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A bidirectional mendelian-randomization analyses of genetically predicted circulating levels of systemic inflammatory regulators with risk of sepsis

Jiaqi Lou, MM[a], Ziyi Xiang, PhD[b], Xiaoyu Zhu, MM[c], Youfen Fan, BM[a], Jiliang Li, MM[a], Guoying Jin, MM[a], Shengyong Cui, MM[a], Neng Huang, MM[a,*]

Abstract

Whether there is a causal relationship between circulating levels of systemic inflammatory regulators and sepsis remains unclear. To determine whether genetically predicted circulating levels of cytokines are associated with risk of sepsis, a bidirectional two-sample Mendelian randomization (MR) analysis based on the a STROBE-compliant cross-sectional observational study was conducted utilizing gene-wide association study (GWAS) data. Selected with rigor, single-nucleotide polymorphisms served as instrumental variables for subsequent MR analysis. The preferred method for the MR analysis was the inverse-variance weighted approach. However, for comprehensive sensitivity analyses, 6 additional MR methods were employed. Cochrane's Q test was performed to examine heterogeneity. A leave-one-out method ensured the stability of MR results. Our findings suggest an inverse association between the levels of beta-nerve growth factor (BNGF) and the risk of sepsis development (OR = 0.769, 95% CI = 0.599–0.987, P = .039). In contrast, higher levels of TNF-related apoptosis-inducing ligand and vascular endothelial growth factor A (VEGF-A) are positively correlated with sepsis risk (OR = 1.094, 95% CI = 1.012–1.183, P = .025; OR = 1.182, 95% CI = 1.016–1.375, P = .031, respectively). Reverse MR Analysis indicated that sepsis risk is linked with lower circulating levels of adenosine deaminase and Interleukin-17A (β = –0.043, 95% CI = –0.085 to –0.002, P = .042; β = –0.061, 95% CI = –0.108 to –0.013, P = .012, respectively), and also with higher circulating levels of BNGF, delta/notchlike epidermal growth factor-related receptor, fibroblast growth factor 23, leukemia inhibitory factor, monocyte chemoattractant protein-1, and osteoprotegerin (β = 0.056, 95% CI = 0.015–0.096, P = .007; β = 0.137, 95% CI = 0.035–0.240, P = .009; β = 0.118, 95% CI = 0.020–0.216, P = .018; β = 0.136, 95% CI = 0.020–0.252, P = .022; β = 0.143, 95% CI = 0.043–0.242, P = .005; β = 0.116, 95% CI = 0.010–0.222, P = .031, respectively). Sum up, our study provides evidence supporting a bidirectional causal relationship between sepsis and genetically predicted circulating levels of systemic inflammatory regulators.

Abbreviations: ADAR1 = adenosine deaminase acting on RNA 1, BNGF = beta-nerve growth factor, CIs = confidence intervals, DNER = delta/notchlike epidermal growth factor-related receptor, FGF23 = fibroblast growth factor 23, GWAS = gene-wide association study, IL = interleukin, IV = instrumental variable, IVW = inverse variance weighted, LIF = leukemia inhibitory factor, MCP-1 = monocyte chemoattractant protein-1, MR = Mendelian randomization, OPG = osteoprotegerin, OPGL = osteoprotegerin ligand, ORs = odds ratios, SES = socio-economic status, SNPs = single nucleotide polymorphisms, TNF = tumor necrosis factor, TRAIL = TNF-related apoptosis-inducing ligand, VEGF-A = vascular endothelial growth factor A.

Keywords: genetic causal association, gwas, inflammatory modulators, mendelian randomization, sepsis, systemic inflammation

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The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Each study incorporated in the GWAS used in the present study was approved by local research ethics committees or Institutional Review Boards, and all participants had given their informed consent.

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[a] Burn Department, Ningbo No. 2 Hospital, Ningbo, China, [b] Institute of Pathology, Faculty of Medicine, University of Bonn, Bonn, Germany, [c] Health Science Center, Ningbo University, Ningbo, China.

** Correspondence: Neng Huang, Burn Department, Ningbo No. 2 Hospital, No. 41 Northwest Street, Haishu District, Ningbo, Zhejiang Province 315010, China (e-mail: 460474225@qq.com).*

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1. Introduction

Sepsis is commonly understood as a disorderly immune response of the host, provoked by an infection.[1] The pathogenesis of sepsis intertwines with numerous pathophysiological changes, such as imbalances in the inflammatory response, irregularities in immune regulation, coagulation dysfunction, mitochondrial damage, and endoplasmic reticulum stress.[2] Given that sepsis lacks specific clinical manifestations, diagnosis in its early stages can be challenging. A delay in detection often leads to swift disease progression and increased mortality rates.[3]

Inflammatory factors refer to a variety of cytokines engaged in the inflammation process. These cytokines, small peptide proteins secreted by cells, serve essential functions in cell proliferation and differentiation, signaling pathways, and the regulation of immune-inflammatory responses.[4] Recent studies[5,6] underscore the crucial role of cytokines in sepsis onset and progression. In early sepsis, pro-inflammatory and anti-inflammatory cytokines coexist, battling for immune homeostasis. If the pro-inflammatory response gains the upper hand, it can trigger an immune imbalance, causing a cytokine storm[7] and initiating a systemic inflammatory response syndrome with microcirculation dysfunction, escalating eventually to severe multiple organ dysfunction syndrome.[8] The levels of cytokines correlate closely with the severity of organ failure and may potentially act as biomarkers for sepsis.[9] However, typical studies often restrict examination to a single cytokine, ignoring the potential influences of other cytokines on sepsis development. Further, substantial clinical trials are lacking that verify the sensitivity and specificity of certain cytokines for early sepsis identification.[10]

Numerous genome-wide association studies (GWASs) have explored the links between genetic variations and diseases or phenotypes.[11] Mendelian randomization, a rigorously statistical method for causation detection, uses genetic variants with significant exposure associations as instrumental variables (IVs) to examine the causal link between the exposure and the outcome.[12] Two-sample Mendelian randomization (MR) analysis can provide causal estimates using single-nucleotide polymorphisms (SNPs) associated with exposure and outcome from independent GWAS studies.[13] MR studies are less likely to be affected by reverse causality and potential environmental-social confounders. MR serves to complement traditional epidemiological approaches by mitigating specific biases such as confounding and reverse causation. Evaluating the associations between cytokine levels and sepsis risk involves not only identifying which cytokines are involved but also understanding the strength and implications of these associations. In our study, we applied MR to assess the causal relationships between genetically predicted cytokine levels and sepsis. The distinctions between weak, moderate, and strong associations are critical. Strong associations signify a robust and potentially causative link, suggesting these cytokines as strong candidates for therapeutic targets or biomarkers for early detection. In contrast, weaker associations, though less direct, should not be overlooked, as they might represent complex interactions within broader immunological pathways or highlight cytokines involved in secondary or tertiary response mechanisms. This study employs GWASs and bidirectional Mendelian randomization analyses to investigate the causal associations between circulating levels of systemic inflammatory regulators and sepsis risk, which provides evidence for a potential causal relationship and is expected to serve as the basis for further longitudinal or intervention studies..

2. Methods

2.1. Ethics statement

Each study incorporated in the GWAS used in the present study was approved by local research ethics committees or Institutional Review Boards, and all participants had given their informed consent.

2.2. Study design

The Mendelian Randomization analysis is predicated on 3 fundamental assumptions[14]: The IVs used in the analysis exhibit a strong association with the variable of interest; The IVs are not associated with any confounding factors that could influence the relationship between exposure and outcome; and The IVs only affect the outcome via their influence on exposure. These assumptions are graphically depicted in Figure 1.

