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Effect of 2 vs 3 Doses of COVID-19 Vaccine in Patients With Inflammatory Bowel Disease: A Population-based Propensity Matched Analysis

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Aim: There are limited data on the impact of 2 vs 3 doses of COVID-19 vaccine in patients with inflammatory bowel disease (IBD). The primary aim of the study was to assess the efficacy of COVID-19 vaccine based on number of administered doses in patients with IBD.

Methods: We conducted a retrospective cohort study using TriNetX, a multi-institutional database to compare patients with IBD who received 1, 2, or 3 doses of BNT162b2 or mRNA-1273 to unvaccinated IBD patients (1.1.2020-7.26.2022) to assess the risk of COVID-19 after 1:1 propensity score matching. We also evaluated the impact of vaccine on a composite of severe COVID-19 outcomes including hospitalization, intubation, intensive care unit care, acute kidney injury, or mortality.

Results: After propensity score matching, vaccinated patients with 2 (adjusted OR [aOR], 0.8; 95% confidence interval [CI], 0.6-0.9) and 3 doses (aOR, 0.7; 95% CI, 0.5-0.9) were found to have a lower risk of COVID-19 compared with unvaccinated patients. Vaccinated patients with IBD had a lower risk of severe COVID-19 outcomes (aOR, 0.7; 95% CI, 0.6-0.9) compared with unvaccinated patients. There was no difference in the risk of COVID-19 in IBD patients with 2 compared with 3 doses (aOR, 0.97; 95% CI, 0.7-1.3). However, IBD patients with 2 doses were at an increased risk for hospitalization due to COVID-19 (aOR, 1.78; 95% CI, 1.02-3.11) compared with those that received 3 doses.

Conclusion: Vaccinated patients with IBD had a lower risk of severe COVID-19 outcomes compared with unvaccinated patients. A third dose of COVID-19 vaccine compared with 2 doses decreases the risk of hospitalization but not breakthrough infection in patients with IBD.

Key Words: inflammatory bowel disease, COVID-19, covid vaccine

Background

Coronavirus disease-2019 (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has impacted the management of patients with inflammatory bowel disease (IBD). There are currently 3 vaccines against SARS-CoV-2 that have been approved in the United States by the Food and Drug Administration (FDA), 2 messenger RNA (mRNA)-based vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna); and the Ad.26.COV2 (Johnson and Johnson) COVID-19 vaccine.[1–3] The primary series of BNT162b2 and MRNA-1273 vaccines require receipt of 2 doses compared with 1 dose of Janssen vaccine. A booster dose was originally recommended 5 months after completing the primary series for BNT162b2 and mRNA-1273 vaccines and 2 months after Ad.26.COV2.[4–6] However, most at-risk individuals, such as those who are immunocompromised, were initially excluded from the pivotal vaccine trials and have thus been understudied. Recent governmental recommendations include consideration of an additional primary shot 28 days after the second dose of mRNA vaccines in those who are moderately to severely immunosuppressed and then a booster dose at least 3 months after additional primary shot for mRNA vaccines.[7]

Multiple studies have shown the safety of vaccines against SARS-CoV-2 in patients with IBD, including those on immunosuppressive therapy.[8–11] Hadi et al showed low incidence of COVID-19 in patients with IBD after vaccination.[10] A study conducted by Lev-Tzion et al using an Israeli administrative database found comparable effectiveness of COVID-19 vaccine in patients with IBD compared with non-IBD patients, up until June 2021.[11] Overall, prospective studies and meta-analyses on the seroconversion after these vaccines

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Key Messages

What is already known?

- COVID-19 vaccine is safe in patients with inflammatory bowel disease including those on immunosuppressive therapy.

What is new here?

- Decreased risk of COVID-19 in patients with IBD who received 2 or 3 doses of the COVID-19 vaccine (BNT162b2 and mRNA-1273).
- Decreased risk of adverse events after COVID-19 compared with unvaccinated patients
- Patients who received 2 doses of COVID-19 vaccine had an increased risk of hospitalization compared with patients who received 3 doses.

How can this study help patient care?

- Our study provides more data on the efficacy of 2 and 3 doses of COVID-19 vaccine in patients with IBD

in patients with IBD have been reassuring.[12–15] However, the magnitude of these antibody responses has been shown to be significantly lower in patients who are on tumor necrosis factor-α inhibitors (TNFi), especially against the B.1.617.2 Delta virus, which may indicate reduced duration of effect and neutralizing activity resulting in reduced infection protection.[16,17] Reassuringly, patients on TNFi who were administered a third mRNA vaccine dose increased their serum neutralizing antibody titers by more than 16-fold.[17] Prior studies mostly predated the emergence of the newest variant of concern, Omicron. There are limited data on the impact of booster doses against SARS-CoV-2 infection in patients with IBD and outcomes of breakthrough COVID-19 after vaccination. There were no data available on the efficacy of booster doses in patients on immunosuppressive medications until a recent retrospective cohort study that found that patients who received 3 doses of either BNT162b2 or mRNA-1273 had a vaccine effectiveness of 87% against hospitalization due to COVID-19.[18]

In this propensity-matched US-based cohort study, our aim was to study the effectiveness of booster doses of COVID-19 vaccines in preventing COVID-19 and assess adverse events related COVID-19 in vaccinated IBD patients.

