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Impact of Atrial Fibrillation on Outcomes in Patients Hospitalized With Nontraumatic Intracerebral Hemorrhage

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Abstract

Objective: To assess the effect of atrial fibrillation (AF) on outcomes in hospitalizations for non-traumatic intracerebral hemorrhage (ICH).

Patients and Methods: We queried the National Inpatient Sample database between January 1, 2016, and December 31, 2019, to identify hospitalizations with an index diagnosis of non-traumatic ICH using ICD-10 code I61. The cohort was divided into patients with and without AF. Propensity score matching was used to balance the covariates between AF and non-AF groups. Logistic regression was used to analyze the association. All statistical analyses were performed using weighted values.

Results: Our cohort included 292,725 hospitalizations with a primary discharge diagnosis of non-traumatic ICH. From this group, 59,005 (20%) recorded a concurrent diagnosis of AF, and 46% of these patients with AF were taking anticoagulants. Patients with AF reported a higher Elixhauser comorbidity index (19.8±6.0 vs 16.6±6.4; $P<.001$) before propensity matching. After propensity matching, the multivariate analysis reported that AF (aOR, 2.34; 95% CI, 2.26-2.42; $P<.001$) and anticoagulation drug use (aOR, 1.32; 95% CI, 1.28-1.37; $P<.001$) were independently associated with all-cause in-hospital mortality. Moreover, AF was significantly associated with respiratory failure requiring mechanical ventilation (odds ratio, 1.57; 95% CI, 1.52-1.62; $P<.001$) and acute heart failure (odds ratio, 1.26; 95% CI, 1.19-1.33; $P<.001$) compared with the absence of AF.

Conclusion: These data suggest that non-traumatic ICH hospitalizations with coexistent AF are associated with worse in-hospital outcomes such as higher mortality and acute heart failure.

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Spontaneous intracerebral hemorrhage (ICH) is associated with 10% of all strokes globally and accounts for more than 50% of stroke-related deaths.[1-3] Two of the major risk factors for spontaneous ICH are age and use of antithrombotic therapy. Patients with AF are prescribed oral anticoagulants (OACs) for the prevention of ischemic stroke, but it can predispose them to spontaneous ICH. The prevalence of AF increases with age, and aging is an independent risk factor for developing spontaneous ICH.[4,5] However, the effect of AF beyond age and OAC use on the prognosis of patients with ICH is unknown.

Although there are studies evaluating the effect of AF on long-term outcomes in patients with spontaneous ICH, data are limited on in-hospital outcomes in patients hospitalized with ICH and have been confined to small cohort studies.[6-8] Therefore, we aimed to assess the prevalence and effect of AF on in-hospital outcomes in patients hospitalized with spontaneous ICH using a large, nationwide, administrative claims database.

PATIENTS AND METHODS

Data Source

We performed a retrospective cohort analysis of all adult (aged 18 years or older) hospitalizations for spontaneous ICH from January 1, 2016, to December 31, 2019, using the National Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project (HCUP). The NIS data used International Classification of Diseases (ICD)-9 codes before 2016 and, hence, were excluded to avoid data discrepancies. Data from NIS are derived from nonfederal hospitals in all states and is used to track, identify, and analyze patterns of major procedures, trends in hospitalizations, quality, charges, and outcomes.[9] Deidentified individual hospitalizations are maintained in the NIS as unique entries with a primary discharge diagnosis and multiple secondary diagnoses during that hospitalization. Moreover, NIS provides discharge weights that are used for the estimation of disease and procedure trends nationally. An institutional review board approval and informed consent were waived because the data was deidentified.

Data Extraction

We identified patients aged 18 years or older who were hospitalized with index diagnosis of spontaneous (atraumatic) ICH using the ICD, 10th revision, Clinical Modification (ICD-10 CM) code I61. We excluded hospitalizations with missing data on age, sex, and mortality. Then, the study population was stratified into 2 groups—those with and those without a diagnosis of AF. Atrial fibrillation diagnosis and patients consuming OACs were identified using the ICD-10 CM codes (Supplemental Data, available online at http://www.mcpiqojournal.org). Selection of the study population is shown in the Figure. Baseline characteristics and in-hospital outcomes were extracted using NIS variables and ICD-10 CM codes for comparison.

