Prognosis of Patients with Crohn's Disease and Ulcerative Colitis Following Percutaneous Coronary Intervention Procedures

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ABSTRACT **Background:** Patients with inflammatory bowel disease (IBD) are at increased risk after percutaneous coronary intervention (PCI).

Objectives: To compare the clinical outcomes within 30 days, one year, and five years of undergoing PCI.

Methods: We conducted a retrospective cohort study of adult patients with IBD who underwent PCI in a tertiary care center from January 2009 to December 2019.

Results: We included 44 patients, 26 with Crohn's disease (CD) and 18 with ulcerative colitis (UC), who underwent PCI. Patients with CD underwent PCI at a younger age compared to UC (57.8 vs. 68.9 years, $P < 0.001$) and were more likely to be male (88.46% of CD vs. 61.1% of UC, $P < 0.03$). CD patients had a higher rate of non-steroidal treatment compared to UC patients (50% vs. 5.56%, $P < 0.001$). Acute coronary syndromes (ACS) and/or the need for revascularization (e.g., PCI) were the most common clinical events to occur following PCI, in both groups. Of patients who experienced ACS and/or unplanned revascularization within 5 years, 25% of UC vs. 40% of CD had target lesion failure (TLF) due to in-stent restenosis and 10% of CD had TLF due to stent thrombosis.

Conclusions: We observed higher rates of TLF in IBD patients compared to the general population as well as differences in clinical outcomes between UC and CD patients. A better understanding of the prognostic factors and pathophysiology of these differences may have clinical importance in tailoring the appropriate treatment or type of revascularization for this high-risk group.

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KEY WORDS: inflammatory bowel disease (IBD), percutaneous coronary intervention (PCI), stent thrombosis, in-stent restenosis (ISR), target lesion failure (TLF)

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are global diseases of the 21st century. These chronic inflammatory conditions have an estimated global prevalence of 0.2–0.8% [1].

As seen in other chronic inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus, patients with IBD present a higher risk of developing cardiovascular diseases such as atrial fibrillation, heart failure, and ischemic heart disease [2-5].

IBD is accompanied by various extraintestinal manifestations, including systemic inflammation and hypercoagulability, which may increase the risk of atherosclerosis and cardiovascular diseases [5,6]. In addition, medications used to treat IBD that target inflammation, such as corticosteroids, may also accelerate the risk of developing cardiovascular diseases [7,8].

Percutaneous coronary intervention (PCI) is the most widely used revascularization strategy for patients with ischemic heart disease. Several studies have focused on the outcomes of PCI in patients with some chronic inflammatory conditions [9-11].

One study showed that patients with autoimmune rheumatic diseases and IBD were at higher risk for cardiovascular events in long-term follow-up after diagnosed with coronary artery disease (CAD) and treated by PCI [12].

Another study that compared procedural outcomes between patients with and without IBD who underwent PCI found that IBD was associated with reduced risk for major adverse cardiovascular events, and specifically mortality and acute cerebrovascular accident (CVA). Nonetheless, IBD patients did show an increased risk for major bleeding, specifically gastrointestinal bleeding [13].

A better understanding of the outcomes and prognostic factors in the IBD population after PCI may have clinical importance in tailoring the appropriate treatment or type of revascularization due to their high risk.

PATIENTS AND METHODS

STUDY POPULATION

We performed a retrospective, observational population-based cohort study using medical records from the Rambam Health Care Campus, a large tertiary center. All adult (≥ 18 years) patients had IBD and underwent coronary angiography and PCI at the Rambam catheterization lab between January 2009 and December 2019. The index date was based on the date of the performed PCI (index PCI). All patient data were coded and anonymized.

DATA COLLECTION

Demographic and clinical data were collected from the hospital's electronic medical file system.

Information on patient demographics was recorded, including age, sex, race, height, and weight. Based on the hospital data and prior hospitalizations of each patient, we identified baseline medical co-morbidities, including hypertension, diabetes mellitus, dyslipidemia, history of CAD or previous revascularization, atrial fibrillation, vascular diseases (peripheral artery disease [PAD] and CVA), valvular disease, and smoking. In addition, we identified the indication for the index PCI (non-ST-elevation myocardial infarction [non-STEMI], ST-elevation myocardial infarction [STEMI], unstable angina [UA], or stable angina) and the procedural information from the catherization performed prior to the index PCI.

