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ORIGINAL ARTICLE

Clinical and Translational Research

Causal association between 731 immunocyte phenotypes and liver cirrhosis: A bidirectional two-sample mendelian randomization analysis

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Abstract

BACKGROUND

Liver cirrhosis is a progressive hepatic disease whose immunological basis has attracted increasing attention. However, it remains unclear whether a concrete causal association exists between immunocyte phenotypes and liver cirrhosis.

AIM

To explore the concrete causal relationships between immunocyte phenotypes and liver cirrhosis through a mendelian randomization (MR) study.

METHODS

Data on 731 immunocyte phenotypes were obtained from genome-wide association studies. Liver cirrhosis data were derived from the Finn Gen dataset, which included 214403 individuals of European ancestry. We used inverse variable weighting as the primary analysis method to assess the causal relationship. Sensitivity analyses were conducted to evaluate heterogeneity and horizontal pleiotropy.

RESULTS

The MR analysis demonstrated that 11 immune cell phenotypes have a positive association with liver cirrhosis [$P < 0.05$, odds ratio (OR) > 1] and that 9 immunocyte phenotypes were negatively correlated with liver cirrhosis ($P < 0.05$, OR < 1). Liver cirrhosis was positively linked to 9 immune cell phenotypes ($P < 0.05$, OR > 1) and negatively linked to 10 immune cell phenotypes ($P < 0.05$; OR < 1). None

of these associations showed heterogeneity or horizontally pleiotropy ($P > 0.05$).

CONCLUSION

This bidirectional two-sample MR study demonstrated a concrete causal association between immunocyte phenotypes and liver cirrhosis. These findings offer new directions for the treatment of liver cirrhosis.

Key Words: Liver cirrhosis; Immune cell; Immunocyte phenotype; Mendelian analysis; Causal association

Core Tip: The causal relationship between immunocyte phenotypes and liver cirrhosis has not been fully elucidated. This bidirectional two-sample mendelian randomization study identified a significant causal association between 731 immunocyte phenotypes and liver cirrhosis. We found that 20 immunocyte phenotypes were associated with liver cirrhosis ($P < 0.05$), whereas liver cirrhosis was associated with 19 immunocyte phenotypes ($P < 0.05$). None of these associations showed heterogeneity or horizontal pleiotropy ($P > 0.05$). These findings provide novel directions for the treatment of liver cirrhosis.

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INTRODUCTION

Liver cirrhosis represents a chronic and advancing stage of liver disease, characterized by widespread fibrosis and the appearance of pseudolobules as a result of the distortion of normal liver structure by excessive connective tissue. This disease has various aetiologies, and it ultimately leads to multiorgan/system dysfunction[1,2]. It is estimated to be the 11th highest cause of death and the 15th highest contributor to disability-associated life years[3]. The progression from the asymptomatic compensated phase to the symptomatic decompensated phase which is characterized by liver function impairment and portal hypertension results in hospitalization, decreased quality of life, and increased mortality[4,5]. There are currently no treatments that normalize the number and function of liver cells; thus, suppressing the aetiological factor(s) that cause liver inflammation and cirrhosis development is the main method of managing decompensated liver cirrhosis[4]. However, in addition to treatments involving aetiologic factor(s), treatments that can prevent or delay disease progression, complications and multiorgan dysfunction based on the pathophysiologic mechanisms should be identified and implemented[6].

The liver possesses a specialized vascular structure and creates a distinctive immune environment for immune cells[7]. In addition to the sinusoids being composed of macrophages, the liver harbors a diverse population of immune cells, comprising dendritic cells (DCs), innate lymphoid cells, B lymphocytes, and T lymphocytes[8]. Liver inflammation and immune microenvironment changes have been identified as crucial factors in the pathogenesis of cirrhosis. Liver sinusoidal endothelial cells perform a vital function by capturing soluble antigens in a living organism and presenting them to cluster of differentiation (CD) 8 + T cells, resulting in the establishment of tolerance specific to these antigens[9,10]. Hepatic stellate cells (HSCs) have been suggested to present antigens and lead to the activation of CD1d-restricted natural killer T cells (NKTs) and CD4 + and CD8 + T cells[11]. Increasing research has demonstrated that immune cells are pivotal in regulating both the advancement and resolution of liver fibrosis[12,13]. Ramachandran *et al*[14] profiled the transcriptomes of over 100000 single human cells from both healthy and diseased livers, revealing an expansion of a scar-associated macrophage subpopulation expressing *TREM2* + CD9 + during liver fibrosis. Nakamoto *et al*[15] reported that durable CD8 + T-cell-dependent liver disease of moderate severity plays an essential role in the development of liver cirrhosis and hepatocellular carcinoma in a mouse model. Furthermore, Rueschenbaum *et al*[16] demonstrated that adaptive cellular immunity plays a role at a relatively early stage in the development of liver cirrhosis and the capacity of CD4 + and CD8 + T cells to produce proinflammatory cytokines is lower in a prospective cohort study of patients with different stages of liver cirrhosis or acute-on-chronic liver failure than in healthy subjects. All of the abovementioned findings indicated that there is a multifaceted relationship between immune cells and liver cirrhosis. A deeper insight into these relationships might foster the innovation of improved therapeutic modalities and assist in pinpointing patients most likely to respond favorably to immunotherapy. Mendelian randomization (MR) is an important analytical method for inferring causal relationships in epidemiology based on Mendelian genetic principles, which are screened for instrumental variables (IVs) strongly associated with exposure factors by strict criteria to evaluate the relationships between exposure factors and outcomes[17,18]. Previous observational studies have suggested that there are complex interactions between immune cell traits and liver cirrhosis, thus providing evidence for their putative association[16]. This study aimed to elucidate the causal link between 731 distinct immunocyte phenotypes and liver cirrhosis through a comprehensive application of bidirectional two-sample MR analysis.