Statistical Analyses

Continuous variables were expressed as mean (±SD) or median (interquartile range) as appropriate. Categorical variables were expressed as percentages. Baseline characteristics were compared using Pearson χ^2 and Fisher exact tests for categorical variables. Continuous variables were analyzed using the Student *t* test or Wilcoxon rank-sum test, as appropriate. A *P* value of <.05 was considered statistically significant. Propensity score matching (PSM) was performed to balance out the differences in significant baseline characteristics and comorbidities between the 2 groups. Age, sex, congestive heart failure, valvular heart disease, peripheral vascular disease, hypertension, diabetes, chronic lung disease, renal failure, liver disease, coagulopathy, hypothyroidism, alcohol abuse, and drug abuse were used in the model for adjustment. After logistic regression, PSM was performed using a 1-to-1 scheme without replacement using the nearest number matching and a caliper width of 0.2. An absolute standardized difference of <10% (0.1) was considered an acceptable difference for adequate balance between the 2 groups. Multivariate logistic regression was used to analyze and identify association between AF and outcomes, including all-cause in-hospital mortality, respiratory failure requiring mechanical ventilation (MV), requiring blood transfusion, discharge home, length of stay, and cost of hospitalization. E-values were calculated for the variables that had significant odds ratio (OR) in the multivariate analysis.[10] Falsification hypotheses were used as an attempt to validate observational associations.[11] All statistical analyses were performed using R version 4.0.3 (R Project for Statistical Computing).

RESULTS

We identified 292,725 hospitalizations with an index discharge diagnosis of spontaneous non-traumatic ICH during the study period. From this cohort, 59,005 (20.2%) reported a concurrent diagnosis of AF. Persistent AF was present in 40,770 (13.9%). Baseline characteristics are summarized in Table 1. Patients hospitalized with ICH and AF were older (76.9±10.3 vs 65.6±15.2; *P*<.001) and more likely to be men (47.9% vs 46.6%; *P*<.001) compared with patients hospitalized with ICH and without AF. None of the patients with ICH and AF recorded left atrial appendage occlusion during their hospital stay.

Patients hospitalized for ICH with concurrent AF reported higher odds of comorbidities; notably, these included hypertension (OR,

