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

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Abstract

Background Recent observational studies have revealed an inconclusive correlation between inflammatory bowel disease (IBD) and sepsis, accompanied by an uncertain understanding of the causal relationship between the two. To investigate the causality between IBD and sepsis, we employed 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 two types of IBD, such as Crohn's disease (CD) and ulcerative colitis (UC). 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 There was a significant association between genetic liability to CD (IVW: OR, 1.246; 95% CI, 1.090–1.423; $P = 0.0012$) with sepsis (28-day death in critical care), but not with sepsis (critical care) and sepsis. Whereas UC showed slightly, yet statistically insignificant, higher risk for sepsis (IVW: OR, 1.031; 95% CI, 0.988–1.064; $P = 0.064$).

Conclusion Our study offers genetic evidence that supports a substantial causal relationship between CD and sepsis (28-day death in critical care). To enhance the specificity and objectivity of future research findings, it is recommended to specify the types of IBD and the severity of sepsis. Furthermore, the genetic risk loci related may become potential drug development targets.

Keywords Sepsis, Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, Mendelian randomization

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Introduction

Sepsis, a global public health issue with significant morbidity and mortality rates, is the main cause of infection-related deaths worldwide [1, 2]. This clinical syndrome arises from an immune response imbalance triggered by an infection [1, 3]. When cytokines are released suddenly by the innate immune system during sepsis, it can result in multiorgan failure, septic shock, and immune-related complications [1, 3, 4]. The overactive pro-inflammatory response, 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 autoimmune disease, wherein the immune response erroneously targets diverse host tissues [8, 9]. Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), was an important autoimmune disease affecting the intestine. Despite differences in their onset and clinical presentation, both IBD 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 IBD can impact those associated with sepsis [10]. According to several researchers, IBD and their treatment could worsen sepsis patients'clinical outcomes because their immune systems were modulated [5–7]. However, the available experimental evidences substantiating a causal relationship between IBD and sepsis are limited and occasionally contradictory. Investigations into septic patients within a population-based IBD cohort revealed that in-hospital patients with CD experienced a lower risk-adjusted mortality (OR, 0.78; 95% CI, 0.63–0.97), while those with UC experienced a higher one (OR, 1.61; 95% CI, 1.35–1.93) [11]. Notably, a recent study conducted by Sheth et al. at a single medical center suggested that IBD did not linked to a reduced risk-adjusted short-term mortality during sepsis (OR: 0.73; 95% CI: 0.57–0.93) [6]. Therefore, taking a closer look at the outcomes of sepsis in individuals with IBD could offer valuable insights into how the immune system copes with infection.

In observational studies, the utilization of genetic variation as instrumental variables (IVs) in Mendelian randomization (MR) analysis is increasingly prevalent, as it enables the elucidation of direct causal association between exposure and outcomes while minifying the influence of confounding factors [12]. Here, through Two-sample MR (TSMR) analysis, we explored the potential causality between IBD 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.

Materials and methods

The design of study

This study followed the reporting guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology Using MR (STROBE-MR) for MR [13]. The workflow of TSMR analysis was depicted in Fig. 1. In brief, the utilization of genetic variants as IVs necessitated adherence to three crucial prerequisites. Firstly, IBD was strongly associated with genetic variants of interest, as evidenced by attaining genome-wide significance ($P < 5\times 10^{-8}$) and meeting the threshold of F-statistic. Secondly, these genetic variations should not demonstrate any linkage with potential confounding factors, thereby avoiding horizontal pleiotropy. Lastly, the influence of genetic variants on the sepsis was mediated only through IBD. To obtain the necessary summary data, published Genome-wide association study (GWAS) pertaining to the exposure of interest and sepsis were utilized.

Data sources for IBD

Table 1 and Supplementary Table 1 contained the summary statistics of IBD obtained from recently published datasets, involving 48,315 participants from Europe [14–17]. In brief, the GWAS assessed two IBD phenotypes, including CD (n = 20,883), and UC ($n = 27,432$).

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.

