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Research Article

Investigation of Shared Molecular Mechanisms Underlying Sepsis and Heart Failure via Integrated Analysis of Multiple Microarray Data

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Abstract:

Background: This study aimed to explore shared genes and related molecular mechanisms of sepsis and heart failure (HF) to identify potential diagnostic biomarkers and therapeutic targets for both diseases.

Materials and methods: Differentially expressed genes (DEGs) in sepsis and HF were identified using datasets GSE28750 and GSE57345. WGCNA was conducted to uncover gene modules related to both diseases. Shared genes were identified and analyzed for function, PPI, and expression validation with datasets GSE65682 and GSE84796. Diagnostic performance, immune cell infiltration, and gene set enrichment analyses were performed on hub-shared genes.

Results: A total of 5407 DEGs in sepsis samples and 2042 DEGs in HF samples were identified based on the discovery datasets GSE28750 and GSE57345. WGCNA revealed five sepsis-related modules encompassing 2972 genes and three HF-related modules containing 982 genes. Notably, 170 shared genes were identified between the two diseases. PPI analysis and expression validation using external datasets led to the identification of four hub-shared genes: RRS1, IMP4, RPLP0, and NOP16. These four hub-shared genes exhibited high diagnostic performance, with Area Under Curve (AUC) values exceeding 0.7 in all four datasets. Furthermore, a significant negative correlation was observed between RRS1 and M0 macrophages, as well as between IMP4 and plasma cells, in both sepsis and HF. Additionally, these genes were significantly enriched in processes related to ribosome assembly and biogenesis.

Conclusion: The study successfully identified four genes, namely RRS1, IMP4, RPLP0, and NOP16, as potential key common regulators in sepsis and HF. These genes may serve as diagnostic biomarkers and therapeutic targets for both diseases, offering promising insights into the shared molecular mechanisms underlying sepsis and HF.

Key words: sepsis; heart failure; WGCNA; hub shared genes; diagnosis; immune infiltration

List of Abbreviations

DEGs: Differentially Expressed Genes

WGCNA: Weighted Gene Coexpression Network Analysis

PPI: Protein-Protein Interaction

AUC: Area Under Curve

UPR: Unfolded Protein Response

HF: Heart Failure

RRS1: Ribosome Biogenesis Regulator 1 Homolog

IMP4: IMP U3 Small Nucleolar Ribonucleoprotein 4

RPLP0: Ribosomal Protein Lateral Stalk Subunit P0

NOP16: NOP16 Nucleolar Protein

MNC: Maximal Neighborhood Component

MCC: Maximal Clique Centrality

EPC: Edge Percolated Component

GO: Gene Ontology

KEGG: Kyoto Encyclopedia of Genes and Genomes

ROC: Receiver Operating Characteristic

GSEA: Gene Set Enrichment Analysis

Introduction

Sepsis, a life-threatening organ dysfunction secondary to infection, affects more than 19 million people annually and is associated with high mortality rates [1][2]. It is also recognized as a significant risk factor for cardiovascular disease [3]. Despite advancements in treatment approaches, sepsis remains a frequent noncardiac diagnosis in the cardiac intensive care unit, highlighting the need for improved diagnostics and therapies [4][5]. Heart failure (HF), characterized by the heart's inability to pump sufficient blood to meet the body's requirements for nutrients and oxygen, is a common complication of sepsis [6]. The prognosis of HF is poor, with morbidity and mortality rates of approximately 50% after one year of follow-up [7]. Alarmingly, the mortality rate of patients with combined sepsis and cardiac dysfunction can be as high as 90% [3]. Therefore, exploring the common pathogenesis of sepsis and HF is crucial for early diagnosis and improvement of clinical outcomes.

Sepsis is a systemic inflammatory response triggered by the excessive secretion of proinflammatory cytokines and reactive oxygen species [8]. This inflammatory response and oxygen depletion during sepsis can activate the unfolded protein response (UPR) in the heart, which is implicated in cardiovascular diseases, including HF [9][10]. Additionally, reactive species and free radicals can exacerbate endothelial deterioration and increase vascular permeability, accelerating the progression to septic HF [11][12]. These findings suggest a shared pathogenesis between sepsis and HF. However, despite clinical and mechanistic evidence of their relationship, the molecular mechanisms underlying this association remain largely unknown.

The advent of bioinformatics has revolutionized our ability to understand complex diseases like sepsis and HF. High-throughput technologies, such as microarray and RNA sequencing, have enabled the simultaneous analysis of thousands of genes, providing insights into disease pathogenesis at the molecular level [13][14]. Weighted gene coexpression network analysis (WGCNA) is one such approach that has been widely used to identify shared risk genes and mechanisms related to diverse disease phenotypes [15][16]. Protein-protein interaction (PPI) analysis further elucidates the functional significance of these genes by mapping their interactions within biological networks [17]. These bioinformatics tools have the potential to uncover the shared molecular mechanisms between sepsis and HF, offering new avenues for diagnosis and treatment.

In this study, our primary objective was to explore and understand the shared genetic mechanisms between sepsis and heart failure (HF). To achieve this, we leveraged multiple microarray datasets sourced from public databases. Our research purposes were two-fold: firstly, to identify the shared genes between sepsis and HF through rigorous differential expression analysis, and secondly, to delve deeper into the biological significance and functional roles of these genes. We employed differential expression analysis to pinpoint the genes that are commonly altered in both sepsis and HF. Subsequent to this, we utilized Weighted Gene Co-expression Network Analysis (WGCNA) to explore the coexpression patterns of these shared genes, aiming to unravel their potential interactions and regulatory networks. Functional enrichment analysis was then conducted to gain insights into the biological pathways and processes in which these genes are involved. Furthermore, we performed Protein-Protein Interaction (PPI) analysis and expression validation using additional validation datasets to identify hub-shared genes that may play pivotal roles in the pathogenesis of both sepsis and HF. These hub-shared genes represent potential biomarkers and therapeutic targets for these conditions. In addition to identifying and characterizing the shared genes, we also assessed the diagnostic performance of these genes, evaluated their association with immune cell infiltration, and conducted gene set enrichment analyses to further understand their roles in the disease processes. Our findings contribute significantly to expanding the current understanding of the common pathogenesis of sepsis and HF.

The significance of this study lies in its potential to pave the way for the development of novel biomarkers and therapeutic strategies for these conditions, which remain major health burdens worldwide. By unraveling the shared genetic mechanisms, we hope to facilitate more targeted and effective interventions, ultimately improving patient outcomes.

Materials and Methods

Data acquisition and preprocessing

The sepsis-related gene expression profiles GSE28750 and GSE65682 and HF-related gene expression profiles GSE57345 and GSE84796 were downloaded from the NCBI Gene Expression Omnibus (GEO) database [18]. GSE28750 and GSE57345 were utilized as discovery datasets, whereas GSE65682 and GSE84796 were used as validation datasets. The GSE84796 dataset includes 21 sepsis and 20 control samples, the GSE65682 dataset 760 sepsis and 42 control samples, the GSE57345 dataset 177 HF and 136 control samples, and the GSE84796 dataset 10 HF and 7 control samples. The mRNA probe expression matrix and corresponding platform annotation file were also downloaded[18]. Gene symbol transformation was performed, and probes that did not match the gene symbol were removed. For different probes mapped to the same gene, the average value was taken as the expression value of the gene. Since the data were downloaded from the public database GEO, ethical approval was not applicable and informed patient consent was not required.

Differential expression analysis

Based on the GSE28750 and GSE57345 discovery datasets, differentially expressed genes (DEGs) between disease and control samples were analyzed using the R limma package (version 3.48.3) [19]. The cutoff value was p.value adjusted by Benjamini–Hochberg (BH) procedure < 0.05 and $|\log \text{fold change (FC)}| > 0.263$.

WGCNA

Based on the GSE28750 and GSE57345 discovery datasets, the DEGs identified in sepsis and HF were subjected to WGCNA using the R WGCNA package (version 1.71) [20]. In brief, an adjacency matrix was built, and the power β was calculated to render R2 approximately 0.85. Gene coexpression modules were then obtained by a gene hierarchical clustering dendrogram. Genes were matched with different color modules

by a dynamic tree cut, and the gene number in a module was more than 30. Genes that did not match the module were assigned to gray modules. Clinically related modules associated with sepsis and HF were identified by analysis of the correlation between the modules and clinical traits. Overlapping genes in the sepsis- and HF-related modules were obtained using Venn diagram analysis and were considered shared genes of the two diseases.

