

pISSN 1598-9100 • eISSN 2288-1956 https://doi.org/10.5217/ir.2022.00094 Intest Res 2023;21(3):392-405

INTESTINAL RESEARCH

Prevalence of hepatitis B virus and hepatitis C virus infection in patients with inflammatory bowel disease: a systematic review and meta-analysis

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Background/Aims: The data on the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection in patients with inflammatory bowel disease (IBD) are conflicting. The present systematic review was thus conducted to study the prevalence of HBV and HCV markers in patients with IBD. **Methods:** A comprehensive literature search of 3 databases was conducted from 2000 to April 2022 for studies evaluating the prevalence of HBV or HCV in patients with IBD. Pooled prevalence rates across studies were expressed with summative statistics. **Results:** A total of 34 studies were included in the final analysis. The pooled prevalence of hepatitis B surface antigen (HBsAg) and hepatitis B core antibodies were 3.3% and 14.2%, respectively. In HBsAg positive IBD patients, hepatitis B e antigen positivity and detectable HBV DNA were seen in 15.3% and 61.0% of patients, respectively. Only 35.6% of the IBD patients had effective HBV vaccination. The pooled prevalence of anti-HCV and detectable HCV RNA were 1.8% and 0.8%, respectively. The pooled prevalence of markers of HBV infection was higher in Asian studies, while the prevalence of markers of HCV infection was higher in European studies. The prevalence of viral hepatitis markers was similar between IBD patients and the general population and that between ulcerative colitis and Crohn's disease. **Conclusions:** The prevalence of markers of viral hepatitis remains same as the general population with significant regional variations, although the quality of evidence remains low due to publication bias. Only a small proportion of IBD patients had an effective HBV vaccination practices. **(Intest Res 2023;21:392-405)**

Key Words: Inflammatory bowel disease; Colitis, ulcerative; Crohn disease; Hepatitis B; Hepatitis C

INTRODUCTION

Inflammatory bowel disease (IBD), which encompasses 2 clinical forms, namely ulcerative colitis (UC) and Crohn's disease (CD), is a heterogeneous group of inflammatory disorders of the gastrointestinal tract.¹ Though the disease is more

Received July 19, 2022. Revised August 24, 2022. Accepted August 30, 2022. Correspondence to Aditya Kale, Department of Gastroenterology, King Edward Memorial Hospital and Seth Gordhandas Sunderdas Medical College, New OPD Building, Parel, Mumbai 400012, India. Tel: +91-89622-63999, Fax: +91-44-2410-7585, E-mail: adityapkale@yahoo.com prevalent in the West, there has been an increasing incidence in Asian countries in the last two decades.^{2,3} The treatment of IBD primarily involves immunosuppressive and immunomodulatory drugs. This not only increases the chance of prevalence of various chronic infective diseases like chronic hepatitis C virus (HCV) and hepatitis B virus (HBV) but also may lead to reactivation of the latter disease.^{4,6} This will have more impact on Asian countries due to the moderately high prevalence of HBV infection.⁷ Therefore, screening for chronic HBV and HCV is crucial before starting the immunosuppressive treatment in IBD. Nonalcoholic fatty liver disease is becoming more com-

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mon in patients with IBD.⁸ On the other hand, the drugs like thiopurines may provoke liver damage even in the normal liver or may increase the viremia in chronic hepatitis C, leading to the progression of liver fibrosis.⁹ Therefore, to prevent the progression of liver disease due to the interplay in the management of IBD and viral hepatitis, identification of viral hepatitis is important in while treating IBD.¹⁰

Although there are scarce case-control data on prevalence of chronic viral infections in IBD patients, the prevalence is thought to be similar to the general population.¹¹ The European Crohn's and Colitis Organisation guideline recommends the measurement of IgG antibodies against HBV, and HCV for all IBD patients, either at the initial disease diagnosis or while starting treatment with immunosuppressive agents.¹² There is large data on overall prevalence of HBV and HCV infection among general population. However, to the best of our knowledge, there is hardly any previously published systematic review or meta-analysis on prevalence among IBD patients. The main objective of this meta-analysis was to evaluate the prevalence of HBV and HCV infection in patients with IBD.

METHODS

The present systematic review and meta-analysis were conducted as per the Meta-analysis Of Observational Studies in Epidemiology (MOOSE)¹³ and the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIS-MA)¹⁴ guidelines. Institutional review board approval and informed patient consent were not applicable for systematic review and meta-analysis.

1. Information Source and Search Strategy

Electronic databases of MEDLINE, Embase, and Science Direct were searched from 2000 to April 2022 for the title and abstracts of all relevant studies using the keywords: (IBD or "Inflammatory bowel disease" or "Crohn's disease" or CD or "Ulcerative colitis" or UC) and (Hepatitis B or HBV or Hepatitis C or HCV). Two independent reviewers (S.G. and S.A) screened the title and abstract of the retrieved studies and assessed the full texts for eligibility before including them. The bibliographies of the included studies were searched for any relevant studies. A third reviewer (A.K.) resolved any disagreement.

2. Eligibility Criteria

Studies included in this meta-analysis were prospective or retrospective studies fulfilling the following criteria: (1) Study population–patients with IBD; (2) Diagnostic test–markers of HBV infection (hepatitis B surface antigen [HBsAg], hepatitis B core antibody [anti-HBc], hepatitis B e antigen [HBeAg], and HBV DNA), markers of immunity against HBV (anti-HBs), and markers of HCV infection (anti-HCV and HCV RNA); and (3) Outcomes–seroprevalence of HBV and HCV, effective immunization. Conference abstracts, case series, review articles, correspondences, and editorials were excluded.

3. Data Extraction and Quality Assessment

Data were entered into a structured data extraction form with the following parameters: first author, year of publication, location of study, number of patients, study population description, risk factors for viral hepatitis, history of vaccination, and serological markers. The quality of the included studies was assessed by two reviewers (S.G. and S.K.) using the Joanna Briggs Institute (JBI) critical appraisal tools for use in systematic reviews (Supplementary Table 1).¹⁵ JBI appraisal for incidence/prevalence data includes questions about the appropriateness of study sample and selection, description of setting and subjects, completeness of provided data and analysis, and the appropriateness of measuring the condition. The quality of study was determined as per the score (high: 7–9, medium: 4-6, and low: <4). A third independent individual (A.K.) was consulted to determine the best score based on any discrepancy in the study quality assessment.

4. Data Synthesis

The pooled proportions were computed using a random-effect method with an inverse variance approach.¹⁶ Prior to statistical analysis, a continuity correction of 0.5 was applied when the incidence of an outcome was zero in a study. Dichotomous variables were analyzed using the odds ratio (OR) and Mantel-Haenszel test. The heterogeneity was assessed by I^2 and the p-value of heterogeneity. A P-value of < 0.10 was taken as statistically significant while I^2 values of 25%, 50%, and 75% were considered as cutoffs for low, moderate, and considerable heterogeneity, respectively.¹⁷ The assessment of publication bias was done by evaluating the asymmetry of the funnel plot and quantified using Egger's test. Sensitivity analysis was performed by analyzing prevalence data based on continent and study design and by leave-one-out meta-analysis. Meta-regression was used to explore heterogeneity induced by the relationship between moderators and study effect sizes. All statistical analvses were performed using RevMan version 5.4 and STATA software version 17 (StataCorp., College Station, TX, USA).

RESULTS

1. Study Characteristics and Quality Assessment

The search strategy yielded 2,194 records from which 1,267 studies were screened after removal of duplicates. Fig. 1 shows the flow chart for study selection and inclusion process. A total of 34 studies¹⁸⁻⁵¹ were included in the final analysis. Table 1 shows the characteristics of the included studies. Among these, 17 studies were prospective^{18-25,30,31,34,39,45,48-51} and 17 were retrospective in nature.^{26-29,32,33,35-38,40-44,46,47} The majority of the studies were from Europe^{18,20,24-27,31,34,36,39,40,47,49} and Asia.^{28,30,33,35,37,38,41,42,45,} ^{46,51} The number of patients in the studies varied from 74 to 5,096 with a mean age from 32.9 to 50.8 years. Majority of the studies included consecutive patients with IBD while 7 studies^{20,29,31,34,36,40,44} analyzed data of patients being planned for biologicals. Prior risk factors for viral hepatitis and vaccination history were reported in 9 studies^{21,25,26,30,31,33,38,43,51} and 10 studies,^{25,30,31,33,34,37,39,41,45,49} respectively. The study quality assessment is summarized in Supplementary Table 1. Among the included

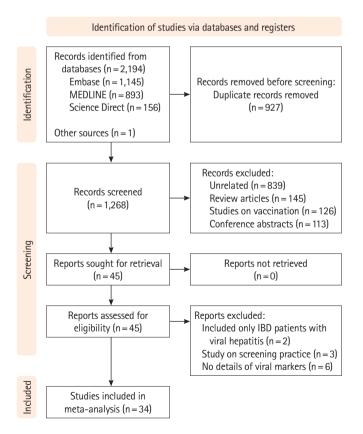


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart showing the study screening and selection process. IBD, inflammatory bowel disease.

studies, 22 studies were of high quality while 12 studies were of medium quality.

