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ORIGINAL RESEARCH

Primary Biliary Cholangitis and Seropositive Rheumatoid Arthritis: A Two-Sample Mendelian Randomization Study

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Background: Observational studies indicated potential associations between primary biliary cholangitis (PBC) and rheumatoid arthritis (RA). However, the causal relationship between RA and PBC remains unclear and controversial. The aim of this study was to evaluate the causal relationships among seropositive RA (SPRA), seronegative RA (SNRA) and PBC.

Methods: This study employed a Mendelian randomization (MR) framework to analyze genome-wide association study (GWAS) data from a European population. The dataset included 802 cases and 16,489 controls for PBC, 18,019 cases and 991,604 controls for SPRA, and 8,515 cases and 1,015,471 controls for SNRA, retrieved on June 11, 2024. Instrumental variables (IVs) were selected based on genome-wide significance ($P < 5.0E-08$) and independence ($R^2 < 0.001$). Palindromic and incompatible SNPs were excluded, and weak instruments ($F < 10$) were removed. Inverse variance weighting (IVW) was the primary analysis method, complemented by Bayesian weighted MR (BWMR), robustly adjusted profile scores (MR-RAPS), MR-Egger, and weighted median approaches. Sensitivity analyses included Cochran's Q test, MR-Egger regression, MR-PRESSO global test, and leave-one-out analysis to assess the robustness of the results.

Results: SPRA increased the risk of genetic susceptibility to PBC (OR=1.28, 95% CI 1.10–1.4, P =0.001). No causal effect of the SNRA on PBC risk was observed.

Conclusion: Our findings show that SPRA increases the risk of developing with PBC. This will help inform future screening guidelines for associated PBC in patients with RA.

Keywords: primary biliary cholangitis, rheumatoid arthritis, causal effect, Mendelian randomization

Introduction

Rheumatoid arthritis (RA) is a persistent autoimmune disease in which the immune system targets the synovial membranes of joints, leading to long-term inflammation, joint damage, and even disability. RA can be either seropositive or seronegative, depending on the presence of RA-specific antibodies in the serum, such as anti-citrulline protein antibodies (ACPA) or rheumatoid factor (RF).[1] Moreover, RA not only causes joint damage but can also develop to autoimmune liver disease (AILD) especially primary biliary cholangitis (PBC).[2,3]

Several large cohort studies have reported that the prevalence of PBC combined with RA ranges from 1.8% to 13%.[4,5] Notably, a study involving 1032 PBC patients and 1041 unrelated controls revealed that PBC coexisted with other autoimmune diseases in 32% of patients, with RA being the most frequently associated autoimmune disease.[6] Increasing evidence suggests that shared immune dysregulation contribute to the co-occurrence of RA and PBC. It is characterized by abnormal immune responses such as cytotoxic or helper T cells, expansion of autoantibody producing B cells, and disorder of bone marrow profiles. In addition, PBC and RA have been shown to share genetic enrichment in multiple

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T cell subpopulations, such as follicle-helper T (Tfh) cells, tissue-resident Th1/17 cells, and tissue-resident gamma-delta T cells.[7] These findings highlight the need to investigate the causal relationship between RA and PBC, which remains poorly understood.

Because observational studies are susceptible to confounders, they are limited in their ability to establish strong causal relationships.[8] Mendelian randomization (MR) is a novel and powerful method for studying causality in epidemiology and genetics. MR uses single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) for inferring causality. MR is not affected by external influences since genetic variation is randomly distributed during meiosis and remains stable throughout an individual's lifetime.[9,10] The causal relationship between RA and PBC has been studied using MR analysis in recent years, but the conclusions are controversial. One study found no causal relationship between RA and PBC,[11] while another study suggested that RA is a significant risk factor for PBC.[12] These conflicting results highlight the uncertainty about whether RA contributes to the development of PBC. Notably, no previous studies have specifically explored the causal relationship between seropositive RA (SPRA) or seronegative RA (SNRA) and PBC. Establishing causal links between SPRA, SNRA, and PBC could help identify RA patients at higher risk for PBC, guiding earlier screening and more targeted treatments. Understanding the lack of a causal relationship in SNRA could help refine clinical management and reduce unnecessary interventions. Therefore, we determined the causal relationship between SPRA, SNRA and PBC using MR analysis.

Materials and Methods

Study Design

Figure 1 offers a concise overview of the research. This study is founded on three assumptions of MR:[13](i) The genetic instrument should be highly related to exposure. (ii) The genetic instrument and potential confounders should be independent of each other. (iii) The results should be linked to the genetic instrument solely through the impact of exposure.

