Causal associations between autoimmune disease and sepsis: a two-sample Mendelian randomization study

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Abstract

Background

Recent observational studies have revealed an inconclusive correlation between autoimmune disease (AID) and sepsis, accompanied by an uncertain understanding of the causal relationship between the two. The objective of this study was to investigate the causality between AID and sepsis by employing a two-sample Mendelian randomization (MR) approach.

Methods

A genome-wide significant threshold ($P < 5 \times 10^{-8}$) was achieved in order to identify single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) for various common types of AID, such as Crohn's disease (CD), ulcerative colitis (UC), systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), and ankylosing spondylitis (AS). Subsequently, the selected SNPs were assessed in relation to three categories of sepsis, namely sepsis, sepsis (critical care), and sepsis (28-day death in critical care). An inverse-variance weighted (IVW) estimation of MR was conducted, followed by sensitivity analysis on multiple dimensions.

Results

In the context of the study, a significant causal correlation was observed between genetic susceptibility and sepsis (28-day death in critical care) in patients with CD (OR, 1.246; 95% CI, 1.090–1.423; $P = 0.0012$). On the other hand, UC patients showed a slightly higher risk for sepsis, although this difference was not statistically significant (OR, 1.031; 95% CI, 0.988–1.064; $P = 0.064$). Additionally, there was evidence of a suggestive significant association between genetic liability to SLE (OR, 1.025; 95% CI, 1.009–1.043; $P = 0.0029$) and MS (OR, 1.038; 95% CI, 1.002–1.076; $P = 0.041$) with sepsis, but not specifically with sepsis (critical care) and sepsis (28-day death in critical care). However, there was no significant association of the genetic vulnerability to RA or AS with any of three types of sepsis.

Conclusion

Our study offers genetic evidence that supports a substantial causal relationship between CD and sepsis (28-day death in critical care), as well as a suggestive significant association between SLE/MS and sepsis. To enhance the specificity and objectivity of future research findings, it is recommended to specify the types of AID and the severity of sepsis. Furthermore, the identified genetic risk loci may serve as promising targets for drug development.

Introduction

Sepsis, a global public health issue with significant morbidity and mortality rates, is responsible for the majority of infection-related deaths worldwide.\[1, 2\] This clinical syndrome arises from an immune response imbalance triggered by an infection.\[1, 3\] The sudden release of cytokines by the innate immune system during sepsis can result in multiorgan failure, septic shock, and immune-related complications.\[1, 3, 4\] The overactive pro-inflammatory response, considered a major contributor to sepsis mortality, has been the focus of therapeutic
interventions. However, the effectiveness of treatments targeting this response has been shown to be unsuccessful in human trials.\[5–7\]

In a septic condition, inadequate clearance of pathogens and toxins may lead to the escalation of a localized infection into systemic inflammation. Therefore, accurate identification of pathogens is crucial for the host to mount an efficient immune response against the insult. However, inadvertent recognition of autoantigens can have catastrophic implications, giving rise to AID, wherein the immune response erroneously targets diverse host tissues.\[8, 9\] Depending on the specific antigens involved, various forms of AID, such as CD, UC, SLE, MS, RA, AS, etc., can manifest. Despite differences in their onset and clinical presentation, both AID and sepsis share a common characteristic: dysregulated immune function. Given the intricate nature of the immune system and its extensive interconnections within the body, it is reasonable to hypothesize that immune disorders caused by AID can impact those associated with sepsis.\[10\] Actually, AID has been reported by several researchers to lead to worse clinical outcomes among sepsis patients as a result of the modulated immune response associated with AID and their treatment.\[5–7, 11\] However, the available experimental evidences substantiating a causal relationship between AID and sepsis are limited and occasionally contradictory. Notably, a recent study conducted by Sheth et al at a single medical center suggested that AID may be linked to a reduced risk-adjusted short-term mortality in individuals with sepsis (OR: 0.73; 95% CI: 0.57–0.93).\[6\] Nevertheless, the underlying factors responsible for these improved clinical outcomes remain unclear. Furthermore, investigations into septic patients within a population-based IBD cohort revealed that the risk-adjusted in-hospital mortality rate was lower for individuals with CD (OR, 0.78; 95% CI, 0.63–0.97), while those with UC exhibited a higher mortality rate (OR, 1.61; 95% CI, 1.35–1.93).\[12\] Taking a closer look at the outcomes of sepsis in individuals with AID could offer valuable insights into how the immune system copes with infection. Consequently, there is an immediate need to undertake fresh investigations and employ innovative approaches to analyzing patient records.

