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Multi-omic studies on the pathogenesis of Sepsis

Hongjie Tong[1,2†], Yuhang Zhao[3†], Ying Cui[4], Jiali Yao[1*] and Tianlong Zhang[4*]

Abstract

Background Sepsis is a life-threatening inflammatory condition, and its underlying genetic mechanisms are not yet fully elucidated. We applied methods such as Mendelian randomization (MR), genetic correlation analysis, and colocalization analysis to integrate multi-omics data and explore the relationship between genetically associated genes and sepsis, as well as sepsis-related mortality, with the goal of identifying key genetic factors and their potential mechanistic pathways.

Methods To identify therapeutic targets for sepsis and sepsis-related mortality, we conducted an MR analysis on 11,643 sepsis cases and 1,896 cases of 28-day sepsis mortality from the UK Biobank cohort. The exposure data consisted of 15,944 potential druggable genes (expression quantitative trait loci, eQTL) and 4,907 plasma proteins (protein quantitative trait loci, pQTL). We then performed sensitivity analysis, SMR analysis, reverse MR analysis, genetic correlation analysis, colocalization analysis, enrichment analysis, and protein-protein interaction network analysis on the overlapping genes. Validation was conducted using 17,133 sepsis cases from FinnGen R12. Drug prediction and molecular docking were subsequently used to further assess the therapeutic potential of the identified drug targets, while PheWAS was used to evaluate potential side effects. Finally, mediation analysis was conducted to identify the mediating role of related metabolites.

Results The MR analysis results identified a significant causal relationship between 24 genes and sepsis. The robustness of these causal associations was further strengthened by SMR analysis, sensitivity analysis, and reverse MR analysis. Genetic correlation analysis revealed that only two of these genes were genetically correlated with sepsis. Colocalization analysis showed that only one gene was closely associated with sepsis, while validation using the FinnGen dataset identified three genes. In the MR analysis of 28-day sepsis mortality, seven genes were found to have significant associations, with reverse MR analysis excluding one gene. The remaining genes passed sensitivity analysis, with no significant genes identified in genetic correlation and colocalization analyses. Molecular docking demonstrated excellent binding affinity between drugs and proteins with available structural data. PheWAS at the gene level did not reveal any potential side effects of the related drugs.

†Hongjie Tong and Yuhang Zhao are contributed equally to this work.

*Correspondence:
Jiali Yao
yaojiali0706@163.com
Tianlong Zhang
zhangtianlong@zju.edu.cn

Full list of author information is available at the end of the article

Conclusions The identified drug targets, associated pathways, and metabolites have enhanced our understanding of the complex relationships between genes and sepsis. These genes and metabolites can serve as effective targets for sepsis treatment, paving new pathways in this field and laying a foundation for future research.

Keywords Sepsis, eQTL, pQTL, Mendelian randomization, Genetic correlation, Colocalization

Background

Sepsis is defined as a life-threatening organ dysfunction resulting from a dysregulated host response to infection [1]. It can be triggered by various pathogens, including bacteria, viruses, fungi, parasites, and others [2]. According to a 2017 analysis of the global burden of disease, sepsis-related deaths accounted for approximately 19.7% of all deaths worldwide [3]. Despite advancements in antibiotic treatments and supportive care, the mortality rate for sepsis remains high [4]. The underlying mechanisms are still not fully understood, presenting a major challenge to human health and safety. This highlights the urgent need for further research into its pathophysiological mechanisms and the development of new therapeutic interventions.

In recent years, the emergence of multi-omics research has enabled the integration of data from various biological fields, such as genomics (expression quantitative trait loci, eQTL) [5] and proteomics (protein quantitative trait loci, pQTL) [6], facilitating cross-validation among diverse components. These approaches have provided compelling evidence for identifying potential biomarkers and therapeutic targets [7]. Additionally, metabolites, as the final products or intermediates of metabolism, reflect the intricate interplay among genomic, epigenomic, transcriptomic, and proteomic processes, while also capturing the system's response to environmental influences [8]. Metabolomics, by uncovering the biochemical activities within cells, tissues, and organs, offers a critical framework for understanding disease mechanisms and devising preventive strategies [9].

In this study, we combined expression eQTL and pQTL with genome-wide association study (GWAS) datasets to link gene expression and protein levels with disease risk, providing a powerful tool for identifying disease-related therapeutic targets. Traditional proteomics and genomics research has often been limited by high costs and ethical challenges associated with participant recruitment. To overcome these limitations, Mendelian randomization (MR) analysis has emerged as a widely adopted approach for drug target development and the repurposing of existing drugs [10]. As a powerful tool for investigating causal relationships between genetic variation and disease, MR uses genetic variants as instrumental variables to minimize common biases in observational studies, such as confounding and reverse causation, thereby elucidating the relationship between relevant factors and disease [11]. Previous studies have utilized multi-omics MR analysis to identify therapeutic targets for genes associated with migraine [12] and sarcopenia [13]. However, no studies to date have combined eQTL and pQTL data to investigate sepsis and its 28-day mortality. In this study, we selected instrumental variables (IVs) associated with eQTLs and pQTLs to directly infer the causal relationship between gene expression and protein levels in sepsis. Additionally, we conducted reverse MR analysis, summary-data-based Mendelian randomization (SMR), genetic correlation analysis, colocalization analysis, and mediation analysis of gene-related metabolites. The objectives of this study are: [1] to identify genes that may influence sepsis and 28-day sepsis mortality, and [2] to uncover potential gene pathways and associated metabolites that may help elucidate the mechanisms underlying sepsis and 28-day sepsis mortality. Our findings aim to use MR in a multi-omics context to advance our understanding of the mechanisms driving sepsis and ultimately contribute to the development of new therapeutic strategies.

Methods

Study design

This MR study aims to investigate the causal relationship between eQTL, pQTL, and sepsis. Figure 1 presents a schematic representation of the study design. The MR methodology is based on three essential conditions (Fig. 1): (A) The genetic variants selected as instrumental variables (IVs) must be strongly associated with eQTL and pQTL; (B) The genetic instruments must be unrelated to sepsis outcomes and independent of potential confounding factors; (C) The genetic variants should influence sepsis risk specifically through certain genes, rather than through other pathways.

The sources of eQTL and pQTL data and the selection of instrumental variables

The eQTL data for potential drug target genes were obtained from a previously published study in a European population [14], identifying a total of 15,944 genes. The pQTL data were derived from GWAS summary statistics of 4,907 plasma proteins in a cohort of 35,559 Icelandic individuals [15]. All IVs underwent a rigorous filtering process: (i) SNPs were required to be robustly associated with gene expression levels ($P < 5 \times 10^{-8}$); (ii) SNPs were filtered to ensure minimal linkage disequilibrium (LD) (R^2 < 0.001, distance = 10,000 kb), indicating that each selected SNP is largely independent of the others; and (iii) the R^2 and F-statistics were calculated to assess

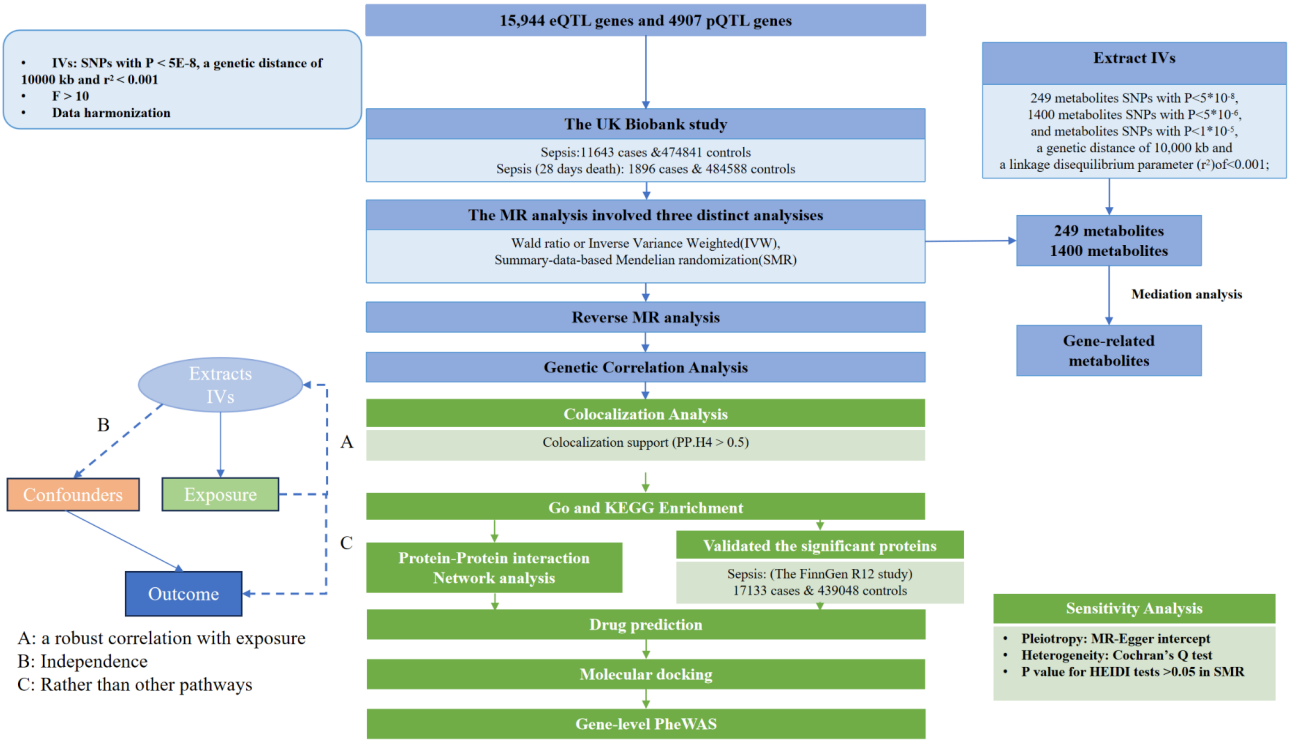


Fig. 1 A schematic representation of the study design

the strength of the IVs, with F-statistics greater than 10 selected to avoid potential bias caused by weak IVs [16].