Data Source

The publicly available large-scale genome-wide association study (GWAS) summary data were retrieved on June 11, 2024. The data for PBC were acquired from five cohorts of European ancestry (n = 8,021 cases and 16,489 controls).[14] The data for RA were taken from the published study by Dr. Saevarsdottir S, who reported separate GWASs for SPRA (18,019 cases and 991,604 controls) and SNRA (8,515 cases and 1,015,471 controls) of European ancestry[15] (Table S1).

All data were derived from open-access sources and contained no identifiable personal information. According to Article 32, Items 1 and 2 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (National Health Commission of China, 2023), this study qualifies for exemption from ethical review as it utilized (1) publicly available non-identifiable data and (2) anonymized summary statistics unlinked to individuals.

Instrumental Variable Selection

The IVs were identified according to the following criteria. First, we selected SNPs highly correlated with exposure ($P <$ 5.0E-08). Subsequently, strict clumping was implemented to eliminate the linkage imbalance, with a window size = 10 MB and $R^2 < 0.001$, based on the data from the European 1,000 Genomes Reference Panel. During the harmonization process, the palindromic SNPs were excluded. In addition, the F-statistic ($F = \beta^2/se^2$) was calculated for each SNP, and an F-statistic less than 10 indicates a weak IV.[16]

Statistical Analyses

Five different MR analysis methods were used to conduct our study. For the primary method, we employed inverse-variance weighted (IVW) with multiplicative random effects (IVW-MRE), was chosen for its precision and unbiased estimates under the assumption of no horizontal pleiotropy, which served as the primary analytical method. This approach involves a meta-analysis of each SNP's Wald ratio between the exposure and the outcome. The analysis uses a random-effects inverse-variance system, and each balance is weighted based on its corresponding standard error, which

