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Systematic Review and Meta-Analysis of the Effects of Intestinal Microbiota on Liver Disease Using Mendelian Randomization

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ABSTRACT

Background and Objective: The global incidence of liver diseases is on the rise, and targeting gut microbiota has become a new strategy for treating liver diseases. This study provides a comprehensive and objective analysis of the potential protective role of gut microbiota in liver disease, highlighting the need for continued research in this area.

Methods: After literature screening, 24 related articles were included in the study. After article quality and risk of bias assessment, data extraction and data collation were carried out, and then comprehensive analysis was carried out using stata12.0 software.

Results: From the perspective of microbial community, most of the microbial communities at the phylum level are risk factors; from the perspective of the top ten families, the intestinal microbial communities play an obvious harmful role in Primary Biliary Cholangitis.From the perspective of disease, the microbial communities at the genus level mostly have protective effects on Chronic Hepatitis B ,Fatty Liver;and Primary Liver Cancer.

Conclusion: Gut microbiota plays a significant role in the occurrence of liver diseases, and different bacterial levels play different roles in the disease.

1 | Introduction

Liver disease is one of the most common diseases in humans, causing approximately 2 million deaths annually and accounting for 4% of all deaths worldwide [1]. Liver diseases encompass a range of conditions, including chronic hepatitis B, cirrhosis, alcoholic fatty liver, primary liver cancer (PLC), and autoimmune liver disease [1–3]. The development of liver disease is often the result of complex interactions between genetic and environmental factors. Early-stage liver disease typically presents with few symptoms, leading to diagnoses often made during the middle or late stages when the disease has progressed significantly [4]. Therefore, early diagnosis and treatment are crucial for improving patient outcomes and delaying disease progression.

Recent research has increasingly recognized the intestinal microbiota as a critical environmental factor closely linked to metabolic disorders, immune dysregulation, and cancer development, with a potential correlation to liver diseases as well [5, 6]. The gut-liver axis, describing the bidirectional relationship between the gut microbiota and the liver, operates through metabolites and signals produced by dietary, genetic, and

Abbreviations: AIH, autoimmune hepatitis; CHB, chronic hepatitis B; CI, confidence interval; FL, fatty liver; GWAS, genome-wide association study; LC, liver cirrhosis; MR, mendelian randomization; OR, odds ratio; PBC, primary biliary cholangitis; PLC, primary liver cancer; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PSC, primary sclerosing cholangitis.

environmental factors [7]. Disruptions in the host–microbe interaction can disturb this balance, leading to the onset of various diseases.

Studies have shown [8, 9] that patients with autoimmune liver disease, such as primary biliary cholangitis (PBC), exhibit reduced intestinal microbial diversity and an increased relative abundance of Lactobacillus compared to healthy individuals, potentially contributing to the development of liver fibrosis. An observational study in 2019 revealed that patients with primary sclerosing cholangitis (PSC), an autoimmune liver disease, exhibited a significantly increased abundance of fecal bacteria such as Haemophilus, Clostridium, Enterococcus, and Streptococcus compared to healthy controls [10]. Additionally, while previous studies have consistently indicated that Bifidobacteriaceae exerts a beneficial effect on cirrhosis, this protective effect was not confirmed in Mendelian randomization (MR) studies. Conversely, Erysipelothrix has been associated with a reduced risk of cirrhosis and autoimmune liver diseases, warranting further in-depth analysis [11–13].

In this context, MR is an emerging method to investigate the causal role of gut microbiota in the development of diseases such as cirrhosis, non-alcoholic fatty liver disease, and autoimmune liver disease through genetic prediction. Despite the growing interest, no relevant meta-analysis has produced consistent and conclusive results regarding the impact of gut microbiota on liver diseases using MR. This gap in knowledge underscores the necessity of synthesizing existing studies to provide more definitive insights into the gut-liver axis.

The primary objective of this systematic review and meta-analysis is to provide quantitative insights into the effects of gut microbiota on human liver diseases through MR studies. Specifically, we aim to synthesize results from existing MR studies examining the association between gut microbiota and specific liver diseases, evaluate the potential protective and adverse effects of different gut microbiota on liver health, identify key bacterial families and genera that significantly influence liver disease outcomes, and offer recommendations for leveraging specific microbiota for clinical treatment and further research.

By achieving these objectives, this review aims to enhance our understanding of the gut-liver axis and inform future clinical trials and therapeutic strategies.

2 | Methods

2.1 | Eligibility Criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, all studies included from the initial search strictly adhered to the Population, Intervention, Comparison, Outcome, and Study Design (PICOS) framework standards [14]. The included articles were MR studies focusing on a specific disease within the gut microbiota and liver disease context. Excluded were purely review articles, randomized controlled trial articles, and articles lacking full text or primary data findings that could not be resolved using the Engauge Digitizer tool (Table 1).

2.2 | Information Sources

We performed a systematic literature search across four electronic databases: PubMed, Embase, the Cochrane Library, and Web of Science. We also searched reference lists of the included studies to identify additional relevant articles. The date of the last search for each database is as follows: PubMed (June 10, 2024), Embase (June 10, 2024), Cochrane Library (June 10, 2024), and Web of Science (June 10, 2024).

