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Short Communication

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# Rheumatoid Arthritis and Its Implications on Inflammatory Bowel Disease

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## Abstract

**Background:** The association between inflammatory bowel disease (IBD) and arthritis has long been known, but it was not until the 1950s that IBD-associated arthritis was recognized as a distinct pathology independent from rheumatoid arthritis (RA). There is evidence that RA and other autoimmune conditions exist at higher rates in patients with IBD compared to the general population. We aimed to determine if the presence of RA in IBD patients is a factor for mortality and IBD-related surgery in this population.

**Methods:** Using Epic's Slicer Dicer function, we queried the International Classification of Diseases, 10th Revision (ICD-10) codes K50 and K51 to identify patients with IBD. Duplicates and those with incomplete information were excluded, leaving a total of 3,613 patients. Data collected included basic demographic information, surgical history, and the presence of RA. We used Student's *t*-test to analyze between group differences for the continuous variables. When it was determined that variances for the comparisons of continuous data were unequal, Welch-Satterthwaite *t*-test statistics were used. We used the Chi-square test to analyze between group differences for the categorical variables. The Fisher's exact test was employed when any of the expected frequencies was 5 or less. All tests were two-sided with criterion for statistical significance at a P value less than 0.05. All the analyses were done by SAS 9.4 (SAS Institute, Cary, NC).

**Results:** Of the approximately 2.7 million adults in Slicer Dicer, there were 3,613 patients (0.13%) identified with IBD. Patients with ulcerative colitis (UC) accounted for 37% of the total group (n = 1,343) and 2,270 patients (62.8%) had Crohn's disease (CD). From the total, 2,084 were women (57.68%) and 1,529 (42.32%) were men. More than 90% of the patients were white (n = 3,321). The mean age was 53.3 ± 18.5. Eight hundred forty-eight patients (23.47%) had documented RA. Mortality was higher in patients with IBD and RA than those with IBD alone (7.31% vs. 3.98%, P value ≤ 0.0001).

**Conclusions:** IBD patients with RA have higher mortality rates and need for IBD-related surgery than patients with IBD alone.

**Keywords:** Rheumatoid arthritis; Mortality; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

## Introduction

Rheumatoid arthritis (RA) is an autoimmune disease of unknown origin characterized by chronic inflammation of synovial joints, causing a gradual destruction of periarticular cartilage and bones. Extra-articular manifestations are possible [1, 2]. Inflammatory bowel disease (IBD) encompasses two distinct disorders: Crohn's disease (CD) and ulcerative colitis (UC), which differ from each other on grounds of pathophysiology, clinical manifestations, extent of gastrointestinal tract involvement, complications, and prognosis [3, 4]. In addition to their gastrointestinal signs and symptoms, these diseases also have extraintestinal manifestations in multiple organ systems, of which the musculoskeletal system is the most affected [5].

Arthritis has long been associated with IBD. In the 1950s, IBD-associated arthritis was recognized as an independent entity, along with the rest of the spondyloarthropathies [6]. The other spondyloarthropathies are reactive arthritis, psoriatic arthritis, and ankylosing spondylitis [7]. The association between arthritis and IBD was originally thought to be a coincidental overlap, but it is now understood that IBD has an associated arthropathy that falls under the umbrella of spondyloarthropathies. This distinction was further emphasized by the discovery of the association between human leukocyte antigen (HLA)-B27 and spondyloarthropathies. Colbert et al [8] found a correlation between a high copy number of B27 and the development of arthritis, gastrointestinal inflammation, psoriasis-skin lesions, nails, and testicular inflammation. HLA-B27 in bone marrow should be expressed to present colitis/peripheral arthritis [8]. Furthermore, spondyloarthropathies are commonly referred to as "seronegative" due to their lower rates of positive rheumatoid factor (RF) when compared to RA. The main clinical differences between IBD-related arthritis and RA are