Information was also collected on the use of cardiac risk factor medications, including antiplatelets, anticoagulants, statins, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, and potassium-sparing diuretics, as well as steroidal and non-steroidal chronic anti-inflammatory medication for treatment of IBD. In addition, we identified procedural information from the index PCI including multivessel versus single-vessel procedure, type of stent deployed (bare metal stent [BMS] or drug eluting stent [DES]), and echocardiography data.

Patient records were reviewed longitudinally from the index date until the first event: acute coronary syndromes (ACS) and/or unplanned revascularization, heart failure, or all-cause mortality. For patients who underwent revascularization due to ACS, two types of target lesion failure (TLF) were recorded: in-stent restenosis (ISR) and stent thrombosis.

Table 1. Patient demographic characteristics from included hospital records, stratified by IBD diagnosis (ulcerative colitis and Crohn's disease)

Patient characteristic	IBD (all patients) (n=44)	Ulcerative colitis (n=18)	Crohn's disease (n=26)	*P*-value
Age at reference event, in years, mean ± SD	62.18 ± 12.39	68.9 ± 9.3	57.8 ± 12.3	0.001
Height (cm)	164.6 ± 29.9	157 ± 42.1	171 ± 8.2	NS
Weight (kg)	76.9 ± 15.05	75.3 ± 16.5	78.1 ± 14.2	NS
Sex				0.03
Female	10 (22.72%)	7 (38.9%)	3 (11.54%)	
Male	34 (77.27%)	11 (61.1%)	23 (88.46%)	
Ethnicity				NS
Jew	26 (59.1%)	9 (50.0%)	17 (65.4%)	
Arab Muslim	7 (15.9%)	3 (16.7%)	4 (15.38%)	
Druze	2 (4.55%)	2 (11.11%)	0	
Other/ Unknown	9 (20.45%)	4 (22.22%)	5 (19.23%)	

IBD = inflammatory bowel disease, SD = standard deviation

ETHICS ASPECTS

The study was approved by the institutional review board at Rambam Health Care Campus. The need for written informed consent was waived due to the specific study design.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 26 (SPSS, IBM Corp, Armonk, NY, USA). Continuous variables are presented as mean and standard deviation and were compared by using 2-sample *t*-tests. Categorical data are presented as frequencies and percentages and were compared using chi-square statistics or Fisher's exact test. Missing data were assumed to be missing at random.

OBJECTIVES

Our main objective was to compare the clinical outcomes within 30 days, 1 year, and 5 years between patients with CD and UC who underwent PCI, including ACS (UA, STEMI, or non-STEMI) and/or unplanned revascularization (PCI or coronary artery bypass graft [CABG]), heart failure, and mortality.

Table 2. Patient co-morbidities and medications from included hospital records, stratified by IBD diagnosis (ulcerative colitis and Crohn's disease)

Patient characteristic	IBD (all patients) (n=44)	Ulcerative colitis (n=18)	Crohn's disease (n=26)	*P*-value
Co-morbidities				
History of CAD or previous revascularization procedure (PCI or CABG)	11 (25%)	7 (38.9%)	4 (15.38%)	NS
Atrial fibrillation	8 (18.18%)	4 (22.22%)	4 (15.38%)	NS
Hypertension	31 (70.45%)	15 (83.3%)	16 (61.54%)	NS
Dyslipidemia	36 (81.81%)	15 (83.3%)	21 (80.77%)	NS
Diabetes mellitus	16 (36.36%)	8 (44.44%)	8 (30.77%)	NS
Vascular disease (PAD, CVA)	7 (15.9%)	5 (27.78%)	2 (7.7%)	NS
Valvular disease	5 (11.36%)	2 (11.11%)	3 (11.54%)	NS
Smoking	22 (50%)	6 (33.33%)	16 (61.54%)	NS
Medication for cardiac risk factors				
Antiplatelets (at admission for index PCI)	31 (70.45%)	13 (72.2%)	18 (69.23%)	NS
Antiplatelets (at discharge after index PCI)	42 (95.45%)	18 (100%)	24 (92.3%)	NS
Anticoagulants	16 (36.36%)	6 (33.33%)	10 (38.5%)	NS
Statins	34 (77.27%)	14 (77.78%)	20 (76.92%)	NS
ACEi/ARB/ Entresto	35 (79.54%)	16 (88.89%)	19 (73.08%)	NS
Spironolactone	11 (25%)	4 (22.22%)	7 (26.92%)	NS
Chronic anti-inflammatory treatment				
Steroids	9 (20.45%)	3 (16.7%)	6 (23.1%)	NS
Non-steroids (e.g., methotrexate, sulfasalazine, azathioprine, anti-TNF)	14 (31.81%)	1 (5.56%)	13 (50.0%)	0.001