Data sources on metabolites and IVs selection for Circulating metabolites

To include a more comprehensive range of metabolites, we selected data from two sources. One dataset included 249 circulating metabolites measured in 121,000 participants of European ancestry, provided by Nightingale Health, focusing mainly on lipids and lipoprotein particles [17]. The second dataset included 1,091 metabolites and 309 metabolite ratios from 8,091 individuals in the Canadian Longitudinal Study on Aging (CLSA) cohort, covering a broad spectrum of substances such as lipids, amino acids, xenobiotics, nucleotides, cofactors and vitamins, carbohydrates, peptides, and energy-related metabolites [18]. In the analysis of the 249 metabolites, SNPs with a p-value below the genome-wide significance threshold (5×10^{-8}) were selected as IVs. In the analysis of the 1,400 metabolites, it was not possible to fully extract SNPs at the 5×10^{-8} threshold. To enhance sensitivity and achieve more comprehensive results, we selected SNPs with p-values below the genome-wide significance thresholds of 5×10^{-6} and 1×10^{-5} as IVs. Subsequently, all IVs underwent LD clumping (r^2 = 0.001; distance = 10,000 kb) to reduce the impact of correlated SNPs.

Sources of Sepsis outcome data

The primary analysis of sepsis and 28-day sepsis mortality outcomes was conducted using data from the UK Biobank, which included 11,643 sepsis cases and 474,841 controls of European ancestry, as well as 1,896 cases of 28-day sepsis mortality and 484,588 controls [19]. Validation of these findings was performed using sepsis data from the FinnGen R12 biobank, consisting of 17,133 cases and 439,048 controls [20]. Unfortunately, there is no available GWAS data on 28-day sepsis mortality in the FinnGen study or other studies, so we were unable to perform validation for this specific outcome.

MR analysis

We initially employed a two-sample MR analysis to assess the causal relationship between eQTL, pQTL, and sepsis, as well as 28-day sepsis mortality. The primary methods used were the inverse variance weighted (IVW) fixed-effects method and the Wald ratio method in MR analysis. For genes with multiple SNPs, the IVW method was applied, while for genes with only a single SNP, the Wald ratio method was used. The Cochran Q test was employed to assess heterogeneity in causal effects, while the MR-Egger intercept assessed horizontal pleiotropy. A p-value below 0.05 in these tests generally suggests the existence of heterogeneity or pleiotropy [21]. Since MR analysis with a single SNP does not allow for heterogeneity testing, we performed summary data-based

Mendelian randomization (SMR) analysis (https://cnsgenomics.com/software/smr/#Overview) on genes with a single SNP to generate effect estimates. This approach provides significance levels to reinforce the evidence from the primary analysis. The heterogeneity in dependent instrument (HEIDI) test was used to differentiate between pleiotropic and linkage models, with a p-value below 0.05 indicating potential pleiotropy. Such results were excluded from further analysis [22]. To identify additional potentially relevant genes in eQTL and pQTL, we did not apply multiple testing correction, instead considering a p-value of less than 0.05 as indicative of significance. All MR analyses were performed using R software (version 4.4.2) with the TwoSampleMR package.

Reverse MR analysis

To prevent the influence of reverse causation, we performed reverse MR analysis to explore the potential causal effects of sepsis and 28-day mortality on significantly associated genes.

Genetic correlation analysis

We utilized linkage disequilibrium score regression (LDSC) to evaluate the shared polygenic architecture between genes and sepsis, using LD scores calculated from European ancestry samples in the 1000 Genomes Project as a reference panel. This approach evaluates genetic correlations using GWAS summary statistics, ensuring no bias is introduced due to sample overlap [23]. To pinpoint genes more strongly linked to sepsis, we conducted genetic correlation analysis based on the results of the MR analysis, considering a p-value below 0.05 as significant.

Colocalization analysis

We further performed colocalization analysis on the identified positive genes using the **coloc** R package to strengthen the genetic findings by identifying shared genetic variants associated with sepsis. Bayesian analysis was employed to evaluate the support for five mutually exclusive hypotheses, where H4 represents the hypothesis that both traits are associated and share the same causal variant [24]. Posterior probabilities (PP) were calculated for each hypothesis, and colocalization was considered supported when the posterior probability for H4 (PP.H4) exceeded 0.5.

GO and KEGG enrichment analysis

We performed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses on the significant genes. These analyses aimed to gain a deeper understanding of the biological functions and metabolic pathways of the genes. GO analysis examines the shared characteristics of genes in three categories: biological processes (BP), cellular components (CC), and molecular functions (MF). It evaluates the enrichment of genes within each GO annotation by comparing the analyzed genes against a reference genome, generating results for enrichment analysis. KEGG enrichment analysis, on the other hand, focuses primarily on the enrichment of genes within metabolic pathways [25].

Protein-Protein interaction network

To better understand how a protein interacts with another protein within the cell, we conducted a protein-protein interaction (PPI) network analysis. In this study, the PPI network was constructed using STRING (https://cn.string-db.org/), with a confidence score of 0.15 set as the minimum interaction threshold, while other parameters were kept at their default settings [26]. The PPI results were further visualized using Cytoscape (v3.10.3) [27].

Validation set

We validated the 24 genes identified in the UKB sepsis results using the latest R12 version of the FinnGen sepsis dataset (17,133 cases and 439048 controls) [20]. Currently, there are no other GWAS studies on 28-day sepsis mortality, so we could not validate the results related to 28-day sepsis mortality.

Drug target prediction

Evaluating protein-drug interactions is crucial for determining whether target genes can serve as practical drug targets. In this study, we utilized the Drug Signatures Database (DSigDB, http://dsigdb.tanlab.org/DSigDBv1.0/) [28] to accomplish this task. This database links drugs and other chemical compounds to target genes, enabling the prediction of candidate drugs to assess the therapeutic potential of the target genes.

Molecular Docking

To gain deeper insights into the impact of drug candidates on target genes and evaluate their druggability, we conducted molecular docking at the atomic level to determine the binding energy and interaction patterns between drug candidates and their respective targets. These molecular docking simulations allowed us to assess the binding affinity and interaction mechanisms between ligands and drug targets. By identifying ligands that exhibit strong binding affinity and favorable interaction profiles, we can prioritize drug targets for subsequent experimental validation and refine the design of potential drug candidates.

Phenome-wide association analysis

To further evaluate horizontal pleiotropy and potential side effects of candidate drug targets, we conducted a

phenome-wide association study (PheWAS) using the AstraZeneca PheWAS Portal (https://azphewas.com/) [29]. Gene expression data were used as the exposure variable, while outcome measures included approximately 15.5 K binary and 1.5 K continuous phenotypes from about 450,000 exome-sequenced participants in the UK Biobank cohort.

Additional mediation analysis

We conducted a two-step Mendelian randomization (MR) analysis to estimate the mediating role of circulating metabolites in the association between significant genes and sepsis. In the first step of the two-step MR, we assessed the effect of significant genes on circulating metabolites (β1). In the second step, we evaluated the effect of circulating metabolites on sepsis (β2). The proportion of the gene-sepsis association mediated by metabolites was calculated as the product of β1 and β2, divided by the total effect of the gene on sepsis (β3). The 95% confidence interval (CI) of the mediation proportion was calculated using the coefficient product method, and a p-value less than 0.05 was considered significant.

Results

eQTL, pQTL and Sepsis

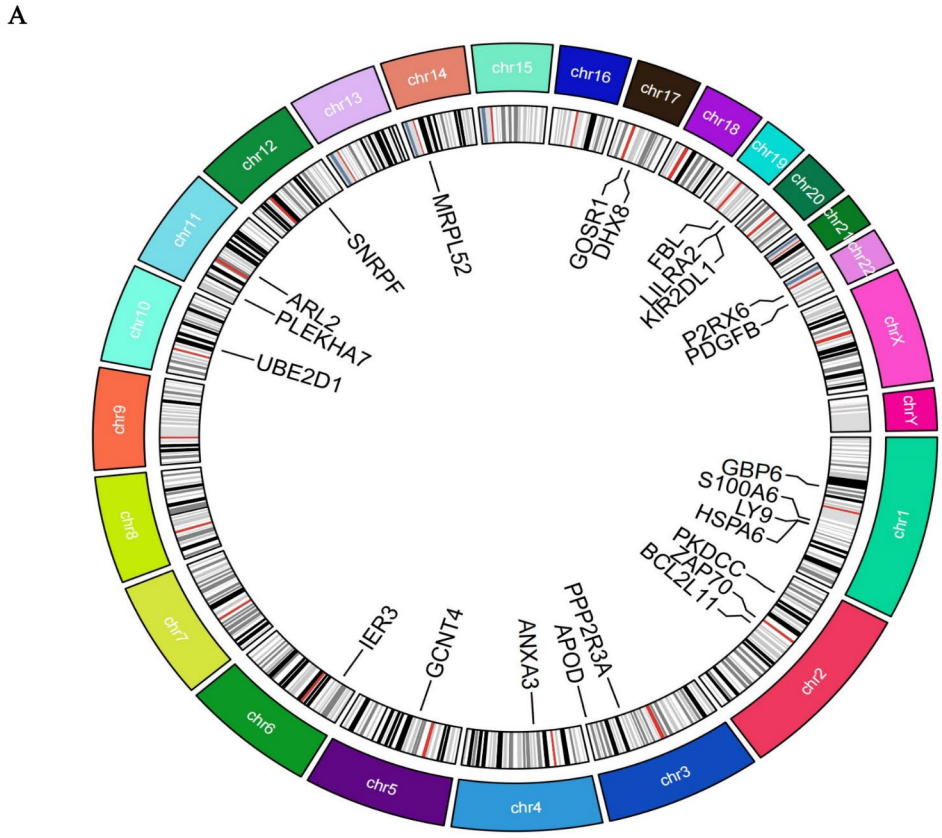
Our findings revealed suggestive associations ($P<0.05$) between sepsis and 742 eQTL genes, along with 766 pQTL genes (Table S1 and S2). To better identify genes more closely associated with sepsis, we examined the overlap between these two sets of genes and found that only 24 genes were strongly linked to sepsis. Among the 24 eQTL genes, 13 were identified as protective genes, including: APOD (OR: 0.775, 95% CI: 0.640–0.938, $P=9.03\times10^{-3}$), DHX8 (OR: 0.815, 95% CI: 0.677–0.982, $P=3.15\times10^{-2}$), FBL (OR: 0.782, 95% CI: 0.657–0.931, $P=5.79\times10^{-3}$), HSPA6 (OR: 0.866, 95% CI: 0.784–0.957, $P=4.65\times10^{-3}$), LY9(OR: 0.808, 95% CI: 0.711–0.918, $P=1.03\times10^{-3}$), MRPL52(OR: 0.909, 95% CI: 0.840–0.984, $P=1.81\times10^{-2}$), P2RX6(OR: 0.869, 95% CI: 0.775–0.974, $P=1.60\times10^{-2}$),PDGFB (OR: 0.864, 95% CI: 0.796–0.938, $P=5.21\times10^{-4}$),

