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Meta-Analysis

Safety of SARS-CoV-2 vaccination in patients with inflammatory bowel disease: A systematic review and meta-analysis

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ABSTRACT

Introduction: Risk of adverse effects and flare of inflammatory bowel disease (IBD) are frequently cited reasons for COVID-19 vaccine hesitancy.
Methods: Electronic databases were searched to identify studies reporting the use of COVID-19 vaccine in IBD. We selected studies reporting the incidence of various adverse effects (local or systemic) and flares of IBD after COVID-19 vaccination. The pooled incidence rates for various adverse effects, stratified for the dose and the type of vaccine (adenoviral or mRNA) were estimated.
Results: Nine studies (16 vaccination cohorts) were included. The pooled incidence rate of overall adverse events was 0.55 (95%CI, 0.45–0.64, I^2= 95%). The pooled incidence rate of local adverse events was 0.64 (0.47–0.78, I^2= 100%). The pooled incidence rates of fatigue, headache, myalgia, fever and chills were 0.30 (0.21–0.40, I^2= 99%), 0.23 (0.17–0.30, I^2= 99%), 0.18 (0.13–0.24, I^2= 99%), 0.10 (0.06–0.17, I^2= 98%) and 0.15 (0.06–0.3, I^2= 86%), respectively. The pooled incidence rates of severe adverse events, adverse events requiring hospitalization and flares of IBD following COVID-19 vaccination were 0.02 (0.00–0.12, I^2= 97%), 0.00 (0.00–0.01, I^2= 27%) and 0.01 (0.01–0.03, I^2= 45%), respectively.
Conclusion: COVID-19 vaccination in patients with IBD appears to be safe with only mild adverse events. Flares of IBD and severe adverse events requiring hospitalization were infrequent.
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1. Introduction

COVID-19 vaccination is recommended as an important strategy to control the pandemic. Various society guidelines recommend a full course of COVID-19 vaccination along with a booster dose [1–4]. The management of patients with IBD has been a challenge amidst the COVID-19 pandemic [1]. Regardless of biological therapies or immunomodulators use, the non-live vaccines are generally considered safe in patients with IBD. The trials of the vaccines which led to the emergency approval had excluded patients of both ulcerative colitis (UC) and Crohn's disease (CD). The response to vaccination in patients with IBD on various immune modifying drugs, was variable [5,6]. The concerns regarding adverse events of COVID-19 vaccination increased after reports of thrombotic events following vaccination. The FDA had to issue a statement suggesting that the benefits outweigh the risks. The adverse events following vaccination are an important concern among the patients with IBD [7,8]. The concerns include possible adverse events, flaring of the underlying IBD and decreased responsiveness to vaccines. The concern for adverse events has been a major reason for vaccine hesitancy among patients with IBD [7,8].

Despite encouraging data on vaccine efficacy in IBD, there is limited information on adverse effects of various COVID-19 vaccines. We performed a systematic review and single-arm meta-analysis on the various adverse events following COVID-19 vaccination in patients with IBD in order to inform the clinicians and patients regarding the (lack of) risks) of COVID vaccination.

2. Methods

This meta-analysis was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group recommendations and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance [9,10].

2.1. Database search

A literature search was done in electronic databases using PubMed and Embase (recent till 17 December, 2021) using the key-

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words inflammatory bowel disease, ulcerative colitis, Crohn's disease combined using the operator 'AND' COVID-19, SARS-COV-2 AND Vaccine or Vaccination or Immunization. The detailed strategy is described in **Supplementary Table 1.** The bibliographies of eligible studies were also searched for additional papers. Preprint servers medRxiv and bioRxiv were also searched for any additional papers. The eligible titles were combined and the duplicates were removed. The titles and abstracts were then reviewed by two reviewers (DJ and PB). After screening of titles and abstracts, full text screening was done (DJ, AJ, AC). Any differences were resolved after discussion with a third reviewer (VS).

2.2. Inclusion and exclusion criteria

We included all relevant articles (uncontrolled, single-arm prospective / retrospective studies including abstracts) pertaining to adverse events of COVID-19 vaccines or the language of publication, in the systematic review. We included studies reporting at least one of following outcomes in IBD-

1. Adverse events or side effects following COVID-19 vaccination.
2. Flare of underlying disease following COVID-19 vaccination.

We excluded case reports, case series (< 10 cases), surveys, reviews, guidelines, editorials and studies which did not report relevant data about adverse events after vaccination. Studies which reported seroconversion rates after COVID vaccination were included in full text screening to look for any additional information regarding adverse events.

