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Association between circulating inflammatory proteins and the risk of autoimmune liver diseases

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Abstract

Background: Autoimmune Liver Diseases (AILDs) are chronic liver diseases that affect the liver and biliary tract mediated by abnormal autoimmune mechanisms. The pathogenesis of AILDs is intricate, involving a multitude of inflammatory factors and confounding variables. Therefore, it is imperative to conduct a Mendelian Randomization (MR) study to elucidate this correlation.

Materials and methods: The associations between 91 circulating inflammatory proteins and AILDs, including autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis, were examined using two-sample MR analysis, utilizing genetic variants predominantly of European ancestry obtained from genome-wide association studies databases. Inverse variance weighted randomization methods, MR-Egger, and weighted median were used to analyze the causal association between 91 circulating inflammatory proteins and AILDs. The Steiger test was employed to infer the direction of causality.

Results: Our findings indicated that C-C motif chemokine 23, T-cell surface glycoprotein CD6, C-X-C motif chemokine (CXCL)10, CXCL9, monocyte chemoattractant protein-1, and tumor necrosis factor ligand superfamily member 12 were positively associated with the risk of AILDs. In contrast, CUB domain-containing protein 1, fibroblast growth factor 19, interleukin-18 receptor 1, IL-6, and Oncostatin-M were identified as protective factors.

Conclusion: CXCL10, combined with CXCL9, exhibits strong potential to predict patients with AILDs.

Introduction

Autoimmune Liver Diseases (AILDs) are chronic liver diseases that affect the liver and biliary tract mediated by abnormal autoimmune mechanisms, including Autoimmune Hepatitis (AIH), Primary Biliary Cholangitis (PBC), and Primary Sclerosing Cholangitis (PSC), which may occur individually or in combination [1]. The etiology of AILDs primarily stems from aberrant immune functionality, leading to non-suppurative inflammatory liver disease and the subsequent involvement of hepatocytes and bile duct epithelial cells [2]. Although AILDs are relatively uncommon in the general population, epidemiological statistics show that their incidence and prevalence are still on the rise, with an incidence of 0.1-4.39 per 100,000 people and a prevalence of 0.78-42.9 per 100,000 people [3].

The clinical characteristics of different AILDs vary, and their onset is often insidious, with a wide age distribution. The diagnosis of AILDs is complex and sometimes requires a liver biopsy for confirmation [4]. Prolonged and intricate diagnostic processes often lead to poor patient cooperation, with some patients presenting with cirrhosis at the time of diagnosis, significantly impacting prognosis [5]. Therefore, early identification and diagnosis of AILDs are crucial, as timely intervention

can effectively mitigate disease progression to end-stage liver disease and greatly improve the overall prognosis [6].

Due to the elusive pathogenesis of AILDs, comprehensive assessment typically involves combining biochemical markers, one or more autoantibodies, and histopathology [7]. Although liver needle biopsy is an important component in diagnosing patients with AILD, it carries risks and cannot be performed continuously [8]. Moreover, in developing countries, where acquiring autoantibodies can be challenging, diagnosis depends entirely on clinical presentation, along with biochemical and histological criteria for AILD evaluation [9]. Consequently, identifying easily obtainable biomarkers for assessing and aiding the diagnosis and treatment of AILDs is crucial for enhancing patient outcomes. Clinical studies have demonstrated that complex aberrant immune responses mediated by T cells and inflammatory cytokines play pivotal roles in the development and progression of AILDs [10].

Cytokines can be easily obtained and quantified, and current research has indicated their significant involvement in the pathogenesis and progression of AILDs [11]. Serum Interleukin (IL)18 levels were found to be significantly elevated in clinically untreated patients with PBC and showed a significant decrease following treatment [12]. The cytokine IL10 exerts a downregulatory effect on the pro-inflammatory response, attenuates the hepatitis response, and retards liver fibrosis [13]. Concurrently, experimental studies in mice demonstrated that helper T cell (TH)1 and TH17 cells facilitate the upregulation of C-X-C motif chemokine (CXCL)9 and CXCL10 expression within the liver, thereby instigating the progression of AIH in murine models [14].