In observational studies, the utilization of genetic variation as IVs in MR analysis is increasingly prevalent, as it enables the elucidation of direct causal relationships between exposure and outcomes while minimizing the influence of confounding factors.\[13\] In this particular study, we employed TSMR analysis to explore the potential causality between several commonly occurring AID and sepsis, in which sepsis was categorized into three types based on clinical outcomes, namely sepsis, sepsis (critical care), and sepsis (28-day death in critical care), which roughly corresponded to mild, moderate, and severe sepsis, respectively. Our findings revealed that IBD had varying impacts on sepsis outcomes. Specifically, there was a significant causal association between the genetic susceptibility of CD and sepsis (28-day death in critical care). On the other hand, UC exhibited a slightly higher risk for sepsis, although this association was not statistically significant. Furthermore, there was a suggestive significant association between SLE and MS with sepsis. However, no significant causal associations was observed between RA and AS with any of the three types of sepsis.

**Materials and Methods**

**Study design**

The analysis of the TSMR was depicted in Fig. 1. In brief, the utilization of genetic variants as IVs necessitated adherence to three crucial prerequisites. Firstly, the genetic variants must exhibit a strong association with the exposure of interest, as evidenced by attaining genome-wide significance ($P<5\times10^{-8}$) and meeting the F-statistic threshold. Secondly, these genetic variations should not demonstrate any linkage with potential confounding factors, thereby avoiding horizontal pleiotropy. Lastly, the influence of the genetic variants on the outcome was
solely mediated through the exposure of interest. To obtain the necessary summary data, published GWAS pertaining to the exposure of interest and sepsis were utilized in this study.

**Data sources for AID**

The summary statistics of AID obtained from recently published datasets were presented in Table 1 and Supplementary Table 1, involving 149519 participants from Europe.[14–17] In brief, the GWAS assessed six common AID phenotypes, including CD (n = 20883), UC (n = 27432), SLE (n = 14267), MS (n = 38582), RA (n = 25708) and AS (n = 22647).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>SNPs used in MR study</th>
<th>SNPs after removing SNPs associated with confounders</th>
<th>Proxy SNP</th>
<th>Sample size</th>
<th>Population</th>
<th>GWAS</th>
<th>Year</th>
<th>PMID</th>
</tr>
</thead>
<tbody>
<tr>
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<td>120/120/120</td>
<td>98/98/98</td>
<td>8</td>
<td>20883</td>
<td>European</td>
<td>Liu et al</td>
<td>2015</td>
<td>26192919</td>
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<tr>
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<td>71/71/71</td>
<td>8</td>
<td>27432</td>
<td>European</td>
<td>Liu et al</td>
<td>2015</td>
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<tr>
<td>SLE</td>
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<td>38/38/38</td>
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<td>14267</td>
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<td>Beecham et al</td>
<td>2013</td>
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<tr>
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<tr>
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<td>European</td>
<td>Cortes et al</td>
<td>2013</td>
<td>23749187</td>
</tr>
</tbody>
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**Selection of IVs**

The first hypothesis of the MR analysis was tested using the PINK CLUMBING algorithm, with the following parameters: $R^2$ threshold of 0.001, window size of 10 Mb, and a significance level of $P<5\times10^{-8}$. Independent SNPs associated with six AID were selected based on these criteria. To assess the effectiveness of the selected SNPs, the F-statistic was calculated using the following formula: . The $R^2$ value represented the proportion of variability in AID explained by the selected SNPs, while the sample size (N) indicated the number of subjects included in the GWAS. A F-statistic greater than 10 indicated a low risk of weak instrument bias in the MR analysis.[18]

**Data sources for sepsis**

From the UK Biobank, we extracted GWAS summary statistics regarding sepsis (10,154 cases versus 454,764 controls), sepsis (critical care) (1,380 cases versus 429,985 controls), and sepsis (28-day death in critical care) (347
cases and 431,018 controls). Supplementary Table 1 presented a detailed description of each dataset used in the analysis.