PKDCC (OR: 0.745, 95% CI: 0.588–0.946, $P=1.55\times10^{-2}$), PPP2R3A (OR: 0.719, 95% CI: 0.562–0.921, $P=8.86\times10^{-3}$), S100A6 (OR: 0.748, 95% CI: 0.567–0.986, $P=3.95\times10^{-2}$),and UBE2D1(OR: 0.913, 95% CI: 0.860–0.969, $P=2.62\times10^{-3}$),ZAP70(OR: 0.854, 95% CI: 0.742–0.983, $P=2.79\times10^{-2}$). Additionally, 11 were identified as risk genes, including: ANXA3 (OR: 1.128, 95% CI: 1.018–1.250, $P=2.21\times10^{-2}$), ARL2 (OR: 1.205, 95% CI: 1.021–1.422, $P=2.71\times10^{-2}$),BCL2L11 (OR: 1.236, 95% CI: 1.028–1.485, $P=2.41\times10^{-2}$), GBP6 (OR: 1.298, 95% CI: 1.007–1.673, $P=4.37\times10^{-2}$),GCNT4 (OR: 1.238, 95% CI: 1.010–1.517, $P=3.40\times10^{-2}$),GOSR1 (OR: 1.592, 95% CI: 1.111–2.283, $P=1.13\times10^{-2}$),IER3(OR: 1.075, 95% CI: 1.007–1.147, $P=2.89\times10^{-2}$), KIR2DL1(OR: 1.120, 95% CI: 1.002–1.252, $P=4.65\times10^{-2}$), LILRA2(OR: 1.053, 95% CI: 1.003–1.107, $P=3.88\times10^{-2}$), PLEKHA7(OR: 1.183, 95% CI: 1.050–1.332, $P=5.68\times10^{-3}$), and SNRPF (OR: 1.237, 95% CI: 1.006–1.521, $P=4.40\times10^{-2}$).

Among the 24 pQTL genes, 20 proteins were identified as protective, including: ANXA3 (OR: 0.735, 95% CI: 0.592–0.914, $P=5.52\times10^{-3}$), APOD (OR: 0.863, 95% CI: 0.783–0.950, $P=2.72\times10^{-3}$), ARL2 (OR: 0.890, 95% CI: 0.837–0.947, $P=2.22\times10^{-4}$),

BCL2L11 (OR: 0.739, 95% CI: 0.556–0.982, $P=3.72\times10^{-2}$), DHX8 (OR: 0.783, 95% CI: 0.620–0.990, $P=4.10\times10^{-2}$), FBL (OR: 0.883, 95% CI: 0.798–0.976, $P=1.54\times10^{-2}$),GBP6 (OR: 0.901, 95% CI: 0.830–0.977, $P=1.16\times10^{-2}$),GCNT4 (OR: 0.716, 95% CI: 0.579–0.886, $P=2.10\times10^{-3}$),GOSR1 (OR: 0.861, 95% CI: 0.764–0.970, $P=1.42\times10^{-2}$),HSPA6 (OR: 0.856, 95% CI: 0.745–0.983, $P=2.79\times10^{-2}$),IER3(OR: 0.856, 95% CI: 0.770–0.952, $P=4.09\times10^{-3}$),KIR2DL1(OR: 0.871, 95% CI: 0.786–0.965, $P=8.09\times10^{-3}$),MRPL52(OR: 0.786, 95% CI: 0.648–0.954, $P=1.46\times10^{-2}$),P2RX6(OR: 0.732, 95% CI: 0.586–0.915, $P=6.09\times10^{-3}$),PKDCC (OR: 0.895, 95% CI: 0.815–0.983, $P=2.09\times10^{-2}$),PPP2R3A (OR: 0.887, 95% CI: 0.803–0.979, $P=1.76\times10^{-2}$),S100A6 (OR: 0.795, 95% CI: 0.661–0.955, $P=1.45\times10^{-2}$),UBE2D1(OR: 0.886, 95% CI: 0.811–0.968, $P=7.57\times10^{-3}$),and ZAP70(OR: 0.897, 95% CI: 0.828–0.972, $P=7.94\times10^{-3}$). In addition, 4 proteins were identified as risk factors, including: LILRA2(OR: 1.072, 95% CI: 1.006–1.143, $P=3.09\times10^{-2}$),LY9 (OR: 1.082, 95% CI: 1.008–1.161, $P=2.89\times10^{-2}$), PDGFB (OR: 1.188, 95% CI: 1.006–1.402, $P=4.28\times10^{-2}$), PLEKHA7(OR: 1.099, 95% CI: 1.004–1.203, $P=4.18\times10^{-2}$), and SNRPF (OR: 1.237, 95% CI: 1.006–1.521, $P=4.40\times10^{-2}$). Figure 2 presents the 24 significant associations between eQTL, pQTL, and sepsis.

MR-Egger regression did not indicate any evidence of horizontal pleiotropy ($P>0.05$). Cochran's Q test revealed no significant heterogeneity ($P>0.05$) (Table S3). For genes with only a single SNP, heterogeneity testing could not be performed. To address this limitation, we conducted SMR analysis, which further strengthened the robustness of our findings. The HEIDI test P-values for these genes were all greater than 0.05, indicating no evidence of heterogeneity (Table S4). The results of the reverse MR analysis did not find any association between sepsis and the 24 genes (Table S5). Genetic correlation analysis of these 24 genes revealed that only DHX8 ($rg=0.137$, $P=4.50\times10^{-2}$) and LILRA2 ($rg=0.520$, $P=4.24\times10^{-2}$) had significant genetic correlations with sepsis (Table S6 and Figure S1). Colocalization analysis of the 24 genes identified that only PDGFB (PP.H4 = 0.664) showed evidence of colocalization (Table S6 and Fig. 3).



B

eQTL and Sepsis

exposure	nsnp	method	pval	OR(95% CI)
ANXA3	3	Inverse variance weighted	**0.021**	1.128 (1.018 to 1.250)
APOD	1	Wald ratio	**0.009**	0.775 (0.640 to 0.938)
ARL2	2	Inverse variance weighted	**0.027**	1.205 (1.021 to 1.422)
BCL2L11	4	Inverse variance weighted	**0.024**	1.236 (1.028 to 1.485)
DHX8	1	Wald ratio	**0.032**	0.815 (0.677 to 0.982)
FBL	1	Wald ratio	**0.006**	0.782 (0.657 to 0.931)
GBP6	1	Wald ratio	**0.044**	1.298 (1.007 to 1.673)
GCNT4	1	Wald ratio	**0.040**	1.238 (1.010 to 1.517)
GOSR1	1	Wald ratio	**0.011**	1.592 (1.111 to 2.283)
HSPA6	4	Inverse variance weighted	**0.005**	0.866 (0.784 to 0.957)
IER3	8	Inverse variance weighted	**0.029**	1.075 (1.007 to 1.147)
KIR2DL1	2	Inverse variance weighted	**0.047**	1.120 (1.002 to 1.252)
LILRA2	4	Inverse variance weighted	**0.039**	1.053 (1.003 to 1.107)
LY9	2	Inverse variance weighted	**0.001**	0.808 (0.711 to 0.918)
MRPL52	3	Inverse variance weighted	**0.018**	0.909 (0.840 to 0.984)
P2RX6	2	Inverse variance weighted	**0.016**	0.869 (0.775 to 0.974)
PDGFB	3	Inverse variance weighted	**<0.001**	0.864 (0.796 to 0.938)
PKDCC	1	Wald ratio	**0.016**	0.745 (0.588 to 0.946)
PLEKHA7	2	Inverse variance weighted	**0.006**	1.183 (1.050 to 1.332)
PPP2R3A	1	Wald ratio	**0.009**	0.719 (0.562 to 0.921)
S100A6	2	Inverse variance weighted	**0.040**	0.748 (0.567 to 0.986)
SNRPF	1	Wald ratio	**0.044**	1.237 (1.006 to 1.521)
UBE2D1	5	Inverse variance weighted	**0.003**	0.913 (0.860 to 0.969)
ZAP70	2	Inverse variance weighted	**0.028**	0.854 (0.742 to 0.983)

