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Article

Exploring the Causal Relationship between Plasma Metabolites and Liver Cirrhosis: A Mendelian Randomization Study

Luyang Liu [1] and Guangwen Zhou [1,*]

[1] Shanghai Sixth People's Hospital Affiliated to Shanghai Jiaotong University, Shanghai, China
* Correspondence: Guangwen Zhou, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiaotong University, Shanghai, China

Abstract: Liver cirrhosis constitutes a major global health challenge, yet the precise metabolic pathways underlying its development remain inadequately defined. This study employed a bidirectional two-sample Mendelian randomization (MR) framework to rigorously assess the causal association between circulating plasma metabolites and the risk of cirrhosis. We integrated summary-level data for liver cirrhosis from the IEU Open GWAS database with statistics for 1,400 plasma metabolites and ratios obtained from the GWAS catalog. The inverse variance weighted (IVW) method served as the primary analytical tool, supplemented by four additional robust MR techniques. To ensure the reliability of our findings, sensitivity analyses—including tests for pleiotropy, heterogeneity, and leave-one-out validation—were performed. Forward MR analysis identified ten specific metabolites and two metabolite ratios with suggestive causal links to liver cirrhosis. Specifically, eight metabolites exhibited significant positive causal associations (increasing disease risk), while negative causal relationships (suggesting a protective effect) were observed for two metabolites and two metabolite ratios. Conversely, reverse MR analysis indicated no significant causal effect of liver cirrhosis on these metabolic markers. Sensitivity analyses confirmed the absence of significant horizontal pleiotropy or heterogeneity. By merging genomic and metabolomic insights, this study identifies twelve metabolites or ratios causally linked to cirrhosis, providing novel perspectives on metabolic influences and highlighting potential therapeutic targets.

Keywords: mendelian randomization; liver cirrhosis; metabolites; genomics; metabolomics

1. Introduction

Liver cirrhosis (LC) constitutes the terminal phase of chronic hepatic deterioration, marked by the structural supplanting of healthy liver parenchyma with regenerative nodules and fibrotic scarring. These pathological shifts trigger compromised organ performance and the onset of severe portal hypertension. The clinical progression of LC typically correlates with a significant drop in patient well-being and elevated mortality rates. At present, LC is a premier global health challenge, responsible for nearly one million fatalities annually. Its worldwide prevalence is driven by diverse etiologies, including chronic hepatitis virus infections, excessive alcohol intake, autoimmune or cholestatic disorders, and metabolic syndrome (obesity). As a multifaceted pathological phenomenon, LC involves a complex interplay of immune dysregulation, chronic inflammation, and metabolic shifts.

Since the liver serves as the primary metabolic center of the human body, various biochemical compounds are processed here before entering the systemic circulation to preserve physiological homeostasis [1, 2]. Consequently, metabolic disturbances act as both a driver and a consequence of LC advancement, creating a deleterious feedback loop. Identifying the definitive causal pathways between circulating metabolites and LC risk is therefore of critical scientific importance.

Previous investigations have demonstrated that specific metabolic reconfigurations are central to cirrhosis development. Metabolomic profiling of decompensated LC has

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revealed shifts such as diminished mitochondrial oxidative glucose metabolism, increased reliance on extramitochondrial glycolysis, and accelerated protein and lipid breakdown; these changes result in the accumulation of amino and fatty acids [1, 3]. Additionally, prospective observational data have linked alcohol-induced fibrosis to the progressive depletion of specific lipids, particularly sphingomyelins. While the correlation between lipid profiles and nonalcoholic fatty liver disease (NAFLD) is well-documented, a more rigorous and systematic evaluation is essential to clarify the causal mechanisms linking these metabolic markers to liver cirrhosis.

