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Association between primary biliary cholangitis and risk of Sjögren's syndrome: a systematic review and meta-analysis

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Abstract

Background: Primary biliary cholangitis (PBC) is associated with certain autoimmune diseases.

Objectives: This study aims to investigate the association between PBC and the risk of Sjögren's syndrome by applying a systematic review and meta-analysis.

Method: Databases such as ProQuest, PubMed, Web of Science, Cochrane, and Google Scholar were searched up to July 17, 2024, using keywords like "Sjögren's Syndrome," "Sicca Syndrome," "Liver Cirrhosis, Biliary," "Primary Biliary Cirrhosis," "Primary Biliary Cholangitis," "Obstructive Liver Cirrhosis," and their MeSH equivalents. No time or language restrictions were applied to the search. Studies directly addressing the association between PBC and the risk of Sjögren's syndrome were included. For low heterogeneity, a fixed-effects model was used. For moderate and severe heterogeneity, a random-effects model was used. Also, I^2=85.6% for cohort studies, I^2=0% for Mendelian randomization studies, and I^2=0% for case-control studies. STATA 14 software was used for data analysis, and P<0.05 was considered significant.

Results: In the 8 studies reviewed (two case-control studies, four Mendelian randomization studies, and two cohort studies), primary biliary cholangitis increased the risk of Sjögren's syndrome (OR: 1.17, (95%CI: 1.11, 1.25)), systemic lupus erythematosus (OR: 1.42, (95%CI: 1.35, 1.49)), and rheumatoid arthritis (OR: 1.14, (95%CI: 1.03, 1.27)). However, there was no statistically significant correlation between PBC and the risk of psoriasis (OR: 1.45, 95% CI: 0.71, 2.95) or systemic sclerosis (OR: 1.23, 95% CI: 0.96, 1.58). Sjögren's syndrome increased the risk of PBC (OR: 1.73, 95% CI: 1.12, 2.70). In Mendelian randomization studies (OR: 1.17, 95% CI: 1.13, 1.21) and case-control studies (OR: 8.47, 95% CI: 1, 71.58), PBC was shown to increase the risk of Sjögren's syndrome; however, cohort studies did not find a significant association between PBC and the risk of Sjögren's syndrome (OR: 1.43, 95% CI: 0.19, 10.69).

Conclusions: PBC is recognized as a risk factor for rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus; moreover, there is a significant risk that Sjögren's syndrome will lead to PBC.

Keywords: Sjögren's Syndrome, Sicca Syndrome, Liver Cirrhosis, Biliary, Primary Biliary Cholangitis, Obstructive Liver Cirrhosis.

1. Introduction

The disease name was updated from "Primary Biliary Cirrhosis" to "Primary Biliary Cholangitis" in 2016 (1, 2). PBC is characterized by the death of biliary epithelial cells lining the intrahepatic bile ducts. It is a chronic form of cholestatic liver disease with a likely autoimmune etiology (3-5). PBC's pathogenesis is still not completely understood. Genetically predisposed individuals may experience immune dysfunction due to environmental factors, which could ultimately result in PBC (6). End-stage liver disease and its related complications may develop from this illness (6, 7). PBC is more common in middle-aged and older women; in the European population, its prevalence ranges from 6.7 to 492 per 100,000 people (8).

Autoimmune diseases are a common cause of mortality and morbidity, with an estimated prevalence of 5 to over 500 per 100,000 individuals (9). PBC is often associated with other autoimmune diseases such as Sjögren's syndrome, systemic sclerosis, rheumatoid arthritis, and systemic lupus erythematosus (10-12). The clinical manifestations of Sjögren's syndrome primarily include dry eyes, dry mouth, and fatigue (13, 14). On the other hand, liver

involvement, with an incidence of 9-20%, is considered the most common non-exocrine feature in Sjögren's syndrome (15), and approximately 3-9% of patients with Sjögren's syndrome have PBC (5, 16). Similar to other autoimmune diseases, Sjögren's syndrome and PBC are significantly more common in women than in men (17-19). Extra-glandular organ involvement in patients with Sjögren's syndrome can lead to conditions such as interstitial lung disease, arthritis, and lymphoma, which severely impact patients' quality of life (13, 14). According to studies (20, 21), PBC is regarded as a risk factor for Sjögren's syndrome; However, a study (22) found no significant correlation between PBC and the risk of Sjögren's syndrome. As a result, the current study used a systematic review and meta-analysis to bring together the contradictory findings of earlier research and present an updated and thorough conclusion.

2. Materials and Methods

2.1. Study Protocol

This study examined the association between PBC and the risk of Sjögren's syndrome, following the PRISMA reporting guidelines (23). Additionally, the study protocol was registered on the PROSPERO website (CRD42024573778).

2.2. PICO Components

Population: All research examining the relationship between PBC and the risk of Sjögren's syndrome was encompassed.

Exposure/Intervention: PBC.

Comparison: Healthy individuals.

Outcomes: The primary outcome was the association between PBC and the risk of Sjögren's syndrome. Secondary outcomes included the association between PBC and the risk of systemic lupus erythematosus, psoriasis, rheumatoid arthritis, and systemic sclerosis.

2.3. Search Strategy

Databases such as ProQuest, PubMed, Web of Science, Cochrane, and Google Scholar were searched up to July 17, 2024, using keywords like "Sjögren's Syndrome," "Sicca Syndrome," "Liver Cirrhosis, Biliary," "Primary Biliary Cirrhosis," "Primary Biliary Cholangitis," "Obstructive Liver Cirrhosis," and their MeSH equivalents. Advanced searches combined keywords with operators (AND, OR), and manual searches included reviewing reference lists of primary studies. No time or language restrictions were applied to the search.

