

Association of atrial fibrillation with outcomes in patients hospitalized with inflammatory bowel disease: an analysis of the National Inpatient Sample

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Abstract

Introduction: We aimed to determine in-hospital outcomes, length of hospital stay (LOS) and resource utilization in a contemporary cohort of patients with inflammatory bowel disease (IBD) and atrial fibrillation (AFIB).

Material and methods: The National Inpatient Sample database October 2015 to December 2017 was utilized for data analysis using the International Classification of Diseases, Tenth Revision codes to identify the patients with the principal diagnosis of IBD.

Results: Of 714,863 IBD patients, 64,599 had a diagnosis of both IBD and AFIB. We found that IBD patients with AFIB had a greater incidence of in-hospital mortality (OR = 1.3; 95% CI: 1.1–1.4), sepsis (OR = 1.2; 95% CI: 1.1–1.3), mechanical ventilation (OR = 1.2; 95% CI: 1.1–1.5), shock requiring vasopressor (OR = 1.4; 95% CI: 1.1–1.9), lower gastrointestinal bleeding (LGIB) (OR = 1.09, 95% CI: 1.04–1.1), and hemorrhage requiring blood transfusion (OR = 1.2, 95% CI: 1.17–1.37). Mean LOS ± SD, mean total charges and total costs were higher in patients with IBD and AFIB.

Conclusions: In this study, IBD with AFIB was associated with increased in-hospital mortality and morbidity, mean LOS and resource utilization.

Key words: inflammatory bowel disease, atrial fibrillation, NIS, propensity-matched, outcomes.

Introduction

Inflammatory bowel disease (IBD) is characterized by non-infectious chronic inflammation of the gastrointestinal tract, and primarily includes Crohn's disease (CD) (which can affect any segment of the gastrointestinal tract from the mouth to the anus), ulcerative colitis (UC) (which is limited to the colonic mucosa), and indeterminate colitis [1]. The incidence and prevalence of IBD are increasing worldwide with the peak of occurrence usually happening in the second to fourth decade of life, and a second smaller peak occurring between 50 and 70 years of age [1, 2]. IBD is

associated with an increased risk of cardiovascular diseases such as stroke, myocardial infarction, and early atherosclerosis with increased intimal thickness of the common carotid artery [3, 4]. High levels of C-reactive protein (CRP), a major marker reflecting activity and severity of inflammation in IBD, are also associated with atherogenesis, atherosclerotic cardiovascular disease and atrial arrhythmia [5–7].

Atrial fibrillation (AFIB) is the most common type of arrhythmia observed in clinical practice, with an estimated prevalence of 0.4% to 1% in the general US population [8–10]. The burden of AFIB in the US has been on the rise, with 2.3 million adults with AFIB in 2000 to an expected value of 12.1 million adults in 2030 [10, 11]. AFIB mostly affects the elderly and is more prevalent in men and white Caucasians [10, 12, 13]. AFIB like other cardiac arrhythmias is significantly associated with increased risks of cardiovascular complications, consequently leading to decreased quality of life, disability, healthcare expenses, and high mortality [14]. Recently, inflammation is being recognized as a pathogenic contributor to the development of AFIB [15]. Previous research has shown a significant association between serum inflammatory mediators such as CRP, tumor necrosis factor- α , interleukin (IL)-2, IL-6, and IL-8, and the development and persistence of AFIB [16, 17]. Several cardiovascular disorders, notably coronary atherosclerosis, are associated with inflammation, and cytokines are known to affect plaque rupture and thrombus formation, resulting in myocardial infarction [18].

Considering that pathogenesis of AFIB is being increasingly linked to systemic inflammation, IBD may be a potential risk factor for AFIB, and the co-existence of the diseases could substantially lead to worsening outcomes (such as disability, health care utilization, medical costs, mortality). However, there is limited information regarding the association between comorbid AFIB and in-hospital outcomes, length of hospital stays, and resource utilization in people with IBD. To date, there are no data on how AFIB affects inpatient outcomes of IBD patients who are at the greatest risk for frequent hospitalizations. In this paper, we aim to study these parameters and other outcomes from a population database.