Methods

Database

A retrospective cohort study was performed using the TriNetX (Cambridge, USA), a multi-institutional database that provides real-time access to de-identified electronic health records (EHRs) of more than 85 million patients within 52 health care organizations (HCOs) in the United States. The de-identification process is determined and performed at a network-level, in addition to being certified through a formal determination by a qualified expert, as defined in the HIPAA Privacy Rule. Robust quality assurance is achieved at the time of extraction of clinical variables from EHRs before inclusion in the database in a systematic and standardized format. The interface provides aggregate counts and statistical summaries to protect patient health information and ensures that the data remain de-identified at all levels of data retrieval and dissemination.[4,19]

Study Cohorts

We utilized the US Collaborative Network in the TriNetX platform from January 1, 2020, to July 26, 2022. There were approximately 75 million patients from 47 HCOs during the study period. TriNetX captures data on COVID-19, their pre-existing risk factors, treatments, and outcomes. We identified patients who had received a COVID-19 vaccine using Current Procedural Terminology (CPT) relevant codes (Supplement Table 1). We identified patients with IBD using the International Classification of Disease, Ninth and Tenth Revision, Clinical Modification (ICD-10-CM) codes for ulcerative colitis (K51.*) OR Crohn's disease (K50.*), plus Rxnorm codes for any one of the following IBD medications: mesalamine, TNFi, vedolizumab, ustekinumab, tofacitinib, azathioprine, mercaptopurine, methotrexate, prednisone, or budesonide (Supplement Table 1).

Inclusion criteria for the vaccinated cohort were adults 18 years and older with a diagnosis code for either ulcerative colitis (UC) or Crohn's disease (CD) before January 2021 who received any COVID-19 vaccine. The vaccinated cohort was further subdivided into patients who had received 1, 2, or 3 doses. We only included patients who had CPT codes for BNT162b2 (0002A) or mRNA-1273 (0012A), as only these vaccines have distinctions available for 1, 2, or 3 doses in the TriNetX platform (Figure 1). We excluded patients with a CPT code for Ad.26.COV2 (0031A) vaccine, as the cohort had a small sample size and did not have information on the number of vaccine doses. Only vaccine doses administered up until 3 months prior to the end of the study period were included to analyze the risk of COVID-19 between cohorts to allow for a minimum of a 3 month follow-up. Inclusion criteria for the unvaccinated IBD cohort was similar, except all CPT codes related to COVID-19 vaccines, including the CPT code for Ad.26.COV2 (0031A), were excluded. A vaccinated non-IBD control cohort included patients who had CPT codes for BNT162b2 or MRNA-1273 and excluded patients who had immune-mediated inflammatory diseases (IMIDs): UC, CD, rheumatoid arthritis, psoriasis, and ankylosing spondylitis. The vaccinated non-IBD control cohort was further subdivided into patients who had received 1, 2 or 3 doses.

Study Outcomes

Primary outcome

The primary outcome was the risk of COVID-19 after 1, 2, or 3 doses of COVID-19 vaccine IBD patients compared with unvaccinated patients with IBD and the non-IBD control cohort.

The diagnosis of COVID-19 was made using criteria provided by TriNetX based on Centers of Disease Control and Prevention (CDC) coding guidelines.[20] Patients with COVID-19 were identified using either an ICD-10-CM code for COVID-19 (U07.1) or a Logical Observation Identifiers Names and Codes (LOINCs) for a positive SARS coronavirus 2 and related RNA test (TNX:LAB:9088). TriNetX allows defining index events and excluding patients with outcomes prior to the index event. This functionality allowed us to identify patients who had SARS-CoV-2 infection after the COVID vaccine. Risk of COVID-19 was also compared based on IBD medications in vaccinated patients who received 2 doses and 3 doses of COVID-19 vaccine. Risk was compared between

