Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Risk of Venous Thromboembolism Among Patients With Inflammatory Bowel Disease Who Contract Severe Acute Respiratory Syndrome Coronavirus 2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic affecting more than 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 coronavirus 2019 (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 patients with IBD in the Veterans Affairs (VA) healthcare system.

See the 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 with themselves at other times. We identified all patients with IBD prior to March 1, 2020 (index date) who were actively followed in the VA and who developed an incident VTE event between April 1, 2020 and March 30, 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 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 10 30-day window control periods (nonoverlapping with the case period, also between April 1, 2020 and March 30, 2021) for each patient using a random number generator. Control periods could occur before or after case periods because 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 (OR) 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 use of chronic anticoagulation medications prior to VTE.

In this study, 428 patients with IBD developed VTE during the study period. The patients in the cohort had a median age 69 years, 93.9% were male, 79.4% were white, and there was 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; $P < .001$). When limited to patients taking chronic anticoagulation medications, there was no significant association between SARS-CoV-2 infection and VTE (OR, 0.63; 95% CI, 0.08–5.15; $P = .66$). However, the association was stronger among patients not previously on anticoagulation (OR, 14.31; 95% CI, 6.90–29.66; $P < .001$).

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- to 3-fold increased odds of developing VTE in patients with IBD compared with 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 promote 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

Abbreviations used in this paper: CI, confidence interval; COVID-19, coronavirus 2019; IBD, inflammatory bowel disease; OD, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VA, Veterans Affairs; VTE, venous thromboembolism.

Most current article

Published by Elsevier Inc. on behalf of the AGA Institute.
0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2021.06.012

Table 1. Cohort Characteristics

Variable	Value (N = 428)
Age (*y*), 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)

5-ASA, 5-aminosalicylic acid; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; TNF, tumor necrosis factor.

versus –negative individuals ($P < .001$).[8] This is in stark contrast to the 8.15-fold increased odds of VTE observed in our cohort of patients with IBD, 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 anticoagulation 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 because 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 up 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 patients with IBD who contract SARS-CoV-2 have a substantially increased risk of VTE and, therefore, may benefit from prophylaxis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2021.06.012.

NADIM MAHMUD
Department of Gastroenterology
Corporal Michael J Crescenz VA Medical Center
Philadelphia, Pennsylvania, *and*
Division of Gastroenterology
University of Pennsylvania
Perelman School of Medicine
Philadelphia, Pennsylvania

ALEXANDRA WEISS
Division of Gastroenterology
University of Pennsylvania
Perelman School of Medicine
Philadelphia, Pennsylvania

CHINMAY TRIVEDI
Department of Gastroenterology
Corporal Michael J Crescenz VA Medical Center
Philadelphia, Pennsylvania

YU-XIAO YANG
Department of Gastroenterology
Corporal Michael J Crescenz VA Medical Center
Philadelphia, Pennsylvania, *and*
Center of Clinical Epidemiology and Biostatistics
University of Pennsylvania
Perelman School of Medicine
Philadelphia, Pennsylvania

JAMES LEWIS
Division of Gastroenterology
University of Pennsylvania
Perelman School of Medicine
Philadelphia, Pennsylvania

NABEEL KHAN
Department of Gastroenterology
Corporal Michael J Crescenz VA Medical Center
Philadelphia, Pennsylvania, *and*
Division of Gastroenterology
University of Pennsylvania
Perelman School of Medicine
Philadelphia, Pennsylvania

References

1. WHO. https://covid19.who.int/.
2. Alatab S, et al. Lancet Gastroenterol Hepatol 2020;5:17–30.
3. Yuhara H, et al. Aliment Pharmacol Therapeutics 2013; 37:953–962.
4. Middeldorp S, et al. J Thromb Haemostasis 2020; 18:1995–2002.
5. Grainge MJ, et al. Lancet 2010;375:657–663.
6. Miehsler W, et al. Gut 2004;53:542–548.
7. Levi M, et al. Thromb Res 2017;149:38–44.
8. Roubinian NH, et al. JAMA Intern Med 2021;181:997–1000.

Received July 22, 2020. Accepted June 7, 2021.

Correspondence
Address correspondence to: Nabeel Khan, MD, 3900 Woodland Avenue, Philadelphia, Pennsylvania 19104. e-mail: nabeel.khan@va.gov and nabeelk@pennmedicine.upenn.edu.