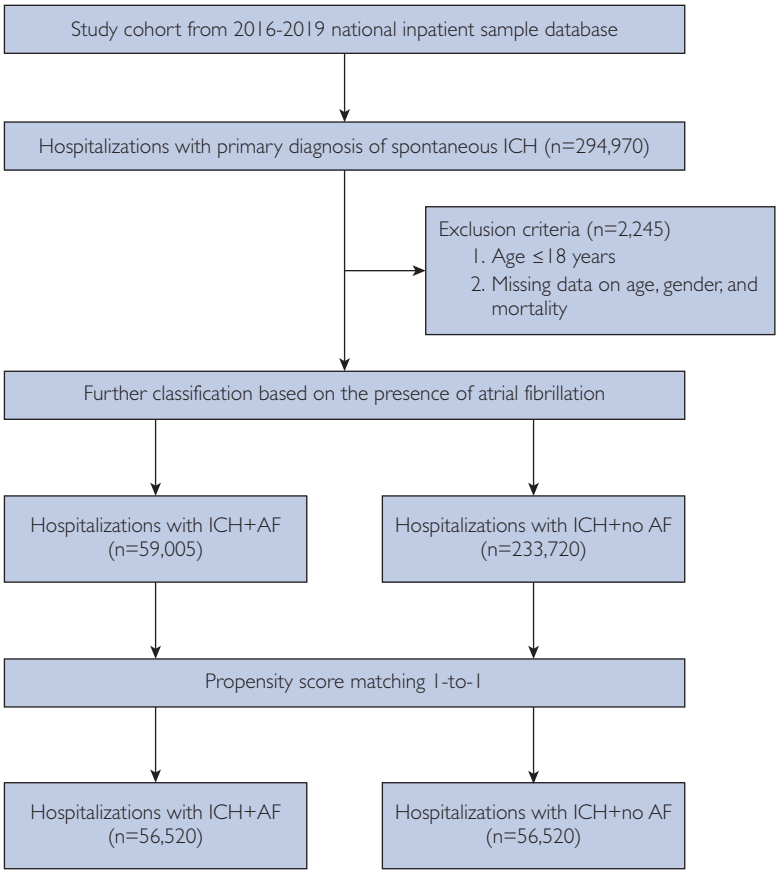

FIGURE. Study population selection—algorithm. Study population has been selected from the National Inpatient Sample (NIS) database 2016-2019 using the ICD-10 codes to select hospitalizations with a primary diagnosis of spontaneous intracerebral hemorrhage (ICH). After applying relevant exclusion criteria, 2245 hospitalizations were excluded, and 292,725 hospitalizations were included in the final analysis. They were further divided into 2 groups on the basis of the diagnosis of atrial fibrillation (AF). A 1-to-1 propensity matching was performed to balance and compare between the 2 groups.

1.9; 95% CI, 1.8-2.0; $P<.001$), diabetes (OR, 1.3; 95% CI, 1.2-1.4; $P<.001$), peripheral vascular disorder (OR, 2.0; 95% CI, 1.9-2.1; $P<.001$), and valvular heart disease (OR, 3.7; 95% CI, 3.6-3.9; $P<.001$) (Table 1). After the propensity score–matched analysis, each group included 56,520 hospitalizations, and differences in demographic variables and comorbidities between patients with and without AF were consistently <10% (Table 2).

We found that in patients hospitalized for ICH, concurrent AF was significantly associated with higher all-cause in-hospital mortality (OR, 2.63; 95% CI, 2.54-2.71; $P<.001$), respiratory failure requiring MV (OR, 1.59; 95% CI, 1.54-1.63; $P<.001$), and acute heart failure (OR, 1.39; 95% CI, 1.33-1.46; $P<.001$) compared with those without AF. Patients with AF were also less likely to be discharged to home (OR, 0.67; 95% CI, 0.65-0.69; $P<.001$) and recorded a higher cost of hospitalization (Table 3). Other variables associated with mortality on univariate analyses included age, male sex, congestive heart failure, valvular heart disease, peripheral vascular disease, chronic lung disease, renal failure, liver disease, coagulopathy, National Institutes of Health Stroke Scale on admission, and

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TABLE 1. Baseline Characteristics of ICH Hospitalizations With and Without AF Before Propensity Matching

Baseline characteristic	AF, n=59,005 (%)	No AF, n=233,720 (%)	*P*
Age (y), mean ± SD	76.9±10.3	65.6±15.2	<.001
Race			<.001
White	43,910 (77)	130,660 (58.1)	
Black	5010 (8.8)	45,390 (20.2)	
Hispanic	3670 (6.4)	25,950 (11.5)	
Female sex	27,470 (46.6)	111,965 (47.9)	<.001
Obesity	6580 (11.2)	26,535 (11.4)	.16
Hypertension	52,515 (89)	188,905 (80.8)	<.001
Diabetes	20,090 (34)	64,820 (27.7)	<.001
Peripheral vascular disease	5955 (10.1)	12,235 (5.2)	<.001
Valvular heart disease	7655 (13)	8970 (3.8)	<.001
Coagulopathy	10,940 (18.5)	23,175 (9.9)	<.001
Gastrointestinal bleeding	635 (1.1)	2695 (1.2)	.11
Hypothyroid	10,215 (17.3)	24,845 (10.6)	<.001
Congestive heart failure	17,335 (29.4)	21,715 (9.3)	<.001
Chronic liver disease	1440 (2.4)	10,075 (4.3)	<.001
Renal failure	13,110 (22.2)	37,080 (15.9)	<.001
Chronic lung disease	10,520 (17.8)	29,805 (12.8)	<.001
Deficiency anemia	1275 (2.2)	5660 (2.4)	<.001
Alcohol abuse	2120 (3.6)	18,845 (8.1)	<.001
Drug abuse	735 (1.2)	14,710 (6.3)	<.001