2.3. Data extraction

The data was extracted from the appropriate studies by two reviewers (DJ and PB) and any disagreement was resolved by discussion with the third reviewer (VS). The data was extracted irrespective of the type (mRNA or Adenoviral) or dose of vaccine. We extracted data regarding the details of the publication (name of author and location), underlying population (ulcerative colitis or Crohn's disease), underling disease activity, characteristics of patients (age, gender, concomitant drugs), type of vaccine (mRNA or AAV), number of doses (first or second dose) and details of adverse events.

2.4. Outcomes

We performed a single-arm meta-analysis (pooled data analysis) in absence of control arms. The pooled incidence rates of adverse events after COVID-19 vaccine were calculated. We calculated the pooled incidence rates of both the local and systemic adverse events following vaccination. The definitions of local or systemic adverse event were used as defined in individual studies. We also calculated the pooled rates of flare of underlying disease activity in IBD, severe adverse events and adverse events requiring hospitalization after COVID vaccination. The analysis was performed separately for single and double dose vaccine regimens.

2.5. Data analysis

The analysis was conducted using the R statistical software, version 4.0.1. In addition to it, meta and metafor packages for R were also used [11,12]. The pooled rates of each adverse event was calculated using the random effects model with inverse variance approach. The random effects model was chosen because of the underlying heterogeneity in the studies, included population, vaccines and doses, and the reported outcomes. Subgroup analysis was conducted for calculating the pooled adverse events rate depending on the type and dose of vaccine. The heterogeneity was determined by I^2 and P value of heterogeneity. A standard continuity correction of 0.5 was applied when the number of events was zero.

2.5.1. Methodological quality and risk of bias assessment

Two of the investigators (DJ and AJ) independently assessed the methodological quality and risk of bias of studies using the Newcastle Ottawa Scale (NOS) for cohort studies [13]. Any discordance in risk of bias, was settled with mutual agreement with a third reviewer (VS). The included studies were rated as having good/ fair or poor quality as per the scale provided along with the NOS table (Supplementary Table 3).

3. Results

The search yielded 429 citations. **(**Fig. 1**, PRISMA flow chart)** Of the total of 429 studies, there were 95 duplicates. We excluded 302 citations after abstract screening. We obtained 3 further studies after manual searching of the references of included studies. After full text screening of 35 articles, we excluded 26 studies not fulfilling inclusion criteria. Eventually, 9 studies (8 full texts and one abstract) with 16 cohorts were included in the final analysis. The details of the included studies are illustrated in Table 1 [14–22]. The details of the excluded studies with the reason for exclusion is shown in **Supplementary Table 2** [23–48].

3.1. Total adverse events in patients with IBD following vaccination

There were 6 studies (9 cohorts, 3930 patients) reporting adverse events following COVID-19 vaccination in patients with IBD. The pooled incidence rate of adverse events in IBD patients following COVID-19 vaccination was 0.55 (95%CI, 0.45–0.64, I^2 = 95%) **(**Fig. 2**)**. There were 3 studies (4 cohorts, 2944 patients) reporting adverse events following m-RNA based COVID-19 vaccination in patients with IBD. The pooled incidence rate of adverse events in IBD patients following only m-RNA based COVID-19 vaccination was 0.52 (95%CI, 0.33–0.71, I^2 = 95%) **(**Fig. 2**)**. There were 4 studies of 1948 patients and 4 studies of 1946 patients reporting adverse events following single and double dose vaccination, respectively. The pooled incidence rate of adverse events in IBD patients following single dose COVID-19 vaccination was 0.47 (95%CI, 0.36–0.58, I^2 = 93%) **(**Fig. 3). The pooled incidence rate of adverse events in IBD patients following double dose COVID-19 vaccination was 0.57 (95%CI, 0.45–0.69, I^2 = 89%) **(**Fig. 3).

3.2. Local adverse events following vaccination in patients of IBD

There were 5 studies (8 cohorts, 9710 patients) reporting local injection site adverse events following COVID-19 vaccination. The pooled incidence rate of local adverse events in IBD patients following COVID-19 vaccination was 0.64 (95%CI, 0.47–0.78, I^2 = 100%) **(**Fig. 4). The pooled incidence rate of local adverse events following mRNA based COVID-19 vaccination was 0.53 (95%CI, 0.40–0.66, I^2 = 97%) **(**Fig. 4). The pooled incidence rate of local adverse events following a single dose COVID-19 vaccination was 0.60 (95%CI, 0.32–0.83, I^2 = 100%) **(Supplementary Fig. 1).** The pooled incidence rate of local adverse events following a double dose of COVID-19 vaccination was 0.71 (95%CI, 0.47–0.87, I^2 = 100%) **(Supplementary Fig. 1)**. The pooled incidence rate of soreness of the arm was 0.52 (95%CI, 0.43–0.60, I^2 = 98%) **(Supplementary Fig. 2). Supplementary Table 4** provides definitions for local and systemic adverse events as used in individual studies.