MATERIALS AND METHODS

Study design

We examined the causal associations between 731 immune cell characteristics and liver cirrhosis *via* a bidirectional two-sample MR analysis. All genetic variations used as IVs must satisfy three fundamental assumptions: (1) IVs are directly associated with the exposure; (2) IVs are unrelated to confounders of the exposure-outcome connection; and (3) IVs do not affect outcome through pathways other than exposure[19]. Figure 1 provides an overview of the study design. The data used in this study were obtained from the Finngen and OPEN genome-wide association studies (GWAS) public databases in this study. This database is publicly accessible, thus eliminating the need for additional ethical approval.

Data sources

Source of immune cell data: The GWAS catalogue (GCST90001391 to GCST90002121) provides summary statistics for all immunologic characteristics[20]. GWASs of immune-related traits involve extensive data derived from 3757 non-overlapping European participants. Through the use of a high-density array generated from Sardinian sequence data, we ascertained approximately 22 million single-nucleotide polymorphisms (SNPs) and examined their associations, taking into account covariates like sex, age, and age squared. In total, 731 immunophenotypic parameters were investigated, comprising 118 absolute cell counts, 389 median fluorescence intensities indicative of surface antigen expression, 32 morphological attributes, and 192 relative cell counts[21].

Source of liver cirrhosis data: We acquired a compendium of GWAS summary statistics pertaining to liver cirrhosis from FinnGen database (https://www.finngen.fi/en). This dataset encompassed a total of 214403 samples (case number = 213592, control number = 811), and the GWAS integrated over 21306350 phenotypic datapoints linked to liver cirrhosis, thereby uncovering in excess of 23 million independent SNPs.

Selection of IVs

These standards must be fulfilled by the candidate IVs. First, SNPs with a P value < 1^{e-05} were needed. Second, we excluded any SNPs with significant linkage disequilibrium (r^2 < 0.001 and kb < 10000) to ensure that the analysis results would not be compromised by SNP interdependencies. Moreover, the PhenoScanner online tool was used to exclude SNPs related to immune cell and liver cirrhosis confounders. In addition, to avoid bias from weak IVs and evaluate the statistical power of the relationship between each SNP and the exposures, we utilized the F statistic [calculated as $F = R^2 (N-2)/(1-R^2)$, with R^2 being the variance in exposure explained by the genetic variant, approximated as $2 \times EAF \times (1 - EAF) \times \beta$; here, EAF is the effect allele's frequency, β is the genetic effect estimate on exposure, and N is the sample size from the exposure GWAS][22,23]. IVs with an F statistic > 10 were considered strong instruments. Finally, harmonization of the SNP exposures and outcomes was conducted to ensure that the effect alleles for each SNP on the exposure matched their corresponding effect alleles on the outcome. We excluded SNPs that had mismatched alleles from our analysis. Additionally, palindromic SNPs and those with ambiguous genotyping were identified and excluded during the harmonization process.

Statistical analysis

The MR analyses in this study were performed using R 4.4.0 software (https://www.r-project.org/) using the two sample MR package. First, significant SNPs were identified according to the above criteria. Moreover, the exposure and outcome data were harmonized, and the two-sample MR effect was calculated. Five distinct MR analysis techniques were employed: Inverse variance weighted (IVW), weighted median, simple mode, weighted mode, and MR-Egger regression. The IVW serves as the primary analytical approach, which involves computing a weighted average of the ratio estimates for each genetic variant. Next, sensitivity analyses were conducted to test potential pleiotropy, such as heterogeneity and horizontal multiple validity. We employed Cochran's Q test to measure the heterogeneity among the IVs and utilized MR-Egger regression for weighted linear regression with intercepts to detect potential horizontal pleiotropy within the IVs. Heterogeneity and pleiotropy were considered not present if the P value was larger than 0.05. In addition, a leave-one-out analysis was conducted by iteratively excluding each genetic variant from the analysis and recalculating the causal effect to determine if any single SNP exerted a substantial influence on the overall causal effect. The outcomes are expressed as odds ratios (OR) accompanied by 95% confidence intervals. Statistical significance was defined as a P value less than 0.05.