2. HBsAg Positivity

A total of 30 studies^{19-21,23-43,44-51} with 17,022 patients reported on HBsAg positivity in patients with IBD. The pooled prevalence of HBsAg was 3.3% (95% confidence interval [CI], 2.5– 4.0; I^2 = 91.6%) with significant heterogeneity among the studies (Fig. 2). Fig. 3A shows the geographic heat map for HBsAg positivity in IBD patients. On subgroup analysis, the pooled prevalence of HBsAg in patients with UC and CD were 3.3% (95% CI, 2.3–4.4; I^2 = 86.5%) and 2.9% (95% CI, 2.0–3.8; I^2 = 88.2%) (Supplementary Figs. 1 and 2), respectively. There was neither any difference in the odds of HBsAg positivity between patients with UC and CD (OR, 1.15; 95% CI, 0.96–1.37; I^2 = 0%) nor between IBD and general population (OR, 1.08; 95% CI, 0.93– 1.24; I^2 = 0%) (Supplementary Figs. 3 and 4).

3. HBeAg Positivity and Detectable HBV-DNA

Overall, 9 studies^{19,23,24,26,31,35,36,39,47} reported on the presence of detectable HBeAg in patients with HBsAg positivity. The pooled prevalence of HBeAg positivity in HBsAg positive cases was 15.3% (95% CI, 6.9–23.7; I^2 = 67.9%) (Supplementary Fig. 5). The presence of detectable HBV DNA was reported in 15 studies with 10,663 patients.^{21,24-26,28,31-34,38,40,41,43,50,51} The pooled prevalence of detectable HBV DNA in patients with IBD and IBD with HBsAg positive cases were 1.0% (95% CI, 0.6–1.4; I^2 = 75.0%) and 61.0% (95% CI, 42.1–79.9; I^2 = 91.6%), respectively (Supplementary Fig. 6).

4. Anti-HBc Positivity

The prevalence of anti-HBc (with or without HBsAg) in patients with IBD was reported in 25 studies with 12,265 patien ts.^{19-21,23-25,27,29-34,37,39-41,43-45,47-51} The pooled anti-HBc positivity in IBD patients was 14.2% (95% CI, 10.6–17.8; $I^2 = 98.2\%$), with significant heterogeneity among the studies (Supplementary Fig. 7). On subgroup analysis, the pooled anti-HBc positivity in patients with UC and CD were 20.3% (95% CI, 12.8–27.8; $I^2 =$ 98.1%) and 16.1% (95% CI, 10.0–22.1; $I^2 = 97.8\%$), respectively (Supplementary Figs. 8 and 9). Patients with IBD had a higher prevalence of anti-HBc positivity compared to controls (OR, 1.48; 95% CI, 1.02–2.13; $I^2 = 90\%$) and among patients with IBD (Supplementary Fig. 10), UC was associated with higher odds of anti-HBc positivity compared to CD (OR, 1.29; 95% CI, 1.03– 1.61; $I^2 = 49\%$) (Fig. 4).

