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.

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BRIEF COMMUNICATIONS

COVID-19 Vaccination Is Safe and Effective in Patients With Inflammatory Bowel Disease: Analysis of a Large Multi-institutional Research Network in the United States

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In December 2020, the US Food and Drug Administration issued Emergency Use Authorizations, followed by interim recommendations, for the use of 2 messenger (m)RNA-based vaccines (Pfizer-BioNTech [Pfizer, New York, NY] and Moderna, [Cambridge, MA]) for the prevention of COVID-19.[1] More than 300 million doses of COVID-19 vaccines have been administered in the United States as of May 2021.[2] Large clinical trials reported efficacy of the mRNA COVID-19 vaccines[3]; however, data for specific patient populations, such as those with inflammatory bowel disease (IBD), are lacking.

mRNA COVID-19 vaccines use novel mechanisms of action that limit extrapolation of safety and efficacy data from other vaccines previously studied in patients with IBD. Moreover, a recent study reported reduced antibody responses to COVID-19 vaccines in patients with IBD on biologic therapies,[4] raising concerns regarding effectiveness. Safety of COVID-19 vaccines in patients with IBD has not yet been investigated in detail.

Methods

We used the TriNetX (Cambridge, MA) research network to retrospectively analyze data from multiple institutions in the United States. Patients with a diagnosis of IBD (Crohn's disease [CD] or ulcerative colitis [UC]) who received a COVID-19 vaccination until April 30, 2021, were identified and included. Details of the database are described in the Supplementary Methods and previous studies.[5]

Study definitions and selection criteria are detailed in the Supplementary Methods. Safety and efficacy of COVID-19 vaccination in patients with IBD was studied in comparison with the general population without IBD who received a COVID-19 vaccination. Safety outcomes included immediate adverse events within 1 day and adverse events of special interest purported by Centers for Disease Control and Prevention, including acute myocardial infarction, anaphylaxis, facial nerve palsy, coagulopathy, deep vein thrombosis, pulmonary embolism, Guillain-Barré syndrome, transverse myelitis, immune thrombocytopenia, disseminated intravascular coagulation, myocarditis/pericarditis, hemorrhagic/nonhemorrhagic stroke, appendicitis, narcolepsy, and encephalomyelitis, up to 30 days after any dose of a COVID-19 vaccination.[6] All-cause hospitalization rates at 30 days after COVID-19 vaccination were also compared between cohorts with and without IBD.

Efficacy was assessed by comparing the rates of a new COVID-19 diagnosis any time after receiving the COVID-19 vaccination. Time-to-event analysis was performed using log-rank tests. Groups with and without IBD were also compared using 1:1 propensity-score matching (PSM) based on demographic variables and comorbidities detailed in the Supplemental Methods. Steroid prescriptions at the 30-day follow-up were compared between vaccinated and non-vaccinated patients with IBD in matched and unmatched analyses.

Subgroup analysis based on the type of IBD (UC/CD), and medications (biologics or immunomodulators, or both) was also performed. Patient counts $\leq$10 were obfuscated to safeguard protected health information. Detailed methodology can be found in the Supplementary Methods.

Results

We identified 864,575 patients who received the COVID-19 vaccination during the study period. Of these, 5562 patients had a prior diagnosis of IBD (2933 UC, 2629 CD). The patients with IBD were a mean age of 57.3 $\pm$ 17.5 years, and 59.67% were women (Table 1). Before vaccination, 2939 patients (52.84%) were on biologics/thiopurines. Among the patients with IBD, 1822 received 1 vaccine dose, and 3740 received 2 doses. Pfizer and Moderna vaccines were administered to 3104 and 762 IBD patients, respectively, and the manufacturer was not specified in the remaining patients.

Among the patients with IBD, $\leq$10 developed any immediate reaction to the vaccine. New instances of the Centers for Disease Control and Prevention-reported adverse events of special interest developed in 113 patients (2.03%) in the IBD cohort, whereas these events were noted in 6992 patients (0.81%) without IBD (risk ratio [RR], 2.50; 95% confidence interval [CI], 2.07–3.00).