RESULTS

Causal effects of immunocytes on liver cirrhosis

From the GWAS data encompassing 731 immunocyte phenotypes, we identified candidate IVs. Our analysis confirmed that the F-statistic for these IVs was above 10, ruling out the likelihood of weak instrument bias. All SNPs with positive results are shown in Table 1. IVW analysis revealed 20 immune cell phenotypes with potential causal relationships with liver cirrhosis. The following 11 phenotypes of immune cells were positively associated with the development of liver cirrhosis (OR > 1, P < 0.05). Treg panel: CD28 + CD45 receptor alpha (RA) + CD8 bright% T cell; B-Cell panel: CD25 on memory B cell, CD25 on sw mem, CD38 on CD20-, and B-cell-activating factor (BAFF)-R on CD20-; Myeloid cell panel: CD33 on CD66b ++ myeloid cell, CD33 on Im myeloid-derived suppressor cells (MDSC), CD33 on CD33dim human

Table 1 Number of single-nucleotide polymorphisms screened in each step

ID exposure	Panel	Immune traits	Number of SNPs after LD	Number of SNPs after F > 10	Number of final IVs
Ebi-a-GCST90001433	B cell	IgD- CD27-% lymphocyte	18	18	18
Ebi-a-GCST90001706	B cell	BAFF-R on IgD + CD38- naive	29	29	28
Ebi-a-GCST90001762	B cell	CD20 on IgD +	23	23	19
Ebi-a-GCST90001790	B cell	CD25 on memory B cell	27	27	24
Ebi-a-GCST90001830	B cell	BAFF-R on CD20-	14	14	14
Ebi-a-GCST90001793	B cell	CD25 on sw mem	21	21	20
Ebi-a-GCST90001809	B cell	CD38 on CD20-	20	20	19
Ebi-a-GCST90002110	Myeloid cell	HLA DR on CD33dim HLA DR + CD11b +	24	24	23
Ebi-a-GCST90001954	Myeloid cell	CD33 on basophil	23	23	22
Ebi-a-GCST90001952	Myeloid cell	CD33 on Mo MDSC	21	21	21
Ebi-a-GCST90001951	Myeloid cell	CD33 on CD66b + + myeloid cell	19	19	18
Ebi-a-GCST90001521	Myeloid cell	CD33 bright HLA DR + CD14 dim% CD33 bright HLA DR +	26	26	25
Ebi-a-GCST90001953	Myeloid cell	CD33 on CD33 dim HLA DR-	21	21	19
Ebi-a-GCST90001955	Myeloid cell	CD33 on Im MDSC	25	25	22
Ebi-a-GCST90002031	Treg	CD39 on CD39 + secreting Treg	24	24	23
Ebi-a-GCST90001901	Treg	CD28 on CD39 + resting Treg	23	23	22
Ebi-a-GCST90001688	Treg	CD28 + CD45 RA + CD8 bright% T cell	112	91	88
Ebi-a-GCST90001630	TBNK	CD8 bright NKT AC	27	27	26
Ebi-a-GCST90002076	TBNK	SSC-A on NK	24	24	23
Ebi-a-GCST90002014	cDC	CCR2 on CD62L++ myeloid DC	15	15	14

TBNK: T cells, B cells, and natural killer cells; ID: Identification; cDC: Conventional dendritic cells; CD: Cluster of differentiation; DR: Dweller region; AC: Absolute count; SSC-A: Side scatter-A; LD: Linkage disequilibrium; BAFF: B-cell-activating factor; HLA: Human leukocyte antigen; MDSC: Myeloid-derived suppressor cells; NKT: Natural killer T cells; NK: Natural killer; CCR2: C-C motif chemokine receptor 2; SNPs: Single-nucleotide polymorphisms; IVs: Instrumental variables.

leukocyte antigen (HLA) dweller region (DR)-, CD33 on basophil, CD33 bright HLA DR + CD14dim %CD33 bright HLA DR +, CD33 on monocytic (Mo) MDSC. The remaining 9 phenotypes were negatively associated with the progression of liver cirrhosis (OR < 1, P < 0.05). Conventional DC (cDC) panel: C-C motif chemokine receptor 2 (CCR2) on CD62L++ myeloid DC; Treg panel: CD39 on CD39 + secreting Treg, CD28 on CD39 + resting Treg; B panel: BAFF-R on IgD + CD38- naive, IgD- CD27- % lymphocyte, CD20 on IgD +; Myeloid cell: HLA DR on CD33dim HLA DR + CD11b +; T cells, B cells, and natural killer cells (TBNK) panel: CD8 bright NKT absolute count (AC), side scatter (SSC)-A on NK. The results of IVW analysis are provided in Figure 2, and the weighted median, simple mode, weighted mode, and MR-Egger regression methods used for MR analysis are depicted in Supplementary Figure 1.

Forward sensitivity analyses

Table 2 presents the results from our sensitivity analysis, which confirmed that there was no significant heterogeneity present (P > 0.05 for the Q test) or directional pleiotropy (P > 0.05 for the MR-Egger intercept method) for 20 immune cell immunocytes in the MR analysis of liver cirrhosis patients. Moreover, the leave-one-out method and funnel plots indicated that the data were robust, as shown in Supplementary Figure 2 and Supplementary Figure 3.

Causal effects of liver cirrhosis on immunocytes

The GWAS data for liver cirrhosis patients were screened for IVs, and all selected IVs exhibited F values exceeding 10, indicating a lower possibility of weak instrument bias. The SNPs that showed positive associations are summarized in Table 3.