The search strategy for PubMed is detailed below: ("sjögren s syndrome"[Title/Abstract] OR "sicca syndrome"[Title/Abstract]) AND ("liver cirrhosis biliary"[Title/Abstract] OR "primary biliary cirrhosis"[Title/Abstract] OR "primary biliary cholangitis"[Title/Abstract] OR "obstructive liver cirrhosis"[Title/Abstract])

2.4. Inclusion and Exclusion Criteria

Studies directly addressing the association between PBC and the risk of Sjögren's syndrome were included. Low-quality studies, duplicate studies, review articles, studies with qualitative data (Only quantitative studies were sought; it is better to clarify that the exclusion of "qualitative studies" is because the meta-analysis focuses on quantitative associations (ORs/HRs)), studies lacking sufficient data for analysis, conference abstracts, case reports, and studies without full-text availability were excluded.

2.5. Qualitative Assessment

Two authors independently assessed observational studies using the Newcastle-Ottawa Scale (NOS). All questions may be rated one star, except the comparison question, which may be rated two stars. The minimum score was zero (poorest quality), and the maximum score was ten (highest quality). A cutoff score of six was used in this

study (24). **Strengthening** the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) checklist was also used to evaluate the quality of Mendelian randomized studies. This checklist has 20 items that cover different aspects of research (25).

2.6. Data Extraction

This step was conducted independently by two authors. Extracted data included author names, study type, year, study location, and odds ratios for the association between Sjögren's syndrome and PBC, and for the association between PBC and each of the diseases (systemic lupus erythematosus, psoriasis, rheumatoid arthritis, and systemic sclerosis) for statistical analysis.

2.7. Statistical Analysis

Data analysis involved using the logarithms of OR and HR indices, and studies were combined. Heterogeneity was assessed using the Cochrane Q test and the I^2 index. For low heterogeneity, a fixed effects model was used, and for moderate and severe heterogeneity, a random effects model was used (I^2=48.8% and tau^2 =0.002 for PBC→SS, I^2=95.8% and tau^2 =0.222 for SS→PBC, I^2=0% and tau^2 =0.000 for PBC→SLE, I^2=80.1% and tau^2 =0.005 for PBC→RA, I^2=39% and tau^2 =0.219for PBC→psoriasis, I^2=97.2%and tau^2 =0.051 for PBC→systemic sclerosis). Additional analyses included meta-regression, publication bias, and sensitivity analysis. Data analysis was performed using STATA 14, with a significance level of $P < 0.05$.

3. Results

3.1. Study Selection

After searching databases and Google Scholar, 907 studies were found. Of these, 403 were duplicates and were removed. Then, 504 studies entered the next stage, and after reviewing the information in the abstracts, 83 studies, whose abstracts were incomplete and did not include full text, were removed. The full texts of 421 studies were reviewed, and 79 studies that did not report the necessary data for data analysis were removed. Consequently, 342 studies were removed based on the remaining 334 criteria, and 8 studies remained (Figure 1).

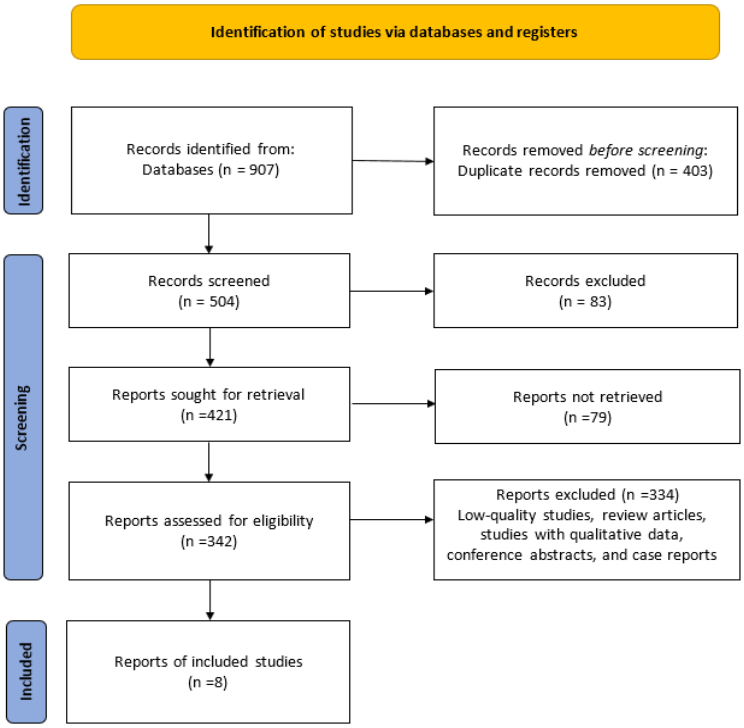

Figure 1. Chart of PRISMA

Eight studies were reviewed for this meta-analysis, encompassing two case-control studies, four Mendelian randomization studies, and two cohort studies (Table 1).

Table 1. Characteristics of articles

Author, Year	Place	Type of Study	Risk of Sjögren's Syndrome			Risk of primary biliary cirrhosis			Risk of SLE			Risk of RA			Risk of psoriasis			Risk of systemic sclerosis		
			OR	Low	UP	OR	Low	UP	OR	Low	UP	OR	Low	UP	OR	Low	UP	OR	Low	UP
Wang N, 2024 (20)	Europe	Mendelian randomization	1.17	1.1	1.24	1.73	1.28	2.35	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Li Y, 2024 (21)	Europe	Mendelian randomization	1.15	1.09	1.22	0.98	0.79	1.22	NR	NR	NR	NR	NR	NR	18.1	1.2	268.5	NR	NR	NR
Liu Z, 2024 (26)	Canada-UK, USA, Italy	Mendelian randomization	1.18	1.12	1.24	0.92	0.79	1.07	1.43	1.3	1.58	1.09	1.04	1.14	NR	NR	NR	1.25	1.08	1.45
Ma G, 2024 (27)	Europe	Mendelian randomization	1.27	1.04	1.57	1.82	1.65	2.01	1.41	1.33	1.49	1.2	1.16	1.24	1.06	1.02	1.09	1.44	1.35	1.53
Braga MH, 2023 (28)	Brazil	Cohort	4.3	1.16	16.2	NR	NR	NR	2.75	0.49	15.38	7	0.79	56.6	1.35	0.19	9.71	1.02	0.99	1.04
Efe C, 2021 (22)	Europe, USA and Canada	Cohort	0.55	0.25	1.19	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mantaka A, 2012(29)	Greece	Case-Control	8.47	1	71.43	NR	NR	NR	2.16	0.79	5.9	0.51	0.13	2.08	1.7	0.53	5.38	1.37	0.55	3.37
Corpechot C, 2010(30)	France	Case-Control	NR	NR	NR	11.9	5.4	26.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

NR: Not reported; OR: Odds ratio; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis.