Functional enrichment analysis

To elucidate the potential function of the shared genes of the two diseases, Gene Ontology (GO) functions and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were conducted using the R cluster Profiler package (version 4.44) [21][22].

PPI network analysis

Using the STRING (version 11.0) database [23], a PPI network was constructed by the shared genes of two diseases and visualized using Cytoscape (version 3.9.2) [24]. The topological properties of nodes in the PPI network were analyzed using the cytoHubba plug-in, including maximal neighborhood component (MNC), maximal clique centrality (MCC), degree, and edge percolated component (EPC), and candidate hub-shared genes were obtained by intersection analysis of the top 10 genes obtained by four topological properties.

Validation of expression of candidate hub-shared genes

Differential expression of candidate hub-shared genes was validated using validation datasets (GSE65682 and GSE84796). Differential expression of candidate hub-shared genes between disease and control samples was analyzed using the Wilcoxon rank sum test; genes with the same expression difference in the discovery and validation datasets were considered hub-shared genes.

Evaluation of the diagnostic performance of hub-shared genes

Based on the gene expression data in the four datasets, receiver operating characteristic (ROC) analysis was conducted using the R pROC package (version 1.18.0) [25] to analyze the diagnostic performance of the hub-shared genes. A higher area under the ROC curve (AUC) indicated better diagnostic performance of the hub-shared genes.

Construction of the PPI network of hub-shared genes

Using the Gene MANIA database (http://genemania.org/), PPI analysis of hub-shared genes at the gene level was conducted to explore interconnections between proteins.

Association analysis of hub-shared genes and immune cell infiltration

Based on the GSE28750 and GSE57345 discovery datasets, the proportions of 22 kinds of immune cells in each sample were analyzed using the CIBERSORT algorithm [26]. The relationship between the hub-shared genes and 22 immune cells was explored with Spearman correlation analysis.

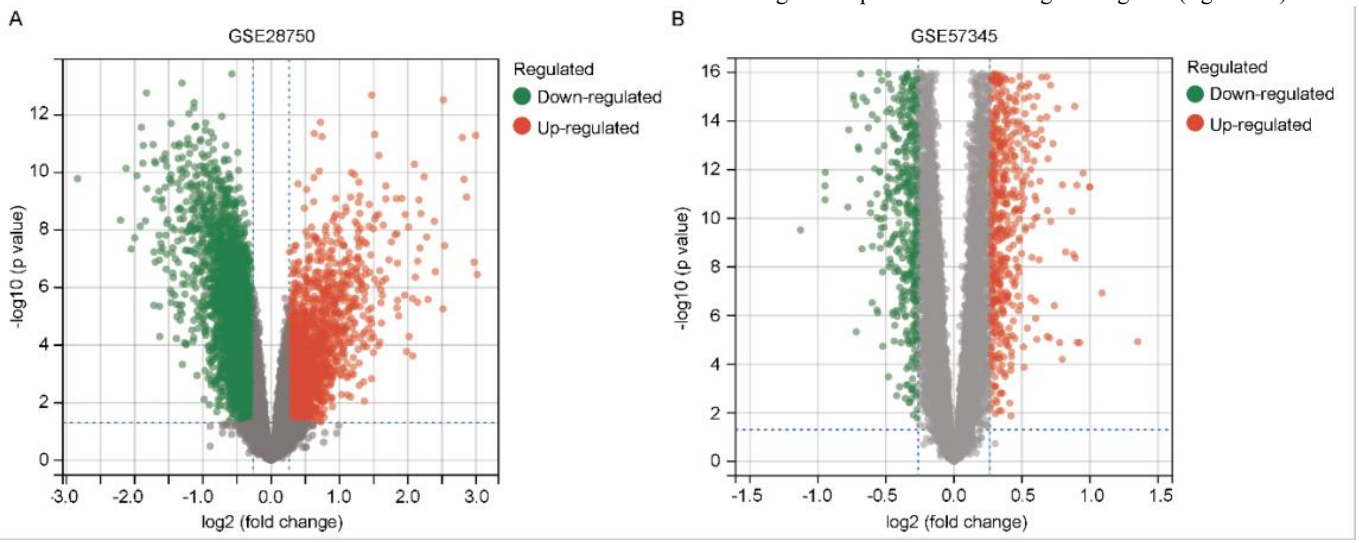
GSEA for hub-shared genes

Samples were divided into high- and low-expression groups based on each hub-shared gene. Differentially activated pathways between different expression groups were analyzed using GSEA. Specifically, with the KEGG and GO datasets in MSigDB v7.1 [27] as the enrichment background, GSEA for each gene was performed using GSEA (version 4.2.3) [28]. The cutoff value was $p < 0.05$.

Results

Identification of DEGs in sepsis and HF

We performed differential expression analysis on the discovery datasets GSE28750 and GSE57345. Based on the GSE28750 dataset, 5407 DEGs between sepsis and control samples were identified, including 2040 up- and 3367 downregulated genes (figure. 1a). Based on the GSE57345 dataset, 2042 DEGs between HF and control samples were screened out, including 1067 up- and 975 downregulated genes (figure. 1b).



Figures: 1a,1b: Volcano plot showing differentially expressed genes between treatment conditions, with up-regulated genes (red) and down-regulated genes (blue) meeting significance thresholds of |log2FC| > 1 and -log10(p.adjust) > 1.3 (FDR-corrected $p < 0.05$).

Coexpression module analysis and identification of shared genes of sepsis and HF

We applied WGCNA to DEGs for construction of a coexpression network associated with sepsis based on GSE28750, and DEGs with similar expression features were assigned to modules. In this study, a power of 20 (scale-free $R2 = 0.85$) was selected to ensure a scale-free network (figure. 2a).

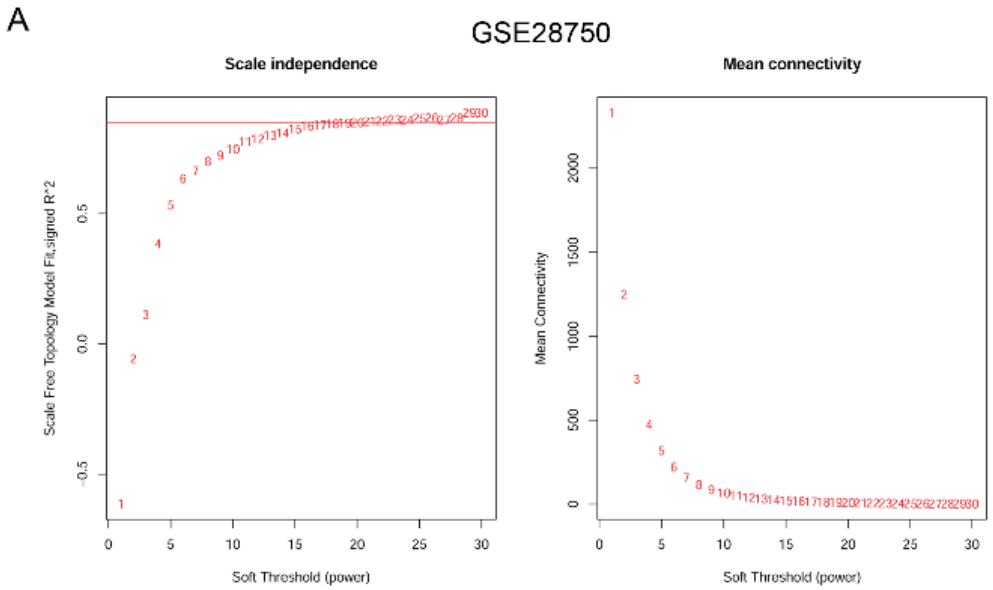


Figure: 2a: Analysis of Scale Independence and Mean Connectivity for GSE28750 with Different Soft Thresholds (powers)

Ten sepsis-related modules were obtained, with each color representing a different module (figure. 2b).