3.3. Systemic adverse events following vaccination in patients of IBD

The pooled incidence rate of fever and chills following COVID-19 vaccination in patients of IBD was 0.10 (95%CI, 0.06–0.17,

Table 1
The included studies with details regarding the included population and vaccination.

Authors	Country	Type of study	Vaccine type, Vaccination status (Complete/ Incomplete/ Mixed)				Total	Mean Age (SD) (years)	Number of patients					Dose breakup		Adverse events				Follow up duration
			mRNA	mRNA type	AAV	AAV type			Female	CD	UC	Disease activity	Drugs	D1	D2	Total	Local	Systemic	Miscellaneous	
Dailey et al. [14]	USA	Prospective longitudinal cohort study	28 Mixed	21 - Pfizer-BioNTech 7 - Moderna	5 Complete	Johnson & Johnson 5	33	NA	NA	NA	NA	Not mentioned	NA	33	28	NA	NA	NA	NA	2 weeks to 6 months
Botwin et al. [15]	USA	Prospective longitudinal study	246 Mixed	141- Pfizer-BioNTech, 105 - Moderna	0	0	246	47.4 (15.5)	139	165	81	Not mentioned	Oral/ rectal Sulfasalazine/ mesalamine, Budesonide, Oral/ parenteral steroids, 6MP/ Azathioprine, Methotrexate, Anti TNF, Anti integrin, IL12/23 inhibitor, JAK inhibitor	246	NA	96	93	NA	NA	At least 7 days
Wong et al. [16]	USA	Longitudinal nested case-control study	48 Mixed	23 – Pfizer-BioNTech, 25 -NIH-Moderna	0	0	48	49.1 (20.2)	25	23	25	Not mentioned	Infliximab, Adalimumab, Vedolizumab, Ustekinumab, Tofacitinib, Oral steroids, Immunomodulator, Mesalamine, No medications	48	26	29	19	NA	NA	85 days
Edelman-Klapper et al. [17]	Israel	Multicenter prospective observational study	185 Mixed	Pfizer-BioNTech	0	0	185	38.1(14.3)	73	122	53	120 – remission 65 - active disease	Infliximab, Adalimumab, Vedolizumab, Ustekinumab, 5-ASA, Steroids, Immunomodulators, JAK inhibitor	185	185	Expressed dose-wise				30 days median
Garrido et al. [18]	Portugal	Single center longitudinal cohort study	190 Mixed	141 - Pfizer-BioNTech, 49 - Moderna	49 Mixed	34 - Johnson & Johnson, 15 - AstraZeneca	239	NA	NA	NA	NA	Not mentioned	Anti TNF, Ustekinumab, Vedolizumab	239	173	Expressed dose-wise				NA

(*continued on next page*)

Table 1 (*continued*)

Authors	Country	Type of study	Vaccine type, Vaccination status (Complete/ Incomplete/ Mixed)				Total	Mean Age (SD) (years)	Number of patients					Dose breakup		Adverse events				Follow up duration
			mRNA	mRNA type	AAV	AAV type			Female	CD	UC	Disease activity	Drugs	D1	D2	Total	Local	Systemic	Miscellaneous	
Cannatelli et al. [19]	Italy	Prospective study	470 Mixed	320 - Pfizer-BioNTech, 150 - Moderna	18 Mixed	AstraZeneca	488	55.3 (14.4)	270	233	246	397 – remission, 91 – active disease	No treatment, Mesalamine, Corticosteroids, Azathioprine, Infliximab, Adalimumab, Golimumab, Vedolizumab, Ustekinumab, Tofacitinib	488	433	228	Expressed dose-wise			NA
Weaver et al. [10]	USA	Prospective observational cohort study	3155 Mixed	1908 - Pfizer-BioNTech, 1247 - Moderna	161 Complete	Johnson & Johnson	3316	43.7 (15.1)	2378	1811	NA	1077 – remission 2239 – active disease	Oral/parenteral steroids, Oral budesonide, Oral mesalamine, Sulfasalazine, Thiopurine, Methotrexate, Infliximab, Adalimumab, Certolizumab, Golimumab, Vedolizumab, Ustekinumab, Tofacitinib, Cyclosporine, Tacrolimus	3316	3080	Expressed dose-wise				Up to 7 days
Mujukian et al. [21]	USA	longitudinal case control study	1391 Mixed	828 - Pfizer-BioNTech, 563 - Moderna	0	0	1391	NA	873	904	487	Not mentioned	NA	1391	1271	Expressed dose-wise				On Day 7
Classen et al. [22]	Germany	Retrospective observational		Heterogeneous data			72	48.4 (15.2)	38	40	32	Not mentioned, One case was in flare	Steroids, Mesalazine, Azathioprine, Methothrexate, Calcineurin inhibitor, Anti TNF, Anti integrin, JAK inhibitors, Ustekinumab	NA	NA	Expressed dose-wise				NA