ACEi/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, CABG = coronary artery bypass graft surgery, CAD = coronary artery disease, CVA = cerebrovascular accident, IBD = inflammatory bowel disease, PAD = peripheral artery disease, PCI = percutaneous coronary intervention

RESULTS

A total of 44 patients with IBD were included, all of whom underwent PCI. The number of patients with CD and UC were 26 (59%) and 18 (41%), respectively [Table 1].

We found that patients with CD underwent PCI at a younger age compared to those with UC: 57.8 years and 68.9 years on average, respectively ($P < 0.001$). Patients with CD were more likely to be male (88.46%) when compared to the UC group (61.1%) ($P < 0.03$). In addition, there were more male than female patients for both UC (61.1% male and 38.9% female) and CD (88.46% male and 11.54% female); however, this result was not statistically significant. Most patients in this study were Jewish (65.4% of CD and 50.0% of UC) [Table 1].

In general, we did not find significant differences in baseline co-morbidities and medications between the groups. We observed that patients with UC had higher rates of co-morbidities, such as a history of CAD, atrial fibrillation, hypertension, dyslipidemia, and diabetes mellitus, whereas CD patients had higher rates of vascular diseases (PAD and CVA) and smoking [Table 2]; however, these results were not statistically significant.

CD patients had a higher rate of steroidal drug use as their chronic anti-inflammatory medication for treatment of IBD compared to UC patients; however, the results were not statistically significant. CD patients also had a higher rate of non-steroidal medication (methotrexate, sulfasalazine, azathioprine, anti-TNF) in comparison to UC patients; 50.0% of CD and 5.56% of UC ($P < 0.001$) [Table 2].

We did not observe significant differences between patients with CD and UC with regard to their diagnosis at the time of the index PCI [Table 3].

We did not find significant differences in the number of vessel diseases or involvement of proximal LAD or left main artery between the two groups. For both UC and CD, most of the patients underwent intervention in a single vessel during the index PCI (72.2% and 84.62% respectively) [Table 3]. There were no significant differences between the UC and CD patients regarding the type of stent used (DES or BMS). DES was used for most of the patients: 55.56% of UC patients and 42.3% of CD patients.

In both groups, most of the patients had normal LV systolic function (22.22% of UC patients and 15.38% of CD patients), and only 11.11% of UC and 11.54% of CD patients had severe LV systolic dysfunction found in the echocardiogram; however, this finding was not statistically significant. We found no significant differences in rates of significant valvular diseases or in ejection fraction (EF%) between the UC and CD patients.

In terms of the clinical outcomes following PCI, 50% of the patients in both UC and CD groups experienced any kind of event ACS (UA, STEMI, or non-STEMI) and/or unplanned revascularization (PCI or CABG), heart failure, all-cause mortality within 5 years of the index PCI [Table 4].