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**Table 1.** Population Characteristics and Results

| | All patients | | RA | | No RA | | P value |
|---|---|---|---|---|---|---|---|
| Total number of patients | 3,613 | | 848 | 23.47% | 2,765 | 76.53% | |
| Disease type, n, % | | | | | | | 0.0077 |
| Crohn's disease | 1,343 | 37.17% | 348 | 41.04% | 995 | 35.99% | |
| Ulcerative colitis | 2,270 | 62.83% | 500 | 58.96% | 1,770 | 64.01% | |
| Age, mean (SD), range | 53.3 (18.5) | 8 - 99 | 63.2 (15.6) | 18 - 97 | 50.2 (18.2) | 8 - 99 | < 0.0001 |
| Gender, n, % | | | | | | | < 0.0001 |
| Male | 1,529 | 42.32% | 299 | 35.26% | 1,230 | 44.48% | |
| Female | 2,084 | 57.68% | 549 | 64.74% | 1,535 | 55.52% | |
| Mortality, n, % | 172 | 4.76% | 62 | 7.31% | 110 | 3.98% | < 0.0001 |
| Ethnic (Hispanic or Latino), n, % | 72 | 1.99% | 11 | 1.30% | 61 | 2.21% | 0.0791 |
| Race, n, % | | | | | | | 0.0058 |
| White | 3,321 | 91.92% | 801 | 94.46% | 2,520 | 91.17% | |
| Black | 178 | 4.93% | 32 | 3.77% | 146 | 5.28% | |
| All others | 113 | 3.13% | 15 | 1.77% | 98 | 3.55% | |
| BMI, mean (SD), range | 29.3 (7.2) | 15.6 - 57.4 | 30.6 (7.0) | 17.0 - 54.4 | 28.9 (7.2) | 15.6 - 57.4 | < 0.0001 |
| Alcohol use (at least 1 drink per week), n, % | 461 | 12.76% | 105 | 12.38% | 356 | 12.88% | 0.7065 |
| Surgical history, n, % | 1,045 | 28.92% | 277 | 32.90% | 768 | 28.16% | 0.0083 |

The Chi-square and Fisher's exact tests were used to analyze between-group differences for the categorical variables. The student's *t*-test was used to analyze group differences for numerical variables. RA: rheumatoid arthritis; BMI: body mass index; SD: standard deviation.

the asymmetrical joint involvement, lower incidence and degree of joint deformity, and the absence of rheumatoid nodules in patients with IBD [6, 9].

There has been relatively little research into IBD and its comorbidities, specifically RA [10]. However, there is evidence that RA and other autoimmune conditions exist in higher rates in patients with IBD compared to the general population. The distinction is important because the management, prognosis, and complications of RA and IBD-related arthropathy differ [3]. This text is meant to offer further insight into the relationship of these diseases by analyzing the demographic and clinical characteristics of a sizable population of patients with IBD.

## Materials and Methods

This study is a retrospective analysis of patients from seven hospitals belonging to University of Pittsburgh Medical Center of Central Pennsylvania (UPMC Central PA). This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. It was reviewed and approved by the UPMC Central PA Review Board. Using Epic's Slicer Dicer function, patients with IBD were identified using the International Classification of Diseases, 10th Revision (ICD-10) codes (K50 and K51). The database was cleaned, and duplicates or records with incomplete information were excluded from the study, resulting in a total of 3,613 patients. Basic demographic information was collected in addition to surgical history and the presence of RA. We reported continuous variables as mean (range) and categorical variables as number (percent). We used Student's *t*-test to analyze between group differences for the continuous variables. When it was determined that variances for the comparisons of continuous data were unequal, Welch-Satterthwaite *t*-test statistics were used. We used the Chi-square test to analyze between group differences for the categorical variables. The Fisher's exact test was employed when any of the expected frequencies was 5 or less. All tests were two-sided with criterion for statistical significance at a P value less than 0.05. All the analyses were done by SAS 9.4 (SAS Institute, Cary, NC).