CRediT Authorship Contributions
Nadim Mahmud, MD (Conceptualization: Equal; Formal analysis: Lead; Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; Interpretation of data: Equal)

Alexandra Weiss, MD (Writing – original draft: Equal; Interpretation of data: Equal) Chinmay Trivedi, MBBS (Writing – original draft: Equal; Interpretation of data: Equal)

James Lewis, MD (Conceptualization: Equal; Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; Data interpretation: Equal)

Yu-Xiao Yang, MD (Formal analysis: Lead; Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; Interpretation of data: Equal)

Nabeel Khan, MD (Conceptualization: Equal; Funding acquisition: Lead; Methodology: Equal; Supervision: Lead; Writing – original draft: Supporting; Writing – review & editing: Equal; Data interpretation: Equal)

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. Nabeel Khan has received research funding from Pfizer, Luitpold, and Takeda Pharmaceuticals as well as from Samsung BioEpis. All other authors disclose no conflicts.

Funding
This study was supported by an unrestricted research grant from Pfizer Pharmaceuticals. Pfizer had no role in study concept and design, acquisition and interpretation of data, or preparation of the manuscript. Nadim Mahmud is supported by an American College of Gastroenterology Junior Faculty Development Award (ACG-JR-010-2020).

Supplementary Methods

Cohort Creation

To identify a cohort of patients with IBD actively managed in the Veterans Health Administration (VHA), we applied the following criteria. First, we only included adult patients (age ≥18 years) classified as having IBD using a previously validated algorithm based on administrative codes for Crohn's disease or ulcerative colitis, which has been used in prior studies.[1,2] Second, we only included patients taking an IBD-related medication within 3 months prior to the index date (March 1, 2020), as ascertained through centralized VHA pharmacy records. These included the following medication categories: 5-aminosalicylic acid (5-ASA) alone, thiopurines (azathioprine or mercaptopurine, with or without 5-ASA), anti–tumor necrosis factor (anti-TNF) agents alone, anti-TNF plus immunomodulators (methotrexate or thiopurines), methotrexate alone, vedolizumab, ustekinumab, or tofacitinib. Finally, we only included patients with at least 6 months of outpatient visit data prior to the index date. For the purposes of this study, the analytic cohort was restricted to patients with IBD who developed an incident thrombosis event (detailed as follows) between April 1, 2020 and March 30, 2021.

Ascertainment of Anticoagulation Medications

We used the centralized VHA pharmacy data tables to identify patients filling outpatient prescriptions for anticoagulant medications. These were identified with regular expression searches for the following medications: enoxaparin, warfarin, apixaban, dabigatran, edoxaban, and rivaroxaban. In this study, patients were considered to be on anticoagulation medication as a covariate if they filled a prescription for an associated medication more than 30 days prior to a thrombosis event in the study period.

Ascertainment of Thrombosis Events

We used inpatient or outpatient International Classification of Diseases, 10th revision (ICD-10) codes to identify thrombosis events (eg, deep venous thrombosis or pulmonary embolism) during the study window. The following codes were used: I26.01, I26.02, I26.09, I26.90, I26.92, I26.93, I26.94, I26.99, I80.00, I80.01, I80.02, I80.03, I80.10, I80.11, I80.12, I80.13, I80.201, I80.202, I80.203, I80.209, I80.211, I80.212, I80.213, I80.219, I80.221, I80.222, I80.231, I80.232, I80.241, I80.242, I80.251, I80.252, I80.253, I80.291, I80.292, I80.293, I80.299, I80.3, I80.8, I80.9, I82.0, I82.1, I82.210, I82.211, I82.220, I82.221, I82.290, I82.291, I82.3, I82.401, I82.402, I82.403, I82.409, I82.411, I82.412, I82.413, I82.419, I82.421, I82.422, I82.423, I82.429, I82.431, I82.432, I82.433, I82.439, I82.441, I82.442, I82.443, I82.449, I82.451, I82.452, I82.453, I82.459, I82.461, I82.462, I82.463, I82.469, I82.491, I82.492, I82.493, I82.499, I82.4Y1, I82.4Y2, I82.4Y3, I82.4Y9, I82.4Z1, I82.4Z2, I82.4Z3, I82.4Z9, I82.601, I82.602, I82.603, I82.609, I82.611, I82.612, I82.613, I82.619, I82.621, I82.622, I82.623, I82.629, I82.811, I82.812, I82.813, I82.819, I82.890, I82.891, I82.90, I82.91, I82.A11, I82.A12, I82.A13, I82.A19, I82.A21, I82.A22, I82.A23, I82.A29, I82.B11, I82.B12, I82.B13, I82.B19, I82.B21, I82.B22, I82.B29, I82.C11, I82.C12, I82.C13, I82.C19, I82.C21, I82.C22, I82.C23, and I82.C29.

References

1. Khan N, et al. Clin Gastroenterol Hepatol 2018;16:1919–1927.
2. Khan N, et al. Gut 2021;70:1657–1664.