Figure 2 briefly portrays the bidirectional MR design. Genetic instruments for 91 systemic inflammatory regulators were sourced from the latest GWAS Catalog (https://www.ebi.ac.uk/

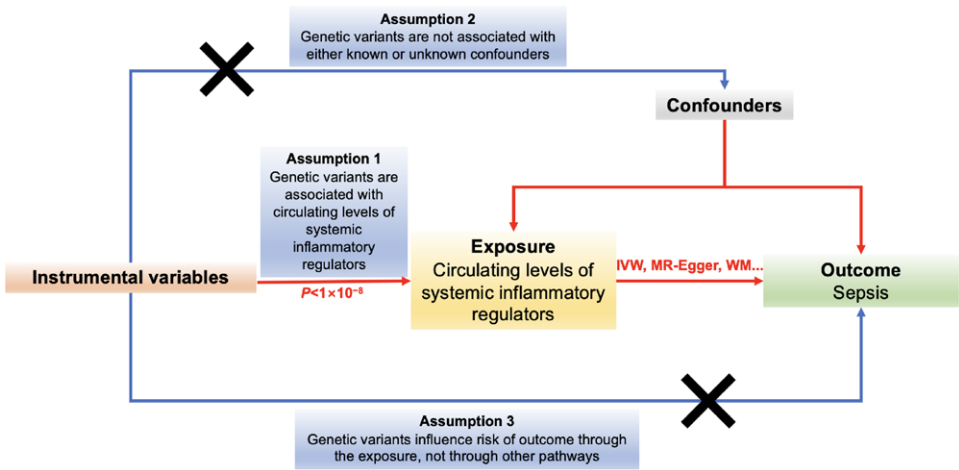

Figure 1. The Directed Acyclic Graph (DAG) representing the Mendelian Randomisation (MR) framework employed to investigate the causal relationship between the circulating levels of systemic inflammatory regulators and sepsis. The MR analysis is guided by 3 crucial instrumental variable assumptions: (1) The instrumental variables must exhibit an association with the circulating levels of systemic inflammatory regulators ($P < 5 \times 10^{-8}$). (2) The instrumental variables must not be associated with any potential confounders that could influence the relationship between the circulating levels of systemic inflammatory regulators and sepsis. (3) The instrumental variables should solely impact the risk of sepsis through their influence on the the circulating levels of systemic inflammatory regulators. The instrumental variables are represented by SNPs, and the MR analysis employs the IVW method, Wald ratio, MR-Egger, Weighted-Median, Simple Mode, Weighted Mode and MR-PRESSO methods to estimate causal relationships. IVW = inverse variance weighted, SNPs = single nucleotide polymorphisms.

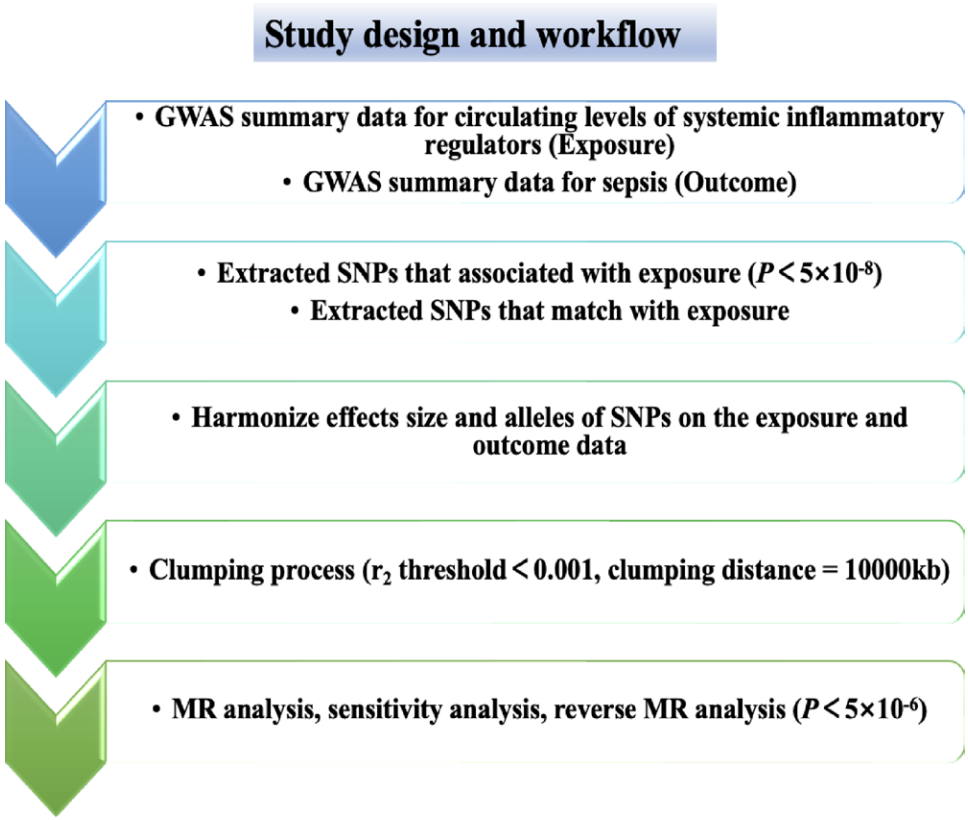

Figure 2. Flow chart of this study.

gwas/publications/37563310) and IEU Open GWAS (https://gwas.mrcieu.ac.uk/).[15–17] Initially, genetic variants for each inflammatory regulator were chosen to deduce the causality from each regulator to sepsis. Subsequently, genetic variants linked with sepsis were used to deduce the causality from sepsis to inflammatory regulators. Lastly, estimates from the sepsis source were amalgamated using the meta-analysis method. All the studies incorporated in the original GWASs obtained approval from the appropriate institutional review board. The study's flowchart is delineated in Figure 2.

2.3. Data source for inflammatory regulators

This study draws upon a published large-scale GWAS meta-analysis, involving up to 91 inflammation-related proteins across 14,824 participants,[17] with some contributions from Chinese populations. Despite being predominantly European, the inclusion of these datasets enhances the study's scope by integrating findings across different ethnic backgrounds and geographic origins. Distributions of these 91 cytokines underwent normalization through a two-step inverse transformation. The cytokine distributions were initially normalized by inverse transformation. Then, inverse transformation was applied to residuals of the linear regression model of the transformed cytokines, considering age, gender, body mass index (BMI), and genetic principal components.[18] To amalgamate genetic associations across multiple cohorts, meta-analyses were conducted.

2.4. Data sources for sepsis

Summary-level data on sepsis was obtained from the GWAS catalog and the IEU Open GWAS project (https://gwas.mrcieu.ac.uk; https://www.ebi.ac.uk/gwas/).[19] The use of multiple data sources was intended to enhance the credibility of the findings due to high sensitivity and specificity. The chosen GWAS in the UK Biobank encompasses 11,643 sepsis cases and 474,841 controls (with a maximum 16% overlap with insomnia GWAS). Case definition adhered to the explicit sepsis criteria set out in the most recent Global Burden of Disease Study of Sepsis.[20] This European-centric composition reflects a substantial portion of our data, providing meaningful insights into genetic associations within this demographic. Sepsis admissions within the UK Biobank were identified using linked secondary care data coded by the International Classification of Diseases (ICD). ICD-10 codes A02, A39, A40, and A41 were utilized to diagnose sepsis, aligning with contemporary literature.[21] Cases were included if the code appeared in the primary or secondary diagnostic position in Hospital Episode Statistics (HES) data or comparable datasets in the devolved nations, as provided by the UK Biobank. Study participants were predominantly of European ancestry, including both genders. The GWAS catalog included 1573 cases and 454,775 controls as outcomes.[22] Self-reported cases or cases presenting solely in primary care were excluded from the study.

2.5. The selection of instruments

Under bidirectional mendelian-randomization (BIMR), the genetic variants serving as instrumental variables for exposure X (Gx) and those serving as instrumental variables for outcome Y (Gy) were entirely distinct. In the initial stage, a forward MR analysis was conducted using a genome-wide threshold of significance ($P < 5 \times 10^{-8}$) to shield against the selection of false-positive instruments. Subsequently, conducting a reverse MR analysis, we studied the relationship of sepsis to the circulating levels of systemic inflammatory regulators. The positions of sepsis and the circulating levels of systemic inflammatory regulators were designated as exposure and outcome, respectively. As we did not screen sites when we imposed a threshold of 5×10^{-8},

the *P* value for exposure IVs was set at 5×10^{-6} to investigate the causative impact of sepsis on systemic inflammatory regulators. All SNPs in linkage disequilibrium ($r^2 < 0.001$ within 10 Mb in the European 1000G reference panel)[23] were pruned, retaining the SNPs with the lowest *P* value as independent variables. Following the harmonization of the selected SNPs with outcome data, all 91 systemic inflammation regulators were chosen. To mitigate the presence of weak IVs, the F-statistics of the SNPs were averaged, considering IVs with F-statistics over 10 as strong.[24] This method helps to avoid the problem of weak instrumental variables, so as to improve the accuracy of causal effect estimation.

2.6. Statistical analysis

Table S1, Supplemental Digital Content, http://links.lww.com/MD/O687 encapsulates details of the MR analyses based on summary-level data from GWAS used in this BIMR analysis. The table outlines exposure numbers, exposure names, outcome numbers, outcome names, SNP names, and the chromosome and position of the SNP in the outcome and exposures data. Subsequently, it presents effect alleles, other alleles, beta values, standard error (SE) values, *P* values, sample size, gene frequencies, R^2 values, and *F* values in sequence.