Mendelian Randomization (MR) is an approach employed to investigate causal relationships between exposure and outcomes of interest [15]. This methodology utilizes single nucleotide polymorphisms (SNPs) as unconfounded proxies for exposure, thereby circumventing the residual confounding and reverse causality commonly encountered in conventional observational studies [16]. The MR design represents a crucial strategy for inferring causality without relying on Randomized Clinical Trials (RCTs), as genetic variants are randomly assorted during meiosis, emulating the principles of an RCT [17]. The pathogenesis of AILDs is intricate, involving a multitude of inflammatory factors and confounding variables. Therefore, it is imperative to conduct an MR study to elucidate this correlation.

Materials and methods

In this study, all data were derived from the Genetic Alliance's publicly available compilation of statistical data from Genome-Wide Association Studies (GWAS). All original studies received specific ethical review and informed consent.

Study design

Summary statistics were collected on circulating inflammatory proteins and AILDs from published GWAS. We aimed to explore the causal effect of circulating inflammatory proteins on the risk of AILDs using two-sample MR.

The MR Approach was built on the following three main assumptions: (1) Genetic variants as Instrumental Variables (IVs) should be robustly associated with the risk factor of interest. (2) The genetic variants used should not be associated with potential confounding factors. (3) Selected genetic variants affect the risk of outcome only by risk factors and not through other pathways (Figure 1).

This MR study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology using MR guidelines.

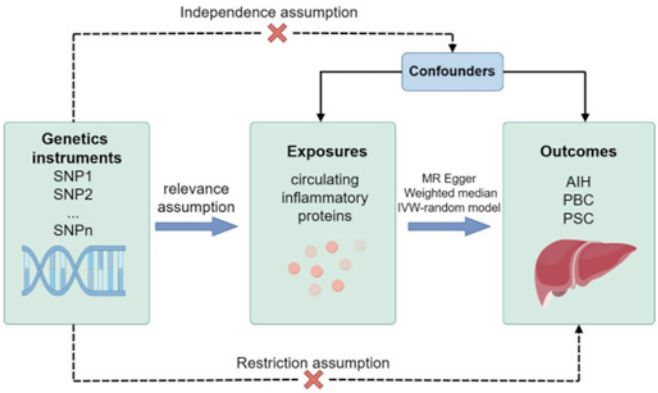

Figure 1: Assumptions of MR analysis for circulating inflammatory proteins and the AILD's risk.

Outcome and exposure data source

The pooled data on circulating inflammatory proteins [18] and AILDs (AIH [19], PBC [20], PSC [21]) utilized in this study were obtained from publicly available GWAS datasets, predominantly comprising individuals of European ancestry. The GWAS Catalog database is publicly available for download at https://www.ebi.ac.uk/gwas/. The details of the GWAS outcomes are presented in (Table 1).

Table 1: Characteristics of GWASs on inflammatory factors and AILDs.

Phenotype	Year	PMID	Discovery ancestry	Sample size
Autoimmune hepatitis [19]	2021	34594039	European, East Asian	906 cases 650942 control
Primary biliary cholangitis [20]	2012	22961000	European	2861 case 8514 control
Primary sclerosing cholangitis [21]	2017	27992413	Utah residents with Northern and Western European, African, Han Chinese and Japanese	2871 case 12019 control

Genetic variants selection criteria

Genetic instruments for each exposure trait or disease were selected at the genome-wide significance threshold ($P<5\times10^{-5}$) from the corresponding GWASs. Independent SNPs were defined by $R2<0.01$ and clump window >5 kb, and correlated SNPs (linkage disequilibrium) with the lowest P-values were retained.

Statistical analysis

In the primary analysis, we employed Inverse Variance Weighted (IVW) MR methods to estimate the association between 91 circulating inflammatory proteins and three AILDs along with their potential causal links [22]. Simultaneously, the MR-Egger and weighted median were used to assist in the judgment of causality. The MR-Egger method was used to determine

whether instrumental SNPs exhibited multiple effects [23]. The presence of potential horizontal pleiotropy and heterogeneity was considered and the intercept term in the MR-Egger regression was used for testing significant horizontal pleiotropy. Additionally, MR-Egger regression was utilized to identify any existing heterogeneity. Furthermore, MR Steiger filtering was employed to examine the causal association between each identified SNP and both the exposure and outcome variables.

