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ORIGINAL ARTICLE

Increased prevalence of gout in patients with inflammatory bowel disease: A population-based study

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Abstract

Background and Aim: Arthritis is a recognized extra-intestinal manifestation of inflammatory bowel disease (IBD). Studies show altered uric acid metabolism in IBD. This study aims to investigate the association between IBD and gout.
Methods: We used a multi-center database (Explorys Inc.) consisting of data from several US healthcare systems. We identified adults diagnosed with Crohn's disease (CD) and ulcerative colitis (UC) between 1999 and 2022. In this cohort, we identified patients diagnosed with gout. We collected demographic data and identified patients diagnosed with IBD-associated arthritis and those who had intestinal resection. Risk factors associated with gout were collected. Multivariate analysis was used.
Results: Out of the 69 260 780 patients in the database, we identified 209 020 patients with UC (0.30%) of whom 9130 had gout (4.3%). Additionally, 249 480 had CD (0.36%) of whom 14 000 had gout (5.61%). Males were more prevalent in the UC and gout group than in the CD and gout group (58% *vs* 51%). After adjustment, CD was significantly associated with gout (odds ratio [OR] 1.68, confidence interval [CI]: 1.60–1.75). UC was also significantly associated with gout (OR 1.38, CI: 1.31–1.44). In subgroup analysis with intestinal resection, CD patients who had intestinal resection had higher association with gout *versus* those without surgery (OR 2.34, CI: 2.25–2.43). Similar increase was observed in the UC group with intestinal resection (OR 1.53, CI: 1.49–1.56).
Conclusion: IBD is strongly associated with gout, with higher correlation observed with CD. Intestinal resection is associated with an increase in the risk of gout. Patients with IBD who present with new-onset arthritis should be investigated for gout.

Introduction

Inflammatory bowel disease (IBD) is a long-standing inflammatory condition that incorporates two major phenotypes: Crohn's disease (CD) and ulcerative colitis (UC). The prevalence of IBD has been increasing globally, with the highest rate observed in North America.[1] Although IBD affects primarily the bowel, the disease is characterized by manifestations in other organ systems. It is estimated that 25% of IBD patients experience an extraintestinal manifestation (EIM) in their lifetime.[2] It is well known that arthritis is associated with IBD, and is considered one of the most frequent EIMs.[3,4] There has been no pathognomonic factor to confirm that arthritis is due to IBD; thus it remains a diagnosis of exclusion.

Gout is a clinical syndrome that occurs as a result of increased extracellular urate concentration, reflected in the blood as hyperuricemia (usual uric acid exceeds 6.8 mg/dl).[5] This manifests as monosodium urate crystals disposition in bones, joints, and soft tissues, which may result in acute arthritis, chronic arthritis, or tophi, or a combination thereof. The prevalence of gout in the United States is estimated to be around 3.9% in adults.[6] Gout and hyperuricemia are not interchangeable terms, but it is important to note that gout is a common clinical outcome of hyperuricemia. Uric acid is the end product of purine nucleoside catabolism by xanthine dehydrogenase. It is mainly produced in the liver and intestine as well as other tissues such as muscles, kidneys, and vascular endothelium as a result of degradation of dietary and endogenously synthesized purine compounds. Therefore, secondary hyperuricemia can be induced by excessive purine-rich food intake (e.g. red meat, seafood), cellular degradation processes, and high cell turnover in the context of malignancy or cancer therapy. About one-third of uric acid is excreted through the gut, with the remaining two-thirds disposed through urine.[7] It is established that the intestinal tract is a crucial organ for both the production and excretion of uric acid.[8]

Uric acid metabolism in IBD has been investigated in several studies. Literature suggests that hyperuricemia is a well-remarked condition in IBD patients. Since gout represents the clinical expression of hyperuricemia, the main aim of this study

was to evaluate the association between IBD and gout using a large database.