Table 2 Forward mendelian randomization sensitivity analysis

Exposure panel	Exposure traits	Inverse variance weighted		MR-Egger	
		Q value	*P* value	Intercept	*P* value
B cell	IgD- CD27-% lymphocyte	11.20	0.846	0.008	0.707
B cell	BAFF-R on IgD+ CD38- naive	19.98	0.831	0.002	0.880
B cell	CD20 on IgD+	18.76	0.407	-0.004	0.662
B cell	CD25 on memory B cell	21.52	0.549	-0.002	0.854
B cell	BAFF-R on CD20-	9.74	0.715	-0.005	0.795
B cell	CD25 on sw mem	17.72	0.541	0.004	0.771
B cell	CD38 on CD20-	14.73	0.680	0.012	0.521
Myeloid cell	HLA DR on CD33dim HLA DR+ CD11b+	25.66	0.266	-0.011	0.303
Myeloid cell	CD33 on basophil	29.56	0.101	0.014	0.248
Myeloid cell	CD33 on Mo MDSC	23.26	0.276	-0.007	0.490
Myeloid cell	CD33 on CD66b+ myeloid cell	18.20	0.376	-0.029	0.065
Myeloid cell	CD33 bright HLA DR+ CD14 dim% CD33 bright HLA DR+	29.63	0.197	0.011	0.294
Myeloid cell	CD33 on CD33 dim HLA DR-	18.45	0.427	0.018	0.184
Myeloid cell	CD33 on Im MDSC	30.80	0.077	0.013	0.354
Treg	CD39 on CD39+ secreting Treg	10.76	0.978	-0.005	0.554
Treg	CD28 on CD39+ resting Treg	21.59	0.423	0.013	0.220
Treg	CD28+ CD45 RA+ CD8 bright% T cell	80.46	0.676	0.009	0.252
TBNK	CD8 bright NKT AC	25.19	0.452	-0.014	0.225
TBNK	SSC-A on NK	27.35	0.198	0.004	0.771
cDC	CCR2 on CD62L+ myeloid DC	9.06	0.768	0.011	0.547

TBNK: T cells, B cells, and natural killer; cDC: Conventional dendritic cells; CD: Cluster of Differentiation; AC: Absolute count; BAFF: B-cell-activating factor; HLA: Human leukocyte antigen; MDSC: Myeloid-derived suppressor cells; NKT: Natural killer T cells; NK: Natural killer; CCR2: C-C motif chemokine receptor 2; SNPs: Single-nucleotide polymorphisms; IVs: Instrumental variables; MR: Mendelian randomization.

Table 3 Number of Single-nucleotide polymorphisms screened in each step

ID exposure	Number of SNPs after LD	Number of SNPs after F > 10	Number of final IVs
Finn-b-CIRRHOSIS_BROAD	31	31	31

ID: Identification; LD: Linkage disequilibrium; SNPs: Single-nucleotide polymorphisms; IVs: Instrumental variables.

The results of IVW for the causal effects of liver cirrhosis on immunocytes are provided in Figure 3, and other analytical methods are provided in Supplementary Figure 4. The immune cell immunocytes with a positive association were as follows (OR > 1, $P < 0.05$): B-cell panel: CD20 on CD24 + CD27+ and CD20 on sw mem; TBNK panel: CD4 + %leukocyte, forward scatter (FSC)-A on B cell, and SSC-A on B cell; Myeloid cell panel: Im MDSC% CD33 dim HLA DR- CD66b-, Im MDSC AC; Monocyte panel: *CX3CR1* on monocyte, *CX3CR1* on CD14- CD16+ monocyte. The remaining 10 immunocytes of immune cells with a negative correlation were as follows (OR < 1, $P < 0.05$): B Cell Panel: IgD + CD38 bright AC, IgD + CD38 dim AC, IgD + AC, naive-mature B cell AC, IgD + CD24- AC; cDC panel: CD62L-plasmacytoid DC AC; TBNK panel: CD3- lymphocyte% leukocyte; Myeloid cell: CD33- HLA DR + AC; Treg panel: CD8 on CD28- CD8 bright, CD28 + CD45RA- CD8 dim AC.

Reverse sensitivity analysis

The results of the sensitivity analysis (Table 4) showed that there was no heterogeneity ($P > 0.05$ for the Q test) or directional pleiotropy ($P > 0.05$ for MR-Egger's intercept method) in the 19 immunocytes from the MR analysis of liver