2.3 | Search Strategy

We performed a systematic literature search to identify MR studies of the effects of gut microbiota on liver disease. We searched four electronic databases (PubMed, Embase, the Cochrane Library, and Web of Science) using Medical Subject Headings (MeSH) and free-text terms “Gastrointestinal Microbiomes” or “Gut Microbiome” or “Intestinal Microbiome” and “Disease, Liver” or “Liver Dysfunction” or “Liver Disease” and “Mendelian randomization” or “Mendelian randomization analysis” for potentially relevant articles up to June 2024. The study language was limited to English. We screened the returned titles to exclude duplicate studies and reviews, and then selected articles to exclude inappropriate ones and include appropriate titles and abstracts. Subsequently, we determined final inclusion by reviewing the full text of the remaining studies. In addition, we searched the references of the included articles for additional studies to ensure that our search strategy identified all relevant studies.

2.4 | Selection Process

Two reviewers independently screened the titles and abstracts of the retrieved articles to assess their eligibility. Full-text articles of potentially eligible studies were then reviewed independently by the same two reviewers. Discrepancies between reviewers were resolved through discussion, and if necessary, a third reviewer was consulted. No automation tools were used in the selection process.

2.5 | Data Collection Process

Two reviewers independently extracted data from each included study using a standardized data extraction form. The extracted data included information on the author, year of publication, country, sample size, intestinal flora species, and types of liver diseases. When specific data were unavailable, we contacted the study authors to request the missing information. Discrepancies in data extraction were resolved through discussion, with a third reviewer consulted if necessary.

2.6 | Data Items

We sought data on various outcomes related to the gut microbiota and liver diseases, including the abundance of specific bacterial species and their association with different liver conditions. The primary outcomes included measures of liver disease severity and progression. We also collected data on participant

TABLE 1 | Basic information of literature.

Country	Expose	Database(Expose)	Sample size (Expose)	SNP	Outcome	Database(Outcome)	Sample size(Outcome)	Method	References (author, year)
China	c. Actinobacteria et al.	MiBioGen consortium	18340	9	CHB	GWAS	NR	IVW; Maximum likelihood; MR; Weighted median	Zhang et al. (2023)
China	f. Enterobacteriales et al.	MiBioGen consortium	18340	10	NAFLD; NASH	FinnGen	NR	IVW; MR;Weighted mode; simple mode; Weighted median	Zhai et al. (2023)
China	c. Coriobacteriia et al.	MiBioGen consortium	18340	17	NAFLD	GWAS	NR	IVW; MR; Weighted mode; simple mode; Weighted median	Li etal, (2023)
China	g. Bacteroides et al.	MiBioGen consortium	7738	7	NAFLD	FinnGen	NR	IVW	Yan et al. (2024)
Italy	f. Lactobacillaceae et al.	GWAS	18340	NR	NAFLD	GWAS	NR	IVW	Roberta Forlano et al. (2023)
China	o. Actinomycetales et al.	GWAS	18340	4	NAFLD	GWAS	NR	IVW; MR; Weighted mode; simple mode; Weighted median	Pan et al. (2024)
China	f. Ruminococcaceae et al.	GWAS	8596	19	HCC; ICC	GWAS	456348	IVW; MR; Radial MR; Weighted median; MR-RAPS; MR-PRESSO	Ma et al. (2023)
China	g. Oscillospira et al.	MiBioGen	18340	8	PLC	FinnGen	BiobNR	IVW; Maximum likelihood; MR; Weighted mode; MR-PRESSO; Weighted median	Jiang et al. (2023)
China	p. Actinobacteria et al.	MiBioGen	18340	18	FL; LC; PLC	FinnGen	NR	IVW; MR; Weighted mode; Weighted median	Zhu et al. (2023)
China	g. Butyricicoccus et al.	MiBioGen	18340	8	LC	FinnGen	NR	IVW	Yuan et al. (2023)
China	f. ClostridialesvadinBB60group et al.	MiBioGen	18340	15	LC	FinnGen	NR	IVW; MR; Weighted mode; simple mode; Weighted median	Zhou et al. (2023)
China	f. Lachnospiraceae et al.	MiBioGen	18340	14	LC	FinnGen	214403	IVW; MR; Weighted mode; Weighted median	Li et al. (2024)

(Continues)

TABLE 1 | (Continued)