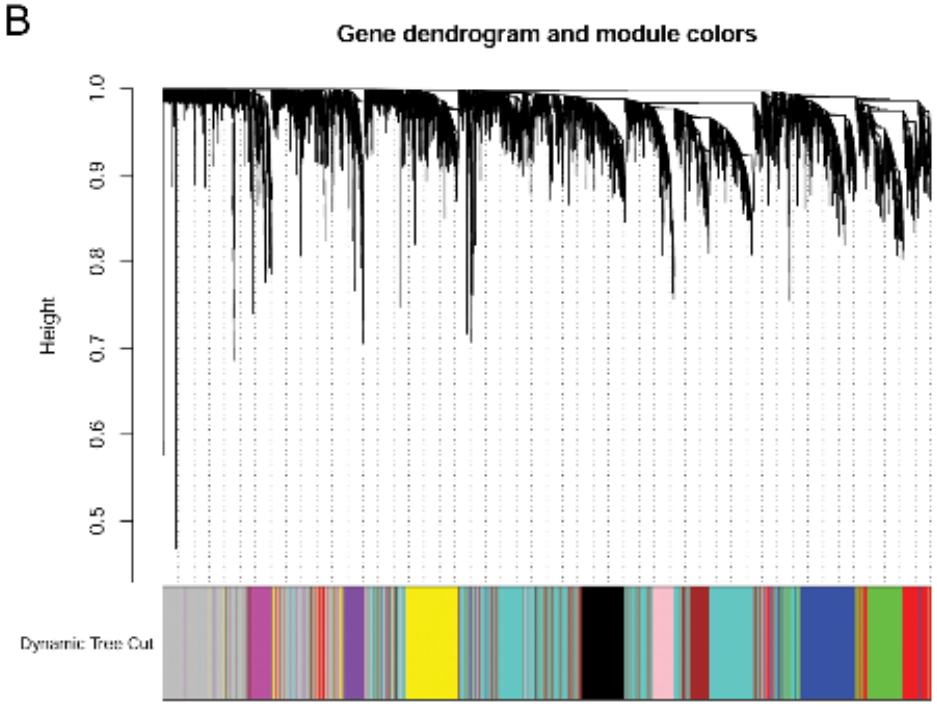


Figure: 2b: Dynamic Gene Modules Identification through Hierarchical Clustering Dendrogram with Modular Color Coding

Subsequently, the association between each module and the disease was evaluated by Spearman correlation analysis. The heatmap of module–trait relationships is shown in figure. 2c.

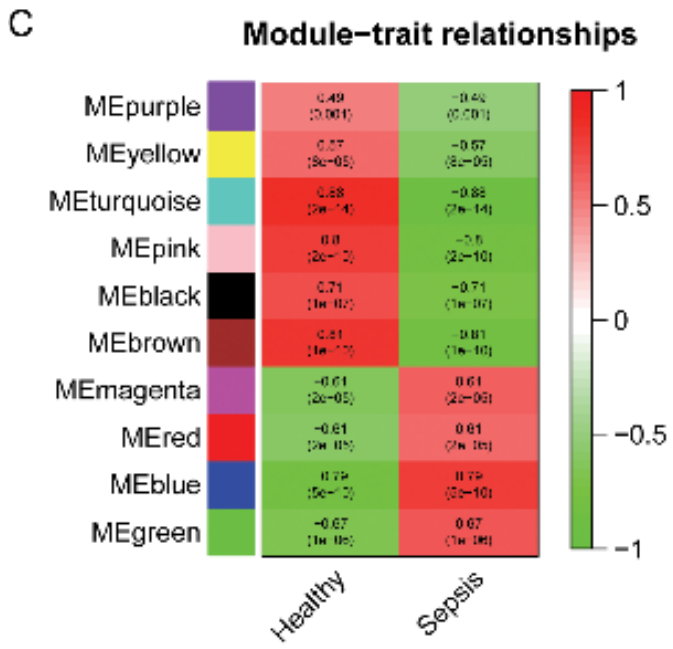


Figure: 2c: Correlation between gene - expression modules and health/sepsis traits

Five modules, including MEturquoise, MEpink, MEblack, MEbrown, and MEblue, had a high association with sepsis ($|r| > 0.7$, $p < 0.05$) and were considered sepsis-related modules. A total of 2972 genes were included in these modules. Similarly, the coexpression network associated with HF was established based on GSE57345. A power of 9 (scale-free $R^2 = 0.85$) was selected to ensure a scale-free network (figure. 2d), and 9 HF-related modules were identified (figure. 2e).

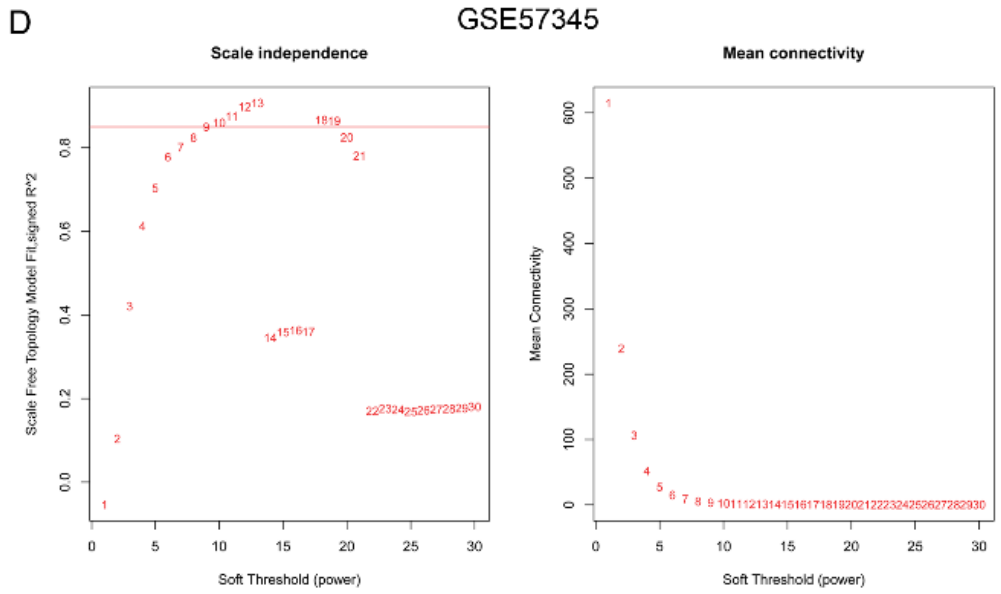


Figure: 2d: Analysis of Scale - independence and Mean Connectivity for GSE57345 Dataset at Different Soft Threshold Powers

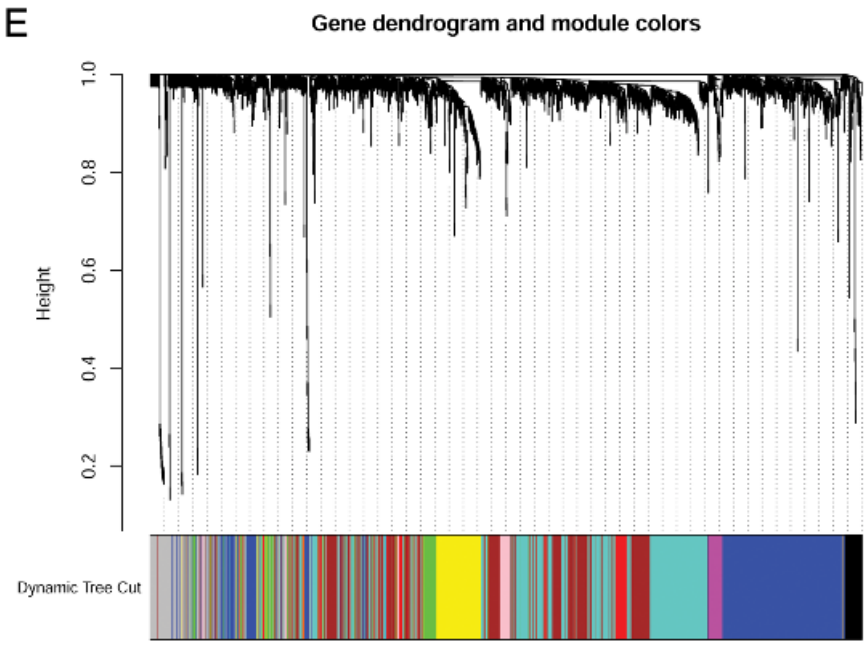


Figure: 2e: Dynamic Tree Cut Identifies Distinct Gene Modules via Hierarchical Clustering and Modular Coloring

Subsequent correlation analysis showed that three modules, namely, Megreen, Mebrown, and Meblue, correlated significantly with HF ($|r| > 0.7$, $p < 0.05$) (figure. 2f).