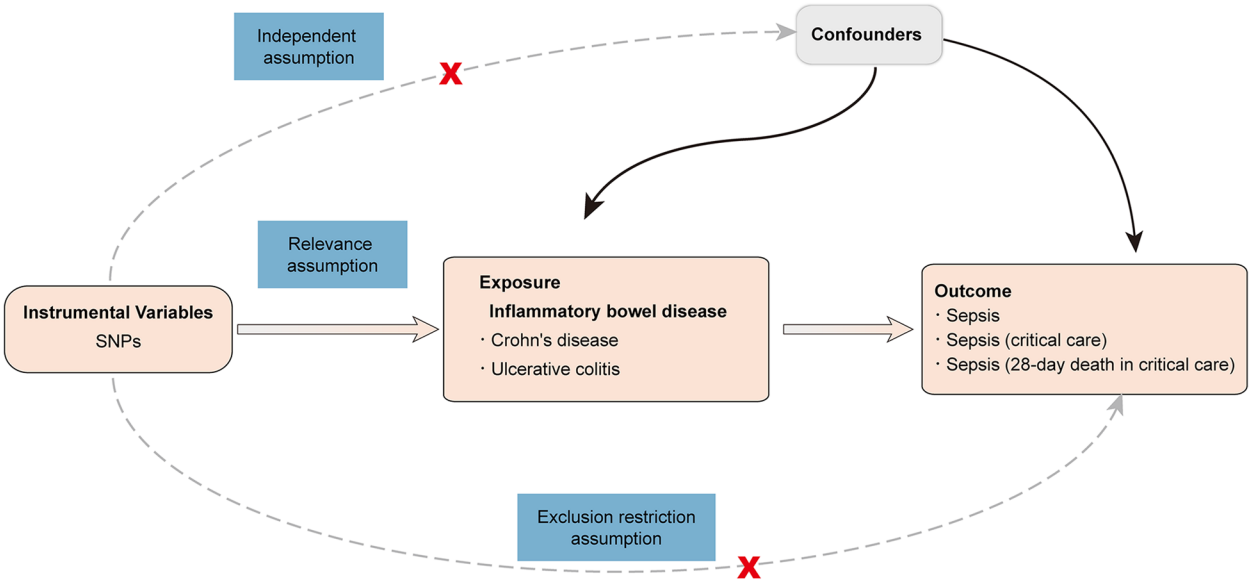

Fig. 1 MR is a wide applied method which determines genetic variation as IVs to elucidate causality between exposure (IBD, including CD and UC) and outcome (sepsis, critical care sepsis (critical care), and sepsis (28-day death in critical care)). Three assumptions should be satisfied beforehand: 1. the genetic variants (i.e. SNPs) should be firmly linked to IBD; 2. the genetic variants can not be affected by any confounding factors; 3. IVs influence the risk of sepsis exclusively via the pathway involving IBD. Abbreviations: CD, Crohn's disease; IBD, Inflammatory bowel diseases; IVs, instrumental variables; MR, Mendelian randomization; SNPs, Single nucleotide polymorphisms; UC, Ulcerative colitis

Table 1 Description of the IVs associated with IBD used in the TSMR study

Risk factor	SNPs used in MR study (Sepsis/critical care sepsis/28-day death in critical care sepsis)	SNPs after removing SNPs associated with confounders (Sepsis/critical care sepsis/28-day death in critical care sepsis)	Proxy SNP	Sample size	Population	GWAS	Year	PMID
CD	120/120/120	98/98/98	8	20,883	European	Liu et al	2015	26,192,919
UC	86/86/86	71/71/71	8	27,432	European	Liu et al	2015	26,192,919

Abbreviations: *CD* Crohn's disease, *GWAS* Genome-wide association study, *IBD* Inflammatory bowel disease, *IVs* instrumental variables, *PMID* PubMed unique identifier, *SNPs* Single-nucleotide polymorphisms, *TSMR* Two-sample Mendelian randomization, *UC* Ulcerative colitis

Genetic instrumental variable selection

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 $P < 5 \times 10^{-8}$. The associated Single nucleotide polymorphisms (SNPs) with IBD were selected based on these criteria. To assess the effectiveness of these SNPs, following is the formula used to calculate the F-statistic: $F = \frac{R^2(N-2)}{(1-R^2)}$. The R^2 value represented the proportion of variability in IBD explained by the selected SNPs, while the sample size (N) indicated the number of subjects included in GWAS. When the F-statistic was over 10, there was a low chance of weak instrument bias [18].