Country	Expose	Database(Expose)	Sample size (Expose)	SNP	Outcome	Database(Outcome)	Sample size(Outcome)	Method	References (author, year)
China	c. Clostridia et al.	MiBioGen	18340	12	AIH; PBC; PSC	GWAS	NR	IVW; MR; Weighted mode; simple mode; Weighted median	Fu et al. (2023)
China	p. Actinobacteria et al.	MiBioGen	18340	5	PBC	GWAS	NR	IVW; MR; Weighted mode; simple mode; Weighted median	Luo et al. (2023)
China	c. Betaproteobacteria et al.	MiBioGen	14306	7	PSC	FinnGen	195922	IVW; MR; Weighted median	Liang et al. (2023)
China	o. Bacillales et al.	MiBioGen	18340	5	PBC; PSC	GWAS	NR	IVW; MR; Weighted mode; simple mode; Weighted median	Yang et al. (2024)
China	c. Coriobacteriia et al.	MiBioGen	18340	10	ALC; LC; PBC	FinnGen	Buch 4208	IVW	Xiao et al. (2023)
China	c. Actinobacteria et al.	MiBioGen	14306	67	NAFLD; ALD; PLC	FinnGen	NR	IVW; MR; Weighted mode; simple mode; Weighted median	Wu et al. (2024)
China	g. Actinomyces et al.	MiBioGen	18340	7	NAFLD;ALD; VH	GWAS	NR	IVW; MR; Weighted median	Zhang et al. (2023)
China	p. Tenericutes et al.	MiBioGen	18340	12	NAFLD	FinnGen	NR	IVW; Weighted median	Dai et al. (2024)
China	c. Actinobacteria et al.	MiBioGen	18340	2699	MLC;PBC	IEU Open GWAS	463010/399920	IVW	Li et al. (2023)
China	g. *Clostridium innocuum* group et al.	MiBioGen	18340	8	PBC; PSC	FinnGen	281127	IVW	Cui et al. (2024)
China	f. Veillonellaceae et al.	MiBioGen	18473	12	ICC	GWAS	NR	IVW; MR; Weighted mode; simple mode; Weighted median	Chen et al. (2023)
China	p. Actinobacteria et al.	MiBioGen	18340	11	PBC	genome-wide meta-an	NR	IVW; Maximum likelihood; MR; Weighted mode; Weighted median	Zhang et al. (2023)

characteristics, study design, and funding sources. In cases of missing or unclear information, we made assumptions based on the available data and context.

2.7 | Study Risk of Bias Assessment

The risk of bias in the included studies was assessed independently by two reviewers using the Cochrane Collaboration tool. This tool evaluates various domains of bias, including selection bias, performance bias, detection bias, attrition bias, and reporting bias [15]. Discrepancies between reviewers were resolved through discussion, with a third reviewer consulted if necessary.

2.8 | Effect Measures

For each outcome, we calculated the standardized mean difference (Hedge's g) as the effect measure. This measure was chosen due to its suitability for synthesizing results from studies with different scales. The results were considered significant when $p < 0.05$, and significance was also indicated when the confidence interval range was either below or above zero.

2.9 | Synthesis Methods

To assess the impact of gut microbiota on liver diseases, we conducted a comprehensive analysis of the selected studies. Subsequently, subgroup analyses were performed to identify sources of heterogeneity and to evaluate significant variables. For each comparison, the standardized mean difference was calculated using Hedge's g as a measure of effect size. These values were categorized as small (0.2–0.5), medium (0.5–0.8), and large (0.8 and higher) according to standard convention [16]. A result was considered significant when the P-value was less than 0.05. Significance was also determined when the confidence interval range was either entirely above or below zero. The heterogeneity of effect sizes within each comparison was assessed using Cochran's Q test and the I^2 statistic, with heterogeneity classified as low ($I^2 < 30\%$), moderate ($I^2 < 60\%$), and high ($I^2 > 60\%$). Data were presented as effect sizes with 95% confidence intervals. All calculations were conducted using Stata software (version 12.0).

2.10 | Reporting Bias Assessment

To assess the risk of bias due to missing results, we utilized funnel plots and Egger's test. Egger's test revealed no significant publication bias ($p = 0.18$), and funnel plots appeared symmetric, suggesting minimal publication bias. We also performed sensitivity analyses excluding studies with smaller sample sizes to confirm the robustness of our conclusions. These methods help identify the presence of publication bias and other reporting biases that might affect the synthesis results.

2.11 | Certainty Assessment

The certainty of the evidence for each outcome was assessed using the GRADE approach. This method considers factors such as study design, risk of bias, consistency of results, and precision of effect estimates to rate the overall confidence in the body of evidence.