A bidirectional two-sample MR procedure, utilizing summary association data, was employed to examine the causal relationship between inflammatory regulators and sepsis. We executed data harmonization meticulously to ensure the same allele corresponded to the effect of an SNP on the exposure and the outcome. For SNPs with varying effect alleles due to different strands, we adjusted the strand to align the effect allele in both datasets. However, harmonizing palindromic SNPs poses challenges due to the allele uniformity on both strands. To preclude ambiguity regarding whether exposure and outcome GWAS report the same effect allele,[25] such SNPs were deleted. In the primary analysis, a Wald ratio estimate was computed for each genetic variant, and these estimates were synthesized using the inverse variance weighted (IVW) procedure. The IVW with a multiplicative random effects strategy offers an efficient estimate, taking into account possible heterogeneity among the Wald ratio estimates from SNPs.[26] Therefore, if heterogeneity is observed, random-effects IVW models are applied; otherwise, fixed-effect IVW models are used. The Cochran Q test and I^2 evaluated the heterogeneity of the meta-analysis. Scatter plots were provided to illustrate the causal associations of systemic inflammatory regulators with sepsis. The effects in 91 cytokines are reported as changes in inverse normalized cytokine concentrations per effect allele dosage. The impact of 91 cytokines on sepsis are presented as odds ratios (ORs) with 95% confidence intervals (CIs) per 1 SD genetically predicted cytokine change. The influences of sepsis on systemic inflammatory regulators are reported as β coefficients with 95% CIs.[13] Given the exploratory nature of this study and the high dimensionality of cytokine data (n = 91), we prioritized sensitivity analyses over strict multiple testing correction. While this approach increases the risk of Type I errors, it aligns with recent MR guidelines for hypothesis generation.[12] Future confirmatory studies should apply methods such as Benjamini-Hochberg correction to control false discovery rates.

2.7. Sensitivity analysis

The Inverse-Variance Weighted (IVW) method was employed as the primary method of analysis. When the number of instrumental variables was limited to one, we utilized the Wald ratio analysis method. Heterogeneity in IVW estimates was then scrutinized via the Cochran Q test. Horizontal pleiotropy was evaluated by the intercept *P* value of the MR-Egger. Additionally, MR-Egger, Weighted Median, Simple Mode, Weighted Mode, and MR-PRESSO methods served as sensitivity analysis methods. The *P* value from the pleiotropy test was adopted to examine the presence of pleiotropy. If the obtained *P* value exceeded .05, this indicated a negligible risk of pleiotropy in the causal analysis, allowing it to be overlooked. To ascertain the consistency of the results, a leave-one-out analysis was implemented. MR-Egger analysis measures instrumental variable pleiotropy, wherein a non-zero intercept demonstrates that the IVW estimate may be skewed.[27] A weighted median, conversely, can deliver a consistent estimate for the causal effect even if up to half of the SNPs infringe on horizontal pleiotropy.[28] As this study's large sample size accommodated the exploration of numerous potential positives, we did not perform multiple testing correction for adjusting significance levels. All analyses were two-sided and executed using the TwoSampleMR (version 0.5.6) packages in R software (version 3.6.3). The report adhered to the STROBE-MR statement.

3. Results

3.1. Causal effects of circulating levels of systemic inflammatory regulators on sepsis

We did not find any potential correlation between genetically predicted circulating levels of systemic inflammatory regulators in the GWAS Catalog data (All $P > .05$) (Fig. 3), but based on the IEU-open GWAS project, lower beta-nerve growth factor levels is inversely associated with decreased risks of sepsis (OR = 0.769, 95% CI = 0.599–0.987, $P = .039$), because there are too few sites of SNPs (n = 2), MR analysis other than IVW cannot be performed. And we also found that higher Tumor Necrosis Factor (TNF)-related apoptosis-inducing ligand levels and vascular endothelial growth factor A level are inverselyassociated with decreased risks of sepsis (OR = 1.094, 95% CI = 1.012–1.183, $P = .025$; OR = 1.182, 95% CI = 1.016–1.375, $P = .031$, respectively) (Fig. 4), the MR-Egger for them were OR = 1.135, 95% CI = 0.996–1294, $P = .107$, and OR = 1.522, 95% CI = 0.917–2.525, $P = .246$, respectively. Furthermore, Q values based on MR-Egger and IVW tests showed that there was no obvious heterogeneity (all $P > .05$).

3.2. Causal effects of sepsis on circulating levels of systemic inflammatory regulators

After MR Analysis of the data from the GWAS Catalog, we found that the lower circulating level of adenosine deaminase and Interieukin-17A (IL-17A) were related to an increased risk of sepsis (β = –0.043, 95% CI = –0.085 to –0.002, $P = .042$; β = –0.061, 95% CI = –0.108 to –0.013, $P = .012$, respectively) using IVW methods, and higher circulating level of beta-nerve growth factor was found to be related to an increased risk of sepsis (β = 0.056, 95% CI = 0.015–0.096, $P = .007$) (Fig. 5). MR analysis based on IEU-open GWAS project data showed that the higher circulating level of Delta/Notch-like EGF-related receptor (DNER), Fibroblast growth factor 23, leukemia inhibitory factor, monocyte chemoattractant protein-1 and Osteoprotegerin were related to an increased risk of sepsis (β = 0.137, 95% CI = 0.035–0.240, $P = .009$; β = 0.118, 95% CI = 0.020–0.216, $P = .018$; β = 0.136, 95% CI = 0.020–0.252, $P = .022$; β = 0.143, 95% CI = 0.043–0.242, $P = .005$; β = 0.116, 95% CI = 0.010–0.222, $P = .031$, respectively) (Fig. 6). MR-Egger Intercept did not detect potential horizontal pleiotropy for them (OR = 1.008, 95% CI = 0.923–1.102, $P = .858$; OR = 0.099, 95% CI = 0.916–1.090, $P = .991$; OR = 0.909, 95% CI = 0.821–1.006, $P = .106$; OR = 0.927, 95% CI = 0.753–1.140, $P = .486$; OR = 1.165, 95% CI = 0.945–1.437, $P = .178$; OR = 1.129, 95% CI = 0.872–1.463, $P = .375$; OR = 1.168, 95% CI = 0.943–1.445, $P = .180$; OR = 0.974,

