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Original Article

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Causal relationship between primary biliary cholangitis and inflammatory bowel disease: a Mendelian randomization study

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Abstract

Background: Several studies indicated that inflammatory bowel disease (IBD) may contribute to increased susceptibility to primary biliary cholangitis (PBC). However, the causal relationship between IBD and PBC remains unclear.

Methods: The genetic variant data of patients with IBD and PBC were obtained from published genome-wide association studies (GWASs). The IBD data were further divided into a discovery dataset and a validation dataset depending on the data source. We conducted a two-sample Mendelian randomization (MR) analysis using the inverse variance weighting (IVW), MR-Egger, weighted median (WM), MR robust adjusted profile score (MR-RAPS), and maximum likelihood (ML) methods, with IVW being the main focus, to verify the causal relationship between IBD and PBC. Additionally, a series of sensitivity analyses were performed to ensure the reliability of the results.

Results: In the discovery cohort, the IVW analysis results (OR = 1.114, $P = 0.011$) indicated a significant association between IBD and PBC. The MR-RAPS (OR = 1.130, $P = 0.007$) and ML (OR = 1.115, $P = 0.011$) analyses yielded results consistent with those of IVW in confirming IBD as a risk factor for PBC. In the validation cohort, consistent findings were observed regarding the causal relationship between IBD and PBC using IVW, MR-RAPS, and ML analyses; all three methods identified IBD as a risk factor for developing PBC. By the IVW analysis, Crohn's disease (CD) emerged as the most prominent subtype of IBD associated with an increased risk of developing PBC in both the discovery cohort (OR = 1.068, $P = 0.049$) and the validation cohort (OR = 1.082, $P = 0.019$).

Conclusion: The results of the MR analysis suggest a causal relationship between IBD and PBC, highlighting the necessity for proactive PBC prevention in patients with IBD, particularly those with CD.

Keywords: primary biliary cholangitis; inflammatory bowel disease; ulcerative colitis; Crohn's disease; Mendelian randomization

Introduction

Primary biliary cholangitis (PBC) is a rare autoimmune liver disease formerly known as primary biliary cirrhosis. The main histologic features of PBC are periportal lymphoplasmacytic infiltration of hepatic interlobular ducts and progressive destruction of interlobular bile ducts, and the main clinical features are fatigue, itching, and jaundice, accompanied by elevated levels of circulating gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and antimitochondrial antibodies (AMAs). The diagnosis is typically established in a clinical setting through the detection of specific antibodies and/or characteristic histological alterations [1, 2]. The annual incidence of PBC ranges from 0.23 to 5.31 cases per 100,000 people, and the prevalence ranges from 1.91 to 40.2 cases per 100,000 people. The majority of patients with PBC are from North America and Northern Europe, and 92% of them are women [3–7]. The prevalence of PBC has exhibited a consistent upward trend over the past decade, and the progression of PBC can culminate in cirrhosis and hepatic failure, underscoring the imperative nature of clinical management for this condition [2, 8]. The pathogenesis of PBC involves a complex interplay between genetic susceptibility and environmental factors, including IL-12, HLA, pathogens, smoking, and radiation. Furthermore, PBC is closely associated with various extrahepatic immune diseases such as rheumatoid arthritis and thyroid disease [9–12].

Inflammatory bowel disease (IBD) is an immune-mediated, chronic, recurrent inflammatory disease of the gastrointestinal tract, with subtypes including ulcerative colitis (UC) and Crohn's disease (CD) [13]. Several studies have demonstrated a correlation and shared susceptibility genes between IBD and PBC [14]. Furthermore, common metabolites have been identified in both diseases that play crucial roles in their progression [15, 16]. Additionally, individuals with IBD exhibit an elevated vulnerability to and risk of developing PBC, suggesting a potential causal association between these two conditions [17]. However, these findings are based solely on observational studies, which are limited by confounding factors and reverse causality.