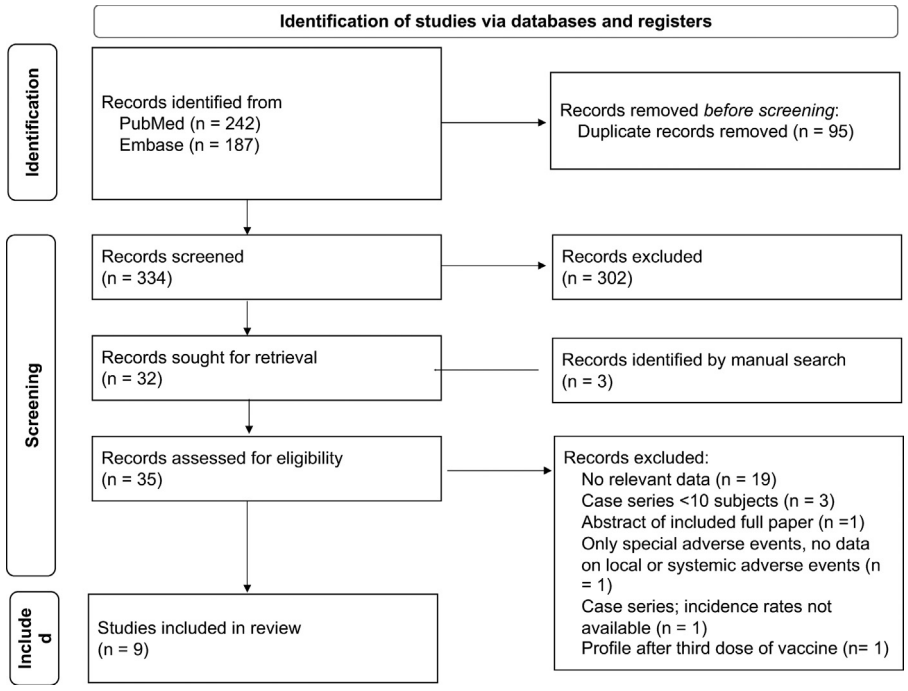

Fig. 1. PRISMA flow chart depicting the study screening and selection of the systematic review.