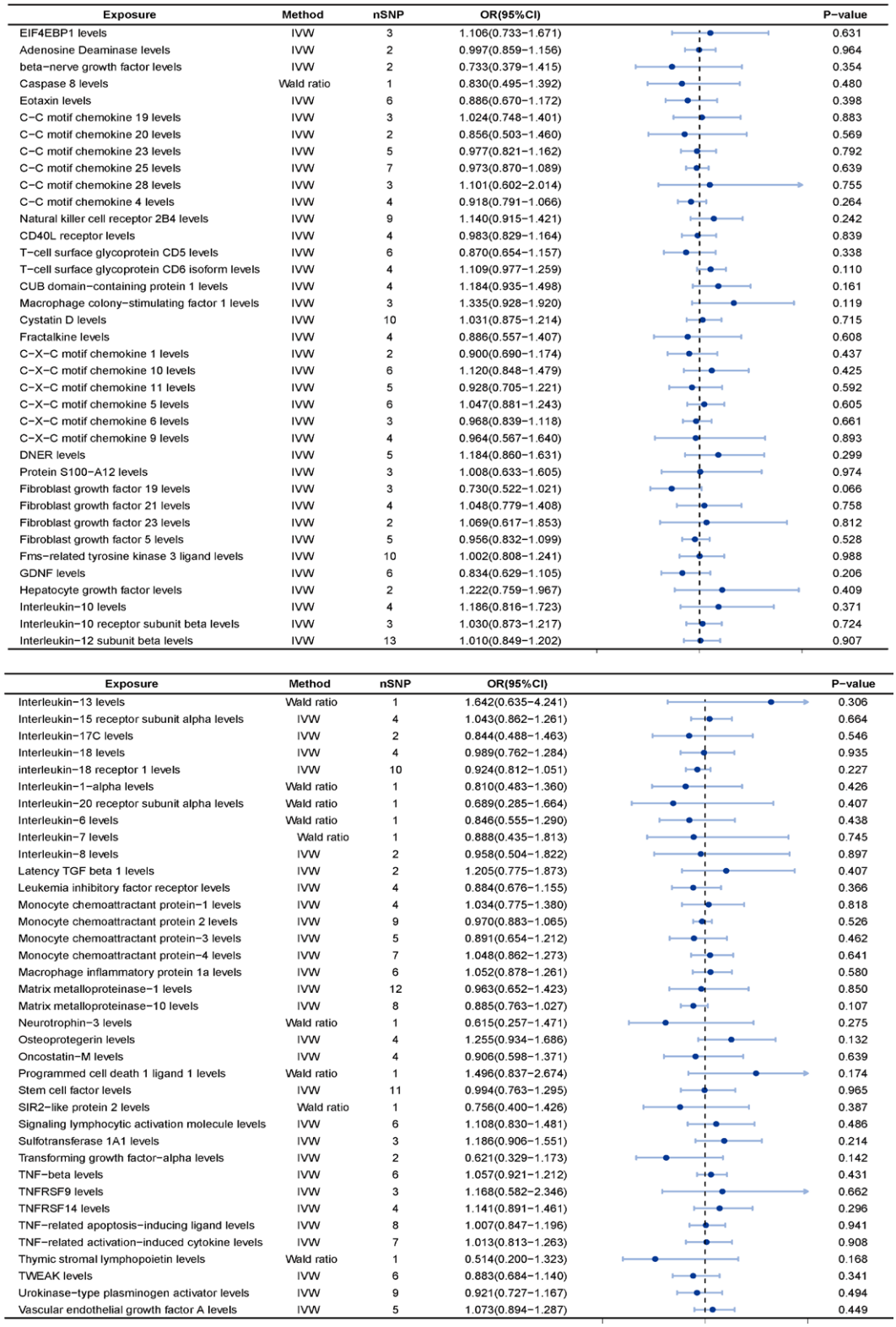

Figure 3. The causal association between between sepsis and circulating inflammatory factors when exposures were circulating inflammatory factors based on GWAS catalog. Inverse-variance weighting was regarded as the major method in this study. *P* value for heterogeneity based on Cochran's Q statistic for IVW. CI = confidence internal, GWAS = gene-wide association study, IVW = inverse variance weighted, MR = mendelian randomization, nSNP = numbers of single nucleotide polymorphism, OR = odds ratio.

95% CI = 0.785–1.209, $P = .816$, respectively). Furthermore, there was also no obvious heterogeneity (all $P > .05$). Leave-one out studies were used for sensitivity analysis and demonstrated no influence of individual studies.

3.3. Sensitivity analyses

The results produced by MR-Egger, simple mode, weighted mode, weighted median, and MR-PRESSO methodologies provided consistent estimates regarding both the magnitude and direction

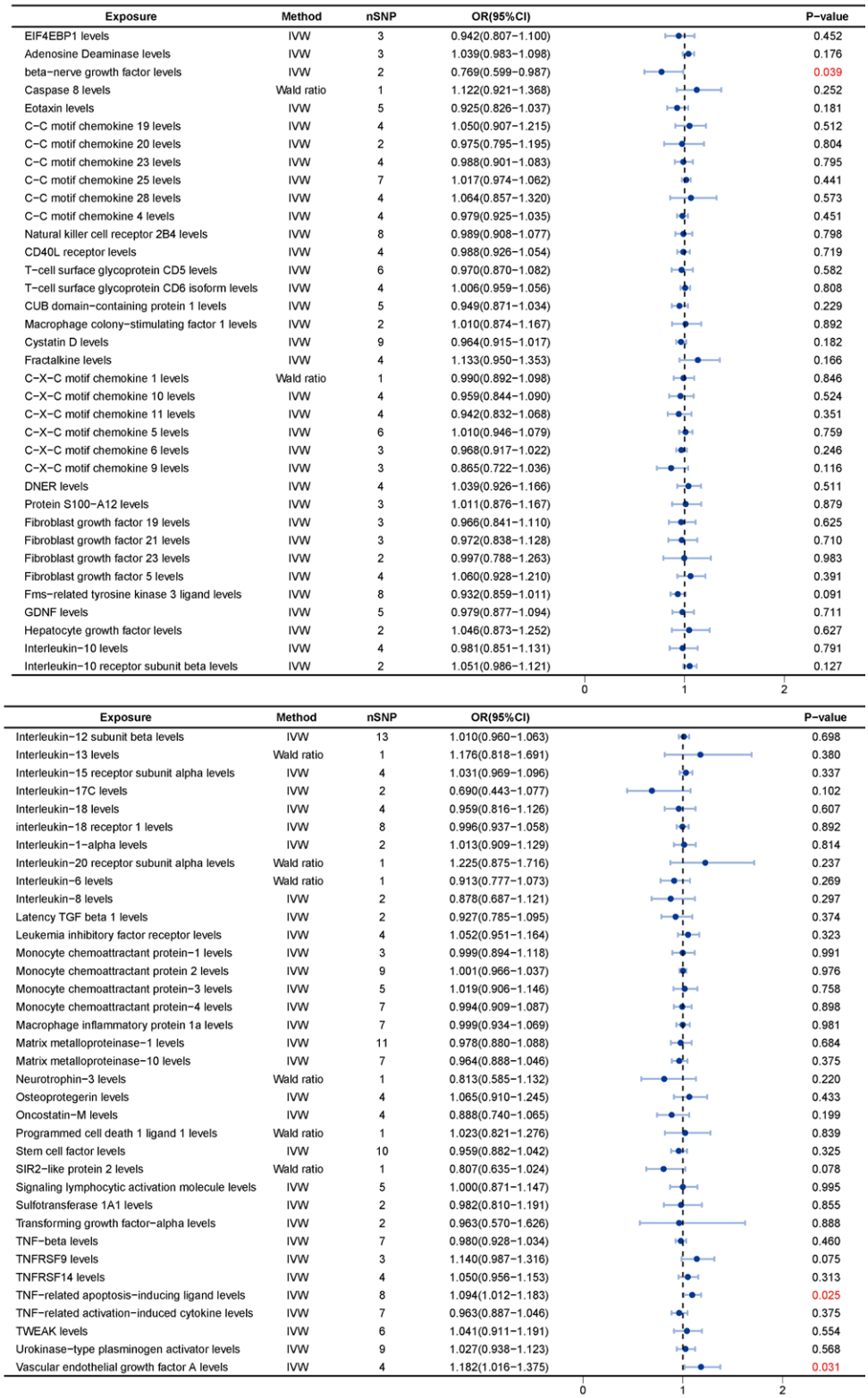

Figure 4. The causal association between between sepsis and circulating inflammatory factors when exposures were circulating inflammatory factors based on IEU-open GWAS project. Inverse-variance weighting was regarded as the major method in this study. *P* value for heterogeneity based on Cochran's Q statistic for IVW. CI = confidence internal, GWAS = gene-wide association study, IVW = inverse variance weighted, MR = mendelian randomization, nSNP = numbers of single nucleotide polymorphism, OR = odds ratio.

of causality. MR-Egger's regression intercept approach revealed no significant evidence of horizontal pleiotropy relevant to the susceptibility of sepsis due to circulating inflammatory factors with $P > .05$. The absence of outliers detected by MR-PRESSO posits a lack of substantive evidence to affirm the presence of heterogeneity in the research outcomes. Furthermore, no significant heterogeneity was observed from the conclusions extracted from Cochrane's Q Statistics, with all $P > .05$ (Figs. 7 and 8).