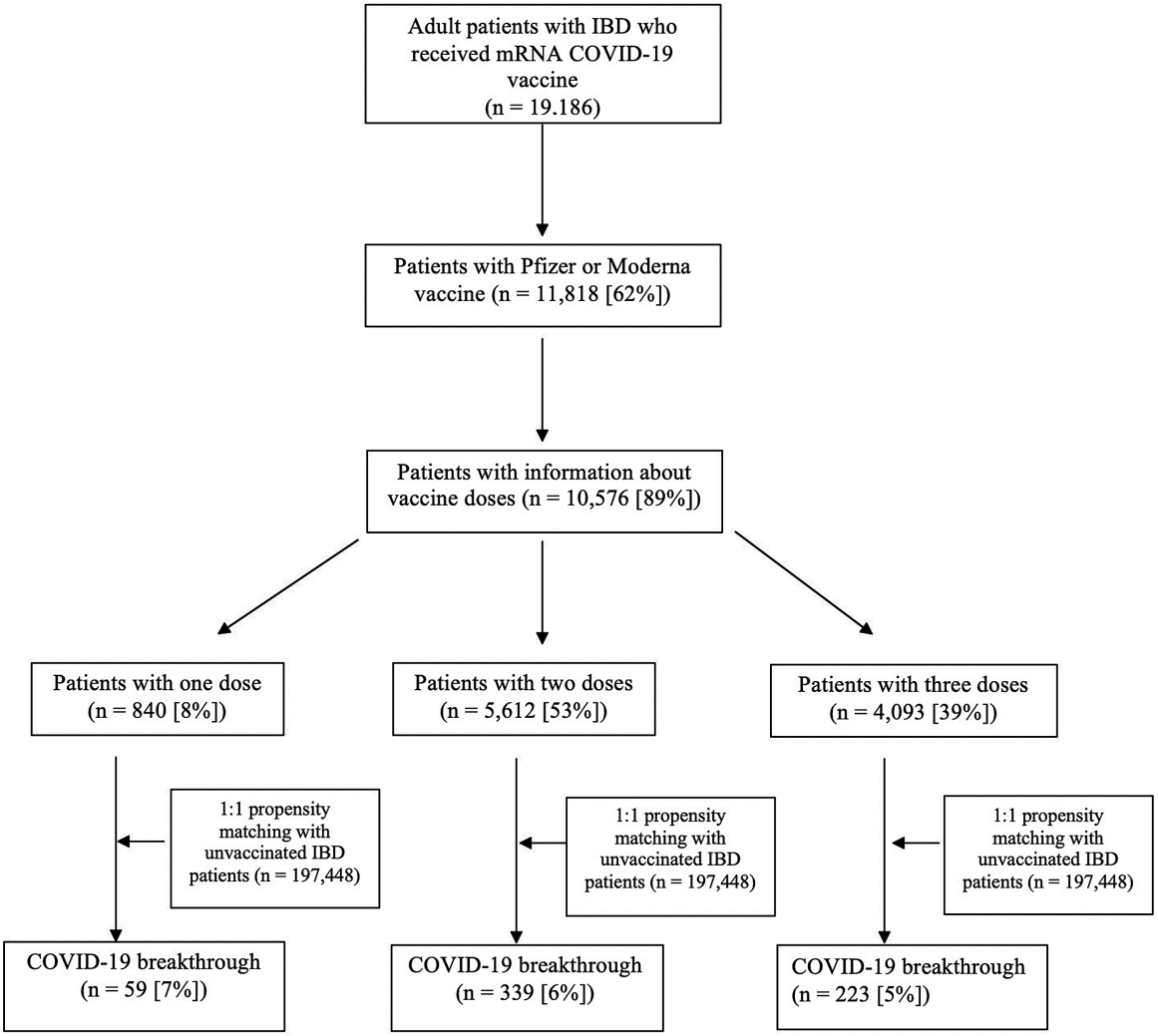

Figure 1. Flowchart of patient identification in the database.

patients on TNFi vs mesalamine cohorts and between TNFi vs non-TNFi cohorts. The non-TNFi cohort included patients on azathioprine, 6-mercaptopurine, methotrexate, vedolizumab, ustekinumab, and tofacitinib.

The secondary outcome was a composite of any adverse event due to COVID-19 infection in vaccinated patients with IBD compared with unvaccinated IBD patients. Adverse events included 30-day risk of hospitalization, endotracheal intubation, intensive care unit care, acute kidney injury (AKI), renal replacement therapy (RRT), and mortality after COVID-19. Patients requiring hospitalization were identified using the CPT code "Hospital Inpatient Services" (1013659). Patients who were deceased were identified on the basis of their vital status "Deceased" from the database. This is regularly imported from the Social Security Death index.[21] Endotracheal intubation was identified based on CPT code 31500 "Intubation, endotracheal, emergency procedure" or mechanical ventilation CPT code 5A09. Intensive care unit care was identified using CPT code 1013729 "Critical Care Services." Acute kidney injury was identified using diagnosis code "Acute kidney failure" (N17), and patients who required RRT were identified by the CPT code 1012740 "Dialysis Services and Procedures."

Statistical Analysis

We conducted all statistical analysis using the TriNetX software using the browser-based real-time analytics feature, TriNetx Live (TriNetX LLC, Cambridge, MA). One-to-one (1:1) propensity score matching was performed for age, sex, ethnicity, race, IBD subtype, obesity, diabetes mellitus, tobacco abuse, and all IBD medications between the vaccinated and unvaccinated IBD cohorts. In the IBD medication analysis, patients were matched for age, sex, ethnicity, race, obesity, diabetes mellitus, and tobacco abuse. TriNetX platform utilizes input matrices of the user-identified covariates to conduct logistic regression analysis to obtain propensity scores for all individual subjects. TriNetX randomizes the order of rows to eliminate bias resulting from nearest-neighbor algorithms. After propensity matching, the risk of each outcome was calculated and expressed as adjusted odds ratios (aORs) with 95% confidence intervals (CIs).

