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# Risk of Venous Thromboembolism among Inflammatory Bowel Disease patients who contract SARS-CoV-2

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**Potential Competing Interests:**

Nadim Mahmud has nothing to disclose regarding conflicts of interest. Alexandra Weiss has nothing to disclose regarding conflicts of interest. Chinmay Trivedi has nothing to disclose regarding conflicts of interest. James Lewis has served as a consultant for Merck, AbbVie, Lilly, Janssen, Johnson & Johnson Consumer Inc., and Takeda, has served on Data Safety Monitoring Boards for Pfizer, Gilead and UCB, and has received research support from Takeda and Nestle Health Science. Yu-Xiao Yang has nothing to disclose regarding funding interests. Nabeel Khan has received research funding from Pfizer, Luitpold and Takeda Pharmaceuticals as well as from Samsung BioEpis.

**Specific Author Contributions:**

Nadim Mahmud has participated in study concept and design, acquisition of data, formal statistical analysis, interpretation of data, preparation of the manuscript, and critical review of the manuscript for important intellectual content. Alexandra Weiss has participated in interpretation of data and preparation of the manuscript. Chinmay Trivedi has participated in interpretation of data and preparation of the manuscript. James Lewis has participated in study concept and design, data interpretation, manuscript preparation, and critical review of the manuscript for important intellectual content. Yu-Xiao Yang has participated in statistical

analysis, data interpretation, preparation of the manuscript, and critical reviewing of the manuscript for important intellectual content. Nabeel Khan has participated in study supervision, study concept and design, data interpretation, manuscript preparation, and critical review of the manuscript for important intellectual content.

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## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic affecting over 166 million people worldwide. **(1)** Inflammatory bowel disease (IBD) is a common disorder affecting more than 6.8 million people globally, **(2)** and the association between IBD and the development of venous thromboembolism (VTE) has been well described. **(3)** The association between COVID-19 disease and VTE has also been described, **(4)** however to date there are no published data addressing the incremental risk of VTE in patients with underlying IBD who contract SARS-CoV-2. To evaluate this, we studied a nationwide cohort of IBD patients in the Veterans Affairs (VA) healthcare system.

## Methods

See Supplement for extended methods. This was a case crossover study of patients with IBD and VTE in an established VA cohort. The case crossover design only uses data from patients with the outcome of interest and compares the prevalence of exposure immediately prior to the outcome to other times, such that each patient is compared to themselves at other times. We identified all patients with IBD prior to March 1st, 2020 (index date) who were actively followed in the VA and who developed an incident VTE event between April 1$^{st}$, 2020 and March 30$^{th}$, 2021. Demographics, IBD medication, corticosteroid use, anticoagulation medication, and comorbidity data were obtained for each patient, in addition to dates of SARS-CoV-2 infection (via polymerase chain reaction). Descriptive statistics were reported as medians and interquartile ranges (IQRs) for continuous variables and as percentages for categorical variables. For the primary analysis, we established a 30-day window prior to VTE for each patient (case period), and subsequently generated ten 30-day window control periods (non-overlapping with the case period, also between April 1$^{st}$, 2020 and March 30$^{th}$, 2021) for each patient using a random number generator. Control periods could occur before or after case periods, as the outcome of thrombosis was not thought to impact future risk of SARS-CoV-2 infection, and it was important to include periods throughout the study duration given a fluctuating national burden of COVID-19. For each case and control window, the presence or absence of SARS-CoV-2 infection was designated as the exposure. Conditional logistic regression using a 1:10 case:control ratio was used to estimate the odds ratio and 95% confidence interval (CI) for the association of VTE with SARS-CoV-2 infection, adjusting for all-cause hospitalization at the start of the 30-day window and time-updated corticosteroid use in the prior 30 days. Stratified analyses were performed based on usage of chronic anticoagulation medications prior to VTE.

## Results

428 patients with IBD developed VTE during the study period. The cohort had median age 69 years, was 93.9% male, 79.4% white, and with a slight predominance of ulcerative colitis (54.4%, Table 1). The majority of patients were being treated with 5-aminosalicylic acid alone (49.8%) or anti-tumor necrosis factor agents alone

(15.7%). During the study window, there were 58 SARS-CoV-2 infections, 21 of which occurred within 30 days prior to a VTE. In conditional logistic regression models adjusted for recent hospitalization and steroid exposure, SARS-CoV-2 infection was associated with 8.15-fold increased odds of VTE (95% CI 4.34-15.30, p<0.001). When limited to patients taking chronic anticoagulation medications, there was no significant association between SARS-CoV-2 infection and VTE (odds ratio [OR] 0.63, 95% CI 0.08-5.15, p=0.66). However, the association was stronger among patients not previously on anticoagulation (OR 14.31, 95% CI 6.90-29.66, p<0.001).