Methods

Study design. This is a retrospective analysis of a large multicenter electronic health record (EHR)-based commercial database developed by IBM (Explorys Inc., Cleveland, OH, USA), This platform aggregates the EHRs from 26 nationwide major healthcare systems in the United States. It stores over 70 million unique health records. Patient information is then de-identified, standardized, and stored in a cloud database. The Explorys platform uses the Systemized Nomenclature of Clinical Medical Terms (SNOMED-CT) for medical terms, diagnoses, and procedures. For diagnoses, the International Classification of Disease, 10th Revision, Clinical Modification (ICD-10-CM) codes are mapped into the SNOMED-CT hierarchy. This platform is compliant with the Health Insurance Portability and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health Act (HITECH). The Cleveland Clinic Institutional Review Board considers studies using Explorys as a recorded dataset exempt from approval because all patient information is de-identified. Explorys preserves patient confidentiality by approximating each cohort's count to 10. All counts between 0 and 10 are treated equally.

Patient selection and covariates. Adult patients (age above 18 years) with active EHRs between 1999 and 2022 were identified using the search tool in Explorys. Using the SNOMED-CT diagnosis terms "Crohn's disease" and "Ulcerative colitis," we identified patients diagnosed with IBD. The control group was identified as patients without these SNOMED-CT diagnoses. The SNOMED-CT diagnosis term "gout" was used to identify patients with the diagnosis of gout. We adjusted the search tool to delineate the diagnosis of gout AFTER the UC/CD diagnosis. Our goal was to estimate the prevalence of gout after IBD diagnosis in light of the altered uric acid metabolism in IBD patients. We excluded patients who were on thiazides or loop diuretics. The platform does not provide specific laboratory data including uric acid levels. We collected cross-sectional information on patient demographics such as gender, age, and race. Comorbidities known to be associated with gout, such as chronic kidney disease (CKD), malignancy, alcohol abuse, and smoking, by searching the database for their respective SNOMED-CT terms. Moreover, we identified patients with diagnosed IBD-associated arthritis and those who needed intestinal resection for further analysis. We used the SNOMED-CT term "intestinal resection," which is the nomenclature that includes both small bowel resection and colectomy.

Statistical analysis. Gout patients diagnosed with IBD (CD or UC) were compared with patients without IBD (control group). To calculate the overall period prevalence, we divided the total number of patients with IBD by the total number of individuals in Explorys; by doing so, we ensured that all patients in the denominator had an equal chance of being diagnosed with IBD. The prevalence rates of gout in patients with IBD and control patients were calculated by dividing the total number of patients with gout by the total number of individuals with and without (CD or UC), respectively. To adjust for possible confounding factors, a multivariate regression model was constructed using binary logistic regression, with gout as the dependent variable. To assess for independence within covariate risk factors, we used the variance inflating factor, with a cutoff of significant collinearity set at a variance inflating factor >1.5. Goodness of fit was evaluated for the regression model by applying the Hosmer–Lemeshow test, with P >0.05 indicating a good fit. We used IBM SPSS Statistics version 28.0.1 to perform the multivariate regression analysis. A two-sided P-value of <0.05 was considered statistically significant for all analyses.

This study was exempt from approval by the Cleveland Clinic Institutional Review Board as the dataset obtained from the Explorys platform is de-identified.

Results

Out of the 69 260 780 adult patients in the database between 1999 and 2022, there was a total of 458 500 diagnosed with IBD (0.66%). Among those patients, 209 020 individuals were diagnosed with UC (0.30%), of whom 9130 had gout (4.3%) compared to 3.51% in the general population with no history of UC, $P < 0.001$. In addition, 249 480 patients had CD (0.36%), of whom 14 000 had gout (5.61%) in comparison to 3.53% of the general population without diagnosis of CD, $P < 0.001$. The majority of patients in both UC with gout and CD with gout were >65 years old (70% *vs* 61%), respectively. Males were more prevalent in the UC and gout group than in the CD and gout group (58% *vs* 51%). Caucasians were predominant across the two groups, with nearly 83% in each group, followed by African Americans (9–11%), Table 1. Adjusting for demographics

Table 1 Characteristics of patients in cohort.