Table 4 Reverse mendelian randomization sensitivity analysis

Outcome panel	Outcome traits	Inverse variance weighted		MR-Egger	
		Q value	*P* value	intercept	*P* value
B cell	IgD+ CD38 bright AC	35.51	0.224	-0.014	0.401
B cell	IgD+ CD38 dim AC	30.73	0.429	-0.030	0.068
B cell	IgD+ AC	33.15	0.316	-0.028	0.094
B cell	Naive-mature B cell AC	27.47	0.599	-0.022	0.160
B cell	IgD+ CD24- AC	29.82	0.475	-0.019	0.250
cDC	CD62L- plasmacytoid DC AC	29.39	0.497	0.029	0.075
Myeloid cell	Im MDSC AC	29.23	0.506	0.019	0.249
Myeloid cell	Im MDSC% CD33 dim HLA DR- CD66b-	24.09	0.768	0.009	0.568
Myeloid cell	CD33- HLA DR+ AC	30.39	0.446	-0.004	0.790
TBNK	CD4+% leukocyte	16.12	0.982	0.007	0.670
TBNK	CD3- lymphocyte% leukocyte	17.10	0.971	0.013	0.443
Treg	CD28+ CD45RA- CD8 dim AC	37.39	0.166	0.000	0.997
B cell	CD20 on CD24+ CD27+	22.52	0.834	0.026	0.231
B cell	CD20 on sw mem	32.59	0.341	0.020	0.381
TBNK	FSC-A on B cell	25.61	0.695	0.017	0.345
Monocyte	*CX3CR1* on monocyte	39.69	0.111	0.002	0.891
Monocyte	*CX3CR1* on CD14- CD16+ monocyte	19.80	0.922	0.008	0.641
TBNK	SSC-A on B cell	32.70	0.336	-0.003	0.844
Treg	CD8 on CD28- CD8 bright	37.59	0.106	-0.003	0.877

TBNK: T cells, B cells, and natural killer cells; DC: Dendritic cells; AC: Absolute count; FSC-A: Forward scatter-A; SSC-A: Side scatter-A; CD: Cluster of differentiation.

cirrhosis patients. Moreover, the leave-one-out method and funnel plots indicated that the results were robust, as shown in Supplementary Figure 5 and Supplementary Figure 6.

DISCUSSION

We first performed a bidirectional MR investigation, which examined the causal associations between 731 immune cell phenotypes and liver cirrhosis based on a large amount of publicly available genetic data. We found that 20 immunophenotypes had significant causal effects on liver cirrhosis, and liver cirrhosis had a causal effect on 19 immunophenotypes. Moreover, no single immune cell phenotype was observed to have a bidirectional causal association.

B cells play diverse roles in liver cirrhosis by mediating antigen presentation and cytokine release, which trigger the activation of various immune cell phenotypes[24]. In our study, CD25 on memory B cell, CD25 on sw mem cell, CD38 on CD20- cell, and BAFF-R on CD20- cell in the B-cell panel were shown to be associated with increased liver cirrhosis risk. Moreover, we also found that the risk of liver cirrhosis decreased with increasing proportions of BAFF-R on IgD + CD38- naive cell, IgD- CD27-% lymphocyte cell, and CD20 on IgD + cell. BAFF has been identified as a crucial regulator of peripheral B-cell survival, homeostasis, and antibody-mediated responses[25,26]. Yang *et al*[27] reported that BAFF levels are elevated in individuals with chronic hepatitis B virus (HBV) infection and that BAFF upregulation in patients with liver cirrhosis is more prominent. The serum levels of BAFF are also elevated in patients with non-alcoholic steatohepatitis (NASH) and are correlated with the degree of fibrosis[28]. Furthermore, there is evidence that CD20 + B cells are also related to the occurrence and progression of cirrhosis and that the depletion of CD20 + B cells plays a crucial role in improving cirrhosis[29,30].

Tregs constitute a population of CD4 + T helper cells that mainly express the transcription factors forkhead box P3 and signal transducer and activator of transcription 5. The number of Tregs is increased in patients with liver disorders[12]. In the liver, *CXCR6* + CD8 T cells were found to exhibit reduced activity of the *FOXO1* transcription factor. However, they are abundant in patients with NASH and are related to self-directed immune responses[31]. Our study revealed that CD28 + CD45RA + CD8 bright% T cell increased the risk of liver cirrhosis, and CD39 on CD39 + secreting Treg and CD28 on CD39 + resting Treg decreased the risk of liver cirrhosis. A study based on a bile duct ligation rat model suggested

