

# An Investigation into the Association Between Inflammatory Bowel Disease and Cardiac Arrhythmias: An Examination of the United States National Inpatient Sample Database

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## ABSTRACT

**BACKGROUND:** Inflammatory bowel diseases (IBD) associated-chronic inflammation and autonomic dysregulation may predispose to arrhythmias. However, its exact prevalence is unknown. Thus, we aimed to ascertain the prevalence of arrhythmias in patients with IBD.

**METHODS:** We queried the Nationwide Inpatient Sample (the largest publicly available all-payer inpatient USA database) from 2012 to 2014. We used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) discharge codes to identify adult patients (≥18 years) with IBD and dysrhythmias (supraventricular tachycardia (SVT), atrial fibrillation, atrial flutter, ventricular tachycardia (VT), or ventricular fibrillation). Furthermore, we identified risk factors for cardiovascular disease. We divided patients into 2 cohorts, IBD cohorts, and non-IBD cohort. The independent effect of a diagnosis of IBD on the risk of dysrhythmias was examined using a multivariable logistic regression model controlling for multiple confounders.

**RESULTS:** We identified 847 235 and 84 757 349 weighted hospitalizations among patients with IBD and non-IBD cohorts, respectively. Patients with IBD were less likely to be hospitalized for dysrhythmias than the non-IBD (9.7% vs 14.2%,  $P < .001$ ). The hospitalization odds for dysrhythmias among patients with IBD were less than the general population (OR 0.87; 95% CI 0.85–0.88). However, the prevalence of SVT and VT was indifferent between the 2 groups. Male sex, age of over 60, and white race were risk factors for dysrhythmias.

**CONCLUSION:** Despite prior reports of a higher prevalence of arrhythmias among patients with IBD, in a nationwide inpatient database, we found lower rates of hospitalization-related-arrhythmias in the IBD population compared to that of the general population.

**KEYWORDS:** Inflammatory bowel disease, arrhythmias, Nationwide Inpatient Sample, Crohn's disease, ulcerative colitis

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## Introduction

Sudden cardiac death (SCD) remains a public health crisis, accounting for up to 15% to 20% of all deaths worldwide, despite advances in the treatment of coronary artery disease.<sup>1</sup> The development of malignant tachyarrhythmias is the predominant mechanism of sudden cardiac death (SCD). The pathogenesis of cardiac arrhythmias has been increasingly linked to systemic inflammation.<sup>2</sup> Previous studies have established the association between cytokines (such as interleukin IL-2, IL-6, and IL-8), inflammatory mediators such as CRP, tumor necrosis alpha, and the occurrence and persistence of atrial fibrillation (AF).<sup>3</sup> Chronic autoimmune and inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, and psoriasis are linked to an increased risk of AF.<sup>4,5</sup>

Despite the growing evidence of the role of inflammation in the pathogenesis of cardiac diseases, uncertainty remains as to the exact relationship between inflammatory bowel disease (IBD) and cardiovascular disease (CVD); or if indeed it increases its prevalence and impacts on mortality associated with it.<sup>6–11</sup> So far, most of the current work had centered on the implication of inflammatory mechanisms in the development of atrial fibrillation in chronic inflammatory conditions such as rheumatoid arthritis and IBD. There is, therefore, an urgent need to comprehensively examine the exact association between IBD and other arrhythmias, including the clinical and demographic determinants of this association. Ascertaining this relationship will have significant implications for morbidity and mortality thus far reported for patients with IBD. In this



study, we have comprehensively examined the comparative rates of arrhythmias among patients with IBD compared to that of the US general population utilizing the national inpatient sample database.

## Methods

### Data source

We utilized the Agency for Healthcare Research and Quality (AHRQ's) National Inpatient Sample database, which was developed as part of the Healthcare Cost and Utilization Project (HCUP). The National (Nationwide) Inpatient Sample (NIS) has been exhaustively described elsewhere. In brief, it is the largest publicly available database in the United States that captures a 20% sample of non-federal hospitals of the US. The NIS is a beneficial tool in studying rare and uncommon diseases given its large sample size.