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	Tolentino et al. $(2008)^{21}$	Brazil	Prospective	176 (74 UC/102 CD)	68/108	ı	Consecutive patients with IBD	29.3/26.7	I
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0^{α} Retrospective 41531(1,228 UC/h,521 CD) 2,523/h,530 55.1±84 Conscutive patients with IBD 0^{α} Retrospective 371 (61 UC/223 CD/3 IBD-U) 139/h48 41.7±12.3 Oh/requiring anti-NF therapy 1^{α} Prospective 371 (17 UC/184 CD) 139/h48 41.7±12.3 Oh/requiring anti-NF therapy 1^{α} Retrospective 301 (11 UC/182 CD)2 IBD-U) 139/h36 2.55±165 Oh/requiring anti-NF therapy 1^{α} Retrospective 500 (10 1 UC/323 CD)2 IBD-U) 149/529 3.25±918 Consecutive patients with IBD $^{\alpha}$ Retrospective 339 (11 UC/397 CD) 205/184 40 ± 0.7 Pion to anti-INF therapy $^{\alpha}$ Retrospective 338 (12 UC/307 CD) 205/184 40 ± 0.7 Pion to anti-INF therapy $^{\alpha}$ Retrospective 338 (12 UC/307 CD) 209/129 3.24±313 Pion to anti-INF therapy $^{\alpha}$ Retrospective 341 (10 G) 598 (16 UU/201 CD) 298/136 Dion to anti-INF therapy $^{\alpha}$ Retrospective 341 (16 G) 348 ± 15 Pion to anti-INF th	Morisco et al. $(2012)^{27}$	Italy	Retrospective	5,096 (2,611 UC/2,485 CD)	ı	ı	Consecutive patients with IBD	ī	ı
1° USA Retrospective 37 (61 UC/223 CD/3 IBD-U) $139/148$ 4.7 ± 123 Only requiring anti-TNF therapy Italy Prospective 513 (722 UC/241 CD) $330/183$ 3.3 ± 136 Disease duration > 6 mo Italy Prospective 501 (117 UC/184 CD) $142/189$ 41.5 ± 132 Pror to anti-TNF therapy Italy Retrospective 500 (206 UC/232 CD/2 IBD-U) $195/305$ 42.5 ± 165 Consecutive patients with IBD Prospective 301 (117 UC/194 CD) $415/329$ 42.5 ± 165 Consecutive patients with IBD Poland Retrospective 381 UC/337 CD) $217/19$ 938 ± 162 Prospective patients with IBD China Retrospective 510 UC/136 CD) $217/19$ 938 ± 162 Prospective patients with IBD Vintaly Netherlands Retrospective 512 UC/194 CD) 2168 32.5 ± 135 Prior to anti-TNF therapy China Retrospective 512 UC/136 CD) 21673 32.5 ± 135 Prior to anti-TNF therapy China Retrospective 5122 UC/136 CD) 216737	Park et al. (2012) ²⁸	Korea	Retrospective	4,153 (1,728 UC/1,521 CD)	2,523/1,630	35.1 ± 8.4	Consecutive patients with IBD	'	ı
Korea Prospective 513 (272 UC/241 CD) 330/183 373 ± 13.6 Discase duration > 6mo 11aly Prospective 301 (117 UC/184 CD) 142/153 413 ± 13.2 Prior to anti-TMF therapy 11aly Prospective 301 (117 UC/184 CD) 195/305 42.5±16.5 Consecutive patients with BD 11al Prospective 301 (117 UC/184 CD) 195/305 42.5±16.5 Consecutive patients with BD 11al Prospective 301 (127 UC/397 CD) 205/193 40.512 Prior to anti-TMF therapy 11al Retrospective 318 (12/037 CD) 205/194 40.517 Prior to anti-TMF therapy 12014) ¹⁶ Netherlands Retrospective 55 (26 UC/449 CD) 216/116 418 ± 13.5 Prior to anti-TMF therapy 101a Retrospective 57 (21 UC/185 CD) 216/116 418 ± 13.5 Prior to anti-TMF therapy 101a Retrospective 505 (201 UC/185 CD) 241/166 448 ± 13.5 Prior to anti-TMF therapy 101a Retrospective 503 UC/37 CD) 291/1265 38 ± 16.5 Prior to anti-TMF therapy </td <td>Vaughn et al. (2012)²⁹</td> <td>USA</td> <td>Retrospective</td> <td>287 (61 UC/223 CD/3 IBD-U)</td> <td>139/148</td> <td>41.7±12.3</td> <td>Only requiring anti-TNF therapy</td> <td>·</td> <td>ı</td>	Vaughn et al. (2012) ²⁹	USA	Retrospective	287 (61 UC/223 CD/3 IBD-U)	139/148	41.7±12.3	Only requiring anti-TNF therapy	·	ı
ItalyProspective301 (117 UC/184 CD)142/153413 ± 132Pior to anti-TNF threapy114) ¹² USARetrospective500 (206 UC/292 CD/2 IBD-U)195/305 4.25 ± 16.5 Consecutive patients with BD12ChinaRetrospective510 (203 CD)215/13937.2 ± 9.8Consecutive patients with BD12Prospective389 (23 UC/397 CD)205/184 40 ± 0.7 Pior to anti-TNF threapy12ChinaRetrospective389 (23 UC/397 CD)205/184 40 ± 0.7 Pior to anti-TNF threapy12ChinaRetrospective56 UC177/11950.8 ± 16.2Pior to anti-TNF threapy13ChinaRetrospective61 CD215/1393.2 ± 11.5Pitients with UC16] ¹⁰ PiolandRetrospective147 (63 UC/57 CD)205/184 40 ± 0.7 Bio duration > 3 mo16] ¹⁰ PiolandRetrospective590 (230 UC/389 CD)209/15332 ± 11.5Pitients screened for biologic and/16] ¹⁰ PiolandRetrospective590 (230 UC/389 CD)200/23339 ± 16.5Hospitalized BD patients16] ¹⁰ PiolandRetrospective590 (201/230 CD)591/3537.7 ± 12.5Consecutive patients with BD16] ¹⁰ Retrospective596 (100 UC/195 CD)591/3532.3 ± 11.5Piorito anti-NF threapy16] ¹⁰ PiolandRetrospective590 (2430 CD)541/3537.7 ± 12.5Consecutive patients with BD16] ¹⁰ Retrospective596 (100 UC/195 CD)591/35<	Kim et al. (2013) ³⁰	Korea	Prospective	513 (272 UC/241 CD)	330/183	37.3 ± 13.6	Disease duration >6 mo	17.3/25.5	Yes
1141*USARetrospective500 (206 UC/292 CD/2 IBD-U)195/305 $4.2.5 \pm 16.5$ Conscutive patients with IBD27ChinaRetrospective339 (82 UC/307 CD)205/184 40 ± 0.7 Piror to arti-TNF therapy20ChinaRetrospective339 (82 UC/307 CD)205/184 40 ± 0.7 Piror to arti-TNF therapy2014Retrospective389 (82 UC/307 CD)205/184 40 ± 0.7 Piror to arti-TNF therapy2014Retrospective61 (CD20149 CD)205/184 40 ± 0.7 Piror to arti-TNF therapy2014Retrospective61 (CD230 (250 CD)236/13573.2 \pm 13.5Piror to arti-TNF therapy2014Retrospective61 (CD249/23023.4 ± 13.5B1 duration > 3 mo2016PolandProspective60 (221 UC/185 CD)20/630 42.3 ± 11.5 B1 duration > 3 mo2016Retrospective60 (221 UC/185 CD)20/630 42.3 ± 11.5 B1 duration > 3 mo2016Retrospective60 (231 UC/185 CD)20/269 33.4 ± 15.5 B1 duration > 3 mo2016Retrospective60 (231 UC/185 CD)20/260 33.4 ± 15.5 B1 duration > 3 mo2016Retrospective60 (231 UC/392 CD)20/7 CD) 30.73 ± 12.5 Conscutive patients with BD2016Retrospective60 (63 UC/293 CD)20/2 260 (73 3 27 \pm 12.5Conscutive patients with BD2016Retrospective80 (63 UC/393 CD)20/2 260 (73 9 200 (73 9 20) 23.77 ± 12.5 Conscutive patients with BD<	Papa et al. (2013) ³¹	Italy	Prospective	301 (117 UC/184 CD)	142/159	41.9±13.2	Prior to anti-TNF therapy	53.1/ -	Yes
ChinaRetrospective714 (317 UC/397 CD)415/299372 ± 9.82 Consecutive patients with IBDSpainProspective389 (20 UC/307 CD)205/184 40 ± 0.7 Prior to anti-TNF threapyChinaRetrospective56 UC256 UC205/184 40 ± 0.7 Prior to anti-TNF threapyNetherlandsRetrospective611 CD215/39632.9 ± 13.5 Prior to anti-TNF threapyNetherlandsRetrospective675 (226 UC/449 CD)215/39632.9 ± 13.5 Prior to anti-TNF threapyNetherlandsRetrospective675 (226 UC/449 CD)241/165 448 ± 13.5 BD duration $> 3 mo$ PolandProspective60 (221 UC/185 CD)241/165 448 ± 13.5 BD duration $> 3 mo$ PolandProspective509 (220 UC/289 CD)291/165 448 ± 13.5 BD duration $> 3 mo$ PolandRetrospective509 (234 UC/37 CD)241/165 38 ± 16 Hospitalized BD patientsItalyRetrospective508 (334 UC/327 CD)241/367 37.4 ± 12.5 Consecutive patients with BDIndiaRetrospective508 (334 UC/327 CD)241/367 37.4 ± 12.5 Consecutive patients with BDIndiaRetrospective508 (334 UC/327 CD)241/367 37.4 ± 12.5 Consecutive patients with BDIndiaRetrospective508 (107 UC/354 CD)241/367 37.4 ± 12.5 Consecutive patients with BDIndiaRetrospective508 (107 UC/354 CD)241/367 37.4 ± 12.5 Consecutive patients with BDIndia	Ben Musa et al. (2014) ³²	NSA	Retrospective	500 (206 UC/292 CD/2 IBD-U)	195/305	42.5 ± 16.5	Consecutive patients with IBD	I	ı
SpainProspective389 (82 UC/3O7 CD) $205/184$ 40 ± 0.7 Pior to anti-TNF threapyChinaRetrospective 56 UC $127/119$ 50.8 ± 16.2 Patients with UCNetherlandsRetrospective 611 CD $215/396$ 32.9 ± 13.5 Pior to anti-TNF threapyNetherlandsRetrospective $675(226 UC/49 CD)$ $215/396$ 32.9 ± 13.5 Pior to anti-TNF threapyChinaRetrospective $675(226 UC/49 CD)$ $79/68$ 38 ± 16 Hospitalized IBD patientsPolandProspective $147(63 UC/57 CD)$ $79/68$ 38 ± 16 Hospitalized IBD patientsPolandRetrospective $900(324 UC/57 CD)$ $79/68$ 38 ± 16 Hospitalized IBD patientsPolandRetrospective $900(324 UC/57 CD)$ $79/68$ 38 ± 16 Hospitalized IBD patientsItalyRetrospective $900(324 UC/377 CD)$ $79/68$ 38 ± 16 Hospitalized IBD patientsIndiaRetrospective $900(324 UC/327 CD)$ $509/382$ 39.4 ± 15.5 Positalized IBD patientsIndiaRetrospective $500(236 UC/337 CD)$ $539/382$ 33.4 ± 15.6 Hospitalized IBD patientsIndiaRetrospective $300(7397 CD)$ $249/560$ 35.4 ± 11.6 Consecutive patients with IBDVorceRetrospective $357/75 UC/1.954 CD/628 IBD-U)30.377 \pm12.5Consecutive patients with IBDUSARetrospective357/75 UC/1.954 CD/628 IBD-U)30/313450.6Only requiring anti-TNF threapyUSARetrospective357/75 UC/1.$	Huang et al. (2014) ³³	China	Retrospective	714 (317 UC/397 CD)	415/299	37.2±9.8	Consecutive patients with IBD	22/ -	Yes
ChiaRetrospective256 UC $127/119$ 50.8.4.16.2Patients with UCNetherlandsRetrospective611 CD $215/396$ $3.2.9.4.13.5$ Pior to anti-TNF therapyChinaRetrospective $675(226 UC/449 CD)$ $296/329$ $-$ Consecutive patients with IBDChinaRetrospective $606(221 UC/185 CD)$ $29/68$ $38.4.16$ Hospitalized IBD patientsPolandProspective $606(221 UC/289 CD)$ $79/68$ $38.4.16$ Hospitalized IBD patientsPolandRetrospective $609(220 UC/289 CD)$ $79/68$ $38.4.16$ Hospitalized IBD patientsItalyRetrospective $609(220 UC/289 CD)$ $79/68$ $38.4.16$ Hospitalized IBD patientsItalyRetrospective $609(220 UC/289 CD)$ $79/68$ $38.4.16$ Hospitalized IBD patientsIndiaRetrospective $609(220 UC/289 CD)$ $59/306$ $3.3.4.15$ Hospitalized IBD patientsIndiaRetrospective $608(231 UC/327 CD)$ $54/367$ $3.7.7.12.5$ Consecutive patients with IBDUSARetrospective $3557(775 UC/1954 CD/628 IBD-U)$ $3.07.312.6$ $600/797 CD)$ $3.07.312.6$ $600/797 CD)$ USARetrospective $606(61 UC/101 CD)$ 3.073344 50.6 $001/7$ requiring rati-TNF therapyVoreeRetrospective $600(100 UC/101 CD)$ 3.073344 50.6 $001/7$ requiring rati-TNF therapyUSARetrospective $600(100 UC/101 CD)$ 13377 $3.49.153$ $001/7$ requiring rati-TNF therapyUS	Loras et al. (2014) ³⁴	Spain	Prospective	389 (82 UC/307 CD)	205/184	40 ± 0.7	Prior to anti-TNF therapy	I	Yes
NetherlandsRetrospective611 CD $215/396$ 32.3 ± 13.5 Pior to anti-TNF therapyChinaRetrospective $675(226 UC/449 CD)$ $436/239$ $-$ Consecutive patients with IBDChinaRetrospective $406(221 UC/185 CD)$ $241/165$ 44.8 ± 13.5 IBD duration $> 3 mo$ PolandProspective $147(63 UC/57 CD)$ $79/68$ 38 ± 16 Hospitalized IBD patientsItalyRetrospective $509(220 UC/289 CD)$ $79/68$ 38 ± 16 Hospitalized IBD patientsItalyRetrospective $509(220 UC/289 CD)$ $79/68$ 38 ± 16 Hospitalized IBD patientsItalyRetrospective $509(220 UC/289 CD)$ $79/68$ 38 ± 16 Hospitalized IBD patientsItalyRetrospective $908(581 UC/327 CD)$ $59/382$ 39.4 ± 15.5 Hospitalized IBD patientsIndiaRetrospective $908(581 UC/327 CD)$ $541/367$ 37.4 ± 12.5 Consecutive patients with IBDIndiaRetrospective $337(175 UC/1954 CD/628 IBD-U)$ 30.4 ± 15.5 Consecutive patients with IBDUSARetrospective $337/775 UC/1954 CD/628 IBD-U)$ 30.4 ± 15.5 Consecutive patients with IBDUSARetrospective $337/775 UC/1954 CD/628 IBD-U)$ 30.4 ± 15.5 Consecutive patients with IBDUSARetrospective $337/775 UC/1954 CD/628 IBD-U)$ 30.4 ± 15.5 Consecutive patients with IBDUSARetrospective $307(175 UC/1954 CD/628 IBD-U)$ 30.4 ± 15.5 Retrospective $306(106 UC/101 CD)$ USARetrospecti	Sui et al. (2014) ³⁵	China	Retrospective	256 UC	127/119	50.8 ± 16.2	Patients with UC	,	ı
ChinaRetrospective $675 (226 UC/490 CD)$ $436/239$ $-$ Consecutive patients with BDChinaRetrospective $406 (221 UC/185 CD)$ $241/165$ 4.8 ± 1.35 BD duration $> 3 mo$ PolandProspective $147 (63 UC/57 CD)$ $79/68$ 38 ± 16 Hospitalized BD patientsItalyRetrospective $509 (220 UC/289 CD)$ $79/68$ 38 ± 16 Hospitalized BD patientsItalyRetrospective $900 (324 UC/327 CD)$ $59/68$ 38 ± 16 Hospitalized BD patientsIndiaRetrospective $900 (581 UC/327 CD)$ $59/3382$ 39.4 ± 15.5 Hospitalized BD patientsIndiaRetrospective $900 (581 UC/327 CD)$ $544/367$ 37.7 ± 12.5 Consecutive patients with BDMorroccoRetrospective $3,357 (775 UC/1954 CD/628 IBD-U)$ $3/013/344$ 50.66 $0nh$ requiring anti-TNF therapyUSARetrospective $3,357 (775 UC/1954 CD/628 IBD-U)$ $3/013/344$ 50.66 $0nh$ requiring anti-TNF therapyUSARetrospective $3,357 (775 UC/1954 CD/628 IBD-U)$ $3/013/344$ 50.66 $0nh$ requiring anti-TNF therapyUSARetrospective $3,357 (775 UC/1954 CD/628 IBD-U)$ $3/013/344$ 50.66 $0nh$ requiring anti-TNF therapyUSARetrospective $3,367 (775 UC/1954 CD/628 IBD-U)$ $3/013/344$ 50.66 $0nh$ requiring anti-TNF therapyUSAProspective $200 (100 UC/1001 CD)$ $133/77$ 34.9 ± 15.9 $0nh$ requiring anti-TNF therapyInvianRetrospective $306 (165 UC/101 CD$	van der Have et al. (2014) ³⁶	Netherlands	Retrospective	611 CD	215/396	32.9 ± 13.5	Prior to anti-TNF therapy	ı	ı