Abbreviations used in this paper: **CI, confidence interval; CD, Crohn's disease; IBD, inflammatory bowel disease; mRNA, messenger RNA; PSM, propensity score matching; RR, risk ratio; UC, ulcerative colitis..**

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Table 1. Characteristics and Outcomes After COVID-19 Vaccination in Patients With and Without IBD

Variable	IBD (N = 5562)	Non-IBD (N = 859,017)	Standardized mean difference	IBD (n = 5561)	Non-IBD (n = 5561)	Standardized mean difference
	Before matching			After matching		
Demographics						
Age, mean (SD), *y*	57.3 (17.5)	57.9 (18.1)	0.04	57.3 (17.5)	57.4 (17.4)	0.008
Male	2299 (41.33)	360,857 (42.01)	0.01	2298 (41.32)	2300 (41.36)	0.001
BMI, mean (SD), kg/m^2	28.4 (6.4)	29.2 (6.77)	0.13	28.4 (6.4)	28.9 (6.19)	0.09
African American	630 (11.36)	114,493 (13.33)	0.06	630 (11.33)	624 (11.22)	0.003
Caucasian	4450 (80.01)	601,483 (70.02)	0.23	4449 (80.00)	4473 (80.44)	0.01
Comorbid conditions						
Hypertension	2742 (49.30)	288,540 (33.59)	0.32	2741 (49.29)	2468 (44.38)	0.09
Chronic lower respiratory diseases	1658 (29.81)	119,685 (13.93)	0.39	1657 (29.80)	1650 (29.67)	0.003
Diabetes mellitus	1110 (19.96)	114,510 (13.33)	0.17	1109 (19.94)	1117 (20.09)	0.004
Ischemic heart disease	1020 (18.34)	90,578 (10.54)	0.22	1019 (18.32)	1026 (18.45)	0.003
Nicotine dependence	643 (11.56)	50,741 (5.91)	0.20	642 (11.55)	642 (11.55)	0.0001
Heart failure	493 (8.86)	39,655 (4.62)	0.17	492 (8.85)	418 (7.52)	0.048
	Vaccine-related outcomes in study cohorts					
	IBD cohort	Non-IBD cohort	RR (95% CI)	IBD cohort	Non-IBD cohort	RR (95% CI)
New COVID-19 diagnosis[a]	19 (0.36)	2277 (0.28)	1.3 (0.83–2.05)[b]	19 (0.36)	20 (0.38)	0.95 (0.51-1.78)[c]
Immediate adverse events[d]	≤10[e]	519 (0.06)	…	≤10[e]	≤10[e]	…
Special adverse events of interest[f]	113 (2.03)	6992 (0.81)	2.50 (2.08–3.00)	113 (2.03)	98 (1.76)	1.15 (0.88–1.51)
Hospitalization within 30 days	53 (0.95)	4090 (0.48)	2.00 (1.53–2.62)	52 (0.94)	35 (0.63)	1.49 (0.97–2.28)

NOTE. Categorical data are presented as n (%) and continuous data as indicated.
BMI, body mass index; SD, standard deviation.
[a]The denominator for this analysis excluded patients with history of COVID-19 diagnosis before vaccination: 5300 for patients with IBD and 828,461 for the cohort without IBD in unmatched analysis and 5300 in each group in the matched analysis
[b]Log-rank test $P = .93$.
[c]Log-rank test $P = .59$.
[d]Anaphylactic reaction, shock, or poisoning.
[e]Exact number obfuscated because patient count was <10.
[f]Special adverse events of interest include: acute myocardial infarction, anaphylaxis, facial nerve palsy, coagulopathy, deep vein thrombosis, pulmonary embolism, Guillain-Barré syndrome, transverse myelitis, immune thrombocytopenia, disseminated intravascular coagulation, myocarditis, pericarditis, hemorrhagic stroke, non-hemorrhagic stroke, appendicitis, narcolepsy, and encephalomyelitis.

After the COVID-19 vaccination, 19 patients (0.36%) with IBD were diagnosed with COVID-19 compared with 2277 individuals (0.28%) in the cohort without IBD (RR, 1.3; 95% CI, 0.83–2.05). Kaplan-Maier survival analysis with the log-rank test revealed no difference in new COVID-19 diagnoses between the 2 unmatched and matched cohorts (log-rank test $P = .93$ and $P = .59$, respectively). Of 19 new cases of COVID-19 in the IBD cohort, 14 were diagnosed within 1 month of the first vaccine dose.

After PSM, a matched cohort of 5561 patients without IBD who received the COVID-19 vaccine was identified and compared with the patients with IBD. No residual imbalance in the 2 cohorts was noted (standardized mean difference was <0.1 for all assessed covariates; Table 1). After PSM, there was no significant difference in adverse events of special interest (RR, 1.15; 95% CI, l 0.88–1.51) and a new diagnosis of COVID-19 in the 2 cohorts (RR, 0.95; 95% CI, 0.51–1.78). Also similar in the matched cohorts was 30-day hospitalization (RR, 1.49; 95% CI, 0.97–2.28) after the COVID-19 vaccination (Table 1).