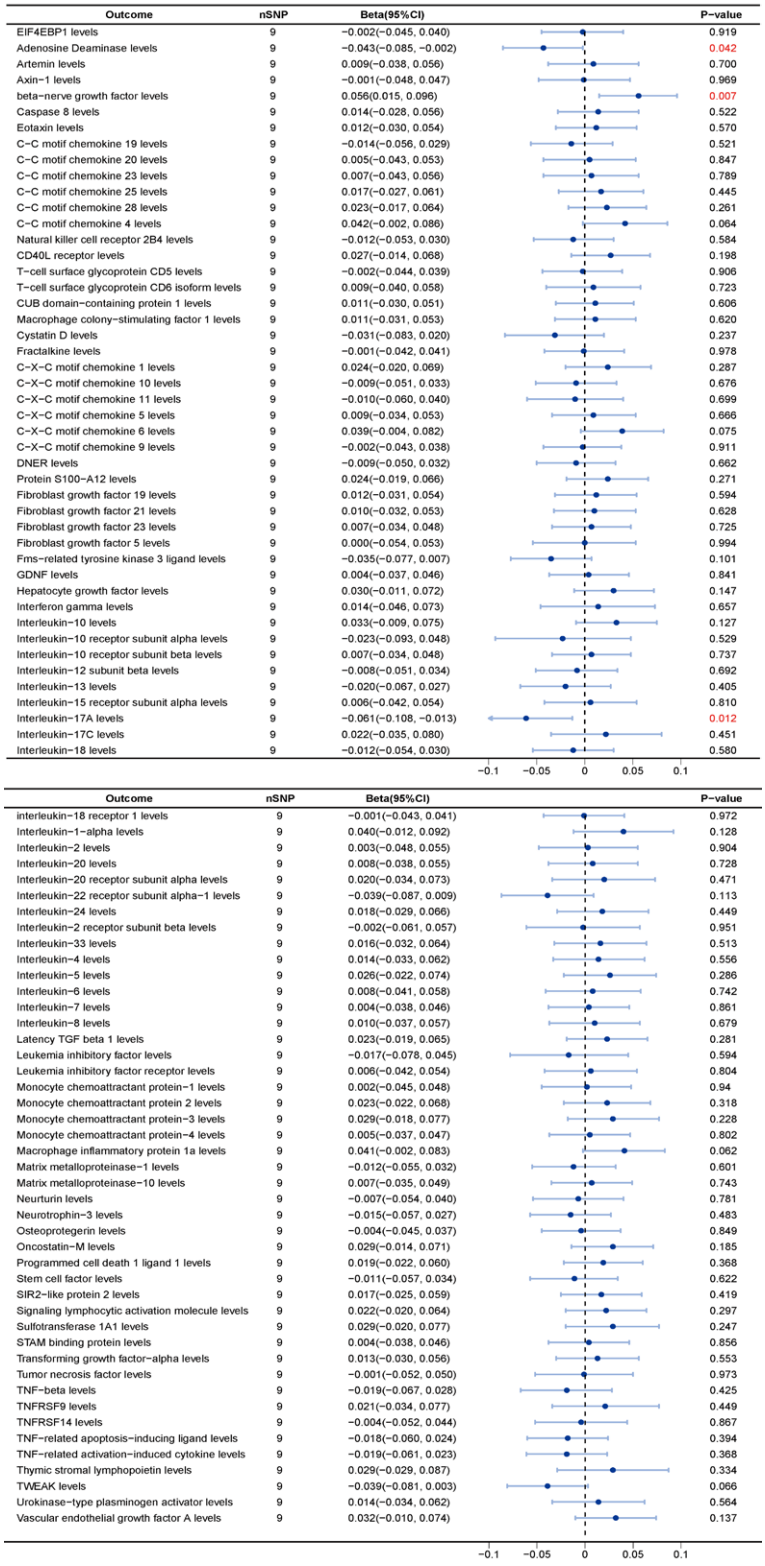

Figure 5. The causal association of sepsis on circulating levels of systemic inflammatory regulators based on GWAS catalog. Inverse-variance weighting was regarded as the major method in this study. *P* value for heterogeneity based on Cochran's Q statistic for IVW. CI = confidence internal, GWAS = gene-wide association study, IVW = inverse variance weighted, MR = mendelian randomization, nSNP = numbers of single nucleotide polymorphism, OR = odds ratio.

4. Discussion

In this bidirectional two-sample Mendelian randomization study, we employed pooled GWAS data from a European demographic to scrutinize the causal relationships between 91 biomarkers and sepsis. The results unequivocally established a causal relationship between the genetically predetermined levels of systemic inflammatory regulators and sepsis susceptibility.

Our analysis revealed an inverse relationship between increased beta-nerve growth factor (BNGF) levels and sepsis incidence. NGF, a polypeptide indispensable to normal neural

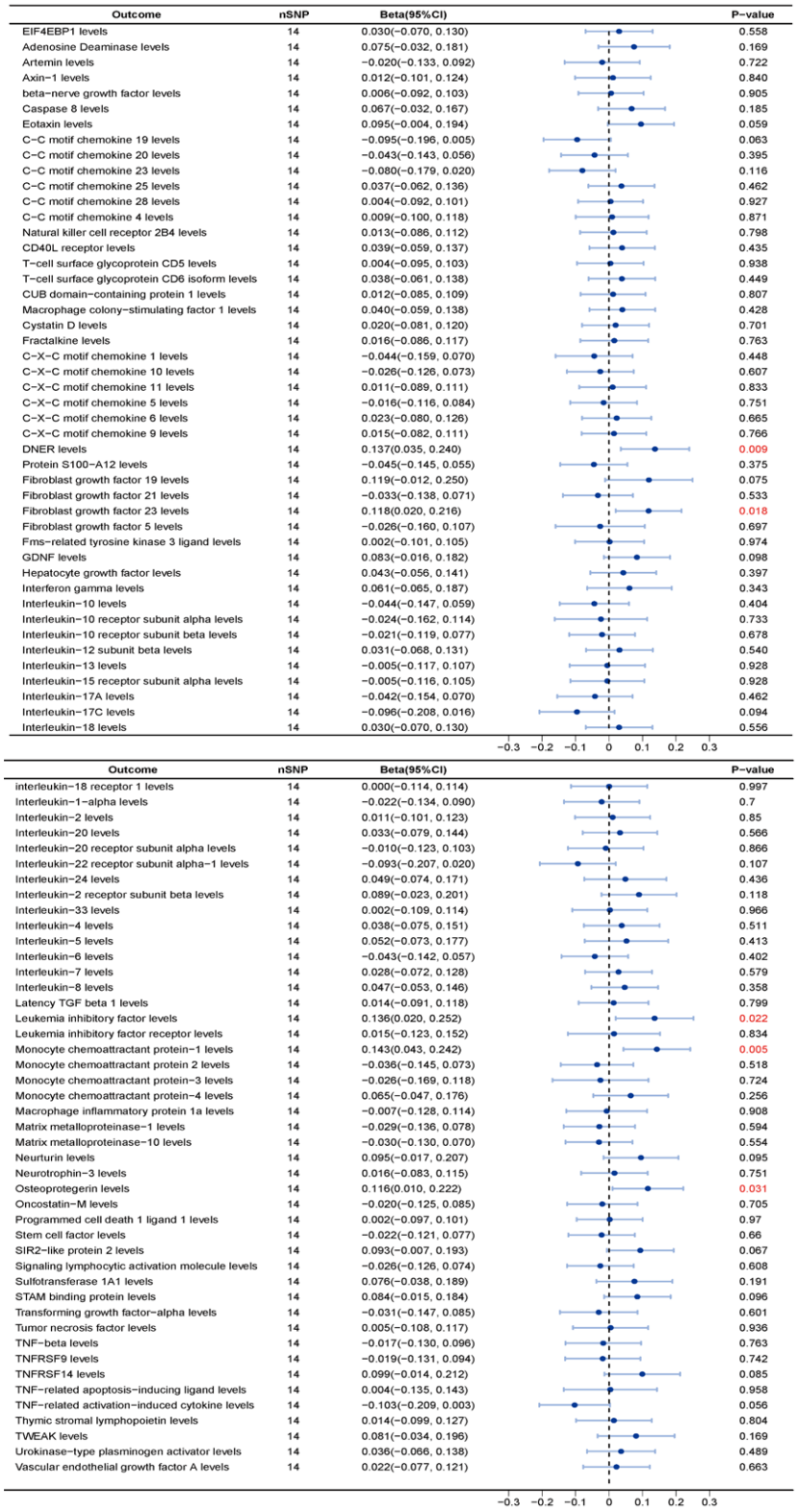

Figure 6. The causal association of sepsis on circulating levels of systemic inflammatory regulators based on based on IEU-open GWAS project. Inverse-variance weighting was regarded as the major method in this study. *P* value for heterogeneity based on Cochran's Q statistic for IVW. CI = confidence internal, GWAS = gene-wide association study, IVW = inverse variance weighted, MR = mendelian randomization, nSNP = numbers of single nucleotide polymorphism, OR = odds ratio.

development, fosters the sustenance and differentiation of sensory and sympathetic neurons in culture.[29] Additionally, it has been associated with cognitive alterations following brain damage.[30] Sepsis-induced dysfunction of the central nervous system often results from a localized generation of inflammatory cytokines, cerebral microcirculation disruption, imbalances in neurotransmitters, and apoptosis.[31] Our study uncovers an inverse causality between B-NGF and sepsis, linking an augmented risk