Figure 2 demonstrates that across the reviewed studies, PBC increases the risk of Sjögren's syndrome (OR: 1.17, 95% CI: 1.11, 1.25). Moreover, cohort studies show no significant association between PBC and the risk of Sjögren's syndrome (OR: 1.43, 95% CI: 0.19, 10.69). However, the risk was higher in case-control studies (OR: 8.47, 95% CI: 1, 71.58) and Mendelian randomization studies (OR: 1.17, 95% CI: 1.13, 1.21).

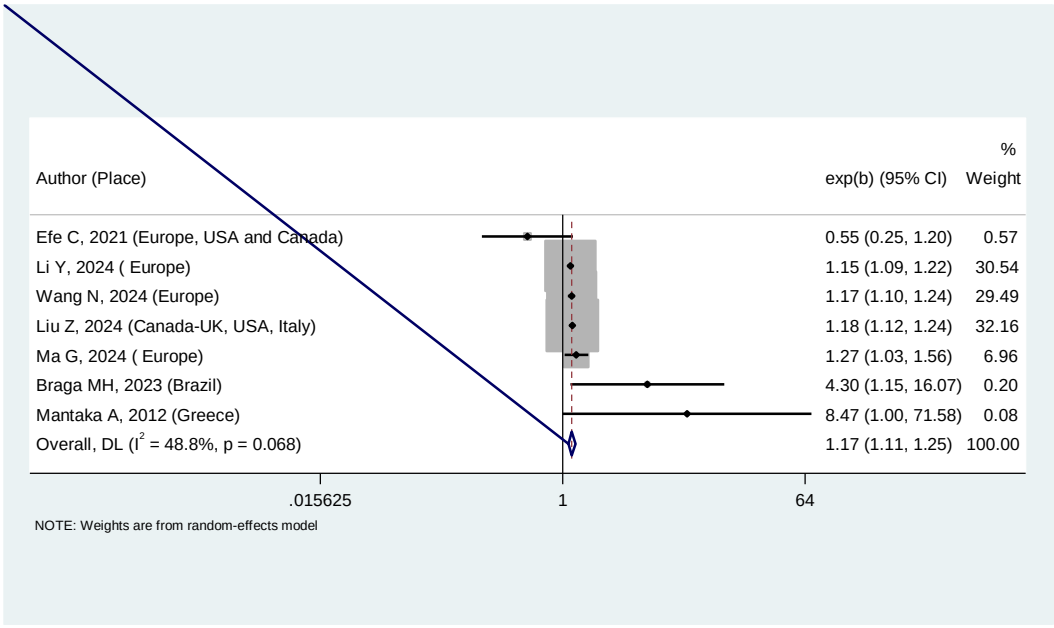

Figure 2. Forest plot showing the relationship between PBC and the risk of Sjögren's syndrome

Similarly, Figure 3 depicts that Sjögren's syndrome increased the risk of PBC (OR: 1.73, 95% CI: 1.12, 2.70);

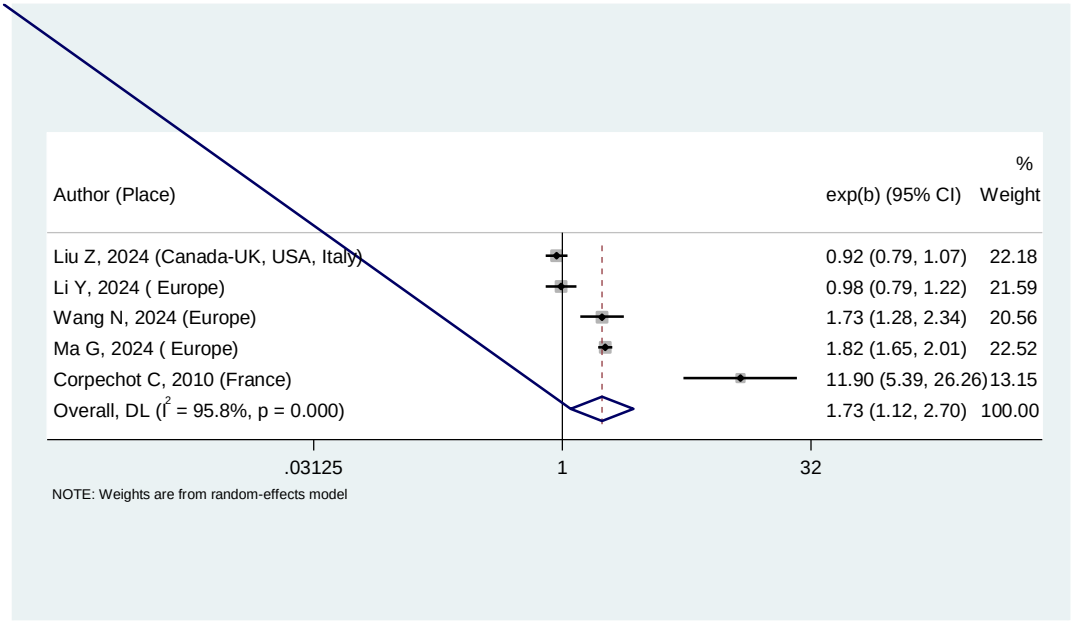

Figure 3. Forest plot showing the relationship between Sjögren's syndrome and the risk of PBC

Additionally, PBC increased the risk of systemic lupus erythematosus (OR: 1.42, 95% CI: 1.35, 1.49) and rheumatoid arthritis (OR: 1.14, 95% CI: 1.03, 1.27) (Figures 4 and 5).