**Statistical analysis**

This study utilized a TSMR approach to examine the influence of AID on sepsis. The Wald estimates were employed to estimate the impact of AID on sepsis after extracting the necessary data and harmonizing the effect alleles across GWASs. To account for potential measurement error, the delta method was employed to adjust the causal relationship between AID and sepsis.[19, 20] The IVW method was used as part of the primary analysis to evaluate the final effect estimate. Additionally, an analysis of the MR effects based on each method was shown visually in scatter plots.[21]

In the IVW analysis, the presence of SNPs with pleiotropic effects can introduce bias into causal estimates. We evaluated the heterogeneity of different SNPs in the fixed effect IVW analysis by calculating Cochran's Q.[21] The detection of heterogeneity, indicated by a Cochran's Q $P$ value less than 0.05, suggested the presence of horizontal pleiotropy. In cases where potential horizontal pleiotropy was suspected, the random-effects IVW method was employed. To identify potential pleiotropy, we conducted an MR-Egger intercept test, where a $P$ value less than 0.05 for the intercept indicated significant pleiotropic bias.[22]

In order to enhance the robustness of our findings, we conducted a variety of sensitivity analyses, including simple median analysis, weighted median analysis, MR-Egger regression analysis, MR Pleiotropy Summary (MR-PRESSO) analysis, and the leave-one-SNP-out method.[22, 23] It was important to note that even if all SNPs were considered unreliable, the MR-Egger regression method could still produce reliable estimates, albeit with reduced statistical power compared to the IVW method.[22] Additionally, we evaluated $I^2_{GX}$ to investigate the potential presence of weak IVs bias in the MR-Egger regression analysis. The risk of bias was considered to be low when the $I^2_{GX}$ value exceeds 95%.[24] In order to ensure the reliability of our findings, we utilized Phenoscanner and the GWAS catalog to examine each selected SNP and its proxies for any previously established associations ($P < 5 \times 10^{-6}$) with relevant confounders or sepsis. If such associations were confirmed, the selected SNPs were excluded from the analysis as a precautionary measure against potential confounding effects. The confounders considered in this study encompassed cancer, cholesterol levels, type 1 diabetes, body mass index, and coronary heart disease. Subsequently, the MR analysis described earlier was repeated after taking out SNPs that were linked to confounders or sepsis.

The statistical significance was determined by considering a $P$ value less than 0.05 on both sides. To account for multiple comparisons, the Bonferroni-correction was employed, resulting in a corrected threshold of 0.0028 (0.05 / (6×3)). The analysis in this study utilized R software (version 3.5.4; www.r-project.org) and three R packages specifically designed for MR: "Mendelian Randomization", "MRPRESSO", and "Two-Sample MR".

**Results**

A summary of the characteristics of correlated SNP for several common AIDs was presented in Table 1 and Supplementary Table 1. A total of 120, 86, 40, 46, 9, and 25 independent SNPs that achieved genome-wide significance were extracted for CD, UC, SLE, MS, RA, and AS, respectively (Supplementary Table 2–7). The majority of these SNPs were available in the GWAS of sepsis, while any SNPs that were not available in the GWAS were substituted with proxy-SNPs (Supplementary Table 2–7). Among the selected SNPs, the F statistics exceeded 10 (ranging from 30 to 1460) (Supplementary Table 2–7). PhenoScanner analysis allowed us to identify 22, 15, 2, 6, 4,
and 7 selected SNPs that appeared to have an association with confounding factors or sepsis in the context of CD, UC, SLE, MS, RA, AS, respectively (Supplementary Table 8).