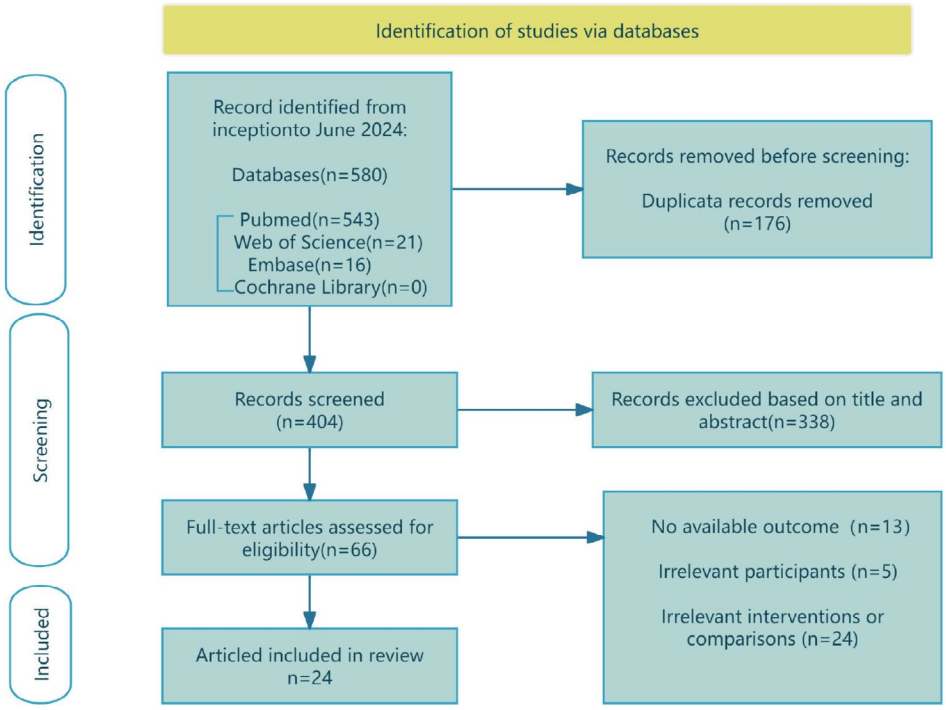

FIGURE 1 | Search strategy for trials included in the meta-analyses.

3 | Results

3.1 | Study Characteristics

Our search strategy retrieved 580 articles from four electronic databases: PubMed, Embase, the Cochrane Library, and Web of Science. After removing duplicates, we screened 543 articles based on their titles and abstracts. Following this initial screening, 43 articles were retained for full-text review. After excluding articles due to the absence of control groups ($n = 9$), insufficient original data for meta-analysis ($n = 6$), and full-text inaccessibility ($n = 4$), a total of 24 articles met the inclusion criteria and were ultimately included in this meta-analysis. The flow diagram in Figure 1 illustrates the study selection process.

3.2 | Article Quality

The included MR articles all conducted an MR study using the most comprehensive GWAS data to overcome common limitations in epidemiological studies. The results highlighted the causal effect of the abundance of specific bacterial signatures on the risk of liver disease, which may provide an important basis for studying the association between the gut microbiome and liver disease (Figure 2).

4 | Significance of Meta-Analysis

From the perspective of the microbial community, most of the microbial communities at the phylum level are risk factors. For example, Actinobacteria, Cyanobacteria, Lentisphaerae, Proteobacteria, and Verrucomicrobia all show negative correlation levels. From the class level, it is in a state where probiotics and harmful bacteria coexist. Some bacteria play a protective role against liver disease, such as Alphaproteobacteria, Bacteroidia, Clostridia, etc.; while Betaproteobacteria, Gammaproteobacteria, etc., have a negative impact. From the order level, there are many microbial communities that are positively correlated between the two, such as Bacillales and Bacteroidales, but there is one type of bacteria that is an absolute risk factor, and this type of bacteria is Burkholderiales. (Figure 3).

From the perspective of the top 10 families, intestinal flora plays an obviously harmful role in PBC. Among them, the main bacterial groups are Acidaminococcaceae, Bifidobacteriaceae, Clostridiaceae1, and Methanobacteriaceae. Interestingly, these bacteria showed a positive correlation level with PLC, and some bacteria even played a significant protective role, such as Family XI bacteria, Lactobacillaceae bacteria, and Lachnospiraceae bacteria. From the level of the top 10 genera, both FL and LC diseases are in a state of bacterial flora interaction and do not show particularly significant significance. However, from the perspective of CHB, Butyricicoccus bacteria are obviously negatively correlated, while Dorea bacteria have significant protective significance. (Figure 4).