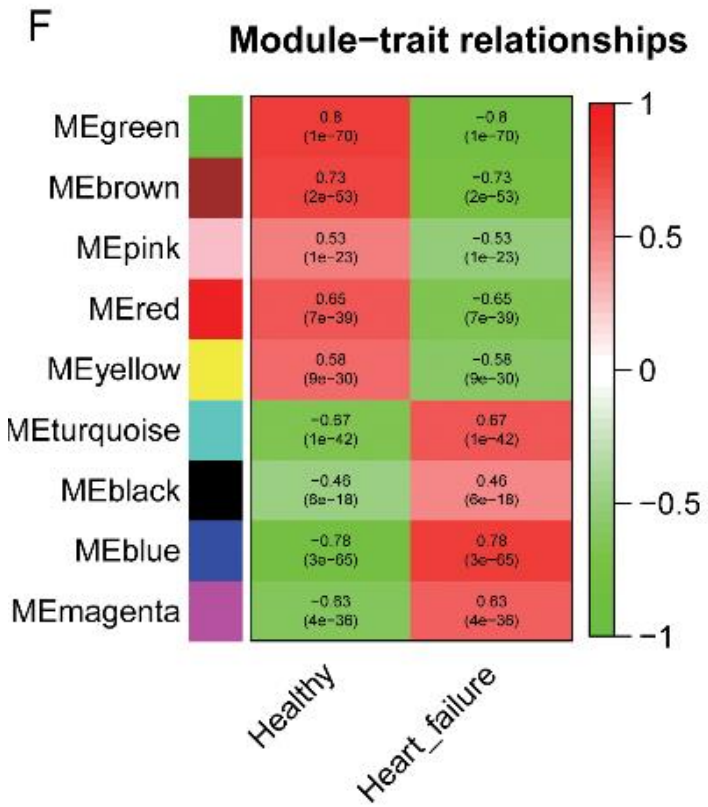


Figure: 2f: Module - trait relationships between healthy and heart - failure states

These modules were selected as HF-related modules and contained 982 genes. A total of 170 shared genes of two diseases were obtained based on Venn diagram analysis of genes in sepsis- and HF-related modules (figure. 2g).

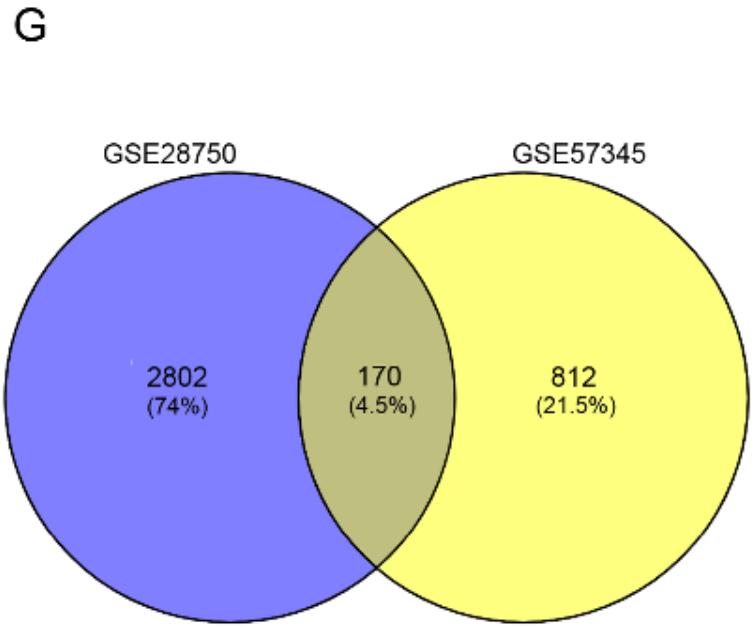


Figure: 2g: Overlap of gene - related data between GSE28750 and GSE57345 datasets, with 74% of genes unique to GSE28750, 21.5% unique to GSE57345, and 4.5% common to both.

Functional enrichment analysis

Functional enrichment analyses were conducted to elucidate the potential function of shared genes of the two diseases. As a result, 6 GO biological process terms, such as macrophage activation, and 11 pathways, such as metabolic pathways, were significantly enriched by the shared genes of the two diseases (figure. 3a).

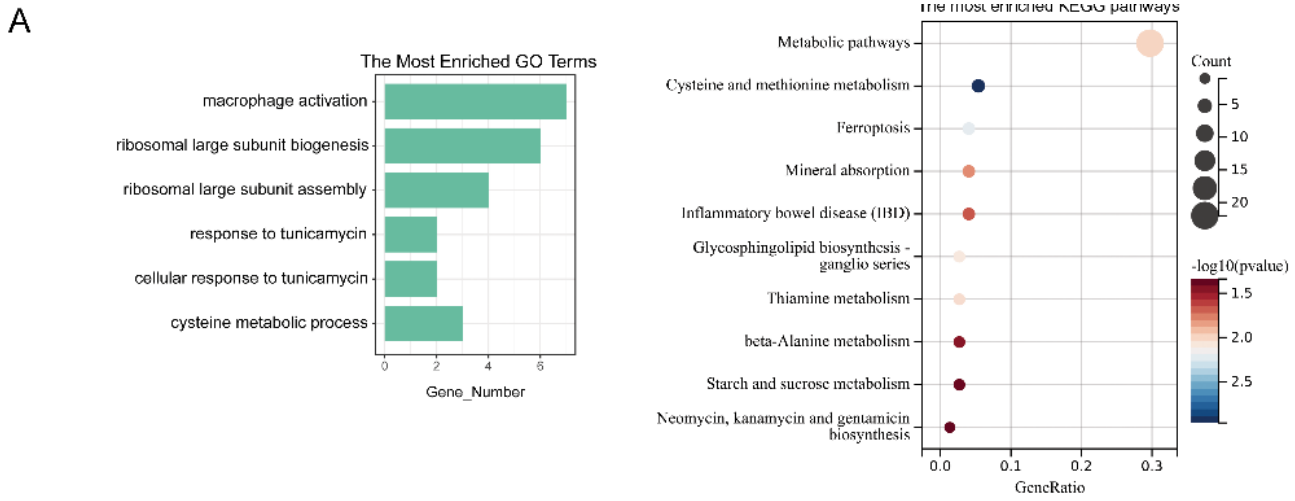


Figure: 3a: Enriched GO Terms and KEGG Pathways Analysis Results

Screening candidate hub-shared genes by PPI network analysis

Using the STRING database, a PPI network was constructed using the shared genes of the two diseases (figure. 3b).

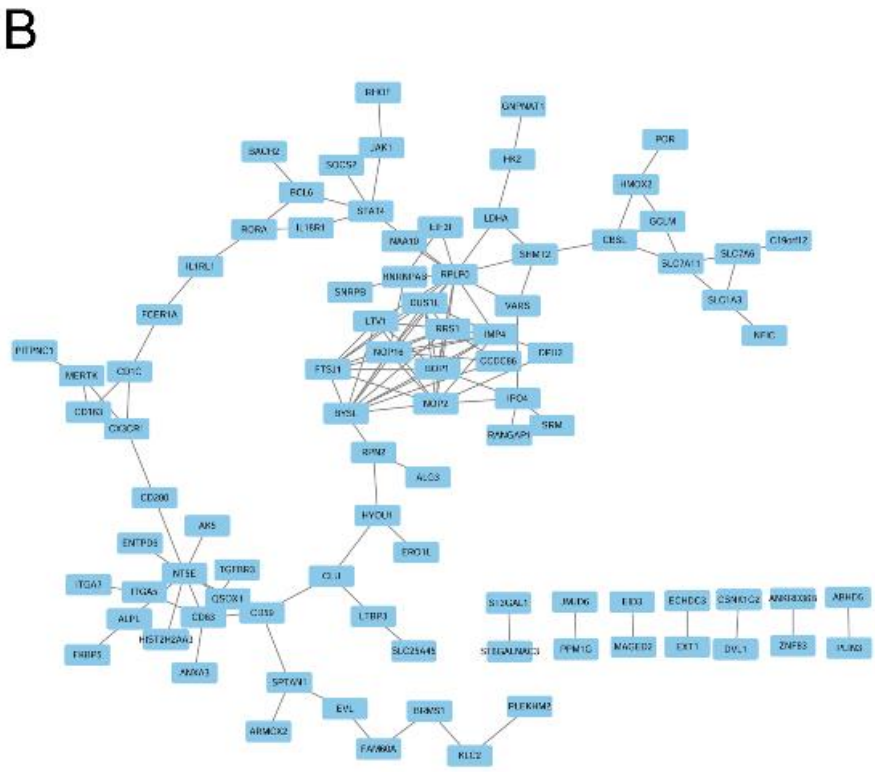


Figure: 3b: Protein-Protein Interaction Network Analysis

The top 10 genes in the PPI network were screened based on four topological properties (MCC, MNC, degree, and EPC) (figure. 3c).