Table 3. Patient procedural and electrocardiographic characteristics from included hospital records, stratified by IBD diagnosis (ulcerative colitis and Crohn's disease)

Patient characteristic	IBD (all patients) (n=44)	Ulcerative colitis (n=18)	Crohn's disease (n=26)	*P*-value
Diagnosis at index PCI				
Non-STEMI	8 (18.18%)	1 (5.56%)	7 (26.92%)	NS
STEMI	12 (27.27%)	4 (22.22%)	8 (30.77%)	
Unstable angina	9 (20.45%)	6 (33.33%)	3 (11.54%)	
Number of vessel disease in catheterization				
1	20 (45.45%)	5 (27.78%)	15 (57.7%)	NS
2	17 (38.63%)	9 (50%)	8 (30.77%)	
3	7 (15.9%)	4 (22.22%)	3 (11.54%)	
Involvement of proximal LAD > 75%	7 (15.9%)	4 (22.22%)	3 (11.54%)	NS
Number of vessels intervened with in PCI				
1	35 (79.54%)	13 (72.2%)	22 (84.62%)	NS
2	5 (11.36%)	4 (22.22%)	1 (3.85%)	
3	4 (9.09%)	1 (5.56%)	3 (11.54%)	
Type of stent used				
Drug eluting stent	21 (47.72%)	10 (55.56%)	11 (42.3%)	NS
Bare metal stent	7 (15.9%)	2 (11.11%)	5 (19.23%)	
Echo data exists	23 (52.27%)	9 (50%)	14 (53.85%)	NS
Left ventricle systolic dysfunction				
Normal	8 (18.18%)	4 (22.22%)	4 (15.38%)	
Mild	7 (15.9%)	2 (11.11%)	5 (19.23%)	NS
Moderate	3 (6.81%)	1 (5.56%)	2 (7.7%)	
Severe	5 (11.36%)	2 (11.11%)	3 (11.54%)	
Significant valvular disease (AR, AS, MR, MS), moderate TR	4 (9.09%)	3 (16.7%)	1 (3.85%)	NS
Ejection fraction				
20–40%	7 (15.9%)	3 (16.7%)	4 (15.38%)	NS
41–60%	6 (13.63%)	0	6 (23.1%)	
> 60%	5 (11.36%)	4 (22.22%)	1 (3.85%)	

AS = aortic stenosis, AR = aortic regurgitation, IBD = inflammatory bowel disease, LAD = left anterior descending, MR = mitral regurgitation, MS = mitral stenosis, non-STEMI = non-ST-elevation myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-elevation myocardial infarction, TR = tricuspid regurgitation

Most of the events that both groups experienced were ACS and/or revascularization procedures: 44.44% of UC and 38.5% of CD patients within 5 years of the index PCI. Heart failure was the second most common event to occur in both groups, with 5.56% of UC and 7.7% of CD patients within 5 years of the index PCI. Mortality was the least common event in both groups, with no patients in the UC group and only 1 patient (3.85%) in the CD group who died within 5 years of the index PCI [Table 4].

More patients in the UC group had an adverse outcome during the 30-day follow-up period when compared to CD patients; 11.11% compared to 3.85%, respectively, and 38.9% compared to 23.1%, respectively, within 1 year of the index PCI. However, these differences were statistically insignificant [Table 4].

A total of 8 patients in the UC group (44.44%) and 10 patients in the CD group (38.5%) experienced recurring ACS and/or revascularization (PCI or CABG) within 5 years of the index PCI. Of these patients, 6 UC patients (33.33%) and 9 CD patients (34.61%) underwent revascularization procedures (PCI or CABG); 25% and 40% of UC and CD patients, respectively, who experienced recurring ACS and/or revascularization within 5 years had TLF due to ISR; 10% of CD patients who experienced recurring ACS and/or revascularization within 5 years had TLF due to stent thrombosis [Table 4].