We used random-effects IVW methods because Cochran's Q test in Supplementary Table 9 revealed significant heterogeneity ($P < 0.05$) in several subgroup (Supplementary Table 9). The IVW analysis demonstrated that different types of AID had varying effects on the outcomes of three sepsis types (Fig. 2). Specifically, the genetic susceptibility of CD was found to be significantly causally associated only with sepsis (28-day death in critical care) (OR, 1.246; 95% CI: 1.090–1.423; $P = 0.0012$), but not with sepsis (OR, 1.012; 95% CI: 0.987–1.038; $P = 0.354$) and sepsis (critical care) (OR, 1.065; 95% CI: 0.997–1.139; $P = 0.062$) (Fig. 3). In contrast to CD, UC showed slightly, yet statistically insignificant, higher risk for sepsis (OR, 1.031; 95% CI, 0.988–1.064; $P = 0.064$) (Fig. 3). Moreover, there was a suggestive significant association between genetic liability to SLE (OR, 1.025; 95% CI, 1.009–1.043; $P = 0.0029$) and MS (OR, 1.038; 95% CI, 1.002–1.076; $P = 0.041$) with sepsis, but not with sepsis (critical care) and sepsis (28-day death in critical care) (Fig. 4). However, there was no significant association observed between AS and RA and any of the three types of sepsis (Fig. 5).

In sensitivity analysis, the confirmation of the causal association between CD and sepsis (28-day death in critical care) was achieved through the weighted median, simple median, MR-PRESSO, (Supplementary Table 10–12) and leave-one-SNP-out method (Supplementary Fig. 1–3). Similarly, the causal association between SLE and sepsis was confirmed by employing the MR-Egger, MR-PRESSO, (Supplementary Table 10–12) and leave-one-SNP-out method (Supplementary Fig. 1–3). Additionally, the causal association between MS and sepsis was established by employing the MR-Egger, weighted median, MR-PRESSO, (Supplementary Table 10–12) and leave-one-SNP-out method (Supplementary Fig. 1–3). In the MR-Egger regression, the $I^2_{GX}$ for each AID was found to be greater than 0.98, suggesting a low likelihood of bias from weak IVs (Supplementary Table 13–14). It is worth noting that the presence of directional pleiotropy was solely observed in the association between RA and sepsis, which has the potential to influence the obtained results (Supplementary Table 13–14). Supplementary Figs. 4–6 exhibited scatter plots that depicted the MR effect according to each method.

**Discussion**

A TSMR analysis was used in our study to determine the causal link between AID and different types of sepsis. Firstly, the impact of IBD on sepsis outcomes was found to be differential. Specifically, the genetic susceptibility of CD was significantly and causally linked to sepsis (28-day death in critical care), whereas UC exhibited a slightly higher risk for sepsis, albeit statistically insignificant. Secondly, a suggestive significant association between SLE and sepsis with MS with sepsis was observed. Thirdly, no significant associations were identified between RA/AS and any of the three types of sepsis. Collectively, these findings provided evidence that certain AID can causally influence the outcomes of specific sepsis types.

When the body experiences an infection, the resulting inflammatory response leads to varying levels of fluctuation in pro-inflammatory and anti-inflammatory cytokines.[1, 3] Insufficient clearance of pathogens and toxins can lead to the escalation of a localized infection into a severe systemic inflammatory response. Therefore, it is crucial to accurately identify and promptly eliminate pathogens. Accidental recognition of autoantigens can result in detrimental outcomes, such as the development of AID, where the immune response become directed against the host.[8] AID encompasses a range of conditions, including CD, UC, SLE, MS, RA, AS, and others, in which the immune response malfunctions and targets normal substances or tissues within the body.[9] The levels of inflammatory cytokines exhibit variability based on the specific AID.[1, 3, 4] This variability in cytokine levels among individuals
with autoimmune conditions may impact the outcomes of sepsis patients. It has been hypothesized that AID contributed to poorer clinical outcomes in sepsis patients due to alterations in immune reactivity associated with AID and its immune-related treatments.[6, 7, 11] However, recent studies have yielded divergent and even contradictory findings across different types of AID.[5, 6, 8, 12, 25] Not to mention confirming the causal relationship between AID and sepsis, which could have been achieved through MR.