Mendelian randomization (MR) has emerged as a potent epidemiological methodology for inferring causality by utilizing genome-wide association study (GWAS) data. This technique utilizes single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to estimate the causal impact of an exposure on a clinical outcome. Because alleles are randomly distributed during meiosis, MR effectively minimizes common pitfalls of observational studies, such as reverse causation and confounding factors. By leveraging genetic inheritance, MR allows researchers to validate phenotypic associations at the genotypic level. While some MR studies have explored LC in relation to factors like gut microbiota, smoking, or iron status, and others have examined metabolites in NAFLD, there remains a significant research gap regarding the comprehensive causal landscape between the broad plasma metabolome and liver cirrhosis.

To bridge this gap and uncover the metabolic drivers of LC, we performed a large-scale two-sample MR analysis encompassing 1,400 plasma metabolites and ratios. Furthermore, recognizing that metabolites may serve as either precursors to or markers of disease, we incorporated a reverse MR framework [4]. This bidirectional strategy aims to provide a definitive understanding of the causal directions and the complex metabolic networks underlying liver cirrhosis.

2. Materials and Methods

2.1. Study Design

In our Mendelian randomization (MR) research framework, liver cirrhosis was designated as the primary outcome, while 309 metabolite ratios and 1,091 plasma metabolites were utilized as exposure factors. To reinforce the reliability of the identified associations, every significant exposure-outcome pair was subsequently subjected to a reverse MR analysis. The scientific validity of this bidirectional MR framework was contingent upon three fundamental requirements. First, the chosen genetic instrumental variables (IVs) are required to exhibit a significant and robust correlation with the exposures [5]. Second, these IVs must remain completely independent of any potential confounding factors that might distort the causal estimate. Finally, the selected instruments should influence the cirrhosis outcome strictly through the exposure pathway, precluding any alternative pleiotropic mechanisms. Figure 1 offers a comprehensive visual overview of the bidirectional study design and the complete analytical procedure.

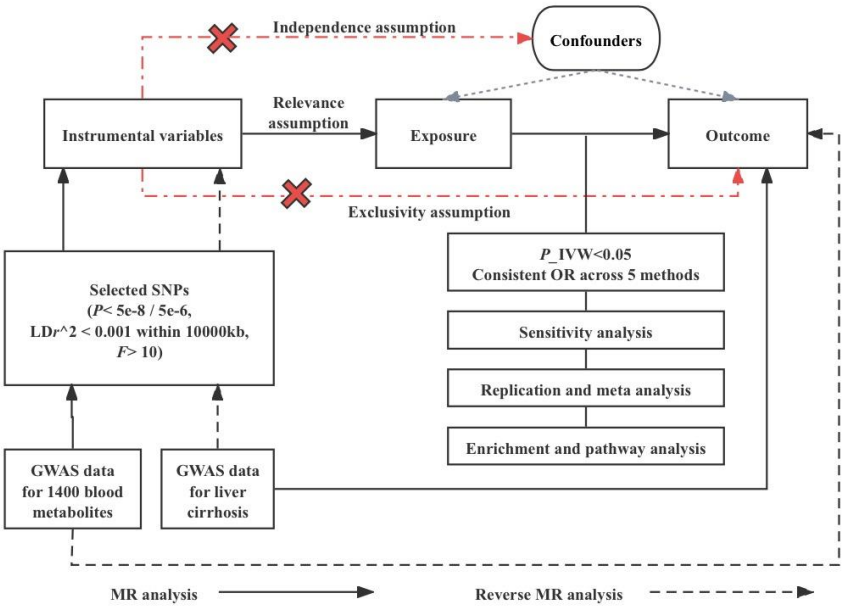

Figure 1. Illustration of the bidirectional Mendelian randomization (MR) study architecture. The diagram outlines the fundamental MR prerequisites: (1) Relevance: genetic instruments must demonstrate a robust connection to the exposure; (2) Independence: IVs must be independent of any confounding variables; (3) Exclusivity: the outcome must be influenced by IVs solely through the exposure pathway. Abbreviations: SNPs, single nucleotide polymorphisms; IVW, inverse variance weighted; OR, odds ratio; LD, linkage disequilibrium; GWAS, genome-wide association studies.