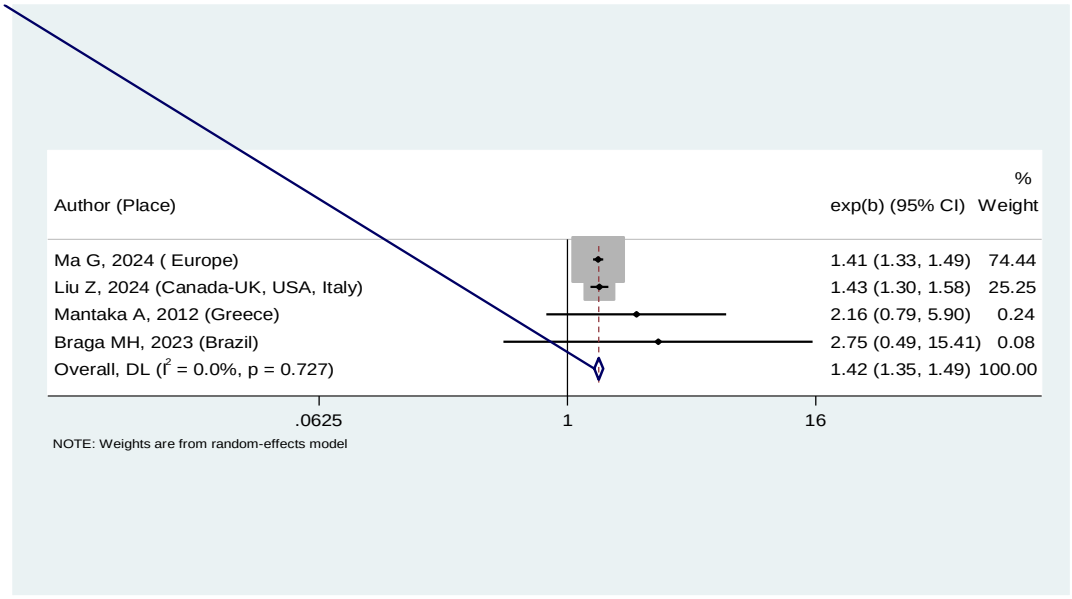

Figure 4. Forest plot showing the relationship between PBC and the risk of systemic lupus erythematosus

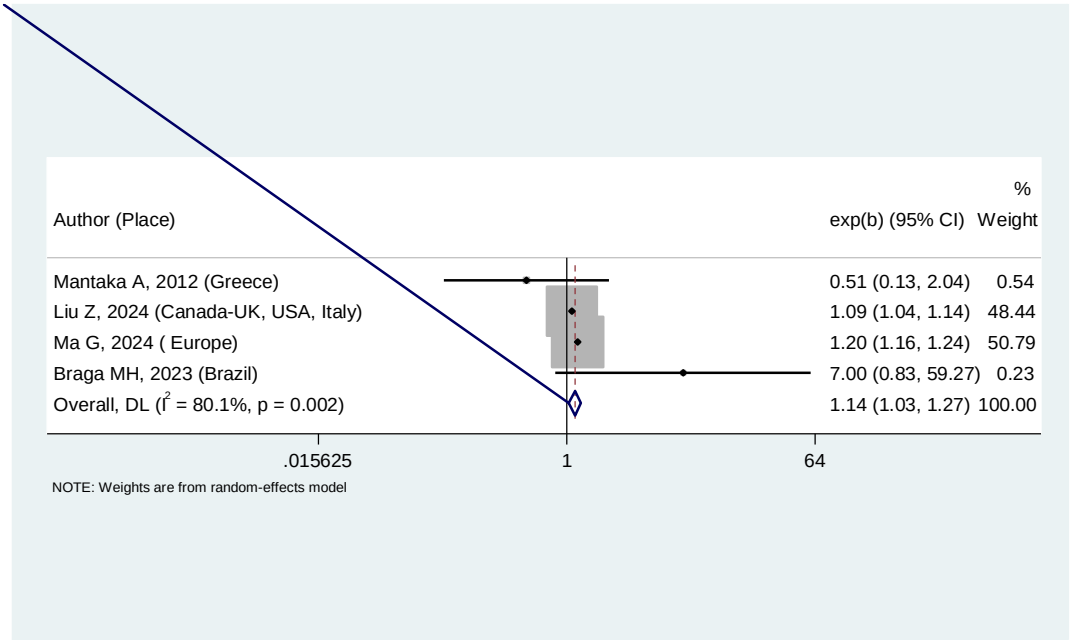

Figure 5. Forest plot showing the relationship between PBC and the risk of rheumatoid arthritis

However, Figures 6 and 7 indicated no statistically significant association between PBC and increased risk of psoriasis (OR: 1.45, 95% CI: 0.71, 2.95) or systemic sclerosis (OR: 1.23, 95% CI: 0.96, 1.58).

