States. It is stratified by geographic region, urban/rural location, teaching status, and hospital bed size to minimize sampling bias. Each admission is weighted to make NIS representative of nationwide hospital systems. Patient's demographics, primary and secondary diagnoses, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, resource utilization and clinical outcomes are reported in the database. The data within the NIS are available to the public without personal identifiers, making this retrospective study exempt from review by the Institutional Review Board.

Admissions were included in the study if they had a principal diagnosis of ET. The current procedural terminology code (CPT) for ET and stroke were utilized to ensure inclusion of all patients with ET who were hospitalized with stroke. Patient demographics of age, gender and race were collected, and hospital characteristics of location and size were correlated to outcomes. The extent of common medical comorbidities such as hypertension, diabetes, chronic kidney disease and atrial fibrillation was studied in ET patients who died with and without stroke. Comorbidities were itemized and assessed using the Charlson Comorbidity Index (CCI) [15, 16]. CCI is a composite measure of the patient's health status based on chronic conditions.

Hospitals were classified based upon size.

Statistical analysis

Categoric group comparisons to compare patients with ET were carried out using Pearson χ^2 tests. Stepwise multiple logistic regression analyses were used to determine independent predictors of mortality over the years. Covariates for logistic regression included age, race, sex, comorbidities, hospital characteristics, insurance, and year. Statistical significance was defined as a P value of <0.05. All statistical analysis was performed using STATA software (College Station, Texas).

Results

Patient demographics

Between the years of 2006 to 2014, a total of 552422 hospitalizations involved patients with a diagnosis of ET, 20650 of which were due to stroke. Of the entire cohort of patients with stroke, 64.9% were females (13400 vs. 7251). The prevalence of stroke in these hospitalizations ranged from 3.64% to 4.29% over 9 years with no significant changes in mortality observed. The prevalence of stroke was highest amongst Asians and Caucasians (4.7% and 3.86%) with a statistically significant difference ($P<0.0001$). The age group of 80+ years and the difference in prevalence between different age groups (18-34 vs. 35-49 vs. 50-64 vs. 75-79) was statistically significant ($P<0.0001$) with Medicare being the insurance for most of these patients ($P<0.001$). Notably, mortality

was highest in the same group but was not significantly different from other age groups. Large sized hospitals were noted to have a higher proportion of ET patients with stroke compared to smaller and medium sized hospitals (P=0.0002). No difference in such proportions was noted in hospitals varying by region (Northeast vs. Midwest vs. South vs. West). Burden of medical comorbidities as measured by Charlson's comorbidity index was noted to be in the 4-6 range. Similarly, hypertension, hyperlipidemia, diabetes, atrial fibrillation, smoking status were also found to be more frequent in ET patients with stroke. A majority of ET patients with stroke were discharged to skilled nursing facilities. **Table 1** shows the summary statistics for demographic, clinical, and hospital factors.

Multivariate analysis

Multiple regression showed that female gender, atrial fibrillation, stroke, higher Charlson's comorbidity score and 80+ age were statistically significant independent predictors of mortality (OR: 0.75, 1.35, 1.8, 2 to 5.7, 13.9 respectively). The year of hospitalization, race, presence of comorbidities such as hypertension, diabetes, chronic renal failure, patient insurance, and hospital characteristics were not found to have statistically significant association with the prevalence of stroke. These data are summarized in **Table 2**.

Discussion

Essential thrombocythemia is a highly prevalent form of myeloproliferative neoplasms that increases a patient's risk for strokes. The NIS provides data on outcomes for patients with ET in hospitals across the United States. We specifically focused upon patients with a history of ET who were hospitalized for strokes. Our findings show that patients with ET who were hospitalized with stroke have significantly worse outcomes. The majority of patients were discharged to long-term skilled nursing facilities or died during their hospitalization. Our results also demonstrate that strokes were more prevalent in patients of old age, female gender, and Asian and Caucasian ethnic origin. Old age and female gender have been known to be major risk factors for stroke even among the general population [17, 18]. Our study corroborates such a trend exists in ET patients as well. What is more interesting to note is the significant prevalence of Asian and Caucasian patients with ET who were hospitalized for strokes. In the US, the largest racial disparity in stroke risk is in black individuals [19, 20], but our study revealed a different trend, possibly revealing that ET may invariably outweigh ethnic risk factors. When comparing outcomes across the different age groups, we found a marked difference in the prevalence of strokes. Particularly, patients over the age of 80 were more likely to have a stroke with the highest mortality. However, mortality due to stroke was not significantly different when compared to other age groups. This may be due to the devastating complications associated with stroke specifically in ET patients. The majority of these patients were noted to be covered by Medicare, which seems valid since many of the patients qualify for coverage based upon age.