ChinaRetrospective $406 (221 UC/185 CD)$ $241/165$ $4.8\pm 1.3.5$ BD duration $> 3mo$ PolandProspective $147 (63 UC/57 CD)$ $79/68$ 38 ± 16 Hospitalized BD patientsItalyRetrospective $509 (220 UC/289 CD)$ $300/209$ 4.3 ± 11.5 Patients screened for biologic and/ItalyRetrospective $509 (220 UC/289 CD)$ $300/209$ 4.3 ± 11.5 Patients screened for biologic and/ItalyRetrospective $980 (334 UC/646 CD)$ $598/382$ 39 ± 15.5 Patients screened for biologic and/IndiaRetrospective $980 (334 UC/646 CD)$ $598/382$ 39 ± 15.5 Patients screened for biologic and/IndiaRetrospective $980 (334 UC/639 CD)$ $598/382$ 39 ± 15.5 PatientsIndiaRetrospective $357 (775 UC/1954 CD/628 IBD-U)$ $3(73 12.5)$ Consecutive patients with IBDUSARetrospective $357 (775 UC/1954 CD/628 IBD-U)$ $3(0334 6.5)$ 5.66 Only requiring anti-TNF therapyUSARetrospective $357 (775 UC/1954 CD/628 IBD-U)$ $3(0334 6.5)$ 36 ± 11.6 Only requiring anti-TNF therapyUsaRetrospective $357 (775 UC/1954 CD/628 IBD-U)$ $3(0334 6.5)$ 36 ± 11.6 Only requiring anti-TNF therapyUsaRetrospective $357 (775 UC/1954 CD/628 IBD-U)$ $3(0334 6.5)$ 36 ± 11.6 Only requiring anti-TNF therapyUsaRetrospective $357 (775 UC/1954 CD/628 IBD-U)$ $3(0334 6.5)$ 36 ± 11.6 Only requiring anti-TNF therapyInvoFarive	He et al. (2015) ³⁷	China	Retrospective	675 (226 UC/449 CD)	436/239	ı	Consecutive patients with IBD	I	Yes
** Poland Prospective 147 (63 UC/57 CD) 79/68 38±16 Hospitalized IBD patients Italy Retrospective 509 (220 UC/289 CD) 300/209 4.3.±11.5 Patients screened for biologic and/or thiopurine therapy China Retrospective 980 (334 UC/387 CD) 598/382 39.4±15.5 Patients screened for biologic and/or thiopurine therapy India Retrospective 980 (334 UC/397 CD) 541/367 37.7±12.5 Consecutive patients with IBD India Retrospective 3,57 (775 UC/1,954 CD)/5327 CD) 249/506 35.4±11.6 Consecutive patients with IBD USA Retrospective 3,57 (775 UC/1,954 CD)/534 3,013/344 50.6 Only requiring anti-TNF therapy USA Retrospective 3,73 (775 UC/1,954 CD)/534 3,013/344 50.6 Only requiring anti-TNF therapy USA Retrospective 3,07 (101 CD) 13/77 34.9±15.9 Bouration > 3 mo Iaiwan Retrospective 190 (110 UC/80 CD) 13/77 34.9±15.9 Bouration > 3 mo Iaiwan Retrospective 190 (110 UC/80 CD) 13/77 <td>Chan et al. (2016)³⁸</td> <td>China</td> <td>Retrospective</td> <td>406 (221 UC/185 CD)</td> <td>241/165</td> <td>44.8±13.5</td> <td>IBD duration >3 mo</td> <td>14.3/ -</td> <td>ı</td>	Chan et al. (2016) ³⁸	China	Retrospective	406 (221 UC/185 CD)	241/165	44.8±13.5	IBD duration >3 mo	14.3/ -	ı
ItalyRetrospective509 (220 UC/289 CD)300/209 42.3 ± 11.5 Patients screened for biologic and/ or thiopurine therapyChinaRetrospective980 (334 UC/646 CD)598/382 39.4 ± 15.5 Hospitalized IBD patientsIndiaRetrospective908 (581 UC/327 CD) $591/367$ 37.7 ± 12.5 Consecutive patients with IBDMoroccoRetrospective $3.357 (775 UC/1,954 CD/628 IBD-U)$ $3.013/344$ 50.66 Only requiring anti-TNF therapyUSARetrospective $3.357 (775 UC/1,954 CD/628 IBD-U)$ $3.013/344$ 50.66 Only requiring anti-TNF therapyUSARetrospective $2.10 (109 UC/101 CD)$ $1.33/77$ 34.9 ± 15.3 Newly diagnosed IBDUSARetrospective $90 (110 UC/80 CD)$ $1.33/77$ 34.9 ± 15.3 Newly diagnosed IBDTaiwanRetrospective $90 (110 UC/80 CD)$ $1.33/77$ 34.9 ± 15.3 Newly diagnosed IBDTaiwanRetrospective $90 (110 UC/80 CD)$ $1.33/77$ 34.9 ± 15.3 Newly diagnosed IBDTaiwanRetrospective $90 (100 UC/101 CD)$ $1.33/77$ 34.9 ± 15.3 Newly diagnosed IBDTaiwanRetrospective $90 (110 UC/80 CD)$ $1.33/77$ 34.9 ± 15.3 Newly diagnosed IBDTaiwanRetrospective $90 (110 UC/80 CD)$ $1.33/77$ 34.9 ± 15.3 Newly diagnosed IBDTaiwanRetrospective $306 (165 UC/141 CD)$ $1.7/189$ $$ Consecutive patients with IBDIndixProspective $807 (369 UC/438 CD)$ $474/333$ 46	Waszczuk et al. (2016) ³⁹	Poland	Prospective	147 (63 UC/57 CD)	79/68	38±16	Hospitalized IBD patients	ı	Yes
ChinaRetrospective 980 (334 UC/646 CD) $598/382$ 39.4 ± 15.5 Hospitalized IBD patientsIndiaRetrospective 908 (581 UC/327 CD) $541/367$ 37.7 ± 12.5 Consecutive patients with IBDMoroccoRetrospective 755 (364 UC/391 CD) $249/506$ 35.4 ± 11.6 Consecutive patients with IBDUSARetrospective 3.557 (775 UC/1,954 CD/628 IBD-U) $3,013/344$ 50.6 Only requiring anti-TNF therapyUSARetrospective $3,357$ (775 UC/1,954 CD/628 IBD-U) $3,013/344$ 50.6 Only requiring anti-TNF therapyUSARetrospective $3,357$ (775 UC/1,954 CD/628 IBD-U) $3,013/344$ 50.6 Only requiring anti-TNF therapyUSARetrospective $3,357$ (775 UC/1,954 CD/628 IBD-U) $3,013/344$ 50.6 Only requiring anti-TNF therapyUSARetrospective 900 (100 UC/80 CD) $133/77$ 34.9 ± 15.3 Newly diagnosed IBDTaiwanRetrospective 602 (346 UC/256 CD) $135/55$ 38.4 ± 15.9 IBD duration > 3 modelBrazilProspective 807 (369 UC/438 CD) $177/189$ $$ Consecutive patients with IBDItalyProspective 807 (369 UC/438 CD) $474/333$ 46.2 ± 13.2 Consecutive patients with IBDIndiaProspective 74 (12 UC/62 CD) $36/38$ 43.5 ± 14.2 Consecutive patients with IBDInaitiProspective 74 (12 UC/62 CD) $36/38$ 43.5 ± 14.2 Consecutive patients with IBDInaitiaProspective 74 (12 UC/62 CD)	Ardesia et al. (2017) ⁴⁰	Italy	Retrospective	509 (220 UC/289 CD)	300/209	42.3±11.5	Patients screened for biologic and/ or thiopurine therapy	I	I
India Retrospective 908 (581 UC/327 CD) 541/367 37.7 ± 1.25 Consecutive patients with IBD Morocco Retrospective 755 (364 UC/391 CD) 249/506 35.4 ± 11.6 Consecutive patients with IBD USA Retrospective 3,357 (775 UC/1,954 CD/628 IBD-U) 3,013/344 50.6 Only requiring anti-TNF therapy Korea Prospective 210 (109 UC/101 CD) 133/77 34.9 ± 15.3 Newly diagnosed IBD Taiwan Retrospective 190 (110 UC/80 CD) 135/55 38.4 ± 15.9 IBD duration > 3 mo Greece Retrospective 600 (160 UC/101 CD) 135/55 38.4 ± 15.9 IBD duration > 3 mo Brazil Prospective 306 (141 CD) 117/189 - Consecutive patients with IBD Italy Prospective 807 (369 UC/438 CD) 360/242 36.2 ± 13.2 Consecutive patients with IBD Italy Prospective 807 (369 UC/438 CD) 36/323 36.2 ± 13.2 Consecutive patients with IBD Italy Prospective 807 (369 UC/438 CD) 36/323 46.2 ± 13.2 Consecutive patients with IB	Chen et al. (2017) ⁴¹	China	Retrospective	980 (334 UC/646 CD)	598/382	39.4±15.5	Hospitalized IBD patients	ı	Yes
Morocco Retrospective 75 (364 UC/391 CD) 249/506 35.4±11.6 Consecutive patients with IBD USA Retrospective 3,357 (775 UC/1,954 CD/628 IBD-U) 3,013/344 50.6 Only requiring anti-TNF therapy Korea Prospective 3,357 (775 UC/1,954 CD/628 IBD-U) 3,013/344 50.6 Only requiring anti-TNF therapy Korea Prospective 210 (109 UC/101 CD) 133/77 34.9±15.3 Newly diagnosed IBD Taiwan Retrospective 190 (110 UC/80 CD) 135/55 38.4±15.9 IBD duration > 3 mo Greece Retrospective 602 (346 UC/256 CD) 135/72 34.9±15.9 IBD duration > 3 mo Brazil Prospective 602 (46 UC/256 CD) 360/242 39±17.4 Consecutive patients with IBD Brazil Prospective 807 (458 UC/141 CD) 117/189 - Consecutive patients with IBD Italy Prospective 807 (458 CD) 36/242 39±17.4 Consecutive patients with IBD Italy Prospective 807 (438 CD) 117/189 - Consecutive patients with IBD <tr< td=""><td>Harsh et al. (2017)⁴²</td><td>India</td><td>Retrospective</td><td>908 (581 UC/327 CD)</td><td>541/367</td><td>37.7±12.5</td><td>Consecutive patients with IBD</td><td>,</td><td>ı</td></tr<>	Harsh et al. (2017) ⁴²	India	Retrospective	908 (581 UC/327 CD)	541/367	37.7±12.5	Consecutive patients with IBD	,	ı
USA Retrospective 3,357 (775 UC/1,954 CD/628 IBD-U) 3,013/344 5.0.6 Only requiring anti-TNF therapy Korea Prospective 210 (109 UC/101 CD) 133/77 34.9 ± 15.3 Newly diagnosed IBD Taiwan Retrospective 190 (110 UC/80 CD) 135/55 38.4 ± 15.9 IBD duration > 3 mo Greece Retrospective 602 (346 UC/256 CD) 360/242 39 ± 17.4 Consecutive patients with IBD Brazil Prospective 602 (165 UC/141 CD) 117/189 - Consecutive patients with IBD Italy Prospective 807 (369 UC/438 CD) 36/3242 36.5 ± 13.2 Consecutive patients with IBD Italy Prospective 807 (369 UC/338 CD) 36/33 46.2 ± 13.2 Consecutive patients with IBD Innisia Prospective 74 (12 UC/62 CD) 36/38 43.5 ± 14.2 Consecutive patients with IBD India Prospective 74 (12 UC/62 CD) 36/38 43.5 ± 14.2 Consecutive patients with IBD	Abid et al. (2018) ⁴³	Morocco	Retrospective	755 (364 UC/391 CD)	249/506	35.4±11.6	Consecutive patients with IBD	19.7/22.2	I
Korea Prospective 210 (109 UC/101 CD) 133/77 34.9±15.3 Newly diagnosed IBD Taiwan Retrospective 190 (110 UC/80 CD) 135/55 38.4±15.9 IBD duration > 3 mo Greece Retrospective 602 (346 UC/256 CD) 360/242 39±17.4 Consecutive patients with IBD Brazil Prospective 306 (165 UC/141 CD) 117/189 - Consecutive patients with IBD Italy Prospective 360 (165 UC/141 CD) 117/189 - Consecutive patients with IBD Italy Prospective 807 (369 UC/438 CD) 36/33 46.2±13.2 Consecutive patients with IBD Innisia Prospective 74 (12 UC/62 CD) 36/38 43.5±14.2 Consecutive patients with IBD India Prospective 76 (42 UC/33 CD) 36/38 43.5±14.2 Consecutive patients with IBD	Shah et al. (2018) ⁴⁴	USA	Retrospective	3,357 (775 UC/1,954 CD/628 IBD-U)	3,013/344	50.6	Only requiring anti-TNF therapy		ı
Taiwan Retrospective 190 (110 UC/80 CD) 135/55 38.4±15.9 IBD duration > 3 mo Greece Retrospective 602 (346 UC/256 CD) 360/242 39±17.4 Consecutive patients with IBD Brazil Prospective 306 (165 UC/141 CD) 117/189 - Consecutive patients with IBD Italy Prospective 807 (369 UC/438 CD) 47/333 46.2±13.2 Consecutive patients with IBD Tunisia Prospective 74 (12 UC/62 CD) 36/38 43.5±14.2 Consecutive patients with IBD India Prospective 76 (42 UC/33 CD) 48/28 37.5±13.3 Consecutive patients with IBD	Yeo et al. (2018) ⁴⁵	Korea	Prospective	210 (109 UC/101 CD)	133/77	34.9 ± 15.3	Newly diagnosed IBD	I	Yes
Greece Retrospective 602 (346 UC/256 CD) 360/242 39±17.4 Consecutive patients with IBD Brazil Prospective 306 (165 UC/141 CD) 117/189 - Consecutive patients with IBD Italy Prospective 807 (369 UC/438 CD) 474/333 46.2±13.2 Consecutive patients with IBD Italy Prospective 74 (12 UC/62 CD) 36/38 43.5±14.2 Consecutive patients with IBD India Prospective 76 (42 UC/33 CD) 48/28 37.5±13.9 Consecutive patients with IBD	Chou et al. (2019) ⁴⁶	Taiwan	Retrospective	190 (110 UC/80 CD)	135/55	38.4±15.9	IBD duration > 3 mo		ı
Brazil Prospective 306 (165 UC/141 CD) 117/189 - Consecutive patients with IBD Italy Prospective 807 (369 UC/438 CD) 47/4/333 46.2 ± 13.2 Consecutive patients with IBD Tunisia Prospective 74 (12 UC/62 CD) 36/38 43.5 ± 14.2 Consecutive patients with IBD India Prospective 76 (42 UC/33 CD) 48/28 37.5 ± 13.9 Consecutive patients with IBD	Fousekis et al. (2019) ⁴⁷	Greece	Retrospective	602 (346 UC/256 CD)	360/242	39±17.4	Consecutive patients with IBD	ı	I
Italy Prospective 807 (369 UC/438 CD) 474/333 46.2±13.2 Consecutive patients with IBD Tunisia Prospective 74 (12 UC/62 CD) 36/38 43.5±14.2 Consecutive patients with IBD India Prospective 76 (42 UC/33 CD) 48/28 37.5±13.9 Consecutive patients with IBD	Silva et al. (2019) ⁴⁸	Brazil	Prospective	306 (165 UC/141 CD)	117/189	ı	Consecutive patients with IBD	ı	ı
Tunisia Prospective 74 (12 UC/62 CD) 36/38 43.5±14.2 Consecutive patients with IBD India Prospective 76 (42 UC/33 CD) 48/28 37.5±13.9 Consecutive patients with IBD	Losurdo et al. (2020) ⁴⁹	Italy	Prospective	807 (369 UC/438 CD)	474/333	46.2 ± 13.2	Consecutive patients with IBD	·	Yes
India Prospective 76 (42 UC/33 CD) 48/28 37.5±13.9 Consecutive patients with IBD	Sabbah et al. (2020) ⁵⁰	Tunisia	Prospective	74 (12 UC/62 CD)	36/38	43.5±14.2	Consecutive patients with IBD		ı
	Patil et al. (2021) ⁵¹	India	Prospective	76 (42 UC/33 CD)	48/28	37.5 ± 13.9	Consecutive patients with IBD	13.1/ -	I