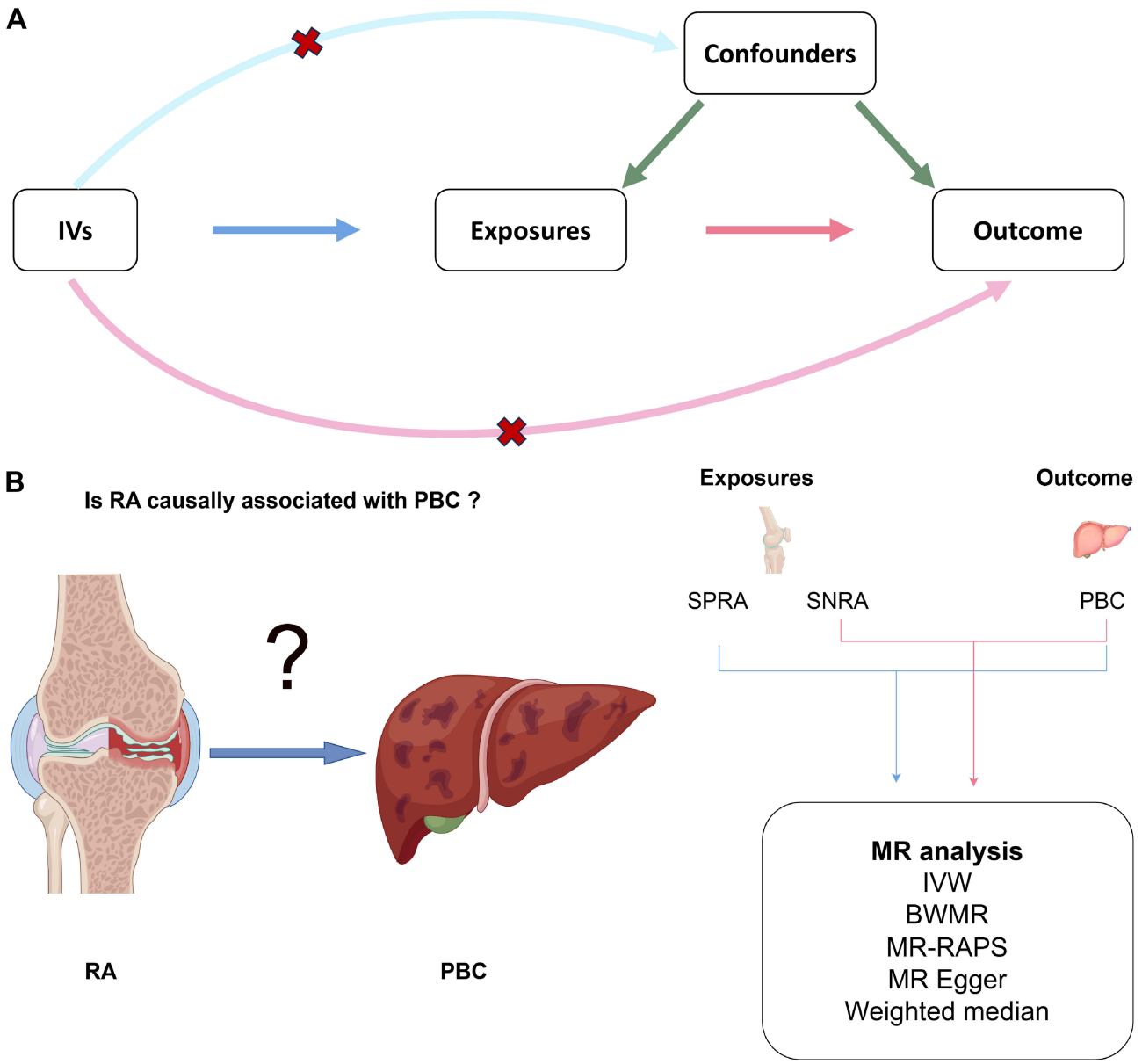

Figure 1 Study design of this research; (**A**) The directed acyclic graph visualizes the three key assumptions of Mendelian randomization. (**B**) Conduct a comprehensive MR analysis using large-scale GWAS datasets, and then apply IVW, BWMR, MR-PAPS, MR Egger, and Weighted median tests to determine the causal relationship between SPRA, SNRA and PBC.

Abbreviations: IVs, Instrument variables; RA, Rheumatoid arthritis; PBC, Primary biliary cholangitis; SPRA, Seropositive rheumatoid arthritis; SNRA, Seronegative rheumatoid arthritis; IVW, inverse-variance weighted; BWMR, Bayesian weighted Mendelian randomization; MR-RAPS, Robust adjusted profile score.

accounts for potential heterogeneity across the analyzed SNPs.[17] Four methods were used for complementary analyses, the Bayesian weighted MR (BWMR) account the uncertainty of weak effects caused by polygenicity, further enhancing the robustness of causal inference,[18] the robust adjusted profile score (MR-RAPS) can permits the incorporation of weak instrumental variables, enabling robust statistical estimation of MR even when utilizing such variables,[19] the MR-Egger method can assess whether genetic variations have pleiotropic effects on outcomes with means different from zero and provide consistent estimates of causal effects under weaker assumptions,[20] and weighted median can provide consistent estimates even if up to 50% of the IVs are invalid.[21] MR estimates are reported as odds ratios (ORs) because the outcome was binary or dichotomous, such as the presence or absence of PBC. A threshold of $P < 0.05$ was considered to indicate a significant causal relationship.

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For the robustness of our analysis results, the Cochran Q test was used to assess the presence of heterogeneity.[22] The MR–Egger regression intercept test[20] and MR-PRESSO global test[23] were utilized to detect potential horizontal pleiotropy. If pleiotropy was detected, estimates were recalculated after removal of outlier SNPs identified by MR-PRESSO or Radial MR.[24] A threshold of $P > 0.05$ indicated no heterogeneity or horizontal pleiotropy. Finally, the leave-one-out (LOO) test was conducted.[22]

Our statistical analyses were conducted in R software (version 4.3.1). MR analyses were conducted using the TwoSampleMR, Radial MR and MRPRESSO packages.

Results

The number of SNPs used as IVs ranged from 6–12. Weak IVs were not considered, as the F-statistics for all SNPs were greater than 30.10. (Tables S2 and S3)

MR Estimates of Rheumatoid Arthritis on the Development of Primary Biliary Cholangitis

Seropositive Rheumatoid Arthritis

Our analyses revealed that SPRA significantly promoted the risk of PBC (IVW-MRE, OR: 1.28, 95% CI: 1.10–1.49, P = 0.001). Consistent findings were obtained using the other four MR methods (Table S4). The tests for pleiotropy showed mixed results, and the MR–Egger regression test indicated no evidence of pleiotropy (P = 0.408). The MR-PRESSO global test result indicated that there may be pleiotropy (P = 0.001) (Table S4); however, MR-PRESSO did not highlight any SNPs as outliers. We used Radial MR to identify and remove outliers contributing to heterogeneity and then reperformed the statistical analyses.