No difference was found in steroid prescription at the 1 month follow-up in vaccinated and unvaccinated patients with IBD in unmatched (6.26% vs 6.92%; RR, 0.90; 95% CI, 0.81–1.01) and PSM analysis (6.26% vs 6.44%; RR, 0.97; 95% CI, 0.84–1.12).

Subgroup analysis revealed no difference in 30-day adverse events of special interest after the COVID-19 vaccination between patients with IBD with and without biologic or immunomodulator use (2.2% vs 1.67%; RR, 1.32; 95% CI, 0.85–2.06) and between patients with CD and UC (2.07% vs 1.98%; RR, 1.04; 95% CI, 0.70–1.54). No difference in steroid use after vaccination was found between patients with and without biologic or immunomodulator use, or both (6.55% vs 5.28%; RR, 1.24; 95% CI, 0.97–1.59) and between patients with CD and UC (6.37% vs 6.16%; RR, 1.03; 95% CI, 0.83–1.29). Among patients on biologics or immunomodulators, or both, $\leq$10 patients were diagnosed with COVID-19 after vaccination.

Discussion

SARS-CoV-2 vaccine development and approval has been completed in a remarkably swift manner, allowing public administration within 1 year. Our data provide the first large analysis of the safety and efficacy of mRNA SARS-CoV-2 vaccines in patients with IBD in the United States. Immediate adverse events after vaccination were rare in both cohorts. The incidence of adverse events of special interest in IBD patients after COVID-19 vaccination was small and similar to a matched cohort of patients without IBD. Furthermore, there was no signal toward increased steroid need in vaccinated patients with IBD compared with unvaccinated patients with IBD. Thus, we conclude that the benefits of COVID-19 vaccination in patients with IBD probably outweigh the minimal risks.

There is some concern that patients with IBD, especially those using immunosuppressive medications, may be at risk of suboptimal vaccine response.[4] We found that the incidence of COVID-19 in patients with IBD after vaccination is very low, including patients on immunosuppressive agents, and is similar to population without IBD. Further studies including a larger cohort with longer follow-up duration are needed.

Our study has several limitations inherent to retrospective studies based on electronic health record data. However, several factors lend strength to our conclusions, including the first large real-world data on IBD patients undergoing vaccinations. Our study findings are reassuring and support the continued use of these vaccines in patients with IBD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2021.06.014.

References

1. Fortner A. Discoveries (Craiova) 2021;9:e122.
2. Centers for Disease Control and Prevention. COVID Data tracker 2021.
3. Polack FP, et al. N Engl J Med 2020;383:2603–2615.
4. Wong S-Y, et al. Gastroenterology. Published online ahead of print, April 20, 2021, doi:10.1053/j.gastro.2021.04.025.
5. Singh S, et al. Risk of severe coronavirus disease 2019 in patients with inflammatory bowel disease in the United States: a multicenter research network study. Gastroenterology 2020;159:1575–1578.e4.
6. Center for Biologics Evaluation and Research. CBER Surveillance Program Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring Protocol January 12, 2021. Accessed April 4, 2021. https://www.bestinitiative.org/wp-content/uploads/2021/02/C19-Vaccine-Safety-AESI-Background-Rate-Protocol-FINAL-2020.pdf.

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provided on the TriNetX cloud-based platform. Codes for creating cohorts of patients are included in the Supplementary Methods.

CRediT Authorship Contributions

Yousaf Bashir Hadi, MD (Formal analysis: Equal; Methodology: Equal; Writing – original draft: Lead; Writing – review & editing: Equal). Shyam Thakkar, MD (Conceptualization: Equal; Formal analysis: Equal; Writing – original draft: Supporting). Sardar Momin Shah-Khan, MD (Formal analysis: Equal; Writing – review & editing: Supporting). William Hutson, MD (Writing – original draft: Supporting; Writing – review & editing: Equal). Arif Sarwari, MD (Writing – original draft: Supporting; Writing – review & editing: Equal). Shailendra Singh, MD (Conceptualization: Equal; Formal analysis: Equal; Methodology: Equal; Supervision: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).

Conflicts of interest

The authors disclose no conflicts.