Table 4. Patient events after the index PCI, stratified by IBD diagnosis (ulcerative colitis and Crohn's disease)

Event after index PCI	IBD (all patients) (n=44)	Ulcerative colitis (n=18)	Crohn's disease (n=26)	*P*-value
Any event (ACS and/or revascularization, heart failure, mortality)				
Within 30 days	3 (6.81%)	2 (11.11%)	1 (3.85%)	NS
Within 1 year	13 (29.54%)	7 (38.9%)	6 (23.1%)	
Within 5 years	22 (50%)	9 (50%)	13 (50%)	
ACS and/or revascularization (PCI or CABG)				
Within 30 days	3 (6.81%)	2 (11.11%)	1 (3.85%)	
Within 1 year	11 (25%)	7 (38.9%)	4 (15.38%)	
Within 5 years	18 (40.9%)	8 (44.44%)	10 (38.5%)	NS
Any target lesion failure	7 (15.9%)	2 (11.11%)	5 (19.23%)	
In-stent restenosis	6 (13.63%)	2 (11.11%)	4 (15.38%)	
Stent thrombosis	1 (2.27%)	0	1 (3.84%)	
Heart failure				
Within 30 days	0	0	0	
Within 1 year	2 (4.54%)	0	2 (7.7%)	NS
Within 5 years	3 (6.81%)	1 (5.56%)	2 (7.7%)	
All-cause mortality				
Within 30 days	0	0	0	
Within 1 year	0	0	0	NS
Within 5 years	1 (2.27%)	0	1 (3.85%)	

ACS = *acute coronary syndrome*, CABG = coronary artery bypass graft surgery, IBD = inflammatory bowel disease, PCI = percutaneous coronary intervention

DISCUSSION

We conducted a single-center retrospective cohort study of patients with IBD who underwent PCI. We presented their demographic, clinical, angiographic, and echocardiographic data, as well as their clinical outcomes.

Patients with IBD are at a higher risk of ischemic heart disease, for which they may require coronary revascularization [5].

In this population-based study, we showed that patients with CD were more likely to be male when compared to UC patients. In addition, CD patients underwent PCI at a younger age compared to UC patients. This finding could possibly be attributed to the higher degree of systemic inflammation that CD patients are prone to, evidenced by a higher level of serum C-reactive protein [8].

We showed that the diagnosis at the time of the index PCI was different between the two groups. CD patients were more likely to undergo PCI due to non-STEMI or STEMI, whereas UC patients were more likely to undergo PCI due to unstable angina. However, this observation needs further examination in a larger cohort.

In this study, we observed a higher rate of non-steroidal medications for treatment of IBD (methotrexate, sulfasalazine, azathioprine, and anti-TNF drugs) in CD patients compared to UC. This treatment is in accordance with the American Gastroenterological Association's guidelines for treatment of UC [14] and CD [15]. Previous studies showed an increased risk of acute myocardial infarction (AMI) and heart failure among systemic corticosteroid users [2]. Therefore, we presume that a study in which the follow-up on clinical outcomes is stratified by type of treatment for IBD would be beneficial to identify different treatments for IBD as potential prognostic factors predicting outcomes of these patients after PCI.

Patients with UC had a relatively high ratio of multivessel CAD, possibly due to older age at the time of the index PCI, which is characterized by more diffuse atherosclerosis and calcification [16].

Most of the events that occurred after the index PCI were related to ACS and/or the need for unplanned revascularization (PCI or CABG). The rates of these events within 5 years of the index PCI (44.44% for UC and 38.5% for CD) were higher than those of the general population, as shown in previous studies [17]. This finding is in accordance with conclusions from previous studies that showed that patients with IBD are at increased risk for cardiovascular disorders, such as AMI or heart failure, despite a lower prevalence of traditional risk factors [2]. Our results showed that this increased risk may persist for years.

It seems that this high-event rate of ACS and unplanned revascularization might be related to TLF, ISR, or stent thrombosis; 25% of UC patients and 50% of CD patients with ACS and/or revascularization within 5 years of the index PCI were shown to have TLF during revascularization. These percentages of TLF in IBD patients following PCI are much higher than of the general population, which has also been observed in previous studies [18]. Those authors found that IBD patients faced higher rates of ISR compared to the general population.

The endothelial dysfunction seems to be the principal common pathogenic pathway for ISR and is attributed to both the immune system disorder and the systemic inflammation. According to Doornum and colleagues [18], the damage of the coronary endothelium could alter the physiological repair after PCI and to favor ISR. The augmented carotid intima-media thickness test, an independent risk indicator for ISR, further supports the concept of systemic arterial involvement in IBD patients.