SPRA can increase the risk of PBC was confirmed in the final analysis (IVW-MRE, OR: 1.19, 95% CI: 1.05–1.36, P = 0.009) (Figure 2). The results of the Cochran's Q test (MR–Egger P = 0.230, IVW P = 0.119), MR–Egger intercept

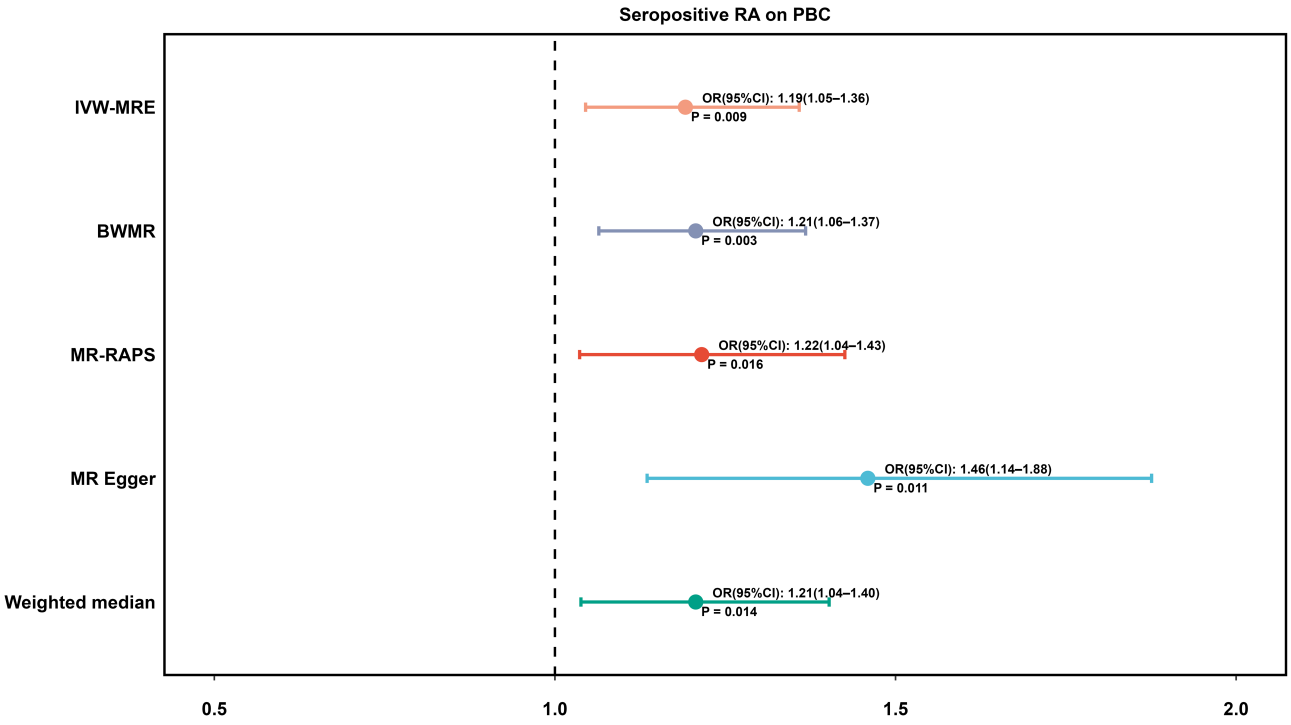

Figure 2 Estimated causal effect of the SPRA on PBC. Error bars show 95% CI for overall estimates (OR) from each MR method (left).
Abbreviations: RA, rheumatoid arthritis; PBC, Primary biliary cholangitis; IVW-MRE, multiplicative random-effect inverse-variance weighted; BWMR, Bayesian weighted Mendelian randomization; OR, odds ratio; CI, confidence interval.

(P = 0.091) and MR-PRESSO global test (P = 0.142) did not provide any evidence of heterogeneity or horizontal pleiotropy (Table S5). Similarly, LOO analysis supplemented the reliability of the results. (Figure 3).

Seronegative Rheumatoid Arthritis

No significant association between SNRA and PBC was detected (IVW-MRE, OR: 1.21, 95% CI: 0.99–1.47, P = 0.060) (Figure 4). The results of the Cochran's Q test (MR–Egger P = 0.004, IVW P = 0.009) show that there is heterogeneity in IVs. However, MR–Egger intercept (P = 0.875) and MR-PRESSO global test (P = 0.062) did not indicate horizontal pleiotropy (Table S6). LOO analysis also supports the reliability of the results (Figure 5).

