Unravelling the Link Between Primary Sclerosing Cholangitis and Sepsis: A Mendelian Randomization Study

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Abstract

Background: autoimmune diseases (ADS) are associated with sepsis. This study aims to investigate the causalities between ADs and sepsis using Mendelian randomization (MR). Methods: we extracted single-nucleotide polymorphisms (SNPs) closely associated with 10 ADs, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), type 1 diabetes (T1D), multiple sclerosis (MS), inflammatory bowel disease (IBD), celiac disease (CD), psoriasis (PsO), primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), and ulcerative colitis (UC) from the GWAS. Two-sample MR analysis was conducted using GWAS data from the UK Biobank to assess the association between the liability of each ad and sepsis and sepsis-related 28-day mortality. The inverse variance-weighted (IVW) method was used as the primary analysis. If sig-nificant causal relationships are found (considering multiple comparisons) in the univariate MR analysis, multivariate MR (MVMR) analysis is performed to adjust for body mass index (BMI) and smoking. A series of sensitivity analyses were conducted to validate the robustness of the results. Results: after adjusting for multiple testing, MR analysis revealed that PSC patients are responsible for increased susceptibility to sepsis using the IVW method (OR:1.033, 95%CI:1.007-1.060, PFDR = 0.020). Further sensitivity analyses validated the robustness of the above association. Even after adjusting for BMI and smoking, the MVMR-IVW still displayed a positive correlation(OR:1.043, 95%CI:1.022-1.064, P-value for IVW = 3.32E-05) between PSC patients and susceptibility to sepsis. However, no significant causal relationship was observed between SLE, RA, T1D, MS, IBD, CD, PsO, PBC, and UC with susceptibility to sepsis or short-term death risk. Conclusions: our MR analysis revealed a genetic susceptibility of PSC to sepsis. However, no causal relationship was observed between SLE, RA, T1D, MS, IBD, CD, PsO, PBC, and UC with suscep-tibility to sepsis or short-term death risk. Keywords: autoimmune diseases; sepsis; primary sclerosing cholangitis; Mendelian randomization

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Autoimmune diseases (ADS) are associated with sepsis. This study aims to investigate the causalities between ADs and sepsis using Mendelian randomization (MR).

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We extracted single-nucleotide polymorphisms (SNPs) closely associated with 10 ADs, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), type 1 diabetes (T1D), multiple sclerosis (MS), inflammatory bowel disease (IBD), celiac disease (CD), psoriasis (PsO), primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), and ulcerative colitis (UC) from the GWAS. Two-sample MR analysis was conducted using GWAS data from the UK Biobank to assess the association between the liability of each ad and sepsis and sepsis-related 28-day mortality. The inverse variance-weighted (IVW) method was used as the primary analysis. If significant causal relationships are found (considering multiple comparisons) in the univariate MR analysis, multivariate MR (MVMR) analysis is performed to adjust for body mass index (BMI) and smoking. A series of sensitivity analyses were conducted to validate the robustness of the results.

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After adjusting for multiple testing, MR analysis revealed that PSC patients are responsible for increased susceptibility to sepsis using the IVW method (OR:1.033, 95%CI:1.007-1.060, PFDR = 0.020). Further sensitivity analyses validated the robustness of the above association. Even after adjusting for BMI and smoking, the MVMR-IVW still displayed a positive correlation(OR:1.043, 95%CI:1.022-1.064, P -value for IVW = 3.32E-05) between PSC patients and susceptibility to sepsis. However, no significant causal relationship was observed between SLE, RA, T1D, MS, IBD, CD, PsO, PBC, and UC with susceptibility to sepsis or short-term death risk.

Conclusions:

Our MR analysis revealed a genetic susceptibility of PSC to sepsis. However, no causal relationship was observed between SLE, RA, T1D, MS, IBD, CD, PsO, PBC, and UC with susceptibility to sepsis or short-term death risk.

Keywords:

Autoimmune diseases, sepsis, primary sclerosing cholangitis, Mendelian randomization

Introduction

Sepsis is the dysregulated immune response to infection that leads to life-threatening organ dysfunction,[1] which is a medical emergency associated with high mortality and long-term disability in survivors.[2] Based on epidemiological data, there are over 30 million cases of sepsis worldwide annually, with an overall mortality rate of about 17%.[3] This creates a substantial burden on healthcare systems globally. Consequently, identifying underlying pathologies that could trigger sepsis might point to avenues for new treatments.