	Gout without IBD	UC + gout	CD + gout
Total cohort	2 400 990	9130	14 000
Age			
18–65	979 600 (40.8%)	2740 (30%)	5340 (38%)
>65	1 421 390 (59.2%)	6350 (70%)	5870 (61%)
Gender			
Male	1 378 170 (57.4%)	5290 (58%)	7120 (51%)
Female	1 022 820 (42.6%)	3820 (42%)	6850 (49%)
Race			
Caucasian	1 248 510 (52%)	7480 (82%)	11 570 (83%)
AA	962 790 (40.1%)	960 (11%)	1220 (9%)
Asian	31 200 (1.3%)	110 (1%)	350 (3%)
Hispanic	48 000 (2%)	30 (0.3%)	120 (1%)
Unknown	110 400 (4.6%)	550 (6%)	740 (5%)
Comorbidities			
Tobacco smoking	456 180 (19%)	1910 (21%)	3010 (21.5%)
Alcohol abuse	288 100 (12%)	1460 (16%)	2380 (17%)
Obesity	1 032 400 (43%)	4190 (46%)	6370 (45.5%)
DM	768 310 (32%)	3240 (35.5%)	4900 (35%)
CKD	432 170 (18%)	2550 (28%)	4060 (29%)
Hypertension	1 087 640 (45.3%)	4380 (48%)	6720 (48%)
Hyperlipidemia	744 300 (31%)	3100 (34%)	4620 (33%)

AA, African American; CD, Crohn's disease; CKD, chronic kidney disease; DM, diabetes mellitus; IBD, inflammatory bowel disease; UC, ulcerative colitis.

including age, race, and gender, as well as known gout risk factors including CKD, malignancy, IBD-associated arthritis, intestinal resection, alcohol intake, and smoking, CD was significantly associated with gout (odds ratio [OR] 1.68, confidence interval [CI]: 1.60–1.75) $P < 0.001$. UC was also found to be significantly associated with gout (OR 1.38, CI: 1.31–1.44) $P < 0.001$, Figure 1. In subgroup analysis in both groups against intestinal resection, the UC group that had intestinal reaction had a higher association with gout compared to those who did not have surgery (OR 2.34, CI: 2.25–2.43) $P < 0.001$. A similar relationship was observed in the CD group that had intestinal resection *versus* that with no surgery (OR 1.53, CI:1.49–1.56) $P < 0.001$.

