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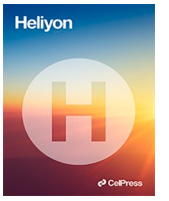

Efficacy of COVID-19 vaccines in inflammatory bowel disease patients receiving *anti*-TNF therapy: A systematic review and meta-analysis

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ABSTRACT

Background and objectives: There are concerns about the serological responses to Coronavirus disease 2019 (COVID-19) vaccines in inflammatory bowel disease (IBD) patients, particularly those receiving *anti*-TNF therapy. This study aimed to systematically evaluate the efficacy of COVID-19 vaccines in IBD patients receiving *anti*-TNF therapy.
Methods: Electronic databases were searched to identify relevant studies. We calculated pooled seroconversion rate after COVID-19 vaccination and subgroup analysis for vaccine types and different treatments were performed. Additionally, we estimated pooled rate of T cell response, neutralization response, and breakthrough infections in this population.
Results: 32 studies were included in the meta-analysis. IBD patients receiving *anti*-TNF therapy had relatively high overall seroconversion rate after complete vaccination, with no statistical difference in antibody responses associated with different drug treatments. The pooled positivity rate of T cell response was 0.85 in IBD patients receiving *anti*-TNF therapy. Compared with healthy controls, the positivity of neutralization assays was significantly lower in IBD patients receiving *anti*-TNF therapy. The pooled rate of breakthrough infections in IBD patients receiving *anti*-TNF therapy was 0.04.
Conclusions: COVID-19 vaccines have shown good efficacy in IBD patients receiving *anti*-TNF therapy. However, IBD patients receiving *anti*-TNF have a relatively high rate of breakthrough infections and a low level of neutralization response.

1. Introduction

Coronavirus disease 2019 (COVID-19) pandemic is an ongoing global health crisis with high transmission rate, vaccine distribution challenges, and emerging variants that continue to cause concerns. Although COVID-19 is no longer a public health emergency of

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international concern, it does not mean the end of the epidemic in COVID-19. As of May 10, 2023, the World Health Organization (WHO) has reported over 760 million confirmed cumulative cases of COVID-19 worldwide, with more than 6 million cumulative deaths [1]. Currently, the global epidemic of COVID-19 continues to spread and the virus continues to mutate, we are still in an epidemic process of COVID-19 and efforts to suppress the epidemic should continue. The outbreak of COVID-19 offers many lessons for handling future public health events, the most important of which is vaccination. The development and distribution of effective vaccines have been key in reducing the severity and mortality of COVID-19 in many parts of the world. The current vaccines for syndrome coronavirus 2 (SARS-CoV-2) remain effective in preventing severe illness, hospitalizations, and fatalities [2].

Inflammatory bowel disease (IBD) is an immunocompromised disease of the digestive system, comprising Crohn' s disease (CD), ulcerative colitis (UC), and IBD-unclassified [3], which has a combined prevalence of 0.5%–1% in Western Europe [4]. With the rapid increase of prevalence in developing countries, IBD is now regarded as a global disease [5]. The pathogenesis of IBD involves a complex interplay between genetic, environmental, and immunological factors, resulting in the activation of various immune cells and the release of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) [6,7]. Biologic agents have revolutionized the treatment of IBD, particularly *anti*-TNF therapy which has become increasingly prevalent in induction and maintain of remission in patients with moderate-severe IBD [8]. It has been showed that IBD patients have weakened immune responses to COVID-19 vaccines, leading to higher rate of breakthrough infections and lower vaccine effectiveness [9]. In addition, patients with IBD taking different drugs do not respond consistently to vaccination. Studies have shown treatment with *anti*-TNF therapy, such as infliximab, may impair antibody responses to SARS-CoV-2 infection [10,11]. However, efficacy of COVID-19 vaccines in IBD patients receiving *anti*-TNF therapy has not been fully determined. To address this knowledge gap and provide experience for dealing with public events in the future, a systematic review and meta-analysis was conducted.

2. Materials and methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the study protocol was registered in the International Prospective Register of Systematic Reviews, under the identification number CRD42023384870.

2.1. Search strategy

We conducted a comprehensive search of the following databases: PubMed, EMBASE, and Cochrane Library for articles published from inception to December 31, 2022, without any language restrictions. To enhance the accuracy of data, we excluded non-peer-reviewed articles. In addition, we manually examined the reference lists of all the articles that met our inclusion criteria to identify any potentially relevant studies. The search terms included keywords relevant to "COVID-19" "severe acute respiratory syndrome coronavirus 2" "SARS-CoV-2" combined with "Inflammatory bowel disease" "ulcerative colitis" "Crohn's disease" and "vaccination" (Table S1).

2.2. Study selection

We employed a two-stage screening process to identify relevant studies: firstly, we screened the title and abstract of each study, and secondly, we assessed the full-text. Two researchers (DD and XD) screened each study independently, and any discrepancies were resolved through consensus with a third researcher. This process was designed to minimize bias and ensure the inclusion of the most relevant studies.

We included all studies that reported on COVID-19 vaccines in patients with IBD who were treated with *anti*-TNF therapy and provided information on at least one of the following: (1) seroconversion rate after COVID-19 vaccination, (2) T-cell response in patients with IBD after COVID-19 vaccination, (3) breakthrough infections after COVID-19 vaccination, and (4) the positivity of neutralization assays after COVID-19 vaccination. We included studies from all regions, publication types, vaccine types, and vaccine dosages. We excluded studies that reported only the median titers of antibodies or studies that failed to provide categorical data on seroconversion.

2.3. Data extraction

Two researchers (DD and XD) independently extracted data according to a predetermined data extraction form. To ensure the accuracy of the extracted data, a third researcher checked all key information at the end of the data extraction phase.

We extracted data on various study characteristics, including context (author, date of publication, and location of study), and sample size. In addition, we collected participant data including age, gender for IBD patients and healthy controls, type of IBD, and current drug regimen. Information on the interventions was also gathered, including the type and brand of vaccines, number of participants receiving each type and brand of vaccine, and the mean interval between doses. Finally, we collected outcome-related data, such as assay method, sample collection interval, seroconversion rate for different drug treatments, T cell response, neutralization response, and breakthrough infections.

2.4. Risk of bias assessment

Since the included studies were all non-randomized observational studies, the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used to assess the risk of bias for studies [12]. Specifically, two reviewers (DD and XD) independently evaluated the risk of bias for each study across seven domains, including confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and reported results selection. Any discrepancies were resolved through discussion with a third reviewer.

2.5. Outcomes

The primary outcome of this study was seroconversion rate after COVID-19 vaccination in IBD patients receiving *anti*-TNF therapy, defined as the proportion of participants who are serologically positive for *anti*-SARS-CoV-2 antibodies. The secondary outcomes involved T cell response, neutralization response, and breakthrough infections in IBD patients receiving *anti*-TNF therapy. Pooled analysis was conducted only when there were at least three studies with more than five participants available for each individual analysis.