To promote research transparency and facilitate the replication of our findings, we exclusively utilized publicly accessible datasets for this analysis. All GWAS summary statistics incorporated into this study were generated in compliance with the ethical principles defined in the Declaration of Helsinki. Since the original research cohorts obtained informed consent from all participants and were approved by their respective institutional review boards, no additional ethical clearance was required for the present analysis. This strict adherence to established ethical protocols ensures the reliability and integrity of our data handling procedures [6, 7].

2.2. Metabolic GWAS Data Source

Summary-level statistics for the human plasma metabolome, covering 309 metabolite ratios and 1,091 individual metabolites, were extracted from the GWAS Catalog. These data originated from 8,299 individuals in the Canadian Longitudinal Study on Aging (CLSA) cohort, which constitutes one of the most comprehensive resources for metabolic GWAS currently available. Among the 1,091 analyzed metabolites, 850 were stratified into eight primary biochemical categories, such as xenobiotics, lipids, carbohydrates, and amino acids [8, 9]. The intricate nature of the plasma metabolome is reflected in the remaining 241 features, which were classified as unknown or partially identified molecules.

2.3. Liver Cirrhosis GWAS Dataset

For the liver cirrhosis (LC) outcome, we accessed GWAS summary statistics for 216,861 controls and 1,931 cases of European ancestry. This dataset, which encompasses an all-cause definition of cirrhosis based on standard diagnostic thresholds [10, 11], was retrieved from the GWAS Catalog using the identifier "finn-b-CIRRHOSIS_BROAD." This expansive cohort serves as a powerful foundation for identifying genetic markers associated with cirrhosis risk.

2.4. Selection of Instrumental Variables (IVs)

Rigorous selection criteria were applied in this study to identify valid and reliable instrumental variables (IVs). Specifically, potential candidate IVs included single nucleotide polymorphisms (SNPs) reaching genome-wide significance ($P < 5 \times 10^{-8}$) in relation to plasma metabolites. To address the bias of linkage disequilibrium, we performed a clumping procedure with an r^2 threshold of 0.001 and a 10,000 kb distance. Furthermore, we only retained SNPs with an F-statistic > 10 to prevent weak instrument bias, while manually excluding any variants associated with potential confounders or the cirrhosis outcome itself [7, 12]. The standard significance threshold ($P \leq 5 \times 10^{-8}$) proved overly restrictive for the reverse MR analysis, yielding only a single qualified SNP. To facilitate a more robust assessment, the significance threshold was relaxed to $P \leq 5 \times 10^{-6}$ for the reverse analysis, while keeping all other clumping and filtering parameters constant. This adjustment ensured an adequate pool of SNPs for stable causal estimation. Finally, we calculated the R^2 and F-statistics for each instrument using established formulas to further validate their strength and enhance the overall reliability of the findings [13, 14].

$$\boldsymbol{R^2} = \frac{\boldsymbol{2*\beta^2 \times EAF \times (1-EAF)}}{\boldsymbol{[2\times\beta^2 \times EAF \times (1-EAF) + 2(se(\beta))^2 \times N \times EAF \times (1-EAF)]}} \;;$$

$$\mathrm{F} = \frac{\boldsymbol{N-k-1}}{\boldsymbol{k}} \times \frac{\boldsymbol{R^2}}{\boldsymbol{1-R^2}}$$

Within these equations, the fraction of exposure variance accounted for by the IVs is represented by R^2, whereas β signifies the effect magnitude of the genetic variant under investigation **[7, 15]**. EAF refers to the frequency of the effect-associated allele; $se(\beta)$ denotes the standard error of the β coefficient; N reflects the total sample size of the exposure cohort, and k represents the number of analyzed SNPs. We defined genetic instruments with an F-statistic below 10 as weak IVs and eliminated them from the analysis. Furthermore, any SNPs associated with potential confounders—including obesity, hepatitis virus infection, and alcohol consumption—or those showing a direct link to cirrhosis outcomes were rigorously identified and removed using the Phenoscanner V2 online resource (http://www.phenoscanner.medschl.cam.ac.uk/).