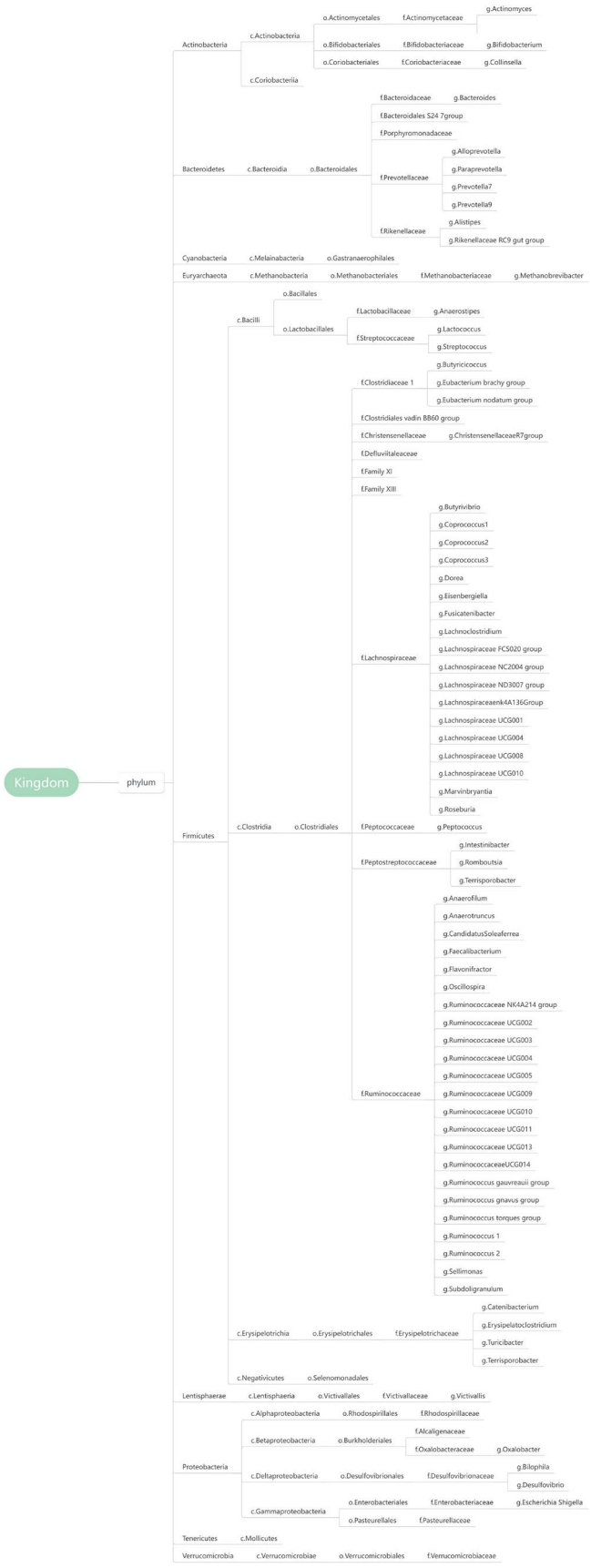

FIGURE 2 | Taxonomic relationship of intestinal flora.