### Study population

We captured longitudinal patients' data from 2012 to 2014. All patients with a discharge diagnosis of IBD, either Crohn's or ulcerative colitis, were included using the International classification of diseases-9th edition (ICD-9). From this cohort, we selected IBD patients (ICD-9:555.xx, 556.xx) who had a diagnosis of cardiac arrhythmias, including AF, atrial flutter (A.flutter), SVT, VT, VF using codes 427.3, 427.32, 427.0, 427.1, 427.41, respectively.

### Patient and hospital characteristics

We abstracted the following demographic and multi-morbidity covariates from NIS database: age, gender, race, smoking, alcohol intake, obesity, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), diabetes, heart failure, hypertension,

dyslipidemia, coronary artery disease, acute coronary syndrome, stroke, chronic kidney disease (CKD), obstructive sleep apnea (OSA), peripheral vascular disease (PVD), and the hospital region.

### Outcomes

The primary outcomes of this study were the prevalence of hospitalization related-cardiac arrhythmias as a whole, as well as the prevalence of each cardiac arrhythmia subgroup (AF, A.flutter, SVT, VT, V.fib) amongst IBD patients versus non-IBD Patients. The secondary outcome was a correlation between cardiac arrhythmias and demographic as well as the geographical disposition of patient cohorts (baseline hospital region).

### Statistical analysis

The comorbidities were classified using the Charlson Comorbidity Index. Demographic characteristics, co-existing disease distribution were compared using  $\chi^2$  or *t*-test, as appropriate. Multiple logistic regression was used to obtain risk-adjusted odds ratio (OR) to compare dysrhythmia prevalence between IBD and non-IBD patients, with adjusting baseline characteristics, including comorbidities and different hospital status. All tests were 2-sided with an a priori  $\alpha$  of 0.05.

## Results

A total of 169 447 discharges of patients with IBD and 16 951 470 discharges of the general population of  $\geq 18$  years of age were reviewed, representing 847 235 hospitalizations among the IBD patients, and 84 757 349 hospitalizations among the general population. Baseline characteristics of the study population are summarized in (Table 1). Compared to the general population, patients with IBD tended to be younger

**Table 1.** Baseline demographic and clinical characteristics among hospitalized patients in the nationwide inpatient sample.

	PATIENTS WITHOUT IBD (84 757 349)	PATIENTS WITH IBD (847 235)	P VALUE
Age (mean)	57.41	52.45	<.001
Female	50 085 109 (59.10%)	482 125 (56.91%)	<.001
Race			<.001
White	58 039 425 (68.48%)	675 320 (79.71%)	
Black	12 510 579 (14.76%)	91 295 (10.78%)	
Hispanic	8 947 061 (10.56%)	47 435 (5.60%)	
Asian or Pacific Islander	2 107 545 (2.49%)	8 855 (1.10%)	
Native American	534 919 (0.63%)	3 470 (0.41%)	
Other	2 617 820 (3.10%)	20 860 (2.46%)	

(Continued)

Table 1. (Continued)