2.6. Data analysis

The analysis was performed using R statistical software version 4.2.2, and the meta package was also utilized in addition to the base package [13]. Pooled seroconversion rate was computed by random effect method with inverse variance approach, and pooled relative risk (RR) was computed by Mantel-Haenszel random effect method. Before computing the pooled summary, logit transformations were performed on the individual seroconversion rate. For each outcome, DerSimonian-Laird estimator was used to estimate the between-study variance τ^2. The χ^2 test and I^2 statistic were used to assess heterogeneity between studies, and heterogeneity was considered significant if the p-value was <0.1 or the I^2 statistic was $\geq 50\%$. We also planned to use Baujat plot to determine the studies that lead to heterogeneity and whether there are biologically reasonable reason to explain the heterogeneity. Subgroup analysis were conducted to determine if seroconversion rate was affected by vaccine type, vaccine dose (single versus two doses) and drug exposure. Funnel plots and Egger's test were used to assess publication bias. Unless otherwise specified, a bilateral $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study selectin and characteristics

Our search across three databases yielded 1058 citations, out of which 194 were identified as duplicates. Following an initial screening of 864 articles, 725 were excluded. After browsing the full texts, 32 studies [14–45] were ultimately included in the meta-analysis (Fig. 1). Table 1 presents additional details on these 32 studies, including the study site, study type, type of vaccine administered, and other relevant information. Detailed information of various vaccines for IBD patients is shown in Table S2.

3.2. Seroconversion rate after COVID-19 vaccination

30 studies comprising 3245 participants reported pooled seroconversion rate after complete COVID-19 vaccination in IBD patients receiving *anti*-TNF therapy. The pooled seroconversion rate was 0.94 (95% CI 0.91–0.96, $I^2 = 81\%$, Fig. 2). We conducted a subgroup analysis of vaccine types and found that the pooled seroconversion rate after complete mRNA vaccine (19 studies: 1836 participants) was 0.96 (95% CI 0.93–0.98, $I^2 = 74\%$). However, the pooled seroconversion rate after complete adenovirus vector vaccine (AVV) (3 studies: 643 participants) was lower at 0.87 (95% CI 0.69–0.95, $I^2 = 83\%$). Across 9 studies, we pooled data from 735 IBD patients and 1594 healthy controls, and found that the pooled RR of seroconversion rate in IBD patients treated with *anti*-TNF therapy compared with healthy controls after complete COVID-19 vaccination was lower (pooled RR 0.98, 95% CI 0.94–1.02, $I^2 = 79\%$, Fig. S1). Furthermore, we observed no significant difference in the seroconversion rate between IBD patients and healthy controls ($p = 0.11$).

9 cohorts from 8 studies, comprising 585 participants, were analyzed to determine the seroconversion rate in IBD patients receiving *anti*-TNF therapy after incomplete COVID-19 vaccination. The pooled seroconversion rate was 0.59 (95% CI 0.41–0.75, $I^2 = 92\%$, Fig. S2). When compared to healthy controls (3 studies, n = 121), IBD patients receiving *anti*-TNF therapy (n = 100) showed a lower pooled RR of seroconversion after incomplete COVID-19 vaccination (pooled RR 0.87, 95% CI 0.77–0.98, $I^2 = 29\%$, Fig. S3). Notably, there was a significant difference in the seroconversion after incomplete COVID-19 vaccination between IBD patients receiving *anti*-TNF therapy and healthy controls ($p = 0.02$). These findings highlight the importance of administering a second dose of the COVID-19 vaccine to improve seroconversion rate in IBD patients.

3.3. Seroconversion rate of IBD patients stratified by treatments

We conducted further analysis on the seroconversion rate in IBD patients who underwent different treatments after complete vaccination. As depicted in Fig. 3, among patients with IBD who received no treatment (215 participants), the pooled seroconversion rate was 0.97 (95%CI 0.93–0.98, $I^2 = 0\%$). The pooled rate of seroconversion for those on 5-ASA (531 participants), steroid (272

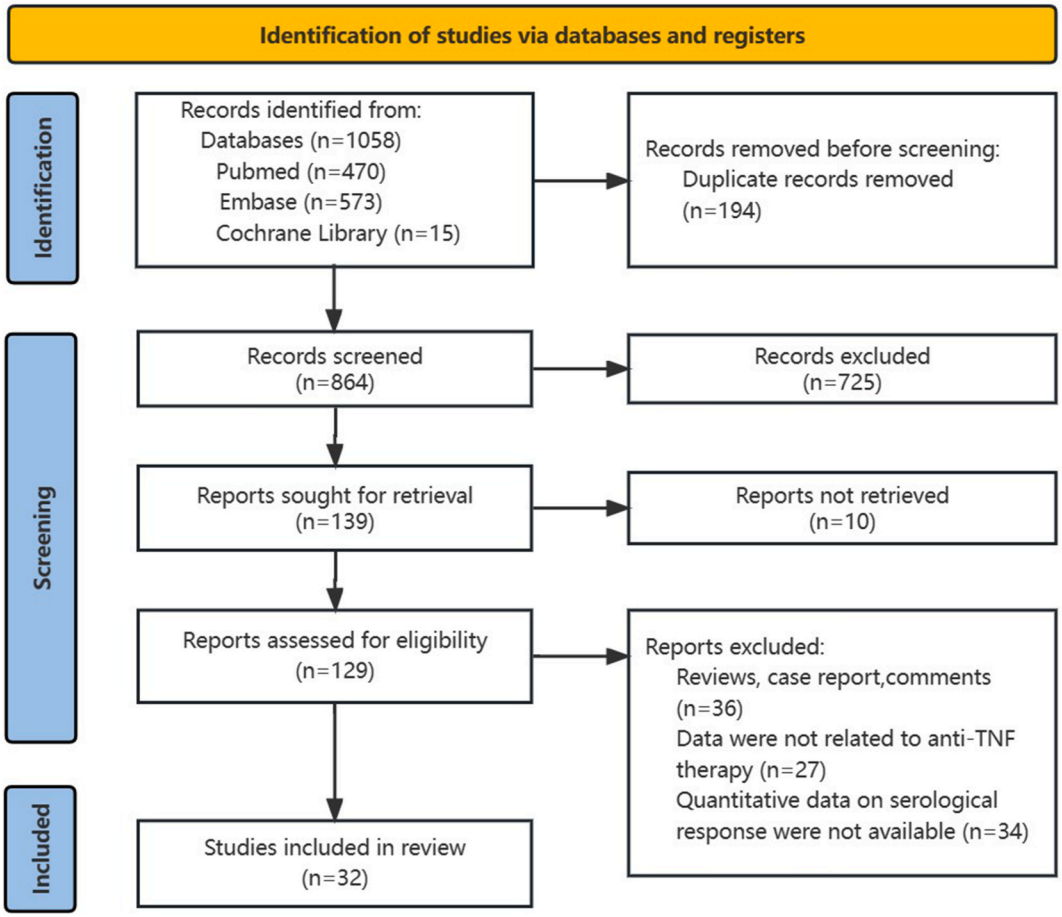

Fig. 1. PRISMA flow chart depicting the process of screening and selection of studies for the meta-analysis.