AF, atrial fibrillation; ICH, intracerebral hemorrhage.

taking anticoagulants (Table 4). After adjustment for other variables associated with mortality on the univariate analysis, the multivariate analysis reported that AF (adjusted odds ratio [aOR], 2.34; 95% CI, 2.26-2.42; *P*<.001), National Institutes of Health Stroke Scale (aOR, 1.21; 95% CI, 1.19-1.23; *P*<.001), and use of anticoagulants (aOR, 1.32; 95% CI, 1.28-1.37; *P*<.001) were independently associated with all-cause in-hospital mortality in patients admitted with ICH (Table 4). E-values for the variables significant in the multivariate analysis are summarized in Table 5. Atrial fibrillation recorded the highest E-value of 2.43 and lower CI of 2.37. Falsification hypotheses reported no association of pancreatitis (OR, 0.6; 95% CI, 0.35-1.02; *P*=.06) or cardiac sarcoidosis (OR, 1.01; 95% CI, 0.29-3.45; *P*=.99) with mortality.

Subgroup Analysis

The subgroup analysis reported that in patients with AF, persistent AF was significantly associated with mortality (OR, 1.68; 95% CI, 1.61-1.76; *P*<.001) when compared with that in patients with paroxysmal AF. There was a graded increase in OR for mortality when comparing patients with ICH and AF on OACs and those with no AF (OR, 1.69; 95% CI, 1.55-1.84; *P*<.001) vs patients with ICH and AF on OACs and those with AF but not taking OACs (OR, 1.30; 95% CI, 1.25-1.35; *P*<.001).

DISCUSSION

This study compared the in-hospital outcomes of patients admitted with spontaneous ICH with and without a concurrent diagnosis of comorbid AF. In our analysis on the basis of a large, contemporary, sample representative of the US population, we found that in patients hospitalized with spontaneous non-traumatic ICH, comorbid AF was associated with the following:

1. Significantly higher all-cause in-hospital mortality

TABLE 3. In-Hospital Outcomes of ICH Hospitalizations With and Without AF After 1-to-1 Propensity Matching

In-hospital outcome	AF, n=56,520 (%)	No AF, n=56,520 (%)	*P*
All-cause mortality	14,040 (24.8%)	6305 (11.2%)	<.001
Mechanical ventilation	15,950 (28.2%)	11,195 (19.8%)	<.001
Requiring blood transfusion	1070 (1.9%)	1135 (2%)	.16
Acute heart failure	4635 (8.2%)	3395 (6%)	<.001
Discharge home	5745 (10.2%)	8120 (14.4%)	
Length of stay (d), mean	7.3	7.5	<.001
Cost of hospitalization ($), mean	101,929	91,537	<.001

A, atrial fibrillation; ICH, intracerebral hemorrhage.

2. Higher rates of respiratory failure requiring MV and heart failure
3. Lower likelihood of discharge to the home setting.

Our study reported that AF is associated with worse in-hospital outcomes, such as higher all-cause in-hospital mortality, even after PSM and adjusting for univariate covariates of mortality in patients admitted with ICH. This association is independent of age and OAC use. Moreover, AF recorded a significantly higher E-value compared with other variables in the multivariate analysis. This could infer that the observed aOR of 2.34 could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of 2.4-fold each, higher and lower than the measured confounders, but weaker confounding could not do so. The traditional risk factors for ICH are advanced age, hypertension, OACs, smoking, and alcohol abuse.[12] In older people, cerebral amyloid angiopathy (CAA) is an important cause of ICH.[13] β-Amyloid peptide fragments in CAA predominantly deposit in the leptomeningeal and cortical blood vessels, which weaken the vessel wall and eventually result in hemorrhage.[14,15] Because AF is also more prevalent in older people, older

TABLE 2. Baseline Characteristics of ICH Hospitalizations With and Without AF After Propensity Matching