The association between IBD and PBC has yet to be established. Investigating their relationship will contribute to a

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deeper understanding of their pathogenesis and enhance treatment and management strategies for both diseases. A randomized controlled trial (RCT) is the most reliable method for causal inference. However, RCTs are difficult to carry out due to the strict implementation requirements and control of confounding factors. Mendelian randomization (MR) is an emerging epidemiological approach that can assess causal associations with disease outcomes by using genetic variants strongly associated with the exposure as instrumental variables (IVs) [18]. Genetic variation is not subject to confounding factors, and causality is estimated chronologically because the variation is transmitted randomly to offspring during meiosis following Mendelian inheritance principles [19]. In this study, we used summary statistics from large-scale genome-wide association studies (GWASs) and applied two-sample MR to reveal the causal relationship between IBD and PBC.

Materials and methods

Mendelian randomization analysis and study design

The present study is based on three Mendelian assumptions: (1) genetic IVs are strongly associated with exposure variables, (2) genetic IVs are independent of confounders, and (3) genetic IVs are associated with outcome variables only through exposure variables [20]. We used two sets of genetic variant data from different databases (discovery set and validation set) to reveal the causal relationship between IBD and PBC (Figure 1).

Data sources for instrumental variables

Associated genetic variants of IBD, patients with CD, and UC in the discovery dataset were identified from the IEU OpenGWAS online database. The summary data included European and non-European cohorts, but only the European population was selected to avoid racial bias. Single-nucleotide polymorphisms (SNPs) associated with IBD were derived from 34,652 European participants, including 12,882 cases and 21,770 controls. SNPs associated with CD were derived from 20,883 European participants, including 5,956 cases and 14,927 controls. SNPs associated with UC were derived from 27,432 European participants, including 6,968 cases and 20,464 controls [21]. In the validation dataset, genetic variants associated with IBD, CD, and UC were obtained from the International Inflammatory Bowel Disease Genetics Consortium (IIBDGC). The study involved a total of 75,000 participants, all of European ancestry, with 14,763 cases and 15,977 controls for CD and 10,920 cases and 15,977 controls for UC [22].

The PBC data were obtained from a meta-analysis of more than 1 million SNPs in a European population consisting of 2,764 cases and 10,475 controls. The diagnosis of PBC was based on the International Classification of Diseases-10 (ICD-10) criteria [23]. The presence of potential sample overlap between exposure variables and outcome variables within the same database is acknowledged. However, it has been argued in the study conducted by Bulik-Sullivan *et al.* [24] that this sample overlap does not impact the estimation of β values. The data utilized in this study were exclusively sourced from publicly available databases, and all GWAS summary data were anonymized and made public. Therefore, there is no requirement for additional ethical approval or informed consent. Detailed information regarding the specific sources of the data can be found in Table 1.

Selection of instrumental variables

First, we screened SNPs that were strongly correlated with the exposure variables ($P < 5e\text{-}8$), which satisfied the first Mendelian hypothesis. Second, SNPs with a linkage disequilibrium (LD) of $r^2 < 0.001$ were removed, and a window size of 10,000 kb was used to ensure that the SNPs were valid and independent; in addition, palindromic SNPs with effect alleles were excluded. The SNPs associated with PBC and potential confounding factors, including exposure to environmental pollutants, radiation, infectious agents, chemical xenobiotics, and smoking, were systematically excluded according to the third hypothesis. The *F*-statistic was used to assess the strength of the IVs, and an *F*-statistic greater than 10 indicated good predictive potential of the IV [25].

MR analysis method

The main method used in this study was the random effects model inverse variance weighted (IVW) method. MR-Egger, weighted median (WM), MR robust adjusted profile score (MR-RAPS), and maximum likelihood (ML) were used as complementary methods. The IVW method for calculating the Wald ratio of each SNP of the IVs provides precise causal estimates [26]. MR-Egger is a causal hypothesis test and provides a causal impact estimation when all SNPs are assumed to be invalid [27]. The WM method can be used to estimate causality when 50% of SNPs are invalid [28]. To reduce the bias of weak IVs, the newly developed MR-RAPS method was used to evaluate the causal effect [29]. ML is a reliable traditional method for assessing causality [30]. In addition, the MR pleiotropy residual sum and outlier (MR-PRESSO) method was used to correct for horizontal pleiotropy and remove outliers to obtain a more robust estimation of causal effects [31].