participants), and JAK inhibitor (77 participants) were 0.94 (95%CI 0.76–0.99, $I^2 = 89\%$), 0.90 (95%CI 0.79–0.96, $I^2 = 46\%$), and 0.91 (95%CI 0.82–0.96, $I^2 = 0\%$), respectively. Patients who received *anti*-TNF treatment (3245 participants) had a pooled seroconversion rate of 0.94 (95%CI 0.91–0.96, $I^2 = 81\%$), while those on immunomodulator (484 participants) had a pooled seroconversion rate of 0.93 (95%CI 0.88–0.96, $I^2 = 41\%$). Among patients treated with vedolizumab (1561 participants) and ustekinumab (823 participants), the pooled seroconversion rate was 0.96 (95%CI 0.94–0.98, $I^2 = 31\%$) and 0.97 (95%CI 0.95–0.98, $I^2 = 0\%$) respectively, indicating excellent seroconversion. Furthermore, the pooled seroconversion rate for patients who received *anti*-TNF monotherapy was higher than those who received a combination of *anti*-TNF and immunomodulator (azathioprine, mercaptopurine, methotrexate) (pooled RR 1.02, 95%CI 0.99–1.06, $I^2 = 72\%$, Fig. S4) in 13 included studies (4637 participants). As depicted in Fig. S5, among patients with IBD who have not received *anti*-TNF therapy (3963 participants), the pooled seroconversion rate was 0.95 (95%CI 0.93–0.96, $I^2 = 55\%$) , which was slightly higher than IBD patients receiving *anti*-TNF therapy (see Fig. 3).

3.4. T cell response

4 studies reported T cell response after complete vaccination in IBD patients receiving *anti*-TNF therapy. The pooled positivity rate of T cell response was 0.85 (95%CI 0.75–0.92, $I^2 = 59\%$, FigureS6). Table S3 presents the methods and time points of T cell response determination used in these studies.

3.5. Neutralization response after complete vaccination

In total, there were 7 studies (1162 patients) that reported positive results for neutralization assays after complete vaccination, but only 4 of these studies included corresponding data for healthy controls who were also vaccinated. The pooled positivity rate of neutralization response in IBD patients receiving *anti*-TNF therapy was 0.78 (95%CI 0.57–0.91, $I^2 = 94\%$, Fig. 4). Compared with healthy controls, the positivity of neutralization assays after complete vaccination was significantly lower in IBD patients receiving *anti*-TNF therapy (pooled RR 0.65, 95%CI 0.49–0.88, $I^2 = 79\%$, Fig S7). Table S4 presents the definitions of positive neutralization assays reported in these studies and the time points at which they were measured.

Table 1
Characteristics of included studies.

Author (Place of study)	Type of study	Type of Vaccine (patients)	Number of Patients receiving *anti*-TNF therapy	Age and gender	Response	Definition of Response	Response With other Drugs	Endpoints of testing response	Breakthrough Infections	T cell response	Number With Neutralization
Alexander(a) et al. (United Kingdom)	Multicenter prospective case-control	Mixed: BNT162b2, ChAdOx1 nCoV-19, complete vaccination	49(CD:35,UC:13, Unclassified:1)	Median age:47.5 (36.1–56.4)y, Female:22 (48%)	IBD patients treated with *anti*-TNF:44/49	*Anti*-SARS-CoV-2 spike protein antibodies on the ElecSys assay of at least 15 U/mL	IMM (64/64), *anti*-TNF + IMM(49/56), Vedolizumab (50/50), ustekinumab (47/49), JAK inhibitor (19/19)	53–92 d after 2nd dose	–	–	–
Alexander(b) et al. (United Kingdom)	Multicenter prospective case-control	Mixed: BNT162b2 or ChAdOx1 nCoV-19, complete vaccination	46(CD:31,UC:13, Unclassified:2)	Median age:41.4 (31.8–55.0)y, Female:22 (46%)	–	–	–	–	–	*Anti*-TNF(30/30), *anti*-TNF + IMM (30/34), IMM (39/41), vedolizumab (30/31), ustekinumab (24/25), JAK inhibitor (10/12)	–
Algaba et al. (Spanish)	Single-centre observational cross-sectional	Mixed : BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, Ad26. COV2, complete vaccination	–	–	IBD patients treated with *anti*-TNF:48/73	The SR of the vaccine was tested by determination of IgG antibodies specific to the RBD of the S1 protein subunit of the viral spicule. Seroconversion defined as IgG levels of >30 AU/mL	5-ASA (34/52)	2–4 mo after 2nd dose	–	–	–
Avni Biron et al. (Israel)	Multicentre prospective cohort	BNT162b2 complete vaccination	11	–	IBD patients treated with *anti*-TNF:11/11	IgG(S) detected by using the SARS-CoV-2 IgG-II assays. IgG(S) level >50 AU/mL positive result	No treatment (4/4), 5-ASA (15/15), vedolizumab (4/4), ustekinumab (2/2), steroids (2/2), IMM(8/8)	21–35 d after 2nd dose	–	–	–
Ben-Tov et al. (Israel)	Prospective cohort	BNT162b2 complete vaccination	1323	–	–	–	–	–	After 7 days post 2nd dose BNT162b2 mRNA vaccination. *Anti*-TNF(3/1323),	–	–

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Table 1 (*continued*)

Author (Place of study)	Type of study	Type of Vaccine (patients)	Number of Patients receiving *anti*-TNF therapy	Age and gender	Response	Definition of Response	Response With other Drugs	Endpoints of testing response	Breakthrough Infections	T cell response	Number With Neutralization
									ustekinumab (0/225), vedolizumab (0/454)		
Chen et al. (United States)	Prospective cohort	BNT162b2 complete vaccination	9	–	–	–	–	–	–	–	*Anti*-TNF(3/9), healthy con trols (23/25) tested against delta strain
Classen et al. (Germany)	Single-centre retrospective cohort	Mixed: BNT162b2, mRNA-1273, Ad26. COV2, complete vaccination	27	–	IBD patients treated with *anti*-TNF:27/27	Detection of IgG SARS-CoV2 antibody to RBD-S protein using immuno assay Elecsys *anti*-SARS-CoV-2S (Roche Diagnostics)	5-ASA (24/24), vedolizumab (19/19), ustekinumab (14/14)	56.4 ± 31.485 d after 2nd dose	–	–	–
Edelman-Klapper et al. (Israel)	Multicentreprospective observational	BNT162b2	67	Mean age: 37.8 (14.3) y, Female:24 (36%)	IBD patie Nts treated with *anti*-TNF: First dose: 57/63, Second dose: 51/51	Quantitative detection of SARS-CoV-2 IgG II by Abbott architect i2000sr platform.IgG level >50 AU/mL positive result.	–	2–3 wk after 1st dose,4 wk after 2nd dose	–	–	*Anti*-TNF (43/55), healthy controls (38/39)
Frey et al. (United States)	Prospective	BNT162b2, mRNA-1273, complete vaccination	24	–	IBD patients treated with *anti*-TNF:24/24	Roche Elecsys *anti*-RBD pan Ig > 0.8 units/mL for seroconversion	IMM(17/18), *anti*-TNF + IMM(8/8), JAK inhibitor (2/2), ustekinumab (17/17), vedolizumab (6/6), steroids (23/23)	179 (165, 202) d after 2nd dose	Reported at 2 mo after 2nd dose mRNA vaccination. *Anti*-TNF(0/24),steroids (1/23), vedolizumab (0/6), ustekinumab (0/17), JAK inhibitor (0/2)		
Kappelman et al. (United States)	Prospective observational cohort	BNT162b2, mRNA-1273, Ad26. COV2, complete vaccination	691	–	IBD patients treated with *anti*-TNF: mRNA (634/660), AVV(24/31)	Quantitative determination of *anti*-RBD IgG antibodies against SARS-CoV-2 using the LabCorp Cov2Quant IgG method.	mRNA:no treatment (114/117),5-ASA (385/391), steroids (140/151), IMM(158/160), *anti*-TNF + IMM	67.2 d after 2nd dose mRNA, 91.3 d after 1 dose AVV	–	–	–

