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Impact of atrial fibrillation on inflammatory bowel disease hospitalizations—a nationwide retrospective study

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ABSTRACT

Systemic inflammation seen in inflammatory bowel disease (IBD) may cause electrophysiological changes in the atria leading to atrial fibrillation (AF). We analyzed data from the National Inpatient Sample for 2018 to identify all adult hospitalizations with a primary diagnosis of IBD, which were further divided based on the presence or absence of AF. The primary outcome was inpatient mortality while the secondary outcomes included inpatient complications, mean length of stay, and mean total hospital charge. We identified 92,055 IBD hospitalizations, of which 3900 (4.2%) had AF and 88,155 (95.8%) served as controls. IBD hospitalizations with AF were older (70.9 vs. 45.0 years, $P < 0.001$) and had a higher association with comorbidities compared to the non-AF cohort. Furthermore, the AF cohort had significantly higher adjusted odds of inpatient mortality (2.05% vs. 0.24%; adjusted odds ratio 2.07; 95% confidence interval [CI] 1.09–3.90; $P = 0.025$), longer length of stay (6.5 vs. 4.9 days; incidence rate ratio 1.23; 95% CI 1.14–1.33; $P < 0.001$), and higher total hospital charge ($14,587 vs. $11,475; incidence rate ratio 1.26; 95% CI 1.15–1.38; $P < 0.001$). Additionally, complications such as acute respiratory failure, pulmonary embolism, and necessity of blood product transfusion were more common for IBD hospitalizations with AF than those without.

KEYWORDS Atrial fibrillation; inflammatory bowel disease; mortality; National Inpatient Sample; outcomes

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract and can be subdivided into ulcerative colitis and Crohn's disease based on the pattern of mucosal involvement and characteristics of the chronic inflammatory process.[1,2] IBD is not a leading cause of mortality but severely impacts patients' quality of life.[3–6] The presence of continuous chronic systemic inflammation in IBD patients is linked to numerous pathophysiological processes within the cardiomyocytes leading to electrophysiological and structural remodeling for the atria, promoting the development and maintenance of atrial fibrillation (AF).[7] Although AF is the most common arrhythmia encountered in clinical practice and a leading cause of morbidity and mortality, there is a paucity of data on the impact of AF on IBD hospitalizations. In this study, we assessed biodemographic distribution, adverse outcomes, and system-based complications of IBD hospitalizations with concurrent AF and compared it with IBD hospitalizations without AF. Furthermore, we detailed the geographical distribution and burden of the disease on the US health care system in terms of health care costs and resource utilization.

METHODS

We used the National Inpatient Sample (NIS) database, which consists of hospitalizations derived from billing data from hospitals across the US covering more than 97% of the population.[8] It approximates a 20% stratified sample of discharges from US community hospitals, excluding rehabilitation and long-term acute care hospitals. This dataset is

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weighted to obtain national estimates.[9] In 2018, the database was coded using the International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS). Using these ICD-10 codes, we identified all adult hospitalizations with a primary diagnosis of IBD (ulcerative colitis and Crohn's disease) for 2018. Patients <18 years of age and elective admissions were excluded. The cohort was further subdivided into two groups based on the presence or absence of AF. The primary outcome was to estimate inpatient mortality for IBD hospitalizations with AF. Additionally, we also compared the inpatient mortality rates for IBD hospitalizations with AF to those without AF to assess the impact of AF on IBD mortality. The secondary outcomes included system-based complications such as sepsis, renal failure, pulmonary embolism, acute respiratory failure, acute myocardial infarction, need for blood product transfusion, and the impact of the disease on the US health care system in terms of health care costs and resource utilization.

The analysis was conducted using weighted samples for national estimates and Stata Version 16 software (StataCorp, College Station, TX). Comorbidities were calculated as proportions and the chi-squared test was used to compare characteristics between the groups. A multivariate regression analysis was performed to adjust for possible confounders such as age, gender, race, hospital region, household income, and grouped Charlson Comorbidity Index while estimating the primary and secondary outcomes. Additionally, a negative binomial regression model was used to adjust for count data including length of stay (LOS) and total hospital charge, expressed as incidence rate ratios (IRR). P values ≤ 0.05 were considered statistically significant. As the NIS database lacks identifiers at an individual and hospital level, this study was exempt from institutional review board approval.