0.5 1 1.5

pQTL and Sepsis

exposure	nsnp	method	pval	OR(95% CI)
ANXA3	3	Inverse variance weighted	**0.006**	0.735 (0.592 to 0.914)
APOD	6	Inverse variance weighted	**0.003**	0.863 (0.783 to 0.950)
ARL2	13	Inverse variance weighted	**<0.001**	0.890 (0.837 to 0.947)
BCL2L11	2	Inverse variance weighted	**0.037**	0.739 (0.556 to 0.982)
DHX8	9	Inverse variance weighted	**0.041**	0.783 (0.620 to 0.990)
FBL	6	Inverse variance weighted	**0.015**	0.883 (0.798 to 0.976)
GBP6	11	Inverse variance weighted	**0.012**	0.901 (0.830 to 0.977)
GCNT4	5	Inverse variance weighted	**0.002**	0.716 (0.579 to 0.886)
GOSR1	7	Inverse variance weighted	**0.014**	0.861 (0.764 to 0.970)
HSPA6	6	Inverse variance weighted	**0.028**	0.856 (0.745 to 0.983)
IER3	7	Inverse variance weighted	**0.004**	0.856 (0.770 to 0.952)
KIR2DL1	7	Inverse variance weighted	**0.008**	0.871 (0.786 to 0.965)
LILRA2	14	Inverse variance weighted	**0.031**	1.072 (1.006 to 1.143)
LY9	14	Inverse variance weighted	**0.029**	1.082 (1.008 to 1.161)
MRPL52	4	Inverse variance weighted	**0.015**	0.786 (0.648 to 0.954)
P2RX6	4	Inverse variance weighted	**0.006**	0.732 (0.586 to 0.915)
PDGFB	5	Inverse variance weighted	**0.043**	1.188 (1.006 to 1.402)
PKDCC	10	Inverse variance weighted	**0.021**	0.895 (0.815 to 0.983)
PLEKHA7	7	Inverse variance weighted	**0.042**	1.099 (1.004 to 1.203)
PPP2R3A	7	Inverse variance weighted	**0.018**	0.887 (0.803 to 0.979)
S100A6	8	Inverse variance weighted	**0.015**	0.795 (0.661 to 0.955)
SNRPF	9	Inverse variance weighted	0.050	0.883 (0.780 to 1.000)
UBE2D1	9	Inverse variance weighted	**0.008**	0.886 (0.811 to 0.968)
ZAP70	6	Inverse variance weighted	**0.008**	0.897 (0.828 to 0.972)

0.5 1 1.5

Fig. 2 MR analysis results of eQTL and pQTL for sepsis risk. **A**: Circular plot of the loci for 24 sepsis-associated genes. **B**: Forest plot showing the MR associations between eQTL, pQTL, and sepsis risk

eQTL, pQTL and Sepsis (28-day mortality)

Our results showed that sepsis 28-day mortality was associated with 667 eQTL genes and 111 pQTL genes ($P < 0.05$) (Table S7 and S8). After overlapping these two sets, we found that only 7 genes were strongly associated with 28-day sepsis mortality. Among the 7 eQTL genes, 5 were identified as protective genes, including CNRIP1(OR: 0.737, 95% CI: 0.552–0.983, $P = 3.80 \times 10^{-2}$),

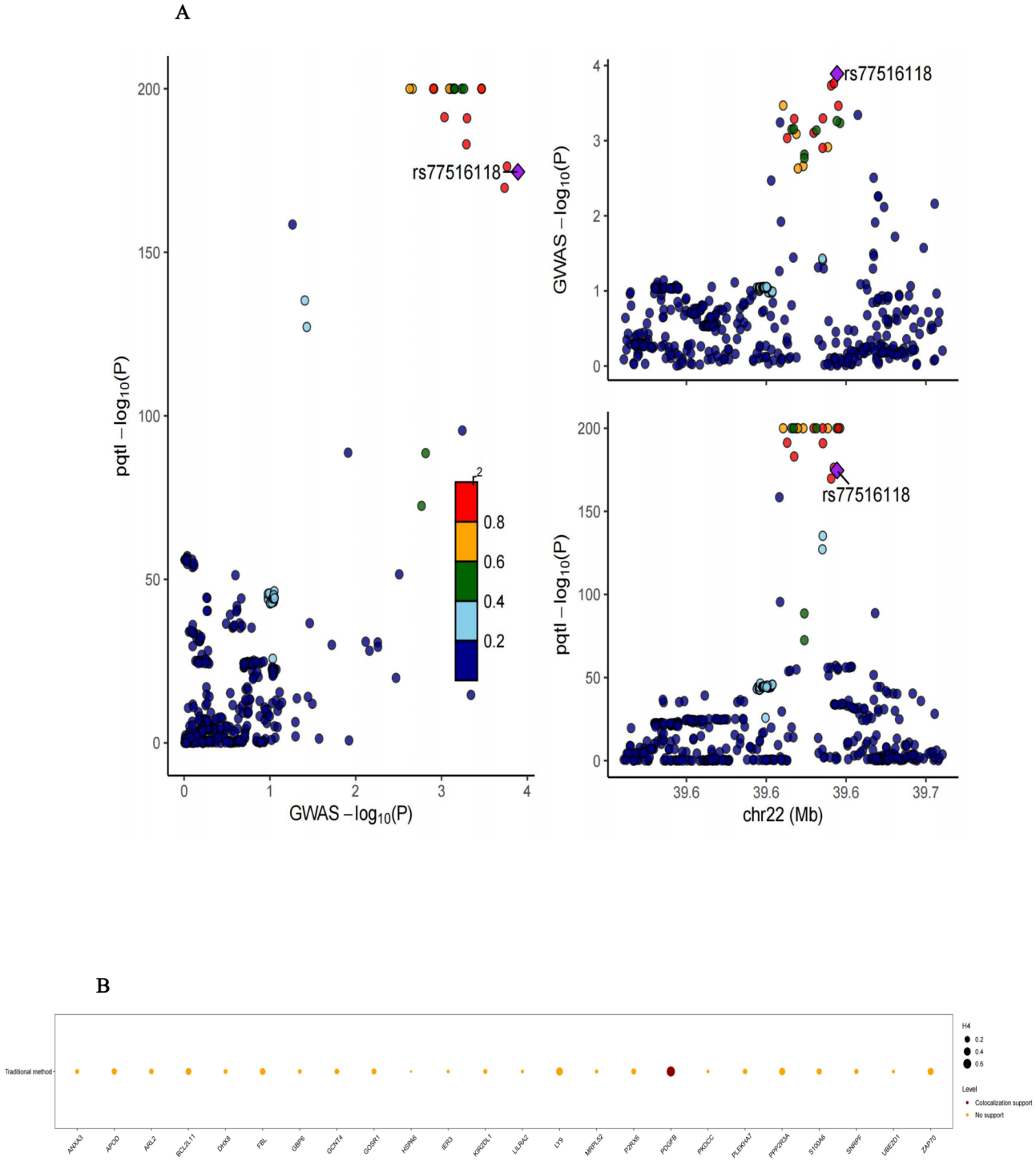


Fig. 3 The colocalization analysis of these genes. **A**: Colocalization results for the PDGFB gene (PP.H4 = 0.664), where the r^2 value represents the linkage disequilibrium (LD) between the variants and the leading SNPs. **B**: Colocalization analysis of the identified 24 genes

COL6A2(OR: 0.802, 95% CI: 0.663–0.970, $P = 2.27 \times 10^{-2}$), FN1(OR: 0.624, 95% CI: 0.421–0.924, $P = 1.87 \times 10^{-2}$),PPP3R1(OR: 0.765, 95% CI: 0.608–0.962, $P = 2.21 \times 10^{-2}$), and IL18R1(OR: 0.785, 95% CI: 0.649–0.950, $P = 1.27 \times 10^{-2}$). The remaining 2 genes were associated with increased risk, namely C5 (OR: 1.246, 95% CI: 1.024–1.515, $P = 2.78 \times 10^{-2}$), and IGFLR1(OR: 1.215, 95% CI: 1.033–1.430, $P = 1.86 \times 10^{-2}$). Among the 7 pQTL genes, 1 was identified as a protective gene: CNRIP1(OR: 0.824, 95% CI: 0.699–0.972, $P = 2.16 \times 10^{-2}$).

Six genes were identified as risk genes, including C5 (OR: 1.549, 95% CI: 1.093–2.195, $P = 1.40 \times 10^{-2}$), IGFLR1(OR: 1.247, 95% CI: 1.011–1.537, $P = 3.89 \times 10^{-2}$),COL6A2(OR: 1.720, 95% CI: 1.239–2.389, $P = 1.20 \times 10^{-3}$),FN1(OR: 1.707, 95% CI: 1.125–2.588, $P = 1.19 \times 10^{-2}$),PPP3R1(OR: 1.768, 95% CI: 1.087–2.875, $P = 2.16 \times 10^{-2}$), and IL18R1(OR: 1.188, 95% CI: 1.013–1.392, $P = 3.37 \times 10^{-2}$). Figure S2 presents the 7 associations between eQTL, pQTL, and sepsis 28-day mortality.

MR-Egger regression showed no evidence of horizontal pleiotropy ($P > 0.05$). Additionally, Cochran's Q test did not detect any significant heterogeneity ($P > 0.05$) (Table S9). Since the number of SNPs for the above genes exceeds 3, we did not conduct SMR analysis. Reverse MR analysis revealed an association between IL18R1 and 28-day sepsis mortality ($P = 2.92 \times 10^{-2}$) (Table S10). Therefore, IL18R1 was excluded from further analysis. Subsequent genetic correlation and colocalization analyses on the remaining six genes found no evidence of association (Table S11).