2.5. Analytical MR Framework

To strictly assess the causal associations between the plasma metabolome and liver cirrhosis (LC), we utilized five distinct MR estimation techniques: the inverse variance weighted (IVW) approach, the weighted median, MR-Egger regression, and both weighted and simple modes. Among these, the IVW technique was prioritized as the primary analytical tool due to its superior statistical power, provided that all instruments satisfy the core MR assumptions. The remaining four models provided essential validation checks to confirm the consistency and robustness of our findings **[16, 17]**. To ensure analytical stability, we excluded any metabolites linked to fewer than three SNPs. A suggestive causal association was only established if the direction of the odds ratios (ORs) was consistent across all five estimators and the IVW-derived P-value was below 0.05.

2.6. Bidirectional Assessment (Reverse MR)

We implemented a reverse MR framework to determine whether liver cirrhosis itself induces changes in metabolic profiles. In this secondary analysis, the roles of the variables were switched: LC was defined as the exposure, while the identified metabolites were treated as outcomes **[18, 19]**. To maintain methodological uniformity, the reverse MR utilized the same statistical models and filtering parameters as the forward analysis.

2.7. Sensitivity and Reliability Testing

Given the risk of bias from statistical heterogeneity and horizontal pleiotropy, we performed a series of rigorous sensitivity assessments. Horizontal pleiotropy was

evaluated through the MR-Egger intercept test; an intercept with $P > 0.05$ indicated an absence of directional pleiotropy. For heterogeneity assessment, we utilized Cochran's Q test. In the absence of significant heterogeneity ($P > 0.05$), we employed a fixed-effects IVW model; otherwise ($P < 0.05$), a random-effects model was applied to account for the variance. Furthermore, we conducted a leave-one-out analysis to identify whether any single genetic instrument exerted a disproportionate influence on the overall causal estimate, thereby verifying the stability of our findings.

2.8. Computational Software and Multiple Testing

All statistical computations were performed using R (version 4.3.1). The bidirectional MR was primarily executed through the "Two-Sample MR" package. To minimize false-positive discoveries arising from multiple comparisons, we implemented a conservative Bonferroni correction, adopting a threshold of $P < 3.57 \times 10^{-5}$ (calculated as $0.05/1400$). Metabolites with IVW P-values between 3.57×10^{-5} and 0.05 were categorized as suggestively significant **[20]**. We acknowledge that while Bonferroni correction is stringent, it may be overly conservative in high-dimensional testing, potentially limiting the detection of some meaningful associations.

3. Results

3.1. Instrumental Variables for Metabolites and Cirrhosis

Following a rigorous screening protocol, we identified 47 single nucleotide polymorphisms (SNPs) for use as instrumental variables (IVs) to evaluate the causal link between metabolites and cirrhosis. Each metabolite in the MR analysis was proxied by three to five SNPs. For the reverse MR, 19 SNPs were selected as instruments for cirrhosis based on a threshold of $P < 5 \times 10^{-6}$. Comprehensive characteristics of these SNPs, including their F-statistics, are detailed in Table S1 and Table S2. Crucially, all instruments exhibited F-statistics above 10, confirming the absence of weak instrument bias and supporting the robustness of the results.

3.2. Causal Associations of Plasma Metabolites with LC

Metabolites were considered potential candidates if they yielded an IVW P-value <0.05 and showed consistent OR directions across the five MR methods. Among the 1,400 features analyzed, several demonstrated a causal link to LC, as shown in Figure 2. Our analysis indicated that an increased risk of LC was associated with higher concentrations of 1-(1-enyl-palmitoyl)-GPC (p-16:0) (OR=1.54, 95% CI: 1.16-2.05, P=0.0203), 2-hydroxy-4-(methylthio) butanoic acid (OR=1.53, 95% CI: 1.08-2.16, P=0.0163), and homocitrulline (OR=1.31, 95% CI: 1.04-1.65, P=0.0230). Similarly, higher levels of sphingomyelin (specifically d18:1/25:0, d19:0/24:1, d20:1/23:0, and d19:1/24:0) (OR=1.31, 95% CI: 1.11-1.53, P=0.0012), X-24337 (OR=1.29, 95% CI: 1.04-1.60, P=0.0206), bilirubin degradation products, campesterol (OR=1.22, 95% CI: 1.02-1.47, P=0.0339), and biliverdin (OR=1.15, 95% CI: 1.01-1.31, P=0.0360) were linked to elevated disease risk **[21]**. Conversely, the ratio of glucuronate to androsterone glucuronide (OR=0.79, 95% CI: 0.65-0.96, P=0.0172) appeared to act as a protective factor. These findings highlight the role of metabolic profiles in LC etiology and point toward promising biomarkers.