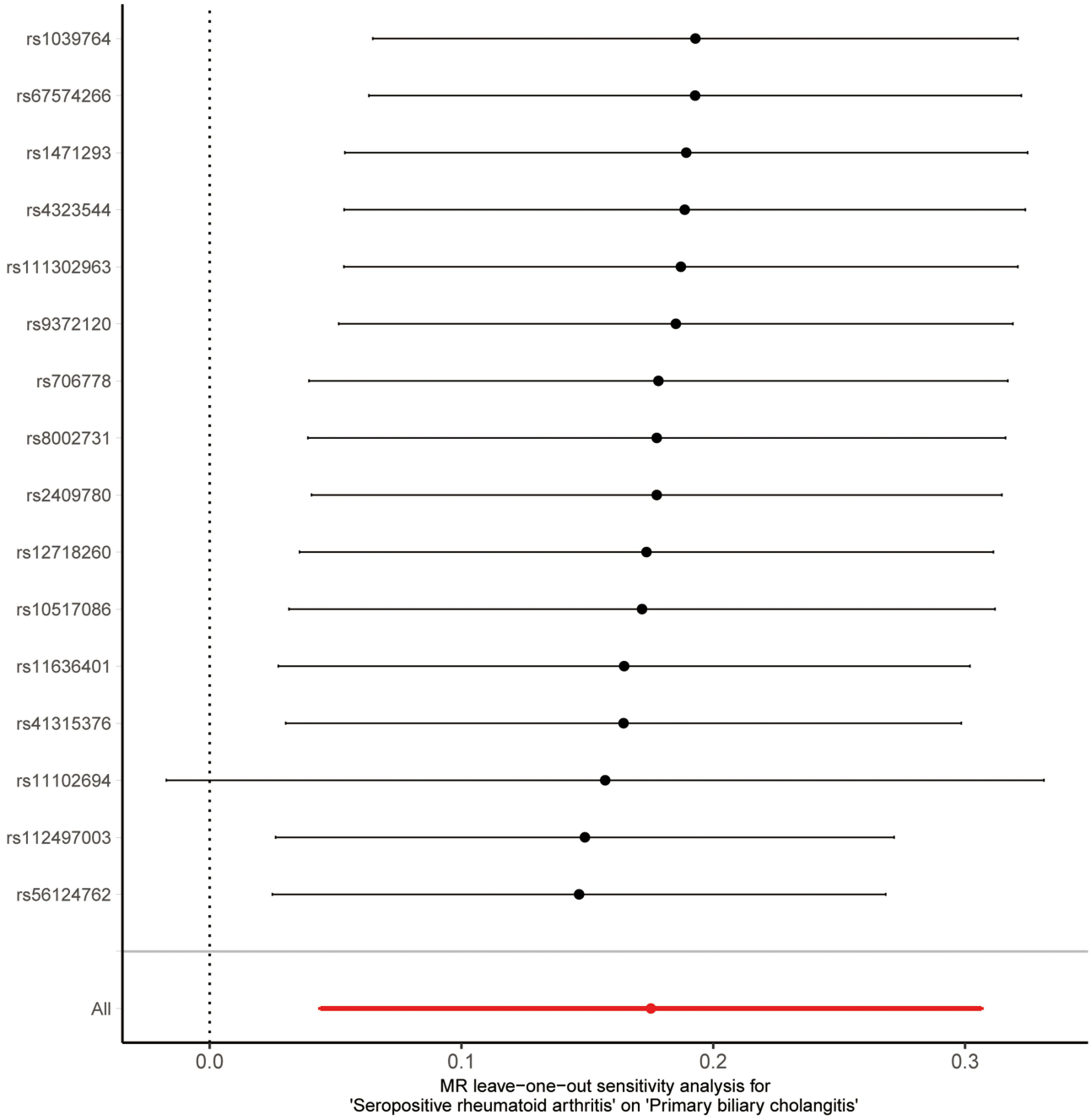

Figure 3 Leave-one-out analysis plot of SPRA on PBC. Error bars show 95% CI for estimates from each SNP.
Abbreviation: MR, Mendelian randomization.