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Table 1 (*continued*)

Author (Place of study)	Type of study	Type of Vaccine (patients)	Number of Patients receiving *anti*-TNF therapy	Age and gender	Response	Definition of Response	Response With other Drugs	Endpoints of testing response	Breakthrough Infections	T cell response	Number With Neutralization
							(176/202), vedolizumab (210/212), ustekinumab (270/272), JAK inhibitor (29/30); AVV:5-ASA (18/23), steroids (5/10),*anti*-TNF + IMM(5/8), IMM(4/4), vedolizumab (10/12), ustekinumab (17/18), JAK inhibitor (1/2)				
Kashiwagi et al. (Japen)	Single-centre retrospective cohort	BNT162b2 complete vaccination	11	Median age:13.3 (9.6–17.9)y, Female:45.5% (5/11)	IBD patients treated with *anti*-TNF:7/8	The Roche Elecsys *anti*-SARS-CoV-2 spike (S) electrochemiluminescence immun oassay was used to identify vaccin ation-specific antibody respons es. 15 U/mL was defined as the threshold of seroconversion.	5-ASA (13/13)	20–28 wk after 2nd dose	After 2nd dose mRNA vaccination, the exact date was not mentioned. *Anti*-TNF(1/11),5-ASA (4/21)		
Kastl et al. (United States)	Prospective observational cohort	BNT162b2 complete vaccination	161	–	IBD patients treated with *anti*-TNF:53/53	Quantitative determination of *anti*-RBD IgG antibodies against SARS-CoV-2 using the LabCorp Cov2Quant IgG method.	Ustekinumab (10/10), vedolizumab (8/8), *anti*-TNF + IMM (15/15)	after 2nd dose			
Kennedy et al. (United Kingdom)	Multicentre prospective observational cohort	First dose: BNT162b2 (387/865), ChAdOx1 nCoV-19 (478/865); Second dose: BNT162b2 (20)	First dose:865, Second dose:20	Median age:41.4 (31.5–54.8)y, Female: (434/863) 50.3%	IBD patients treated with *anti*-TNF: first dose 103/328, second dose 17/20	*Anti*-SARS-CoV-2 anti-spike (S) protein RBD antibodies using Roche Elecsys *anti*-SARS CoV-2 spike (S) immunoassay13 and the nucleocapsid (N) immunoassay.	First dose: *anti*-TNF + IMM(125/537) vedolizumab (218/330); Second dose: vedolizumab (6/7)	3–10 wk after 1st dose	–	–	–
Levine et al. (United States)	Single-centre prospectivecohort	BNT162b2, mRNA-1273,	10	–	IBD patients treated with	ELISA assay for both the COVID-19 nucleocapsid and spike domain	Ustekinumab (5/5), vedolizumab	–	–	–	–

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Table 1 (*continued*)

Author (Place of study)	Type of study	Type of Vaccine (patients)	Number of Patients receiving *anti*-TNF therapy	Age and gender	Response	Definition of Response	Response With other Drugs	Endpoints of testing response	Breakthrough Infections	T cell response	Number With Neutralization
		complete vaccination			*anti*-TNF:9/10	antibodies (Roche) ≥0.80 U/mL indicating positive results	(2/2), JAK inhibitor (1/1), IMM(1/1)				
Liu et al. (United Kingdom)	Multicentreprospective observational cohort	BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, complete vaccination	871 (614CD,257UC)	Median age:43.6 (32.5–55.5)y, Female: 401/871 (46%)	–	–	–	–	After 14 days post 3rd dose vaccination. *Anti*-TNF (119/871), vedolizumab (29/417)	–	*Anti*-TNF (809/871), vedolizumab (408/417)
Lin et al. (United Kingdom)	Multicentre prospective, Observational cohort	BNT162b2, ChAdOx1 nCoV-19, complete vaccination	2279 (1531CD,748UC)	Median age:40.2 (30.1–53.1)y, Female: 45.9% (1040/2267)	IBD patients treated with *anti*-TNF:904/952 (BNT162b2 (347/356), ChAdOx1 nCoV-19 (557/596))	Roche Elecsys *anti*-SARS-CoV-2 spike (S) immunoassay and nucleocapsid (N) immunoassay. Electrochemiluminescence immunoassay. Values ≥ 15 U/mL considered positive.	Vedolizumab (807/818), *anti*-TNF + IMM(1241/1327)	14–70 d after 2nd dose	After 14 days post 2nd dose vaccination. *Anti*-TNF (201/3441), vedolizumab (66/1682)	*Anti*-TNF(78/97), vedolizumab (21/26)	–
López-Marte et al. (Puerto Rico)	Prospectivecohort	BNT162b2, mRNA-1273, complete vaccination	30	–	IBD patients treated with *anti*-TNF:30/30	Anti-Spike IgG levels were measured with an indirect in-house ELISA for the semi-quantitative determination of human IgG antibody class	No treatment (3/3), 5-ASA (2/2), ustekinumab (12/12), vedolizumab (7/7), IMM (2/2), steroids (1/1)	60 ± 7 d after 2nd dose	–	–	*Anti*-TNF(13/30)
Macaluso et al. (Italy)	Multicentreprospectivecohort	Mixed: BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, Ad26. COV2, complete vaccination	437	–	IBD patients treated with *anti*-TNF:409/447	The ELISA assay to detect IgG uses a fragment of the SARS-CoV-2 Spike glycoprotein (S protein) as antigen. Positivity threshold levels were determined by ROC curves.	Ustekinumab (61/66), vedolizumab (170/183), IMM(89/100), *anti*-TNF + IMM (9/10)	8 wk after 2nd dose	–	–	–
Mayorga Ayala et al. (Spain)	Prospective observational	mRNA (No type of vaccine described)	57	–	IBD patients treated with *anti*-TNF:57/57	Positive antibodies to the Spike(S), SARS-CoV-2 protein were analyzed by CLIA	IMM(38/38), *anti*-TNF + IMM(53/53)	6 ± 2 wk after 3rd dose	–	*Anti*-TNF(49/53),IMM(33/38)	
Melmed et al. (United States)	Multicentreprospective cohort	BNT162b2, mRNA-1273,	183	Mean age:41.5 (13.36)y, Female:130/183	IBD patients treated with *anti*-	Antibodies to the RBD of the spike protein S1 subunit IgG(S) and to the viral nucleocapsid protein using	No treatment (85/87), IMM (12/12), *anti*-TNF + IMM	2 wk after 2nd dose	–	–	–