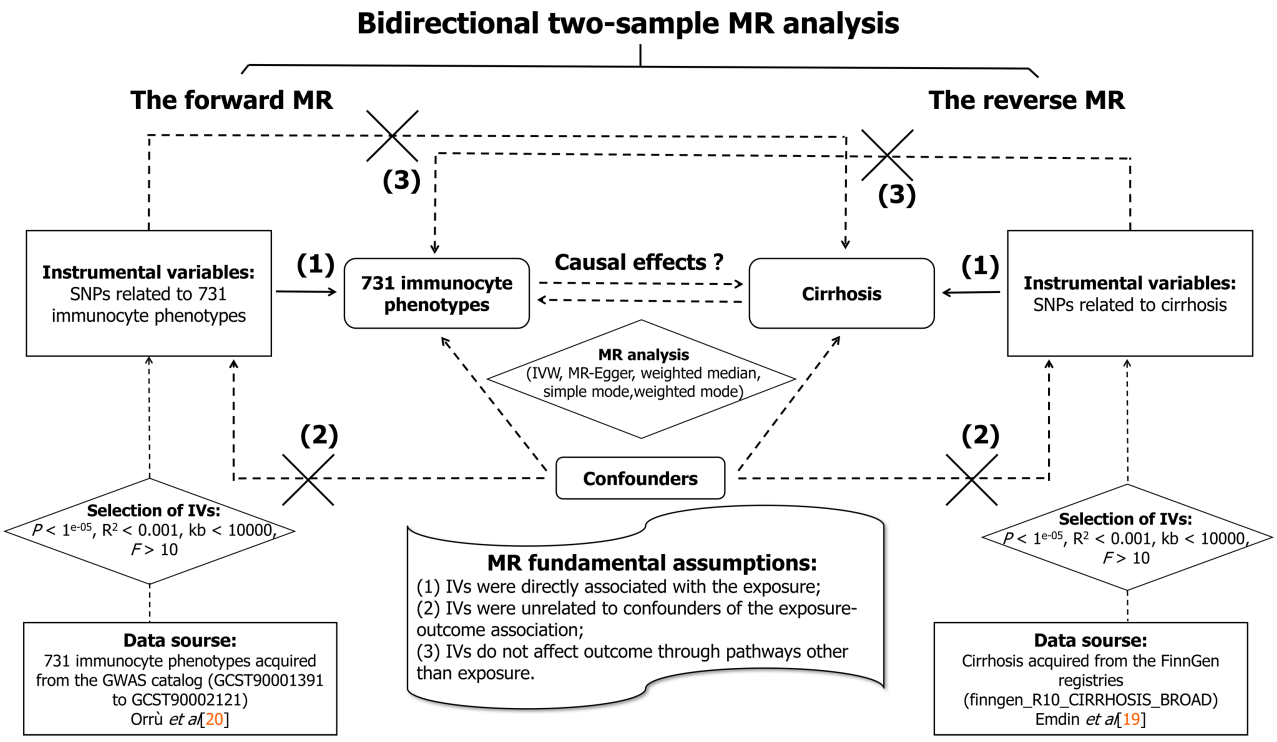

Figure 1 Diagram of this bidirectional mendelian randomization study design. The arrows indicate bidirectional causal relationships between liver cirrhosis and immunocyte phenotypes, and the causal pathway is blocked if a "fork" is placed in the arrowed line. IVW: Inverse variance weighting; MR: Mendelian randomization; SNPs: Single-nucleotide polymorphisms; IVs: Instrumental variables.

Exposure panel	Immune cell	Methods	nsnp	β	SE	*P* value	OR (95%CI)
B cell	IgD- CD27- %lymphocyte	Inverse variance weighted	18	-0.117	0.037	0.002	0.89 (0.83 - 0.96)
B cell	BAFF-R on IgD+ CD38- naive	Inverse variance weighted	28	-0.035	0.017	0.043	0.97 (0.93 - 1.00)
B cell	CD20 on IgD+	Inverse variance weighted	19	-0.033	0.016	0.040	0.97 (0.94 - 1.00)
B cell	CD25 on memory B cell	Inverse variance weighted	24	0.053	0.022	0.017	1.05 (1.01 - 1.10)
B cell	BAFF-R on CD20-	Inverse variance weighted	14	0.070	0.033	0.032	1.07 (1.01 - 1.14)
B cell	CD25 on sw mem	Inverse variance weighted	20	0.079	0.035	0.026	1.08 (1.01 - 1.16)
B cell	CD38 on CD20-	Inverse variance weighted	19	0.090	0.046	0.049	1.09 (1.00 - 1.20)
Myeloid cell	HLA DR on CD33dim HLA DR+ CD11b+	Inverse variance weighted	23	-0.039	0.016	0.014	0.96 (0.93 - 0.99)
Myeloid cell	CD33 on basophil	Inverse variance weighted	22	0.028	0.013	0.031	1.03 (1.00 - 1.06)
Myeloid cell	CD33 on Mo MDSC	Inverse variance weighted	21	0.034	0.017	0.042	1.03 (1.00 - 1.07)
Myeloid cell	CD33 on CD66b++ myeloid cell	Inverse variance weighted	18	0.042	0.017	0.015	1.04 (1.01 - 1.08)
Myeloid cell	CD33br HLA DR+ CD14dim %CD33br HLA DR+	Inverse variance weighted	25	0.047	0.023	0.041	1.05 (1.00 - 1.10)
Myeloid cell	CD33 on CD33dim HLA DR-	Inverse variance weighted	19	0.053	0.016	0.001	1.05 (1.02 - 1.09)
Myeloid cell	CD33 on Im MDSC	Inverse variance weighted	22	0.054	0.020	0.006	1.06 (1.02 - 1.10)
Treg	CD39 on CD39+ secreting Treg	Inverse variance weighted	23	-0.032	0.014	0.025	0.97 (0.94 - 1.00)
Treg	CD28 on CD39+ resting Treg	Inverse variance weighted	22	-0.030	0.015	0.044	0.97 (0.94 - 1.00)
Treg	CD28+ CD45RA+ CD8br %T cell	Inverse variance weighted	88	0.009	0.003	0.002	1.01 (1.00 - 1.01)
TBNK	CD8br NKT AC	Inverse variance weighted	26	-0.080	0.033	0.016	0.92 (0.86 - 0.99)
TBNK	SSC-A on NK	Inverse variance weighted	23	-0.068	0.029	0.021	0.93 (0.88 - 0.99)
cDC	CCR2 on CD62L+ myeloid DC	Inverse variance weighted	14	-0.092	0.034	0.006	0.91 (0.85 - 0.97)