Autoimmune diseases (ADs) arise from an abnormal host immune response against substances and tissues usually present in the body. Sepsis results from a dysregulated host response to an infection associated with an imbalance between pro- and anti-inflammatory cytokines.[4] Certain ADs have been linked to alterations in the expression levels of pro-inflammatory and anti-inflammatory cytokines, which are involved in the pathophysiology of sepsis.[5] ADs may impact the occurrence and progression of sepsis through the modulation of cytokine levels.

The relationship between ADs and sepsis has been studied to some extent, yet the results remain uncertain. Previous research evidence has shown that certain ADs, such as systemic lupus erythematosus(SLE), Type 1 Diabetes(T1D), multiple sclerosis(MS), and celiac disease(CD), may be associated with an increased risk

of sepsis.[6-9]Furthermore, one study suggested a decreased short-term mortality risk of sepsis with certain ADs, while another study found an increased mortality risk of sepsis with rheumatoid arthritis(RA).[5, 10] However, epidemiological studies suggest associations between sepsis and ADs; whether these associations are causal remains unknown. The epidemiological research investigating the connection between sepsis and ADs is vulnerable to confounding factors, particularly immunosuppressive therapy for ADs, which hampers the ability to establish causal relationships.

Mendelian randomization (MR) allows exploring the causality between an exposure of interest (here, an autoimmune disease) and an outcome (here, sepsis) using an instrumental variables (IVs) approach.[11] In MR, genetic variants strongly associated with exposure and satisfying specific assumptions are used as IVs to study the causal association with an outcome. Since these variants are randomly assigned at conception, it could reduce bias due to environmental confounders. As such, the MR design is analogous to a randomized controlled trial. In the current study, we employed MR to investigate the potential causal relationship between ADs (SLE, RA, T1D, MS, inflammatory bowel disease (IBD), CD, psoriasis (PsO), primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), ulcerative colitis (UC)) and susceptibility to and short-term mortality risk from sepsis using summary statistics from the most extensive available genome-wide association studies (GWAS) in European populations for the above traits.

Methods

Study design

In order to perform any MR study, the single nucleotide polymorphisms (SNPs) used as instruments should satisfy three criteria: (1) instrumental variables were strongly associated with the exposure; (2)instrumental variables were independent of the confounders of exposure and outcome; and (3) instrumental variables only affect the outcome via the exposure and not through any other pathways, including selection bias (i.e., the exclusion restriction assumption) (Figure 1).[12]