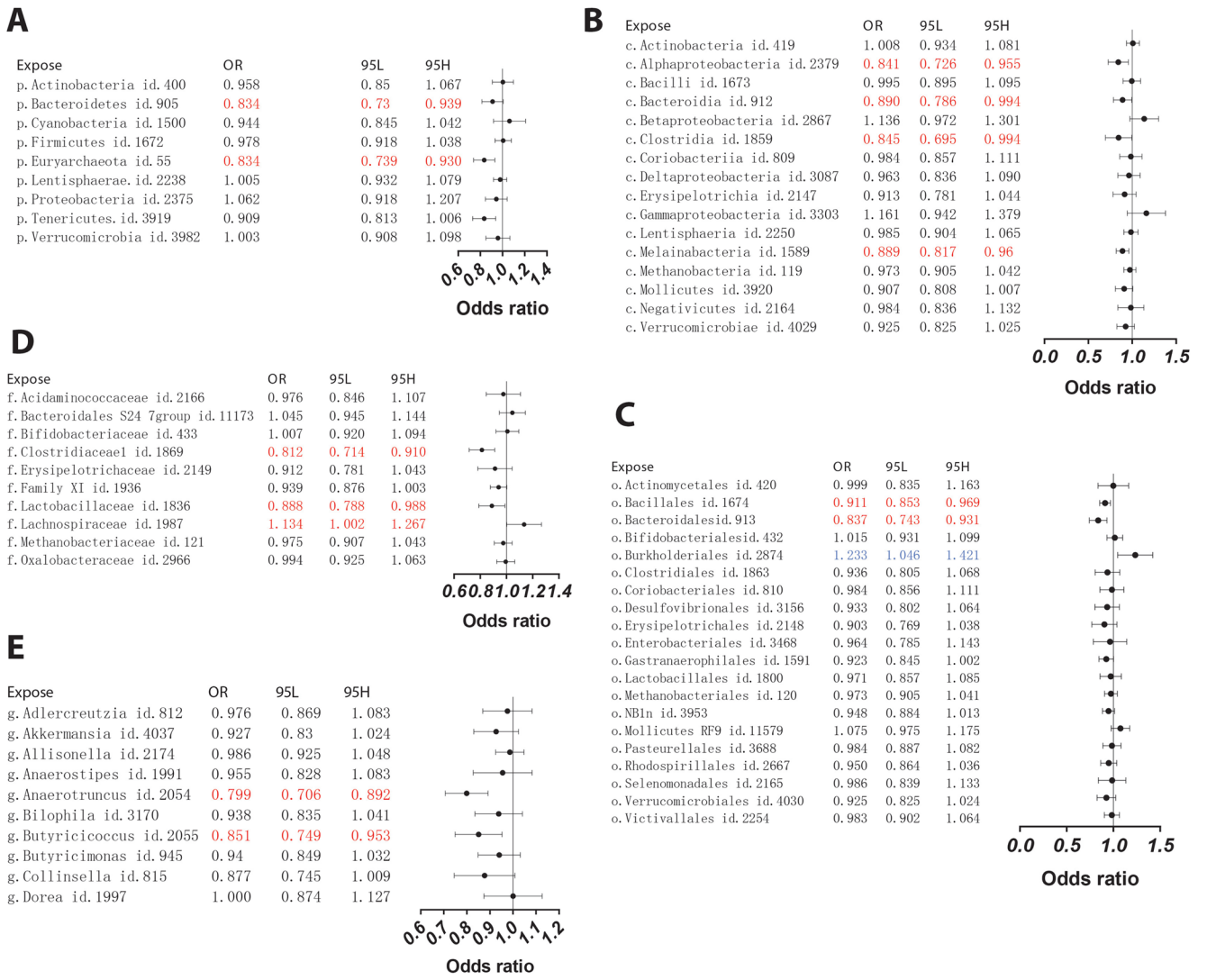

FIGURE 3 | The relationship between gut microbiota and five liver diseases at various taxonomic levels. Red indicates microbiota positively correlated with increased liver disease risk, whereas blue indicates microbiota associated with reduced risk or protective effects. (A–C) Associations between phylum (A), class (B), and order (C) levels of intestinal flora and five liver diseases. (D-E) Relationship between the top ten family (D) and genus (E) level gut microbiota and five liver diseases.

From the perspective of disease analysis, most of the bacterial flora at the genus level have a protective effect on CHB, FL, and PLC. For example, Christensenellaceae R7 group bacteria, Dorea bacteria, *Eubacterium rectale* group bacteria, Family XIII AD3011 group bacteria, Flavonifractor bacteria, and Parabacteroides bacteria, etc., play a role in reducing the risk level of CHB. In addition, bacteria such as Clostridium sensustricto1, FamilyXIIIUCG001, and *Ruminococcus gauvreauii* group are risk factors for CHB; Prevotella7, Roseburia, and Veillonella are risk factors for FL; Oscillospira is a risk factor for PLC. Bacteria at the genus level are basically in a state of coexistence of protection and danger for PBC and LC. Among them, Coprococcus2 and Veillonella showed significant risk to LC, and Ruminococcaceae UCG003, Ruminococcaceae UCG010, and Ruminococcaceae UCG013 also had the same impact on PBC. (Figure 5).

5 | Discussion

Many studies have previously conducted MR to investigate the causal relationship between specific liver diseases and intestinal flora [17], but few have combined their results into a meta-analysis. This study investigated the impact of intestinal microorganisms on liver disease through a comprehensive meta-analysis. Our discussion primarily focuses on findings at the genus level, as these results are both concentrated and more clinically relevant. By examining the genus-level data, we aim to provide insights that are directly applicable to clinical settings, facilitating the identification of potential microbial targets for therapeutic intervention.

The significance of the microbiome in the etiology of liver disease has attracted considerable attention. Take bile acids as an