Mendelian randomization analysis

This study utilized a TSMR approach to examine the influence of IBD on sepsis. The Wald estimates were employed to estimate the impact of IBD on sepsis after extracting the necessary data and harmonizing the effect alleles across GWASs. To account for potential measurement error, the delta method was applied to adjust the causal relationship between IBD and sepsis [19, 20]. Final effect estimates were evaluated using the inverse-variance weighted (IVW) method during the primary analysis. Additionally, an analysis of MR effects based on each method was shown visually in scatter plots [21].

Statistical analysis

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

To enhance the robustness of our findings, we conducted several sensitivity analyses, including simple median analysis, weighted median analysis, MR-Egger regression analysis, 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 through MR-Egger regression analysis. The risk of bias was low when the I^2_{GX} value exceeds 95% [24]. Our findings were verified by using Phenoscanner and the GWAS database 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 body mass index, cholesterol levels, diabetes, and coronary heart disease and cancer. 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 0.0083 (0.05/(2 ×3)). The analysis in this study utilized R software (version 3.5.4) 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 IBD was presented in Table 1 and Supplementary Table 1. A total of 120 and 86 independent SNPs that achieved genome-wide significance were extracted for CD and UC, respectively (Supplementary Table 2–3). 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 2–3). Among the selected SNPs, the F statistics exceeded 10 (ranging from 30 to 1460) (Supplementary Table 2–3). PhenoScanner analysis allowed us to identify 22 and 15 selected SNPs that appeared to have an association with confounding factors or sepsis in the context of CD and UC, respectively (Supplementary Table 4).

Cochran's Q test in Supplementary Table 5 revealed no significant heterogeneity ($P < 0.05$). The random-effects IVW analysis demonstrated that different types of IBD had varying effects on the outcomes of three sepsis types (Fig. 2). Specifically, the genetic susceptibility of CD was found to be significantly and 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).

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, (Tables 2, 3, 4) and leave-one-SNP-out method (Supplementary Fig. 1–3). In the MR-Egger regression, the I^2_{GX} for each IBD was found to be greater than 0.98, indicating a low chance of bias from weak IVs (Supplementary Table 6–7). No directional pleiotropy was observed in the association between IBD and different sepsis (Supplementary Table 6–7). Supplementary Figs. 4–6 exhibited scatter plots that depicted the MR effect according to each method. Table 1

Discussion

A TSMR analysis was used in our study to determine the causal link between IBD and different types of sepsis. 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. These findings provided evidence that certain IBD 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 IBD, where the immune response become directed against the intestine [8]. The levels of inflammatory