Results

Mendelian estimations

The associations between 91 circulating inflammatory proteins (Supplementary Table 1) and AILDs (AIH, PBC, and PSC; Table 1) were examined using two-sample MR analysis, utilizing genetic variants predominantly from European ancestry obtained from GWAS databases.

The IVW randomization methods, MR-Egger, and weighted median were used to analyze the causal association between 91 circulating inflammatory proteins and AIH (Figure 2A). The IVW randomization methods result as the primary outcome indicators (Supplementary Table 1). Outcomes with a P<0.05 for IVW randomization method outcomes were screened, and an OR was further used to express the association between exposure and outcome (Figure 2B). The results demonstrated a positive correlation between AIH risk and tumor necrosis factor ligand superfamily member (TNFRSF)9 (OR: 2.67), IL1A, IL12B, CXCL9, CXCL11, IL17A, CXCL10, IL18, Caspase8, SCF, STAMBP, IL10RA, C-C motif chemokine (CCL)28, HGF, NRTN, IL33, Fractalkine, IL13, IL8, IL2, T-cell surface glycoprotein CD6 (CD6), DNER, TNFSF12, NKR2B4, VEGFA, fibroblast growth factor (FGF)5, CD40L receptor, MMP 1, C-C motif chemokine 23 (CCL23), TRAIL, monocyte chemoattractant protein (MCP)1, IL10RB, ADA, CXCL5, GDNF, and TNFβ levels. Conversely, OPG, MMP10, CCL4, IL15RA, IL18R1, MCP2, IL6, FGF21, Cystatin D, CSF1, FGF23, CXCL1, CXCL6, S100A12, FGF19, MCP1a, SULT1A1, IL7, TRANCE, FLT3LG, TGFα, MCP4, TNFSF14, EIF4EBP1, CUB domain-containing protein 1 (CDCP1), Oncostatin-M (OSM), MCP3, CCL19, IL4, SLAM, IL5, CD5, IL10 (OR: 0.27) were identified to be negatively correlated with the risk of AIH. The detailed outcomes of the IVW randomization method are presented in (Supplementary Table 2). The MR-Egger test results indicated the absence of heterogeneity in several SNPs (Supplementary Table 3). Reversal of causality was not observed in any of the analyses conducted using the MR Steiger's test (Supplementary Table 3).

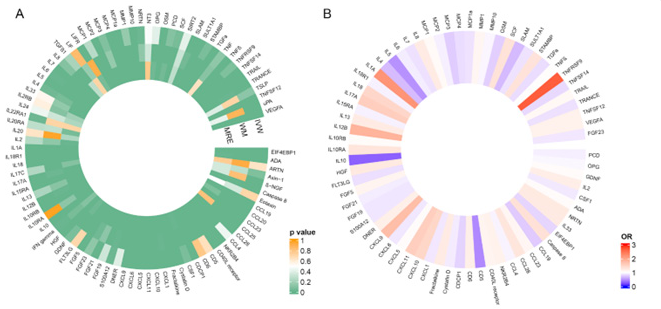

Figure 2: MR analyses for the associations between circulating inflammatory proteins and the risk of autoimmune hepatitis.

We analyzed the correlation between circulating inflammatory proteins and PBC development risk (Figure 3A). Outcomes with a P<0.05 for IVW randomization method outcomes were screened, and an OR was further used to express the association between exposure and outcome (Figure 3B). The results demonstrated a positive correlation between PBC risk and the levels of CXCL9 (OR: 6.90), CXCL10 (OR: 5.67), CXCL11, SLAM, CCL20, CD5, FGF21, Caspase 8, MMP10, IL15RA, CCL23, FLT3LG, TNFSF12, Cystatin D, Eotaxin, MCP1, CD6, MCP3, MCP2. Conversely, IL18R1, ADA, CCL4, IL12B, MCP4, CCL25, CD40L receptor, IL7, FGF19, DNER, CSF1, TNFβ, IL6, OSM, TGFα, CCL28, LIFR, TRANCE, CDCP1, Fractalkine (OR: 0.27) were identified to be negatively correlated with the PBC risk. The detailed outcomes of the IVW randomization method are presented in (Supplementary Table 4).