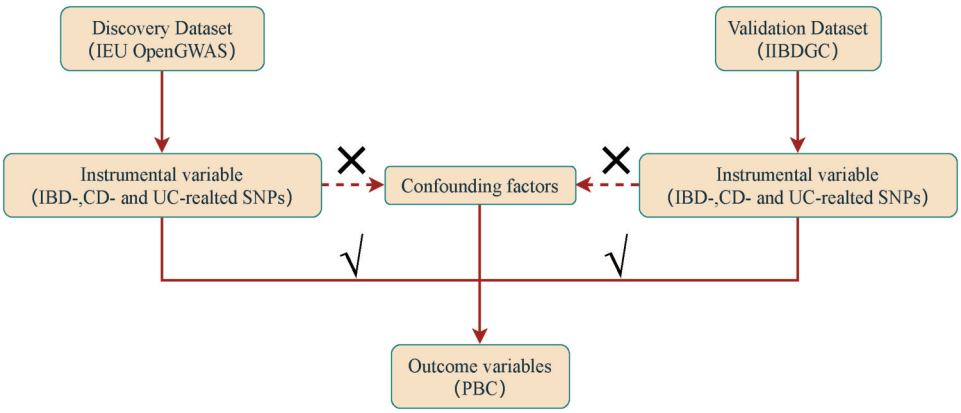

Figure 1. Three hypotheses of Mendelian randomization. IBD = inflammatory bowel disease, CD = Crohn's disease, UC = ulcerative colitis, IIBDGC = International Inflammatory Bowel Disease Genetics Consortium.

Table 1. Data sources for IVs information

Variable	Ancestry	Sample size (case/control)	Data source	SNP	r^2 (%)	*F*-statistic
IBD (Discovery)	European	12,882/21,770	IEU OpenGWAS	73	3.83	50.90
CD (Discovery)	European	5,956/14,927	IEU OpenGWAS	69	5.30	58.88
UC (Discovery)	European	6,968/20,464	IEU OpenGWAS	46	4.20	48.58
IBD (Validation)	European	75,000/75,000	IIBDGC	67	3.97	52.01
CD (Validation)	European	14,763/15,977	IIBDGC	72	4.18	57.60
UC (Validation)	European	10,920/15,977	IIBDGC	44	3.66	44.29
PBC (Outcome variables)	European	2,764/10,475	IEU OpenGWAS	/	/	/

IBD = inflammatory bowel disease, CD = Crohn's disease, UC = ulcerative colitis, IIBDGC = International Inflammatory Bowel Disease Genetics Consortium.

We used pleiotropy, heterogeneity, and sensitivity analyses for data quality control. MR-PRESSO and MR-Egger regressions were used to evaluate the potential pleiotropy of the SNPs. The presence of pleiotropy ($P < 0.05$) indicates that a single SNP may affect multiple phenotypes, which violates the third hypothesis of Mendelian randomization. Cochran's Q statistic was used to assess heterogeneity. The leave-one-out method determines whether an individual SNP affects the causal estimates of MR and assesses the stability of the results by removing individual SNPs one at a time and recalculating the results [31].

Statistical analysis

MR estimates are expressed as odds ratios (ORs) and 95% confidence intervals (CIs), with a two-tailed *P* value of less than 0.05 indicating statistical significance. The MR-Steiger directivity test was used to test the causal direction between the exposure variable and the outcome variable to verify the credibility of the results. All the statistical analyses were performed in RStudio (version 4.2.2) using the R packages "TwoSampleMR" and "MRPRESSO".