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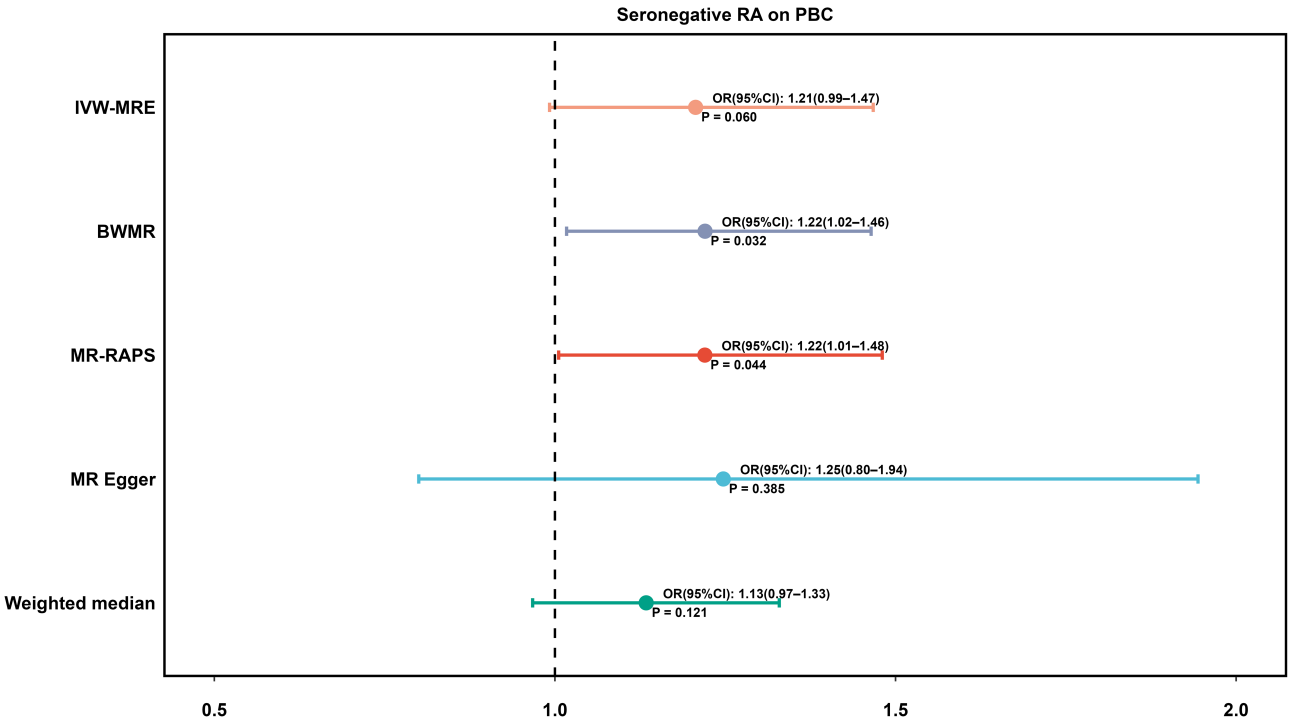

Figure 4 Estimated causal effect of the SNRA on PBC. Error bars show 95% CI for overall estimates (OR) from each MR method (left).
Abbreviations: RA, Rheumatoid arthritis; PBC, Primary biliary cholangitis; IVW-MRE, multiplicative random-effect inverse-variance weighted; BWMR, Bayesian weighted Mendelian randomization; OR, odds ratio; CI, confidence interval.

Discussion

RA is an autoimmune disorder characterized by a complex pathogenesis and an unknown etiology. The sensitivity of RF and the specificity of ACPAs are crucial for diagnosing RA. Nevertheless, some RA patients do not present these antibodies in their serum, highlighting the heterogeneity of the disease. This heterogeneity results in varying clinical manifestations, disease severities, and outcomes among RA patients.[25] Consequently, it is essential to investigate the distinct characteristics of rheumatoid arthritis through the analysis of serological markers.

Many patients with PBC also have other autoimmune comorbidities and complications. Delays in diagnosis and treatment can lead to long-term adverse consequences, placing an enormous burden on hospitals and society.[26] Therefore, it is critical to explore autoimmune factors that may impact the risk of PBC. In a study conducted by Sherlock and Scheuer, five percent PBC patients developed RA, and approximately half of the PBC patients tested positive for RF.[27] PBC is the most prevalent AILD among patients with RA. A separate study demonstrated that ACPAs were present in 9% of patients with AILD. The robust association between ACPA and erosive arthritis revealed that patients with both AILD and ACPA had a greater incidence of histological cirrhosis at the time of diagnosis than did those without AILD and ACPA, and these patients also had an elevated mortality rate due to liver failure.[28] Pak's study also suggested that patients diagnosed with RA are at a greater risk of developing PBC than the general population.[29] Therefore, when a patient with RA shows abnormalities in liver function tests, especially if there are no other causative factors, further examination of the patient is needed. These findings urge the need for further research to investigate the genetic relationship between RA subtypes and PBC. In alignment with the aforementioned observational studies, our MR studies based on serological markers of RA confirmed that SPRA is linked to an increased risk of PBC. This result has significant clinical implications and deepens our understanding of the association between RA and PBC.