Material and methods

Study data

In this retrospective analysis, we utilized the National Inpatient Sample (NIS) data from October 2015 to December 2017. The NIS database is sponsored by the Agency for Healthcare Research and

Quality as a part of the Healthcare Cost and Utilization Project (HCUP) and is the largest publicly available all-payer administrative database, containing data on more than 7 million hospitalizations (unweighted); when weighted, it represents about 35 million hospitalizations nationally. It provides information on clinical and resource utilization with safeguards to protect data for individual patients, physicians, and hospitals. Beginning in October 2015, the NIS started using the International Classification of Diseases, Tenth Edition, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS) to reflect the implementation of ICD-10-CM/PCS by hospital systems. Using the Agency for Healthcare Research and Quality sampling and weighting method, national estimates of the entire US hospitalized population were calculated.

Study design

Given the de-identified nature of the NIS data, our study was exempt from approval from the Institutional Review Board. We identified all patients (≥ 18 years of age) who had a principal diagnosis of IBD ($n = 714863$), using their respective ICD-10-CM/PCS codes. We divided the total sample into two groups: IBD with AFIB ($n = 64599$) and IBD alone ($n = 650264$). We identified patients with AFIB using appropriate diagnosis codes. The ICD-10-CM/PCS codes used in this study are displayed in Supplementary Table S1.

For baseline characteristics, we used patient demographics (age, race, and sex), the Charlson comorbidity index, insurance status, hospital characteristics, and relevant co-morbidities coronary artery disease (CAD), hypertension (HTN), obesity, dyslipidemia, diabetes mellitus (DM), congestive heart failure, chronic lung disease, peripheral vascular disease, and chronic kidney disease (CKD) (Table I). Comorbidities were identified using their respective ICD-10-CM/PCS codes (Supplementary Table S1).

Outcomes

The primary outcome of interest was all-cause in-hospital mortality. Secondary outcomes included incidence of acute kidney injury (AKI), peritonitis, intestinal obstruction, lower gastrointestinal bleeding (LGIB), sepsis, acute coronary syndrome, shock requiring vasopressors, disseminated intravascular coagulation (DIC), hemorrhage requiring blood transfusion, venous thromboembolism (VTE), acute respiratory failure, colectomy, and mechanical ventilation. Complications were identified using their respective ICD-10-CM/PCS (Supplementary Table S1). We also studied the length of hospital stay (LOS), hospital costs, and reimbursement.

Table I. Demographics comparing IBD with AFIB vs. IBD alone

Variable	IBD with AFIB (%)	IBD without AFIB (%)	P-value
Total	64599	650264	
Age (mean ± SD)	73.2 ±11.8	50.8 ±19.5	< 0.001*
Female	52.3	55.2	0.22
Race (%):			
Caucasian	88.8	77.2	
African American	5.1	12.1	
Hispanic	3.0	6.5	< 0.001*
Asian	0.9	1.2	
Native American	0.2	0.4	
Others	1.7	2.4	
Hospital bed size (%):			
Small	17.7	18.4	
Medium	30.1	27.8	0.11
Large	52.1	53.7	
Hospital region (%):			
Northeast	23.6	21.6	
Midwest	23.7	24.5	0.06
South	34.1	36.6	
West	18.4	17.1	
Discharge:			
Routine	72.1	42.7	< 0.001*
Skilled nursing facility	1.9	2.8	
Charlson comorbidity index (%):			
0 or 1	31.8	70.9	
2	19.3	11.7	< 0.001*
3	48.8	17.2	
Insurance type (%):			
Medicare	36.5	36.5	
Medicaid	3.6	16.9	< 0.001*
Private	13.97	39.8	
Uninsured	0.8	3.67	
Teaching hospital	69.9	70.9	0.32
Chronic co-morbidity (%):			
DM	30.5	15.0	< 0.001*
HTN	40.3	30.3	< 0.001*
CAD	36.47	9.8	< 0.001*
Anemia	7.7	8.1	0.13
Obesity	12.2	11.2	0.15
Dyslipidemia	45.2	40.9	0.53
CKD	25.7	8.7	< 0.001*
CHF	28.5	4.9	< 0.001*
CLD	14.6	13.5	0.11
PVD	6.2	4.1	0.23

*Statistically significantly different result. DM – diabetes mellitus, HTN – hypertension, CAD – coronary artery disease, CHF – congestive heart failure, PVD – peripheral vascular disease, CLD – chronic lung disease.