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Table 1 (*continued*)

Author (Place of study)	Type of study	Type of Vaccine (patients)	Number of Patients receiving *anti*-TNF therapy	Age and gender	Response	Definition of Response	Response With other Drugs	Endpoints of testing response	Breakthrough Infections	T cell response	Number With Neutralization
		complete vaccination			TNF:175/177	the SARS CoV-2 IgG-II and SARS-CoV–2 IgG assays, respectively. IgG(S) level >50 AU/mL positive result.	(49/49), JAK nhibitor (7/7), vedolizumab (75/76), ustekinumab (113/114), steroids (26/27)				
Quan et al. (Canada)	Multicentreprospective	Mixed: BNT162b2, mRNA-1273, ChAdOx1 nCoV-19	158	Mean age:49.4 (14.6)y, Female:88/158 (55.7%)	IBD patients treated with *anti*-TNF: first dose 48/62, second dose 95/97	SARS-CoV-2 IgG II Quant assay was used to the spike protein of SARS-CoV-2. Seroconversion defined as IgG levels of >50 AU/mL	First dose: IMM(17/20), *anti*-TNF + IMM(15/31), vedolizumab (34/41), ustekinumab (61/70), Second dose: IMM(15/15), *anti*-TNF + IMM(31/33), vedolizumab (47/48), ustekinumab (66/66), steroids (4/7)	2–4 wk after 1st dose, 2–8 wk after 2nd dose	–	–	–
Ramos et al. (Spain)	Single-centre prospectivecohort	Mixed: BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, Ad26. COV2, complete vaccination	50	Median age:47 (43–51)y, Female: 20 (40%)	IBD patients treated with *anti*-TNF:44/50	IgG RBD antibody was measured by chemiluminescent immunoassay from Abbott using a reactive SARS-CoV-2 IgG II Qu- ant, and values > 7.1 BAU/mL (50 AU/mL) considered positive.	Vedolizumab (14/14), ustekinumab (32/32)	5 mo after complete vaccination	–	–	–
Reuken et al. (Germany)	Prospectiveobservational	Mixed: BNT162b2, ChAdOx-1 nCoV-19	9	–	IBD patients treated with *anti*-TNF: first dose 7/9	Liaison SARS-CoV-2 Trimerics IgG CLIA on the LiaisonXL.Cut-off of 33.8 BAU/mL	–	3 wk after 1st dose	–	–	–
Shehab et al. (Kuwait)	Multicentre prospective cohort	Mixed: BNT162b2, ChAdOx1 nCoV-19	96	–	IBD patients treated with *anti*-TNF: first dose 14/19,	SARS-CoV-2–specific IgG antibodies measured by ELISA.Values > 31.5 BAU/mL positive	Second dose: vedolizumab (13/14), ustekinumab (12/13)	3–6 wk after 1st dose, 4–10 wk after 2nd dose	–	–	2 nd dose:*anti*-TNF(55/75), vedolizumab (13/14), ustekinumab (12/13)

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Table 1 (*continued*)

Author (Place of study)	Type of study	Type of Vaccine (patients)	Number of Patients receiving *anti*-TNF therapy	Age and gender	Response	Definition of Response	Response With other Drugs	Endpoints of testing response	Breakthrough Infections	T cell response	Number With Neutralization
					second dose 57/75						
Shiga et al. (Japen)	Prospective	Mixed: BNT162b2, mRNA-1273, complete vaccination	146	–	IBD patients treated with *anti*-TNF:86/89	The anti-novel coronavirus test kit was used to quantitatively determine the high affinity antibodies in serum, including IgA/IgG/IgM specific for novel coronavirus spike protein. Values $\geq$ 0.8 U/mL positive	Ustekinumab (58/58), vedolizumab (36/36), JAK inhibitor (10/10), *anti*-TNF + IMM(53/57)	38.5 ± 31.8 d after 2nd dose	–	–	*Anti*-TNF(88/89),*anti*-TNF + IMM(44/57), JAK inhibitor (10/10), vedolizumab (36/36), ustekinumab (55/58)
Spencer et al. (United States)	Single-centreretrospective cohort	Mixed: BNT162b2, mRNA-1273, Ad26. COV2, complete vaccination	9	–	IBD patients treated with *anti*-TNF:9/9	Semiquantitative SARS-CoV-2 IgG antibody assay by ELISA.Values >5–15 AU/mL positive.	Ustekinumab (10/10), JAK inhibitor (2/2)	14–37 d after complete vaccination	–	–	–
Tsipotis et al. (United States)	Prospective	BNT162b2, mRNA-1273, complete vaccination	70	–	IBD patients treated with *anti*-TNF:70/70	antibody titers on the Roche Elecsys *anti*-SARS-CoV-2 enzyme immunoassay were tested. Values $\geq$ 0.8 units/mL positive.	5-ASA (11/11), ustekinumab (36/36), vedolizumab (10/10), JAK inhibitor (3/3), *anti*-TNF + IMM(7/8), steroids (49/51)	3 mo after 2nd dose	–	–	–
Vollenberg et al. (Germany)	Prospective cohort	BNT162b2, mRNA-1273, complete vaccination	52	Median age:46 (33–55)y, Female:47% (45/95)	IBD patients treated with *anti*-TNF: first dose 21/28, second dose 33/33	IgG antibodies against the SARS-CoV-2 RBD on the spike protein subunit S1 was quantified by the SARS-CoV-2 IgG II Quant assay (Abbott Diagnostics). Values $\geq$ 50.0 AU/mL denoting seropositivity	First dose: ustekinumab (11/12), vedolizumab (6/7); Second dose: ustekinumab (11/11), vedolizumab (9/10)	First test: before 2nd dose; Second test:3 mo afer 2nd dose	–	–	2 nd dose : *anti*-TNF(26/33)
Wasserbauer et al. (Czech Republic)	Prospective observational	BNT162b2	47	–	IBD patients treated with *anti*-TNF: first dose 13/47,	An immune-enzymatic kit (EIA COVID-19 RBD IgG CoRG96) was used to determine IgG antibodies against the RBD of SARS-CoV-2 virus in human	Second dose : IMM (24/28), *anti*-TNF + IMM (9/12)	3 wk after 1st dose,4 wk after 2nd dose	–	–	–

(*continued on next page*)

Table 1 (*continued*)