Country HBsAg + Total Proportion (95% CI) Weight	Country	Continent and Author
		Europe
Italy 7 332 0.021 (0.010, 0.043) 3.6	Italy	Biancone 2001
Spain 3 80 0.037 (0.013, 0.105) 1.9	Spain	Esteve 2004
Spain 15 2076 0.007 (0.004, 0.012) 4.2	Spain	Loras 2009
France 3 315 0.010 (0.003, 0.028) 3.9	France	Chevaux 2010
Greece 11 482 0.023 (0.013, 0.040) 3.7	Greece	Katsanos 2010
Italy 30 1556 0.019 (0.014, 0.027) 4.1	Italy	Morisco 2012
Italy 1 301 0.003 (0.001, 0.019) 4.1		Papa 2013
Spain 4 389 0.010 (0.004, 0.026) 3.9		Loras 2014
Netherlands 1 80 0.013 (0.002, 0.067) 2.9		Van der Have 2014
Poland 3 147 0.020 (0.007, 0.058) 3.1		Waszczuk 2016
Italy 8 450 0.018 (0.009, 0.035) 3.8		Ardesia 2017
Greece 12 225 0.053 (0.031, 0.091) 2.6	•	Fousekis 2019
		Losurdo 2020
	Italy	Subgroup, DL (I ² = 61.8%, p = 0.002)
0.014 (0.009, 0.018) 46.3		Subgroup, DE ($1^2 = 61.6\%$, $p = 0.002$)
		South America
Brazil 4 176 0.023 (0.009, 0.057) 3.1		Tolentino 2008
Brazil 2 182 0.011 (0.003, 0.039) 3.6	Brazil	Silva 2019
0.015 (0.002, 0.027) 6.8		Subgroup, DL ($I^2 = 0.0\%$, p = 0.389)
		Asia
Korea 134 3249 0.041 (0.035, 0.049) 4.1	Korea	Park 2012 🔶
Korea 19 513 0.037 (0.024, 0.057) 3.5	Korea	Kim 2013
China 39 714 0.055 (0.040, 0.074) 3.5	China	Huang 2014
China 12 246 0.049 (0.028, 0.083) 2.8	China	Sui 2014
← China 99 675 0.147 (0.122, 0.175) 2.8	China	He 2015
China 23 406 0.057 (0.038, 0.084) 3.1	China	Chan 2016
China 77 980 0.079 (0.063, 0.097) 3.5		Chen 2017 +
India 20 829 0.024 (0.016, 0.037) 3.9		Harsh 2017
Korea 8 210 0.038 (0.019, 0.073) 2.8		Yeo 2018
Taiwan 21 190 0.111 (0.073, 0.163) 1.7		Chou 2019
India 2 76 0.026 (0.007, 0.091) 2.2		Patil 2021
0.058 (0.042, 0.075) 34.3	India	Subgroup, DL (I ² = 90.0%, p = 0.000)
		North America
USA 33 287 0.115 (0.083, 0.157) 2.1	119.4	Vaughn 2012
USA 33 287 0.113 (0.000, 0.137) 2.1 USA 4 220 0.018 (0.007, 0.046) 3.4		Ben Musa 2014
> 0.065 (-0.030, 0.160) 5.6	USA	Subgroup, DL (l ² = 95.4%, p = 0.000)
		Africa
Morocco 11 755 0.015 (0.008, 0.026) 4.0	Morocco	Abid 2018
Tunisia 1 74 0.014 (0.002, 0.073) 2.8		Sabbah 2020
	rumsia	
0.014 (0.006, 0.023) 6.8		Subgroup, DL (I ² = 0.0%, p = 0.940)
		Heterogeneity between groups: p = 0.000
0.033 (0.025, 0.040) 100.0		Overall, DL (I ² = 91.6%, p = 0.000)
5 1	5	I
.5 1 Proportion	Proportion	0 NOTE: Weights and between-subgroup heterogeneity test are from random-effects m