Statistical analysis

We conducted all statistical analyses as per the recommended methods accounting for the intricate survey design of the NIS database using STATA 15.0 (Stata Corp LLC). Categorical data are reported as frequency and percentage, and continuous data as mean with standard deviation and standard error. Pearson's χ^2 test was used to determine significant differences in categorical variables, and continuous variables were analyzed using Student's *t*-test. Univariable logistic regression analysis was used to calculate unadjusted odds ratios (OR) for the primary and secondary outcomes; then multivariable logistic regression analysis was performed for potential confounders. The multivariate logistic regression model was built by using only variables that were associated with the outcome of interest in univariable regression analysis at $p < 0.2$. All analyses in our study were weighted using provided discharge weights to produce national estimates. Statistical significance was set at a two-sided p -value of < 0.05 . Reported hospital costs and charges were inflation-adjusted for July 2020 using the Consumer Price Index (provided by the U.S. Department of Labor). Sensitivity analysis was performed, excluding the population with CHF and CAD, to determine the accuracy of the results. A full list of covariates used in the regression analysis and confounders in the multivariable regression model is shown in Supplementary Table S1.

Results

Characteristics of the study population

We identified 714,863 patients admitted with the diagnosis of IBD. Of these, 64,599 had concomitant AFIB, and 626,869 had IBD only. The mean age (SD) in the IBD + AFIB group and IBD group was 73.2 (11.8) years and 50.8 \pm 19.5 years, respectively. There was a significant difference between groups for age, race, discharge disposition, Charlson comorbidity index, insurance, DM, HTN, CAD, CKD, and CHF (Table I). There was a higher percentage of patients with DM, HTN, CKD, CAD, and CHF in patients with IBD + AFIB.

Comparison of primary and secondary outcomes

The proportion of primary and secondary outcomes in both groups is shown in Table II. We compared the outcomes between IBD with AFIB and IBD groups. In the univariate analysis, a statistically significant difference was observed for in-hospital mortality (OR = 4.1, 95% CI: 3.7–4.5), AKI (OR = 2.6, 95% CI: 2.5–2.7), sepsis (OR = 2.3, 95% CI: 2.1–2.4), peritonitis (OR = 1.2, 95%

CI: 1.05–1.5), intestinal obstruction (OR = 0.85, 95% CI: 0.57–0.75), colectomy (OR = 0.5, 95% CI: 0.4–0.6), DIC (OR = 2.1, 95% CI: 1.5–2.9), acute respiratory failure (OR = 2.5, 95% CI: 2.3–2.8), mechanical ventilation (OR = 2.8, 95% CI: 2.5–3.1), shock requiring vasopressor (OR = 3.4, 95% CI: 2.8–4.2), LGIB (OR = 1.4, 95% CI: 1.3–1.5), hemorrhage requiring blood transfusion (OR = 3.4, 95% CI: 3.0–3.8), acute myocardial infarction (OR = 3.4, 95% CI: 3.0–3.8) and venous thromboembolism (OR = 1.6, 95% CI: 1.3–1.9). Except intestinal obstruction and colectomy, which were lower, all other complications were higher in the IBD with AFIB group.

Multivariable logistic regression was performed to adjust for potential confounders. After adjusting for confounders, IBD patients with AFIB had a significantly greater incidence of in-hospital mortality (OR = 1.3; 95% CI: 1.1–1.4), sepsis (OR = 1.2; 95% CI: 1.1–1.3), mechanical ventilation (OR = 1.2; 95% CI: 1.1–1.5), shock requiring vasopressor (OR = 1.4; 95% CI: 1.1–1.9), LGIB (OR = 1.09, 95% CI: 1.04–1.1), and hemorrhage requiring blood transfusion (OR = 1.2, 95% CI: 1.17–1.37) (Table II).

A sensitivity analysis where patients with CAD and CHF were excluded to assess whether AFIB was still associated with increased risk of mortality and complications in univariable and multivariable analyses was performed. The results were similar, with increased in-hospital mortality (OR = 1.3; 95% CI: 1.1–1.5), sepsis (OR = 1.2; 95% CI: 1.1–1.4), mechanical ventilation (OR = 1.2; 95% CI: 1.1–1.4), shock requiring vasopressor (OR = 1.5; 95% CI: 1.1–1.9), LGIB (OR = 1.08, 95% CI: 1.03–1.1), and hemorrhage requiring blood transfusion (OR = 1.2, 95% CI: 1.1–1.3) (Table III).