	PATIENTS WITHOUT IBD (84 757 349)	PATIENTS WITH IBD (847 235)	P VALUE
Hospital region			<.001
Northeast	17 103 283 (20.18%)	196 160 (23.15%)	
Midwest	17 397 853 (20.53%)	193 320 (22.82%)	
South	33 903 817 (40.00%)	314 245 (37.09%)	
West	16 352 396 (19.29%)	143 510 (16.94%)	
Supraventricular tachycardia	272 360 (0.32%)	2970 (0.35%)	<.1
Ventricular tachycardia	1 039 405 (1.23%)	7315 (0.86%)	<.001
Atrial fibrillation	10 774 535 (12.71%)	72 565 (8.57%)	<.001
Atrial flutter	1 068 015 (1.26%)	6540 (0.77%)	<.001
Ventricular fibrillation	177 500 (0.21%)	905 (0.11%)	<.001
Cardiac arrhythmias	12 018 995 (14.18%)	81 865 (9.66%)	<.001
Smoking	22 504 186 (26.55%)	253 100 (29.87%)	<.001
Alcohol intake	1 818 725 (2.15%)	10 960 (1.30%)	<.001
Obesity	11 206 652 (13.22%)	81 040 (9.57%)	<.001
Rheumatoid arthritis	1 468 415 (1.73%)	26 740 (3.16%)	<.001
Systemic lupus erythematosus	521 025 (0.62%)	8230 (0.97%)	<.001
Diabetes	21 435 781 (25.29%)	138 090 (16.230%)	<.001
Heart failure	12 106 825 (14.28%)	66 020 (7.79%)	<.001
Hypertension	33 127 161 (39.10%)	265 940 (31.40%)	<.001
Dyslipidemia	25 029 291 (29.53%)	171 285 (20.22%)	<.001
Coronary artery disease	16 680 671 (19.68%)	103 900 (12.26%)	<.001
Acute coronary syndrome	4 138 551 (4.88%)	21 285 (2.51%)	<.001
Stroke	4 065 730 (4.80%)	19 690 (2.32%)	<.001
Chronic kidney disease	11 805 846 (13.93%)	85 400 (10.10%)	<.001
Obstructive sleep apnea	4 470 755 (5.28%)	33 845 (4.00%)	<.001
Peripheral vascular disease	3 704 136 (4.37%)	21 165 (2.50%)	<.001
Modified Charlson Comorbidity Index			<.001
Index score $\geq 1$	54 382 833 (64.16%)	640 425 (75.59%)	
Index score 2	15 309 890 (18.063%)	117 525 (13.87%)	
Index score $\geq 3$	15 064 626 (17.77%)	89 285 (10.54%)	
Year			<.001
2012	28 832 836 (34.02%)	276 985 (32.69%)	
2013	28 005 173 (33.04%)	280 365 (33.09%)	
2014	27 919 340 (32.94%)	289 885 (34.22%)	

(average age of 52.45 years vs 57.41 years,  $P$ -value of  $<.001$ ), less likely to have hypertension, dyslipidemia, diabetes, coronary artery disease, heart failure, chronic kidney disease, history of stroke, PVD or OSA (all  $P$ -values,  $<.001$ ). Smoking, alcohol abuse, and obesity were significantly less prevalent among the IBD patient group.

Overall, IBD patients were less likely to have a diagnosis of cardiac arrhythmias compare with the non-IBD population (9.7% vs 14.2%,  $P$ -value  $<.001$ ), with unadjusted OR, 0.65; 95% CI, 0.63 to 0.66. Except for supraventricular tachycardia, all types of arrhythmias were significantly lower in the IBD population.

Adjusting for covariates using multivariate logistic regression showed that the IBD population had 0.87-fold-odds of diagnosis of cardiac arrhythmias compared to non-IBD population (adjusted OR, 0.87; 95% CI, 0.85-0.88; Table 2). The prevalence of supraventricular tachycardia and ventricular tachycardia was not different between the 2 groups (Table 3). Rheumatoid arthritis and systemic lupus erythematosus were also associated with lower odds of cardiac arrhythmias compared to the general population.

Male sex, age of over 60, and white race and west region residence had significantly higher odds of cardiac arrhythmias.

## Discussion

The relationship between IBD and cardiac arrhythmias other than atrial fibrillation has not been comprehensively examined.<sup>12</sup> As a result, the question of whether IBD was associated with higher rates of cardiac arrhythmias remains unknown. In this study, we have shown that patients with IBD were more likely to be younger, female, smokers, and have an increased prevalence of the morbidities such as SLE and RA. Additionally, they were less likely to have other Cardiovascular (CV) risks factors such as hypertension, alcohol intake, obesity, diabetes mellitus, dyslipidemia, CKD, and OSA. Overall, with the notable exception of SVT, IBD patients had lower rates of arrhythmias.