Results

Characteristics of Study Population

We identified 10 576 patients with IBD who received COVID-19 vaccine (BNT162b2 80.6%, mRNA-1273 19.4%). Of

those patients, 840 (7.9%) received 1 dose; 5612 (53%) received 2 doses; and 4093 (38.8%) received 3 doses. There were 197 448 patients with IBD who did not receive a COVID-19 vaccine. Vaccinated patients with IBD were older (mean age 57.6 +/- 17.7 years) compared with unvaccinated patients with IBD (mean age 53.2 +/- 18.9 years). Vaccinated IBD patients were predominately Caucasian (79%), with a female predominance (58%). Vaccinated IBD patients had more comorbid conditions as outlined in Table 1. Vaccinated IBD patients were also more likely to be on biologic medications compared with unvaccinated patients during the time frame of the study. There were 1 151 287 patients in the control cohort who received a COVID-19 vaccine. In all, 132 291 (12%) patients received 1 dose, 750 365 (65%) patients received 2 doses, and 268 631 (23%) received 3 doses of COVID-19 vaccine.

Risk of COVID-19 Based on Number of Vaccine Doses

The risk of COVID-19 in vaccinated IBD patients with a single dose was not statistically different compared with unvaccinated IBD patients (OR, 1.2; 95% CI, 0.9-1.7). This was unchanged after propensity score matching (aOR, 1.1; 95% CI, 0.7-1.7). Vaccinated IBD patients with 2 doses did not have a significant difference in the risk of COVID-19 compared with unvaccinated IBD patients in crude/unmatched analysis (OR, 0.9; 95% CI, 0.8-1.1). However, after propensity score matching, IBD patients with 2 doses were found to have a lower risk of COVID-19 (aOR, 0.8; 95% CI, 0.6-0.9). Vaccinated IBD patients with 3 doses did not have a lower risk of COVID-19 in unmatched analysis (OR, 0.9; 95% CI, 0.7-1.1). However, after matched analysis, the risk of COVID-19 was lower (aOR, 0.7; 95% CI, 0.5-0.9) compared with unvaccinated IBD patients. Subgroup analysis based on IBD subtype did not reveal a difference in the risk of COVID-19 (Table 2). The risk of COVID-19 in vaccinated patients with IBD with 2 doses was not statistically different compared with 3 doses in unmatched (OR, 0.96; 95% CI, 0.8–1.2) and matched analysis (aOR, 0.97; 95% CI, 0.7–1.3; Table 3). After propensity score matching, vaccinated patients with IBD who received 1 dose (aOR, 2.2; 95% CI, 1.2-3.9), 2 doses (aOR, 2.2; 95% CI, 1.7-2.9), or 3 doses (aOR, 1.9; 95% CI, 1.1-3.2) had an increased risk of COVID-19 compared with the control cohort of vaccinated individuals without IMIDs who received 1, 2, or 3 doses, respectively (Table 4).

There were 739 patients on a TNFi, of whom 459 patients received 2 doses and 280 patients received 3 doses. There were 1777 patients on mesalamine, of whom 1171 patients received 2 doses and 606 patients received 3 doses. There were 1171 patients in the non-TNFi cohort, of whom 710

Table 1. Comparison of characteristics of patients with IBD who received a dose of m-RNA vaccine and unvaccinated patients with IBD.

Demographics	Vaccinated (N = 10576)	Unvaccinated (N = 197 448)	*P*	Standard Difference
Age in years, mean (±SD)	57.6 +/- 17.7	53.2 +/- 18.9	< .0001	0.23
Gender				
Female, *n* (%)	6101 (58)	108 880 (55)	< .0001	0.05
Ethnicity, *n* (%)				
Hispanic or Latino	502 (5)	6472 (3)	< .0001	0.07
Non-Hispanic or Latino	9060 (86)	151 015 (76%)	< .0001	0.23
Race, *n* (%)				
Caucasian	8400 (79)	153 756 (78)	.0002	0.03
African American	1350 (13)	19 445 (10)	< .0001	0.09
Co-morbid conditions, *n* (%)				
Hypertension	5757 (54)	76 738 (39)	< .0001	0.31
Hyperlipidemia	5444 (51)	61 411 (31)	< .0001	0.42
Diabetes mellitus	2602 (25)	33 804 (17)	< .0001	0.18
Obesity	3272 (31)	40 177 (20)	< .0001	0.24
Nicotine dependence	1889 (18)	33 528 (17)	.01	0.02
Chronic kidney disease	1801 (17)	23 884 (12)	< .0001	0.14
Ischemic heart disease	2414 (23)	30 757 (16)	< .0001	0.18
Chronic lower respiratory disease	3768 (36)	52 943 (27)	< .0001	0.19
IBD medications, *n* (%)[a]				
TNFi	3986 (37.6)	67 905 (34.3)	< .0001	0.004
Vedolizumab	1163 (11)	12 755 (6)	< .0001	0.16
Ustekinumab	981 (9)	11 422 (6)	< .0001	0.13
Tofacitinib	256 (2)	2106 (1)	< .0001	0.11
Immunomodulator	3532 (33.3)	61 968 (31.3)	< .0001	0.01
Mesalamine	5402 (51)	105 762 (53.5)	< .0001	0.02

[a]Patients could be on more than 1 medication or switched to a different medication in the period prior to receiving the COVID vaccine.