Fig. 2. Forest plot showing the pooled prevalence of hepatitis B surface antigen (HBsAg) in patients with inflammatory bowel disease with subgroup analysis based on the continent of study. DL, DerSimonian and Laird method; Cl, confidence interval.

5. Effective HBV Vaccination

Effective immunization was defined as the presence of anti-HBs titer ≥ 10 mIU/mL without anti-HBc and HBsAg. The presence of protective antibody against HBV in patients with completed immunization was reported in 10 studies with 4,895 patients.^{2023-25,27,30,31,32,36,38,39,41,46,47} Among patients with IBD, only 35.6% (95% CI, 28.7–42.4; $I^2 = 96.5\%$) of the patients had effective vaccination (Supplementary Fig. 11).

6. Anti-HCV Positivity

Overall, 22 studies with 10,304 patients of IBD reported on anti-HCV prevalence.^{18-20,22-27,31-34,36,39-42,46-50} The pooled prevalence of anti-HCV positivity was 1.8% (95% CI, 1.2–2.4; I^2 = 82.1%) with significant heterogeneity among the studies (Fig. 5). Fig. 3B shows the geographic heat map for anti-HCV positivity in IBD patients. On subgroup analysis, the pooled prevalence of anti-HCV in patients with UC and CD were 1.4% (95% CI, 0.7–

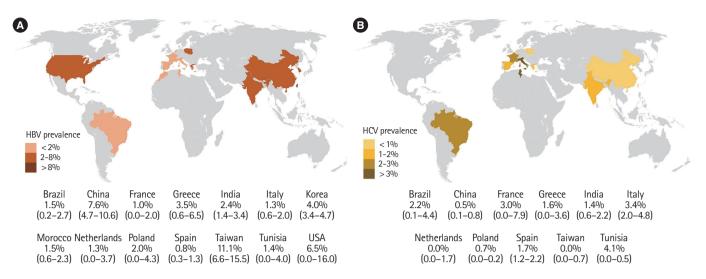


Fig. 3. Geographic heat map for prevalence of (A) hepatitis B surface antigen and (B) anti-HCV in patients with inflammatory bowel disease. HBV, hepatitis B virus; HCV, hepatitis C virus.

	UC		CD			Odds Ratio				Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M	-H, Random, 95%	CI	
Tolentino 2008	17	74	13	102	5.6%	2.04 [0.92, 4.52]	2008					
Loras 2009	74	928	80	1128	14.3%	1.14 [0.82, 1.58]	2009			-		
Kim 2013	68	193	39	164	10.9%	1.74 [1.09, 2.78]	2013					
Papa 2013	9	117	13	184	4.8%	1.10 [0.45, 2.65]	2013					
Huang 2014	132	317	158	397	15.1%	1.08 [0.80, 1.46]	2014			-		
Ben Musa 2014	1	76	6	143	1.0%	0.30 [0.04, 2.58]	2014					
He 2015	68	226	114	449	13.6%	1.26 [0.89, 1.80]	2015			+		
Ardesia 2017	12	188	15	228	5.7%	0.97 [0.44, 2.12]	2017					
Chen 2017	176	334	228	646	16.0%	2.04 [1.56, 2.67]	2017					
Yeo 2018	27	109	26	101	7.9%	0.95 [0.51, 1.77]	2018					
Abid 2018	5	364	10	391	3.5%	0.53 [0.18, 1.57]	2018		_			
Patil 2021	5	41	2	32	1.5%	2.08 [0.38, 11.52]	2021					
Total (95% CI)		2967		3965	100.0%	1.29 [1.03, 1.61]				•		
Total events	594		704									
Heterogeneity: Tau ² =	0.06; Chi ²	= 21.7	5, df = 11	(P = 0	.03); l² = 49	%						
Test for overall effect:	Z = 2.24 (P = 0.0	3)					0.02	0.1		10	50

Fig. 4. Forest plot comparing the prevalence of hepatitis B core antibody in patients with ulcerative colitis (UC) and Crohn's disease (CD). M-H, Mantel-Haenszel; CI, confidence interval.

2.1; $I^2 = 73.3\%$) and 1.4% (95% CI, 0.6–2.1; $I^2 = 80.5\%$), respectively (Supplementary Figs. 12 and 13). The difference in prevalence of HCV between patients with IBD and general population was reported by 5 studies. Presence of IBD was not associated with an increased odd of HCV (OR, 1.42; 95% CI, 0.93–2.18, $I^2 = 0\%$) without any heterogeneity (Supplementary Fig. 14). Overall, 9 studies compared the HCV prevalence between patients with UC and CD. There was no difference in the odds of HCV prevalence between UC and CD (OR, 1.04; 95% CI, 0.54–1.99; $I^2 = 52\%$) with significant heterogeneity (Supplementary Fig. 15).

7. HCV RNA Positivity

Overall, 12 studies with 7,447 patients reported HCV RNA positivity in patients with IBD.^{19,20,24,25-27,31-34,41,47,48} The pooled prevalence of HCV RNA positivity among patients with IBD and IBD patients with positive anti-HCV were 0.8% (95% CI, 0.4–1.3; I^2 = 87.9%) and 78.5% (95% CI, 64.8–92.2; I^2 = 91.4%), respectively (Supplementary Fig. 16).