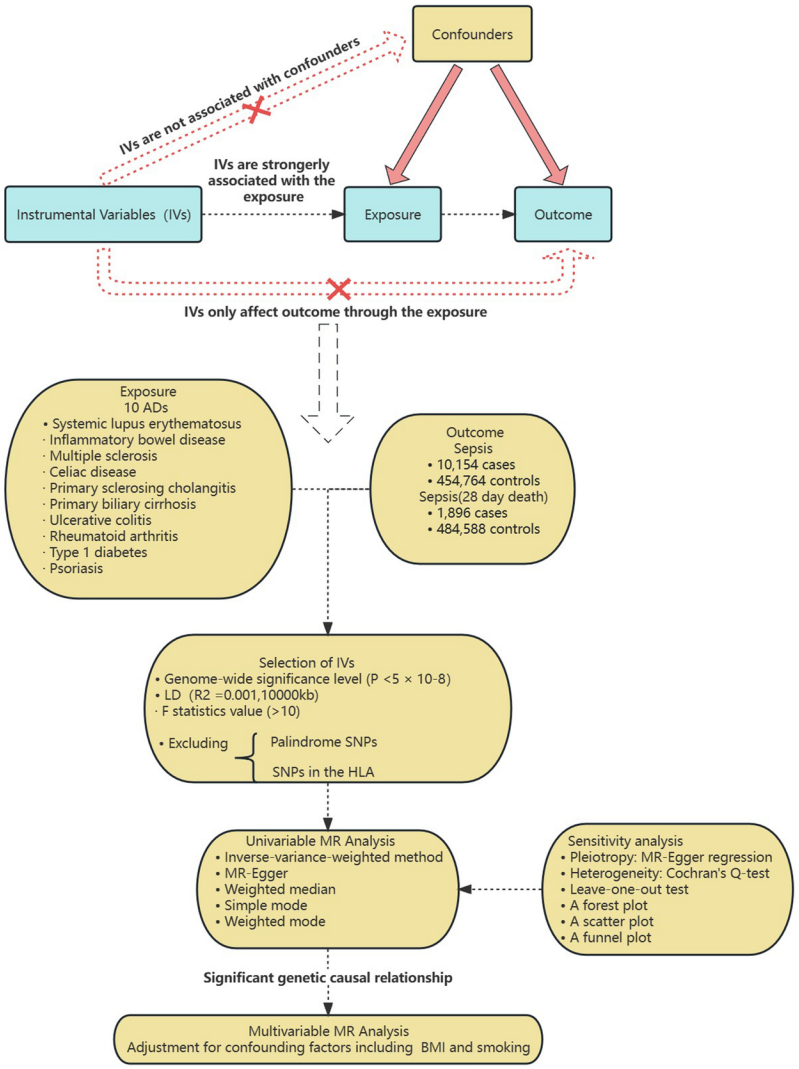

Figure 1 . Study design

ADs autoimmune disease, MR mendelian randomization, LD linkage disequilibrium

Data Source

To conduct our MR analyses, we used summary-level data from the largest publicly available GWAS for each trait (Table 1). Specifically, the 10 ADs GWAS summary statistics are available from prior research and the FinnGen consortium R5 release data.[13] Additionally, the UK Biobank provides the GWAS data for sepsis,[14] encompassing two phenotypes: sepsis and sepsis-related 28-day mortality. These findings, as mentioned above, are publicly available in the Integrative Epidemiology Unit (IEU) GWAS database(https://gwas.mrcieu.ac.uk/).[15]Detailed information regarding recruitment procedures and diagnostic criteria is detailed in the original publications. Furthermore, all cases and control groups included in these studies were exclusively individuals with European ancestry. Moreover, there is minimal overlap between the populations analyzed in the respective GWAS datasets.

Table 1. The characteristics of the MR-GWAS summary statistics data.

Trait
Exposures
SLE
IBD
MS
CD
PSC
PBC
UC
RA
T1D
PsO
Outcomes
Sepsis
Sepsis(28 day death)
Confounders
BMI
Smoking initiation

SLE systemic lupus erythematosus, IBD inflammatory bowel disease, MS multiple sclerosis, CD celiac disease, PSC primary

Mendelian randomization

Selection of Genetic Instruments

For selecting genetic instruments from each of the ten exposure GWASs, we used the default settings in the R package TwoSampleMR.[15, 24] The selection process for eligible genetic instrumental variables proceeded as outlined below: (1) SNPs associated with each exposure trait (SLE, RA, T1D, MS, IBD, CD, PsO, PSC, PBC, UC) were identified using a genome-wide significance threshold of $P < 5\times10^{-8}$; (2) a clumping procedure was performed with a threshold of $R^2 < 0.001$ and a clumping window of > 10,000 kb to account for linkage disequilibrium; (3) only SNPs with a high F statistics value (>10), indicating a substantial estimated effect size on the outcome, were included, while weak genetic variants were excluded from the analysis; F statistics for each SNP were calculated using the equation: $F = R^2 \times (N - 2)/(1 - R^2)$; (4) palindrome SNPs were excluded from the analysis; (6) SNPs within the human leukocyte antigen (HLA) gene were excluded from accounting for the influence of HLA on autoimmune diseases and sepsis[25].

Mendelian randomization analyses

We conducted 20 two-sample MR analyses using the TwoSampleMR R package[15, 24]. After clumping IVs, we performed Steiger filtering to exclude SNPs, explaining more variance in the outcome than in the exposure. Then, we employed five different methods (including random-effects inverse variance-weighted (IVW), MR-Egger regression, weighted median, simple mode, and weighted mode methods to combine the effect of different IVs. IVW was selected as the primary analysis approach among these methods due to its accuracy when all selected SNPs serve as valid instrumental variables. The remaining four methods were used as supplementary analyses in the MR framework. Specifically, we calculated the Wald ratio for each SNP and used IVW to meta-analyze the individual effects, yielding a conclusive βestimate. This estimate was then transformed into an odds ratio (OR)[26-28].

Body mass index (BMI) and smoking are significant confounding factors in the relationship between ADs and sepsis[29-32]. Therefore, in evaluating the independent causal effects of ADs on susceptibility and the short-term mortality risk from sepsis, we conducted a multivariable Mendelian randomization (MVMP) analysis to adjust for BMI and smoking. The genetic predictors for BMI and smoking initiation were derived from published GWAS summary statistics data(Table 1), respectively, from UK Biobank and GWAS and Sequencing Consortium of Alcohol and Nicotine Use (GSCAN) GWAS meta-analyses[33].