Factors associated with mortality in IBD + AFIB group

Multivariate logistic regression was performed to identify the factors associated with mortality in the IBD + AFIB group. Advanced age (OR = 1.05; 95% CI: 1.04–1.06), congestive heart failure (OR = 1.7; 95% CI: 1.3–2.2), and CAD (OR = 1.5; 95% CI: 1.1–1.9) were identified as factors associated with mortality in IBD with AFIB (Table IV).

Length of stay and resource utilization

Statistically significant differences were observed in the mean length of stay (LOS), mean cost of care, and mean total charges between the two groups. Mean LOS (\pm SD) (6.7 \pm 7 vs. 5.2 \pm 6.7, $p < 0.001$), mean total charges (\$ 76104 vs. \$ 54876, $p < 0.001$), and mean total costs (\$ 18926 vs. \$ 13881) were higher in IBD with AFIB (Table V).

Table II. Comparison of primary and secondary outcomes: IBD with AFIB vs. IBD

Variable	Incidence (%)		Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
	IBD with AFIB	IBD without AFIB				
In-hospital mortality	4.7	1.1	4.1 (3.7–4.5)	< 0.001*	1.3 (1.1–1.4)	< 0.001*
AKI	25.0	11.2	2.6 (2.5–2.7)	< 0.001*	1.0 (0.97–1.09)	0.31
Sepsis	10.2	4.7	2.3 (2.1–2.4)	< 0.001*	1.2 (1.1–1.3)	< 0.001*
Peritonitis	0.8	0.6	1.2 (1.05–1.5)	0.01*	1.05 (0.83–1.3)	0.63
Intestinal obstruction	1.7	2.1	0.85 (0.57–0.75)	< 0.001*	0.94 (0.82–1.07)	0.39
Colectomy	2.2	4.1	0.5 (0.4–0.6)	< 0.001*	0.91 (0.79–1.04)	0.20
DIC	0.3	0.1	2.1 (1.5–2.9)	< 0.001*	1.1 (0.75–1.6)	0.6
Acute respiratory failure	3.2	1.2	2.5 (2.3–2.8)	< 0.001*	1.1 (0.96–1.3)	0.12
Mechanical ventilation	4.2	1.5	2.8 (2.5–3.1)	< 0.001*	1.2 (1.1–1.5)	0.001*
Pressor requirements	1.1	0.3	3.4 (2.8–4.2)	< 0.001*	1.4 (1.1–1.9)	0.001*
LGIB	39.1	30.81	1.4 (1.3–1.5)	< 0.001*	1.09 (1.04–1.1)	< 0.001*
Blood requirement	10.0	5.8	1.8 (1.6–1.9)	< 0.001*	1.2 (1.17–1.37)	< 0.001*
AMI	3.6	1.0	3.4 (3.0–3.8)	< 0.001*	0.92 (0.80–1.05)	0.24
VTE	1.0	0.6	1.6 (1.3–1.9)	< 0.001*	1.01 (0.81–1.2)	0.92

*Statistically significantly different results. AKI – acute kidney injury, DIC – disseminated intravascular coagulation, LGIB – lower gastrointestinal bleeding, AMI – acute myocardial infarction, VTE – venous thromboembolism. Variables used in the multivariate logistic regression: age, sex, race, Charlson comorbidity index, congestive heart failure, acute kidney injury, chronic kidney disease, anemia, shock requiring vasopressor, coronary artery disease, chronic lung disease, hypertension, dyslipidemia diabetes mellitus, disseminated intravascular coagulation, acute respiratory failure, peritonitis, colectomy, mechanical ventilation, venous thromboembolism, acute myocardial infarction, hemorrhage requiring blood transfusion, sepsis and intestinal obstruction.

Table III. Sensitivity analysis comparing primary and secondary outcomes: IBD with AFIB vs. IBD