RA has been demonstrated to originate at mucosal sites. Tajik et al were the first to report that intestinal inflammation and loss of permeability precede the onset of arthritis in a collagen-induced arthritis model.[30] The pathogenesis of RA is linked to increased intestinal permeability, dysregulation of the gut microbiota, and activation of antigen-presenting cells and T cells.[31,32] Newkirk's research has indicated that elevated *E. coli* IgM antibodies are associated with early SPRA.[33]

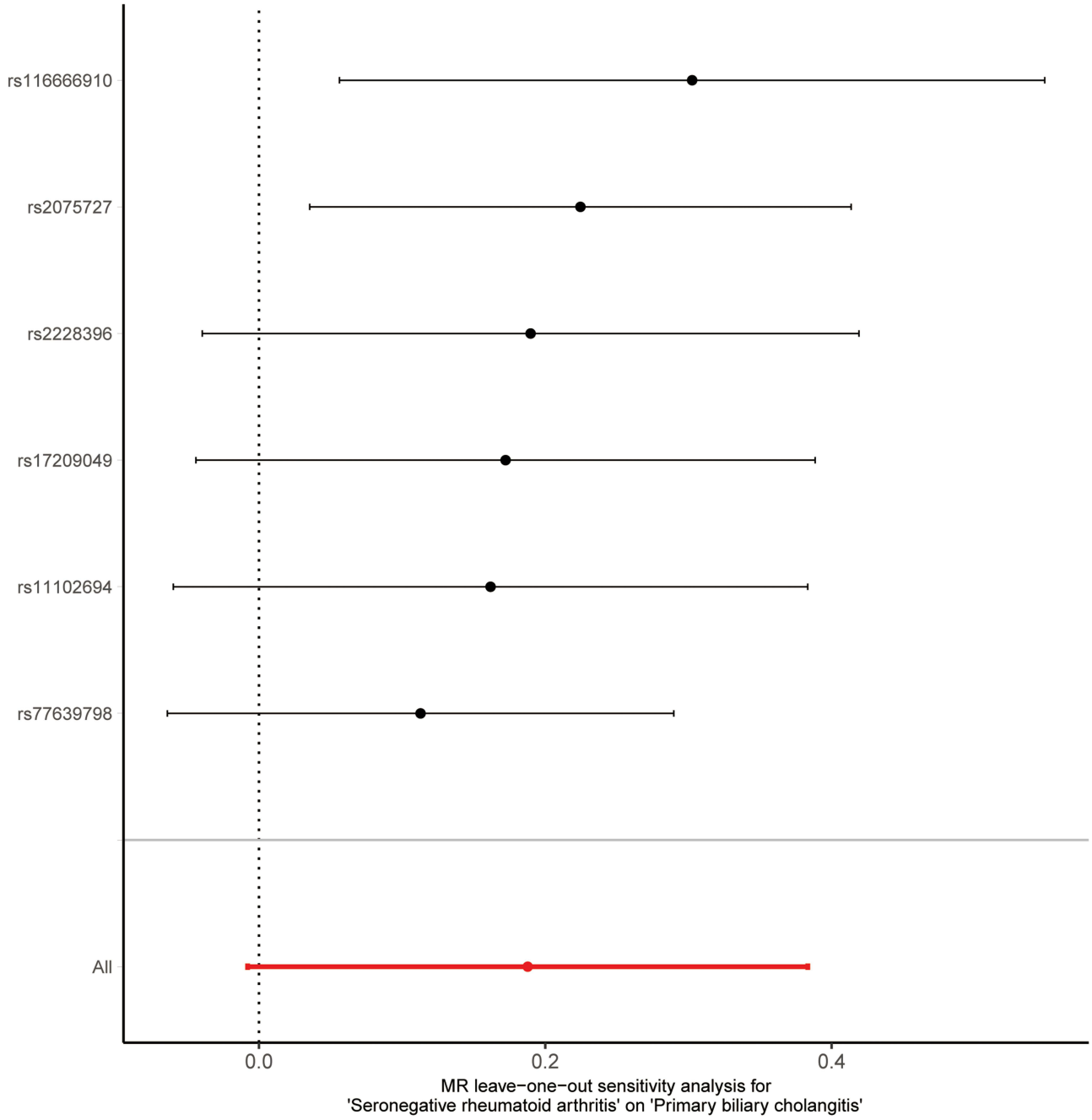

Figure 5 Leave-one-out analysis plot of SNRA for PBC. Error bars show 95% CI for estimates from each SNP.
Abbreviation: MR, Mendelian randomization.

Escherichia coli, a significant infection inducer of PBC, plays a crucial role in its pathogenesis. A study by Yang Y and Choi J showed that *E. coli* is the first step in the development of human PBC through a mechanism that antibodies against the E2 subunit of the *E. coli* pyruvate dehydrogenase complex (ePDC-E2) produced after E. coli infection result in cross-immunization, triggering an autoimmune response against the lipoyl structural domain of the E2 subunit of the human pyruvate dehydrogenase complex (hPDC-E2LD).[34] In addition, Lin CMA examined the levels of the circulating cytokine Interferon Alpha(IFN-α) in patients who were SPRA, SNRA as well as in those who were seropositive for arthralgia and reported that IFN-α was upregulated by as much as 50% in patients who were SPRA but not in those who were SNRA.[35] IFN-α is a cytokine that is critical to immune processes and has been associated with a range of autoimmune conditions.

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Patients with PBC showed significantly increased IFNα levels, and the administration of the IFN-α inducer polyinosine-polycytidylic acid to genetically susceptible mice resulted in PBC-like cholangitis. These findings suggest an association between the IFN-α pathway and the pathophysiology of PBC.[36] The interaction between metabolism and immunity is complex, and these studies serve as a bridge between SPRA and PBC, providing a potential explanation for the causal relationship between the two.

This is the first study to classify RA based on antibody levels and analyze the causal relationship between PBC and these distinct groups. Grouping RA patients by antibody levels enhances the reliability of the results, providing a more nuanced understanding of the relationship between RA and PBC. With large-scale GWAS summary datasets, we utilized a spectrum of analytical methods to verify our conclusions, providing robust evidence