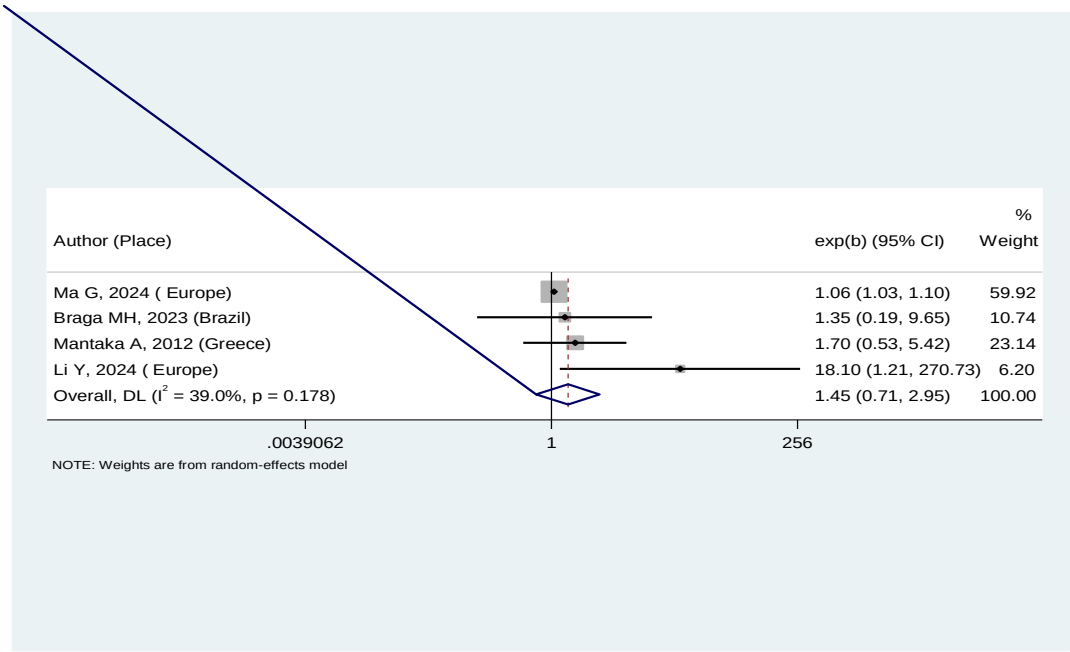

Figure 6. Forest plot showing the relationship between PBC and the risk of psoriasis

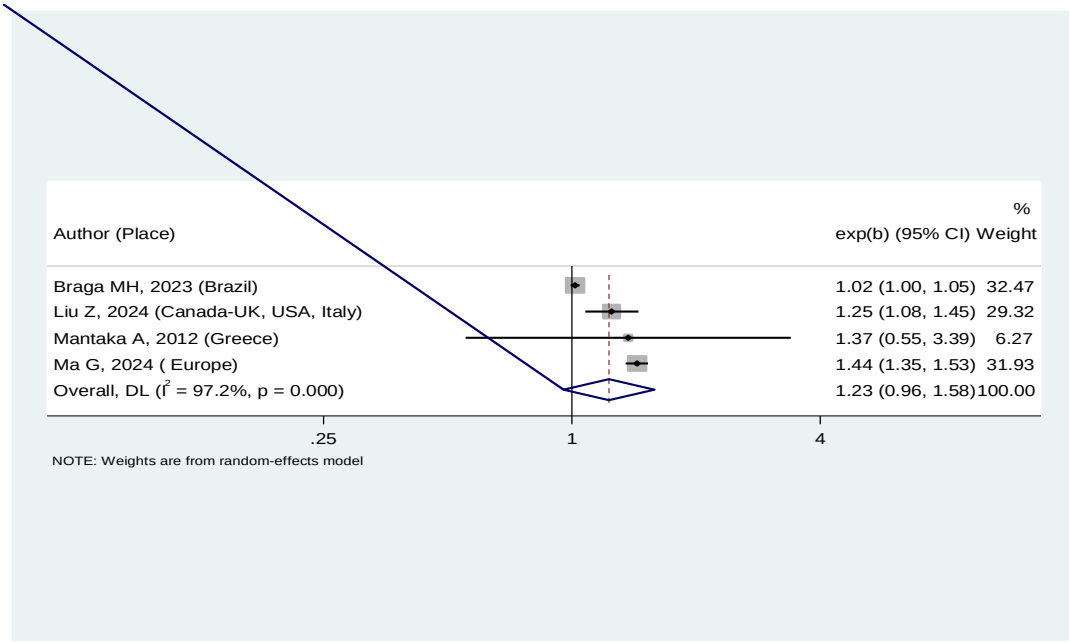

Figure 7. Forest plot showing the relationship between PBC and the risk of systemic sclerosis

Additional Analyses

According to a meta-regression analysis, there is no significant correlation (p-value = 0.687) between the year of study publication and the "relationship between PBC and the risk of Sjögren's syndrome," suggesting that the association has not decreased over time from 2010 to 2024 (Figure 8).

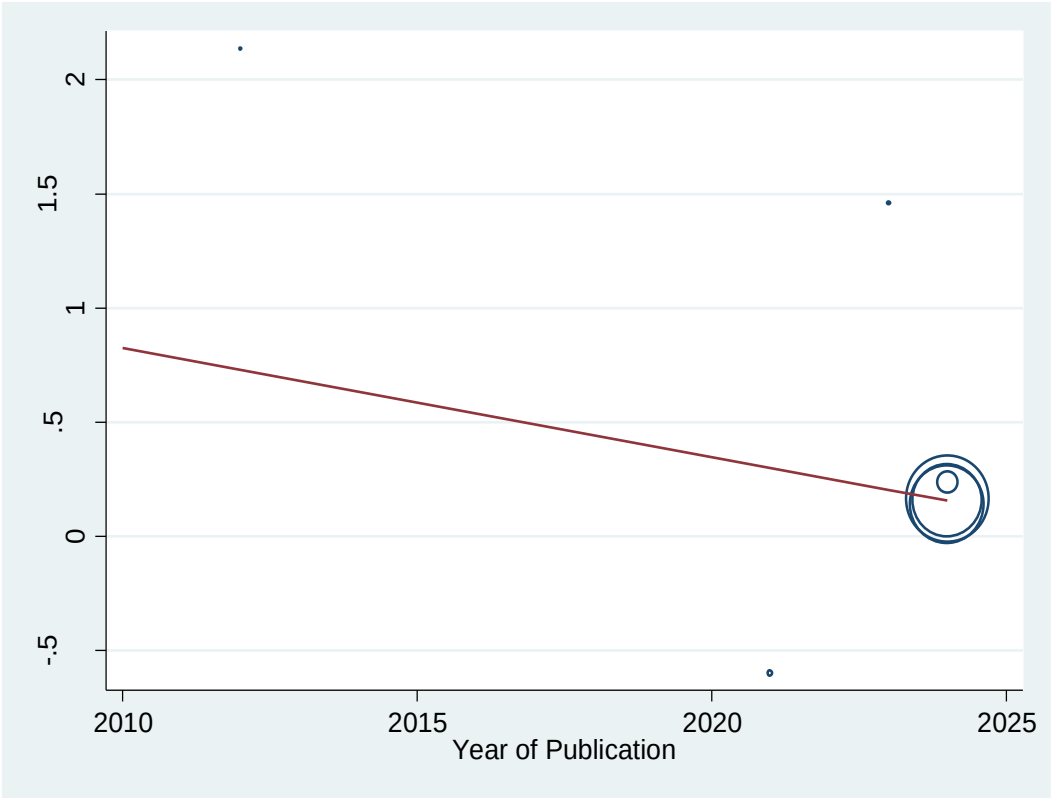

Figure 8. Meta-regression plot of the relationship between "association between PBC and the risk of Sjögren's syndrome" with year of publication

The P-value was not statistically significant (P-value = 0.389). However, because the number of primary studies was small (8 studies), this reduced the precision of Egger's test. It is not possible to definitively confirm the absence of publication bias or guarantee a completely comprehensive or unbiased search process (Figure 9).