IBD are characterized as chronic, relapsing-remitting inflammatory disorders affecting the intestine.[26] Individuals with IBD are at a higher risk of experiencing infectious complications, leading to increased hospitalizations and mortality rates.[26, 27] Several disease- and treatment-related factors, such as aging, severity of illness, compromised barrier function of the inflamed intestine, and impairment of immune dysfunction caused by malnutrition, contribute to the heightened susceptibility to infections in IBD patients.[27, 28] Furthermore, the administration of steroids, immunomodulators, and biological agents for the treatment of IBD has been found to be associated with an elevated risk of serious infections and opportunistic infections.[12, 28, 29] The occurrence of sepsis is a significant concern in the management of patients with IBD. Early evidence from a case report by Foster KJ et al suggested that individuals with UC frequently experienced sepsis.[30] However, recent research has indicated that the age of 65 or older, rather than the presence of IBD or the use of IBD-related medications, was the primary factor associated with the increased incidence of sepsis in IBD patients.[28] In direct opposition, a longitudinal study spanning 9 years conducted by Colbert JF et al revealed that sepsis patients with CD exhibited more favorable outcomes in comparison to the control group, whereas those with UC experienced significantly poorer outcomes.[12] However, Sheth M et al. noted that neither CD nor UC was linked to a significant reduction in 30-day mortality risk.[6] In light of the contradictory research findings aforementioned, there is an urgent requirement for additional elucidation regarding the potential association between IBD or its subtypes with sepsis.

Potential clues may be discovered at the genetic level, as numerous crucial genes implicated in the pathogenesis of IBD and played pivotal roles in pathogen sensing and eliciting an appropriate immune response for their eradication. Consequently, it has been hypothesized that polymorphisms within these genes could potentially impact immune responses. Against this backdrop, Sasidharan et al undertook a genetic analysis to unveil IBD-related immune response loci that could be associated with serious infections.[27] The findings revealed the presence of eight IBD risk loci, with two additional polymorphisms displaying significant associations with serious infections.[27] The findings of the study were partially consistent with our TSMR results. However, the authors did not provide a comprehensive definition and classification of sepsis, nor did they conduct subgroup analysis on the two disease subtypes of IBD. In our TSMR study, sepsis was categorized into three subtypes: sepsis, sepsis (critical care), and sepsis (28-day death in critical care), which roughly corresponded to mild, moderate, and severe sepsis, respectively. Our TSMR analysis demonstrated a significant and causal association between genetic susceptibility of CD and sepsis (28-day death in critical care) (OR, 1.246; 95% CI, 1.090–1.423; \( P = 0.0012 \)). The genetic association of CD with the sepsis (critical care) (OR, 1.065; 95% CI: 0.997–1.139; \( P = 0.062 \)) showed an increased, yet statistically insignificant trend. Additionally, no significant associations were observed between CD and sepsis (OR, 1.012; 95% CI: 0.987–1.038; \( P = 0.354 \)). After evaluating potential pleiotropy of IVs through some sensitivity analysis, genetic susceptibility of CD associated with sepsis (28-day death in critical care) were still robust. It implied that CD may be related to sepsis in severe conditions, although the underlying mechanism remains unclear. It is possible that the hidden onset and insufficient clinical attention contribute to this association. Furthermore, once CD progresses, it can easily lead to severe illness or even death.

Unfortunately, a causal relationship between UC and all three types of sepsis was not established in our study. As one type of IBD, the reason why UC had no causal relationship with sepsis required further research. Some
researchers have suggested that this disparity could be attributed to factors such as population size bias, distinct pathophysiological mechanisms between the two IBD subtypes, a higher prevalence of chronic usage of TNFα immunosuppressive agents in CD compared to UC, variations in genetic polymorphism (although there was significant overlap in genetic risk factors between CD and UC), and other factors.\[12, 31\] It was likely that these factors did not exist independently, but rather exhibited a synergistic effect. Therefore, conducting further detailed research on the differences in pathogenesis between CD and UC during sepsis will help to develop potential drug targets for the treatment of IBD in the future. Interestingly, we noticed that out of the 120 IVs from CD, two specific genetic variants (rs7438704, rs7236492) were also present among the 8 IBD risk loci discovered by Sasidharan S et al (Fig. 6).\[27\] Hence, SLAIN2 (gene potentially associated by rs7438704) and NFATC1 (gene potentially associated by rs7236492) may be important genes involved in the process of CD disease during sepsis, thereby warranting further investigation as potential molecular targets for drug development.