8. Publication Bias, Sensitivity Analysis and Meta-Regression

Significant publication bias for all the outcomes except for the comparison of prevalence of HBV and HCV markers between IBD and general population and patients with UC and CD (Sup-

Continent and Author	Country	Anti-HCV +	Total	Proportion (95% CI)	Weight%
Europe					
Longo 2000	France	7	117	0.060 (0.029, 0.118)	1.47
Biancone 2001	Italy	24	325	0.074 (0.050, 0.108)	2.66
Esteve 2004	Spain	1	80	0.013 (0.002, 0.067)	3.19
Loras 2009	Spain	38	2076	0.018 (0.013, 0.025)	6.66
Chevaux 2010	France	3	315	0.010 (0.003, 0.028)	5.75
Katsanos 2010	Greece	4	482	0.008 (0.003, 0.021)	6.26
Morisco 2012	Italy	60	1513	0.040 (0.031, 0.051)	5.93
Papa 2013 🔶	Italy	4	301	0.013 (0.005, 0.034)	5.28
Loras 2014	Spain	5	389	0.013 (0.006, 0.030)	5.65
Van der Have 2014	Netherlands	0	78	0.000 (0.000, 0.047)	4.35
Waszczuk 2016	Poland	1	147	0.007 (0.001, 0.038)	5.21
Ardesia 2017	Italy	11	437	0.025 (0.014, 0.045)	4.92
Fousekis 2019	Greece	6	201	0.030 (0.014, 0.064)	3.31
Losurdo 2020	Italy	28	807	0.035 (0.024, 0.050)	5.35
Subgroup, DL (l ² = 79.0%, p = 0.000)	98.330 ·			0.021 (0.013, 0.029)	65.99
Multiple					
Agmon-Levin 2009		6	98	0.061 (0.028, 0.127)	1.25
Lidar 2009		7	119	0.059 (0.029, 0.116)	1.51
Subgroup, DL (l ² = 0.0%, p = 0.941)				0.060 (0.028, 0.091)	2.77
Asia					
Huang 2014	China	3	714	0.004 (0.001, 0.012)	6.80
Chen 2017 •	China	5	870	0.006 (0.002, 0.013)	6.76
Harsh 2017	India	11	790	0.014 (0.008, 0.025)	6.25
Chou 2019 🔶	Taiwan	0	190	0.000 (0.000, 0.020)	6.42
Subgroup, DL (l ² = 54.3%, p = 0.087)				0.006 (0.001, 0.010)	26.23
S. America					
Silva 2019 🔶	Brazil	4	181	0.022 (0.009, 0.055)	3.65
Subgroup, DL (l ² = 0.0%, p = .)				0.022 (0.001, 0.044)	3.65
Africa					
Sabbah 2020	Tunisia	3	74	0.041 (0.014, 0.113)	1.37
Subgroup, DL (I ² = 0.0%, p = .)				0.041 (-0.004, 0.085)	1.37
Heterogeneity between groups: p = 0.000					
Overall , DL (I ² = 82.1%, p = 0.000)				0.018 (0.012, 0.024)	100.00
0	 .5			1	
U	ہ. Proportion			1	

Fig. 5. Forest plot showing the pooled prevalence of anti-hepatitis C virus (HCV) in patients with inflammatory bowel disease with subgroup analysis based on the continent of study. DL, DerSimonian and Laird method; Cl, confidence interval.

plementary Fig. 17). On leave-one-out meta-analysis, there was no difference in anti-HBc positivity between UC and CD with the exclusion of the study by Tolentino et al.,²¹ Kim et al.,³⁰ and He et al.³⁷ Similarly, with the exclusion of studies one at time, there was no difference in the anti-HBc positivity between IBD and controls, except for the study by Kim et al.³⁰ Concerning HCV viremic status, HCV RNA positivity rate reduced to 0.5% (0.2–0.8) with the exclusion of the study by Morisco et al.²⁷

Meta-regression analysis was conducted to assess for the source of heterogeneity for various outcomes. For HBsAg positivity and anti-HBc positivity, difference in the continent of study was a significant contributor to heterogeneity (Supplementary Fig. 18). For anti-HCV positivity, the continent of study (P=0.016), publication year (P=0.011) and mean age (P=0.004) of the study population were significant covariates contributing to heterogeneity (Fig. 6).

Table 2 summarizes the pooled events rates with sensitivity analysis based on etiology, study design and continent of study.

DISCUSSION

The present analysis provides updated data on the epidemiology of HBV and HCV infection among IBD patients globally. The pooled prevalence of HBsAg in patients with IBD was 3.3% (2.5–4.2), while HBeAg positivity and detectable HBV DNA were seen in 15.3% (6.9–23.7) and 61.0% (42.1–79.9) of the

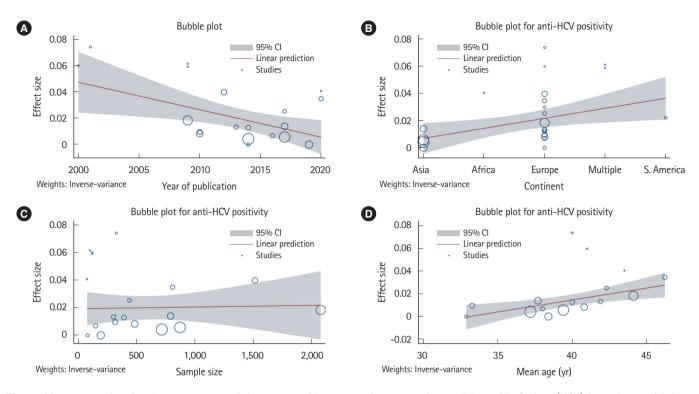


Fig. 6. Meta-regression for the assessment of the source of heterogeneity concerning anti-hepatitis C virus (HCV) in patients with inflammatory bowel disease analyzing (A) year of publication, (B) study continent, (C) sample size, and (D) mean age. CI, confidence interval.

HBsAg positive patients, respectively. The pooled prevalence of anti-HBc in IBD patients was 14.2% (10.6–17.8), while effective HBV vaccination was seen in only 35.6% (28.7–42.4) of the patients. The pooled prevalence of anti-HCV and detectable HCV RNA were 1.8% (1.2–2.4) and 0.8% (0.4–1.3), respectively. The odds of prevalence of HBsAg (OR, 1.08; 95% CI, 0.93– 1.24) and anti-HCV (OR, 1.42; 95% CI, 0.93–2.18) were similar between IBD patients and the general population. Similarly, both patients with UC and CD had a comparable prevalence of HBsAg (OR, 1.15; 95% CI, 0.96–1.37) and anti-HCV (OR, 1.04; 95% CI, 0.54–1.99). Although the prevalence of anti-HBc was higher in patients with IBD compared to controls (OR, 1.48; 95% CI, 1.02–2.13) and in patients with UC compared to CD (OR, 1.29; 95% CI, 1.03–1.61), the odds were comparable on sensitivity analysis.

The reported global prevalence of HBsAg in 2016 was 3.9% (3.4–4.6),⁵² which is similar to the HBsAg prevalence rate of 3.3% (2.5–4.0) among IBD patients in the present analysis. HBV infection may be particularly significant for patients with IBD. Firstly, IBD is no more the disease of the West, with incidence and prevalence increasing across developing countries where HBV infection is more prevalent.⁵³ This would imply that many patients with IBD may be exposed and infected

with HBV. Secondly, HBV vaccination rates are considerably lower in developing countries, especially amongst the IBD population, which puts them at increased risk of HBV infection.⁵⁴ Finally, the immunodeficiency state acquired through immunomodulatory drugs like steroids, thiopurines, biologics, or biosimilars renders patients with IBD more vulnerable to viral reactivation, characterized by viremia with or without clinical manifestations, including fulminant life-threatening hepatitis.

In the study by Loras et al.,⁵⁵ 36% (9/25) of the HBsAg positive IBD patients on immunosuppression developed reactivation, out of which 6 patients (6/9, 75%) developed hepatic failure. Treatment with \geq 2 immunosuppressants was an independent predictor of HBV reactivation, while prophylactic antiviral therapy was protective against reactivation. Interestingly, none of the patients with isolated anti-HBc positivity developed HBV reactivation. The study by Park et al.²⁸ reported liver dysfunction in 25.7% of the HBsAg positive compared to 2.8% of the HBsAg-negative patients receiving immunosuppressive therapy. Lee et al.⁵⁶ reported that the liver dysfunction due to viral reactivation was 7.3% after a median time interval of 32.4 months after anti-tumor necrosis factor (anti-TNF) in IBD patients with HBV infection. The proportion of liver dysfunction