Results

Causal relationship between IBD and PBC in the discovery cohort

In the discovery cohort, 73, 69, and 46 SNPs were selected for the IBD, CD, and UC cohorts, respectively, after rigorous screening (Table 1). The F-statistics for all the instruments were much greater than 10; the median F-statistics for IBD, CD, and UC were 50.90, 58.88, and 48.58, respectively, indicating that IV strength met the MR correlation hypothesis. Random effects IVW analysis showed that IBD had a positive causal effect on PBC (OR = 1.114, 95% CI = 1.026–1.211, $P = 0.011$), and CD was also positively correlated with PBC (OR = 1.068, 95% CI = 1.000–1.140, $P = 0.049$). However, no causal association was found between UC and PBC (OR = 1.001, 95% CI = 0.917–1.094, $P = 0.975$). In addition, MR-RAPS and ML analyses revealed positive causal relationships of IBD and CD with PBC. MR-Egger and WM analyses did not reveal a correlation with PBC. All MR estimation results are shown in Table 2, and the forest diagram is shown in Figure 2. We performed heterogeneity testing using the Cochran Q test, which showed that there was no heterogeneity in the MR estimates. Moreover, the MR-Steiger directivity test showed that the causal directions of the relationship between IBD and PBC were consistent with the predicted directions (Table 2). The leave-one-out method did not reveal any SNPs that significantly affected the results (Supplementary Figure 2A–C). MR-Egger regression and MR-PRESSO global tests showed no horizontal pleiotropy (IBD: intercept = 0.014, $P = 0.256$; CD: intercept = −0.005, $P = 0.644$; UC: intercept = −0.005, $P = 0.725$; Table 2). Scatter plots and funnel plots are shown in Supplementary Figure 1A–C and Supplementary Figure 3A–C, respectively. The Egger intercept did not pass through the origin in the scatter plot, and all estimates exhibited a symmetrical distribution in the funnel plot, indicating the absence of pleiotropy in our exposure variables.

Causal relationship between IBD and PBC in the validation cohort

In the validation dataset from IIBDGC, we identified 67 SNPs for IBD, 72 SNPs for CD, and 44 SNPs for UC, and the *F*-statistics indicated that the SNPs had strong predictive potential (Table 1). The causal association between IBD and PBC remained consistent when replication analyses were performed using validation data. IVW showed that IBD (OR = 1.092, 95% CI = 1.005–1.186, $P = 0.039$) and CD (OR = 1.082, 95% CI = 1.013–1.156, $P = 0.019$) were positively correlated with PBC. MR-RAPS (IBD: OR = 1.112, 95% CI = 1.015–1.218, $P = 0.023$; CD: OR = 1.099, 95% CI = 1.022–1.181, $P = 0.010$) and ML (IBD: OR = 1.0922, 95% CI = 1.009–1.182, $P = 0.030$; CD: OR = 1.084, 95% CI = 1.017–1.155, $P = 0.014$) produced the same results (Table 3, Figure 3). The Cochran Q test for heterogeneity did not reveal heterogeneity, and pleiotropy testing did not reveal evidence of horizontal pleiotropy. In addition, the MR-Steiger directivity test supported a positive causal relationship between IBD and PBC (Table 3). The leave-one-out method also indicated that the results were not driven by a particular SNP (Supplementary Figure 2D–F). The presence of a zero intercept in the scatter plot and the symmetrical estimates in the funnel plot suggested the absence of pleiotropy in genetic variation, thereby supporting the robustness of the results (Supplementary Figure 1D–F, Supplementary Figure 3D–F).

Discussion

Two-sample MR analysis was employed to investigate the presence of a causal relationship between IBD and PBC. The results of our MR analysis revealed a significant causal association between IBD and PBC, with CD exhibiting a significantly positive correlation with PBC. Furthermore, we corroborated these findings by validating them using an independent validation dataset.

Research [15, 17, 32–34] has demonstrated that the incidence of PBC is greater among patients with IBD than in the general population, with IBD-related PBC being more prevalent in males and occurring at a younger age. Several studies [35] have indicated similarities between the pathogenesis of PBC and CD, where dysfunction in IL-12 signaling leads to both liver fibrosis and granuloma formation. Furthermore, TNFSF15 and ICOSLG-CXCR5 have been identified as potential shared pathways for the development of both PBC and CD [36]. Chronic intestinal inflammation results in elevated expression of inflammatory cytokines, leading to increased intestinal permeability, disruption of the

Table 2. The causal relationship between IBD and PBC was assessed using MR analysis in the discovery cohort