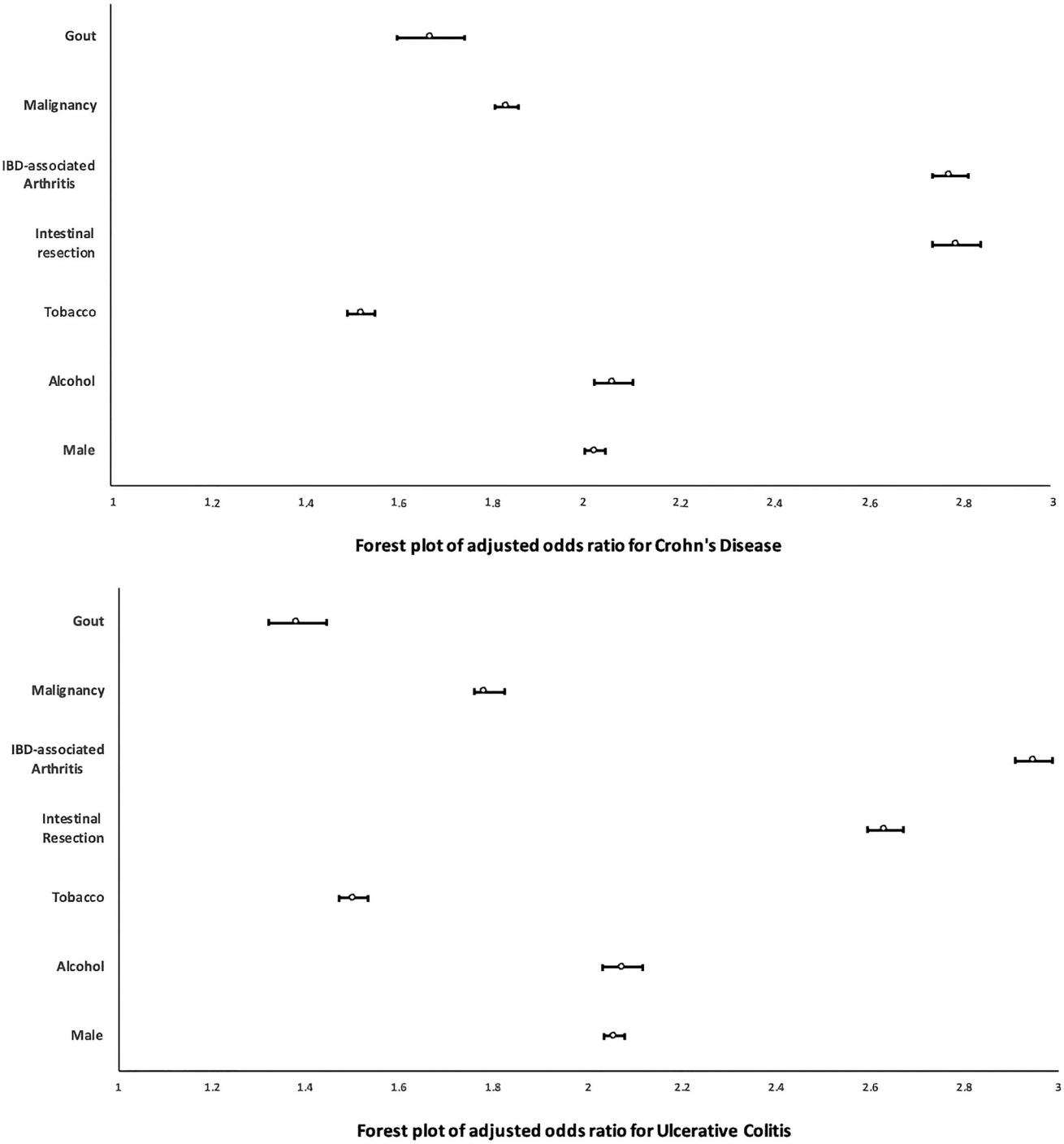

Figure 1 Forest plots for adjusted odds ratio for Crohn's disease and ulcerative colitis. IBD, inflammatory bowel disease.

Discussion

Our study highlights the increased prevalence of gout in the IBD population (4.3% in UC and 5.6% in CD) compared with the general population (prevalence 3.5%). To the best of our knowledge, this is the first large-scale database study to bring out this relationship.

Although the exact pathophysiology of IBD is unknown, several immune, microbial, and genetic factors have been implicated in the pathogenesis of IBD. Out of these factors is the dysregulated immune response to luminal microbiota and/or their products.[9-11] In addition, alteration in intestinal mucus and increase intestinal permeability contribute to the pathogenesis of IBD.[12-14] Excessive immune cell recruitment and activation has been noted in multiple immune subsets such as myeloid cells, natural killer cells, and inmate lymphoid cells. These cells play a crucial role in the observed increased levels of immune-regulatory cytokines.[15,16]

The existence of hyperuricemia in IBD has been linked to some of the above-mentioned pathogenetic mechanisms. Chiaro *et al*. in their study indicated that certain commensal microbiota are found in IBD patients in comparison to healthy individuals. They investigated a fungus *Saccharomyces cerevisiae* hosting purine metabolism, leading to a rise in uric acid production in IBD patients.[17] Also, Lv *et al*. and Xu *et al*. implemented animal models, showing that the abundance of inflammation-related microbiota along with intestinal barrier inflammation resulted in an increase in intestinal permeability and a rise in uric acid level in IBD patients.[18,19]

Gout is characterized biochemically by extracellular fluid urate saturation, which is reflected in the blood by hyperuricemia. The clinical manifestations include recurrent flares of inflammatory arthritis (gout flare), chronic arthropathy, accumulation of urate crystals in the form of tophaceous deposits, uric acid nephrolithiasis, and chronic nephropathy. The diagnosis can be made by clinical presentation and lab work, but preferably by identification of intracellular monosodium urate (MSU) crystals on polarizing light microscopy of the synovial fluid from an affected joint.