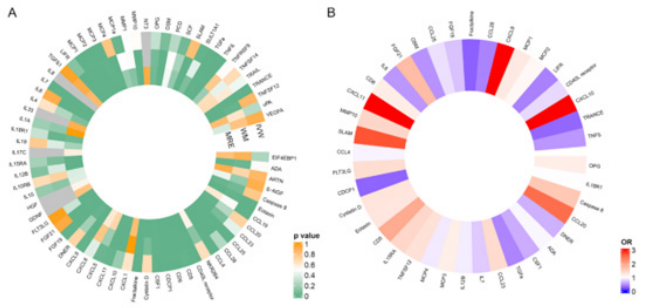

Figure 3: MR analyses for the associations between circulating inflammatory proteins and the risk of primary biliary cholangitis.

We also examined the association between circulating inflammatory proteins and susceptibility to PSC development (Figure 4). The results demonstrated a positive correlation between PSC risk and the levels of TNFRSF9 (OR: 45.16), Fractalkine (OR: 44.80), IL12B (OR: 20.53), CXCL10, IL1A, CSF1, TGFα, TNFβ, IL7, FGF23, CCL20, TNFSF12, MCP1, IL17A, Eotaxin, CXCL9, IL8, IL20, DNER, NRTN, IL10RA, TGFβ1, IL13, NT3, MCP3, NKR2B4, S100A12, HGF, MCP4, IL18, CXCL1, MCP1a, CD6, CCL28, MCP2, CD40L receptor, CCL23, Cystatin D, CCL4. Conversely, IL10RB, FGF5, CXCL6, MMP1, uPA, CXCL11, IL18R1, CCL25, Caspase 8, SCF, MMP10, OPG, GDNF, IL6, Axin-1, IL20RA, IL2, EIF4EBP1, OSM, IL4, SULT1A1, FGF19, PCD, IL5, IL10, CDCP1, CCL19, SLAM, and CD5 (OR: 0.05) were negatively correlated with PSC risk. The detailed outcomes of the IVW randomization method are presented in (Supplementary Table 5).

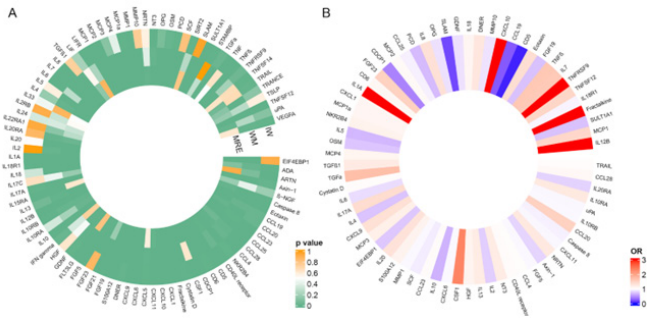

Figure 4: MR analyses for the associations between circulating inflammatory proteins and the risk of primary sclerosing cholangitis.

To comprehensively evaluate circulating inflammatory proteins exhibiting common characteristics in AILDs, we screened for outcomes that were significant for both exposure and outcomes using the IVW random method, ensuring consistency across all AILDs. Our findings indicated that CCL23, CD6, CXCL10, CXCL9, MCP1, and TNFSF12 were positively associated with the risk of AILDs, whereas CDCP1, FGF19, interleukin-18 receptor 1 (IL18R1), IL6, and OSM were identified as protective factors (Figure 5).

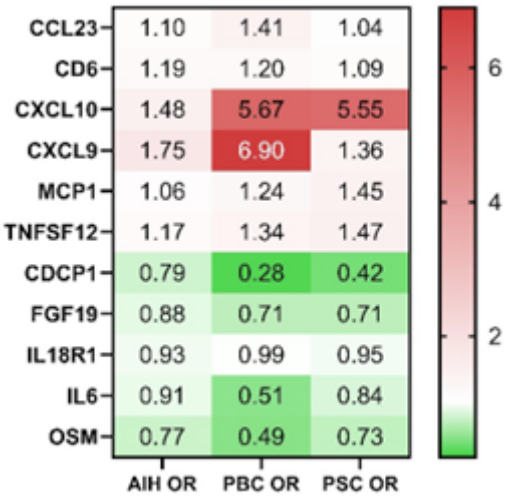

Figure 5: Pooled results of MR analysis of the relationship between circulating inflammatory proteins and the risk of autoimmunity.