Table 2. Risk of COVID-19 in vaccinated patients with IBD based on number of m-RNA vaccine doses compared with unvaccinated patients with IBD before and after propensity score matching.

	Before propensity score matching		After propensity score matching	
Cohort	Outcome n (%)	OR (95% CI)	Outcome n (%)	OR (95% CI)
1 dose				
IBD	43 (6.66%)	1.23 (0.90-1.67)	41 (6.72%)	1.09 (0.69-1.71)
UC	28 (7.69%)	1.33 (0.90-1.96)	27 (7.6%)	0.73 (0.43-1.22)
CD	25 (6.56%)	1.23 (0.81-1.84)	20 (6.64%)	1.17 (0.61-2.24)
2 doses				
IBD	199 (5.07%)	0.92 (0.79-1.06)	180 (5.02%)	0.77 (0.63-0.94)
UC	118 (5.01%)	0.84 (0.70-1.02)	117 (5.02%)	0.84 (0.65-1.08)
CD	111 (5.31%)	0.98 (0.81-1.19)	75 (5.12%)	0.67 (0.50-0.91)
3 doses				
IBD	108 (4.92%)	0.89 (0.73-1.08)	99 (5%)	0.70 (0.54-0.91)
UC	61 (4.57%)	0.76 (0.59-0.99)	60 (4.59%)	0.66 (0.47-0.92)
CD	61 (5.16%)	0.95 (0.73-1.23)	59 (5.15%)	0.67 (0.48-0.94)

Table 3. Risk of COVID-19 in vaccinated patients with IBD with 2 compared with 3 doses of m-RNA vaccine before and after propensity score matching.

		Before propensity score matching		After propensity score matching	
Outcome		n (%)	OR (95%)	n (%)	OR (95% CI)
IBD	2 doses	108 (4.92%)	0.96 (0.76-1.23)	107 (4.94%)	0.97 (0.74-1.27)
	3 doses	199 (5.07%)		113 (5.08%)	
UC	2 doses	61 (4.57%)	0.90 (0.66-1.24)	60 (4.57%)	1.01 (0.70-1.46)
	3 doses	118 (5.01%)		60 (4.50%)	
CD	2 doses	61 (5.16%)	0.97 (0.70-1.33)	58 (5.04%)	0.98 (0.67-1.42)
	3 doses	111 (5.31%)		61 (5.13%)	

Table 4. Risk of COVID-19 in vaccinated patients with IBD based on number of m-RNA vaccine doses compared with vaccinated patients without IBD before and after propensity score matching.

		Before propensity matching		After propensity matching	
Vaccine dose	Cohort	n (%)	OR (95% CI)	n (%)	OR (95% CI)
1 dose	IBD	35 (5.72%)	2.36 (1.70-3.26)	35 (5.72%)	2.15 (1.19-3.89
	Control	3018 (2.42%)		17 (2.74%)	
2 doses	IBD	177 (4.54%)	2.28 (1.97-2.63)	161 (4.07%)	2.19 (1.67-2.88)
	Control	14 110 (1.99%)		74 (1.85%)	
3 doses	IBD	61 (3.81%)	1.75 (1.36-2.24)	37 (2.45%)	1.86 (1.08-3.19)
	Control	3019 (2.17%)		20 (1.31%)	

received 2 doses and 461 received 3 doses. There was also no difference in the risk of COVID-19 between patients on TNFi and non-TNFi after 2 (aOR, 0.8; 95% CI, 0.4-1.8) and 3 doses (aOR, 0.7; 95% CI, 0.3-1.5) of vaccine in propensity-matched analysis (Table 5). There was no difference in the risk of COVID-19 between patients on TNFi and mesalamine after 2 (aOR, 1.1; 95% CI, 0.5–2.4) or 3 doses (aOR, 0.9; 95% CI, 0.4–2.0) of vaccine in propensity-matched analysis.

Outcomes of COVID-19 After Vaccine

There was no difference in the risk of adverse events in terms of composite outcomes between vaccinated and unvaccinated patients with IBD in unmatched/crude analysis (OR, 0.9; 95% CI, 0.7-1.0). After propensity score matching, risk of composite outcomes was lower in vaccinated patients with IBD (aOR, 0.7; 95% CI, 0.6-0.9). Analysis of individual outcomes showed that the risk of hospitalization (aOR, 0.7; 95% CI, 0.5-0.9), intubation (aOR, 0.5; 95% CI, 0.3-0.8), mortality (aOR, 0.5; 95% CI, 0.3-0.8), critical care (aOR, 0.5; 95% CI, 0.3-0.9), and AKI (aOR, 0.5; 95% CI, 0.3-0.8) was lower in vaccinated patients with IBD compared with unvaccinated patients after propensity score matching (Table 6). There was no difference in the risk of RRT (aOR, 1.0; 95% CI, 0.4-2.4) in vaccinated and unvaccinated patients with IBD after matched analysis.