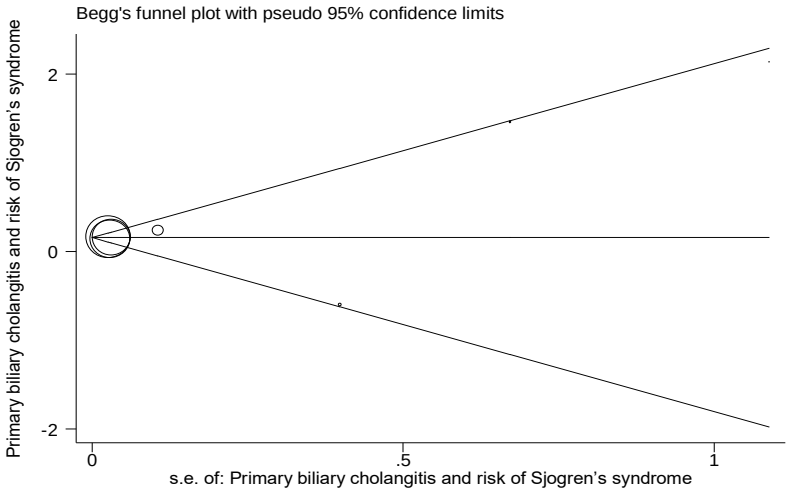

Figure 9. Diagram of publication bias

Sensitivity analysis indicated that the studies by Li Y (2024) (20) and Ma G (2024) (25) were the most influential in the final meta-analysis results. Excluding Li Y (2024) changed the final result to (OR: 0.17, 95% CI: 0.07, 0.26), and excluding Ma G (2024) changed it to (OR: 0.15, 95% CI: 0.08, 0.21) (Figure 10).

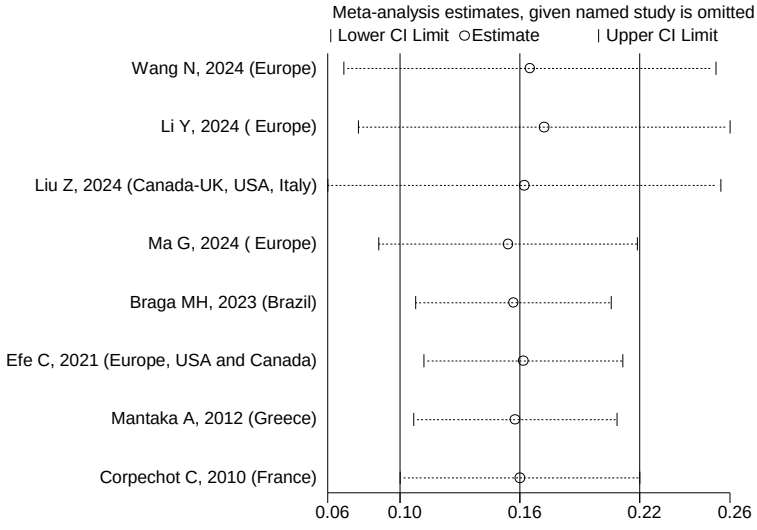

Figure 10. Diagram of sensitivity analysis

"According to Figures 11 and 12, neither the mean age of patients (P-value = 0.856) nor the percentage of female participants (P-value = 0.976) served as a significant confounding factor or effective moderator in the association between PBC and Sjögren's syndrome. In other words, the meta-regression does not support a linear relationship in which increasing patient age elevates the risk of developing Sjögren's syndrome. Nevertheless, it is critical to acknowledge that this analysis included only three studies; therefore, its findings are severely underpowered and lack sufficient clinical and statistical validity to support definitive conclusions."

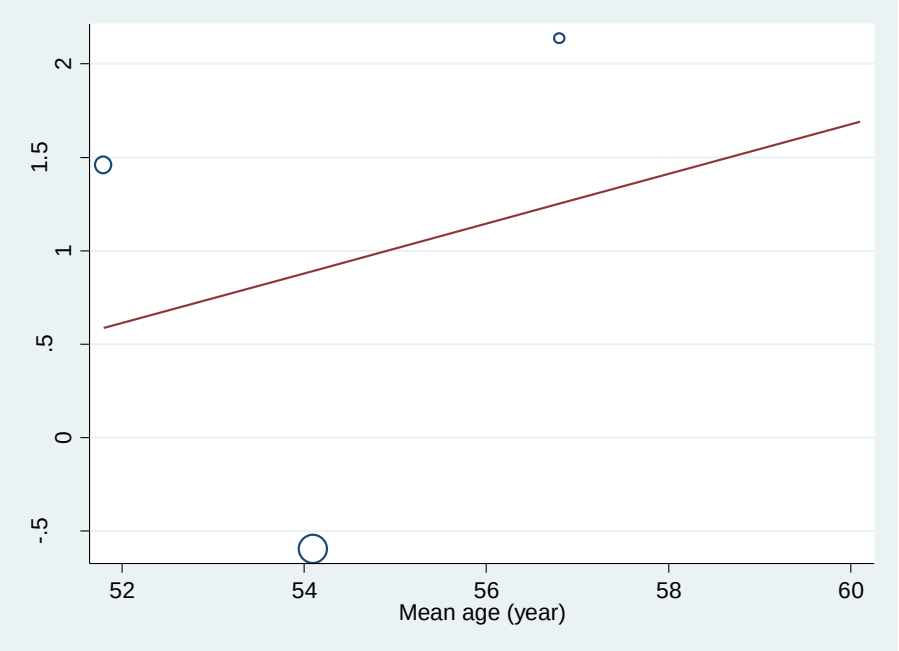

Figure 11. Meta-regression plot of the relationship between "association between PBC and the risk of Sjögren's syndrome" and mean age