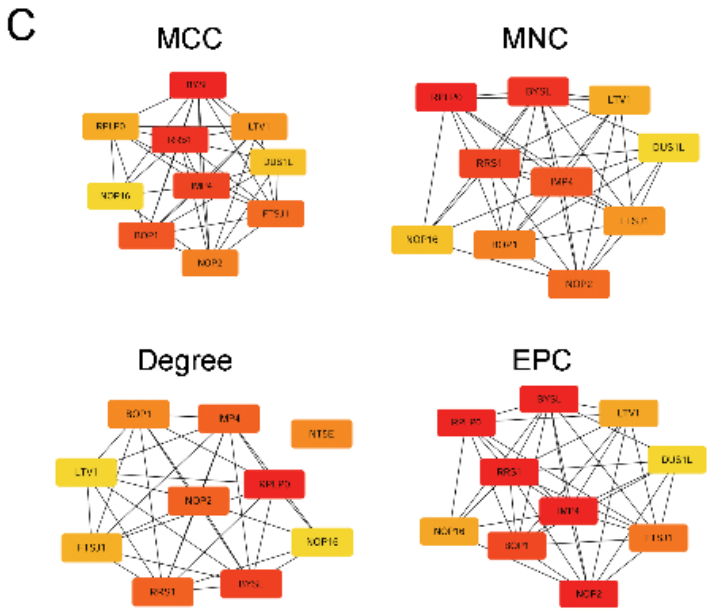


Figure: 3c: Four Network Metrics Visualizations: MCC, MNC, Degree, and EPC Connectivity Patterns

By intersection analysis, 9 overlapping genes were obtained (figure. 3d), including bystin-like (BYSL), ribosome biogenesis regulator 1 homolog (RRS1), IMP U3 small nucleolar ribonucleoprotein 4 (IMP4), BOP1 (ribosomal biogenesis factor (BOP1), FtsJ RNA 2'-O-methyltransferase 1 (FTSJ1), NOP2 nucleolar protein (NOP2), LTV1 ribosome biogenesis factor (LTV1), ribosomal protein lateral stalk subunit P0 (RPLP0), and

NOP16 nucleolar protein (NOP16), which were identified as candidate hub-shared genes of the two diseases.

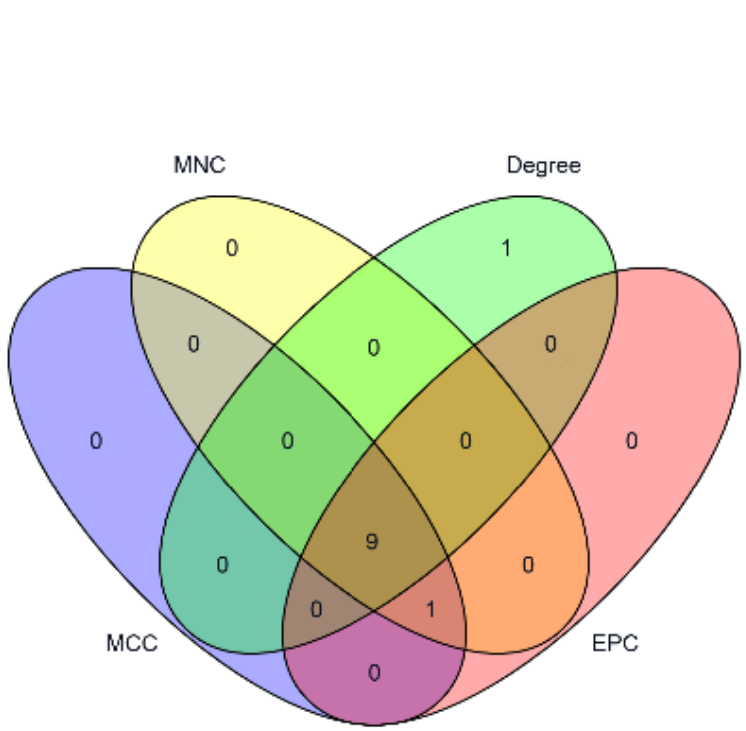


Figure: 3d: Venn Diagram of MNC, Degree, MCC, and EPC Overlaps with Numerical Distributions

Validation of expression of hub-shared genes

Using validation datasets (GSE65682 and GSE84796), we analyzed differential expression of the candidate hub-shared genes. Four candidate hub-shared genes that had the same expression difference in the discovery and validation datasets were identified, including RRS1, IMP4, RPLP0, and NOP16, which were selected as hub-shared genes. These genes were all downregulated in sepsis and HF (figure. 3e).

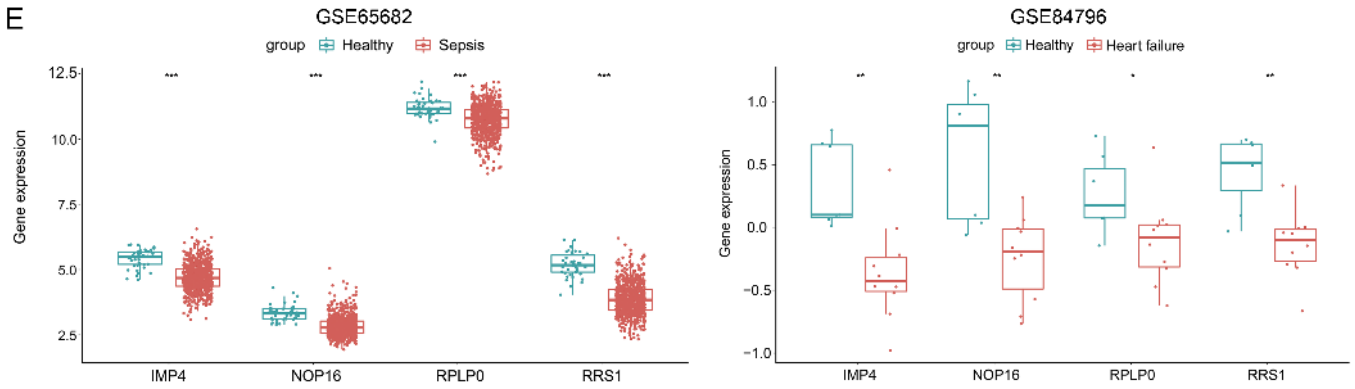


Figure: 3e: Comparative Gene Expression Profiling of IMP4, NOP16, RPLP0, and RRS1 in Sepsis (GSE65682) and Heart Failure (GSE84796) Cohorts

Evaluation of the diagnostic performance of hub-shared genes

The diagnostic performance of the four hub-shared genes was analyzed according to the gene expression data in all datasets. We found that the AUC values of the four hub-shared genes in the four datasets were all higher than 0.7 (figure. 4), revealing that all these hub-shared genes have high diagnostic performance.