RESULTS

For 2018, we identified 92,055 hospitalizations for IBD, out of which 3900 (4.2%) had AF and 88,155 (95.8%) served as controls. Of these IBD hospitalizations, patients with AF were significantly older (70.9 vs. 45 years, $P < 0.001$) compared to those without AF *(Table 1)*. There was no statistically significant difference in the groups' gender distribution. For IBD hospitalizations with AF, Whites (84.7%) made up most of the study population, followed by Blacks (7.2%), Hispanics (3.1%), and other races (5%). A similar distribution was seen for the non-AF cohort, with Whites making up 70.5% of the study population, followed by Blacks (13.7%), Hispanics (8.6%), and other races (7.2%).

Compared to IBD hospitalizations without AF, we noted a higher proportion of patients in the AF cohort with comorbidities such as diabetes mellitus (27.6% vs. 9%, $P < 0.001$), obesity (17.8% vs. 9.6%, $P < 0.001$), dyslipidemia (44% vs. 13.2%, $P < 0.001$), coronary artery disease (32.2% vs. 5.6%, $P < 0.001$), prior cerebrovascular accident (1.5% vs. 0.5%, $P < 0.001$), hypertension (38.5% vs. 23.2%, $P < 0.001$), congestive heart failure (25% vs. 2.4%, $P < 0.001$), chronic kidney disease (24.6% vs. 4.5%, $P < 0.001$), chronic obstructive pulmonary disease (19.1% vs. 5.2%, $P < 0.001$), malnutrition (18.5% vs. 14.5%, $P = 0.002$), and a history of anemia (52.6% vs. 37.3%, $P < 0.001$) *(Table 1)*. However, IBD hospitalizations without AF had more smokers (18.9% vs. 9%, $P < 0.001$) compared to those with AF *(Table 1)*.

A higher proportion of IBD hospitalizations with AF were observed in the South hospital region (35.5%), followed by the Midwest (26.3%), Northeast (24.5%), and West (13.7%). Most of these hospitalizations were at teaching hospitals (70.6%) located in urban areas (91.5%). A similar distribution was noted for IBD hospitalizations without AF *(Table 1)*.

The adjusted odds ratio (aOR) for inpatient mortality was significantly higher for IBD hospitalizations with AF compared to the non-AF cohort (2.05% vs. 0.24%; aOR 2.07; 95% CI 1.09–3.90; $P = 0.025$) *(Table 2)*. IBD hospitalizations with AF also had longer mean LOS (6.5 vs. 4.9 days; IRR 1.23; 95% CI 1.14–1.33; $P < 0.001$) and higher mean total hospital charge ($14,587 vs. $11,475; IRR 1.26; 95% CI 1.15–1.38; $P < 0.001$) compared to the non-AF cohort. Additionally, inpatient complications such as acute respiratory failure (6% vs. 1.1%; aOR 1.69; 95% CI 1.16–2.46; $P = 0.006$), pulmonary embolism (1.7% vs. 0.4%; aOR 2.45; 95% CI 1.16–5.15; $P = 0.018$), and need for blood product transfusion (10.4% vs. 5.4%; aOR 1.86; 95% CI 1.42–2.45; $P < 0.001$) were higher for IBD hospitalizations with AF compared to the non-AF cohort *(Table 2)*. From a payment perspective, Medicaid was the largest insurer (74.8%) for IBD hospitalizations with AF, followed by private insurance (18.3%) and Medicare (5.9%). Only 1% of these patients were uninsured.