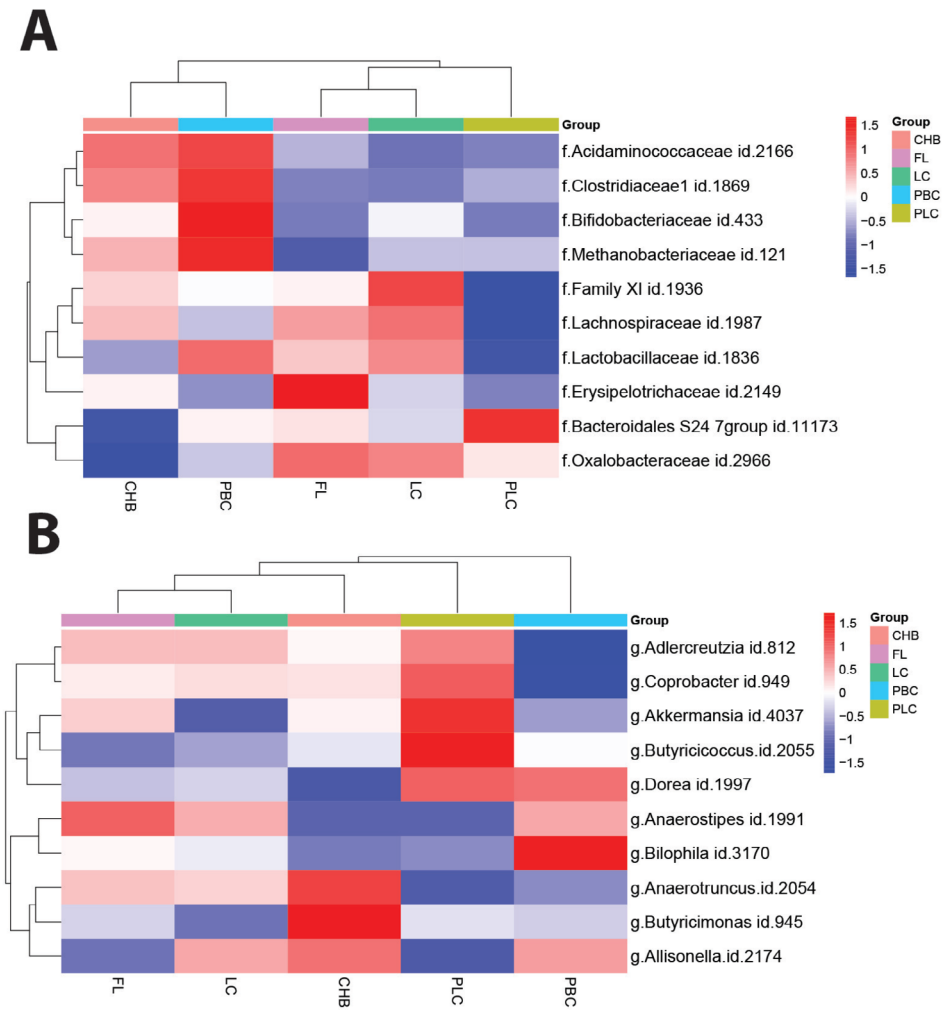

FIGURE 4 | The top 10 family and genus-level gut microbiota associated with five liver diseases. Red indicates microbiota positively correlated with increased liver disease risk, and blue indicates microbiota associated with reduced risk or protective effects. (A) The top 10 families associated with five liver diseases. (B) The top 10 genera associated with five liver diseases.

example. After food is ingested, bile is released into the duodenum, promoting the absorption of intestinal lipids. These bile acids are then transported and reabsorbed at the end of the ileum through passive diffusion and active transport, eventually returning to the liver via the portal vein. This process is known as the enterohepatic circulation of bile acids. Disruptions in the enterohepatic circulation, influenced by changes in the abundance of specific gut microbiota, can significantly impact liver function and health. Protective associations found, such as with Bacteroidetes, could reflect their involvement in bile acid metabolism, immune modulation, and gut barrier integrity. Bacteroidetes produce short-chain fatty acids, such as butyrate, which help reduce hepatic inflammation by modulating immune cell activity and improving gut epithelial integrity [18]. Conversely, an increased abundance of pathogenic bacteria, such as Veillonella, may exacerbate liver conditions by promoting systemic inflammation via impaired intestinal barrier function. In 2022, Herbert Tilg's article [18] mentioned that disturbances in this host–microbe interaction were observed in various experimental liver diseases, and that damage to the intestinal barrier would promote this disturbance, thereby promoting liver inflammation and disease progression. Clinical evidence describes that the gut-liver axis is affected in non-alcoholic fatty liver disease, alcoholic liver disease, and PSC [19, 20].

According to the results of this study, gut microbiota primarily exerts a positive effect on liver diseases. For instance, the Clostridiaceae1 and Lachnospiraceae families are negatively correlated with the risk of PLC, acting as protective factors against PLC. These findings are consistent with the MR study by Cui Yanglin et al. Additionally, both of these bacterial families have been shown to play protective roles in autoimmune liver diseases [21]. In a study, Chen et al. [22] examined the gut microbiota composition of 28 patients with cirrhosis and compared it with that of 16 controls. The analysis revealed that the abundance of Veillonella, Prevotella, and other microbial genera was significantly increased in patients with cirrhosis, which is consistent with the findings of our study. At the genus level, an increased abundance of Adlercreutzia, Coprobacter, and Anaerotruncus was associated with a reduced incidence of PBC. Interestingly, Butyricicoccus was identified as a risk factor solely for PLC, while it either played a protective role or had no significant impact on the other four liver diseases. However, if the abundance of Anaerotruncus increases, it not only protects