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Supplementary Methods

Structure of the Research Network and Data Source

TriNetX (Cambridge, MA) is a multi-institutional cloud-based research network. It allows real-time access to deidentified data from participating institutions to end users. Deidentified data on the network are collected and aggregated from participating health care organizations in real time, which can then be analyzed using statistical and analytical tools available on the network.

The TriNetX platform obtains data directly from electronic health records, and these data include demographic characteristics, clinical diagnoses, medical procedures, laboratory investigations available for patients, medications, and other clinical variables, including vital signs and presenting complaints, among others. The platform can also extract facts directly from clinical documents available in electronic health records through its natural language processing system that is then transformed into standard clinical terminologies.

The health care organizations included in the TriNetX platform are mostly large academic health care centers comprising >1 facility and include tertiary care centers and satellite health care clinics. Health Insurance Portability and Accountability Act compliance is ensured by the platform by including deidentified data or a limited data set, depending on the participating health care organizations. TriNetX obfuscates patient ages at >90 years and patient counts at <10 to ensure anonymity.

The Western Institutional Review Board has granted a waiver to TriNetX as a federated network. The West Virginia University Clinical and Translational Science Institute manages the TriNetX platform at West Virginia University.

Patient Selection Criteria and Study Period

Patients were identified up to April 15, 2021. Study analysis was updated through May 31, 2021.

COVID-19 vaccine administration was identified with the following criteria:

Pfizer COVID-19 vaccine:

1. 91300 "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-lipid nanoparticle (LNP), spike protein, preservative free, 30 μg/0.3 mL dosage, diluent reconstituted, for intramuscular use"
2. 0001A "Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 μg/0.3 mL dosage, diluent reconstituted; first dose"
3. 0002A "Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 μg/0.3 mL dosage, diluent reconstituted; second dose"

Moderna COVID-19 vaccine:

1. 91301 "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 μg/0.5 mL dosage, for intramuscular use"
2. 0011A "Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 μg/0.5 mL dosage; first dose"
3. 0012A "Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 μg/0.5 mL

COVID-19 Diagnosis

COVID-19 diagnosis was identified using Centers for Disease Control and Prevention COVID-19 coding guidance. Patients were identified by using International Classification of Diseases (ICD), Ninth Revision (ICD-9) and Tenth Revision, Clinical Modification (ICD-10-CM) codes as well as Logical Observation Identifiers Names and Codes (LOINC) codes for positive results on the laboratory tests discussed below.

1. ICD-10-CM codes U07.1 (COVID-19, virus identified), *or* B34.2 (Coronavirus infection, unspecified), *or* B97.29 (Other coronavirus as the cause of diseases classified elsewhere), *or* J12.81 (Pneumonia due to SARS-associated coronavirus)

Patients were excluded if they had diagnosis code 079.89 (Other specified viral infection). This code is mapped to ICD-10 code B34.2 and B97.2, and it was used to exclude to prevent false positives because it is used as a catch all code, sometimes for many viral infections.

2. The following LOINC codes were also used to identify COVID-19 patients with positive COVID-19 test results.

94533-7: SARS coronavirus 2 N gene [Presence] in Respiratory specimen by nucleic acid amplification (NAA) with probe detection

94534-5: SARS coronavirus 2 RdRp gene [Presence] in Respiratory specimen by NAA with probe detection

41458-1: SARS coronavirus RNA [Presence] in Unspecified specimen by NAA with probe detection

94309-2: SARS coronavirus 2 RNA [Presence] in Unspecified specimen by NAA with probe detection

94531-1: SARS coronavirus 2 RNA panel-Respiratory specimen by NAA with probe detection

94506-3: SARS coronavirus 2 IgM antibody [units/volume] in Serum or Plasma by Immunoassay

94500-6: SARS coronavirus 2 RNA [Presence] in Respiratory specimen by NAA with probe detection

94315-9: SARS coronavirus 2 E gene [Presence] in Unspecified specimen by NAA with probe detection

94316-7: SARS-CoV-2 (COVID19) N gene [Presence] in Unspecified specimen by NAA with probe detection

94502-2: SARS-related coronavirus RNA [Presence] in Respiratory specimen by NAA with probe detection

3. The patient identification period was limited from January 20, 2020, to August 20, 2020. January 20 was chosen because it was the date of diagnosis of the first case of COVD-19 in the US. August 20 was chosen so that all patients had 1 month of follow-up available, because the primary study end point was a composite outcome at 30 days from diagnosis. The study search was updated on September 20, 2020.
4. Patients aged ≥16 years at the index event were included.