Exposure	Method	OR (95%CI)	P-value	Q test P	Egger_intercept	P-Egger_intercept	MR-PRESSO Global Test P value	MR-Steiger test
IBD					0.014	0.256	0.712	TRUE
	IVW	1.114 (1.026–1.211)	0.011	0.721				
	MR-Egger	0.974 (0.762–1.245)	0.834	0.732				
	WM	1.115 (0.986–1.261)	0.083					
	MR-RAPS	1.130 (1.035–1.234)	0.007					
	ML	1.115 (1.026–1.212)	0.011					
CD					−0.005	0.644	0.700	TRUE
	IVW	1.068 (1.000–1.140)	0.049	0.688				
	MR-Egger	1.107 (0.937–1.309)	0.237	0.664				
	WM	1.076 (0.973–1.189)	0.152					
	MR-RAPS	1.075 (1.005–1.150)	0.036					
	ML	1.068 (1.000–1.140)	0.049					
UC					−0.005	0.725	0.877	TRUE
	IVW	1.001 (0.917–1.094)	0.975	0.871				
	MR-Egger	1.049 (0.817–1.347)	0.709	0.850				
	WM	0.973 (0.817–1.347)	0.681					
	MR-RAPS	1.004 (0.916–1.100)	0.927					
	ML	1.001 (0.917–1.094)	0.975					

IBD = inflammatory bowel disease, CD = Crohn's disease, UC = ulcerative colitis, IVW = inverse variance weighted, WM = weighted median, MR-RAPS = MR robust adjusted profile score, ML = maximum likelihood.

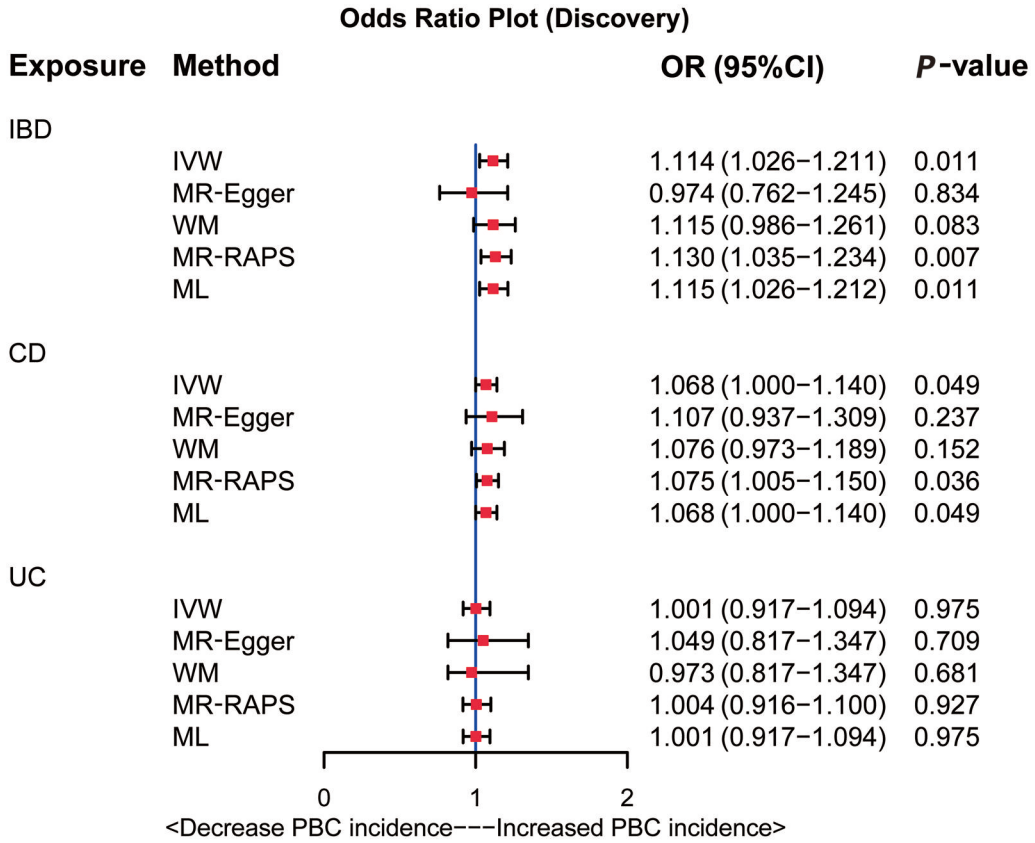

Figure 2. Odds ratio plot for IBD, CD and UC in the discovery cohort. IBD = inflammatory bowel disease, CD = Crohn's disease, UC = ulcerative colitis, IVW = inverse variance weighted, WM = weighted median, MR-RAPS = MR robust adjusted profile score, ML = maximum likelihood.