GO and KEGG analysis

We performed GO and KEGG analyses on the 24 genes associated with sepsis and the 6 genes related to 28-day sepsis mortality. The GO annotation results for sepsis revealed that the BP category was mainly enriched in cell-substrate adhesion, regulation of carbohydrate metabolic processes, and related pathways. The CC category included the U2-type catalytic step 2 spliceosome, among others. The MF category was primarily enriched in non-membrane spanning protein tyrosine kinase activity, and other related functions. For the 28-day sepsis mortality analysis, the BP category was mainly enriched in mesenchymal cell differentiation, along with other processes. The CC category primarily involved the sarcolemma, and the MF category was enriched in collagen binding, among other functions (Table S12, Fig. 4 and Figure S3, S4).

The KEGG enrichment analysis for sepsis revealed that the genes were primarily involved in the Spliceosome pathway, the PI3K-Akt signaling pathway, and other related pathways. For the 28-day sepsis mortality analysis, the genes were mainly associated with ECM-receptor interaction, focal adhesion, and other pathways (Table S13, and Figure S5).

PPI network analysis

The 24 drug target genes identified in sepsis, along with the 7 target genes identified in 28-day sepsis mortality, were uploaded to the STRING database to construct a protein-protein interaction network. The resulting file was then imported into **Cytoscape** for visualization. Figure 5 displays the interactions between the drug targets and other proteins.

Validation set

After validating the 24 genes in the FinnGen sepsis dataset, only 3 genes remained significantly associated. Among these, PDGFB (OR: 0.930, 95% CI: 0.868–0.997, $P = 4.10 \times 10^{-2}$) and SNRPF (OR: 0.708, 95% CI: 0.571–0.878, $P = 1.64 \times 10^{-3}$) were identified as protective, while IER3 (OR: 1.113, 95% CI: 1.051–1.179, $P = 2.51 \times 10^{-4}$).

was identified as a risk gene (Table S14).

Drug target prediction

This study utilized the DSigDB database to predict potential effective intervention drugs. Based on p-values, the top 10 potential compounds are shown for both sepsis and sepsis-related mortality (Table S15 and Fig. 6).

Molecular Docking

To evaluate the affinity of the aforementioned candidate drugs for their targets and understand the druggability of these targets, we assessed the interactions between the binding sites of proteins encoded by genes related to sepsis and 28-day sepsis mortality and the top 10 candidate drugs. In the sepsis analysis, UNII-9XX54M675G and Dichloromercury did not produce docking results with the associated genes. Similarly, in the 28-day sepsis mortality analysis, SILVER, TITANIUM DIOXIDE, and [6-[6-(butanoylamino)purin-9-yl]-2-hydroxy-2-oxo-4a,6,7,7a-tetrahydro-4 H-furo[3,2-d][1,3,2]dioxaphosphinin-7-yl] butanoate did not produce docking results with the associated genes. For the remaining drugs, binding energies were obtained, and successful docking outcomes were achieved (Table S15, Fig. 7 and S6).

PheWAS analysis

To further evaluate whether the successful molecular docking of drug target genes could have beneficial or adverse effects on other traits, and to determine the potential pleiotropy that may not have been captured by the MR-Egger intercept test, we conducted a PheWAS analysis at the genetic level. The PheWAS results indicate associations between protein expression determined by genetics and specific diseases or traits, as illustrated in Figures S7-S30. None of the 12 drug targets identified for sepsis and sepsis-related mortality showed significant associations with other traits at the genetic level at genome-wide significance with $P < 5 \times 10^{-8}$. This indicates that the potential side effects and horizontal pleiotropy of drugs targeting these genes are minimal, thereby supporting the robustness of the study's findings.

Additional mediation analysis

We initially conducted an MR analysis between 1400 metabolites and sepsis. For metabolites with IVs at a threshold of 5×10^{-6}, we identified 83 associations($P < 0.05$). For metabolites with IVs at a

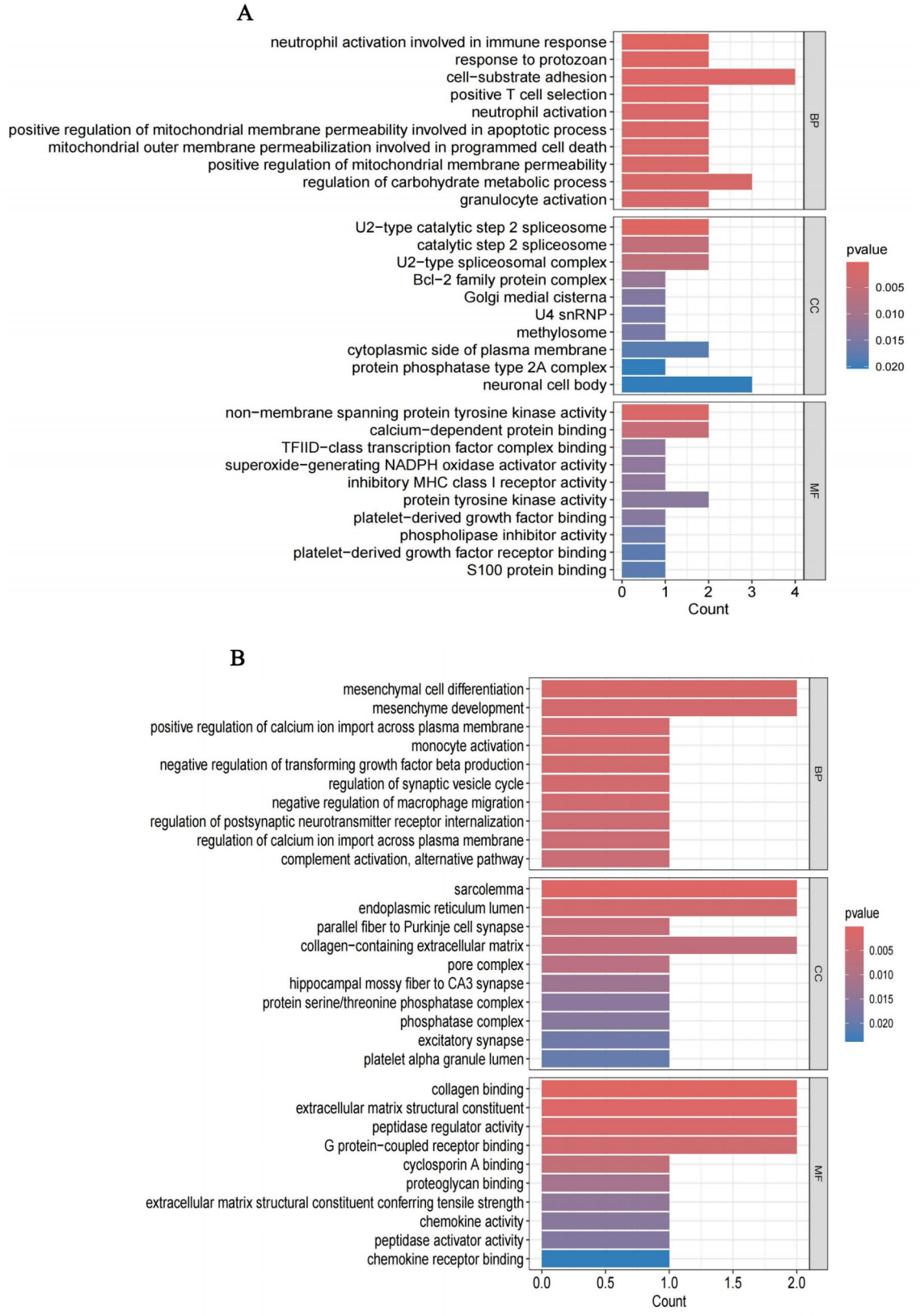


Fig. 4 GO enrichment analysis for sepsis and sepsis (28-day mortality). **A**: Bar plot representing the GO analysis results for sepsis. **B**: Bar plot representing the GO analysis results for sepsis (28-day mortality)