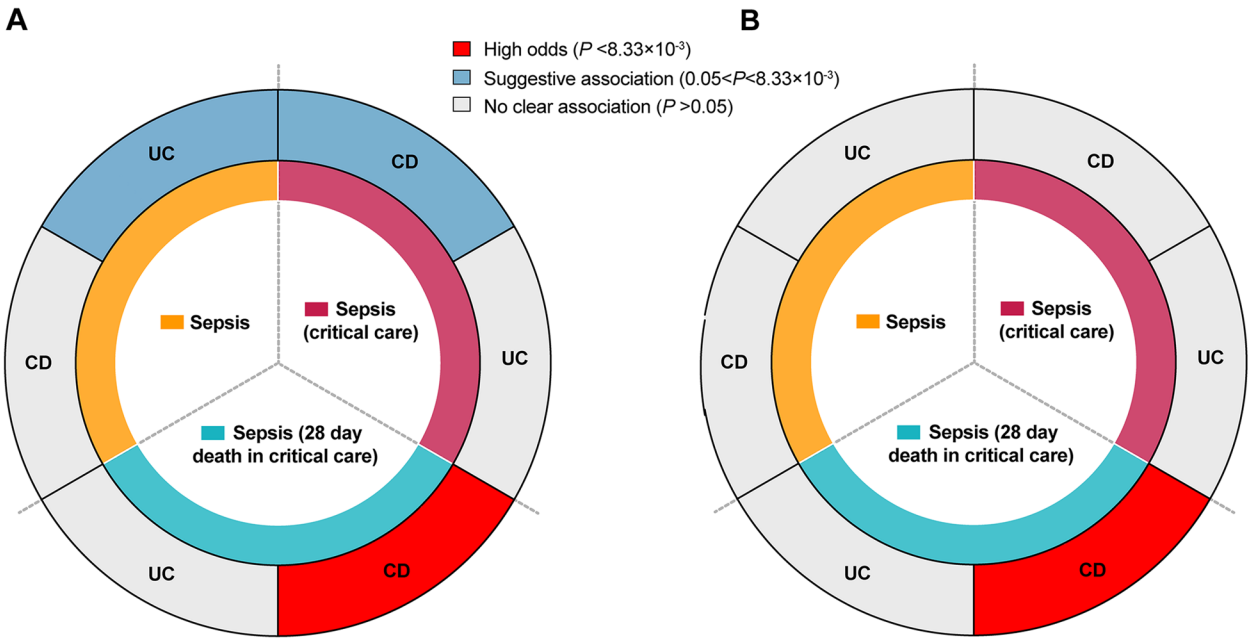

Fig. 2 Overview of the MR results before **(A)** and after **(B)** removing the SNPs potentially associated with confounders. The results were mainly analyzed by IVW method. The genetic susceptibility of CD was significantly causally associated with sepsis (28-day death in critical care). Abbreviations: CD, Crohn's disease; IBD, Inflammatory bowel diseases; MR, Mendelian randomization; SNPs, Single nucleotide polymorphisms; UC, Ulcerative colitis

Exposures	Outcomes	nSNP	OR (95% CI)	P
Crohn's disease				
	All			
	Sepsis	120	1.011 (0.988,1.035)	0.367
	Sepsis (critical care)	120	1.068 (1.005,1.136)	0.035
	Sepsis (28 day death in critical care)	120	1.240 (1.096,1.402)	6.09×10^{-4}
	Remove			
	Sepsis	98	1.012 (0.987,1.038)	0.354
	Sepsis (critical care)	98	1.065 (0.997,1.139)	0.062
	Sepsis (28 day death in critical care)	98	1.246 (1.09,1.423)	1.23×10^{-3}
Ulcerative colitis				
	All			
	Sepsis	86	1.032 (1.001,1.063)	0.041
	Sepsis (critical care)	86	1.033 (0.959,1.113)	0.394
	Sepsis (28 day death in critical care)	86	1.101 (0.948,1.279)	0.208
	Remove			
	Sepsis	71	1.031 (0.988,1.064)	0.064
	Sepsis (critical care)	71	1.029 (0.949,1.116)	0.495
	Sepsis (28 day death in critical care)	71	1.075 (0.914,1.264)	0.385

Fig. 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 associations were estimated using OR and their corresponding 95% CI between CD and UC and the risk of the three types of sepsis. Abbreviations: CD, Crohn's disease; CI, Confidence interval; IVW, Inverse-variance weighted; OR, Odds ratio; SNPs, Single nucleotide polymorphisms; UC, Ulcerative colitis

Table 2 Mendelian randomization estimates between IBD and sepsis

Exposures	Outcomes	No. of SNPs	IVW		MR-Egger		Weighted median		Simple median		MR-PRESSO	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
CD	**All**	**120**	**1.011 (0.988–1.035)**	**0.367**	**0.963 (0.906–1.024)**	**0.225**	**0.993 (0.958–1.03)**	**0.712**	**1.017 (0.983–1.053)**	**0.333**	**1.011 (0.988–1.035)**	**0.369**
	Remove	98	1.012 (0.987–1.038)	0.353	0.965 (0.906–1.027)	0.264	1.003 (0.965–1.042)	0.892	1.019 (0.981–1.058)	0.337	1.012 (0.987–1.038)	0.355
UC	**All**	86	1.032 (1.001–1.063)	0.04	1.032 (0.96–1.109)	0.400	1.019 (0.975–1.064)	0.406	1.033 (0.989–1.079)	0.139	1.032 (1.001–1.063)	0.043
	Remove	71	1.031 (0.998–1.064)	0.063	1.059 (0.982–1.142)	0.135	1.019 (0.971–1.068)	0.443	1.020 (0.972–1.069)	0.419	1.031 (0.998–1.064)	0.068