DISCUSSION

The US Centers for Disease Control and Prevention reported an increase in the prevalence of IBD from 2 million adults (0.9%) in 1999 to 3 million (1.3%) in 2015.[4] These rising rates are concerning as IBD patients are at increased risk of developing early atherosclerosis, cardiovascular diseases such as myocardial infarction, and arrhythmias like AF.[5,6]

Over the past decade, there has been growing evidence of the role of systemic inflammation in the pathogenesis of AF.[7] Systemic inflammation has been associated with numerous pathophysiological processes including oxidative stress, apoptosis, and fibrosis of cardiomyocytes, leading to electrophysiological and structural remodeling of the atria promoting the development of AF.[10,11] Additionally, patients with IBD may have increased levels of interleukin-6 and C-reactive protein, both of which can lead to atrial remodeling.[12] The role of systemic inflammation in the development of AF is further evident by the fact that the incidence rate of AF is

Table 1. Characteristics of inflammatory bowel disease hospitalizations in the presence and absence of atrial fibrillation

Variable	Atrial fibrillation Yes (n = 3900)	Atrial fibrillation No (n = 88,155)	*P* value
Patient characteristics			
Mean age (years)	70.9	45.0	<0.001
Women	54.5%	51.3%	0.081
Racial distribution			<0.001
White	84.7%	70.5%	
Black	7.2%	13.7%	
Hispanic	3.1%	8.6%	
Others	5.0%	7.2%	
Charlson Comorbidity Index score			<0.001
0	25.8%	66.9%	
1	22.7%	19.5%	
2	19.9%	7.2%	
≥3	31.6%	6.4%	
Insurance type			<0.001
Medicaid	74.8%	25.3%	
Medicare	5.9%	19.8%	
Private	18.3%	48.9%	
Uninsured	1.0%	6.0%	
Median annual income*			0.056
≤$43,999	22.9%	25.0%	
$44,000–$55,999	30.3%	25.9%	
$56,000–$73,999	24.6%	26.2%	
≥$74,000	22.2%	22.9%	
Comorbidities			
Diabetes mellitus	27.6%	9.0%	<0.001
Hypertension	38.5%	23.2%	<0.001
Smoking history	9.0%	18.9%	<0.001
Congestive heart failure	25.0%	2.4%	<0.001
Chronic kidney disease	24.6%	4.5%	<0.001
Dyslipidemia	44.0%	13.2%	<0.001
Obesity	17.8%	9.6%	<0.001
Coronary artery disease	32.2%	5.6%	<0.001
Prior cerebrovascular accident	1.5%	0.5%	<0.001
COPD	19.1%	5.2%	<0.001
Malnutrition	18.5%	14.5%	0.002
History of neoplasm	11.5%	6.4%	<0.001
History of anemia	52.6%	37.3%	<0.001
Hospital characteristics			
Hospital region			0.027
Northeast	24.5%	21.3%	
Midwest	26.3%	24.2%	
South	35.5%	37.5%	
West	13.7%	17.0%	
Hospital bed size			0.211
Small	19.6%	20.0%	
Medium	30.8%	27.8%	
Large	49.6%	52.2%	
Urban location	91.5%	93.5%	0.032
Teaching hospital	70.6%	75.6%	0.002

*In patient's zip code for 2018.
COPD indicates chronic obstructive pulmonary disease.

higher in IBD flare-ups and persistent disease compared to periods of remission.[13]

According to the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, the overall prevalence of AF was ≤0.5% in individuals <50 years of age with a gradual increase to 4% to 9% in the 65 to 80 age group and >9% in individuals aged >80 years.[14] In another study from 2001 to 2010, AF was reported in 11.3% of IBD patients with a mean age of 56.4 ± 15.4 years.[15] Most studies have noted a female and Caucasian predominance in this patient population.[16,17] In our study, the prevalence and mean age for IBD hospitalizations with AF was noted to be 4.2% (3900 patients) and 70.9 years, respectively. These findings were in line with current literature. Furthermore, IBD hospitalizations with AF had a White predominance *(Table 1)*. The reasons for this racial/ethnic variance are relatively unknown. However, a combination of genetic factors, host immune response, and environmental factors may contribute to the higher expression of IBD, which in turn may lead to higher rates of AF.[17]

Studies have identified numerous risk factors for AF. Systemic inflammation may serve as an independent factor; however, the presence of additional risk factors may have a synergistic effect. In our study, we noted a higher proportion of patients with comorbidities such as diabetes mellitus, obesity, dyslipidemia, coronary artery disease, prior cerebrovascular accident, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, malnutrition, and history of anemia for IBD hospitalizations with AF compared to the non-AF cohort.