Author (Place of study)	Type of study	Type of Vaccine (patients)	Number of Patients receiving *anti*-TNF therapy	Age and gender	Response	Definition of Response	Response With other Drugs	Endpoints of testing response	Breakthrough Infections	T cell response	Number With Neutralization
					second dose 41/47	serum.Values $\geq$ 100U/mL positive.					
Woelfel et al. (France)	Multicentre prospective observational cohort	BNT162b2, mRNA-1273, complete vaccination	73	Mean age: 44.64 (15.32) y,Female:31 (42.5%)	IBD patients treated with *anti*-TNF:73/73	Concentrations of IgG antibodies targeting the SARS-CoV-2 spike protein were measured using the LIAISON® SARS-CoV-2 TrimericS IgG assay.Values $\geq$ 33.8 BAU/ml seropositive.	–	2–16 wk after 3rd vaccination	–	*Anti*-TNF(58/73)	–
Wong et al. (United States)	Single-centre serosurvey	BNT162b2, mRNA-1273, complete vaccination	8	–	IBD patients treated with *anti*-TNF:8/8	EUA sCOVG assay has for semiquantitative index value results. An index value of 1 equals a positive test.	No treatment (4/4), vedolizumab (12/12), ustekinumab (2/2)	2–85 d after 2nd dose	–	–	–
Zhang et al. (Australia)	Single-centre prospective cohort	Mixed: BNT162b2, ChAdOx1 nCoV-19, complete vaccination	14	–	IBD patients treated with *anti*-TNF:14/14	Antibodies to the S1/2 IgG subunit and RBD were measured	Ustekinumab (16/16), vedolizumab (13/13), JAK inhibitor (1/1), *anti*-TNF + IMM(32/32)	3–6 wk after 2nd dose	–	–	–

Abbreviations: 5-ASA, 5-aminosalicylates; AVV, Adenovirus vector vaccine; COVID-19, Coronavirus disease 2019; CD, Crohn's disease; ELISA, enzyme-linked immunosorbent assay; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM immunoglobulin M; IMM, immunomodulators; IBD, inflammatory bowel disease; JAK, Janus Kinase; mRNA, messenger RNA; RBD, receptor-binding domain; SARS-CoV-2, syndrome coronavirus 2; SR, Seroconversion rate; TNF, tumor necrosis factor; UC, ulcerative colitis.

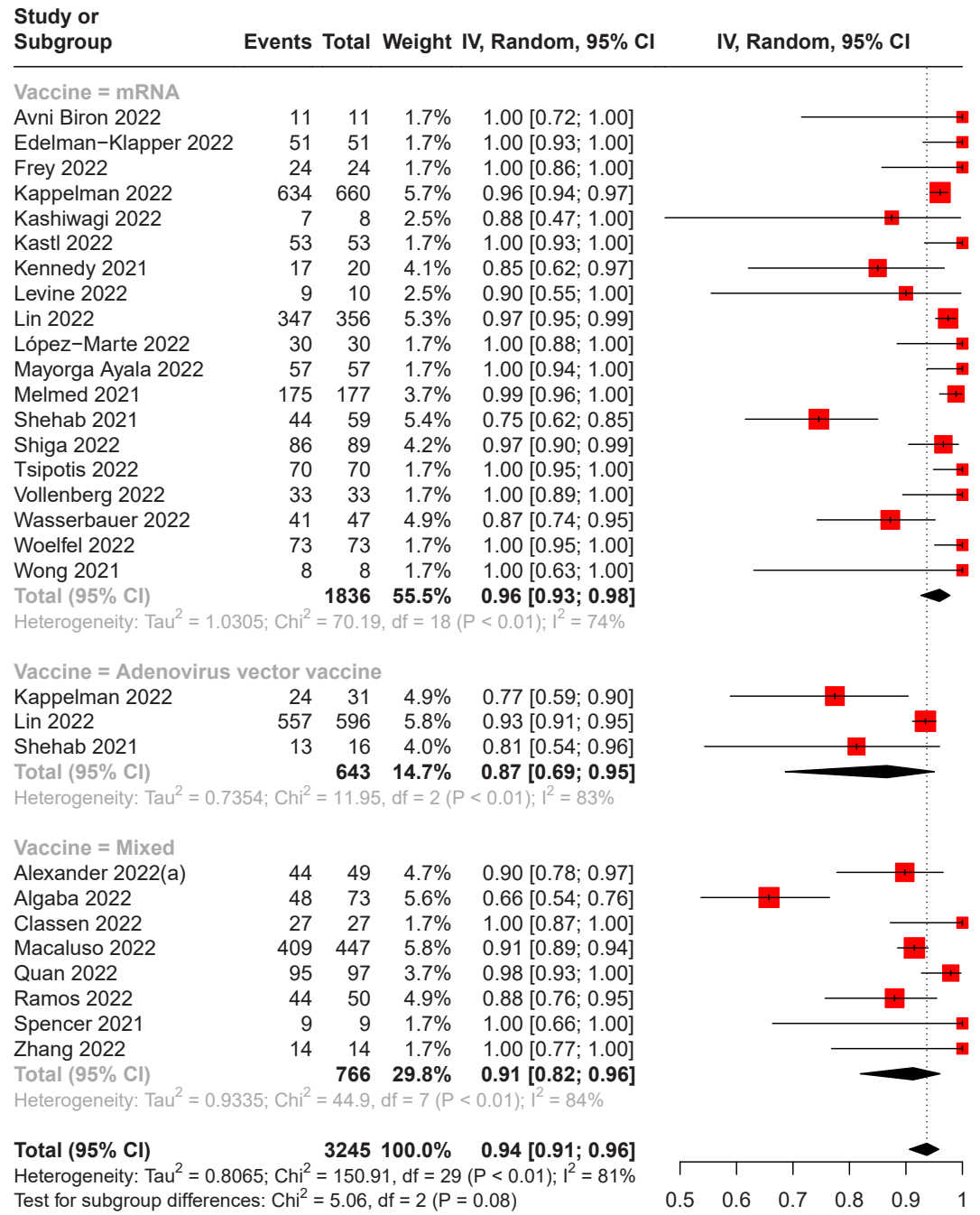

Fig. 2. Pooled seroconversion rate after complete COVID-19 vaccination in IBD patients receiving *anti*-TNF therapy. Abbreviations: mRNA, messenger RNA.

3.6. Breakthrough infections after complete vaccination

A total of 5 studies reported breakthrough infections in IBD patients receiving *anti*-TNF therapy after complete vaccination. These studies included 5670 IBD patients, among whom 324 experienced breakthrough infections. The pooled breakthrough infections rate in IBD patients receiving *anti*-TNF therapy was 0.04 (95%CI 0.02–0.09, $I^2 = 96\%$, Fig. S8). Moreover, the 5 studies also provided corresponding breakthrough infections in vaccinated IBD patients receiving other biological agents such as vedolizumab, ustekinumab, and tofacitinib. The pooled RR of breakthrough infections in vaccinated IBD patients receiving *anti*-TNF therapy was significantly higher than those IBD patients who received other biological agents (pooled RR 1.63, 95% CI 1.31–2.03, $I^2 = 0\%$, Fig S9).