"All" represents analyses with all selected SNPs, "Removed" represents analyses after removing SNPs associated with relevant confounders or sepsis. *Abbreviations*: *CD* Crohn's disease, *CI* Confidence interval, *IBD* Inflammatory bowel diseases, *IVW* Inverse-variance weighted, *MR-PRESSO* MR Pleiotropy Summary, *OR* Odds ratio, *SNPs* Single nucleotide polymorphisms, *UC* Ulcerative colitis

Table 3 Mendelian randomization estimates between IBD and sepsis (critical care)

Exposures	Outcomes	No. of SNPs	IVW		MR-Egger		Weighted median		Simple median		MR-PRESSO	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
CD	**All**	120	1.068 (1.005–1.136)	0.035	1.101 (0.935–1.296)	0.247	1.092 (0.992–1.203)	0.072	1.044 (0.951–1.146)	0.366	1.068 (1.008–1.132)	0.028
	Remove	98	1.065 (0.997–1.139)	0.061	1.094 (0.924–1.294)	0.297	1.101 (0.994–1.219)	0.065	1.030 (0.933–1.138)	0.560	1.065 (1.002–1.132)	0.044
UC	**All**	86	1.033 (0.959–1.113)	0.394	0.865 (0.723–1.036)	0.115	0.982 (0.879–1.098)	0.753	1.058 (0.946–1.184)	0.322	1.033 (0.967–1.104)	0.338
	Remove	71	1.029 (0.949–1.116)	0.494	0.878 (0.726–1.063)	0.183	0.980 (0.869–1.106)	0.746	1.057 (0.936–1.195)	0.371	1.029 (0.954–1.109)	0.462

"All" represents analyses with all selected SNPs, "Removed" represents analyses after removing SNPs associated with relevant confounders or sepsis. *Abbreviations*: *CD* Crohn's disease, *CI* Confidence interval, *IBD* Inflammatory bowel diseases, *IVW* Inverse-variance weighted, *MR-PRESSO* MR Pleiotropy Summary, *OR* Odds ratio, *SNPs* Single nucleotide polymorphisms, *UC* Ulcerative colitis

Table 4 Mendelian randomization estimates between IBD and sepsis (28-day death in critical care)

Exposures	Outcomes	No. of SNPs	IVW		MR-Egger		Weighted median		Simple median		MR-PRESSO	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
CD	**All**	120	1.240 (1.096–1.402)	6.09×10^{-4}	1.140 (0.822–1.58)	0.432	1.230 (1.017–1.488)	0.033	1.241 (1.027–1.501)	0.025	1.240 (1.104–1.392)	4.12×10^{-4}
	Remove	98	1.246 (1.09–1.423)	1.23×10^{-3}	1.071 (0.765–1.501)	0.688	1.241 (1.012–1.521)	0.037	1.246 (1.015–1.53)	0.035	1.246 (1.1–1.411)	8.24×10^{-4}
UC	**All**	86	1.101 (0.948–1.279)	0.207	0.797 (0.556–1.144)	0.218	1.021 (0.818–1.275)	0.851	1.152 (0.919–1.443)	0.219	1.101 (0.962–1.26)	0.164
	Remove	71	1.075 (0.914–1.264)	0.384	0.813 (0.554–1.192)	0.288	1.017 (0.802–1.291)	0.887	1.090 (0.853–1.393)	0.490	1.075 (0.925–1.249)	0.349