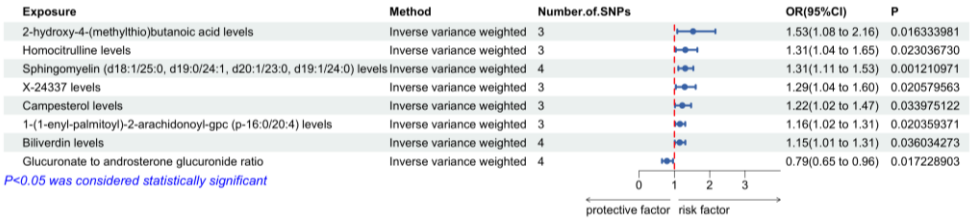

Figure 2. Forest diagram for the impact of plasma metabolites on liver cirrhosis derived from the inverse variance weighted (IVW) analysis. SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

3.3. Sensitivity Analysis of MR

To verify the stability and reliability of our causal estimations, we performed a series of sensitivity evaluations on the metabolites that satisfied the initial selection criteria. The identified MR associations for these 12 metabolic traits are visually represented through scatter plots in Figure 3. According to the MR-Egger regression intercepts (detailed in Table S3), all P-values exceeded 0.05, indicating a complete absence of directional horizontal pleiotropy. This confirms that the observed causal effects were not biased by pleiotropic pathways. Similarly, the results from Cochran's Q test ($P > 0.05$) supported the internal consistency of our findings by demonstrating an absence of significant heterogeneity. Furthermore, the leave-one-out validation (depicted in Figure 4) confirmed that no individual SNP exerted a disproportionate influence or introduced significant bias to the overall causal estimate. Collectively, these rigorous validation steps reinforce the scientific integrity and statistical robustness of the causal links established between these metabolites and liver cirrhosis.

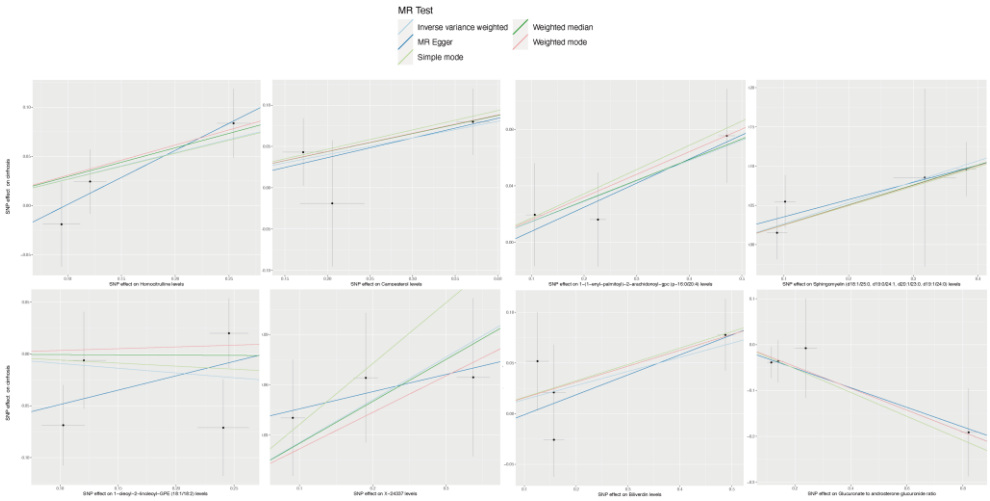

Figure 3. Scatter plots for the significant Mendelian randomization (MR) associations between metabolites and cirrhosis. SNP, single nucleotide polymorphism.