Baseline characteristic	AF, n=56,520 (%)	No AF, n=56,520 (%)	Absolute mean difference (%)
Age (y), mean ± SD	76.5±10.4	76.8±10.5	2.5
Female sex	26,245(46.4)	26,165 (46.3)	0.2
Hypertension	50,130 (88.7)	50,520 (89.4)	2
Diabetes	19,025 (33.7)	19,745 (34.9)	2.4
Peripheral vascular disease	5430 (9.6)	5175 (9.2)	1.4
Valvular heart disease	6435 (11.4)	5605 (9.9)	4.3
Coagulopathy	9925 (17.6)	9105 (16.1)	3.4
Hypothyroid	9605 (17)	9645 (17.1)	0.1
Congestive heart failure	14,930 (26.4)	13,070 (23.1)	7.1
Chronic liver disease	1390 (2.5)	1225 (2.2)	1.6
Renal failure	12,295 (21.8)	12,395 (21.9)	0.2
Chronic lung disease	9795 (17.3)	10,000 (17.7)	0.6
Alcohol abuse	2100 (3.7)	2080 (3.7)	0.3
Drug abuse	735 (1.3)	620 (1.1)	1.5

AF, atrial fibrillation; ICH, intracerebral hemorrhage.

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TABLE 4. Univariate and Multivariate Logistic Regression Analyses Showing Association With All-Cause In-Hospital Mortality

Variable	OR	*P*	Adjusted OR	*P*
Age	1.008 (1.007-1.01)	<.001	1.014 (1.012-1.015)	<.001
Female sex	0.91 (0.88-0.93)	<.001	0.89 (0.86-0.91)	<.001
Congestive heart failure	1.54 (1.49-1.59)	<.001	1.49 (1.43-1.54)	<.001
Valvular disease	1.15 (1.10-1.21)	<.001	1.01 (0.96-1.06)	.50
Peripheral vascular	1.18 (1.13-1.25)	<.001	1.05 (1.00-1.11)	.05
Lung disease	1.24 (1.20-1.29)	<.001	1.23 (1.18-1.28)	<.001
Hypothyroidism	0.91 (0.88-0.95)	<.001	0.90 (0.86-0.94)	<.001
Renal failure	1.14 (1.10-1.18)	<.001	1.08 (1.04-1.12)	<.001
Liver disease	1.26 (1.14-1.38)	<.001	1.22 (1.10-1.35)	<.001
Coagulopathy	1.53 (1.47-1.59)	<.001	1.48 (1.42-1.54)	<.001
Alcohol	0.74 (0.68-0.81)	<.001	0.73 (0.66-0.80)	<.001
Drug abuse	1.24 (1.09-1.41)	.001	1.48 (1.29-1.70)	<.001
Hypertension	0.74 (0.71-0.77)	<.001	0.69 (0.65-0.72)	<.001
Diabetes mellitus	0.96 (0.93-1.01)	.05	—	—
AF	2.63 (2.54-2.71)	<.001	2.34 (2.26-2.42)	<.001
Anticoagulation	2.00 (1.94-2.07)	<.001	1.32 (1.28-1.37)	<.001

AF, atrial fibrillation; ICH, intracerebral hemorrhage.

age is a common risk for both AF and CAA.[16,17]

The association of symptomatic stroke and AF is well known, but recent studies have also shown higher rates of silent cerebral lesions detected by diffusion-weighted magnetic resonance imaging with AF and in patients with a history of AF ablation.[18-20] Anticoagulants are well proven to decrease the risk of stroke and all-cause mortality in patients with AF who are at an increased risk of ischemic stroke, but they carry the risk of ICH.[4] Although we could not measure the size of ICH, we believe this might be higher in those with AF because of anticoagulant use leading to higher mortality. Similar conclusion can be derived from our subgroup analysis that reported a higher mortality in patients with AF on OACs than patients not on OACs. Therefore, the effect of AF on the prognosis of ICH could be mediated by age and OAC use. However, the higher OR in the adjusted analysis of the association with AF when compared with age and OAC use suggests that AF might negatively affect recovery after ICH that is not solely explained by older age or OAC use.