Table 5. Risk of COVID-19 in patients with IBD on TNFi compared with patients on mesalamine and non-TNFi based on number of m-RNA vaccine doses.

		Before propensity score matching		After propensity score matching	
Outcome		*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Total	TNFi	34 (4.7%)	1.14 (0.75-1.73)	33 (4.9%)	1.16 (0.69-1.95)
	Mesalamine	72 (4.1%)		28 (4.2%)	
2 doses	TNFi	17 (3.8%)	0.94 (0.53-1.67)	15 (3.6%)	1.13 (0.53-2.41)
	Mesalamine	45 (4.0%)		13 (3.2%)	
3 doses	TNFi	11 (4.2%)	1.28 (0.60-2.74)	10 (4.3%)	0.85 (0.36-2.01)
	Mesalamine	19 (3.3%)		12 (5.1%)	
Total	TNFi	34 (4.7%)	0.79 (0.52-1.21)	29 (4.3%)	0.68 (0.42-1.12)
	Non-TNFi	66 (5.8%)		41 (6.2%)	
2 doses	TNFi	17 (3.8%)	0.65 (0.36-1.16)	14 (3.4%)	0.84 (0.40-1.75)
	Non-TNFi	39 (5.8%)		16 (4.05%)	
3 doses	TNFi	11 (4.2%)	0.91 (0.43-1.95)	10 (4.2%)	0.66 (0.29-1.50)
	Non-TNFi	20 (4.6%)		15 (6.2%)	

Table 6. Outcomes of COVID-19 in vaccinated patients with IBD compared with unvaccinated patients with IBD before and after propensity score matching.

		Before propensity score matching		After propensity score matching	
Outcome		*n* (%)	OR (95%)	*n* (%)	OR (95% CI)
Composite outcome	Vaccinated	159 (13.71%)	0.87 (0.73-1.04)	159 (13.73%)	0.72 (0.57-0.90)
	Unvaccinated	7742 (15.38%)		209 (18.048%)	
Hospitalization	Vaccinated	105 (9.06%)	0.80 (0.64-0.99)	105 (9.06%)	0.67 (0.51-0.87)
	Unvaccinated	854 (11.03%)		149 (12.86%)	
Mortality	Vaccinated	23 (1.98%)	0.74 (0.48-1.15)	23 (1.98%)	0.47 (0.28-0.79)
	Unvaccinated	204 (2.63%)		47 (4.05%)	
Intubation	Vaccinated	16 (1.38%)	0.59 (0.35-0.99)	16 (1.38%)	0.46 (0.25-0.84)
	Unvaccinated	178 (2.29%)		34 (2.93%)	
Critical care	Vaccinated	26 (2.24%)	0.68 (0.45-1.03)	26 (2.24%)	0.53 (0.32-0.86)
	Unvaccinated	250 (3.22%)		48 (4.14%)	
AKI	Vaccinated	19 (2.14%)	0.68 (0.42-1.09)	19 (2.14%)	0.45 (0.26-0.78)
	Unvaccinated	204 (3.11%)		43 (4.59%)	
RRT	Vaccinated	10 (0.87%)	3.56 (1.65-7.69)	10 (0.88%)	1.007 (0.41-2.42)
	Unvaccinated	19 (0.24%)		10 (0.87%)	

There was no difference in the risk of hospitalization between vaccinated patients with IBD who had COVID-19 after receiving 2 compared with 3 doses of vaccine in unmatched/crude analysis (OR, 1.1; 95% CI, 0.69-1.95). After propensity score matching, IBD patients with 2 doses who had COVID-19 were at an increased risk for hospitalization (aOR, 1.78; 95% CI, 1.02-3.11) compared with 3 doses. There was no difference in the risk of critical care, intubation, mortality, AKI, or RRT between patients with IBD who received 2 doses compared with 3 doses after propensity score matching (Table 7).

Discussion

We utilized a large, propensity-matched, US-based multi-institutional cohort to examine the effectiveness of booster doses of COVID-19 vaccines and adverse events after breakthrough COVID-19 infection in IBD patients. Patients with IBD who were administered 2 or 3 doses of vaccine had a decreased risk for clinical infection compared with unvaccinated patients. Our data suggests a booster dose of vaccine decreases the need for hospitalization after COVID-19 during a minimum follow-up of 3 months compared with patients who completed the primary series of vaccine. In our vaccinated cohort which included patients predominantly with 2 or 3 doses (roughly 90%), vaccinated IBD patients who had COVID-19 were less likely to develop adverse outcomes compared with unvaccinated patients. Patients with IBD on TNFi who were administered 2 or 3 doses of vaccine were protected against COVID-19 with no difference in risk observed in our study when compared with other IBD medications.