SLE is a chronic multisystem AID characterized by a broad range of laboratory and clinical manifestations.\[32, 33\] Patients with SLE were more likely to succumb to sepsis than non-SLE patients.\[25\] Moreover, sepsis patients with SLE were observed to have a higher short-term mortality and unfavorable long-term outcomes.\[34–36\] Regarding the potential influence of SLE on sepsis, several studies indicated that SLE did not act as an independent risk factor for short-term (30-day) or long-term (3-year) mortality in sepsis patients receiving critical care.\[6, 25\] As opposed to that, a population-based case-control study conducted by Chen HH et al revealed that SLE was linked to a higher long-term (5 years) mortality rate in patients with severe sepsis requiring ICU admissions and mechanical ventilation.\[33\] Surprisingly, Oud, L. and J. Garza contradicted these findings by suggesting that SLE was associated with a reduced risk-adjusted odds of short-term mortality, and they contended that the increased likelihood of developing sepsis, rather than the higher fatality rate among SLE patients, was the primary driver of the elevated risk of sepsis-related short-term mortality related to sepsis.\[8\] The conflicting findings mentioned above may be attributed to various factors, including the size of the sample, potential bias in sample selection, cytokine levels at baseline, the use of steroids and immunosuppressive drugs, the severity of sepsis, the methods employed to estimate the cohort's outcome after adjusting for risk, and others.\[6, 8, 25, 37\] It should be noted that there was currently no universally accepted method for determining causal relationships in observational studies. Now, MR analysis may present a more suitable approach for assessing the causal relationships between SLE and sepsis. According to our TSMR results, the genetic predisposition to SLE had a suggestive significant association with sepsis (OR, 1.025; 95% CI, 1.009–1.043; \(P=0.0029\)). This observation aligned with previous reports highlighting a shared genetic overlap of pathogenesis between SLE and sepsis, wherein 27 hub genes were revealed to be the common key genes.\[38\] Further genetic studies may be warranted to characterize the sepsis-associated changes in SLE patients in order to gain mechanistic insights allowing for the development of potential interventions.

MS is a central nervous system disorder involving autoimmune demyelination, which is mediated by various inflammatory cells.\[5, 39\] The association between sepsis and MS is intricate. On one hand, sepsis has been postulated to significantly contribute to the development of MS, as demonstrated by a recent retrospective cohort study conducted in Taiwan, which reported a nearly threefold increased likelihood of MS development among patients with sepsis.\[40\] Paradoxically, recent findings from a mice model of MS have revealed that sepsis actually impeded the progression of experimental autoimmune encephalomyelitis by reducing the population of encephalitogenic CD4+ T cells.\[41\] On the other hand, it is alternately worth evaluating the influence of MS on sepsis, given the limited and inconsistent nature of available epidemiological data. Notably, two studies conducted in Canada demonstrated a heightened susceptibility to severe infection and sepsis-related mortality among individuals with MS.\[42, 43\] In order to further investigate the influence of MS on the vulnerability of hosts to sepsis, Jensen IJ et al developed murine models of MS. Their findings indicated that mice with MS exhibited a significantly
increased susceptibility to mortality induced by sepsis, primarily attributed to elevated cytokine storms.[5] Conversely, statistical analysis conducted by Sheth M et al revealed that MS was linked to a significant decrease in the short-term (30-day) mortality rate in the sepsis cohort and septic shock cohort after adjusting for potential confounding factors.[6] Our MR analysis, which offered the advantage of causal association testing, indicated a suggestive significant association between MS and sepsis, but not with sepsis (critical care) and sepsis (28-day death in critical care). Therefore, further epidemiological data, specifically stratified by sepsis type, is needed to gain a deeper understanding of the direct relationship between MS and the various types of sepsis.