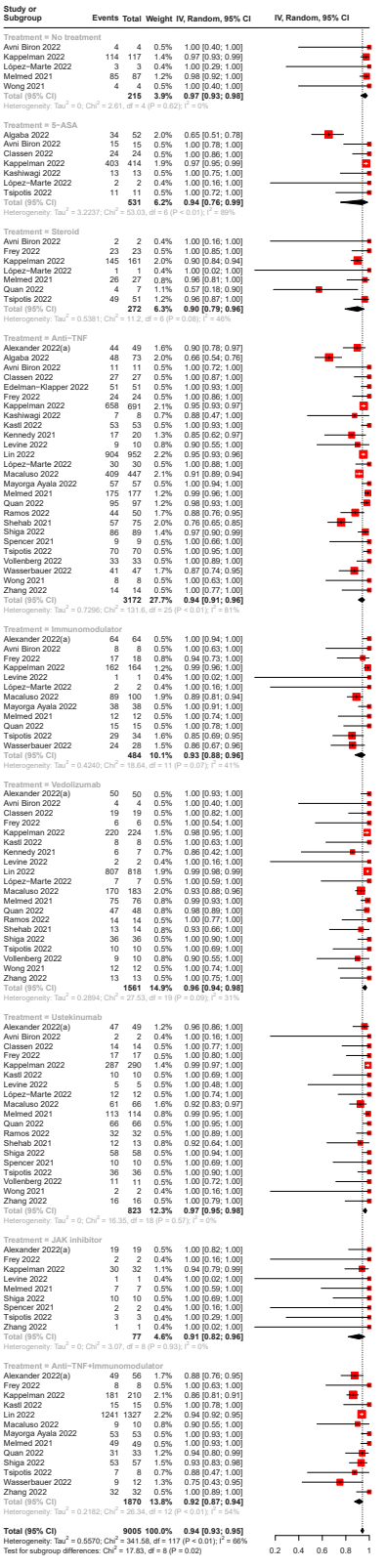

Fig. 3. Pooled seroconversion rate after complete COVID-19 vaccination in IBD patients depending on the different treatment. Abbreviations: 5-ASA, 5-aminosalicylic acid; JAK, Janus Kinase; TNF, tumor necrosis factor.

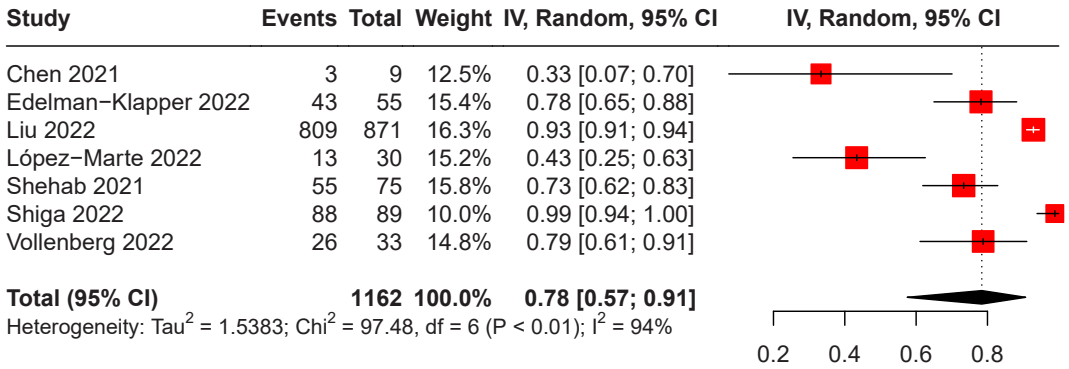

Fig. 4. Pooled positivity rate of neutralization response after complete COVID-19 vaccination in IBD patients receiving *anti*-TNF therapy.

3.7. Risk of bias assessment

According to the ROBINS-I tool, the risk of bias was rated as low in 24 studies, moderate in 8 studies (Table S5). No studies were assessed to be at severe or critical risk of bias. The main sources of bias were related to confounding effects and selective bias. For example, some studies had an unclear exposure history of SARS-CoV-2, and participants were not matched for age and basic diseases, which led to bias in the selection of participants and confounding effects. Furthermore, different antibody detection methods and criteria for determining seropositivity were also factors that led to the bias in measurement of outcomes.

3.8. Publication bias

We assessed publication bias in studies reporting seroconversion rate for complete vaccination. The visual inspection of the funnel plot and the Egger's test ($t = 1.37$, $p = 0.1822$) did not show significant publication bias (Fig. S10).

3.9. Heterogeneity

The Baujat plot, which was performed to analyze the seroconversion rate reported in studies after complete COVID-19 vaccination, indicated that the study by Algaba et al. [16] contributed the most to the heterogeneity of the meta-analysis. The report by Algaba et al. [16] not only had the greatest impact on the overall results but also significantly increased the heterogeneity of the meta-analysis (Fig. S11). Algaba et al. [16] reported seroconversion rate after complete COVID-19 vaccination including mRNA (BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna)) and AVV(ChAdOxl nCoV-19 (AstraZeneca), Ad26.COV2.S (Janssen)). Subgroup analysis of vaccine subtypes revealed high heterogeneity in mRNA, AVV, and mixed vaccines.

4. Discussion

COVID-19 pandemic is an ongoing global public health challenge, with millions of people reported to be infected. The strategy of vaccine development and widespread vaccination is considered to be an important step to curb the pandemic. Owning to immune dysfunction and frequent use of biological agents, the risk of COVID-19 infection in IBD patients is theoretically higher [46,47]. Therefore, the professional association have recommended COVID-19 vaccination in the IBD population [48]. Many advances have been made in the field of IBD treatment over the past two decades, with the mainstream use of *anti*-TNF agents being arguably the most notable. *Anti*-TNF therapy can not only effectively induce and maintain clinical remission and mucosal healing, but also improve the quality of life of IBD patients and reduce the rate of surgery and hospitalization [49–52]. It has become the cornerstone of the treatment of moderate to severe UC and CD, revolutionising the treatment of IBD. TNF-α has a variety of important immunomodulatory effects, including co-stimulation of antigen-activated T cells and driving B cell immunoglobulin synthesis [53]. Therefore, inhibition of TNF-α can have a negative impact on the immune system and may cause a reduced antibody response to COVID-19 vaccination. There have been numerous studies reporting lower COVID-19 vaccines responses in immunocompromised patients, as well as in IBD patients receiving biological agents, specifically *anti*-TNF [21,26,54]. However, there is a lack of systematic evaluation and meta-analysis summarizing current data on the effectiveness of COVID-19 vaccines in IBD patients receiving *anti*-TNF therapy. We summarized the seroconversion rate, neutralization response, T cell response, and breakthrough infections of COVID-19 vaccines in IBD patients receiving *anti*-TNF therapy through systematic evaluation and meta-analysis of the current data to evaluate the efficacy of COVID-19 vaccines in this population.