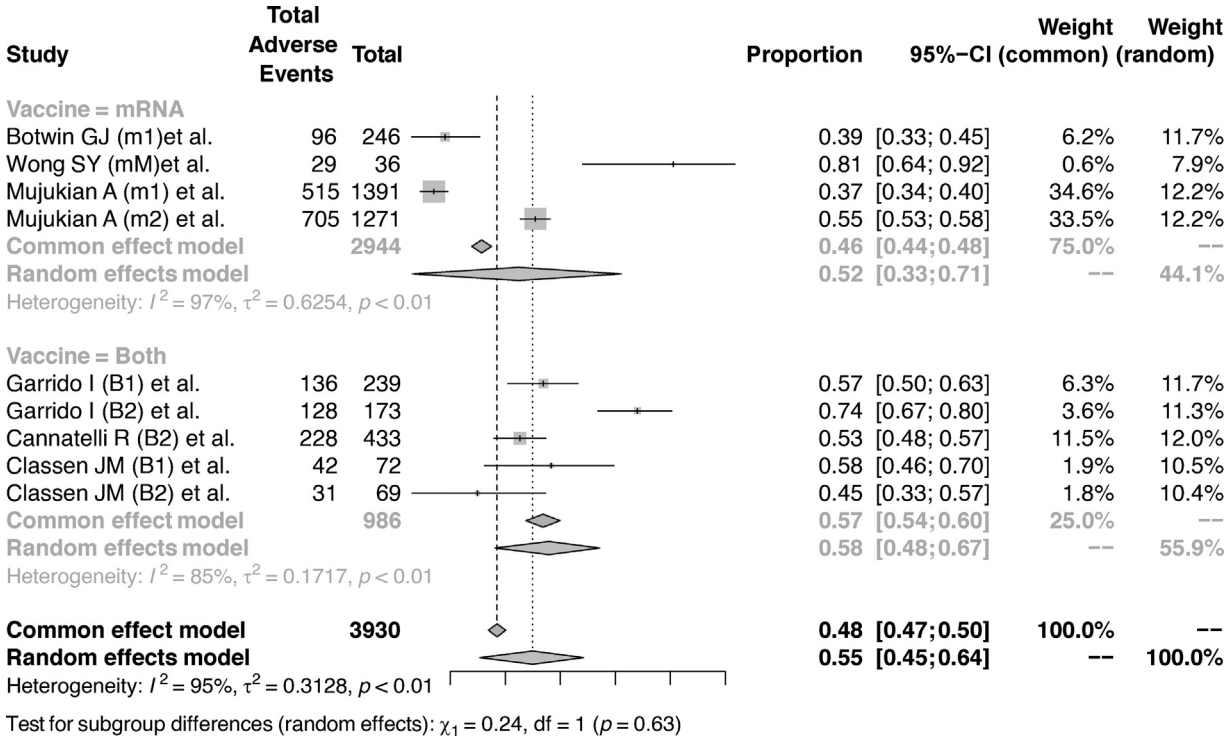

Fig. 2. Adverse events following COVID-19 vaccination in patients with IBD subtyped for type of vaccine.

I^2 = 98%) and 0.15 (95%CI, 0.06–0.3, I^2 = 86%), respectively **(Supplementary Figs. 3 and 4)**. The pooled incidence rate of fatigue and myalgia following COVID-19 vaccination in patients of IBD was 0.30 (95%CI, 0.21–0.40, I^2 = 99%) and 0.18 (95%CI, 0.13–0.24, I^2 = 99%), respectively **(Supplementary Figs. 5 and 6)**. The pooled incidence rate of headache following COVID-19 vaccination in patients of IBD was 0.23 (95%CI, 0.17–0.30, I^2 = 99%) **(Supplementary Fig. 7)** while for joint pain it was 0.10 (95%CI, 0.06–0.17, I^2 = 98%) **(Supplementary Fig. 8)**. The pooled incidence rate of skin rash following COVID-19 vaccination in patients of IBD was 0.01 (95%CI, 0.01–0.01, I^2=29%) **(Supplementary Fig. 9)**. The pooled incidence rate of gastrointestinal adverse events following vaccination in patients with IBD was 0.08 (95%CI, 0.05–0.12, I^2 = 97%) **(Supplementary Fig. 10)**.

3.4. Severe adverse events following vaccination in patients of IBD

Of the 6 studies (7590 total events) the pooled rates of severe adverse events were 0.02 (95%CI, 0.00–0.12, I^2 = 97%) (Fig. 5, **Top Panel).** There were 5 studies (7 cohorts, 7578 patients) reporting