RA, an inflammatory disorder affecting the joints, is distinguished by proliferative synovitis, serositis, and vasculitis, which arise from lymphocytic infiltration and autoantibodies. Previous studies have established a correlation between RA and a heightened susceptibility to infection, particularly severe infections.[44–46] However, the impact of RA on the progression of sepsis has not been sufficiently documented. A retrospective study with a limited sample size conducted multivariate analysis, uncovering that RA alone constituted a significant independent risk factor for in-hospital mortality related to sepsis.[47] However, Sheth M et al and Barrett O et al provided evidence indicating that RA did not pose an independent risk for short-term mortality (within 30 days), but it did serve as a significant independent risk factor for long-term mortality (within 3 years).[6, 45] It was therefore evident that there was still controversy over if RA and sepsis were causally related. Our TSMR study discovered no substantial association between RA and the three types of sepsis. This discrepancy in findings may contribute to the inconsistent conclusions mentioned earlier.

AS is one common kind of AID, which was characterized by back pain and stiffness in the sacroiliac joints. While previous reports suggested that infections were an environmental risk factor in the development of AS,[48] a recent systematic review and meta-analysis found no evidence to support the notion that bacterial infections contribute to the risk of AS.[49] This finding was in line with the research conducted by Sheth M et al, who found no significant association between AS and short-term mortality in sepsis. Consequently, the limited number of reports on the relationship between AS and sepsis may be attributed to the lack of association in reality. Consistent with this, our TSMR analysis found that AS did not have genetic susceptibility to any of the three types of sepsis.

Conclusion

In conclusion, our study offered genetic evidence that supported a causal link between CD and Sepsis (28-day death in critical care), SLE and sepsis, MS and sepsis. Considering the notable associations, it was advisable to exercise caution when managing these AID in terms of infection prevention, particularly by implementing early intervention measures. Despite the shared characteristics among AID, each individual disease exhibited distinct genetic polymorphisms, resulting in varying impacts on the severity of sepsis. Therefore, future investigations should focus on specifying the types of AID and the severity of sepsis to yield more precise and unbiased outcomes. The genetic risk loci related may become important research hotspots and potential drug development targets.

Strengths and limitations

Our study possessed several notable strengths. Firstly, the meticulous categorization of AID and sepsis in our study facilitated subgroup analysis, including sepsis, sepsis (critical care), and sepsis (28-day mortality in critical care). Secondly, confounding variables were effectively minimized through the utilization of multiple SNPs to characterize AID. Thirdly, the robustness of our findings was confirmed through sensitivity analyses, which excluded the influence of pleiotropy using MR-PRESSO.
Besides, it was also important to acknowledge some limitations. Firstly, it was worth noting that the vast majority of individuals included in the GWAS for AID, which were utilized in our MR analysis, were of European descent. This demographic composition could introduce a potential source of bias, thereby limiting the extrapolation of our findings to other ethnic groups. Secondly, the lack of individual data prevented us from assessing possible nonlinear AID-sepsis associations. Thirdly, the reverse causality between AID and sepsis can not be inferred for limited SNPs available. Fourthly, considering the causal association evaluated by MR was based on the genetic information and the experiment lacked direct mechanistic studies to support our findings, the result should be cautiously interpreted. Additional research was warranted to elucidate the effects of AID on the immune system, pathogens and pathogenic pathways during various types of sepsis. Lastly, the genetic influence of AID on long-term sepsis outcomes could not be conducted due to unavailability of certain databases.

**Abbreviations**

AID, Autoimmune disease; AS, Ankylosing spondylitis; CD, Crohn's disease; CI, Confidence interval; GWAS, Genome-wide association study; IBD, Inflammatory bowel diseases; IVs, instrumental variables; IVW, Inverse-variance weighted; MR, Mendelian randomization; MS, Multiple sclerosis; NFATC1, Nuclear factor of activated T-cells, cytoplasmic 1; OR, Odds ratio; PMID, PubMed unique identifier; RA, Rheumatoid arthritis; SLAIN2, SLAIN motif-containing protein 2; SLE, Systemic lupus erythematosus; SNPs, Single nucleotide polymorphisms; TSMR, Two-sample MR; UC, Ulcerative colitis.