Case Definition of Patients With Inflammatory Bowel Disease/Selection Criteria

Patients with IBD were identified using the ICD-9 and ICD-10-CM codes. Patients were included if they had encounters with a diagnosis of UC or CD and were on an IBD-specific medication. Identification criteria were based on study by Kappelman et al.[1]

K50.90: Crohn's disease *or* K51.90: Ulcerative colitis, in conjunction with 1 of the following medication use history:

Biologics: RxNorm Codes

Certolizumab: 709271
Ustekinumab: 847083
Infliximab: 191831
Adalimumab: 327361
Vedolizumab: 1538097
Tofacitinib: 1357536

Immnunomodulators: RxNorm Codes

Methotrexate: 6851
Azathioprine: 1256
Mercaptopurine: 103
Mycophenolic acid: 7145
Mycophenolate mofetil: 68149

Other Agents

Mesalamine: 52582
Sulfasalazine: 9524
Balsalazide: 18747
Budesonide, oral

Unvaccinated Inflammatory Bowel Disease Control

An unvaccinated control group with IBD was identified using the same IBD case definition stated above. Patients were included if they did not have an associated COVID-19 vaccination code and had a health care visit within the study duration (December 1, 2020, to April 15, 2021), which was then taken as index event for this group.

Index Event

Administration of first dose of COVID-19 vaccine according to the criteria defined above was considered the index event for the purposes of our study.

Outcomes

Immediate Adverse Effects After Vaccination. Immediate adverse effects of vaccination were considered up to 1 day after administration of any dose of COVID-19 vaccine.

Anaphylactic shock unspecified	T78.2
Anaphylactic reaction due to vaccination	T80.52
Poisoning by, adverse effects of, and underdosing of drugs, medications, and biological substances	T36-T50

Adverse Effects of Special Interest. Adverse effects of special interest were considered up to 30 days after administration of any dose of COVID-19 vaccine.

Acute myocardial infarction	I21
Anaphylaxis	T78.2 T80.52
Facial nerve palsy	G51
Coagulopathy (deep vein thrombosis, pulmonary embolism)	I82.4 I26
Guillain-Barré syndrome	G61.0
Transverse myelitis	G37.3
Immune thrombocytopenia	D69.59
Disseminated intravascular coagulation	D65
Myocarditis	I51.4
Pericarditis	I30
Hemorrhagic stroke	I60 I61 I62
Non hemorrhagic stroke	I63
Appendicitis	K35 K36 K37
Narcolepsy	G47.41
Encephalomyelitis	G04

Efficacy of COVID-19 Vaccination

Efficacy was assessed by comparing the rates of a new COVID-19 diagnosis any time after receiving the first dose of the COVID-19 vaccination. This analysis excluded patients with a COVID-19 diagnosis on the day of vaccination or before vaccination.

Statistical Analysis

Groups with and without IBD were compared using PSM analysis. One-to-one matching was performed based on age, sex, ethnicity, body mass index, and comorbidities, including hypertension, diabetes, chronic lower respiratory diseases, chronic kidney disease, and ischemic heart disease. Propensity scores were generated using greedy nearest-neighbor algorithms with a caliper width of 0.1 pooled standard deviation. Balance on covariates was assessed using the standardized mean difference, and absolute values >0.1 were considered indicative of residual imbalance. A 2-sided α of $<.05$ was defined a priori for statistical significance. TriNetX obfuscates patient counts when the aggregate count is ≤ 10 to safeguard protected health information.

Sensitivity Analysis

A sensitivity analysis was performed with 1:1 PSM of only those patients with health care visits ≥ 1 month after the vaccine administration to ensure more robust capture of follow-up data/adverse events, among others, and to control/adjust for follow-up. No difference in statistical significance was noted as shown in results of this analysis below.

One-to-one matching performed with the covariates described above resulted in 3438 patients with IBD matched to 3438 patients without IBD. The standardized mean difference after matching in all covariates was <0.05, signifying no residual imbalance. No difference in adverse events of special interest (4.45% vs 4.01%; RR, 1.11; 95% CI, 0.89–1.34) or a new COVID-19 diagnosis (0.44% vs 0.69%; RR, 0.63; 95% CI, 0.33–1.20) was noted. Adverse events developed in <10 patients in each group.

References

1. Kappelman MD, et al. Dig Dis Sci 2013;58:519–525.