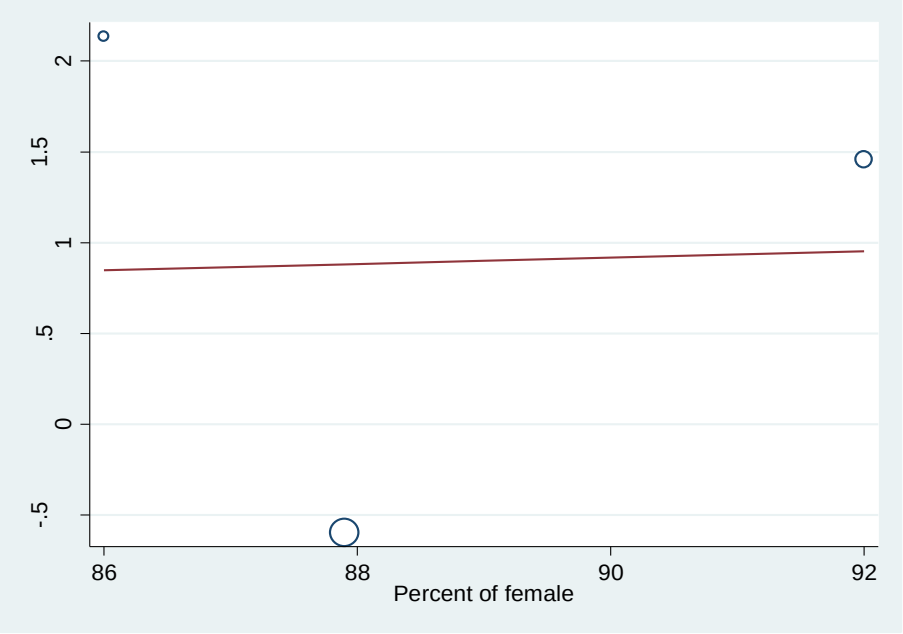

Figure 12. Meta-regression plot of the relationship between "association between PBC and the risk of Sjögren's syndrome" and the percentage of females

4. Discussion

Our meta-analysis showed a statistically significant association between PBC and Sjögren's syndrome (OR: 1.17, 95% CI: 1.11–1.25). This association suggested that having PBC is a risk factor for developing Sjögren's syndrome. However, this finding has major methodological weaknesses that prevent us from speaking with precision and power about this result. These weaknesses are characterized by two issues: 1) PBC raised the risk of Sjögren's syndrome in case-control and Mendelian randomization studies but not in cohort studies. 2) Sensitivity analysis showed that by leaving one out, the overall effect size and direction were overly driven by the studies of Li Y (2024) and Ma G (2024), as their sequential exclusion reversed the pooled estimate from a risk effect (OR=1.17) to a protective effect (ORs of 0.17 and 0.15, respectively). This strong dependence on individual studies suggests that our results are not robust.

Sjögren's syndrome had the most significant incidence (21.4% compared to 3% in non-PBC individuals) in a meta-analysis conducted by Liang et al. (2024) to ascertain the prevalence of extrahepatic conditions and their association with PBC. Raynaud's syndrome (12.3% vs. 1%), rheumatoid arthritis-like arthritis (5% vs. 3%), systemic sclerosis (3.7% vs. 0%), and systemic lupus erythematosus (2% vs. 0%) were the following most common conditions (31). A further meta-analysis conducted in 2022 by Deng et al. looked into the prevalence and effects of Sjögren's syndrome in patients with PBC. The results showed that the condition was present in 3.5% to 73% (35%, 95% CI: 28, 41%) of these patients (32). As demonstrated by this research, the high frequency of Sjögren's syndrome among PBC patients emphasizes the significance of investigating the reciprocal link between these illnesses.

According to the findings of this meta-analysis, PBC raises the possibility of developing SLE, RA, and Sjögren's syndrome. Other research revealed similar results, indicating that PBC raises the risk of SLE, RA, and Sjögren's syndrome but not systemic sclerosis. Wang et al. A 2024 Mendelian randomization study showed that PBC is linked to a higher incidence of Sjögren's syndrome (OR: 1.17, 95% CI: 1.10, 1.24), according to the data analysis (20). Another Mendelian randomization study by Li et al. (2024) investigated the association between Sjögren's syndrome and autoimmune liver disease, showing that PBC increased Sjögren's syndrome risk in the European population (OR: 1.15, 95% CI: 1.09, 1.22) (21). Liu et al. (2024), in a Mendelian randomization study, demonstrated that PBC increases SLE risk (OR: 1.43, 95% CI: 1.30, 1.58), RA (OR: 1.09, 95% CI: 1.04, 1.14), and Sjögren's syndrome (OR: 1.18, 95% CI: 1.12, 1.24), but not systemic sclerosis (26). Zhong et al. (2024) found that PBC is associated with an increased risk of SLE (OR: 1.17, 95% CI: 1.09, 1.25) (33).

An elevated risk of primary biliary cirrhosis was found in case-control research by Corpechot et al. (2010), which sought to uncover risk factors and complications of the disease. Sjögren's syndrome was linked to this increased risk (OR: 11.9, 95% CI: 5.4, 26.3) (30); additionally, Sjögren's syndrome raises PBC risk (OR: 1.73, 95% CI: 1.28, 2.35) (20), according to Wang et al. (2024). Sjögren's syndrome was identified as a risk factor for PBC in the current investigation, consistent with earlier research and supporting our findings.

4.1. Limitation

Our meta-analysis showed a statistically significant positive association between PBC and Sjögren's syndrome. However, it had a major methodological weakness. It is a major limitation of the present meta-analysis. Therefore, it is recommended that future studies conduct large-scale prospective cohort studies to validate the findings of this

meta-analysis.

Inability of meta-regression to find the main source of heterogeneity in the study.