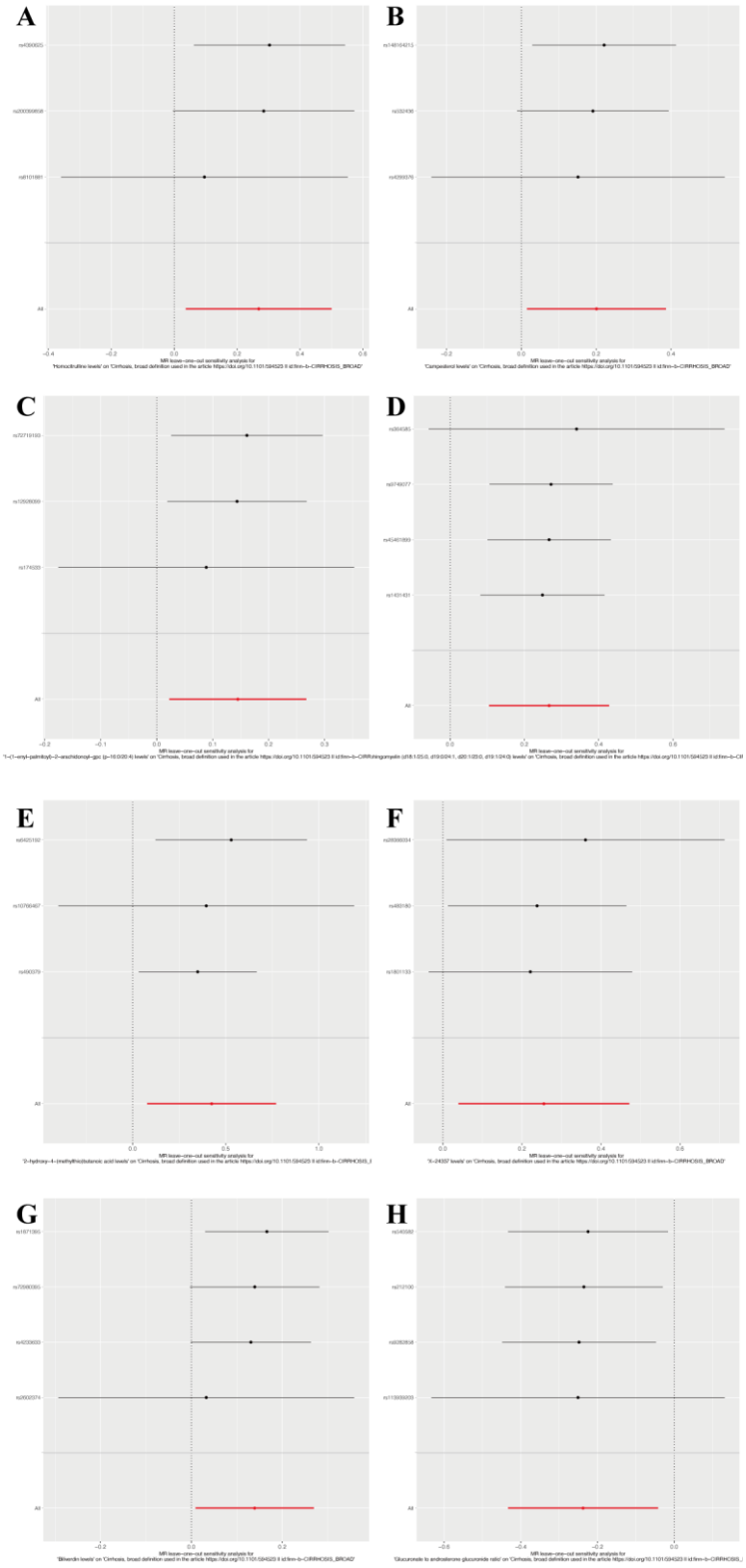

Figure 4. Leave-one-out plots for metabolites on cirrhosis to visualize the causal effect of each metabolite when leaving one SNP out. (A) Leave-one-out plots for homocitrulline levels on cirrhosis; (B) Leave-one-out plots for campesterol levels on cirrhosis; (C) Leave-one-out plots for 1-(1-enyl-palmitoyl)-2-arachidonoyl-gpc (p-16:0/20:4) levels on cirrhosis; (D) Leave-one-out plots for sphingomyelin (d18:1/25:0, d19:0/24:1, d20:1/23:0, d19:1/24:0) levels on cirrhosis; (E) Leave-one-out plots for 2-hydroxy-4-(methylthio)butanoic acid levels on cirrhosis; (F) Leave-one-out plots for X-24337 levels on cirrhosis; (G) Leave-one-out plots for biliverdin levels on cirrhosis; (H) Leave-one-out plots for glucuronate to androsterone glucuronide ratio on cirrhosis.

3.4. Results of Reverse MR Analysis

Estimations from the reverse MR models, utilizing the IVW method, revealed that liver cirrhosis (LC) exerted no significant causal influence on any of the 12 plasma metabolites or their ratios **[22]**. Moreover, these analyses yielded no substantial evidence of horizontal pleiotropy or statistical heterogeneity. Detailed reverse MR outcomes, including the results of various sensitivity tests, are summarized in **Table S4**. These observations indicate that the causal link between LC and the plasma metabolome is unidirectional. Specifically, while the ratios and levels of these plasma metabolites appear to causally drive the development of liver cirrhosis, LC itself does not seem to fundamentally alter these metabolic signatures.

4. Discussion

A profound link exists between metabolic regulation and hepatic function, with numerous observational studies highlighting a correlation between circulating metabolites and cirrhosis risk. In the present research, we performed the first bidirectional MR assessment to explore the causal relationship between LC and 1,091 blood-based metabolites plus 309 metabolic ratios [11, 23]. Our analysis drew upon the most extensive metabolite GWAS summary statistics currently available in public repositories. Using selected SNPs as genetic instruments, we preliminarily identified 12 metabolites or ratios with potential causal effects on cirrhosis, while reverse-directional analysis confirmed that LC did not act as a driver for these candidate metabolites. This study offers a unique perspective on the metabolic architecture of liver cirrhosis and emphasizes the value of integrating metabolomic and genomic insights in medical research.