The IBD patients who received only a single dose of mRNA vaccine had similar risk of COVID-19 compared with unvaccinated IBD patients. This could be due to impaired antibody responses to a single mRNA vaccine dose as part of the disease

Table 7. Outcomes of COVID-19 in vaccinated patients with IBD with 2 doses compared with 3 doses of m-RNA vaccine compared before and after propensity score matching.

		Before propensity score matching		After propensity score matching	
Outcome		***n*** **(%)**	**OR (95%)**	***n*** **(%)**	**OR (95% CI)**
Composite outcome	2 doses	11 (3.1)	0.73 (0.30-1.76)	10 (4.6)	0.99 (0.40-2.43)
	3 doses	10 (4.2)		10 (4.6)	
Hospitalization	2 doses	44 (12.5)	1.1 (0.69-1.95)	38 (17.3)	1.78 (1.02-3.11)
	3 doses	26 (10.8)		23 (10.5)	
Mortality	2 doses	10 (2.8)	0.67 (0.27-1.63)	10 (4.5)	1 (0.40-2.45)
	3 doses	10 (4.1)		10 (4.5)	
Intubation	2 doses	11 (3.1)	0.73 (0.30-1.76)	10 (4.5)	1 (0.40-2.45)
	3 doses	10 (4.1)		10 (4.5)	
Critical care	2 doses	15 (4.2)	1.01 (0.45-2.3)	11 (5)	1.1 (0.46-2.65)
	3 doses	10 (4.1)		10 (4.5)	
AKI	2 doses	10 (3.7)	0.65 (0.26-1.60)	10 (6.1)	0.98 (0.39-2.42)
	3 doses	10 (5.6)		10 (6.2)	
RRT	2 doses	10 (2.9)	N/A	10 (4.6)	N/A
	3 doses	0		0	

itself or the impact of immunosuppressive medications. A recent prospective study by Caldera et al found lower antibody concentrations in patients with IBD after completion of mRNA-based vaccines compared with healthy controls. Additionally, they found lower antibody concentrations in patients on immune-modifying therapies compared with patients on no treatment, aminosalicylates, or vedolizumab.[22] The CLARITY study showed lower rates of seroconversion after a single dose of BNT162b2 vaccine in IBD patients on infliximab compared with vedolizumab.[14]

Inflammatory bowel disease patients who were administered 2 or 3 doses of vaccine were found to have a decreased risk of COVID-19 compared with those with IBD who were not vaccinated. Findings were also noted to be similar after dividing patients based on IBD subtype. Patients who completed the primary vaccine series had similar risk of COVID-19 compared with patients who received 3 doses. These findings are similar to a recent study of mRNA-based vaccines published from Ontario, Canada, where the vaccine effectiveness in IBD patients was similar after 2 (79%; 95% CI, 74%-82%) or 3 (76%; 95% CI, 47%-89%) doses.[23] Vaccinated patients with IBD (including those not on medications) were still at an increased risk for COVID-19 compared with non-IBD control population. Multiple studies have shown reduced immune responses following vaccination in IBD patients compared with the general population.[12,14,15] However, our findings are different from those reported by Lev-Tzion et al who found similar infection rates in vaccinated IBD patients with 2 doses compared with matched non-IBD controls.[11] However, this study did not include a minimum follow-up period for all patients and predated the Delta and Omicron variants.

A lower serologic response has been noted in patients on TNFi following 2 doses of the BNT162b2 vaccine; however, a significant increase in antibody titers were noted after a third dose.[17] Our study, which had a larger proportion of patients who received the BNT162b2 vaccine, showed no difference in the risk of clinical infection in IBD patients on TNFi compared with mesalamine and other biologic and immunosuppressive medications after 2 doses of vaccine. These findings are similar to an Israeli study that also addressed real-world efficacy of COVID-19 vaccines and also did not show an increased incidence of COVID-19 in vaccinated IBD patients on TNFi.[11] Our findings are different from the recent results from CLARITY-IBD, where a weakened serological response was noted after 3 doses of mRNA vaccine and a higher risk of SARS-CoV-2 breakthrough infection and reinfection in IBD patients on infliximab compared with those on vedolizumab.[24] A possible explanation for this is that our cohort received all 3 doses as m-RNA-based vaccine, whereas 58% of patients in CLARITY-IBD received a 3rd dose of m-RNA after the initial 2 doses of ChAdOx1 nCoV-19. Additional differences could be related to case-findings methods for identifying breakthrough infections after vaccination between the 2 studies.