Sensitivity Analyses

We performed a comprehensive sensitivity analysis for the two-sample MR method, incorporating heterogeneity testing, pleiotropy testing, scatter plots, forest plots, leave-one-out analysis (LOO), and funnel plots. Firstly, to assess heterogeneity in the IVW and MR-Egger methods, we computed Cochran's Q statistic, and the significance of Cochran's Q test (p <0.05 indicates heterogeneity) was evaluated[34]. Secondly, we examined potential violations of the instrumental variable assumption due to directional pleiotropy by assessing the intercept of the MR-Egger regression (p <0.05 indicates directional pleiotropy). Next, scatter plots were employed to investigate the potential causal relationship between ADs and susceptibility to sepsis and short-term mortality risk. Additionally, forest plots were utilized to illustrate the effect sizes of individual SNPs of ADs on sepsis. LOO analysis was conducted to assess the influence of each SNP on the overall MR results. Lastly, funnel plots were employed to detect any potential asymmetry.

Statistical Analysis

The causal estimate is the odds ratio (OR) with a 95% confidence interval (CI). To address the issue of multiple testing, we adjusted the statistical significance of the MR effect estimates using the Benjamini-Hochberg false discovery rate (FDR) procedure with a threshold of less than 5%. Analyses were conducted in R (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria). MR analyses were performed using the TwoSampleMR (version 0.5.6)[24] and MendelianRandomization (version 0.7.0) R packages.

Results

Characteristics of Genetic Instrumental Variables

All the genetic instrumental variables selected in our study had an$F$ -statistics of >10, indicating the absence of weak instruments. An overview of the instrumental variables used in each MR analysis is provided in Supplementary Table S1-S10.

Univariable Mendelian Randomization Analysis

Figure 2 and Figure 3 show the causal effects of 10 ADs on susceptibility and short-term mortality risk of sepsis estimated by MR analysis using the IVW method. More specifically, in the general population, genetically predicted T1D was suggestively associated with a lower risk of susceptibility to sepsis (Figure 2; OR:0.972, 95%CI:0.952-0.993, P -value for IVW = 0.009), but was not associated with the short-term mortality risk of sepsis. In addition, genetically predicted PSC was associated with a higher risk of susceptibility to sepsis (Figure 2; OR:1.033, 95%CI:1.007-1.060,P -value for IVW = 0.014) but was not associated with the short-term mortality risk of sepsis. The weighted median and weighted mode methods supported the positive causal relationship between PSC and susceptibility to sepsis (Supplementary Table S11). Our IVW methods revealed that the liability to RA, SLE, IBD, MS, CD, PsO, PBC, and UC does not affect the susceptibility and short-term mortality risk of sepsis, consistent with the findings of other MR methods (Supplementary Table S11-S12, Figure 2, and Figure 3).

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Figure 2 . Univariable Mendelian randomization estimates for each autoimmune disease and sepsis.

Forest plot of MR estimates of 10 autoimmune diseases with sepsis using the multiplicative random-effects inverse variance weighting method. MR estimates are reported as odds ratios per unit of log odds of each autoimmune disease examined. IBD inflammatory bowel disease, RA rheumatoid arthritis, UC ulcerative colitis, MS multiple sclerosis, SLE systemic lupus erythematosus, PBC primary biliary cirrhosis, PSC primary sclerosing cholangitis, T1D type 1 diabetes, PsO psoriasis, CD celiac disease.

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Figure 3 . Univariable Mendelian randomization estimates for each autoimmune disease and sepsis (28-day death).

Forest plot of MR estimates of 10 autoimmune diseases with sepsis using the multiplicative random-effects inverse variance weighting method. MR estimates are reported as odds ratios per unit of log odds of each autoimmune disease examined. IBD inflammatory bowel disease, RA rheumatoid arthritis, UC ulcerative colitis, MS multiple sclerosis, SLE systemic lupus erythematosus, PBC primary biliary cirrhosis, PSC primary sclerosing cholangitis, T1D type 1 diabetes, PsO psoriasis, CD celiac disease.

The results obtained from the Benjamini-Hochberg correction indicate a significant causal relationship between T1D and susceptibility to sepsis (IVW FDR-corrected $P = 0.020$). Similarly, a robust causal relationship between PSC and susceptibility to sepsis (IVW FDR-corrected$P = 0.020$) was also observed.