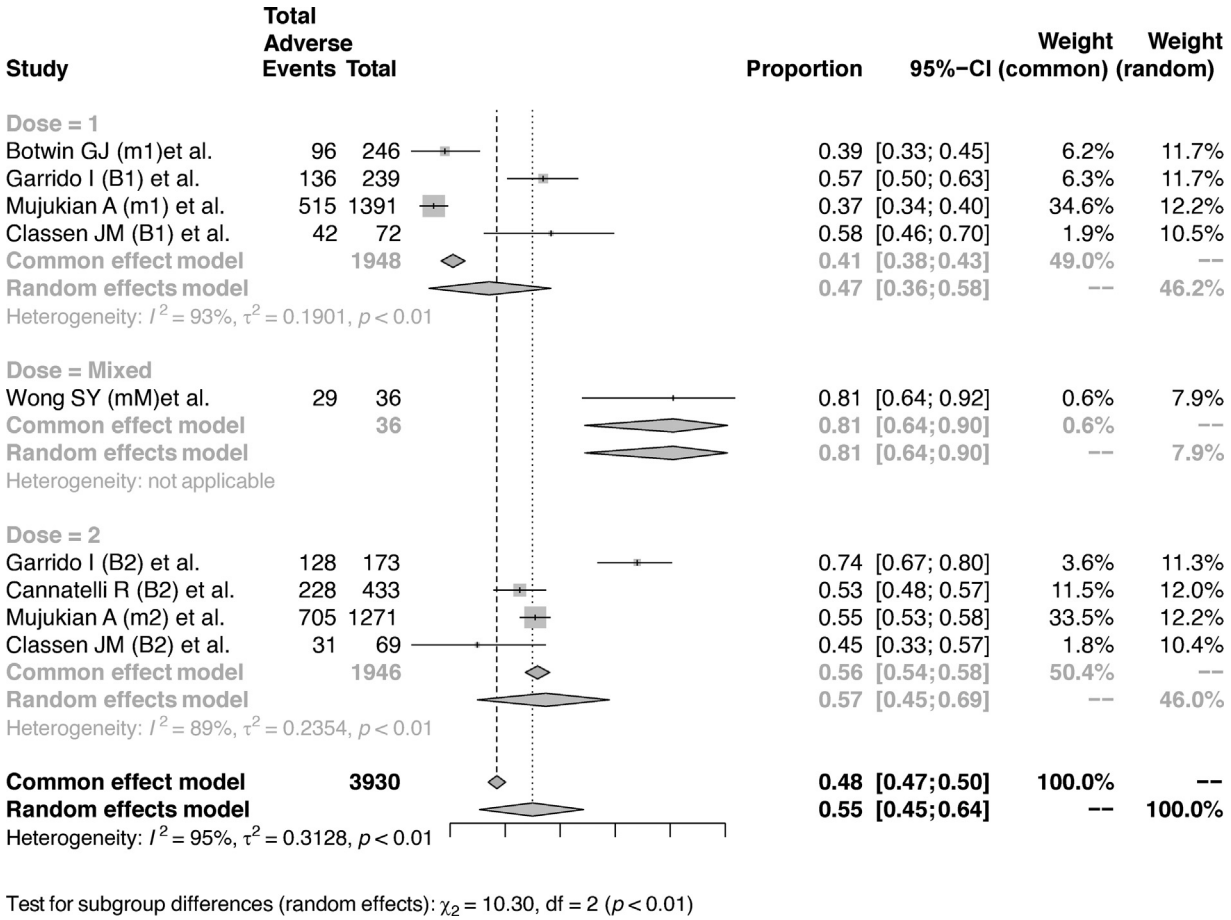

Fig. 3. Adverse events following COVID-19 vaccination in patients with IBD subtyped for dose of vaccine.

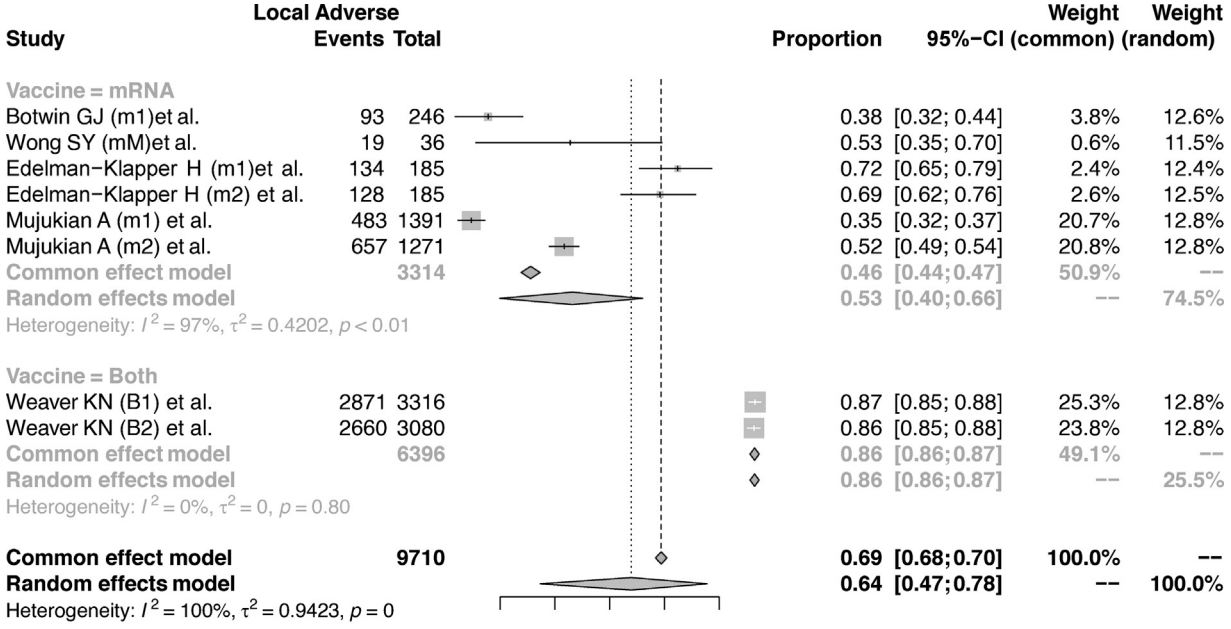

Fig. 4. Local adverse events following COVID-19 vaccination in patients with IBD subtyped for type of vaccine.