"All" represents analyses with all selected SNPs, "Removed" represents analyses after removing SNPs associated with relevant confounders or sepsis. *Abbreviations*: *CD* Crohn's disease, *CI* Confidence interval, *IBD* Inflammatory bowel diseases, *IVW* Inverse-variance weighted, *MR-PRESSO* MR Pleiotropy Summary, *OR* Odds ratio, *SNPs* Single nucleotide polymorphisms, *UC* Ulcerative colitis

cytokines exhibit variability based on the specific IBD [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 IBD contributed to poorer clinical outcomes in sepsis patients due to alterations in immune reactivity associated with IBD and its immune-related treatments [6, 7, 25]. However, recent studies have yielded divergent and even contradictory findings across different types of IBD [5, 6, 8, 11]. Not to mention confirming the causal relationship between IBD 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 greater risk of experiencing infection-related 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 [11, 28, 29]. The occurrence of sepsis is a significant concern in the management of IBD patients. 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 risk of sepsis in IBD individuals [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 [11]. 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 [27]. 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, and 8 loci were identified by them [27]. It was partially in line with the TSMR analysis. 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) (IVW: OR, 1.246; 95% CI, 1.090–1.423; $P = 0.0012$). We utilized the weighted median and the MR-Egger approach as complements to IVW analysis. The weighted median and MR-Egger analyses were consistent with the IVW method, though MR-Egger method with low precision. Due to the less statistical power of MR-Egger than IVW, we concentrated more on the consistency of the estimate direction between MR-Egger and IVW [31]. The genetic association of CD with the sepsis (critical care) (IVW: 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 (IVW: 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. As known, CD was characterized by a transmural inflammation that could affect the entire gastrointestinal tract and was associated with a more severe systemic inflammatory response. The diffuse and severe inflammation may facilitate the dissemination of pathogens and the amplification of systemic inflammatory responses, thereby augmenting the severity of sepsis in patients with CD. Conversely, UC primarily confined its inflammation to the mucosal layer of the colon, demonstrating a more localized inflammatory pattern with lesser systemic implications. 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