## Results

Of the approximately 2.7 million adults analyzed in Slicer Dicer, we found 3,613 patients (0.13%) with IBD. Patients with UC accounted for 37% of the total group (n = 1,343) and 2,270 patients (62.8%) had CD. From the total, 2,084 were women (57.68%) and 1,529 (42.32%) were men. More than 90% of the patients were white (n = 3,321) and 291 patients were either black or Hispanic. The mean age was 53.3 ± 18.5. About 24% of our population (848) had documented RA. IBD-related surgical procedures including bowel resection were more common in patients with IBD + RA compared with those without rheumatologic disease (32.9% vs. 28.16%, P = 0.0083). Near 5% of the total died (n = 172). The mortality rate was higher in patients with IBD and RA than those with IBD alone (7.31% vs. 3.98%, P value ≤ 0.0001) (Table 1).

Infections were the most common cause of death in approximately 20% of patients, including eight patients who died

from severe coronavirus disease 2019 (COVID-19) pneumonia. Thirty-two patients (18.6%) died from complications related to colorectal or hematologic malignancies. In 16 patients (9.3%), bowel perforation was the main cause of death. About 15% of patients died either from cardiovascular or cerebrovascular causes. For the remaining patients, we were unable to determine the cause of death as only the date was documented.

## Discussion

We reaffirm the relationship between IBD and RA. The current investigation contributes valuable insights into the prevalence and implications of coexisting IBD and increased mortality and surgical rates in IBD patients with associated RA, emphasizing the essential connection between these conditions. The association has lacked recognition for the last century, and the relationship between the gut and the musculoskeletal system has remained uncertain [6, 11]. IBD may result from an inappropriate inflammatory response to the intestinal flora in patients who are genetically predisposed. Many of these genes are also found in other immune-mediated diseases. [12]. The presence of TH17 cells (proinflammatory lymphocytes that secrete interleukin-17 that is linked to T-cell activation and neutrophil mobilization and activation) is evident in CD and UC. Although the mechanism by which microbiome leads to arthritis remains unclear, several proposed mechanisms highlight how intestinal microbiota can influence the development of arthritis, such as commensal bacteria driving the local accumulation of TH17 [6, 12].

A limitation of this study pertains to the use of the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes for identifying and categorizing cases of IBD and RA. Variability in coding practices, coding errors, or changes in coding criteria over time can introduce potential inaccuracies in case identification. For instance, cases may be missed if not coded accurately or if milder or atypical presentations are not captured by physicians. Conversely, over-representation of cases may occur if coding is overused. In addition, the ICD-10-CM code used was IBD and included both CD and UC; there was no analysis between either group.

Despite the insights gained from our study, several limitations merit consideration. The lack of information regarding the smoking status from our cohort should be considered. While CD is associated with smoking, which has detrimental effects on the clinical course of the disease, UC is largely a disease of nonsmokers and former smokers [13]. Additionally, the demographic homogeneity of the studied population presents another limitation. Most of the participants (more than 90%) were identified as Caucasian. In addition, our population were more women than men, increasing the availability bias. Another limitation is that our study predominantly involved an elderly patient cohort, which can lead to limited external validity. Moreover, this age distribution can cause age-related confounding, complicating the interpretation of mortality rates. The age distribution within our study cohort raises concerns of the presence of different types of comorbidities than can be the cause of the mortality besides IBD and RA.

In conclusion, we found a strong correlation between higher rates of mortality and need for IBD-related surgical procedures in patients with both comorbidities (IBD and RA) compared to those that do not have RA.

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## Conflict of Interest

The authors have no conflict of interest to disclose.

## Informed Consent

This study was reviewed and approved by the UPMC Central PA Review Board. The need for informed consent was waived as no personally identifiable information was used.

## Author Contributions

EC and EV designed the study. EC participated in the data collection, reviewed the literature, interpreted the data, and drafted the manuscript. DG, WN, and CZ engaged in data interpretation, reviewed the literature, and contributed to drafts of the manuscript. AA provided critical reviews of the manuscript. AG participated in extra data collection and reviewers' comments.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

## Abbreviations

IBD: inflammatory bowel disease; RA: rheumatoid arthritis; UC: ulcerative colitis; CD: Crohn's disease; RF: rheumatoid factor; UPMC Central PA: University of Pittsburgh Medical Center of Central Pennsylvania

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