Variable	Incidence (%)		Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
	IBD with AFIB	IBD without AFIB				
In-hospital mortality	4.6	1.1	4.2 (3.8–4.7)	< 0.001*	1.3 (1.1–1.5)	0.001*
AKI	24	10.9	2.6 (2.5–2.7)	< 0.001*	1.03 (0.97–1.1)	0.23
Sepsis	10.3	4.6	2.3 (2.1–2.5)	< 0.001*	1.2 (1.1–1.4)	< 0.001*
Peritonitis	0.8	0.6	1.2 (1.05–1.6)	0.01*	1.02 (0.80–1.3)	0.81
Intestinal obstruction	1.9	2.3	0.91 (0.58–0.78)	< 0.001*	0.96 (0.92–1.03)	0.07
Colectomy	2.4	3.9	0.5 (0.5–0.64)	< 0.001*	0.89 (0.77–1.03)	0.14
DIC	0.4	0.2	2.3 (1.6–3.2)	< 0.001*	1.1 (0.79–1.7)	0.43
Acute respiratory failure	3.2	1.2	2.6 (2.3–3.0)	< 0.001*	1.1 (0.97–1.3)	0.09
Mechanical ventilation	4.2	1.5	2.8 (2.5–3.2)	< 0.001*	1.2 (1.1–1.4)	0.01*
Pressor requirements	1.1	0.3	3.3 (2.7–4.2)	< 0.001*	1.5 (1.1–1.9)	0.003*
LGIB	39.1	30.7	1.4 (1.3–1.5)	< 0.001*	1.08 (1.03–1.1)	< 0.001*
Blood requirement	9.7	5.7	1.7 (1.6–1.9)	< 0.001*	1.2 (1.1–1.3)	< 0.001*
AMI	3.1	0.9	3.3 (3.0–3.8)	< 0.001*	1.01 (0.86–1.17)	0.88
VTE	1.1	0.7	1.6 (1.3–2.0)	< 0.001*	1.01 (0.77–1.2)	0.88

*Statistically significantly different result. AKI – acute kidney injury, DIC – disseminated intravascular coagulation, LGIB – lower gastrointestinal bleeding, AMI – acute myocardial infarction, VTE – venous thromboembolism. Variables used in the multivariate logistic regression: age, sex, race, Charlson comorbidity index, acute kidney injury, chronic kidney disease, anemia, shock requiring vasopressor, hypertension, dyslipidemia diabetes mellitus, chronic lung disease, disseminated intravascular coagulation, acute respiratory failure, peritonitis, colectomy, mechanical ventilation, venous thromboembolism, acute myocardial infarction, hemorrhage requiring blood transfusion, sepsis and intestinal obstruction.

Table IV. Factors associated with mortality in IBD with AFIB

Variable	Odds ratio	P-value	95% CI
Advanced age	1.05	< 0.001*	1.04–1.06
Congestive heart failure	1.7	< 0.001*	1.3–2.2
CAD	1.5	0.004*	1.1–1.9

*Statistically significantly different result. Variables used in the multivariate logistic regression: age, sex, race, acute myocardial infarction, insurance status, hospital bed size, hospital location, discharge disposition, teaching status of hospital, Charlson comorbidity index, hypertension, diabetes mellitus, peripheral vascular disease, chronic kidney disease, coronary artery disease, obesity dyslipidemia, congestive heart failure, chronic lung disease, acute kidney injury, peritonitis, disseminated intravascular coagulation, acute respiratory failure, peritonitis, colectomy, mechanical ventilation, venous thromboembolism, hemorrhage requiring blood transfusion, sepsis and intestinal obstruction.

Table V. Analysis for length of stay and cost of care

Parameter	IBD with AFIB	IBD without AFIB	P-value
Mean ± SD LOS [days]	6.7 ±7.0	5.2 ±6.7	< 0.001*
Mean total charge [\$]	76104	54876	< 0.001*
Mean total cost [\$]	18926	13881	< 0.001*

*Statistically significantly different result.

The factors associated with increased length of stay in IBD with AFIB were advanced age (adjusted mean difference = 1.2, 95% CI: 1.2–3.6), AKI (adjusted mean difference = 2.9, 95% CI: 1.6–2.4), sepsis (adjusted mean difference = 7.7, 95% CI: 3.6–4.9), and VTE (adjusted mean difference = 1.6, 95% CI: 2.8–6.1) (Table V).

Discussion

The main findings of our current investigation are as follows: (1) IBD patients with comorbid AFIB have increased mortality compared to IBD patients without AFIB, and this difference persisted after adjusting for potential confounders. (2) The presence of AFIB is an independent predictor of mortality in IBD patients even after excluding those with CHF and CAD, and about 9% of patients in our cohort have AFIB. (3) Advanced age, CAD, and CHF were also independently associated with death among IBD patients with AFIB. (4) IBD and AFIB patients have increased risk of sepsis and LGIB, higher cost of hospitalization and increased length of stay compared to IBD patients without AFIB even after adjusting for known confounders.