Our analysis also reported that in patients hospitalized with ICH, comorbid AF was significantly associated with higher rates of respiratory failure requiring MV. These findings are consistent with some previous evidence.[21] The volume and expansion of the hematoma in patients with previous AF is larger than those in patients without AF.[22] Large hematomas are more likely to result in midline shift, which might increase the rates of MV from acute respiratory failure.[23] Altered mental status and pulmonary complications in these patients may in turn lead to prolonged and difficult weaning from MV.[23] Prolonged MV has already been proven to negatively affect hospital outcomes by prolonging hospital stays and increasing the risk of infections.[24]

The HAS-BLED score does not include components that may risk stratify patients for ICH-like imaging features of CAA (cerebral microbleeds, superficial siderosis, increased centrum semiovale perivascular spaces, and spot pattern of white matter hyperintensities) in patients with AF when predicting the risk of bleeding.[25-29] Patients with a history of ICH are traditionally excluded from the

TABLE 5. E-Values for the Variables Significant in the Multivariate Analysis

Variable	E-value	Lower/upper CI
Atrial fibrillation	2.43	2.37
Oral anticoagulation	1.56	1.51
Age	1.09	1.08
Female sex	1.31	1.27
Congestive heart failure	1.74	1.68
Hypertension	1.70	1.64
Lung disease	1.45	1.40
Hypothyroidism	1.29	1.21
Renal failure	1.24	1.16
Liver disease	1.44	1.27
Coagulopathy	1.72	1.67
Alcohol	1.61	1.48
Drug abuse	1.72	1.52

randomized control trials that assessed the safety and efficacy of OACs in patients with AF.[30-32] Previous observational studies of patients with ICH and AF investigating the competing risks of hemorrhage and ischemic stroke have suggested that restarting anticoagulation drugs is generally recommended.[33-35] However, these studies have not particularly analyzed the risk in patients with CAA where the risk of rebleeding may be higher than in those with a hypertensive hemorrhage. Thus, patients with CAA who are at an increased risk of recurrent ICH continue to remain understudied.[36]

Left atrial appendage occlusion devices are promising as a non-pharmacologic alternative in patients with a higher risk of bleeding in AF.[37,38] Patients in our study with concomitant intracranial ICH and AF are perhaps good candidates for left atrial appendage occlusion device evaluation. However, there is a need for studies to develop risk stratification tools or modify the current scoring systems such as HAS-BLED to include more variables such as cerebral microbleeds in patients with AF to further guide anticoagulation drug use decisions.[27]

Limitations

Our study has several limitations. First, although the NIS is a large and powerful repository for hypothesis-generating studies, it lacks information on whether a specific diagnosis was present on admission. Thus, one cannot discriminate between conditions that were present on admission or acquired during the hospitalizations. Because a significant proportion of patients were not on anticoagulation drugs in the non-AF group, we could not include the use of anticoagulation drugs in the initial PSM. However, we included anticoagulation drug use in the multivariate analysis to factor its effect on mortality and MV. Similar to any other administrative registry, NIS is susceptible to coding errors. The size of hematoma is an important determinant of outcome in patients with ICH, including rates of MV, but hematoma volume and location cannot be extracted from NIS.[39] However, we potentially hypothesize that patients with AF experience multiple risk factors such as being at risk of CAA and being on anticoagulation, which lead to more severe ICH and, in turn, worse outcomes. Finally, we were limited in a per-patient analysis taking medications to determine which patients began taking OACs again. Because of these limitations, the associations identified in our analysis should not considered to reflect any causality.

CONCLUSION

These data show that in patients admitted with ICH, a concurrent diagnosis of AF is associated with significantly higher rates of in-hospital mortality, respiratory failure, heart failure, and lower chances of discharge home. The strength of the association of AF with worse outcomes after ICH suggests that the deleterious effect of coexistent AF may not be fully explained by older age or OAC use.

POTENTIAL COMPETING INTERESTS

The authors report no competing interest.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AF,** atrial fibrillation; **CAA,** cerebral amyloid angiopathy; **ICH,** intracerebral hemorrhage; **MV,** mechanical ventilation; **NIS,** National Inpatient Sample; **OAC,** oral anticoagulant; **OR,** odds ratio; **PSM,** propensity score matching

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