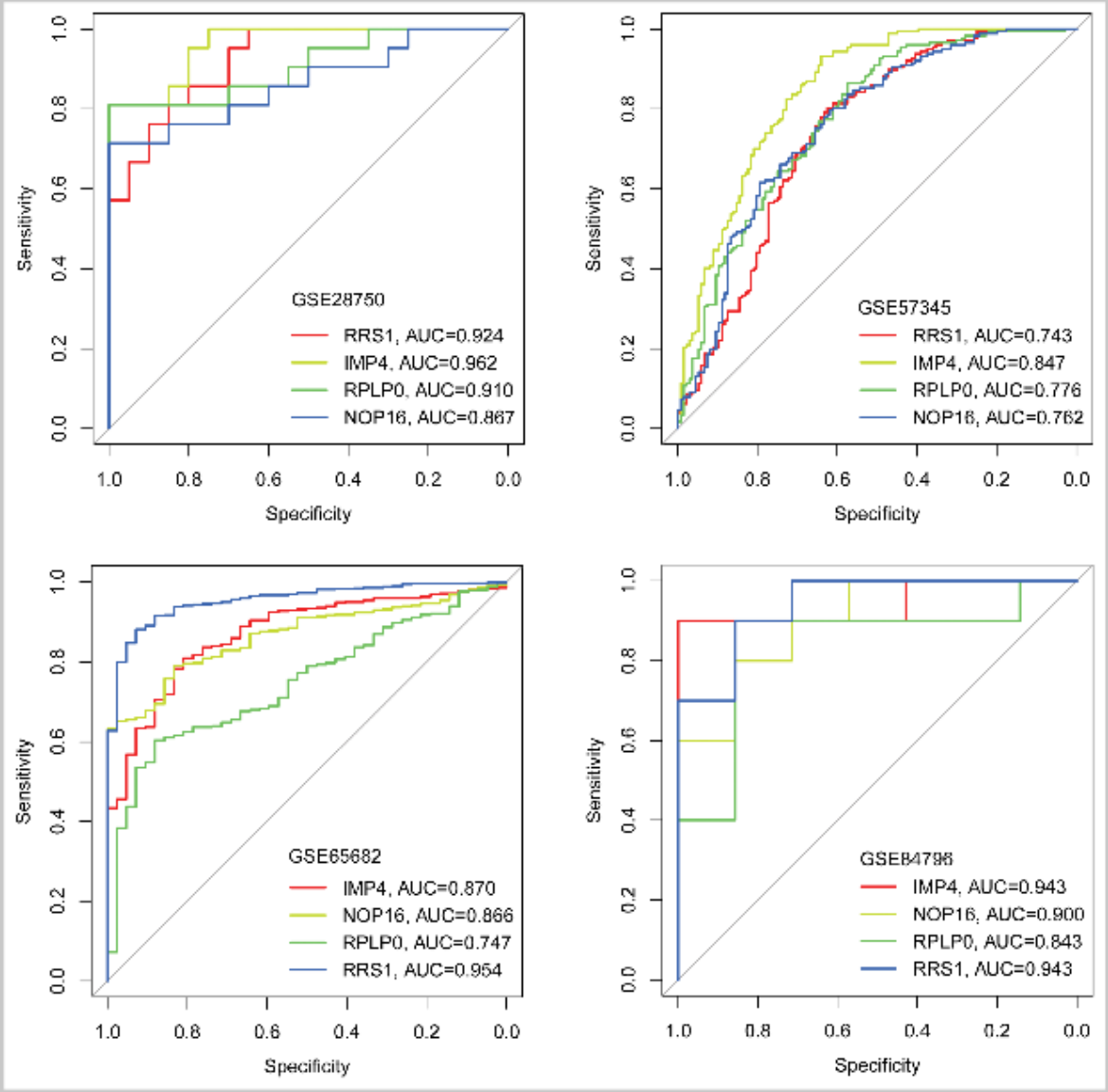


Figure: 4: Comparative Performance of RRS1, IMP4, RPLP0, and NOP16 Biomarkers Across Multiple Datasets: AUC Values and ROC Curves

Construction of the PPI network of hub-shared genes

To explore the potential mechanisms of the hub-shared genes, a PPI network of the hub-shared genes was constructed using the Gene MANIA database (figure. 5). This network, contained20 cooperators of the hub-shared genes, such as mitochondrial ribosomal protein L12 (MRPL12), SEC61 translocon subunit alpha 1 (SEC61A1), and MRT4 homolog, ribosome maturation factor (MRTO4).

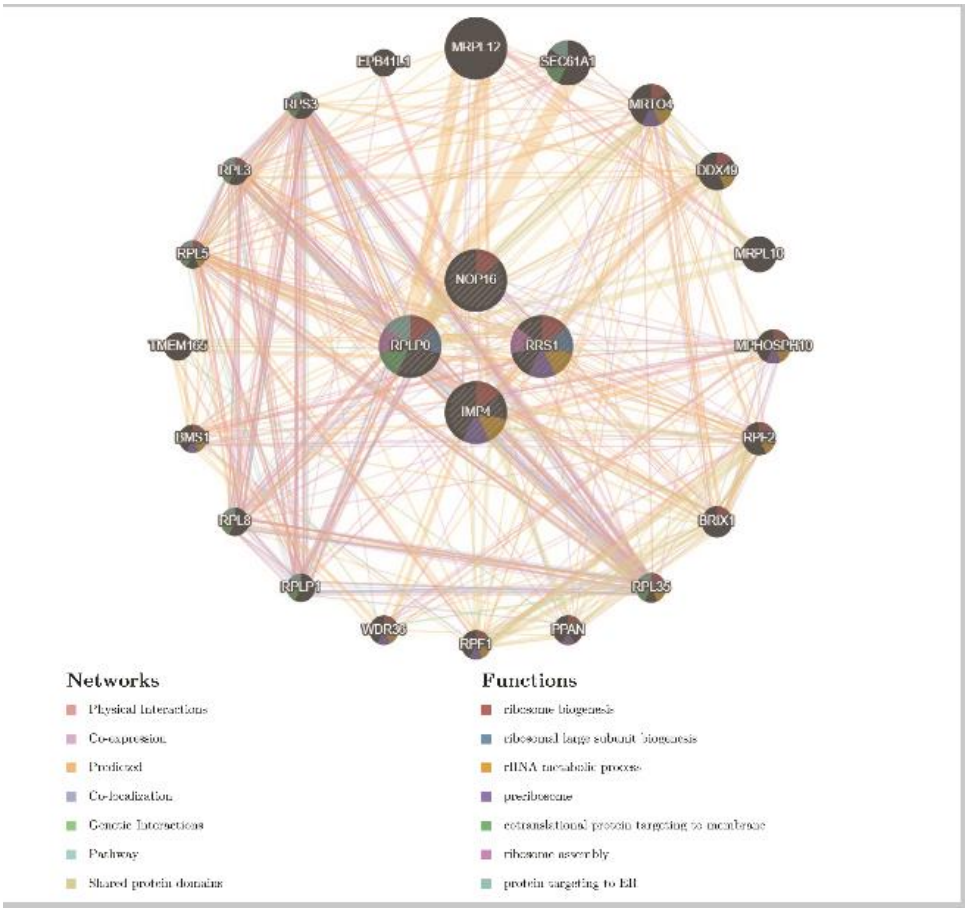


Figure 5: Performance Comparison of Different Biomarkers in Diagnostic Tests Across Multiple Datasets: Sensitivity-Specificity Curves and AUC Values

Association analysis of hub-shared genes and immune cell infiltration

To explore the role of the hub-shared genes in the immune microenvironment, we determined the correlation between the hub-shared gene expression and the proportion of 22 kinds of immune cells based on the GSE28750 and GSE57345 datasets. We observed a significantly negative correlation between RRS1 and M0 macrophages as well as between IMP4 and plasma cells in the two diseases (figure. 6).