Due to the limited number of studies and insufficient data for subgroup analysis, it could not analyze the link between primary biliary cirrhosis and Sjögren's syndrome according to patient age, gender, and type. This resulted in moderate heterogeneity and prevented distinction by gender, between primary and secondary Sjögren's syndrome, and across age groups.

Most studies reported study locations as continents or combinations of countries, preventing country-specific analysis of the association between primary biliary cirrhosis and Sjögren's syndrome.

The wide confidence intervals observed for psoriasis and systemic sclerosis analyses underscore limited statistical power and highlight the need for cautious interpretation of these null findings.

Most studies omitted sample sizes, making it impossible to calculate the total number of patients studied and to perform meta-regression based on sample size. Given that this is a systematic review, missing sample size is a serious omission.

escalating global burden of antimicrobial resistance highlights the urgent need for the development of innovative therapeutic strategies. The declining pipeline of new antibiotic classes, coupled with the rapid evolution of bacterial resistance, has underscored the inadequacy of conventional drug discovery approaches(15, 16). In this context, drug repurposing and the identification of existing non-antibiotic drugs with antimicrobial or antibiotic-adjuvant properties have emerged as a promising strategy to expand available therapeutic options. The present study investigated the in vitro antibacterial activity of the tricyclic antidepressant (TCA), Nortriptyline, alone and in combination with vancomycin, against a VISA isolate of Staphylococcus aureus.

Our findings demonstrate that Nortriptyline exhibits antibacterial activity against the tested isolate and enhances the in vitro activity of vancomycin, as evidenced by a 4-fold reduction in the MICs of both agents when combined and an FICI of 0.5. According to the predefined criteria, this interaction was considered consistent with synergy. A recent study by Cabral et al. (2025) reported antibacterial activity of Nortriptyline against S. aureus, with an MIC value of 128 µg/mL. It demonstrated an additive interaction between Nortriptyline and vancomycin. These findings provide additional support for Nortriptyline's antibacterial potential and further justify investigation of Nortriptyline–vancomycin interactions. However, these findings should be interpreted as preliminary in vitro evidence rather than evidence of clinical applicability at this stage. This observation aligns with a growing body of evidence supporting the antibacterial and adjuvant potential of tricyclic antidepressants (TCAs). Previous studies have reported antibacterial activity of nortriptyline and related TCAs against Gram-positive bacteria, particularly S, aureus (17). Although most available studies have investigated other TCAs such as amitriptyline, these findings provide a rationale for exploring structurally related compounds, including Nortriptyline. For instance, amitriptyline has shown efficacy against a wide range of Gram-positive and Gram-negative bacteria (18) and has demonstrated synergistic effects when combined with colistin against resistant Klebsiella pneumoniae (19). Further supporting this concept, the combination of amitriptyline with tetracycline proved effective against multidrug-resistant Acinetobacter baumannii (20). At the same time, the TCA amoxapine resensitized MRSA to oxacillin, potentially by inhibiting beta-lactamase activity (21). Collectively, these studies support the potential role of

antidepressant compounds as antibiotic adjuvants warranting further investigation.

While this study provides preliminary in vitro evidence for the vancomycin-nortriptyline interaction, several limitations should be considered. First, the findings are based on a single VISA isolate; therefore, they cannot be generalized to other VISA populations and require validation using a larger collection of genetically diverse clinical isolates. Furthermore, the high MIC of Nortriptyline alone (1000 µg/mL) represents a potential limitation for its further development as an antimicrobial agent. It requires additional evaluation of its pharmacological feasibility and safety. Although combination with vancomycin reduced the nortriptyline MIC in vitro, the clinical relevance of this finding remains uncertain. Further pharmacokinetic, pharmacodynamic, and toxicity evaluations are required.

Additionally, although the checkerboard assay is a widely used method for initial evaluation of antimicrobial interactions, time-kill studies and additional validation approaches were not performed in this study and should be considered in future investigations. Therefore, these findings should not be interpreted as evidence for direct clinical use at this stage. Given its reported antimicrobial properties, Nortriptyline may represent a candidate for further exploration; however, additional studies are necessary to evaluate its feasibility and safety.

Scientific literature suggests that TCAs may exert antimicrobial effects through multiple mechanisms. Proposed mechanisms include induction of oxidative stress, effects on bacterial genetic material, disruption of membrane integrity, and modulation of bacterial efflux systems. However, the relative contribution of these mechanisms appears to vary among different TCAs and bacterial species(12, 13). Nevertheless, the precise mechanisms underlying the interaction between Nortriptyline and vancomycin observed in the present study remain unclear and require further experimental investigation.

From a translational perspective, future studies should include multiple VISA isolates, time-kill kinetics, mechanistic investigations, and in vivo models to determine whether the observed in vitro interaction can be reproduced under more clinically relevant conditions.

5. Conclusion

PBC enhances the risk of both conditions. However, PBC is not linked to an elevated risk of systemic sclerosis or psoriasis. However, it does raise the risk of systemic lupus erythematosus and rheumatoid arthritis. The relationship between PBC, systemic sclerosis, and psoriasis should be investigated in more detail.

Appendix: PubMed: (Sjogren's Syndrome[Title/Abstract] OR Sicca Syndrome[Title/Abstract]) AND (" Liver Cirrhosis, Biliary"[Title/Abstract] OR Primary Biliary Cirrhosis[Title/Abstract] OR Primary Biliary Cholangitis[Title/Abstract] OR Obstructive Liver Cirrhosis[Title/Abstract])

Web of Science: Sjögren's Syndrome OR Sicca Syndrome (All Fields) AND " Liver Cirrhosis, Biliary" OR Primary Biliary Cirrhosis OR Primary Biliary Cholangitis OR Obstructive Liver Cirrhosis (All Fields)

Cochrane: Sjögren's Syndrome OR Sicca Syndrome in Title Abstract Keyword AND " Liver Cirrhosis, Biliary" OR Primary Biliary Cirrhosis OR Primary Biliary Cholangitis OR Obstructive Liver Cirrhosis in Title Abstract Keyword.

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Conflict of interest: The authors declare that they have no conflict of interest.

Availability of data and materials: This is a review study, and it is not an original. Data availability is the corresponding author's responsibility.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication: Not applicable.

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