intestinal barrier, bacterial translocation, and liver inflammation, ultimately contributing to the onset and progression of PBC [37]. Additionally, it has been reported that the gut microbiota of patients with IBD may elicit cross-immune responses that contribute to the development of PBC [7, 38]. Although there is a potential correlation between IBD and PBC, the current body of related research primarily consists of retrospective studies with small sample sizes and case reports, leaving the association between IBD and PBC unclear. Consequently, we conducted MR analyses utilizing the available genetic variants to evaluate causality.

In this study, we identified a significant association between IBD and PBC in the discovery dataset. The main MR methods, including IVW, MR-RAPS, and ML, consistently indicated that both

Table 3. The causal relationship between IBD and PBC was assessed using MR analysis in the validation cohort

Exposure	Method	OR (95%CI)	P-value	Q test P	Egger_intercept	P-Egger_intercept	MR-PRESSO Global Test P value	MR-Steiger test
IBD					0.004	0.764	0.246	TRUE
	IVW	1.092 (1.005–1.186)	0.039	0.230				
	MR-Egger	1.056 (0.839–1.330)	0.644	0.254				
	WM	1.099 (0.970–1.245)	0.139					
	MR-RAPS	1.112 (1.015–1.218)	0.023					
	ML	1.092 (1.009–1.182)	0.030					
CD					– 0.005	0.641	0.282	TRUE
	IVW	1.082 (1.013–1.156)	0.019	0.276				
	MR-Egger	1.123 (0.948–1.330)	0.183	0.255				
	WM	1.081 (0.975–1.199)	0.140					
	MR-RAPS	1.099 (1.022–1.181)	0.010					
	ML	1.084 (1.017–1.155)	0.014					
UC					0.005	0.769	0.470	TRUE
	IVW	1.057 (0.969–1.153)	0.212	0.473				
	MR-Egger	1.020 (0.796–1.308)	0.874	0.434				
	WM	1.027 (0.902–1.169)	0.686					
	MR-RAPS	1.073 (0.975–1.180)	0.148					
	ML	1.058 (0.968–1.155)	0.213					

IBD = inflammatory bowel disease, CD = Crohn's disease, UC = ulcerative colitis, IVW = inverse variance weighted, WM = weighted median, MR-RAPS = MR robust adjusted profile score, ML = maximum likelihood.