When adjusted for multiple confounders, including age and gender, we found patients with IBD were less likely to have hospitalization-related-cardiac arrhythmias, including ventricular fibrillation (VF), atrial fibrillation, atrial flutter than the general population, while SVT and VT rates remained the same between the 2 groups. Similarly, other than cardiac arrhythmias, the prevalence of other cardiovascular comorbidities such as coronary artery disease, acute coronary syndrome, and peripheral arterial disease were also comparatively lower in the patients from IBD. This will have substantial implication for amongst others therapeutic commissioning as well as the development of clinical programs for these cohorts of patients.

Our findings are at variance with that reported by Choi et al (utilizing national patient registry data in South Korea), and Kristensen et al reporting from the Danish registry.<sup>13,14</sup> The patient populations in these registries (Korean and Danish) were comparatively younger (mean age of IBD patients was

**Table 2.** Unadjusted and adjusted odds ratios for the relationship between IBD and cardiac arrhythmias.

UNADJUSTED ANALYSIS	OR (95% CI)
IBD (cardiac arrhythmias)	0.65 (0.63-0.66)
Adjusted analysis (multivariate model)	
IBD	0.87 (0.85-0.88)
Age	
40-60	Reference
18-39	0.19 (0.18-0.19)
>60	2.78 (2.76-2.8)
Female	0.75 (0.75-0.76)
Race	
White	Reference
Black	0.56 (0.56-0.57)
Hispanic	0.59 (0.58-0.6)
Asian or Pacific Islander	0.76 (0.74-0.78)
Native American	0.64 (0.6-0.68)
Other	0.73 (0.71-0.75)
Year	
2012	Reference
2013	1.03 (1.02-1.04)
2014	1.06 (1.05-1.07)
Hosp_Region	
Northeast	Reference
Midwest	0.94 (0.93-0.96)
South	0.9 (0.89-0.91)
West	0.95 (0.94-0.97)
Alcohol	1.03 (1.01-1.04)
Smoking	0.85 (0.84-0.85)
Obesity	1.07 (1.07-1.08)
Hypertension	1.22 (1.22-1.23)
Rheumatoid arthritis	0.94 (0.93-0.95)
Systemic lupus erythematosus	0.88 (0.86-0.9)
Diabetes	0.79 (0.79-0.79)
Heart failure	3.7 (3.67-3.72)
Dyslipidemia	1.04 (1.03-1.04)
Coronary artery disease	1.39 (1.38-1.4)
Acute coronary syndrome	1.06 (1.05-1.07)

(Continued)

**Table 2.** (Continued)

UNADJUSTED ANALYSIS	OR (95% CI)
Stroke	1.41 (1.4-1.42)
Chronic kidney disease	1.29 (1.29-1.3)
Obstructive sleep apnea	1.36 (1.35-1.37)
Peripheral vascular disease	0.96 (0.95-0.97)
Charlson	1.09 (1.09-1.1)

**Table 3.** Differential odds ratios for the relationship between IBD and cardiac arrhythmias.

ADJUSTED ANALYSIS (MULTIVARIATE MODEL)	OR (95% CI)
Supraventricular tachycardia	1.26 (1.16-1.37)
Ventricular tachycardia	0.96 (0.91-1.02)
Atrial fibrillation	0.86 (0.85-0.88)
Atrial flutter	0.78 (0.74-0.83)
Ventricular fibrillation	0.69 (0.59-0.79)

39.4 years in Korean study, 43.9 in Danish study compared to 52.45 years in our study). Additionally, both studies reported from registry data comprised of both inpatient and outpatient records in contradistinction to our study, which examined inpatient cohort data exclusively. Furthermore, data from Kristensen et al showed the incidence rate ratio of atrial fibrillation during IBD flare-up, persistent disease, and remission was 2.63, 2.06, and 0.97, respectively. This, they suggested, may indicate that IBD was associated with a higher risk of AF only during the active stage but not during the remission period (which accounts for as high as 85% of the follow-up time in IBD patients). In a comparative retrospective analysis of IBD cohorts within the Metro Health database and the more extensive ATRIA registry, Pattanshetty et al established that the prevalence of AF was higher in IBD patients compared to the general population.<sup>15</sup> Similarly, a comprehensive synthesis of current evidence by way of a meta-analysis by Zuin et al reported an increased risk of atrial fibrillation in IBD patients over and above those of the general population.<sup>12</sup> This study was limited by marked heterogeneity of the included studies resulting in an uncertain point estimate. Previous attempts at determining the subsisting relationship between IBD and risk of arrhythmias such as that by Khan et al were limited by only reporting on the burden of AF in IBD patients, without comparison with the general population.<sup>16</sup> The methodological approach of our study stands in sharp relief to earlier reports. Whilst both our report and those reported earlier demonstrated increasing prevalence of AF in IBD patient cohorts over time, our report is the only one that had a comparative