Multivariable Mendelian Randomization Analysis

BMI and smoking are significant confounding factors in the relationship between ADs and sepsis. To assess the robustness of the causal effects, we performed an MVMR analysis, adjusting for BMI and smoking. The results of the MVMP analysis, which accounted for BMI and smoking, are presented in Supplementary Table S13-S14. After adjusting for BMI and smoking, the IVW results of the MVMR analyses revealed a significant correlation between PSC (OR:1.043, 95%CI:1.022-1.064, P -value for IVW = 3.32E-05) and susceptibility to sepsis. However, BMI and smoking may partially confound the association between T1D and susceptibility to sepsis (OR:0.999, 95%CI:0.971-1.029, P -value for IVW = 0.969).

Sensitivity Analyses

There was no evidence of horizontal pleiotropy between the instrumental variables and the outcome (all P-values for the MR-Egger intercept test were greater than 0.05). However, heterogeneity was observed in Cochran's Q test analysis between susceptibility to PSC and sepsis (MR-Egger, Q P -value=9.7E-03; IVW, Q P -value=1.5E-02). Despite heterogeneity, we employed the random-effects IVW method as the primary analysis for the merged heterogeneity. Subsequently, the scatter plot indicates a potential causal relationship (Supplementary Figure S1-S19 and Figure 4).

Additionally, the forest plot illustrates the effect size of each SNP concerning susceptibility to sepsis and the risk of short-term mortality. Furthermore, the leave-one-out (LOO) analysis revealed that the causality estimates were not driven by any single SNP. Finally, the funnel plot of the MR analysis showed that the data points were evenly distributed around the funnel plot, indicating no substantial asymmetry(Supplementary Figure S1-S19 and Figure 4).

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Figure 4 . The funnel plot (A), scatter plot (B), forest plot (C), and leave-one-out plot (D) illustrate the genetic susceptibility to sepsis risk in primary sclerosing cholangitis.

The funnel plot shows the symmetrical distribution of the selected SNPs (Figure 4A). The scatter plot demonstrates the causal relationship between PSC and increased susceptibility to sepsis (Figure 4B). The forest plot displays the effect size of each SNP on susceptibility to sepsis and indicates a causal relationship between PSC and increased susceptibility to sepsis (Figure 4C). The remaining figure indicates no SNP has an estimated causal association (Figure 4D).

Discussion

Our univariate MR analysis examined the causal genetic relationships between 10 ADs and susceptibility to sepsis and the short-term mortality risk. Multiple comparisons showed a negative correlation between T1D and susceptibility to sepsis (OR:0.972, 95%CI:0.952-0.993, IVW FDR-corrected $P = 0.020$). Conversely, a positive correlation was observed between PSC and susceptibility to sepsis (OR:1.033, 95%CI:1.007-1.060, IVW FDR-corrected $P = 0.020$). These findings were further supported by sensitivity analysis. However, no ADs were found to be responsible for the short-term mortality risk from sepsis. The MVMR analysis revealed a robust causal relationship between PSC and susceptibility to sepsis (OR: 1.043, 95%CI: 1.022-1.064, IVWP -value = 3.32E-05). However, the association between T1D and susceptibility to sepsis lost statistical significance after accounting for BMI and smoking. Consequently, the observed causal relationship between T1D and susceptibility to sepsis in the univariate MR analysis may be susceptible to confounding factors and lacks statistical significance.

The findings of this MR study contradict the results of some observational studies. Previous observational studies faced limitations such as potential confounding variables, selection bias, potential disease-death structure, and heterogeneous dropout groups. Multiple observational studies have reported an increased susceptibility to sepsis in patients with ADs.[6-9] A retrospective study specifically identified patients with MS as having an elevated susceptibility to sepsis.[35] However, BMI and smoking are common risk factors for ADs and sepsis.

Consequently, this study did not account for potential confounders associated with this relationship. One potential source of selection bias is the inclusion of participants with ADs who receive long-term immunosuppressive therapy. These individuals are more likely to use immunosuppressive drugs, which can compromise their host immunity. Additionally, improvements in medical care have led to a longer lifespan for patients with ADs, but they also experience a higher burden of comorbidities, which increases their susceptibility to sepsis in observational studies. A retrospective study revealed a significant rise in sepsis hospitalization rates among SLE patients between 1996 and 2011,[9] at a greater rate than the general population. This finding suggests that more SLE patients live longer but face more complications, including end-stage renal disease, vascular diseases, chronic lung disease, or diabetes, heightening their risk of infection and susceptibility to sepsis. Therefore, patients with ADs and comorbidities frequently display increased susceptibility to sepsis, representing another potential source of selection bias. A cohort study examining the short-term mortality risk of ADs in sepsis revealed a protective effect of ADs on the short-term mortality risk of sepsis.[5] Importantly, this protective effect remained independent of the long-term use of immune-modulating drugs. However, it is essential to acknowledge that this study was also susceptible to diagnostic bias, as the prevalence of ADs among the participants was estimated to be at the higher end of the general population's estimate of ADs. Furthermore, the study participants were generally of advanced age, which is known to elevate the risk of sepsis. Like a randomized controlled trial, an MR study mitigates confounding and reverse causation by leveraging the genetic assignment of exposure from parents to offspring. This approach enables a more robust and dependable inference of causal effects.