AFIB is a complex disease with several potential mechanisms. The prevalence of AFIB in our cohort of IBD patients is 9%, which approximates 11.3% reported by Pattanshetty *et al.* [19] in 141 IBD patients, and significantly higher than the general US population of 0.95% as reported by Go *et al.* [10]. Several studies have shown that the inflammatory process is one of the mechanisms for the occurrence of AFIB [15, 20, 21]. Frustaci *et al.* demonstrated inflammatory

changes in atrial tissues obtained from patients with isolated persistent AFIB [20]. Gedikli *et al.* found a 2 to 3-fold increase in the presence of serum inflammatory markers in AFIB patients compared with controls [22]. It is suggested that inflammation contributes to both occurrence and persistence of AFIB [23]. Inflammation is thought to cause tissue damage by ischemia and oxidative stress, progressively leading to loss of atrial muscle mass with interstitial fibrosis and resulting in structural remodeling [22]. This process also impairs intracellular calcium current, resulting in atrial electrical remodeling, which are known determinants of AFIB [22].

IBD is characterized by chronic inflammation of the digestive tract, affecting the most productive age groups of the population [1, 2]. Proinflammatory cytokines have been involved in regulating the intestinal immune response, causing tissue injury, and mediating complications of IBD [18, 24]. Inflammatory markers such as IL6 have been reproducibly detected in serum of IBD patients and correlate with disease activity [24–28]. IL-6 stimulates the proliferation of mature T cells, enhances the differentiation of cytotoxic T lymphocytes and affects the terminal differentiation and immunoglobulin production of B cells and induces acute phase proteins [29, 30].

IBD patients are more prone to developing AFIB and the co-occurrence of the two diseases could lead to worse outcomes and frequent hospitalizations. This is the first study demonstrating additive effects of AFIB in the population of IBD patients. There is a reasonable body of evidence to support the pathophysiological features for the co-occurrence of IBD and AFIB [19, 29]. The higher

prevalence of AFIB in the IBD population as reported in our study could be attributed to systemic inflammation. Systemic inflammation is known to be a significant contributor to the development of AFIB [15, 30]. Several previous studies have suggested that systemic inflammation is linked to various pathological processes such as oxidative stress, apoptosis, and fibrosis of cardiomyocytes, all of which lead to structural and electrical remodeling of the atria, promoting the development and persistence of AFIB [30–32]. Moreover, increases in the level of serum inflammatory markers, such as CRP and IL-6, were observed in patients with AFIB and IBD, especially CD [16, 17].

In our national cohort of IBD patients, we have also demonstrated that AFIB is associated with worse in-patient survival and that difference persists despite accounting for confounding variables. We also demonstrated that AFIB is an independent predictor of mortality in IBD patients. The strong association of worse outcomes of IBD patients with AFIB poses unique management challenges.

Additionally, the association of worse mortality in IBD patients with AFIB also calls into question measures to screen for AFIB in this patient population. Timely detection of AFIB and subsequent implementation of relevant therapeutic measures could result in improved outcomes in IBD patients.

This study is observational, and residual measured and unmeasured confounding factors may influence these findings. The NIS is an administrative claim-based database that uses ICD-10 CM codes for disease diagnosis that may be subject to error. Secondly, the NIS collects data on in-patient discharges, and each admission is registered as an independent event. It is possible that the same patient may have more than one subsequent admission over time. NIS samples are not designed to follow patients longitudinally, so long-term outcomes could not be assessed from the present dataset. Additionally, data on AFIB management are lacking from the NIS, which has important implications for the conclusions drawn from the study.

In conclusion, our study shows AFIB to be associated with worse outcomes in IBD patients. Given the higher prevalence of AFIB in IBD and a significantly higher incidence of mortality and morbidity in IBD patients with AFIB, it is imperative that treating physicians should have clinical suspicion for AFIB in this specific patient cohort, as timely AFIB detection could result in improved outcomes. Further longitudinal studies are required to explore the temporal trends of AFIB and its comorbidities in IBD patients, and to establish associations with mortality and morbidity due to the arrhythmia complications.

Conflict of interest

The authors declare no conflict of interest.