that better articulates the associations found in previous observational studies.This study is the absence of explicit timeframe information for both exposure and outcome data. However, in MR analysis, genetic variants are determined at conception and remain stable throughout an individual's life, thereby mitigating concerns regarding temporal mismatches. Due to the lack of allele frequency (EAF) data, which is essential for estimating the statistical power. Nevertheless, we ensured that the selected genetic instruments were robust by verifying their strength and performing extensive sensitivity analyses to validate the reliability of our findings.

This study is subject to several limitations that warrant careful consideration. A primary limitation arises from the reliance on RA GWAS datasets exclusively comprising individuals of European descent, which raises questions regarding the applicability of our conclusions across different ethnic groups, necessitating the validation of these findings through GWAS datasets pertinent to those populations. Specifically, while PBC and RA impose considerable societal impacts in China, the extrapolation of our study's outcomes to the Chinese population is not applicable without further dedicated research. Additionally, the absence of individual-level data within the database precludes the possibility of evaluating the impact of variables such as age, sex, and height.

In conclusion, our research suggests a potential association between SPRA and PBC. While these findings provide insights into possible shared mechanisms, further studies are needed to establish causality and evaluate clinical implications.

Abbreviations

PBC, Primary biliary cholangitis; RA, Rheumatoid arthritis; ACPA, Anti-citrulline protein antibodies; RF, Rheumatoid factor; AILD, Autoimmune liver disease; MR, Mendelian randomization; SNPs, Single nucleotide polymorphisms; IV, Instrumental variable; SPRA, Seropositive RA; SNRA, Seronegative RA; GWAS, Genome-wide association studies; IVW, Inverse variance weighted; BWMR, Bayesian weighted MR; MR-RAPS, Robust adjusted profile score; OR, Odds ratios; LOO, Leave-one-out; MR-PRESSO, MR pleiotropy residual sum and outlier; IFNα, Interferon Alpha.

Data Sharing Statement

All data generated or analysed during this study are included in this published article and its supplementary information files.

Acknowledgments

This study would not have been possible without the sharing of GWAS data by Dr. CHJ[14], Dr. SS[15] and all study participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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