Our study identified a negative correlation between T1D and susceptibility to sepsis in the univariable MR analysis. However, after adjusting for BMI and smoking, this relationship lost statistical significance, aligning with previous MR studies.[36]This may suggest that T1D is not responsible for susceptibility to sepsis.

A population-based retrospective cohort study has revealed that PSC in hospitalized patients plays a significant role in developing sepsis and bacteremia.[37] Our study confirmed that individuals with PSC have an increased occurrence of sepsis due to genetic susceptibility. The potential mechanisms underlying the association between PSC and sepsis can be explained through three pathways. First, numerous studies have reported that in patients with PSC, Klebsiella pneumoniae has been identified as a microorganism that disrupts the intestinal epithelial barrier, leading to bacterial translocation in the gut.[38] This pathway may play a crucial role in developing sepsis in PSC patients, and the significant involvement of Enterobacteriaceae further supports this finding.[37]Secondly, PSC can disrupt the ecological balance in the gut-liver axis, adversely affecting gut microbiota and activating NLRP3 inflammasomes. This, in turn, leads to compromised intestinal barrier function, bacterial translocation, and intensified NLRP3-mediated innate immune responses in

the liver.[39] Finally, endotoxins enter the portal vein and lead to more significant liver damage, which may be one of the pathogenic mechanisms leading to liver sepsis or bacteremia. Third, a study has shown that the number of mucosal-associated invariant T cells (MAIT Cells) in peripheral blood is significantly reduced in PSC patients.[40] However, MAIT cells have specific antimicrobial properties and play a role in the early stages of bacterial infection.[41] At the same time, related studies have shown that the proportion of MAIT cells in sepsis patients is significantly reduced,[42] which may imply a common pathogenic mechanism between PSC and sepsis.

Despite these findings, this study has various limitations. Firstly, some ADs were not included due to a lack of relevant GWAS studies, such as Sjögren's syndrome and giant cell arteritis. Secondly, the study may have potential selection bias as only participants with certain ADs who have undergone long-term immunosuppressive therapy were selected, as these patients have lower survival rates.[43] Thirdly, this study is based on a European population; thus, the results may not necessarily be generalizable to other folks.

Additionally, some of our MR analyses may need more power to detect minor effects due to limited exposure variance explained by SNPs or sample size. For this situation, we need to exclude ambiguous or palindromic SNPs to enhance the ability of our MR studies to detect causality. Further larger-scale GWAS studies for these autoimmune traits will also enhance the ability of future MR studies.

Conclusion

Our study found no convincing evidence of a causal relationship between SLE, RA, T1D, MS, IBD, CD, PsO, PBC, UC, and susceptibility to sepsis or short-term death risk. This may suggest that the autoimmune processes in these ADs may not underlie sepsis. However, PSC has a genetic responsibility for the increased risk of sepsis, but there is no genetic responsibility for the increased risk of short-term death due to sepsis. The association results observed in clinical or epidemiological studies could be subject to long-term verification and observation.

Authors' contributions

Authors Ze-jun Chen, Fan-ye Wu, and Zheng-ran Li contributed equally to the study. Ze-jun Chen, conception and design of the study; Ze-jun Chen, Fan-ye Wu, and Zhengran Li made the schedule and supervised the whole project. Ze-jun Chen, Zi-ran Zhang, and Yu-xin Sun performed the data gathering and analysis. Zi-jin Wang, Logistic support. Fan-ke Meng and Xun Xia, conception and design of the study. All authors critically reviewed the article and approved the final manuscript.

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Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Data availability

All prominent figures and tables are shown in the manuscript. More data that support the findings of this study are available on reasonable request from the corresponding author (Fan-ke Meng,*yishuihan123433@163.com*, Xun Xia, xiaxun2101@163.com)

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