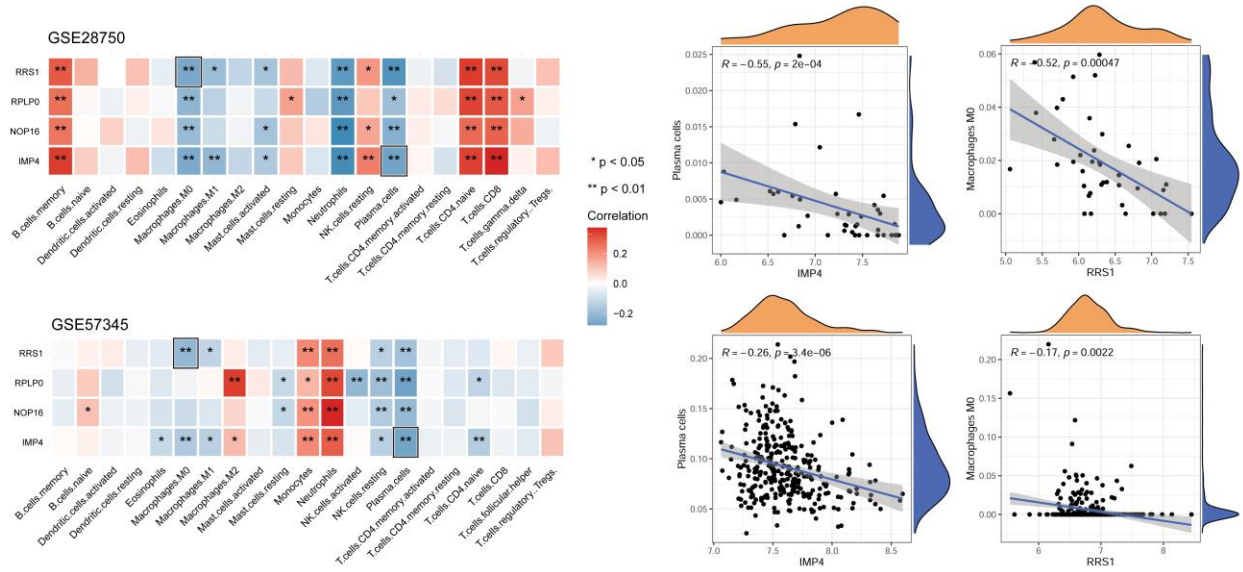


Figure 6: Comprehensive Analysis of RRS1, IMP4, and RPLP0 Expression Profiles and Their Correlations with Immune Cell Subsets in GSE28750 and GSE57345 Datasets

GSEA for hub-shared genes

To explore the potential mechanisms of the hub-shared genes, the top 5 differentially activated pathways between different expression groups of the hub-shared genes were enriched based on the GSE28750 and GSE57345 datasets. Specifically, ribosome biogenesis and RRNA metabolic processes were significantly enriched in the RRS1, IMP4, and NOP16 high-expression groups; ribosome assembly was remarkably enriched in the IMP4 and RPLP0 high-expression groups (figure. 7).

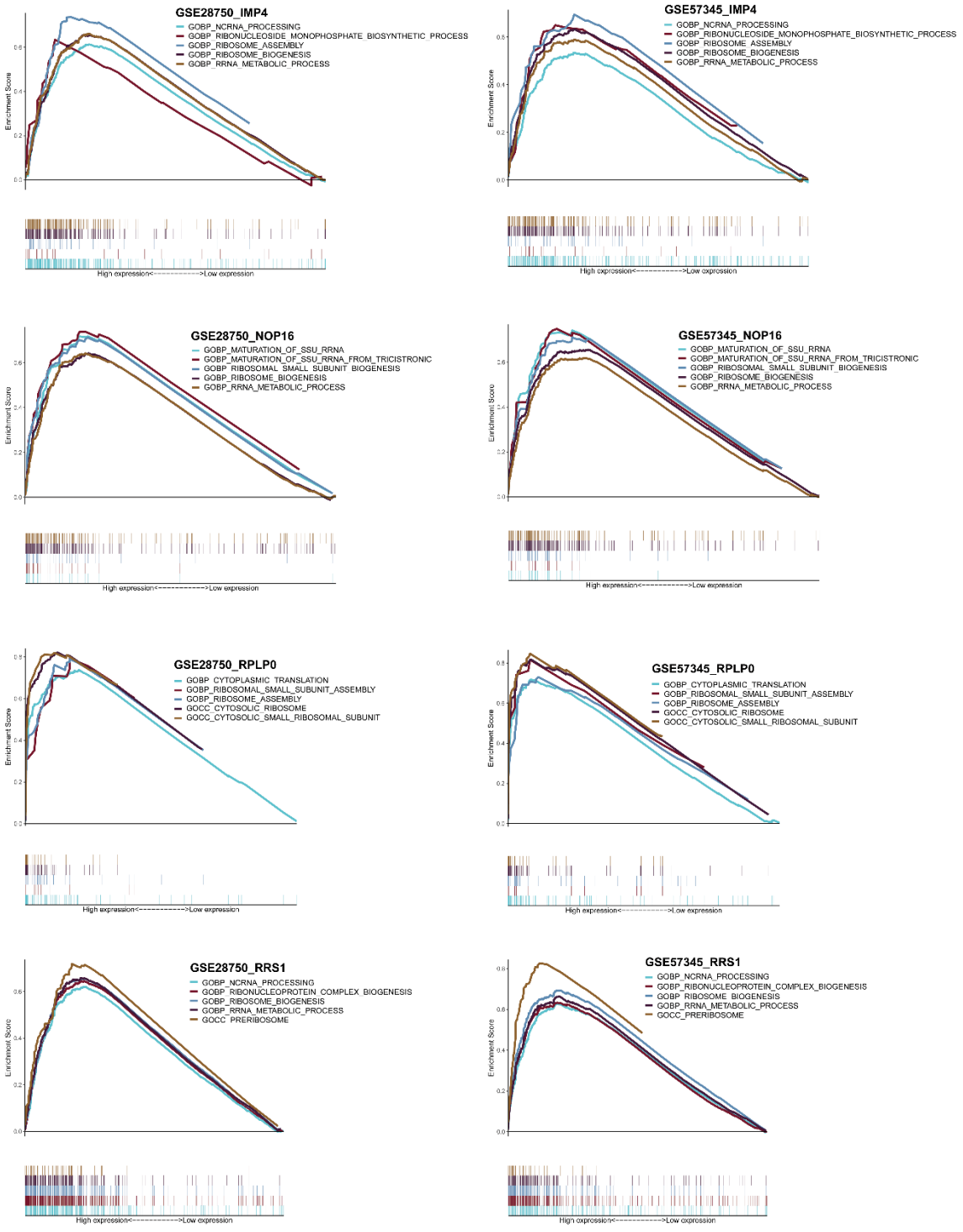


Figure 7: Enrichment analysis of gene - related processes for multiple gene sets across different datasets

Discussion

In this study, we sought to elucidate the regulatory mechanisms of hub-shared genes in sepsis and heart failure (HF), two complex diseases with significant morbidity and mortality. By leveraging bioinformatics approaches and reducing irrelevant data, we aimed to identify potential immunological biomarkers that could predict the risk of these diseases

with greater accuracy. Our research question revolved around understanding the relationship between hub-shared genes and immune cell infiltration in sepsis and HF. This study explored the shared gene signatures of sepsis and HF and elucidated their related regulatory mechanisms via integrated analysis of multiple microarray data and a series of bioinformatics analyses, ensuring that only pertinent information was considered to streamline the process. Four hub-shared genes of the two diseases were identified, including RRS1, IMP4, RPLP0, and NOP16, which had high diagnostic performance, with AUC values higher than 0.7 in the four datasets. Moreover, there was a significantly negative correlation between RRS1 and M0 macrophages and between IMP4 and plasma cells in the two diseases, and the hub-shared genes were significantly enriched in ribosome assembly and biogenesis processes. These findings reveal the common pathogenesis of the two diseases.

HF frequently emerges as a distressing symptom of organ malfunction in sepsis and septic shock scenarios. Despite this, the underlying molecular mechanisms that link sepsis to HF remain elusive. Our comprehensive research delved into the common genetic signatures shared by sepsis and HF, utilizing an integrated approach encompassing the analysis of numerous microarray datasets and a series of bioinformatics techniques, while meticulously excluding redundant or irrelevant data to enhance clarity and focus. Remarkably, we pinpointed four pivotal genes—RRS1, IMP4, RPLP0, and NOP16—that are shared by both conditions and exhibit robust diagnostic capabilities, boasting AUC values surpassing 0.7 across four distinct datasets. Furthermore, our findings indicate a noteworthy negative correlation between RRS1 and M0 macrophages, as well as between IMP4 and plasma cells, in the context of these two diseases. Intriguingly, these hub genes are significantly associated with ribosome assembly and biogenesis processes, providing deeper insights into the shared pathological pathways between sepsis and HF.