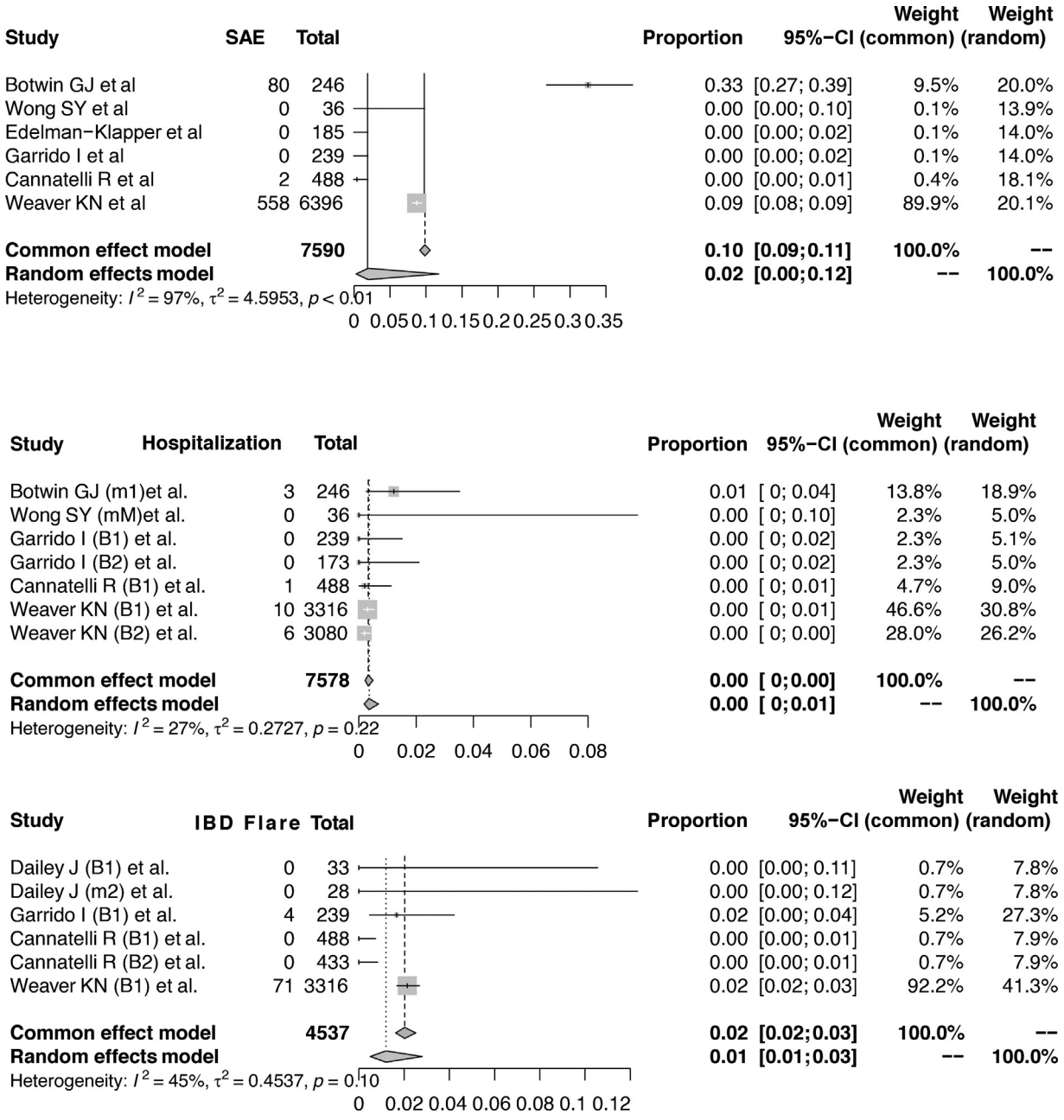

Fig. 5. Top panel: severe Adverse events following COVID-19 vaccination in patients with IBD; Middle Panel: adverse events requiring hospitalization following COVID-19 vaccination in patients with IBD; bottom panel: adverse events causing flare of disease in IBD following COVID-19 vaccination.

adverse events requiring hospitalization in IBD following COVID-19 vaccination. The pooled incidence rate of adverse events requiring hospitalization following COVID-19 vaccination was 0.00 (95%CI, 0.00–0.01, I^2 = 27%) (Fig. 5- **Middle panel**).