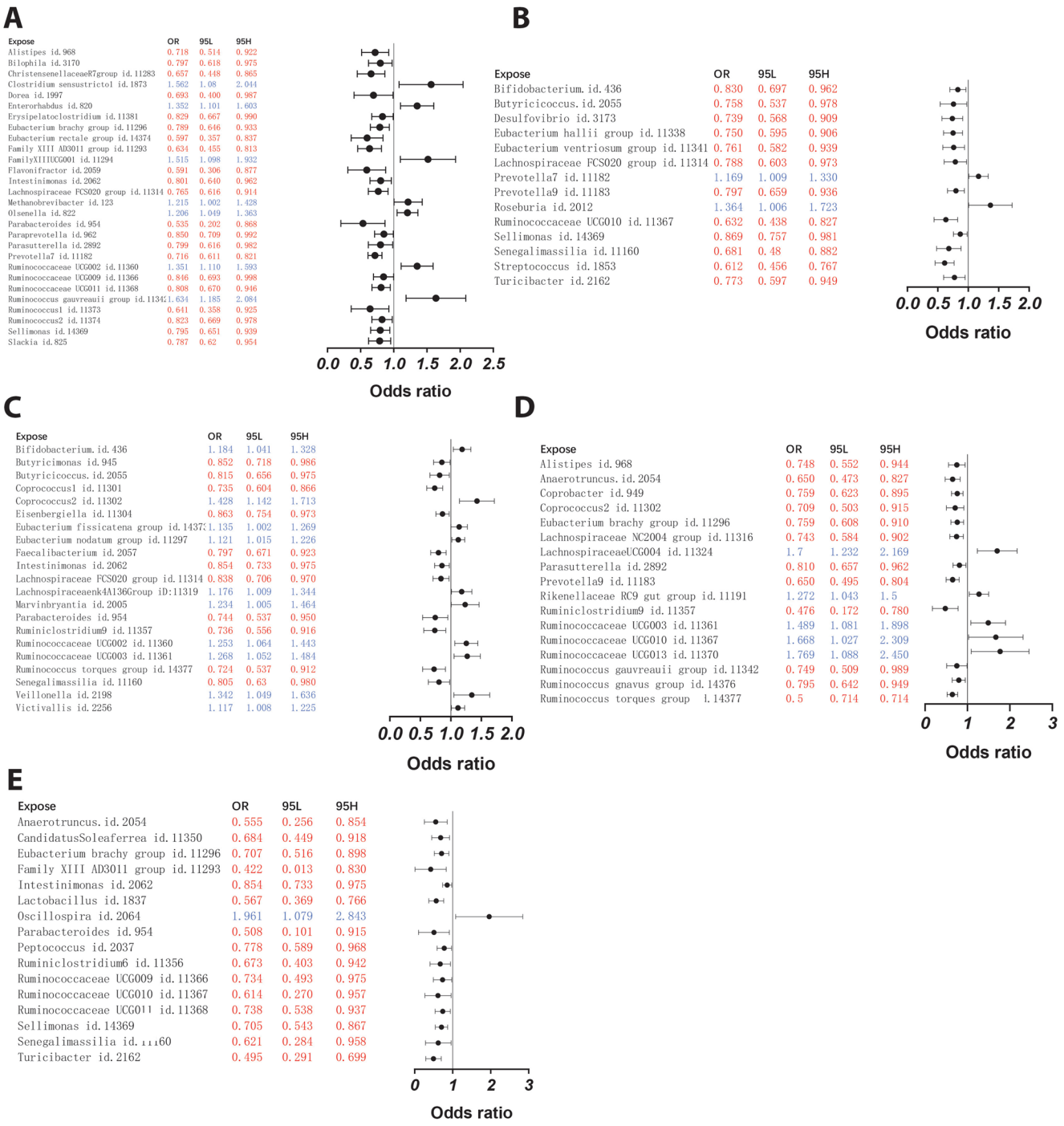

FIGURE 5 | Analysis of the five liver diseases (CHB, FL, LC, PBC, and PLC) across different classification levels of intestinal flora. (A) CHB, (B) FL, (C) LC, (D) PBC, and (E) PLC are analyzed sequentially from phylum, class, order, family, to genus levels.

against PLC but also raises the risk of chronic hepatitis B (CHB), which warrants further consideration.

Although the role of the microbiome in the pathogenesis of inflammatory bowel disease, rheumatoid arthritis, and colorectal cancer has been extensively studied, literature on the causal relationships between the microbiome and liver diseases remains limited. We observed both consistencies and inconsistencies in the associations between bacterial features and different liver diseases. These variations may arise from methodological differences, such as control for horizontal pleiotropy in MR studies, genetic differences among populations, variations in microbiota assessment methods, and dietary habits influencing microbial composition. Dietary patterns significantly affect microbiota composition and could contribute notably to these observed inconsistencies across different populations.

Even so, the study of changes in the gut microbiome has significant clinical implications for the prevention and diagnosis of liver diseases. Firstly, alterations in the gut microbiome can serve as biomarkers for disease screening, diagnosis, and prognosis throughout the course of liver disease [23]. The human

microbiome has been successfully used to develop diagnostic biomarkers for various diseases. Diagnostic models based on the microbiome have been established for AIH and PSC, but there are currently no specific models for PBC, CHB, LC, etc. [24] In the future, more comprehensive data on the gut microbiome will be needed to support the development of screening, diagnostic, and prognostic models for liver diseases.

The limitations of our study include the potential influence of various factors on the abundance of the gut microbiome, such as diet, gender, country, population, and the timing of microbiome collection. Future research will need to conduct more rigorous experimental and clinical validation of our findings. Additionally, it emphasizes the necessity of comprehensive GWAS tailored for Asian populations to deeply investigate host genetic variations associated with the gut microbiome. Lastly, overlapping symptoms among different liver diseases can complicate the diagnostic process, making it more relevant to compare results across diseases rather than relying solely on clinically specific conclusions to draw clear causal inferences about the relationship between the gut microbiome and specific liver diseases.

6 | Conclusion

Our meta-analysis results indicate that the gut microbiota has a significant impact on the occurrence of liver diseases and may serve as a means of prevention or diagnosis. Subgroup analysis revealed that different bacterial levels exert varying effects on diseases; for example, an increase in the abundance of certain bacteria can reduce the risk of one liver disease while simultaneously becoming a risk factor for another. We advocate for customized approaches tailored to specific diseases to improve liver function and delay disease progression. Further high-quality research is needed to elucidate the detailed mechanisms and specific roles of various gut microbiota.

Acknowledgments

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data is provided within the manuscript or supplementary information files.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.