Variable	Overall	Ulcerative colitis	Crohn's disease	Prospective studies	Retrospective studies	European studies	Asian studies	High-quality studies
HBsAg positivity								
No. of patients	17,022	7,012	7,978	5,678	11,344	7,240	8,088	14,371
% (95% CI)	3.3 (2.5–4.0)	3.3 (2.3-4.4)	2.9 (2.0–3.8)	1.3 (0.8–1.8)	4.8 (3.5–6.1)	1.4 (0.9–1.8)	5.8 (4.2–7.5)	3.4 (2.5–4.3)
Anti-HBc positivity								
No. of patients	12,265	3,006	4,297	5,641	6,624	6,644	3,012	8,699
0/0 (950/0 CI)	14.2 (10.6–17.8)	20.3 (12.8–27.8)	16.1 (10.0–22.1)	12.0 (8.9–15.1)	17.0 (9.6–24.5)	8.3 (6.0–10.5)	30.3 (22.9–37.7)	17.1 (11.6–22.5)
HBV-DNA in HBsAg+								
No. of patients	10,663	I	I	3,407	7,256	4,013	5,425	10,117
% (95% CI)	61.0 (42.1–79.9)			70.5 (29.7–100)	56.0 (33.3–78.6)	72.0 (48.7–95.3)	59.9 (29.7–90.1)	60.0 (39.9–80.1)
HBeAg positive in HBsAg+								
No. of patients	7,130	I	I	2,799	4,331	4,279	2,851	5,498
% (95% CI)	15.3 (6.9–23.7)			5.3 (0.0–16.4)	19.6 (9.7–29.4)	8.0 (1.0–15.9)	20.9 (10.4 – 31.3)	16.7 (7.1 – 26.7)
Effective HBV vaccination								
No. of patients	4,895	1,321	2,086	2,526	2,369	1,803	3,092	4,895
% (95% CI)	35.6 (28.7–42.4)	32.7 (23.0–42.4)	32.4 (25.0–39.8)	41.0 (32.2–49.8)	23.6 (18.9–28.4)	42.2 (29.3–55.1)	29.2 (22.4–36.0)	35.6 (28.7–42.4)
Anti-HCV positivity								
No. of patients	10,304	3,642	4,518	5,029	5,275	7,268	2,384	8,122
% (95% CI)	1.8 (1.2–2.4)	1.4 (0.7–2.1)	1.4 (0.6–2.1)	2.4 (1.5–3.2)	1.3 (0.5–2.1)	2.1 (1.3–2.9)	0.6 (0.1–1.0)	1.4 (0.8–1.9)
Detectable HCV RNA								
No. of patients	7,447	1,524	970	3,929	3,518	5,682	1,584	5,673
% (95% CI)	0.8 (0.4–1.3)	0.5 (0.1–1.0)	0.2 (0.0–0.6)	0.7 (0.2–1.2)	0.9 (0.2–1.7)	1.1 (0.4–1.8)	0.2 (0.0–0.5)	0.5 (0.1–0.8)
HBsAg, hepatitis B surface antigen; Cl, confidence interval; Anti-HBc, hepatitis B core antibody; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HCV, hepatitis C virus.	ntigen; Cl, confidence	: interval; Anti-HBc, h	epatitis B core antibc	ody; HBV, hepatitis B	virus; HBeAg, hepatiti	is B e antigen; HCV, h	nepatitis C virus.	



was significantly higher in the non-prophylaxis group (26% vs. 8%, P=0.02). The pooled proportion of anti-HBc positivity (present or past HBV infection) was 14.2% (10.6–17.8). This subset of patients has a moderate risk of HBV reactivation with the use of anti-TNF therapy, anti-integrin therapy or moderate to high-dose corticosteroids.⁶ Therefore, despite having a similar prevalence as the general population, the risk of reactivation or liver dysfunction remains high, which could be prevented by early detection and treatment. For this reason, both ECCO and BSG guidelines recommend that all IBD patients should be tested for HBsAg, anti-HBs, and anti-HBc, preferably at the time of diagnosis.^{12,57}

Immunomodulators and immunosuppressants reduce the effective HBV vaccination response.¹² The study by Kim et al.³⁰ compared HBV markers of IBD patients with age- and sexmatched controls and reported a lower anti-HBs positivity rate (61.8% vs. 73.3%, P<0.001) and effective vaccination in patients with IBD (38.1% vs. 44.4%, P=0.04). They reported that around one-third of the IBD patients were susceptible to HBV and age < 30 years was a risk factor for nonimmune status in the multivariate analysis. Subsequent studies by Papa et al.³¹ and Huang et al.³³ reported a similar lower rate of effective vaccination in patients with IBD, 23.9% and 21.6%, respectively. The present analysis showed that only around one-third of the IBD patients had effective vaccination and this rate was still lower for Asian studies compared to European studies (29.2% [95% CI, 22.4-36.0] vs. 42.2% [95% CI 29.3-55.1]). In a recent meta-analysis, the pooled OR of HBV response in IBD patients was lower compared to controls (OR, 0.13; 95% CI, 0.05-0.33), with pooled proportion of effective immune response being 39.7% (95% CI, 30.7-49.5).⁵⁸

In the study by Morisco et al.²⁷ of the 5,096 patients with IBD, only 30.5% and 29.7% patients were investigated for HBV and HCV markers, respectively. Similarly, Vaughn et al.²⁹ reported that only 25% of the IBD were screened for hepatitis B in the year prior to an anti-TNF being initiated. In a survey from Australia, only 61.3% and 27% of the gastroenterologists screened their patients for HBV infection prior to anti-TNF therapy and corticosteroids, respectively.⁵⁹ In a subsequent study from France, 91% of the gastroenterologists screened IBD patients for HBV while only 46% recommended HBV vaccination for seronegative patients.⁶⁰ Thus, there is considerable uncertainty and disagreement with respect to screening and vaccination practice in IBD patients and this needs to be improved.

Concerning the variation in the prevalence of HBV across various regions, a previous analysis showed a higher prevalence

of HBsAg positive population in the Western Pacific (5.7%; 95% CI, 5.1–6.6) and South-East Asian region (3.5%; 95% CI, 2.9–4.0) compared to European region (1.6%; 95% CI, 1.1–2.1).⁵² The present meta-analysis also showed that Asian studies had a higher pooled prevalence of HBsAg (5.8% [95% CI, 4.2–7.5] vs. 1.2% [95% CI, 0.8–1.6]) and anti-HBc (29.7% [95% CI, 22.1–37.3] vs. 7.5% [95% CI 5.2–9.7]) in the IBD patients compared to European studies.

The global prevalence of viremic HCV infection (HCV RNApositive cases) for the year 2020 was reported as 0.7% (95% uncertainty interval, 0.7–0.9), which had decreased from the prevalence rate of 0.9% (0.8–1.0) for the year 2015.⁶¹ The present analysis also showed a similar prevalence of viremic HCV infection (0.8%; 95% CI, 0.4–1.3). Patients with HCV infection who receive immunosuppressive treatment for IBD raise several interesting concerns. Prednisone may negatively affect HCV infection by increasing the viral load. On the other hand, anti-TNF- α in IBD may not lead to reactivation of hepatitis C. Morisco et al.²⁷ and Loras et al.⁵⁵ reported liver dysfunction in 1 out of 10 (10%) and 8 out of 51 (15.7%) of HCV RNA positive patients, respectively. Thus, IBD patients with HCV viremia should be evaluated and treated actively to prevent hepatic dysfunction.

In a previous meta-analysis, the prevalence of anti-HCV was higher in the Asian studies compared to European studies (2.8% vs. 1.8%), but the viremic rate was higher in the Europeans (72.4% vs. 64.4%).⁶² On the contrary, the present analysis showed a significantly higher anti-HCV positivity (2.1% [95% CI, 1.3-2.9] vs. 0.6% [95% CI, 0.1-1.0]) and viremic rate (1.1% [95% CI, 0.4-1.8] vs. 0.2% [95% CI, 0.0-0.5]) in European studies compared to Asian studies. This may be due to the fact that the prevalence of HCV is higher in central Asia, while the studies included in the present meta-analysis were mostly from east, south, and south-east Asia, where the prevalence remains lower.^{61,62} One interesting finding from the current meta-analysis was the reduction in the effect size of anti-HCV prevalence with publication year (Fig. 6). This decreasing prevalence of HCV in IBD patients suggests that preventative measures such as blood transfusion safety programs, single-use materials, and better aseptic perioperative rules have been effective and explains the diminishing risk for HCV.

One major limitation of this study was the significant heterogeneity between the included studies. Second, the number of primary studies outside of Asia and Europe was small, and that comparisons with other regions were not possible. It is also a concern that the number of included primary studies may affect the results, since different countries in Europe have different prevalence rates due to differences in vaccination policies.⁶³ Third, the data on HBV DNA or HCV RNA were unavailable in most studies. Fourth, the prevalence of chronic hepatitis B and C may be warranted in the subclassified group by age, location, and severity. However, unfortunately, no such data on the prevalence in different age groups were available in the included studies. This study estimated the pooled prevalence of hepatitis B and C among the entire IBD participants irrespective of age. So, it is crucial in future prevalence studies to consider prevalence stratification regarding age and other disease variables. Lastly, most studies did not have data on prior treatment history, risk factors, and vaccination.

Nevertheless, this is the first meta-analysis utilizing data globally to evaluate the prevalence of chronic hepatitis B and C markers in IBD patients. The current evidence suggests that the cumulative prevalence of HBV and HCV in IBD patients is sizeable and parallels the national trends in each country. Physicians should be sensitized to implement guidelines' recommendations in clinical practice to ensure homogeneous screening, prevention, and management of chronic viral hepatitis infection in IBD patients. Further prospective, multicentric and multinational studies are required to understand the actual burden of viral hepatitis in IBD to inform the best possible public health measures and save the direct and indirect costs associated with it.

ADDITIONAL INFORMATION

Funding Source

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability Statement

Not applicable.

Author Contribution

Conceptualization: Giri S. Methodology: Giri S, Agrawal D, Afzalpurkar S, Kasturi S, Gopan A. Formal analysis: Giri S, Kasturi S, Gopan A. Project administration: Giri S, Sundaram S, Kale A. Visualization: Giri S. Writing-original draft: Giri S, Agrawal D, Afzalpurkar S. Writing-review and editing: Giri S, Agrawal D, Afzalpurkar S, Sundaram S, Kale A. Approval of final manuscript: all authors.

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Supplementary Material

Supplementary materials are available at the Intestinal Research website (https://www.irjournal.org).

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