In another study that followed outcomes after a first acute cardiovascular event in patients with rheumatoid arthritis, the authors observed that most stent thrombosis events occurred within 30 days of PCI, showing a strong focus on immediate intensive secondary prophylaxis following PCI in these patients [19]. As an additional systemic inflammatory condition, it is possible that this finding could also be relevant for IBD patients, as shown in some studies [20].

Other studies have suggested that IBD patients who undergo PCI are at a greater risk of sustaining in-hospital major bleeding complications, mainly due to increased gastrointestinal bleeding events [12]. This finding shows the complexity of managing patients with coexisting active IBD and ACS. It is crucial and tricky to correctly assess the balance between hemorrhagic and ischemic risk. Management of these patients includes choosing which type of stent to use and the advantage of using BMS to reduce the bleeding risk [20-22]. DES has been shown to be superior to BMS with respect to long-term outcomes such as target lesion, vessel revascularization, and risk of reinfarction [23]. In addition, decisions on anti-platelet therapy at the time of discharge are important. The use of new stent platforms as well as new antiplatelet therapy strategies with shorter dual antiplatelet therapy duration or use of less potent antiplatelet agents may decrease the bleeding risk further [24,25].

There are several limitations to the present study. First, this single center study included a relatively small number of patients, which did not allow us to reach statistical significance for some of the results. Furthermore, we were not able to stratify by specific anti-inflammatory medication due to the small number of participants. Second, we did not collect data on the severity of the IBD or previous interventions. In addition, in this retrospective observational study, the PCI procedures and adjuvant treatment were not randomized nor unified according to a certain protocol.

CONCLUSIONS

Patients with CD are more likely to be male, to undergo PCI at a younger age, and to be treated with non-steroidal medications for their IBD. In addition, patients with UC may have more extensive coronary artery disease and experience an event sooner after the index PCI, compared to CD patients. Generally, IBD patients have a high rate of adverse events after PCI, especially ACS, and may need unplanned revascularization. This result may be due to high rates of TLF in this population, particularly ISR. A larger cohort is needed to understand the pathophysiology of these findings and to identify potential prognostic factors predicting outcomes of patients with IBD after PCI.

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Capsule

Improving hearing in children

Genetic mutations are an important cause of deafness. Mutations in the Otoferlin (OTOF) gene cause autosomal-recessive deafness 9 (DFNB9). Adeno-associated virus (AAV)-mediated gene therapy has shown positive results in rodents, but safety and efficacy in humans had not been tested. **Qi** et al. reported the first exploratory clinical trial in two children carrying OTOF mutations. Cochlear administration of dual AAV-OTOF vectors restored hearing in the injected ear in one patient and significantly improved hearing in the other individual a month after treatment. The exploratory trial was preceded by safety and efficacy work in mice and nonhuman primates. These results may pave the way for the application of this approach to other forms of deafness caused by genetic mutations.

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Capsule

Health effects associated with exposure to secondhand smoke: a burden-of-proof study

Despite a gradual decline in smoking rates over time, exposure to secondhand smoke (SHS) continues to cause harm to nonsmokers, who are disproportionately children and women living in low- and middle-income countries. **Flor** and colleagues comprehensively reviewed the literature published before July 2022 concerning the adverse impacts of SHS exposure on nine health outcomes. They quantified each exposure–response association accounting for various sources of uncertainty and evaluated the strength of the evidence supporting our analyses using the Burden of Proof Risk Function methodology. The authors found all nine health outcomes to be associated with SHS exposure. They conservatively estimated that SHS increases the risk of ischemic heart disease, stroke, type 2 diabetes, and lung cancer by at least around 8%, 5%, 1%, and 1%, respectively, with the evidence supporting these harmful associations rated as weak (two stars). The evidence supporting the harmful associations between SHS and otitis media, asthma, lower respiratory infections, breast cancer, and chronic obstructive pulmonary disease was weaker (one star). Despite the weak underlying evidence for these associations, these results reinforce the harmful effects of SHS on health and the need to prioritize advancing efforts to reduce active and passive smoking through a combination of public health policies and education initiatives.

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