Biliverdin and bilirubin (along with its degradation byproducts) represent integral elements of the heme metabolism pathway. As the oxidized form of bilirubin, biliverdin is essentially involved in hepatic performance and clinical diagnostics. Traditionally, elevated serum bilirubin concentrations have served as critical biomarkers for liver disorders. Recent research suggests that the redox cycle of bilirubin can exacerbate lipid accumulation and insulin resistance in obese individuals, potentially influencing the progression of non-alcoholic fatty liver disease (NAFLD) or liver cirrhosis. These findings align with previous investigations that identified an association between biliverdin levels and cirrhosis risk. Furthermore, transcriptomic and targeted metabolomic data have revealed an enrichment of porphyrin and lipid metabolites during hepatic fibrosis, with biliverdin showing diagnostic utility in liquid biopsy for distinguishing healthy individuals from patients. Our results are indirectly supported by another recent MR study which found a causal link between elevated biliverdin and increased NAFLD risk. Collectively, these findings underscore biliverdin's potential as both a therapeutic target and a clinical biomarker for liver-related pathologies.

Homocitrulline is a product of carbamoylation, a posttranslational process that significantly alters protein structure and functionality. Such carbamylated proteins have been implicated in various conditions, including chronic kidney disease and atherosclerosis. Previous metabolomic profiling has detected significantly higher homocitrulline levels in individuals with alcoholic hepatitis and NAFLD. Given the established progression from these diseases to cirrhosis, homocitrulline likely plays a pivotal role in fibrotic development, though further experimental validation is necessary **[24]**. Clarifying the pathways through which homocitrulline affects liver pathology could provide fresh insights into its utility as a therapeutic or diagnostic target.