Discussion

This study represents the first MR investigation to explore potential predictive serum markers by examining the association between AILDs and circulating inflammatory proteins. Ninety-one circulating inflammatory proteins exhibited distinct associations with various AILDs. Screening for circulating inflammatory protein markers in different autoimmune livers was conducted. Moreover, overlapping syndromes between AIH, PBC, or PSC constitute the spectrum of autoimmune liver disease [24]. From our results, we concluded that CCL23, CD6, CXCL10, CXCL9, MCP1, and TNFSF12 were positively associated with the risk of AILDs, whereas CDCP1, FGF19, IL18R1, IL6, and OSM were identified as protective factors.

Macrophages are widely acknowledged as a prominent source of pro-inflammatory cytokines [25]. Th1, Th2, and TH17 cells, along with pro-inflammatory factors including IL2, IL17, IL22, IFN-γ, and TNF-α, have a crucial impact on the hepatic inflammation progression [26]. Regulatory T cells (Tregs) exert a protective role by secreting anti-inflammatory cytokines, including IL10, to inhibit effector T cells (Teff) [27]. Consequently, circulating inflammatory proteins can activate inflammatory pathways, affect various inflammatory cells, and cause a complex liver inflammatory response, eventually leading to liver tissue damage and liver disease progression [28].

The macrophages are widely acknowledged as a prominent source of proinflammatory cytokines [25]. TNFSF12, a member of the TNF superfamily, regulates macrophages and induces liver fibrosis and hepatocyte apoptosis, contributing to the occurrence and development of AIH [29]. Knockout of MCP1 in mice attenuates hepatic damage, indicating the crucial role of liver-derived MCP1 in modulating macrophage activation and pro-inflammatory cytokine secretion [30]. A co-stimulatory receptor, CD6, stimulates monocyte antigen presentation and is involved in T-cell development [31]. The CD6 expression is restricted to Teff rather than Tregs, and the CD6/activated leukocyte cell adhesion molecule pathway plays a crucial role in orchestrating immune processes associated with activation, differentiation, and migration of T cells [32].

CCL23/CCR1 governs the migration of monocytes, neutrophils, and T cells, whereas CXCL9/CXCR3 facilitates the recruitment of Teff [33]. CXCL9 and CXCL10 play a pivotal role in the pathogenesis of numerous autoimmune and inflammatory disorders, exerting a potent effect on the recruitment and accumulation of Th1 cells, and are closely associated with the development of autoimmune liver disease [34,35]. The chemokines CXCL9 and CXCL10 facilitate the differentiation of CD4+ T cells into effector Th1/Th17 cells [36]. The increase in TH17 cells may result in a concomitant decrease in the Tregs population, leading to a significant elevation in the Tregs/TH17 ratio and compromised tolerance towards autoantigens, thereby contributing to the initiation and persistence of autoimmune liver injury [37]. The induction of chemokines CXCL10 by IFN-γ is closely associated with liver fibrosis. Therefore, mice with genetic defects in CXCL10 exhibit less hepatic fibrosis induced by CCl4 than wild-type mice [38,39]. Animal experiments also confirmed that the activation of cytokine-induced TH1 and TH17 cells induces the upregulation of CXCL9 and CXCL10 in the liver, thereby facilitating the AIH progression in mice [14]. Therefore, CXCL10, in combination with CXCL9, exhibited a strong potential to identify patients with advanced liver fibrosis [40].