Our study also reports novel findings on adverse events related to COVID-19 after breakthrough infections in IBD patients, including after booster doses of mRNA vaccines. We found decreased risk of all studied outcomes except RRT after COVID-19 in vaccinated IBD patients compared with unvaccinated patients. In subgroup analysis based on number of vaccine doses, we found an increased risk of hospitalization in IBD patients who were administered 2 doses compared with 3 doses. The Omicron variant, which emerged in late 2021 and early 2022, has shown high transmissibility; and partial vaccine escape could have affected the rate of hospitalization in IBD patients who were administered only 2 doses of vaccine. There was no added benefit of a third dose compared with 2 doses in decreasing other severe outcomes related to COVID-19. This finding is limited by the small sample sizes of patients that required hospitalization. We also could not assess outcomes based on IBD medications; however, all patients were matched 1:1 with the unvaccinated cohort for all biologic medications and immunomodulators. Further studies are required to assess the impact of the Omicron variant on IBD patients after a booster dose.

Our study has several notable strengths. Using EHR data from TriNetX, we were able to show the burden of COVID-19 on health care systems in vaccinated patients with IBD

who received booster doses. We utilized a large population-based prospectively maintained database, which allowed for propensity score matching to reduce confounding variables despite the retrospective nature of the database. Clinical data from the Veterans Affairs system and Israel suggest protection against clinical infection from SARS-CoV-2.[11,25] Our study has expanded this to a broader US population and looked at more recent time frames. Additionally, our study has added data in patients who were administered 3 doses of a COVID-19 vaccine in the IBD population and assessed the impact of vaccines on hospitalization and mortality related to COVID-19. We also provide unique data on the risk of COVID-19 in IBD patients on TNFi who received 3 doses of m-RNA vaccine compared with mesalamine.

Our study has several limitations that warrant consideration when interpreting the findings.

The prevalence of COVID-19 vaccine in IBD patients was lower than anticipated in our cohort. This could be related to patients receiving vaccine doses outside of HCOs like pharmacies, health centers, travel clinics, or government distribution centers which could not be captured by the database. The majority of the patients in our study had received the BNT162b2 vaccine. Less information on vaccine efficacy of the mRNA-1273 vaccine in patients with IBD is available; however, 1 study has shown higher antibody concentrations in patients with IBD.[22] Additionally, we were unable to assess the vaccine efficacy of the single-dose Janssen vaccine due to very small sample size. We could not ascertain the duration of follow-up for individual patients who were administered 1 or 2 doses of the vaccine due to limitations of the database. There is a possibility of including patients that were diagnosed with COVID-19 from the first pandemic wave. These patients could be subject to different epidemiological and clinical outcomes compared with patients who developed COVID-19 after receiving COVID-19 vaccine due to the emergency of the Delta and Omicron variants of SARS-CoV-2. It is possible patients with IBD, especially those on immunosuppressive therapy who were vaccinated in early 2021, experienced a faster waning of immunity, leaving them susceptible to SARS-CoV-2 infection during the Delta and Omicron waves. Although propensity score matching was performed for all analysis, there still exists the possibility of residual bias due to an unknown confounder. Patients with IBD who received the booster dose had a short follow-up, as this was not approved until late September; hence the long-term benefit remains unexplored. However, we ensured that all patients had a minimum of 3 months' follow-up. Finally, as with all coding-based studies, results are susceptible to errors in coding, misdiagnosis, or documentation.

In conclusion, our propensity-matched study found a similar decreased risk of COVID-19 in patients with IBD who were administered 2 or 3 doses of the COVID-19 vaccine (BNT162b2 and mRNA-1273). We also found that vaccinated patients with IBD had lower risk of adverse events after COVID-19 infection compared with unvaccinated patients. Additionally, patients who received 2 doses of COVID-19 vaccine had an increased risk of hospitalization from COVID-19 compared with patients that received 3 doses.

Author Contribution

A.D.: Data collection, data analyses, manuscript preparation

P.D., R.U.: Conceptualization of the project, critical revisions of the manuscript

R.C., F.A.F.: Data interpretation, critical revision of the manuscript

J.M.: Literature search, manuscript preparation

G.S.K.: Study conceptualization, study methodology, data interpretation, manuscript preparation, critical revisions

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Conflicts of Interest

A.D., J.M.: No conflict of interest

P.D.: Consultant or on an advisory board for Janssen, Pfizer, Prometheus Biosciences, Boehringer Ingelheim, AbbVie, Arena Pharmaceuticals, Boehringer Ingelheim, CorEvitas LLC and Scipher Medicine Corporation. He has also received funding under a sponsored research agreement unrelated to the data in the article from Takeda Pharmaceutical, Arena Pharmaceuticals, Bristol Myers Squibb-Celgene, and Boehringer Ingelheim.

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R.C.: Advisory board and consulting for Abbvie, Bristol Myers Squib, Fzata, Fresenius Kabi, Janssen, Magellen Health Pfizer, Samsung Bioepis, Sebela, and Takeda.

F.A.F.: Advisory boards for Arena, Bristol-Myers Squibb, Braintree Laboratories, Glaxo Smith Kline, Janssen, Pfizer, and Sebela Pharmaceuticals. He is also a data safety monitoring board member for Adiso Therapeutics, Lilly, and Theravance Biopharma.

G.S.K.: Advisory board-Lilly Pharmaceuticals, CorEvitas research foundation

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