**Declarations**

**Author Contributions**

LL, XL, and ZC were responsible for the conception and design of the study. BX, XL, and DL were involved in the initial drafting of the paper. Data collection was carried out by BX and DL. The analysis and interpretation of the data were conducted by ZC, TR, and YL. Manuscript revisions were made by LL, XL, and ZC.

**Acknowledgments**

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**Supplementary information**

The supplementary tables are available online with this article.

**Declarations of competing interest** None.

**Ethics approval** It was not necessary for this study as it solely relied on publicly available data and did not involve direct patient participation. However, all human studies incorporated in our analysis adhered to the principles outlined in the Declaration of Helsinki.
Consent for publication All authors have thoroughly reviewed the data, ensured its accuracy, and granted their approval for the final manuscript.

References


Figures
Figure 1

MR is an increasingly applied method that can use genetic variation as IVs to elucidate causality between exposure (AID, including CD, UC, SLE, MS, RA, AS) and outcome (sepsis, critical care sepsis (critical care), and sepsis (28-day death in critical care)). Three assumptions should be satisfied beforehand: firstly, the genetic variants (i.e. SNPs) should be firmly linked to AID (CD, UC, SLE, MS, RA, AS); secondly, the SNPs should be unaffected by any confounding factors; and finally, the IVs influence the risk of sepsis exclusively via the pathway involving AID.

Figure 2
Overview of the MR results before (A) and after (B) removing the SNPs potentially associated with confounders. The results were mainly analyzed by IVW method. The genetic susceptibility of CD was significantly causally associated with sepsis (28-day death in critical care). There was a suggestive significant association between genetic liability to SLE and MS with sepsis.

<table>
<thead>
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<th>Exposures</th>
<th>Outcomes</th>
<th>nSNP</th>
<th>OR (95% CI)</th>
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<td>All</td>
<td>120</td>
<td>1.011 (0.988,1.035)</td>
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<td>Sepsis</td>
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<td>1.068 (1.005,1.136)</td>
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<td>120</td>
<td>1.240 (1.096,1.402)</td>
<td>6.09×10⁻⁴</td>
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<tr>
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<tr>
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<td>Sepsis</td>
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<td>1.012 (0.987,1.038)</td>
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<td>1.065 (0.997,1.139)</td>
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<td>Sepsis</td>
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</table>

Figure 3

A forest plot was constructed to examine the causal associations between CD and UC with three different types of sepsis. The analysis included the consideration of SNPs that may be associated with confounding factors in the IVW analyses. The odds ratios (OR) and their corresponding 95% confidence intervals (CI) were utilized to estimate the associations between CD and UC and the risk of the three types of sepsis.
Figure 4

A forest plot was constructed to examine the causal associations between SLE and MS with three different types of sepsis. The analysis included the consideration of SNPs that may be associated with confounding factors in the IVW analyses. The odds ratios (OR) and their corresponding 95% confidence intervals (CI) were utilized to estimate the associations between SLE and MS and the risk of the three types of sepsis.
A forest plot was constructed to examine the causal associations between RA and AS with three different types of sepsis. The analysis included the consideration of SNPs that may be associated with confounding factors in the IVW analyses. The odds ratios (OR) and their corresponding 95% confidence intervals (CI) were utilized to estimate the associations between RA and AS and the risk of the three types of sepsis.

Figure 5

A forest plot was constructed to examine the causal associations between RA and AS with three different types of sepsis. The analysis included the consideration of SNPs that may be associated with confounding factors in the IVW analyses. The odds ratios (OR) and their corresponding 95% confidence intervals (CI) were utilized to estimate the associations between RA and AS and the risk of the three types of sepsis.
**Figure 6**

A Venn diagram was constructed to illustrate the overlapping SNPs between the documented IBD genetic risk loci associated with sepsis (Left ellipse) and the IVs for CD in our TSMR analysis (Right ellipse). Among the 120 IVs from CD, two IVs (rs7438704, rs7236492) were common to the 8 IBD risk loci reported previously.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytable.doc