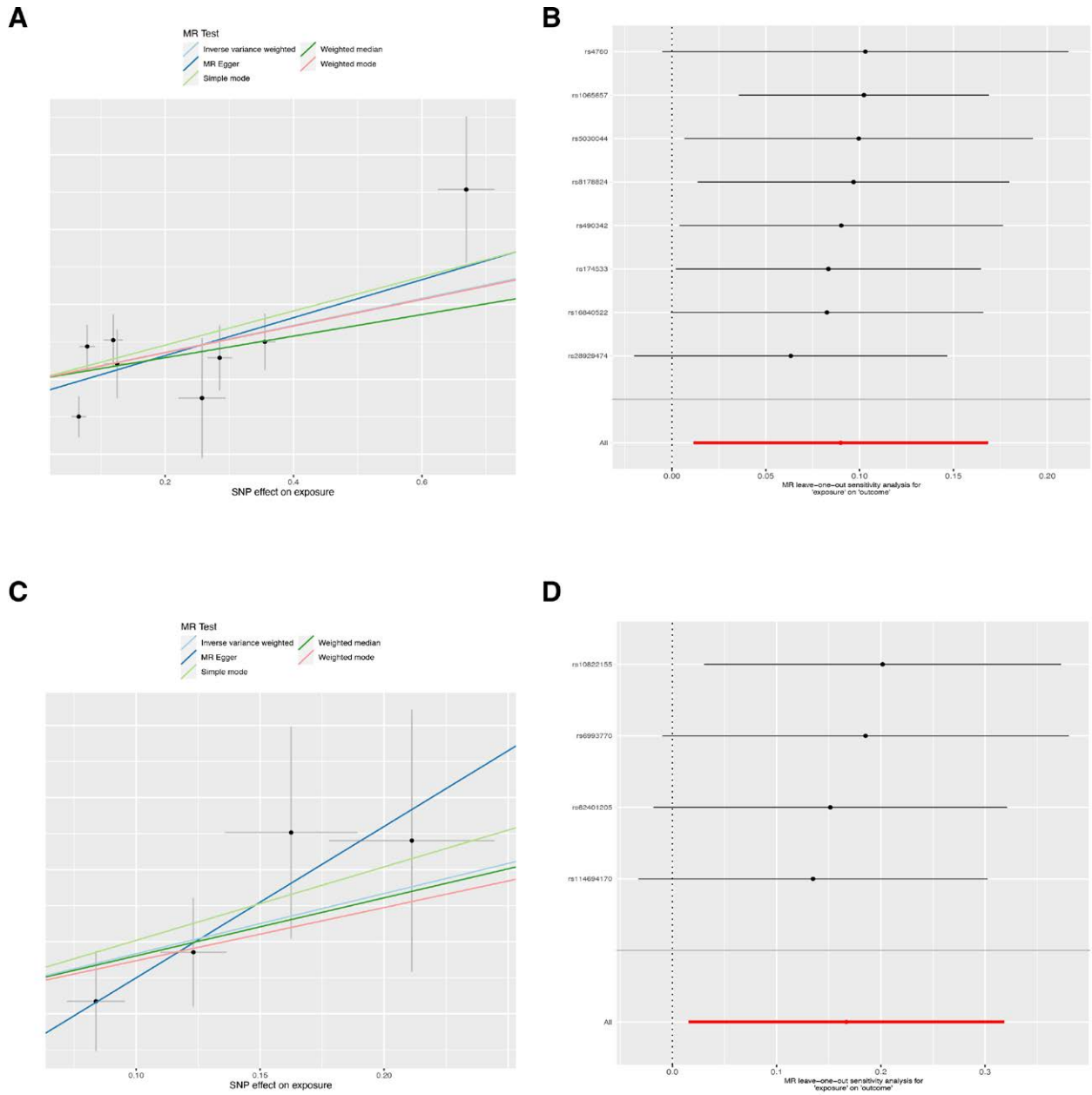

Figure 7. Scatter plots and Leave-one-out plots of circulating levels of systemic inflammatory regulators related SNPs with the risk of sepsis when outcome was spesis. Red lines in leave-one-out plots represent estimations from the IVW test. (A) and (B): Genetic association of TNF-related apoptosis-inducing ligand levels related SNPs and sepsis. (C) and (D): Genetic association of vascular endothelial growth factor A level related SNPs and sepsis. IVW = inverse variance weighted, SNPs = single nucleotide polymorphisms.

of sepsis with decreased circulating BNGF levels, which is also consistent with previous research results. Previous research has unearthed a positive correlation between expansive involutive changes, heightened distribution, and increased NGF immunoreactivity in the mast cells derived from autopsy thymus specimens in pediatric cases of sepsis.[32] Animal studies further demonstrate that elevated NGF levels catalyze cellular activity and expedite bone tissue regeneration.[33] Reports have underscored mitochondrial impairment and reduced NGF levels in the hippocampus of septic diabetic patients.[34] These findings indirectly substantiate our conclusion that genetically predicted higher β-NGF levels may escalate sepsis risk, potentially attributable to its association with excessive inflammatory responses and cellular damage during sepsis. Despite the clear role of NGF in the interplay between the immune and nervous systems, a comprehensive understanding of NGF's influence on immune cells awaits further exploration.[35] While our MR analysis suggests a protective role of BNGF, experimental studies are needed to dissect its dual effects – for instance, whether BNGF modulates neuroinflammation directly or via cross-talk with peripheral immune cells during sepsis.[35]

TNF-related apoptosis-inducing ligand (TRAIL), a cytokine part of the TNF superfamily, triggers apoptosis in transformed or tumor cells upon binding to death receptors 4 or 5, thus playing a pivotal role in sepsis' immune responses.[36,37] TRAIL's multifaceted nature in sepsis involves inducing apoptosis in tissue-invading neutrophils, facilitating organ protection against sepsis-induced damage.[38–40] Our investigation found an increasing trend in sepsis development corresponding to elevated circulating TRAIL levels. Importantly, another study reported an association between plasma TRAIL and worsening prognosis in patients with sepsis.[41] However, a deviation was noted in

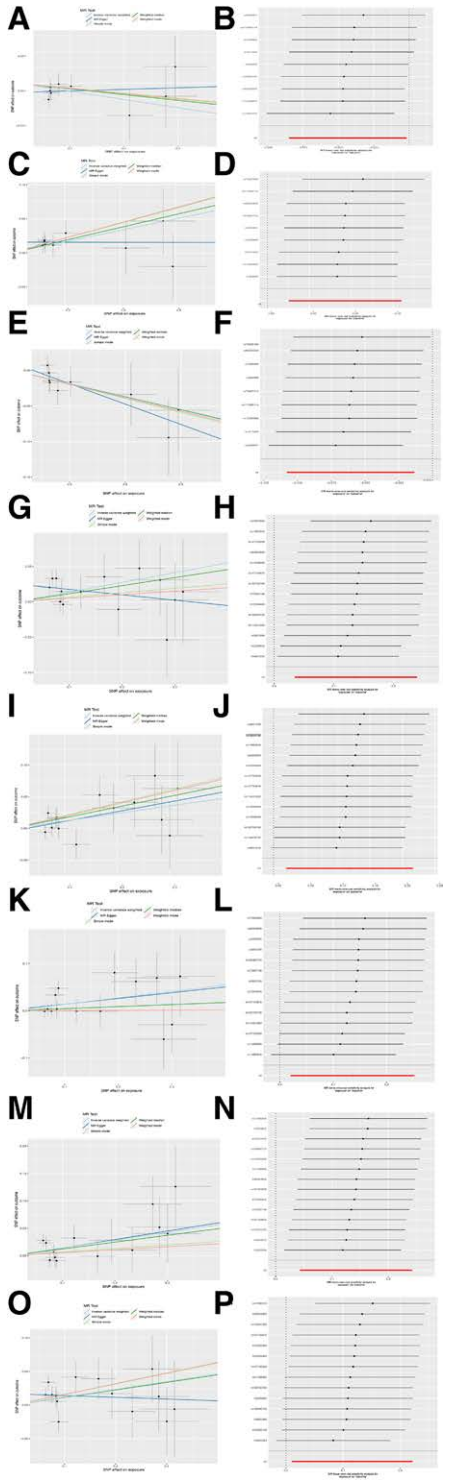

Figure 8. Scatter plots and Leave-one-out plots of circulating levels of systemic inflammatory regulators related SNPs with the risk of sepsis when outcome were circulating levels of systemic inflammatory regulators. Red lines in leave-one-out plots represent estimations from the IVW test. (A) and (B): Genetic association of adenosine deaminase levels related SNPs and sepsis. (C) and (D): Genetic association of Interieukin-17A (IL-17A) level related SNPs and sepsis. (E) and (F): Genetic association of beta-nerve growth factor level related SNPs and sepsis. (G) and (H): Genetic association of DNER level related SNPs and sepsis. (I) and (J): Genetic association of Fibroblast growth factor 23 level related SNPs and sepsis. (K) and (L): Genetic association of Leukemia inhibitory factor level related SNPs and sepsis. (M) and (N): Genetic association of Monocyte chemoattractant protein-1 level related SNPs and sepsis. (O) and (P): Genetic association of Osteoprotegerin level related SNPs and sepsis. IVW = inverse variance weighted, SNPs = single nucleotide polymorphisms.

another recent study where researchers identified a relationship between lower TRAIL levels and septic shock and organ dysfunction across 3 independent Intensive Care Unit cohorts.[42] Likewise, Beyer et al[43] reported that while exogenous and endogenous TRAIL was protective in early sepsis, endogenous TRAIL appeared to have a harmful effect in the later stages. Such contrasting viewpoints emphasize the necessity for a more profound understanding of TRAIL's underlying mechanisms in sepsis progression. This notion underscores the inherent complexity of sepsis and fuels the ongoing pursuit to unravel its multifarious aspects. Further research is needed to determine the precise role of TRAIL in sepsis and its potential as a therapeutic target.