Our comprehensive research delved into the common genetic signatures shared by sepsis and HF, utilizing an integrated approach encompassing the analysis of numerous microarray datasets and a series of bioinformatics techniques. Remarkably, we pinpointed four pivotal genes—RRS1, IMP4, RPLP0, and NOP16—that are shared by both conditions and exhibit robust diagnostic capabilities, boasting AUC values surpassing 0.7 across four distinct datasets. Furthermore, our findings indicate a noteworthy negative correlation between RRS1 and M0 macrophages, as well as between IMP4 and plasma cells, in the context of these two diseases. Intriguingly, these hub genes are significantly associated with ribosome assembly and biogenesis processes. With the rapid development of microarray technology and bioinformatics analysis, expression data of thousands of genes can be quickly measured and analyzed in various diseases, which will help researchers to elucidate disease pathogenesis at the genetic level [25,26]. In this study, we for the first time explored the common mechanisms of sepsis and HF using WGCNA, which is an approach that has been widely applied to identify shared risk genes and mechanisms related to diverse disease phenotypes [27-29]. WGCNA revealed five sepsis-related modules containing 2972 genes and three HF-related modules containing 982 genes, and 170 shared genes of the two diseases were obtained by further intersection analysis. These genes may be common genetic mechanisms of sepsis and HF. To understand their possible biological function, we performed functional enrichment analysis and found that these shared genes were significantly enriched in GO biological process functions such as macrophage activation.

To understand their possible biological function, we performed functional enrichment analysis and found that these shared genes were significantly enriched in GO biological process functions such as macrophage activation. Macrophages are fundamental components of inflammatory and fibrotic responses following myocardial infarction. Abnormal macrophage activation contributes to adverse cardiac events such as exacerbated fibrosis and HF [30,31]. In addition, macrophage activation can cause release of multiple proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α, and production of excessive reactive oxygen species, leading to the inflammatory cascade in sepsis [32]. Given the key role of macrophage activation in sepsis and HF, we speculate that these shared genes may contribute to sepsis and septic HF via regulation of macrophage activation. To explore the core shared genes of the two diseases, we conducted PPI analysis for the shared genes of the two diseases and subsequent expression validation using external validation datasets (GSE65682 and GSE84796). Finally, four hub-shared genes of two diseases were identified, including RRS1, IMP4, RPLP0, and NOP16, which may be core genes mediating development of sepsis and septic HF. RRS1, a ribosomal protein, has been revealed to play a key role in ribosome biosynthesis, the cell cycle, and the ribosomal stress response, which affect the p53 signaling pathway.

RRS1, a ribosomal protein, has been revealed to play a key role in ribosome biosynthesis, the cell cycle, and the ribosomal stress response, which affect the p53 signaling pathway. Aberrant expression of RRS1 is implicated in development of Huntington's disease and multiple cancers [33]. Moreover, the p53 signaling pathway is implicated in sepsis [34], sepsis-induced cardiomyopathy [35] and HF [36,37]. However, it has not been investigated whether RRS1 contributes to sepsis and HF via the p53 signaling pathway, which merits further study. RPLP0 is also a ribosomal protein. Accumulating evidence has revealed that RPLP0 participates in multiple cancers [38,39]. RPLP0 has also been identified as a key regulator of neonatal sepsis [40]. IMP4 is a component of U3 small nucleolar ribonucleoproteins that have been shown to play significant roles at telomeres [41]. IMP4 was recently verified to be involved in the malignancy of lung cancer and is suggested to be a novel target [42,43]. NOP16, also known as HSPC111, is related to poor clinical outcomes in patients with breast cancer [44]. Moreover, GSEA showed that ribosome biogenesis and assembly processes were significantly enriched in the groups with high expression of these hub-shared genes. Ribosomes are the sites of protein synthesis, and ribosome biogenesis is associated with diverse biological functions, such as cell proliferation and apoptosis [45]. Abnormal ribosome biogenesis affects various ribosome-related diseases, such as bacterial resistance and cardiovascular diseases, and targeting ribosome biogenesis may be a potential therapy for these diseases [46]. These data indicate that these hub-shared genes may contribute to sepsis and HF by affecting ribosome biogenesis and assembly processes.

Ribosomes are the sites of protein synthesis, and ribosome biogenesis is associated with diverse biological functions, such as cell proliferation and apoptosis [45]. Abnormal ribosome biogenesis affects various ribosome-related diseases, such as bacterial resistance and cardiovascular diseases, and targeting ribosome biogenesis may be a potential therapy for these diseases [46]. These data indicate that these hub-shared genes may contribute to sepsis and HF by affecting ribosome biogenesis and assembly processes. Furthermore, these genes were found to have high diagnostic performance, with AUC values higher than 0.7 in the four datasets. Therefore, we conclude that these hub-shared genes may serve as novel diagnostic biomarkers and therapeutic targets for sepsis and HF.

During sepsis, microbial infections or necrotic tissues can release harmful substances, leading to excessive activation of immune cells [47]. Indeed, various immune cells, such as neutrophils and macrophages, are involved in the pathogenesis of sepsis [48]. Reinhart, Bauer, Riedemann & Hartog [49] demonstrated that immunological biomarkers can be used to predict the outcome of sepsis. In addition, immune cells are implicated in various cardiovascular diseases, including HF [50], and these immune cells have been used as therapeutic targets for HF [51]. To explore the regulatory mechanism of hub-shared genes, we explored the correlation between hub-shared genes and immune cell infiltration in two diseases in this study and found a significantly negative correlation between RRS1 and M0 macrophages and between IMP4 and plasma cells in the two diseases.

In addition, immune cells are implicated in various cardiovascular diseases, including HF [50], and these immune cells have been used as therapeutic targets for HF [51]. To explore the regulatory mechanism of hub-shared genes, we explored the correlation between hub-shared genes and immune cell infiltration in two diseases in this study and found a significantly negative correlation between RRS1 and M0 macrophages and between IMP4 and plasma cells in the two diseases. These data suggest that RRS1 and IMP4 may participate in the pathogenesis of sepsis and HF by regulating M0 macrophages and plasma cells, respectively. RRS1 and IMP4 are potential immunological biomarkers to predict the risk of the two diseases. However, this study was performed based on pure bioinformatics analysis, without experimental validations. Our study has identified key genes and pathways potentially underlying the shared molecular mechanisms between sepsis and heart failure through integrated bioinformatics analysis. This study identifies RRS1, IMP4, RPLP0, and NOP16 as potential key regulators in sepsis and heart failure, suggesting they may lead to more precise diagnostic and treatment methods, especially for septic heart failure, with future research focusing on validating these genes and translating the findings into clinical practice.

Data availability

The sepsis-related gene expression profiles GSE28750 and GSE65682 and HF-related gene expression profiles GSE57345 and GSE84796 were downloaded from the NCBI Gene Expression Omnibus (GEO) (Barrett et al. 2013) database. GSE28750 and GSE57345 were utilized as discovery datasets, whereas GSE65682 and GSE84796 were used as validation datasets.

The GSE84796 dataset includes 21 sepsis and 20 control samples, the GSE65682 dataset 760 sepsis and 42 control samples, the GSE57345 dataset 177 HF and 136 control samples, and the GSE84796 dataset 10 HF and 7 control samples. The mRNA probe expression matrix and corresponding platform annotation file were also downloaded. Gene symbol transformation was performed, and probes that did not match the gene symbol were removed. For different probes mapped to the same gene, the average value was taken as the expression value of the gene.

Code availability

R	Version：R-4.2.0 https://cran.r-project.org/bin/windows/base/old/4.2.0/	2022-09
WGCNA	Version：WGCNA_1.71 https://cran.r-project.org/src/contrib/Archive/WGCNA/	2022-09
STRING	Version：11.0 https://cn.string-db.org/	2022-09
Cytoscape	Version：3.9.2 https://cytoscape.org/	2022-09
GSEA	Version：4.2.3 https://www.gsea-msigdb.org/gsea/index.jsp	2022-09

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Ethics Approval and Consent to Participate

The data used in this analysis are downloaded from the public database GEO, therefore, ethical approval is not applicable and informed patient consent is not required.

Consent to participate

Yes,

Consent to publish

Yes,

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