GPC and GPE derivatives are formed through the lysophospholipid pathway as degradation products of phosphatidylcholine (PC) and phosphatidylethanolamine (PE), respectively. Existing evidence suggests that GPCs may serve as prognostic markers for various disease outcomes. Research utilizing 31P-MRS has demonstrated that antiviral therapy in patients with hepatitis C-related cirrhosis leads to a decrease in the (PC+PE)/(GPC+GPE) ratio. Other data have linked PE/GPE levels to fibrosis and autoimmune hepatitis. Despite these insights, specific research into the relationship

between GPC/GPE species and liver cirrhosis remains limited. Our study suggests a prospective causal association between cirrhosis risk and levels of 1-palmitoyl-2-linoleoyl-GPC (16:0/18:2), 1-palmitoyl-2-linoleoyl-GPE (16:0/18:2), and 1-(1-enyl-palmitoyl)-GPC (p-16:0). These findings provide new directions for exploring the underlying metabolic networks of liver cirrhosis.

The ratio of glucuronate to androsterone glucuronide was identified as a protective factor against cirrhosis in our analysis, although literature on this specific ratio is currently sparse. Earlier research noted that plasma glucuronate levels are reduced in hepatitis B-related cirrhosis and correlate with the Child–Pugh score, which partially corroborates our results. Because the metabolic role of androsterone glucuronide is not yet fully understood, further research is required to elucidate its impact on cirrhosis.

Overall, this research offers significant innovation across several dimensions. Most notably, it is the first to employ a bidirectional MR framework to integrate metabolomics and genomics in investigating cirrhosis risk. Second, the study provides an exceptionally systematic analysis by covering 1,400 metabolic traits. Finally, our use of rigorous screening and sensitivity analyses ensures that the identified causal links are both stable and reliable. These methodological strengths support the robustness of our findings and their potential to advance the understanding of liver cirrhosis **[25]**.

We must acknowledge certain limitations of this study. First, the GWAS data were sourced primarily from European cohorts, necessitating future research to confirm these findings in diverse ethnic populations. Second, while our analysis was comprehensive, the results are suggestively significant in the context of multiple testing corrections. Finally, due to the aggregate nature of the available datasets, we utilized a broad definition of liver cirrhosis rather than analyzing specific etiologies like alcoholic or viral cirrhosis separately. Thus, while our MR analysis provides robust evidence, further confirmation through clinical trials and basic biological studies is essential **[17]**.

5. Conclusion

To summarize, this study utilized a bidirectional MR framework to evaluate the potential causal links between the plasma metabolome and LC. Our comprehensive analysis identified 12 metabolites or ratios that potentially influence cirrhosis risk, while reverse MR models demonstrated that LC does not fundamentally alter these features. These results emphasize the importance of understanding the metabolic architecture of liver cirrhosis. Furthermore, these identified metabolites may serve as significant biomarkers for preventative and therapeutic strategies. Future investigations should focus on validating these associations in broader populations to enhance their clinical applicability.

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Institutional Review Board Statement: All genome-wide association studies included in the study received prior approval from their respective review boards and informed consent from patients, so no additional ethical approvals or patient consents were required.

Data Availability Statement: The datasets analysed during the current study are available in the IEU open GWAS project (https://gwas.mrcieu.ac.uk/datasets/) and the GWAS Catalog (https://www.ebi.ac.uk/gwas/).

Abbreviation List: LC: Liver cirrhosis; MR: Mendelian randomization; IVW: inverse variance weighted; EBI: European Bioinformatics Institute; NAFLD: nonalcoholic fatty liver disease; GWAS: genome-wide association studies; IV: instrumental variable; SNP: single nucleotide polymorphism; KEGG: Kyoto Encyclopedia of Genes and Genomes; CLSA: Canadian Longitudinal Study on Aging; LD: linkage disequilibrium; OR: odds ratio; SMPDB: Small Molecule Pathway Database; GPC: Glycerylphosphorylcholine.

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