References

1. Thia KT, Loftus EV Jr, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. *Am J Gastroenterol* 2008; 103: 3167-82.
2. Papadakis KA, Targan SR. Role of cytokines in the pathogenesis of inflammatory bowel disease. *Annu Rev Med* 2000; 51: 289-98.
3. Papa A, Danese S, Urgesi R, et al. Early atherosclerosis in patients with inflammatory bowel disease. *Eur Rev Med Pharmacol Sci* 2006; 10: 7-11.
4. Rungoe C, Basit S, Ranthe MF, Wohlfahrt J, Langholz E, Jess T. Risk of ischaemic heart disease in patients with inflammatory bowel disease: a nationwide Danish cohort study. *Gut* 2013; 62: 689-94.
5. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; 107: 499-511.
6. Poullis AP, Zar S, Sundaram KK, et al. A new, highly sensitive assay for C-reactive protein can aid the differentiation of inflammatory bowel disorders from constipation- and diarrhoea-predominant functional bowel disorders. *Eur J Gastroenterol Hepatol* 2002; 14: 409-12.
7. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* 2001; 104: 2886-91.
8. National Heart L, And Blood Institute Arrhythmia 2020.
9. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. *J Am Coll Cardiol* 2001; 37: 371-8.
10. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; 285: 2370-5.
11. Prevention CFDC. Atrial Fibrillation 2020.
12. Blackshear JL, Kopecky SL, Litin SC, Safford RE, Hammill SC. Management of atrial fibrillation in adults: prevention of thromboembolism and symptomatic treatment. *Mayo Clin Proc* 1996; 71: 150-60.
13. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008; 117: e25-146.
14. Murakoshi N, Aonuma K. Epidemiology of arrhythmias and sudden cardiac death in Asia. *Circ J* 2013; 77: 2419-31.
15. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. *Circulation* 2003; 108: 3006-10.
16. Patel P, Dokainish H, Tsai P, Lakkis N. Update on the association of inflammation and atrial fibrillation. *J Cardiovasc Electrophysiol* 2010; 21: 1064-70.
17. Psychari SN, Apostolou TS, Sinos L, Hamodraka E, Liakos G, Kremastinos DT. Relation of elevated C-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation. *Am J Cardiol* 2005; 95: 764-7.

18. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation* 2004; 109: 112-10.
19. Pattanshetty DJ, Anna K, Gajulapalli RD, Sappati-Biyyani RR. Inflammatory bowel "Cardiac" disease: point prevalence of atrial fibrillation in inflammatory bowel disease population. *Saudi J Gastroenterol* 2015; 21: 325-9.
20. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo Ma, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation* 1997; 96: 1180-4.
21. Watanabe T, Takeishi Y, Hirano O, et al. C-reactive protein elevation predicts the occurrence of atrial structural remodeling in patients with paroxysmal atrial fibrillation. *Heart Vessels* 2005; 20: 45-9.
22. Gedikli O, Dogan A, Altuntas I, et al. Inflammatory markers according to types of atrial fibrillation. *Int J Cardiol* 2007; 120: 193-7.
23. Korantzopoulos P, Kolettis T, Siogas K, Goudevenos J. Atrial fibrillation and electrical remodeling: the potential role of inflammation and oxidative stress. *Med Sci Monit* 2003; 9: RA225-9.
24. Atreya R, Neurath MF. Involvement of IL-6 in the pathogenesis of inflammatory bowel disease and colon cancer. *Clin Rev Allergy Immunol* 2005; 28: 187-96.
25. Hirano T, Akira S, Taga T, Kishimoto T. Biological and clinical aspects of interleukin 6. *Immunol Today* 1990; 11: 443-9.
26. Ishihara K, Hirano T. IL-6 in autoimmune disease and chronic inflammatory proliferative disease. *Cytokine Growth Factor Rev* 2002; 13: 357-68.
27. Kishimoto T. Interleukin-6: from basic science to medicine: 40 years in immunology. *Annu Rev Immunol* 2005; 23: 1-21.
28. Mudter J, Neurath MF. Il-6 signaling in inflammatory bowel disease: pathophysiological role and clinical relevance. *Inflamm Bowel Dis* 2007; 13: 1016-23.
29. Kristensen SL, Lindhardsen J, Ahlehoff O, et al. Increased risk of atrial fibrillation and stroke during active stages of inflammatory bowel disease: a nationwide study. *Europace* 2014; 16: 477-84.
30. Harada M, Van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management. *Circ J* 2015; 79: 495-502.
31. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. *J Am Coll Cardiol* 2012; 60: 2263-70.
32. Kourliouros A, Savelieva I, Kiotsekoglou A, Jahangiri M, Camm J. Current concepts in the pathogenesis of atrial fibrillation. *Am Heart J* 2009; 157: 243-52.