evaluation of this in IBD patient cohorts and the general population. Although Sridhar et al utilized the same national inpatient database as our study and reported on similar outcomes, their analysis was limited to 2006.<sup>17</sup> Their finding of an inverse association between IBD, AF, and conduction disorders was consistent with our findings.

Chronic inflammation in patients with IBD is not without morbidity, sometimes affecting various organ systems. For example, Bunu et al suggested that chronic inflammation in IBD patients may be the key driver to a higher risk of cardiac arrhythmias in these patients.<sup>18</sup> Although this hypothesis has been established in other inflammation-driven morbidities (such as rheumatoid arthritis and systemic lupus erythematosus), findings from our study suggest that this may not be the case in IBD.<sup>9,19</sup> A probable explanation for this paradox in our report is that patients with IBD were younger and, therefore, less likely to suffer from other cardiovascular risks (CV) such as hypertension, alcohol intake, obesity, diabetes mellitus, dyslipidemia, CKD, and OSA. It is probable, therefore, that the protection afforded by this low CV risk may be enough to offset the adverse inflammatory tendencies present in the IBD patients.<sup>9</sup> But even when we corrected for these confounders, the dysrhythmia risk was still lower in IBD patients in our study. Additionally, the anti-inflammatory effects of medications such as salicylates and other IBD medications, which are commonly prescribed to IBD, may also play a role in accounting for this inverse relationship.<sup>17</sup> Further studies are needed to evaluate the possible role of new anti-inflammatory and immunomodulatory medications in the prevention of cardiovascular diseases, including cardiac arrhythmias among patients with inflammatory diseases.

The key strength of this study is its comparative exploration of a large national database. To our knowledge, this is the largest study that compared the prevalence of cardiac arrhythmias in IBD patients and perhaps the first study that evaluated the risks of arrhythmias other than atrial fibrillation in IBD patients. Our CV-risk adjusted analyses were seminal (adjusting for other CV risks and confounders such as hypertension, alcohol intake, obesity, diabetes mellitus, dyslipidemia, CKD, and OSA).

This study has limitations that are inherent in observational studies as well as the inherent flaws of the NIS database (extensively discussed elsewhere). These include limited information in the database on the extent, severity, and control of IBD, including a full characterization of the phenotypes of atrial fibrillation (such as paroxysmal, permanent) and lack data on the diagnostic modalities as well as echocardiographic and blood work findings. The time interval between the onset of IBD and dysrhythmia was not adequately captured in the database. There are registry-based inherent drawbacks of ignoring the unmeasured confounders such as blood pressure, concomitant medications including those used in the treatment of the IBD. There were issues with data duplication in the NIS database and is very

much dependent on the coding practices/accuracy of the various contributing hospitals and institutions.

### Conclusion

Despite prior reports of a high prevalence of arrhythmias amongst patients with IBD, in a nationwide inpatient database, we found lower rates of arrhythmias in the IBD patient cohorts compared with the general population.

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### Author Contributions

MM and TS conceived the review idea. The initial manuscript was then critically revised by all other authors. All the authors approved the final manuscript version for publication. Guarantor of integrity of the entire study: MM, MD. Study concepts and design: MM, YZ. Literature research: MM, TS, AH. Clinical studies: NA. Experimental studies/data analysis: NA. Manuscript preparation: MM, TS, AH, MFHM, and MD. Manuscript editing: all authors.

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