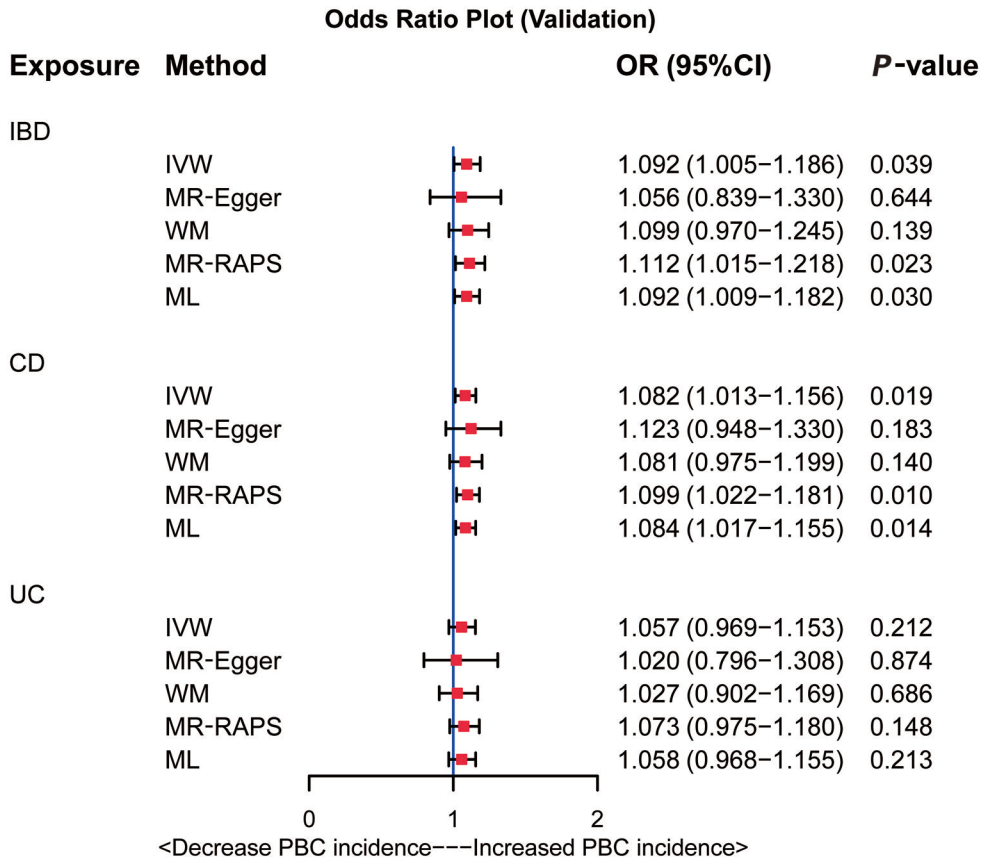

Figure 3. Odds ratio plot for IBD, CD and UC in the validation cohort. IBD = inflammatory bowel disease, CD = Crohn's disease, UC = ulcerative colitis, IVW = inverse variance weighted, WM = weighted median, MR–RAPS = MR robust adjusted profile score, ML = maximum likelihood.

UC and CD significantly increased the incidence of PBC. However, only patients with CD showed an increased risk of PBC in the validation cohort. Therefore, we conclude that IBD clearly elevates the risk of PBC, with CD playing a dominant role in this process. Furthermore, heterogeneity tests and sensitivity analyses yielded *P* values >0.05, indicating stable and reliable results. The MR-Steiger directionality test confirmed the consistency between our causal analysis and directional assumptions without evidence of reverse causality.

The findings of this study have significant implications for future research on the shared mechanisms and potential therapeutic targets of IBD and PBC. Genetic variation plays a crucial role

in the association between IBD and PBC. Recent studies [21, 38–40] have demonstrated an association between PBC and infectious pathogens, while IBD is characterized by 200 risk gene loci, some of which are linked to susceptibility to infection. Therefore, it is essential to monitor diagnostic markers of PBC in patients with IBD, such as antinuclear antibodies and AMAs.

Our study has several strengths. First, the causal relationship between IBD and PBC was estimated by IVs strongly correlated with exposure, without confounders or reverse causality. Second, this study utilized two datasets, a discovery cohort and a validation cohort from different database sources, which increased the reliability of the results. Finally, we applied the MR-Steiger test to determine the direction of causality and repeated the sensitivity analysis to improve the stability of the results. Given the increasing incidence of PBC and the poor prognosis caused by misdiagnosis, revealing the causal relationship between IBD and PBC can improve the diagnosis and treatment of PBC.

However, our study has certain limitations. We included only participants of European ancestry, and differences in genetic and environmental factors between Eastern and Western populations may make it difficult to generalize the results to other populations. Although we rigorously screened the SNPs used as IVs, we could not ensure that each SNP met the three Mendelian hypotheses, and there may be some unknown confounding factors affecting the assessment of the results. In addition, the GWAS dataset of this study could not be stratified by age, sex, or other factors to infer causality; therefore, a broader subgroup study is needed in the future.

This study revealed that there is a close causal relationship between IBD and PBC, where IBD can increase the incidence of PBC. It is necessary to identify and prevent the occurrence of PBC in patients with IBD, especially those with CD.

Ethical Approval

All data for this study were obtained from anonymous publicly available databases, so informed consent was not required.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

Authors' Contributions

Q.Z. substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data and drafting the article; Y.W.X. and Y.F.F. substantial contributions to analysis and interpretation of data; L.Y.G., F.Q.L., and J.H.Q. revised the manuscript; X.D.Z. final approval of the version to be published. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

The datasets [GWAS for Inflammatory bowel disease (IBD) and Primary biliary cholangitis (PBC)] for this study can be found from publicly available databases of large-scale genome-wide association studies.

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