Uric acid is excreted mainly via two routes: two-thirds through the urinary route and one-third through the gastrointestinal tract. Excretion is regulated by multiple types of transporters, mainly ABCG2 (ATP-binding-cassette G2) transporter, which is expressed not only in proximal convoluted tubules but also on the intestinal membrane. It has been suggested that ABCG2 defect, in fact, may have a role in the pathogenesis of primary hyperuricemia.[20] Deuring *et al*. in their study found that the expression of the ABCG2 transporter is downregulated in IBD patients; thus a defect in both renal and extrarenal elimination of uric acid may lead to an increase in the level of uric acid in serum.[21,22] Additionally, several studies have found higher levels of serum uric acid in IBD patients in comparison with the general population. For instance, a recent meta-analysis concurred with the observed higher levels of uric acid in IBD.[23-25]

As noted previously, the etiology of hyperuricemia in IBD has been the subject of extensive research. Another possible explanation is derived from multiple studies showing that low levels of the aromatic amino acid tryptophan (TRP) is associated with a number of immune-mediated diseases including IBD.[26,27] It is speculated that endogenous TRP metabolites offer inflammation protection by preserving intestinal immune hemostasis and microbial diversity. Nikolaus *et al*. examined this phenomenon further and found that IBD patients are essentially deficient in TRP.[28] Interestingly, TRP-deficient subjects were also found to have higher levels of uric acid. It is proposed that low TRP levels lead to a decrease in the urinary excretion of uric acid. In a clinical trial conducted in Japan, combination therapy of glycine and TRP significantly decreased serum uric acid in hyperuricemia patients.[29] Whether TRP deficiency represents a link between gout and IBD is yet to be proven in clinical research.

Our study showed that IBD patients who had intestinal resection have a higher risk of developing gout. We found that UC patients with intestinal resection are more prone to developing gout than CD patients. This relationship has been indirectly established in past studies investigating nephrolithiasis in IBD patients post resection. These patients have a higher tendency for chronic volume contraction and a decrease in urinary excretion. The process of stone formation appears to be different in UC and CD after resection. In CD patients, resection of small bowel may result in bile acid malabsorption and steatorrhea. High levels of intraluminal fatty acids form insoluble soaps after combining with calcium, which leads to a low luminal level of calcium in the gut. In a normal environment, calcium binds with dietary oxalate, forming poorly absorbable calcium oxalate. Therefore, a low intestinal calcium level due to the binding with fatty acids may lead to an increased quantity of free oxalate reaching the colon (i.e. enteric hyperoxaluria). Bile salts and fatty acids increase the permeability of gut mucosa to oxalate, resulting in increased absorption of oxalate, hyperoxaluria, and the formation of oxalate stone. In patients with UC, particularly those who have undergone ileostomy, loss of alkaline fluid can cause chronic metabolic acidosis. Consequently, the urine becomes concentrated and acidic. In the context of hyperuricemic conditions, uric acid stones are noted to be more common in UC patients who have undergone ileostomy.[30-33]

Our study has some limitations. The database used is an EMR-derived data collection from determined healthcare systems. As such, it is vulnerable to selection bias and coding entry, missing data, and follow-up limitations. Validation of the SNOMED-CT diagnostic codes was not possible because the patient information in the database was de-identified. In addition, because of the limitations of ICD-10, Explory's cannot confirm the severity of IBD, which could play a role in hyperuricemia and consequently gout. Similarly, we could not confirm whether the diagnosis of gout was pathologically proven or based on clinical presentation. A crucial factor that may play a role in hyperuricemia is medications. We have excluded patients who are on thiazide or loop diuretics given the well-established, diuretic-induced hyperuricemia and gout. However, we could not address other medications or dietary factors that may positively or negatively contribute to the results. We were unable to perform propensity score-matching because the Explorys platform only provides population-level data and not individual cases. For instance, losartan may have a direct uricosuric effect[34] whereas beta blockers have been reported to increase uric acid levels.[35] IBD patients are advised to avoid NSAIDs, which could potentially suppress gout flares. This may indirectly contribute to the expression of clinical manifestations of gout in IBD. Still and all, the driving force of our study was the large population size

reflecting disease burden at multiple healthcare institutions. The results are therefore generalizable to the population nationwide.

In conclusion, this exploratory analysis of a large database study suggests a strong association between IBD and gout. Several pathophysiological mechanisms could be contributory to this relationship. IBD-related intestinal resection is a significant risk factor for gout in this patient population. We recommend that patients with IBD who present with new-onset arthritis be carefully investigated for gout.

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