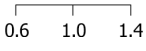

Figure 2 Forest plots showed the causal associations between liver cirrhosis and immune cell traits. CI: Confidence interval; OR: Odds ratio; TBNK: T cells, B cells, and natural killer cells; cDC: Conventional dendritic cells; CD: Cluster of differentiation; BAFF: B-cell-activating factor; HLA: Human leukocyte antigen; DR: Dweller region; AC: Absolute count; MDSC: Myeloid-derived suppressor cells; NKT: Natural killer T cells; NK: Natural killer; CCR2: C-C motif chemokine receptor 2.

that Tregs protect the liver from cholestasis and fibrosis[32]. Additional research indicates that Tregs are essential for protecting the liver from damage in the chronic phase of HBV infection, aiding in the prevention of the disease's progression to cirrhosis and hepatocellular carcinoma[33]. However, Langhans *et al*[34] demonstrated that Tregs activated HSCs and promoted liver fibrogenesis by producing interleukin (IL)-8 in chronic hepatitis C virus (HCV). We postulate that the various roles of Tregs in the pathogenesis of liver cirrhosis might be due to alterations in protein synthesis on their cell surface in response to distinct aetiological factors and immune microenvironments, resulting in the secretion of a

Outcome panel	Immune cell	Methods	nsnp	β	SE	*P* value	OR (95%CI)
B cell	IgD+ CD38dim AC	Inverse variance weighted	31	-0.062	0.023	0.008	0.94 (0.90 - 0.98)
B cell	IgD+ CD24- AC	Inverse variance weighted	31	-0.053	0.024	0.030	0.95 (0.90 - 0.99)
B cell	Naive-mature B cell AC	Inverse variance weighted	31	-0.051	0.025	0.042	0.95 (0.90 - 1.00)
B cell	IgD+ CD38br AC	Inverse variance weighted	31	-0.051	0.025	0.046	0.95 (0.90 - 1.00)
B cell	IgD+ AC	Inverse variance weighted	31	-0.048	0.024	0.044	0.95 (0.91 - 1.00)
B cell	CD20 on CD24+ CD27+	Inverse variance weighted	31	0.048	0.024	0.043	1.05 (1.00 - 1.10)
B cell	CD20 on sw mem	Inverse variance weighted	31	0.051	0.024	0.033	1.05 (1.00 - 1.10)
TBNK	CD3- lymphocyte %leukocyte	Inverse variance weighted	31	-0.052	0.025	0.033	0.95 (0.90 - 1.00)
TBNK	CD4+ %leukocyte	Inverse variance weighted	31	0.049	0.024	0.042	1.05 (1.00 - 1.10)
TBNK	FSC-A on B cell	Inverse variance weighted	31	0.052	0.026	0.048	1.05 (1.00 - 1.11)
TBNK	SSC-A on B cell	Inverse variance weighted	31	0.065	0.026	0.014	1.07 (1.01 - 1.12)
Myeloid cell	CD33- HLA DR+ AC	Inverse variance weighted	31	-0.075	0.037	0.041	0.93 (0.86 - 1.00)
Myeloid cell	Im MDSC %CD33dim HLA DR- CD66b-	Inverse variance weighted	31	0.085	0.032	0.009	1.09 (1.02 - 1.16)
Myeloid cell	Im MDSC AC	Inverse variance weighted	31	0.088	0.034	0.010	1.09 (1.02 - 1.17)
Treg	CD8 on CD28- CD8br	Inverse variance weighted	31	-0.063	0.027	0.020	0.94 (0.89 - 0.99)
Treg	CD28+ CD45RA- CD8dim AC	Inverse variance weighted	31	-0.052	0.026	0.043	0.95 (0.90 - 1.00)
Monocyte	CX3CR1 on monocyte	Inverse variance weighted	31	0.053	0.024	0.030	1.05 (1.01 - 1.11)
Monocyte	CX3CR1 on CD14- CD16+ monocyte	Inverse variance weighted	31	0.066	0.025	0.008	1.07 (1.02 - 1.12)
cDC	CD62L- plasmacytoid DC AC	Inverse variance weighted	29	-0.065	0.029	0.024	0.94 (0.89 - 0.99)

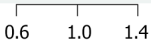

Figure 3 Forest plots showed the causal associations between immune cell traits and liver cirrhosis. CI: Confidence interval; OR: Odds ratio; TBNK: T cells, B cells, and natural killer cells; cDC: Conventional dendritic cells; CD: Cluster of differentiation; AC: Absolute count; DR: Dweller region; FSC-A: Forward scatter-A; SSC-A: Side scatter-A; MDSC: Myeloid-derived suppressor cells.

broad spectrum of cytokines.