Assessing hospital characteristics, we noted a larger prevalence of stroke patients in large hospital systems compared to smaller ones. It is likely that more patients with strokes are sent to larger institutions, which typically have a greater presence of clinical experts with the knowledge, experience, and resources to handle stroke patients. Similar to previous case series [6, 12, 13], our study also suggests that strokes are more likely in patients with ET who also have a predisposition for medical risk factors and comorbidities, including cardiovascular ones. In addition to assessing the prevalence of stroke within various patient demographics, this study attempted to define variables that may predict or increase the risk of in-hospital mortality for ET patients hospitalized with and without stroke. We identified advanced age, female gender, and atrial fibrillation as independent predictors of in-hospital mortality. CCI was also found to have a strong association with in-hospital mortality among hospitalized stroke patients, further supporting its use as a means in predicting in-hospital fatality. As would be expected, sicker patients are more likely to suffer death during hospitalizations - a conclusion that is understandable given the presence of health comorbidities and advanced age at admission. Factors such as older age and female sex have also previously been associated with higher likelihoods of mortality post stroke in the literature [19, 21].

The results of this study help identify modifiable risk factors that can possibly provide guidance in the complex management of ET patients. This study may serve as a foundation to

Table 1. Demographic distribution of hospitalized patients with ET between the years 2006-2014

Hospitalized patients with ET	Gender		Race						Age Group				
	Male	Female	White	Black	Hispanic	Asian	Native American	Unknown	18-34	35-49	50-64	65-79	80+
No Stroke	42856	64625	64919	16890	8562	2026	3194	11897	12661	18572	27476	27465	21314
Stroke	1461	2710	2605	633	243	101	115	474	97	487	845	1334	1408
In-hospital death	77	121	134	17	10	6	8	23	3	13	28	72	82

Table 2. Independent predictors of in-hospital mortality

Predictor	*Odds ratio (95% confidence interval)*	*P Value*
Year	0.98 (0.93-1.05)	0.69
Race	1.00 (0.95-1.06)	0.87
Age group	1.30 (1.11-1.52)	0.001
Sex	0.80 (0.59-1.08)	0.14
Comorbidities		
Atrial fibrillation	0.97 (0.66-1.42)	0.87
Hypertension	0.82 (0.59-1.10)	0.18
Diabetes	1.00 (0.69-1.44)	1
Hyperlipidemia	0.45 (0.31-0.66)	P<0.0001
Chronic renal failure	0.83 (0.51-1.34)	0.44
Smoking	0.48 (0.30-0.77)	0.003
Charlson comorbidity score	1.47 (1.14-1.89)	0.003
Insurance	1.12 (0.93-1.36)	0.23
Hospital region	0.89 (0.77-1.03)	0.11

include additional risk factors to help better risk stratify these patients and potentially decrease or avoid severe complications such as stroke in the future.

Strengths & limitations

There are several important strengths and limitations in this study. A major strength of this study is the large sample size with a nationwide scope, which is representative of a large subset of hospitalizations across the US. Also, the use of the NIS database ensured that the study analyzed only trained clinician-diagnosed stroke data. Limitations include the retrospective nature of the study, possible inaccuracies related to physician and hospital reporting of ICD-9-CM diagnostic and procedural codes, undercoding of possible comorbidities, and an inability to account for strokes that may have occurred shortly after discharge or resulted in patient mortality outside the hospital system. Utilizing the NIS limits the amount of detailed clinical data that can be obtained about outcomes and increases the likelihood of potential coding errors that can skew data results [22].

Conclusions

This large retrospective study allows us to gain an understanding of the prevalence and outcomes of stroke in patients with a history of ET. Our results indicate that patients with ET who suffer stroke are subjected to worse clinical outcomes with higher rates of mortality. Factors such as advanced age, gender, high CCI scores, and comorbid conditions increase the risk of mortality in this patient population. We hope this study may incentivize clinicians to include new risk factors into their risk assessment of patients with ET to reduce the incidence and decrease the morbidity of stroke in these patients.

Disclosure of conflict of interest

None.

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