Table 2. Clinical outcomes for inflammatory bowel disease hospitalizations in the presence and absence of atrial fibrillation

Clinical outcome	Atrial fibrillation		aOR (95% CI)	*P* value*
	Yes (n = 3900)	No (n = 88,155)		
Primary outcome				
Inpatient mortality	2.05	0.24	2.07 (1.09–3.90)	0.025
Secondary outcomes				
Mean length of stay	6.5	4.9	1.23* (1.14–1.33)	<0.001
Mean total hospital costs	$14,587	$11,475	1.26* (1.15–1.38)	<0.001
Sepsis	2.3	1.2	1.29 (0.75–2.22)	0.364
Acute myocardial infarction	1.2	0.2	1.07 (0.43–2.66)	0.877
Transfusion of blood products	10.4	5.4	1.86 (1.42–2.45)	<0.001
Acute renal failure	21.5	7.9	1.05 (0.86–1.28)	0.647
Acute respiratory failure	6.0	1.1	1.69 (1.16–2.46)	0.006
Acute pulmonary embolism	1.7	0.4	2.45 (1.16–5.15)	0.018

*Adjusted incidence rate ratio.
aOR indicates adjusted odds ratio; CI, confidence interval.

These associations were in line with reported risk factors.[18] However, the non-AF cohort had more smokers than the AF cohort *(Table 1)*. The exact reason for this is unknown and may need further investigation. Nonetheless, lifestyle intervention and optimal medical management directed toward modifiable risk factors may be essential to decrease the prevalence of AF in IBD populations.

In 2018, AF was the underlying cause of death for 25,845 patients in the US.[19,20] The 30-day mortality rate for Crohn's disease and ulcerative colitis have been estimated to be 2.7 and 3.8 per 100 hospital stays, respectively.[21] Using a multivariate regression analysis model, we noted a significantly higher adjusted odds of inpatient mortality for IBD hospitalizations with AF compared to the non-AF cohort *(Table 2)*. This finding was expected. Hence, preventing mortality in these patients should focus on better control of the systemic inflammation and optimal pharmacological management of AF.

AF has a wide spectrum of complications if untreated. It can lead to thrombosis, ischemic stroke, pulmonary embolism secondary to thrombus in the right atrium, myocardial infarction, heart failure, and sudden cardiac death.[22–26] We report higher rates of acute respiratory failure, pulmonary embolism, and need for blood product transfusion for IBD hospitalizations with AF. Higher rates of blood product transfusion may correlate with higher rates of bleeding secondary to anticoagulant use in these patients. Therefore, these patients may benefit from early left atrial appendage closure devices, which have become a popular alternative to anticoagulation therapy to prevent strokes and systemic embolism in patients with higher bleeding risks.[27] Hence, we advocate for more studies to evaluate the efficacy of left atrial appendage closure devices and compare outcomes of early vs late closure device placement.

In 2014, the mean cost of inpatient management was noted to be $11,345 for Crohn's disease and $13,412 for ulcerative colitis.[28] From 2006 to 2015, the mean LOS for IBD hospitalizations was 6.7 ± 5.8 days.[29] In our study, IBD hospitalizations with AF had a higher total hospital charge ($14,587) and longer LOS (6.5 days) compared to the non-AF cohort *(Table 2)*. Hence, the presence of AF can be linked to higher costs and longer hospitalizations in a setting of IBD.

This study has several strengths and limitations. A considerable strength of this study was the large multiethnic study population and a study design that focused on numerous facets of the disease. However, we acknowledge the limitations. The NIS database does not include data on the severity, time after hospitalization to AF development, and treatment aspects. Furthermore, all biases present in retrospective studies are applicable to this study. As the NIS is an administrative database that uses codes to gather information, the possibility of coding errors and missing data cannot be excluded. Despite these limitations, we believe that the large sample size, study design, and comprehensive analysis help us better understand the topic in question while promoting future research on AF in IBD.

In conclusion, AF is associated with significant inpatient mortality, higher health care costs, and longer LOS in patients with IBD. Therefore, it is crucial to prevent the development of AF and promptly treat it in an inpatient

setting, thereby reducing adverse outcomes and the burden on the US health care system.

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