MDSCs encompass a heterogeneous mixture of myeloid progenitor cells and immature myeloid cells, and can maintain their suppressive function through the induction of Tregs[35]. MDSCs from inflamed portal tracts and patients with advanced inflammation and hepatic fibrosis are significantly elevated[36]. We found that six MDSC phenotypes, including CD33 on CD66b + myeloid cells, CD33 on Mo MDSCs, CD33 on basophils, CD33 bright HLA DR + CD14 dim% CD33 bright HLA DR +, CD33 on CD33 dim HLA DR-, and CD33 on Im MDSCs have positive causal associations with liver cirrhosis, and HLA DR on CD33dim HLA DR + CD11b + has a negative association with liver cirrhosis. One study revealed an increase in monocytic MDSCs with a phenotype of HLA-DR-/Low CD33 + CD11b + CD14 + CD15- in patients with liver inflammatory diseases compared to healthy controls[36]. In addition, previous studies have shown that the accumulation of CD33 + MDSCs is detected in patients with HCV infection and results in reactive oxygen species-mediated suppression of T-cell responsiveness, which may lead to liver cirrhosis[37]. These observations align with our MR outcomes.

NK cells demonstrate antifibrotic effects by targeting and eliminating HSCs, acting as a critical first line of defense against viral hepatitis. They augment the antiviral immune response by directly killing virus-infected cells or by promoting antigen-specific T cell responses through the release of interferon-γ and tumor necrosis factor-α[38,39]. Our MR analysis findings also suggested that CD8 bright NKT AC and SSC-A on NK cells play a role in improving liver cirrhosis.

DCs, a subset of mononuclear phagocytes that display major histocompatibility complex class II molecules, can be classified into myeloid or classical DCs and plasmacytoid DCs in the blood[40,41]. Our study revealed that CCR2 on CD62L++ myeloid DC was negatively associated with liver cirrhosis. CD62L, an adhesive molecule from the selection family, facilitates interactions with endothelial cells and migration into tissues. Compared with controls, cirrhotic patients presented a marked decrease in cDCs and greater percentages of monocytes expressing CD62L[40,42].

Additionally, we found that the causally associated immunocyte phenotypes were not inversely causally associated. Notably, the presence of liver cirrhosis was associated with increased CD20 on CD24+, CD27+; CD20 on sw mem; CD4 +% leukocyte; FSC-A on B cell; SSC-A on B cell; Im MDSC %CD33dim HLA DR- CD66b-; Im MDSC AC; *CX3CR1* on monocyte; and *CX3CR1* on CD14- CD16+ monocyte levels. Doi *et al*[43] reported that CD27+ memory B cells were markedly less common in cirrhotic patients and that CD70 upregulation, tumour necrosis factor beta secretion, and IgG production were observed. The proportion of total B cells, characterized by a mature phenotype, was found to be elevated, whereas the percentage of memory B cells was significantly reduced in individuals with decompensated cirrhosis compared with healthy individuals. Furthermore, the serum concentrations of IL-10, IL-21, and IL-4 are substantially decreased in patients with decompensated cirrhosis[44].

The role of various immune cell phenotypes in the pathogenesis of liver cirrhosis is complex and multifaceted. Depending on the underlying aetiology and stage of liver cirrhosis, distinct immune cell phenotypes are generated under the guidance of related genes, leading to the secretion of either pro- or anti-liver fibrosis cytokines, which in turn perform diverse functions in the development of liver cirrhosis. Our study offers novel insights into the immune cells participating in the immune response culminating in liver cirrhosis, potentially paving the way for enhanced treatment strategies and aiding in the identification of patients who would derive the greatest benefit from immunotherapy.

We conducted bidirectional two-sample MR analyses utilizing extensive GWAS datasets with large sample sizes, which significantly enhanced the statistical efficiency of our study. By employing genetic variants as IVs and applying various MR techniques, we were able to make robust causal inferences. These methods mitigate the potential impact of horizontal pleiotropy and confounding factors, reinforcing the reliability of our results. There are several limitations in our study. Firstly, we used a screening threshold of $P < 1 \times 10^{-5}$ to identify IVs, which was not strong enough, although a comprehensive assessment of the association between the immune cell phenotype and liver cirrhosis was conducted. Second, the study was based on a European database and genetically differentiated from other populations, so the conclusions cannot be generalized to other ethnic groups. Additionally, owing to the unavailability of individual data, we were unable to perform further stratified analysis of the population. Moreover, confounders could not be eliminated, although we conducted a sensitivity analysis to exclude SNPs associated with potential confounders as much as possible. Finally, to make clinical inferences, these findings need to be further validated in extensive clinical trials.

CONCLUSION

In summary, our research identified causal links between immunocyte phenotypes and liver cirrhosis through comprehensive bidirectional MR analysis, thus highlighting the intricate interplay between the immune system and liver cirrhosis and providing insight into early interventions and therapeutic strategies for liver cirrhosis.

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FOOTNOTES

Author contributions: Li Y and Quan X designed the study, reviewed the literature, and wrote the manuscript; Tai Y and Wu YT performed the data analyses; Wei B downloaded the data from the genome-wide association studies database, and Wu H participated in the drafting and editing of the manuscript; All the authors have read and approved the final manuscript for submission.

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