3.5. IBD flare following vaccination

There were 4 studies (6 cohorts, 4537 patients) reporting flare of disease in IBD following COVID-19 vaccination. The pooled incidence rate of flare of disease following COVID-19 vaccination was 0.01 (95%CI, 0.01–0.03, I^2 = 45%) (Fig. 5- **bottom panel**).

3.6. Risk of bias analysis

The quality analysis of the included studies was done using Newcastle-Ottawa Quality Assessment Form for Cohort Studies. The results of the assessment are shown in **Supplementary Table 3** [14–22]. Of the included studies, two studies were of good quality, three studies were of fair quality and four studies were of poor quality.

4. Discussion

SARS-CoV2 virus, being a mutating virus with emerging variants of concern, vaccination remains the core strategy for control of the pandemic [49]. In the real-world analysis of patients of IBD, adverse events following COVID-19 vaccination were seen in nearly half of the entire cohort irrespective of the dose of vaccine. However, most of these were local adverse events, the majority being injection site related. Systemic adverse events following vaccination were rare with the majority not requiring hospitalization. Fatigue, headache, myalgia, fever and chills were the most common systemic adverse events following COVID-19 vaccination. The find-

ings suggest that COVID-19 vaccination is safe for patients with IBD.

Fear of adverse events especially flare of disease activity in IBD remains a major concern in patients with IBD [7,8,50]. This is one of the important causes of vaccine hesitancy in patients with IBD. A survey in Italy revealed fear of negative impact on the course of IBD was seen in 52% of respondents [51]. To address this, we found gastrointestinal related adverse effects were also low in incidence and a flare of underlying disease activity in IBD following vaccination was seen in extremely small numbers. The data reaffirms the fact that vaccination has minimal impact on the course of disease in IBD.

The risk of adverse events in a survey in China was seen at 88% and was one of the major reasons behind the lack of intention to take vaccines [52]. Other causes include concern that vaccines are being made quickly. The findings of our meta-analysis show a majority of adverse events were limited to injection site side effects. Systemic adverse events were reported only in a small subset. Adverse events of importance like immune mediated thrombocytopenia, Guillain-Barré syndrome, transverse myelitis, stroke, deep vein thrombosis, myocarditis and myocardial infarction were reported in a study and was seen in a minority (2.03%) of patients of IBD [31]. There is a need for close monitoring and reporting of these severe adverse events in patients of IBD.

There were similar adverse events after the first or second dose of COVID-19 vaccine in patients with IBD. The pooled incidence rates were similar between the first and second dose of COVID-19 vaccine. There was only one study reporting about adverse events after the third dose and showed adverse events in 41% of the patients [36]. They found that the adverse events were similar to that of the second dose while post vaccination symptoms were lower than that of the second dose. Data from vaccination in general population suggest that of a cohort with 655 590 doses (mRNA and AAV), systemic side-effects occurred in 13•5% and 33.7% after first dose of mRNA and AAV vaccine, respectively and 22•0% after second dose of mRNA vaccine. Local side-effects were reported 71.9% and 58.7% after first dose of mRNA and AAV vaccine, respectively and 68•5% after the second dose of mRNA vaccine [53]. The local adverse events are comparable to our analysis in IBD patients. We do not have estimates for systemic adverse events overall for IBD patients.

There are some limitations of the study. There is no control arm in most studies. We could not address the impact of age, comorbidities and drugs on the incidence of adverse events by a meta-regression largely due to small number of studies (< 10). There were only two studies reporting AAV related adverse events. Lastly, the included studies were not homogeneous with some studies reporting mixed vaccine schedules. The assessment for publication bias could not be done using the relevant statistical tests due to small number of studies. Also, there could be an overlap in certain definition e.g. gastrointestinal symptoms and flare of IBD. We have used the definitions exactly as provided in individual studies (Supplementary Table 4); it clearly shows that some studies consider flares as a component of gastrointestinal symptoms while others considered these as separate entities. Further although we have done subgroup analysis of adverse events after one or two dose, this is not the same as incomplete or complete vaccination. Certain vaccines like Janssen may have a single dose only in the complete schedule.

To conclude, the meta-analysis confirms that COVID-19 vaccine is safe in patients with IBD and not associated with flares of disease. This study should reduce the vaccine hesitancy among the patients with IBD and the clinicians should affirm that benefits outweigh the risks. Future studies should look into adverse events of each vaccine type and critically look into mechanisms of severe adverse events following vaccination. Post marketing surveillance of vaccine related adverse events especially of patients of pediatric population, elderly and with comorbidities are needed.

Conflict of interest

None declared.

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None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.03.005.

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