Seroconversion is the production of detectable and specific antibodies in serum as a result of a previous infection or vaccination. Seroconversion rate is considered to be an indicator of immunological efficacy of the COVID-19 vaccine. The meta-analysis revealed that only 59% of IBD patients treated with *anti*-TNF achieved a serologic response to incomplete COVID-19 vaccine, which improved to 94% after complete vaccination. The overall data showed that IBD patients receiving *anti*-TNF therapy had lower seroconversion rate

than healthy controls at both stages, especially after incomplete vaccination. Our findings support that a full course of COVID-19 vaccination and booster shots regimen in IBD patients is recommended by the professional societies [55]. The COVID-19 mRNA vaccines represent a new class of vaccine products. When evaluating the effect of different vaccine types on seroconversion rate, the mRNA vaccines seem to be the most effective as compared with AVV and mixed vaccine both the first and the second dose.

We further evaluated the effect of different therapeutic agents on the seroconversion rate of IBD patients. The seroconversion rate were similar for the different therapeutic agents. Although the serological response to steroid and *anti*-TNF combined with IMM therapy was lower relative to other drug treatments, both were also greater than 90%. IBD patients who received different drug treatments such as *anti*-TNF, vedolizumab, and ustekinumab, achieved a higher proportion of seroconversion. Interestingly, we found that the combined use of *anti*-TNF agents and immunomodulators reduced the antibody response compared with the use of *anti*-TNF agents monotherapy, which was consistent with the research results of Jena et al. [56]. In recent years, more and more attention has been paid to the effect of *anti*-TNF drugs on the efficacy of COVID-19 vaccine. There are numerous studies demonstrated that in IBD patients receiving *anti*-TNF, compared to *anti*-TNF untreated and healthy controls, a dramatic reduction in antibody titers and antibody longevity was observed [29]. However, our study did not find that the seroconversion rate statistically differ between different agents. Our results provide a strong basis for evaluating the seroconversion of patients taking biological agents.

The T cell response is also an important part of evaluating the response to COVID-19 vaccines. It is important to note that while the production of antibodies is an important part of the immune response to SARS-CoV-2, T cell response can provide long-lasting protection against the virus even when antibody levels decline over time [36]. Therefore, the induction of T cell response by COVID-19 vaccines is an important aspect of its efficacy. Studies have shown that in some cases, the T cell response may be discordant with the antibody response. This means that even though the antibody response may be low, T cells may still be able to resist the pathogen [33]. Interestingly, studies have also shown that *anti*-TNF therapy could enhance T cell response [57]. This suggests that even in patients with attenuated antibody responses, the T cell response may not be compromised and may still be able to mount an effective immune response against the pathogen. In the included studies, Alexander et al. [15] found that T cell response in IBD patients receiving *anti*-TNF therapy after complete vaccination were not attenuated relative to healthy controls. These data are consistent with observations from Lin et al. [29] and Mayorga Ayala et al. [31], where T cell response were not significantly different between IBD patients receiving *anti*-TNF therapy and other therapies. In contrast, the findings of the Woelfel et al. [43] showed T cell response to complete vaccination were reduced in IBD patients receiving *anti*-TNF therapy compared to healthy controls. Nevertheless, in view of the small number of studies on T cell response included in this review, the analysis of possible differences were limited.

Another important indicator to measure the effectiveness of COVID-19 vaccine is the incidence of breakthrough infections after vaccination. A breakthrough infection was defined as a SARS-CoV-2 infection diagnosed with a positive PCR test more than 14 days after complete COVID-19 vaccine. In the case of COVID-19, breakthrough infections are of particular concern because the virus can cause severe disease, and some variants of the virus may be more resistant to vaccines. Breakthrough infections, which are associated with lower antibody levels after the second dose of vaccine, are more common and occur earlier in IBD patients receiving *anti*-TNF therapy. This meta-analysis showed that the breakthrough infections rate was 4% in IBD patients receiving *anti*-TNF therapy. Furthermore, our research showed that the risk of breakthrough infections in IBD patients receivig *anti*-TNF was significantly higher compared with patients receiving other biological agents such as vedolizumab, ustekinumab, and tofacitinib. Studies have shown that patients with IBD receiving *anti*-TNF therapy have a weaker and less durable vaccine-induced antibody response, which may be associated with an increased risk of breakthrough SARS-CoV-2 infection [28]. It is important to continue the vaccination programmes in COVID-19, such as the third dose of vaccine, especially in patients whose immunogenicity and efficacy may be reduced, such as those receiving *anti*-TNF therapies. However, as only five studies have assessed breakthrough infections after COVID-19 vaccination and fewer studies have set up healthy controls, further studies are needed to assess the risk of breakthrough infections in IBD patients.

Neutralizing antibodies are an important part of the immune response to the COVID-19 vaccine and play a vital role in patient survival and virus control. Studies have shown that higher levels of neutralizing antibodies are associated with greater protection against SARS-CoV-2 [58]. Our meta-analysis shows that the pooled RR for positivity in neutralization assays was significantly lower in IBD patients receiving *anti*-TNF therapy as compared with healthy controls, suggesting that *anti*-TNF therapy may increase the risk of breakthrough infection. However, the neutralization response may vary depending on the type of vaccine and treatments used. Owning to the small number of relevant studies, we failed to perform a subgroup analysis of the effect of various vaccine types and treatments on the neutralization response.

Our meta-analysis has certain limitations. First, factors that may affect the immune response to vaccines, such as age, type of IBD, disease activity, and drug therapies, may not be controlled across different studies, which is one of the reasons for the high heterogeneity of this study. We tried to reduce heterogeneity by subgroup analysis of vaccine types and drug classification. Second, given that the studies included in this meta-analysis were predominantly mRNA vaccines, further research is needed to determine whether the results of our study can be generalized to other types of vaccines. Third, the definition of seroconversion and the serological assays of immune response assessment used were not standardized across the studies. Although some assays are comparable [59], further research is needed to assess the seroconversion between different assays of SARS-CoV-2 antibody detection.

In conclusion, this meta-analysis showed that IBD patients receiving *anti*-TNF therapy had relatively high overall seroconversion rate after complete COVID-19 vaccination, with no statistical difference in antibody responses associated with different drug treatments. However, the breakthrough infections rate of IBD patients receiving *anti*-TNF therapy was significantly higher than that of IBD patients receiving other biological agents. Neutralization response was significantly impaired in IBD patients receiving *anti*-TNF therapy compared to healthy controls. Further research is needed to determine this risk and the associated mechanisms.

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Author contribution statement

Dan Dou: Performed the experiments; Wrote the paper. Fangyi Zhang: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data. Xin Deng: Performed the experiments; Contributed reagents, materials, analysis tools or data. Yun Ma; Xingyu Ji; Shuqing Wang; Xihan Zhu: Analyzed and interpreted the data. Dianpeng Wang: Contributed reagents, materials, analysis tools or data. Shengsheng Zhang; Luqing Zhao: Conceived and designed the experiments; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e19609.

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