Our research determined that increased plasma levels of vascular endothelial growth factor A (VEGF-A) are associated with a heightened risk of sepsis. Sepsis-induced inflammatory responses, complement activation, and coagulation characteristics can trigger severe endothelial dysfunction.[44] This dysfunction could subsequently provoke disorders in hemostasis and vascular reactivity, and tissue edema,[45] thereby exacerbating sepsis severity. VEGF-A impacts several endothelial cell properties, inclusive of Nitrous Oxide and prostacyclin production.[46] It also can induce the production and release of multiple cytokines, such as TNF, NF-κB, IL-4, IL-6, Monocyte chemotactic protein-1 (MCP-1), among others.[47,48] Some studies have noticed an upsurge in VEGF-A and a downswing in VEGF-B in septic children compared to controls.[49–51] One study in adults with sepsis linked elevated serum VEGF to worsening tissue perfusion and oxygenation, and significant influence on tissue fluid accumulation.[52] Additionally, a clinical study revealed septic children exhibiting specific higher concentration levels of IL-6, vascular endothelial growth factor (VEGF), and its soluble decoy receptor II.[53] A multicenter observational clinical trial suggested that dogs with naturally occurring sepsis and organ dysfunction had higher average concentrations of endothelial activation and inflammation biomarkers compared to their healthy counterparts.[54] These research endeavors underscore the pronounced elevation of VEGF, particularly VEGF-A, in sepsis and its pro-inflammatory role. These insights lend credence to its potential utility as a therapeutic target in managing sepsis. Due to the limitations of Mendelian randomization research, future studies should further explore potential mechanisms, mechanistic studies using sepsis models (e.g., cecal ligation and puncture in rodents) are essential to validate these genetic associations and explore therapeutic modulation of key cytokines like TRAIL and VEGF-A.

Adenosine deaminase acting on RNA 1 (ADAR1), a double-stranded RNA-editing enzyme responsible for converting adenosine (A) to inosine (I), plays a significant role in regulating immune responses.[55] A recent study unveiled ADAR1's hitherto unknown protective effect in maintaining intestinal homeostasis.[56] In line with this, Zhao et al[57] demonstrated the regulatory roles of adenosine deaminase in sepsis pathology. Additionally, ADAR1 has been reported to attenuate inflammation and organ damage via the ADAR1-Mir-30a-SOCS3 axis in a mouse model, thereby serving as a protective agent in sepsis.[58] An in vitro study further established ADAR1's role in mitigating IL-1β-induced endothelial activation to prevent sepsis exacerbation.[59] Our study found an inverse correlation between adenosine deaminase and sepsis. However, given the multifaceted nature of downstream targeted molecules of RNA-editing enzyme ADAR1 and miRNA, the potential for other regulatory pathways influencing sepsis' evolution and progression cannot be ruled out. Therefore, further research is warranted to elucidate the precise relationship between adenosine deaminase and sepsis, it should focus on identifying novel ADAR1-dependent pathways and exploring the therapeutic potential of targeting ADAR1 to modulate immune responses in sepsis.

Interleukin (IL)-17A, part of the IL-17 family, may initially reduce the inflammatory response,[60] but subsequently has been reported to interact with specific inflammatory cytokines to amplify inflammation.[61] IL-17A has been implicated in spearheading neutrophil recruitment, host defense, and inflammation, thereby instigating tissue damage and aiding sepsis progression. This has been evidenced by increased IL-17A levels observed in the plasma and tissues of septic animal models.[62,63] Zhao et al[64] have noted a significant increase in IL-17 signaling pathway-related genes in the blood samples of septic patients compared to an age-matched healthy control group. Similarly, another clinical study[65] pointed to a link between heightened IL-17A levels and acute kidney injury in septic patients, further associated with greater renal damage and mortality. Additionally, Mikacenic et al[66] suggested that an uptick in circulating IL-17A levels might signal the onset of Acute Respiratory Distress Syndrome. However, contradictorily, our inverse MR analysis indicated that IL-17A levels inversely corresponded with sepsis incidence. In line with our findings, animal studies[67] have shown that exogenous IL-17A can mitigate the harmful inflammatory response, enhancing the survival rate of septic mice. This apparent discrepancy emphasizes the need for further well-designed trials to comprehensively explore the role of IL-17A in sepsis.

DNER is a transmembrane protein that potentially serves as oncogenic or antioncogenic factors by modulating cellular proliferation, invasion, and metastasis.[68] However, few studies have explored its link to sepsis. Our research identified a potential positive relationship between DNER and sepsis. A cohort study noted that DNER was downregulated in patients with severe infection.[69] These findings suggest that DNER could be involved in lymphopoiesis and apoptosis under pathological conditions. Additionally, an animal experiment highlighted that DNER plays a crucial role in mediating itouch cell-cell interactions and maintaining glucose homeostasis.[70] The possibility of DNER influencing the progression and remission of sepsis through these mechanisms merits further investigation. Future research should focus on elucidating the molecular pathways through which DNER affects sepsis progression and identifying potential therapeutic targets.

In conditions such as sepsis and autoimmune diseases, inflammation is frequently correlated with an upsurge in the fibroblast growth factor (FGF23).[71] As a bone-derived hormone, FGF23 is involved in a positive feedback loop with inflammation – FGF23 stimulates the production of pro-inflammatory cytokines, which in turn induce more FGF23 production.[72] Several studies have drawn a connection between elevated levels of circulating FGF23 and the activation of inflammatory cells in the liver.[73,74] Inflammatory cytokines are directly responsible for inducing FGF23 production in bones and osteoblast/osteocyte lines. Sepsis patients often exhibit transient hypophosphatemia, indicating regulation of FGF23 levels by pro-inflammatory factors.[75] It has been shown that pro-inflammatory stimuli can amplify the secretion of FGF23 by osteocytes.[76] In severe conditions, such as septic shock and myocardial injury, an escalation in inflammation is often accompanied by an abnormal increase in circulating FGF23 levels.[77] However, the biological significance of elevated FGF23 in the context of sepsis remains undefined. Nevertheless, due to its key role in correcting 1,25(OH)2D deficiency,[78] FGF23 may present therapeutic possibilities for enhancing survival rates in sepsis patients. Further research is warranted to explore this hypothesis and elucidate FGF23's functions in sepsis.

We identified a positive correlation between leukemia inhibitory factor (LIF) and sepsis. LIF, an interleukin-6 cytokine family member, mediates a variety of central nervous system (CNS) responses to inflammatory stimuli.[79,80] In patients with sepsis and septic shock, elevated circulating LIF levels were observed[81,82] and these levels were found to correlate with disease severity.[83] In animal models,[84] administering LIF was shown to mitigate the severity of sepsis and septic shock caused by live Escherichia coli infection. Another animal experiment[85] revealed that endogenous LIF enhances the expression of acute phase proteins and the production of IL-10, thus reducing the synthesis and release of TNF-α, providing some protection against sepsis. These findings suggest that changes in LIF are part of the host response to tissue damage induced by endotoxin and sepsis, offering new insights for future exploration of underlying mechanisms. Future research should focus on elucidating the specific pathways through which LIF exerts its protective effects in sepsis and exploring its potential as a therapeutic agent.