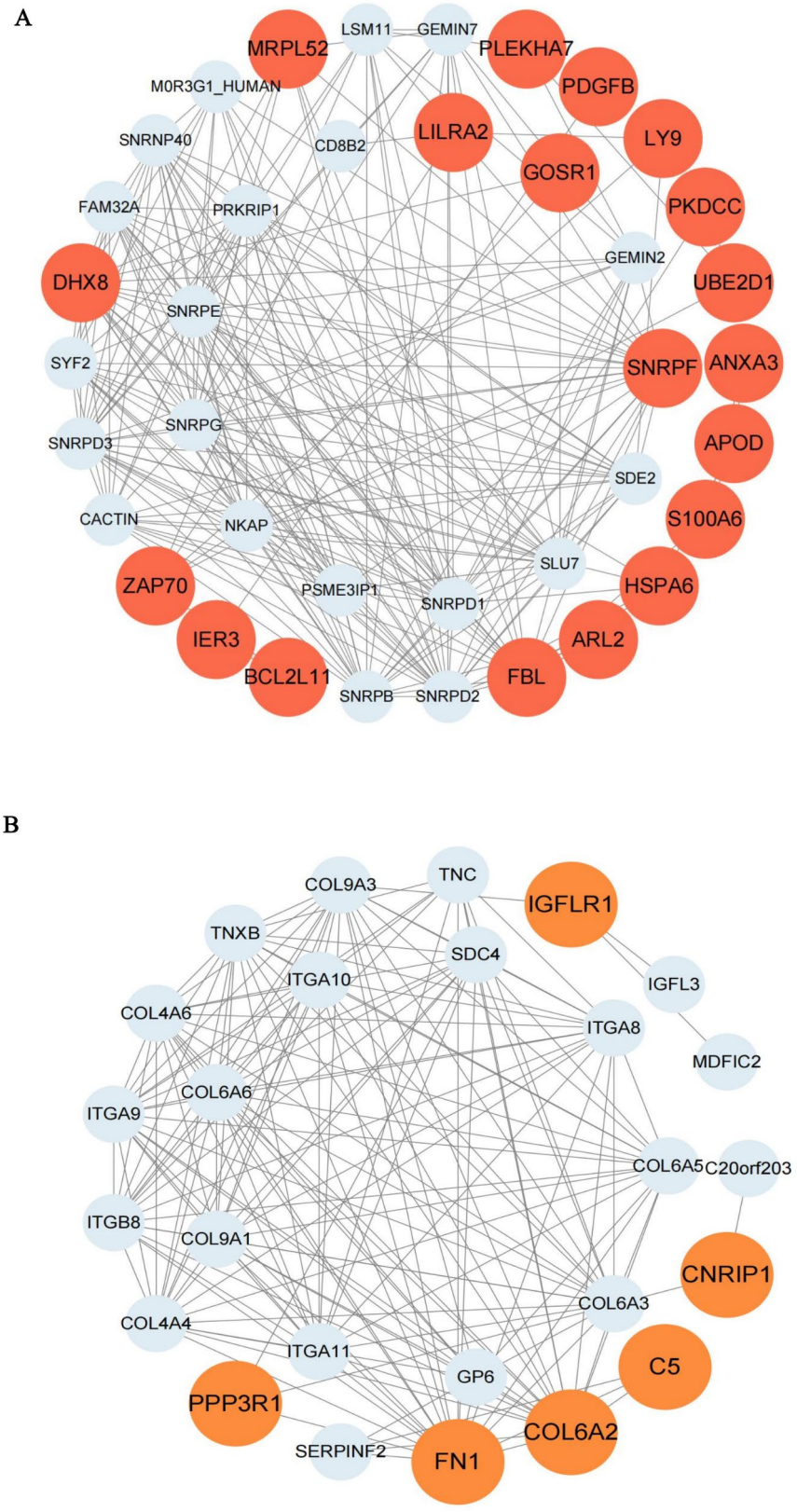


Fig. 5 PPI network analysis. **A**: PPI network constructed using STRING for sepsis. **B**: PPI network constructed using STRING for sepsis (28-day mortality)

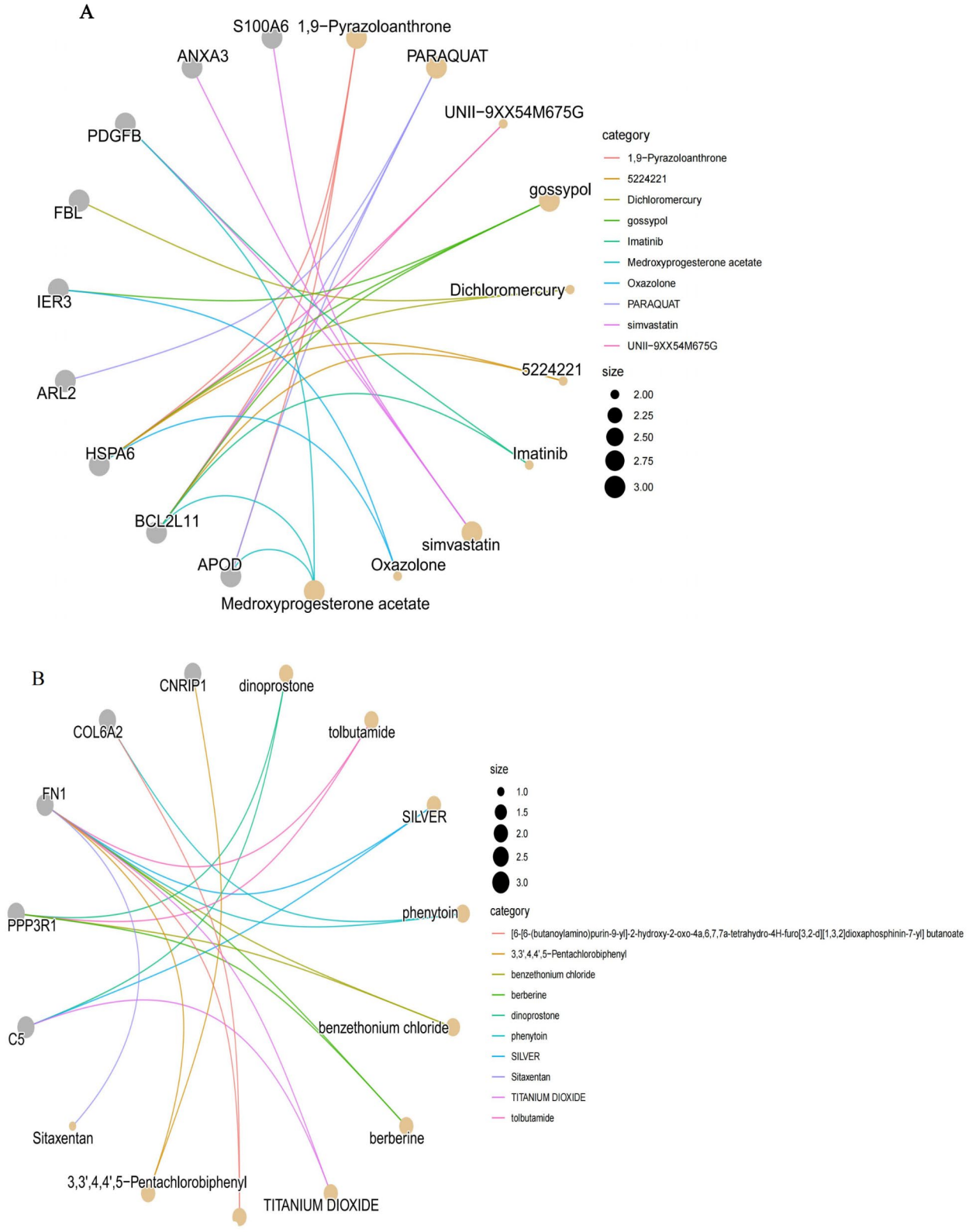


Fig. 6 Candidate drug prediction. A: Enrichment analysis of the top 10 candidate drugs for sepsis. B: Enrichment analysis of the top 10 candidate drugs for sepsis (28-day mortality)

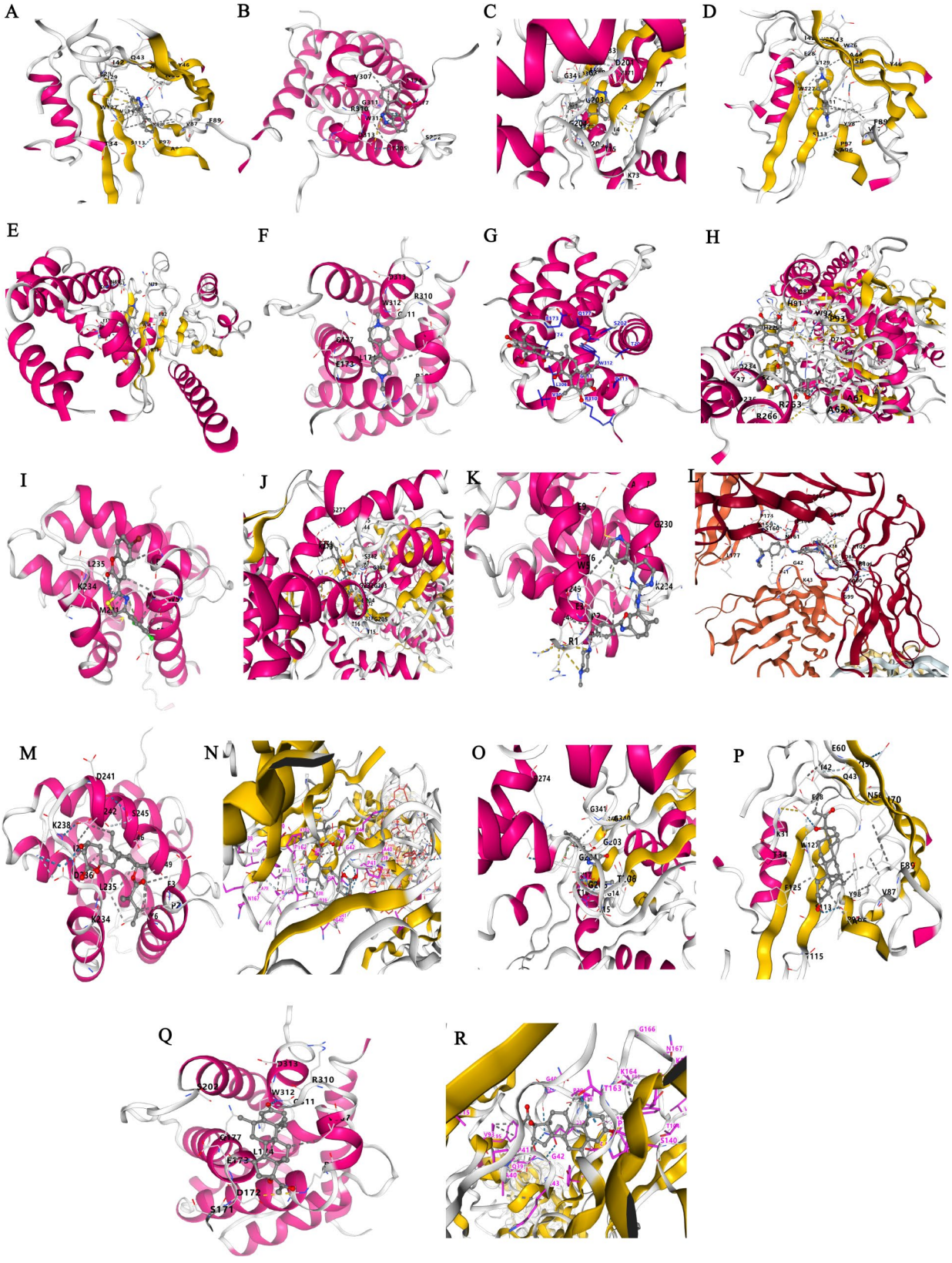


Fig. 7 (See legend on next page.)