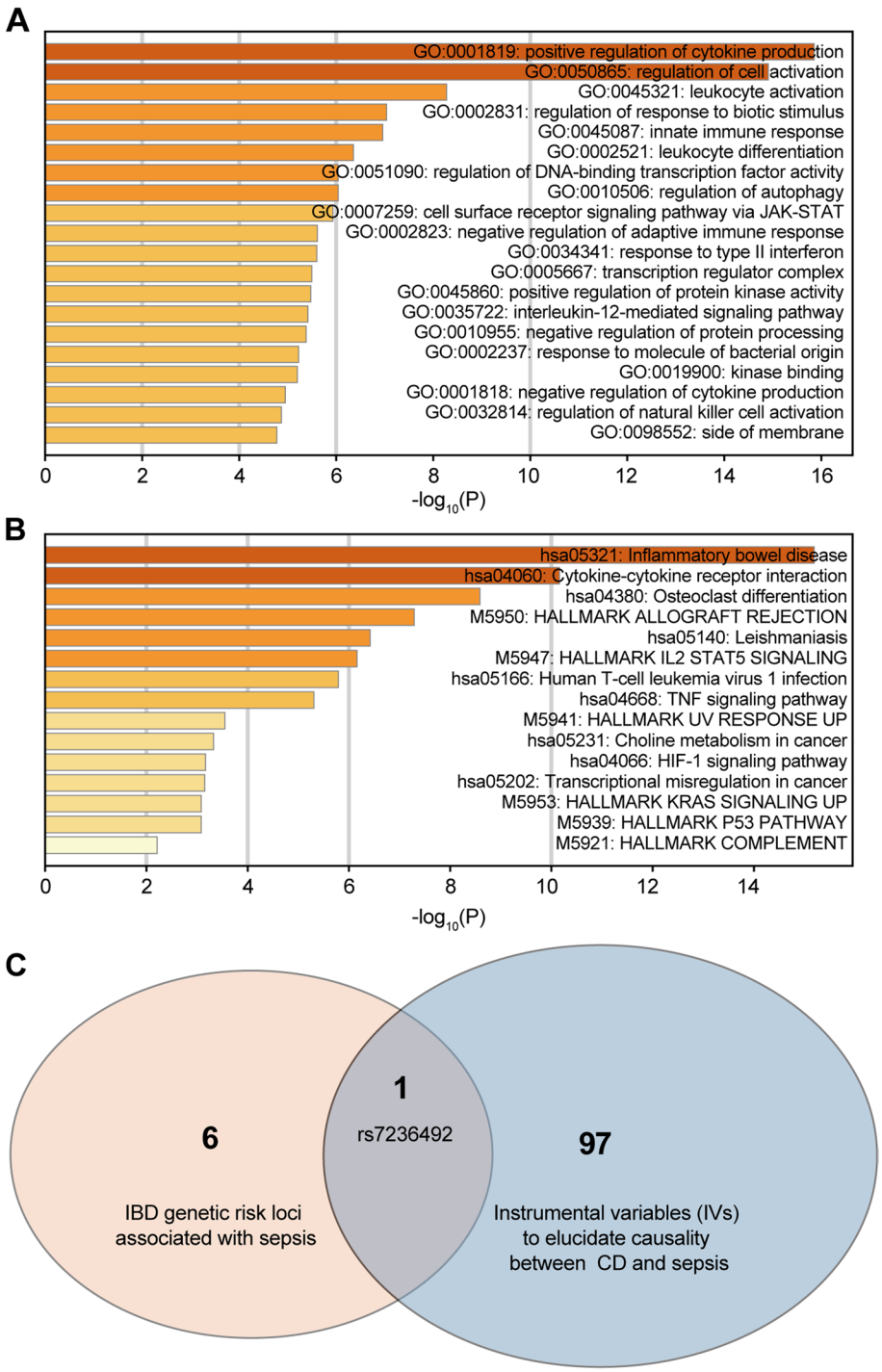

Fig. 4 Functional enrichment analysis of the relevant genes according to SNPs. **(A)**Bar plots showing the top 20 GO terms. **(B)**Bar plots showing the top 15 enriched KEGG and HALLMARK pathways. **(C)** A Venn diagram was constructed to illustrate the overlapping SNPs between the documented IBD genetic risk loci associated with sepsis (Left ellipse) and the IVs for CD in our TSMR analysis (Right ellipse). Among the 98 IVs from CD, one IVs (rs7236492) were common to the 8 IBD risk loci reported previously. Abbreviations: CD, Crohn's disease; IBD, Inflammatory bowel diseases; IVs, instrumental variables; TSMR, Two-sample Mendelian randomization; SNPs, Single nucleotide polymorphisms

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 [11, 32]. 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. To further explore the function of causal SNPs (98 SNPs) identified for Crohn's disease, the relevant genes according to SNPs were subjected to functional enrichment analyses, including KEGG and HALLMARK pathways and GO terms using Metascape database (https://metascape.org/gp/index.html). The results showed that these relevant genes were enriched in the "Inflammatory bowel disease", "TNF signaling pathway" and "positive regulation of cytokine production (Fig. 4A- 4B). Interestingly, we noticed that out of the 98 IVs from CD, one specific genetic variants (rs7236492) were also present among the 8 IBD risk loci discovered by Sasidharan S et al. (Fig. 4C) [27]. Hence, NFATC1 and TST (genes 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.

Conclusion

The present MR study offered genetic evidence that supported a causal link between CD and Sepsis (28-day death in critical care). Considering the notable associations, it was advisable to exercise caution when managing CD in terms of infection prevention, particularly by implementing early intervention measures. Despite the shared characteristics among IBD, 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 IBD 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 some notable strengths. Firstly, the meticulous categorization of 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 IBD. Thirdly, the robustness of our findings was confirmed through sensitivity analyses, which excluded the influence of pleiotropy using MR-Egger intercept and 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 IBD and sepsis, 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 to other ethnic groups. Secondly, the lack of individual data prevented us from assessing possible nonlinear IBD-sepsis associations. Thirdly, considering the causal association was established basing on 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 IBD on the immune system, pathogens and pathogenic pathways during various types of sepsis. Lastly, the genetic influence of IBD on long-term sepsis outcomes could not be conducted due to unavailability of certain databases.

Abbreviations

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
MR-PRESSO	MR Pleiotropy Summary
NFATC1	Nuclear factor of activated T-cells, cytoplasmic 1
OR	Odds ratio
PMID	PubMed unique identifier
SNPs	Single nucleotide polymorphisms
TSMR	Two-sample MR
UC	Ulcerative colitis

Supplementary Information

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Supplementary Material 1.

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Authors' 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 TR, LZ, DY, BX and DL. The analysis and interpretation of the data were conducted by TR, LZ, ZC, and YL. Manuscript revisions were made by DY, LL, XL, and TZ.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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