MCP-1, also known as chemokine ligand 2, is a pro-inflammatory chemokine involved in the recruitment and activation of monocytes and macrophages.[86] Our reverse MR analysis observed a positive correlation between MCP-1 and sepsis mortality. Previous studies[87,88] delineated a relationship between plasma levels of inflammatory cytokines, MCP-1, and outcomes in adults and children with sepsis. Inhibiting MCP-1 or specific MCP-1 antagonists curbed the release of TNF-α, IL-1β, and IL-6 from macrophages.[89] Another clinical study[90] associated the MCP-1/chemokine ligand 2 polymorphisms rs1024611 and rs2857656 with sepsis susceptibility and development. MCP-1 triggers the conversion of blood monocytes from anti-inflammatory IL-10 producing cells to pro-inflammatory TNF-α/IL-6 secreting cells,[91] and its blockers have demonstrated protective effects in animal models of sepsis.[92] Given these results, we propose an anti-MCP-1 strategy[93] for managing sepsis and endotoxin levels, as it might have significant therapeutic implications. Future research should focus on developing and testing MCP-1 inhibitors in clinical trials to determine their efficacy in reducing sepsis mortality.

Osteoprotegerin (OPG) is a soluble protein that, as consistent with our findings, exhibited higher serum levels in some patients with sepsis or septic shock.[94] High levels of OPG were linked to poor sepsis prognosis,[95] which may be partly attributed to OPG's ability to augment inflammation by inhibiting the receptor activator of NF-kappaB.[96] The Osteoprotegerin Ligand (OPGL), a member of the tumor necrosis factor ligand superfamily, has been implicated in T-cell and dendritic cell interactions. Rat experiments have corroborated this, with disease development being suppressed in monocyte/macrophage-mediated conditions following administration of receptor fusion proteins that block OPGL activity.[97] Our study provides additional genomic evidence for the link between osteoprotegerin and sepsis.

Our study highlights the potential of certain cytokines as biomarkers that could transform the way sepsis is diagnosed and managed. The identified associations between cytokine levels and sepsis risk offer a promising avenue for developing new diagnostic tools. By integrating these cytokine profiles into routine clinical assessments, healthcare providers can achieve earlier detection of sepsis, enabling timely interventions that could significantly improve patient outcomes. Additionally, the cytokines identified in our study, such as BNGF, TRAIL, and VEGF-A, may serve as therapeutic targets. Modulating their levels could reduce sepsis risk or severity, presenting a novel therapeutic strategy. This approach requires further investigation through clinical trials to validate efficacy and safety in diverse patient populations.To translate these findings into clinical practice, a few pathways could be considered. Firstly, collaborative efforts between researchers, clinicians, and industry partners are essential for the development and validation of cytokine-based diagnostic assays. Standardization of these assays across healthcare settings will be crucial to ensure reliability and reproducibility. Secondly, pilot studies and clinical trials should be initiated to explore therapeutic interventions targeting specific cytokines, focusing on optimizing treatment regimens and patient selection criteria. By advancing these strategies, the insights gained from this study can contribute to more personalized and effective

management of sepsis, ultimately reducing the burden of this complex and often life-threatening condition.

While this study provides valuable insights into the potential causal relationship between systemic inflammatory regulators and sepsis, several limitations must be acknowledged. First, our reliance on summary statistics, rather than individual-level data, limited our ability to conduct more granular analyses, such as delineating the different etiologies of sepsis or exploring non-linear genetic associations. In our research, the use of summary level GWAS data can improve the statistical efficacy, and it is relatively easy to obtain summary level GWAS data, which can save time and resources. However, the disadvantage is that it depends on the effectiveness of GWAS results reported by other research teams. If there are deviations or errors in these data, it may affect the results of MR analysis, and the use of individual level data can carry out more comprehensive analysis, such as nonlinear MR analysis or analysis of specific subgroups (such as only in smokers). The use of aggregated data limits these more in-depth analyses. In addition, the double sample design requires that 2 samples represent similar basic populations. If the age, sex or other characteristics of the 2 samples are different, the reliability of the instrumental variables may be affected, and there may be overlapping cases in the 2 samples, which will also make the MR estimation biased in the direction of observation correlation, especially when the correlation between genetic and risk factors is not strong. These limitations prompt us to improve in future research. Our inability to stratify sepsis cases by infection source (e.g., pulmonary vs abdominal) or clinical severity scores (e.g., SOFA, APACHE II) due to data availability constraints represents a critical limitation. Future studies with access to granular clinical metadata should prioritize stratified MR analyses to explore subtype-specific causal relationships. Future research could benefit from access to raw data, which would enable more intricate analyses and potentially uncover additional insights. Moreover, the potential for horizontal pleiotropy, where genetic variants influence the outcome through pathways other than the exposure of interest, presents a concern. Although we employed several sensitivity analyses and included a broad array of genetic variants as instrumental variables, identifying and accounting for pleiotropic effects remains a challenge and limits causal inference. Another significant limitation is our inability to dissect subtype-specific effects of sepsis. This is critical given the heterogeneous nature of sepsis, influenced by diverse sources of infection, variations in host genetics, and comorbidities. Subtype-specific analyses could provide more targeted insights and are an important direction for future studies. The population stratification bias is another concern due to the predominance of European ancestry in the GWAS data. This overrepresentation may limit the findings' generalizability to other ethnic groups, highlighting the need for more diverse genetic data in future studies to ensure broader applicability of the results. Future multicenter and multinational collaborations that would include diverse populations to validate our findings across different ethnic backgrounds, particularly in regions with high sepsis burden (e.g., Asia and Africa). Additionally, our focus on circulating cytokine levels, while informative, potentially overlooks significant contributions from local tissue cytokine environments, which may more accurately reflect the inflammatory processes associated with sepsis.[98] Integrated approaches that consider both systemic and local inflammatory responses could further elucidate the complex nature of cytokine involvement in sepsis. Lastly, socio-economic status (SES)[99] is a confounding factor not adequately addressed in this study. SES can affect baseline cytokine levels and sepsis risk through various pathways, yet our study did not find direct associations between SES, the exposures, and the outcomes.[100] Future MR studies should consider stratifying by SES to better understand its potential moderating effects.

In conclusion, addressing these limitations in future research efforts will be crucial to strengthen the understanding of the causal pathways linking systemic inflammatory regulators to sepsis and enhance the generalizability and clinical relevance of such findings across diverse populations. Our findings highlight several cytokines (e.g., TRAIL, VEGF-A) as potential biomarkers for sepsis risk stratification. Integrating these biomarkers into existing diagnostic frameworks (e.g., qSOFA) could improve early detection in high-risk populations. Furthermore, therapies targeting MCP-1 or OPG pathways – already under investigation in autoimmune diseases – may be repurposed for sepsis management. Collaborative efforts between geneticists, clinicians, and pharmaceutical developers are critical to translate these insights into clinical trials.

5. Conclusions

In conclusion, our study found that decreased levels of BNGF, TRAIL, and VEGF-A were inversely associated with sepsis risk. On the other hand, lower circulating levels of adenosine deaminase and IL-17A, coupled with higher circulating levels of BNGF, DNER, FGF23, LIF, MCP-1, and OPG were linked to a heightened risk of sepsis. These findings underscore the pivotal role of cytokines in the pathogenesis of sepsis. Consequently, regulating these inflammatory factors and intervening therapeutically might be a promising strategy for both future treatment and prevention of sepsis. However, further studies are required to confirm whether these biomarkers can indeed be harnessed for sepsis prevention or treatment. Our findings contribute foundational knowledge to the field of sepsis research, emphasizing the need for comprehensive exploration of cytokine interactions. By addressing these limitations and translating these findings into clinical applications, future efforts can enhance the efficacy of sepsis management, paving the way for personalized diagnostic and therapeutic strategies.

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Author contributions

Conceptualization: Jiaqi Lou, Ziyi Xiang, Neng Huang.
Data curation: Jiaqi Lou, Ziyi Xiang.
Formal analysis: Jiaqi Lou, Xiaoyu Zhu.
Funding acquisition: Youfen Fan, Jiliang Li, Shengyong Cui.
Investigation: Jiaqi Lou, Ziyi Xiang.
Methodology: Jiaqi Lou, Ziyi Xiang, Xiaoyu Zhu.
Project administration: Neng Huang.
Resources: Jiaqi Lou, Xiaoyu Zhu, Youfen Fan, Jiliang Li, Guoying Jin.
Software: Jiaqi Lou, Ziyi Xiang, Youfen Fan, Jiliang Li, Guoying Jin, Neng Huang.
Supervision: Youfen Fan, Neng Huang.
Validation: Youfen Fan, Neng Huang.
Visualization: Youfen Fan, Neng Huang.
Writing – original draft: Jiaqi Lou.
Writing – review & editing: Jiaqi Lou, Ziyi Xiang, Neng Huang.

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