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Fig. 7 Molecular docking results of available proteins in sepsis. **A**: APOD docking 1,9-Pyrazoloanthrone; **B**: BCL2L11 docking 1,9-Pyrazoloanthrone; **C**: HSPA6 docking 1,9-Pyrazoloanthrone; D:APOD docking PARAQUAT; **E**: ARL2 docking PARAQUAT; F: BCL2L11 docking PARAQUAT; **G**: BCL2L11 docking gossypol; **H**: HSPA6 2L11 docking gossypol; **I**: BCL2L11 docking 5,224,221;**J**: HSPA6 docking 5,224,221;**K**: BCL2L11 docking Imatinib; **L**:PDGFB docking Imatinib; **M**: ANXA3 docking Simvastatin; **N**: PDGFB docking Simvastatin; **O**:HSPA6 docking Oxazolone; **P**: APOD docking Medroxyprogesterone acetate; **Q**: BCL2L11 docking Medroxyprogesterone acetate; **R**: PDGFB docking Medroxyprogesterone acetate;

threshold of 1×10^{-5}, we found 82 associations. By taking the intersection of these two results, we identified a total of 40 metabolites (Table S16, S17). In the MR analysis of 249 metabolites, we identified 37 associations (Table S18).

We then conducted an MR analysis between the 24 genes and the previously identified metabolites. Through mediation analysis, we ultimately identified an indirect effect of MRPL52 on sepsis mediated by Hypotaurine levels (OR: 0.900, 95% CI: 0.837–0.967, $P = 4.10 \times 10^{-3}$). The mediation proportion was 14.95% (95% CI: 4.97×10^{-3}–0.294, $P = 4.26 \times 10^{-2}$) of the total effect (Fig. 8, Table S19, S20). Similarly, we conducted the same analysis for 28-day sepsis mortality, but no mediating metabolites were identified (Table S21-24).

Discussion

With the rapid advancement of multi-omics research in recent years, better approaches for developing new drugs to treat sepsis have emerged. Currently, there are relatively few multi-omics studies on sepsis, and those that exist are mostly observational, indicating associations without establishing causality. In this study, we used MR to combine eQTL and pQTL data, identifying 24 genes associated with sepsis and 6 genes linked to 28-day sepsis mortality. Subsequently, we conducted reverse MR analysis to mitigate the effects of confounding factors, followed by genetic correlation and colocalization analyses, which offered robust evidence supporting these as potential drug targets. To further understand the biological roles of these drug targets, we carried out enrichment analysis, PPI network analysis, and drug prediction. We also performed molecular docking for the predicted drugs targeting these genes, providing additional support for the druggability of these targets. To evaluate potential pleiotropic effects and side effects of the drugs, we conducted phenome-wide association studies. Mediation analysis revealed specific metabolites mediating the effects of certain genes on sepsis. These comprehensive analyses enhance our understanding of the molecular mechanisms underlying sepsis, paving the way for future advancements in sepsis treatment and the development of new biomarkers for monitoring, ultimately aiming to improve outcomes for sepsis patients.

In our colocalization analysis of sepsis, we identified platelet-derived growth factor B (PDGFB) with supportive evidence for colocalization; however, the directions of effect in eQTL and pQTL analyses were not consistent. PDGFB is a member of the PDGF family, which includes four isoforms: A, B, C, and D. PDGF must form homodimers or heterodimers to exhibit activity, including PDGF-AA, BB [30]. Furthermore, a study has reported that PDGF-BB exerts a protective effect in sepsis by reducing the production of pro-inflammatory cytokines and chemokines [31]. In our study, PDGFB was found to be strongly associated with sepsis, but further investigation is required to understand its precise role in sepsis pathogenesis.

In the genetic correlation analysis of sepsis, DHX8 and LILRA2 were found to be significantly associated. DHX8 is an ATP-dependent RNA helicase, functioning as a molecular winch capable of displacing distal peripheral RNA within the spliceosome, making it a potentially underexplored druggable target in the future [32]. Previous studies have shown a significant association between DHX8 and antidepressant response [33]. Currently, there is no research establishing a relationship between DHX8 and sepsis, indicating a need for further investigation in the future. The leukocyte immunoglobulin-like receptor (LILR) family is a group of specific immune receptors that are widely expressed on most immune cells. LILRA2 recognizes fibrinogen, which is found under certain physiological conditions. Fibrinogen is associated with various diseases, including inflammatory diseases, infections, cancer, thrombotic disorders, and vascular wall diseases [34]. Therefore, blocking the LILRA2-fibrinogen interaction could be a promising therapeutic strategy for treating sepsis. In our study, we found that LILRA2 is associated with an increased risk of sepsis, suggesting its potential involvement in inflammatory responses. However, no direct studies have yet established a link between LILRA2 and sepsis, highlighting the need for further investigation.

In the validation cohort of FinnGen sepsis patients, we identified significant associations for the genes IER3, SNRPF, and PDGFB. Immediate Early Response 3 (IER3) is a stress-inducible gene that plays a crucial role in cell survival under stress conditions, including proliferation, DNA repair, apoptosis, and differentiation. Its response varies depending on the cellular environment. It has been reported that IER3 promotes autophagy and induces the development of acute myeloid leukemia [35]. SNRPF is a protein-coding gene that plays a crucial role in alternative splicing by forming a core component of the spliceosomal small nuclear ribonucleoproteins (snRNP) [36]. In our study, we did not observe consistent directions

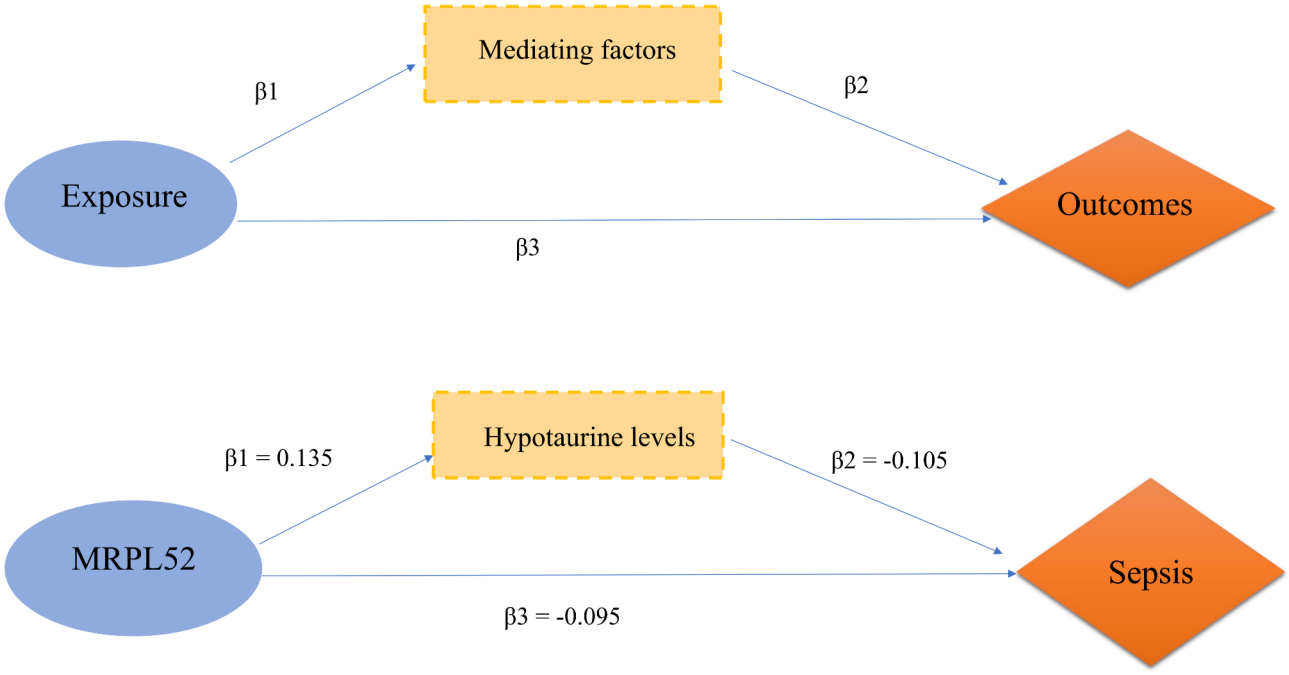

Fig. 8 A schematic diagram of mediation analysis

of effect for these two genes, indicating that further research is needed to explore their roles. Existing literature offers some related insights. A study on sepsis-associated cardiomyopathy found that IER3 is involved in the pathogenesis of cardiovascular and inflammatory diseases, with its expression significantly upregulated in the myocardial tissue of mice under pressure overload. IER3 influences inflammatory responses through the regulation of pathways such as NF-κB and Nrf2 [37]. Another study reported a significant upregulation of IER3 in the peripheral blood of sepsis patients [38]. For SNRPF, no direct link to sepsis has yet been established. However, SNRPF has been identified as being associated with drug sensitivity/resistance in pulmonary squamous cell carcinoma [39]. Among the genes most significantly predicting drugs for sepsis are APOD, ARL2, BCL2L11, and others. Currently predicted drugs include 1,9-Pyrazoloanthrone and gossypol, among others. 1,9-Pyrazoloanthrone, a selective c-Jun N-terminal kinase (JNK) inhibitor, has been shown to slow the progression of osteoarthritis by inhibiting the JNK-related axis [40]. Additionally, gossypol has been reported to improve myocardial dysfunction and increase survival rates in septic mice. This animal study confirmed the anti-inflammatory and antioxidant activities of gossypol, suggesting that it could be a potential therapeutic agent for sepsis [41]. However, research on these genes and drugs in the context of sepsis remains limited, which may pose a challenge for future drug development.