**Discussion**

In this nationwide cohort, we identified a significant positive association between SARS-CoV-2 infection and VTE events in patients with IBD. Prior studies demonstrate 2-3-fold increased odds of developing VTE in patients with IBD compared to the general population, in both hospitalized and ambulatory settings. **(5, 6)** The pathogenesis of VTE in IBD is multifactorial and findings suggest that there is not one particular mechanism that leads to hypercoagulability in IBD, but rather a complex interplay of systems. The mechanisms of hemostatic imbalance in SARS-CoV-2 infection are similarly complex. In patients with infections such as COVID-19, endothelial dysfunction caused by the infectious process increases thrombin production and terminates fibrinolysis, which in turn promotes a hypercoagulable state. **(7)** Although these mechanisms cannot be completely explained by traditional VTE risk factors, it stands to reason that contracting SARS-CoV-2 infection would confer an additional risk on top of the already elevated risk in patients with IBD. Moreover, patients with IBD appear to have a uniquely increased risk in this regard, as recent data from an unselected cohort of 220,588 patients demonstrated a rate ratio of 1.46 for VTE events in SARS-CoV-2 positive versus negative individuals (p<0.001). **(8)** This is in stark contrast to the 8.15-fold increased odds of VTE observed in our cohort of IBD patients, suggesting a strong interaction between SARS-CoV-2 and IBD in conferring increased VTE risk. Importantly, the identified association between SARS-CoV-2 and VTE in the IBD cohort was entirely mitigated among patients who were on anti-coagulation therapy when they contracted SARS-CoV-2. This suggests that there may be a possible role for VTE pharmaco-prophylaxis especially among high-risk IBD patients who contract SARS-CoV-2.

Major strengths of our study include the use of a nationwide study cohort with a geographically diverse patient population, and a self-controlled study design. The VA has devised a system in which all positive SARS-CoV-2 cases are recorded even if they are diagnosed outside the VA. The pharmacy dataset is very comprehensive, and veterans are likely to get their medications filled in the VA as there is little or no co-pay. Limitations include the retrospective nature of the study. We may also have missed thrombotic episodes diagnosed outside the VA

system, but we suspect the numbers would be low as we only included patients who were actively followed in the VA.

To the best of our knowledge, this study is the first to detail the strength of association between SARS-CoV-2 and subsequent VTE in patients with underlying IBD. Our data suggest that IBD patients who contract SARS-CoV-2 have a substantially increased risk of VTE and may therefore benefit from prophylaxis.

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**Table 1 – Cohort Characteristics**

| Variable | Value (N=428) |
|---|---|
| **Age (years), median (IQR)** | 69 (58, 74) |
| **Male Sex** | 402 (93.9%) |
| **Race** | |
| White | 340 (79.4%) |
| Black | 66 (15.4%) |
| Hispanic | 6 (1.4%) |
| Other | 16 (3.7%) |
| **Smoking History** | |
| Unknown | 68 (15.9%) |
| Never | 189 (44.2%) |
| Past | 84 (19.6%) |
| Current | 87 (20.3%) |
| **Alcohol Abuse** | 26 (6.1%) |
| **Drug Abuse** | 26 (6.1%) |
| **IBD Type** | |
| Crohn's Disease | 195 (45.6%) |
| Ulcerative Colitis | 233 (54.4%) |
| **IBD Medication Group** | |
| 5-ASA Alone | 213 (49.8%) |
| Thiopurine alone | 61 (14.3%) |
| Anti-TNF alone | 67 (15.7%) |
| Anti-TNF + immunomodulator | 21 (4.9%) |
| Vedolizumab | 41 (9.6%) |
| Ustekinumab | 9 (2.1%) |
| Tofacitinib | 4 (0.9%) |
| Methotrexate alone | 12 (2.8%) |
| **Steroid Use** | 41 (9.6%) |
| **Obesity** | 77 (18.0%) |
| **Hypertension** | 249 (58.2%) |
| **Diabetes Mellitus** | 134 (31.3%) |
| **Arrhythmia** | 84 (19.6%) |
| **Heart Failure** | 28 (6.5%) |
| **COPD*** | 95 (22.2%) |
| **Renal Failure** | 64 (15.0%) |
| **Metastatic Cancer** | 11 (2.6%) |
| **Chronic Anticoagulation Use** | 133 (31.1%) |
| **SARS-CoV-2 Infection** | 58 (13.6%) |
| **COVID-19 Hospitalization** | 22 (5.1%) |

*Chronic Obstructive Pulmonary Disease