Cytokine IL6 is widely recognized as a pivotal pro-inflammatory and profibrotic factor that drives the progression of liver fibrosis [41]. However, in this study, the opposite results were obtained. The findings demonstrate that IL6 functions in a protective capacity in AILDs. Moreover, emerging evidence suggests that IL6 not only serves as a stimulator of pro-inflammatory cytokines and the acute phase response but also plays a crucial role in liver protection and regeneration. This is supported by observations that IL6 knockout mice display compromised liver regeneration, and inhibition of the IL6 pathway exacerbates liver injury [42]. Furthermore, the activation of Signal Transducer and Activator of Transcription 3 (STAT3) through IL6 signaling plays a crucial role in glycoprotein 130 (gp130)-mediated hepatoprotection in the injured liver [43]. A member of the gp130 cytokine family, OSM, exhibits structural and functional similarities to the IL-6 cytokine family [44]. Therefore, the study revealed that OSM possesses a similar impact on liver function as IL6.

Moreover, IL10 exerts inhibitory effects on macrophages and dendritic cells, leading to the suppression of CD4+ T cell activation and cytokine secretion, along with the facilitation of Treg proliferation and immune regulation [45]. Consequently, IL10 plays a pivotal role in dampening the inflammatory response in liver injury while also contributing to the promotion of autoimmune tolerance and mitigation of liver fibrosis [46]. However, in this study, IL10 exhibited a significant protective effect in AIH and PSC but not in PBC. The inhibitory effects of IL4 and IL10 on inflammation are similar, and increasing their levels can effectively delay the progression of liver fibrosis [47]. A protective effect of IL4 was identified in this study for AIH (OR: 0.68, P<0.01) and PSC (OR: 0.72, P<0.01) but not for PBC (OR: 0.61, P=0.08).

An intestinal hormone, FGF19, reduces bile acid synthesis in the liver by activating the hepatic fibroblast growth factor receptor 4 [48]. In multidrug resistance protein (MDR2)-deficient mice, increased FGF19 expression reduced liver inflammation, alleviated biliary fibrosis, and reversed liver injury [49]. A contrary view has also been reported: in PBC-AIH OS patients with severe cholestasis and a high degree of severity, serum FGF19 levels increase proportionally [50]. The FGF19 augmented secretion under these circumstances is regarded as a defensive, negative feedback mechanism aimed at safeguarding hepatocytes against the cytotoxic effects of bile acids [51]. The findings of our study also demonstrated that elevated concentrations of FGF19 significantly reduced susceptibility to AILDs.

This is the first study to investigate the causal relationship between circulating inflammatory proteins and AILDs using pooled GWAS-level statistics. By aggregating substantial genetic data, this study minimized the possible confounding and reverse causality. However, this study has some limitations. The first step was to use independent SNPs ($P<5\times10^{-5}$) that reached a genome-wide significance level to prevent weak IVs from reducing the validity of the MR study. Moreover, certain SNPs genotypes did not exhibit significant associations with disease outcomes, resulting in missing data points and a potential selection bias in the choice of markers common to AILDs. Notably, the findings of this study may not be generalizable to all populations, as the research only focused on individuals of European descent. Therefore, the conclusions drawn should be made carefully.

Conclusion

In this study, we employed a large-scale sample for exposure and outcome GWAS to conduct MR analysis, aiming to infer causal relationships between circulating inflammatory proteins and AILDs. Our findings revealed distinct associations between various circulating inflammation markers and AILDs. CXCL10, in combination with CXCL9, exhibited a strong potential to predict patients with AILDs. However, the relevance of IL6 as a risk factor for AILDs remains controversial.

Declarations

Ethics approval and consent to participate

- As per the regulations outlined in People's Republic of China's "Notice on the Implementation of Ethical Review Measures for Life Science and Medical Research", our study falls under the exemption criteria specified in Section 4 of the regulation. Therefore, ethics approval was not required for this research, as it met the following conditions:
- **Exemption premise**: This study used only publicly available data, especially summary level data from GWAS, did not involve sensitive personal information, did not cause harm to individuals, and did not compromise their privacy.
- **Exemption provision:** Our research adheres to the exemption circumstances outlined in Section 4 of the regulation: We utilized lawfully obtained publicly available data for our analysis. The data used in this study were fully anonymized, ensuring the privacy and confidentiality of individuals. Our research focuses on analyzing existing data and does not involve interventions, human biological samples, or activities related to reproductive cloning, genetic manipulation, or germ cells.
- Due to the nature of our study and its compliance with the exemption criteria, we did not require explicit ethics approval. And we affirm that this research was conducted in accordance with the applicable laws, regulations, and ethical standards.

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