In our mediation MR analysis, we found that MRPL52 influences sepsis through its effect on hypotaurine levels. Specifically, MRPL52 was shown to reduce the risk of sepsis, with consistent directions of effect observed in both eQTL and pQTL analyses. However, no literature currently establishes a direct relationship between MRPL52 and sepsis. MRPL52 is a component of the mitochondrial ribosomal large subunit, and experiments have demonstrated its role in inhibiting apoptosis and promoting migration and invasion in hypoxic breast cancer cells [42]. Hypotaurine is a sulfur-containing amino acid that serves as a precursor in taurine biosynthesis. It possesses antioxidant properties, scavenging free radicals and protecting cells from oxidative stress [43].Upon uptake, hypotaurine is oxidized to taurine by hypotaurine dehydrogenase. Studies have reported that disturbances in the metabolism of taurine, pantothenic acid, and phenylalanine in the renal cortex are linked to the development of sepsis-induced acute kidney injury (AKI). Correcting these metabolic disturbances could potentially prevent and treat sepsis-induced AKI [44]. In addition, our mediation analysis revealed metabolites such as polyunsaturated fatty acids, omega-3, and DHA with p-values close to 0.05. Given the complexity of metabolic changes in the human body, these metabolites may still play a role in sepsis-related pathways, even though they did not reach strict statistical significance. Furthermore, animal studies have shown that omega-3 PUFAs reduce the incidence of sepsis by activating relevant pathways [45]. Additionally, DHA-derived lipid mediator Resolvin D1 has been reported to improve sepsis-related coagulopathy by regulating associated pyroptosis pathways [46]. These findings suggest a potential biological relevance, which may offer

new insights into sepsis treatment. However, due to the limited evidence, future studies with larger sample sizes are needed to further clarify their role.

In the study of 28-day mortality in sepsis, we identified a total of six genes. Although no significant associations were found in the genetic correlation or colocalization analyses, all six genes passed the sensitivity analysis and successfully predicted drugs and molecular docking interactions. Among these, C5, FN1 and PPP3R1 had the highest number of drug interactions in the molecular docking analysis. According to existing literature, C5 is a component of the complement system, which is part of the innate immune response involved in regulating immunity and inflammation [47]. Previous studies have shown that C5 levels are decreased in both sepsis patients and animal models. In a prospective cohort study, it was found that C5 levels decrease within 48 h after sepsis onset, and following cell injury, C5 levels were significantly correlated with the Sequential Organ Failure Assessment score in sepsis patients [48]. These findings provide strong support for our research results. FN1 is a major component of the extracellular matrix, involved in physiological processes such as cell adhesion, growth, differentiation, migration, and host defense [49]. FN1 has also been implicated in various pathological processes, including cancer, infection, and rheumatoid arthritis [50]. Studies have shown elevated plasma levels of FN1 in sepsis patients [51]. FN1 is also highly expressed in the lungs and actively participates in the pathogenesis of SARS-CoV-2, making it a potential therapeutic target for mitigating infection [52]. Additionally, PPP3R1 has been associated with promoting gastric epithelial-mesenchymal transition, tumor invasion, and drug resistance [53]. In our study, FN1 and PPP3R1 were found to be closely related to sepsis-associated mortality, although their directions of effect were inconsistent. Berberine, the drug predicted by these two genes, is a naturally occurring isoquinoline alkaloid found in various medicinal plants. It has been shown to preserve mitochondrial integrity and inhibit TLR4/NF-κB signaling and NLRP3 inflammasome activation, alleviating sepsis-associated acute kidney injury in aged rats, highlighting its potential therapeutic value [54]. Currently, the relationship between these genes and the predicted drugs with sepsis remains largely unexplored, but they may provide new insights into the potential mechanisms of sepsis for future research.

Molecular docking is a powerful tool for predicting drug-target interactions, offering insights into binding mechanisms. Molecular dynamics simulations can complement this approach by revealing the dynamic interactions between drugs and their targets, providing a deeper understanding of the stability and interaction patterns of these complexes [55]. Despite these advantages, their clinical relevance and predictive accuracy remain limited. One key limitation is that these methods cannot fully replicate the complex human environment, including the pharmacokinetics of drugs, intricate biological interactions (such as protein dynamics), and the possibility that docking predictions may not always align with actual drug effects. Moreover, clinical outcomes are influenced by a variety of factors, such as the drug's properties, the patient's physiological and pathological conditions, individual differences, route of administration, and environmental factors. Consequently, docking alone cannot provide a comprehensive evaluation of a drug's potential. To overcome these limitations, further testing through cell culture experiments and animal models is essential to assess the drug's therapeutic efficacy and safety. We plan to assess the effects of candidate drugs on inflammatory responses and other key biomarkers in the future, while conducting thorough pharmacokinetic and safety evaluations to ensure their feasibility for future clinical applications.

Current treatments for sepsis still lack specific anti-inflammatory strategies. The primary approach involves intravenous antibiotics, along with supportive therapies such as anti-inflammatory and immune-modulating treatments. However, the increasing prevalence of antimicrobial resistance has further exacerbated the clinical burden of sepsis [56]. The pathological progression of sepsis exhibits a biphasic immune response. In the early stages, uncontrolled infectious pathogens can trigger excessive activation of innate immune cells, leading to a systemic cytokine storm. As the disease progresses to later stages, immune cell dysfunction, depletion, and programmed cell death occur, ultimately resulting in persistent immune suppression and dysfunction [57].In our study, we identified novel drug targets such as PDGFB, IER3, and FN1, which are closely linked to sepsis and 28-day mortality. These genes may play a role in regulating inflammatory pathways and cellular stress responses, potentially improving immune regulation and patient prognosis. Drugs targeting these genes could offer therapeutic strategies to prevent or alleviate the systemic inflammation and organ dysfunction observed in sepsis. While these findings are preliminary, we believe they pave the way for more targeted and personalized therapies for sepsis.

A key strength of this study is that we are the first to combine eQTL and pQTL data through MR analysis to identify novel drug targets for sepsis and 28-day sepsis mortality. We employed multiple analytical approaches to uncover direct gene-sepsis relationships. Furthermore, we validated our findings using the FinnGen sepsis dataset to ensure reproducibility in future research. Another strength of our study is that we focused our analysis on individuals of European ancestry, which helps to minimize population stratification bias.

Our study has several limitations. First, our study population is primarily composed of individuals of European ancestry, which results in population homogeneity, meaning genetic consistency within the study group. This could impact the generalizability of our findings to other, more diverse populations. Therefore, further cohort studies are needed to determine whether these findings are applicable to other populations, such as those of Asian ancestry. Second, due to the lack of multiple testing correction methods in our analysis, there is a possibility of false-positive results. However, the overlap between eQTL and pQTL enhances the credibility of our findings. Third, different tissues may have distinct genetic regulatory mechanisms, and relying solely on blood eQTL and pQTL may not provide a comprehensive understanding of the disease and its underlying mechanisms. Fourth, the drug target genes identified through various analytical methods are numerous and not completely overlapping, which presents challenges for future experimental validation. Fifth, MR analysis is still susceptible to potential biases or pleiotropy that could influence the results. Sixth, the reliability of molecular docking is highly dependent on the quality of the protein structures and ligands employed. Although this technique is valuable for identifying potential drug targets, it cannot fully predict their clinical efficacy. Lastly, we only identified one mediating metabolite in our study, but some metabolites had mediation P-values very close to 0.05, suggesting that they may also be potential biomarkers. Therefore, emphasizing the importance of experimental validation and clinical trials in future research is crucial to confirm our findings.

Conclusions

In conclusion, this study utilized a multi-omics approach to identify potential drug targets and mediating metabolites associated with sepsis risk and 28-day sepsis mortality. We identified 24 drug targets and 1 mediating metabolite for sepsis, as well as 6 drug targets for 28-day sepsis mortality, enhancing our understanding of their complex relationships. These genes and metabolites could serve as effective targets for sepsis treatment. Drug prediction and molecular docking provided promising insights for discovering more effective treatments for sepsis and potentially reducing drug development costs. This research paves a new path in the field and lays the groundwork for future studies, although these findings still require further research and clinical trials for validation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06366-w.

Supplementary Material 1

Supplementary Material 2

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Authors' contributions
HT and TZ designed the study, contributed to the data analysis, and wrote the manuscript. YZ and JY were involved in data collection and data analysis. YZ also contributed to manuscript writing and revision. JY assisted with illustrations. YC contributed to the revision of the manuscript in response to reviewers' comments. All authors have read and approved the final version of the manuscript.

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Data availability
Since this study utilized publicly available GWAS summary data, individuals interested in further details are encouraged to contact the corresponding authors for additional information.

Declarations

Ethics approval and consent to participate
In our study, we utilized large-scale GWAS datasets rather than individual-level data. The research conducted by these consortia was approved by local research ethics committees and institutional review boards, with all participants providing written informed consent.

Consent for publication
Not applicable.

Competing interests
All authors declare that the research was conducted without any commercial or financial relationships that could be construed as potential conflicts of interest.

Author details
[1]Department of Critical Care Medicine, Jinhua Hospital Affiliated to Zhejiang University, Jinhua, Zhejiang, China
[2]Zhejiang University School of Medicine, Hangzhou, China
[3]Department of Neurology, the Fourth Affiliated Hospital of School of Medicine, and International School of Medicine, International Institutes of Medicine, Zhejiang University, Yiwu 322000, China
[4]Department of Critical Care Medicine, the Fourth Affiliated Hospital of School of Medicine, and International School of Medicine, International Institutes of Medicine, Zhejiang University, Yiwu 322000, China

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