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ORIGINAL ARTICLE

Identification of Biomarkers and Construction of Predictive Models for Sepsis and Septic Shock

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SUMMARY

Background: **Sepsis is a serious condition resulting from an uncontrolled immune response to infection, often leading to organ dysfunction and septic shock. Current biomarkers have limitations in reflecting disease severity. Recent advances in gene expression analysis suggest that identifying novel biomarkers could improve early diagnosis and intervention, potentially enhancing patient outcomes in sepsis and septic shock.**
Methods: **A whole blood RNA-Seq dataset was obtained from the public database, consisting of samples from sepsis, septic shock, and healthy control groups. Hub genes were identified using differential expression analysis and weighted gene co-expression network analysis. Functional analysis was performed using Gene Ontology and Gene Set Enrichment Analysis. Expression levels of each hub gene across different groups were compared. Biomarkers were identified and predictive models for sepsis and septic shock were constructed using stepwise regression and logistic regression. The models were validated using external datasets.**
Results: **Nine hub genes were identified, with expression levels showing an upward trend in sepsis and septic shock samples. These hub genes were enriched in pathways related to the innate immune system and neutrophils. Predictive models for sepsis (with participating biomarkers ELANE, OLFM4, and MMP8) and septic shock (with participating biomarker COL17A1) demonstrated good diagnostic efficacy during validation.**
Conclusions: **This study identified biomarkers and developed predictive models for early identification of sepsis and septic shock, which could improve patient prognosis. Further investigations are needed to understand the underlying mechanisms of these biomarkers in sepsis.**
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KEYWORDS

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INTRODUCTION

Sepsis is a complex syndrome resulting from a dysregulated immune response to infection, which can lead to life-threatening organ damage. Uncontrolled sepsis, characterized by the massive release of cytokines and inflammatory mediators, may progress to septic shock - a condition of sepsis accompanied by various abnormalities and an increased risk of death [1]. Currently, septic shock and subsequent multi-organ failure are prevalent among patients in intensive care units (ICUs). Studies have reported that the incidence and 90-day

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mortality rates of sepsis in Chinese hospital ICUs are approximately 20.6% and 35.3%, respectively, while the 90-day mortality rates for patients with septic shock can exceed 51% [2]. Despite advances in antibiotics and therapeutic protocols improving sepsis patient prognosis, current survival rates remain low. Given the significantly higher mortality rate associated with septic shock, preventing sepsis patients from developing septic shock is crucial for improving sepsis survival rates. Consequently, early diagnosis and treatment of patients at higher risk of developing septic shock are essential for reducing sepsis mortality.

The primary pathogenesis of sepsis involves a systemic inflammatory response and immune dysregulation, where excessive inflammatory mediators produced during inflammation impair the body's immune function, leading to multiple organ dysfunction [3]. Recent research has demonstrated that both pro-inflammatory and anti-inflammatory responses occur early in the sepsis process [4], followed by significant alterations in non-immune pathways such as metabolism, coagulation, and the cardiovascular system. Due to the complexity of sepsis pathogenic mechanisms and clinical symptoms, screening biomarkers related to disease progression is a valuable monitoring approach. Currently, biomarkers commonly used to monitor sepsis include procalcitonin (PCT) and C-reactive protein (CRP) [5]. In recent years, additional biomarkers, such as serum cytokines, cellular receptors, and coagulation factors, have been employed for sepsis-related diagnosis and prognosis prediction. However, these biomarkers may not adequately reflect the progression and severity of sepsis in real-time and lack potential as therapeutic targets, limiting their preventive effects on the development of sepsis into septic shock. With advancements in microarray and RNA-Seq technologies, emerging studies on sepsis-related biomarkers suggest that identifying markers based on gene expression may offer higher sensitivity and specificity. A recent study utilizing microarray data developed a diagnostic and prognostic model for sepsis based on eight autophagy-related genes [6], while another investigation employing RNA-Seq data proposed NLRC4 as a potential therapeutic target for sepsis treatment [7]. According to these findings, it is feasible to screen biomarkers for sepsis and septic shock and construct diagnostic and predictive models based on the analysis of gene expression data from patients with sepsis and septic shock.

In this study, based on the RNA-Seq dataset of whole blood from patients with sepsis, septic shock, and healthy controls obtained from the public database, hub genes were identified through a combination of differential expression analysis and weighted gene co-expression network analysis (WGCNA). Functional enrichment analyses, including Gene Ontology (GO) and Gene Set Enrichment Analysis (GSEA), were subsequently applied, and the expression levels of each hub gene across different groups were compared. Stepwise regression and logistic regression analyses were employed to identify biomarkers from the hub genes and construct predictive models for sepsis (composed of ELANE, OLFM4, and MMP8) and septic shock (composed of COL17A1) separately. These models were validated using two external RNA-Seq datasets. The ROC curves demonstrated that both constructed prediction models exhibited strong diagnostic performance.

MATERIALS AND METHODS

Data collection

RNA-Seq datasets were obtained from the NCBI Gene Expression Omnibus public database (GEO). GSE154918 contained RNA-Seq data annotated by GPL20301 of whole blood sample from 24 patients with sepsis, 29 septic shock patients, and 40 healthy controls. GSE131411 contained RNA-Seq data of whole blood sample from 63 septic shock patients while GSE185263 contained RNA-Seq data of whole blood sample from 348 patients with sepsis, 82 severe sepsis/septic shock patients, and 44 healthy controls. Both GSE131411 and GSE185263 were annotated by GPL16791.

Differential expression analysis

Differential expression analyses were conducted for sepsis and healthy control samples, septic shock and healthy control samples, as well as septic shock and sepsis samples using the limma package in R software. Genes with a false discovery rate (FDR) < 0.05 and a fold change (FC) > 2 were considered as differentially expressed genes (DEGs).

Construction of the gene co-expression network by WGCNA

The standard deviation (SD) of each gene in the GSE154918 dataset was calculated separately, and the top 50% of genes with the smallest SD were eliminated. Outlier genes and samples were removed using the goodSamplesGenes function of the WGCNA package in R software. A scale-free co-expression network based on the GSE154918 dataset was then constructed using the WGCNA package. The correlation coefficient between each gene pair was calculated to create an adjacency matrix, which was subsequently transformed into a topological overlap matrix (TOM) to further verify network connectivity. To classify genes with similar expression profiles into gene modules, average linkage hierarchical clustering was conducted based on the TOM-derived dissimilarity measure, with a minimum cluster size (gene group) of 50 for the gene dendrogram. The module with the highest absolute value of the correlation coefficient was identified as the key module.

Identification of hub genes and GO analysis

The intersection of DEGs from sepsis and healthy control samples, septic shock and healthy control samples, septic shock and sepsis samples, and genes from the key module of WGCNA was obtained using the jvenn tool. Genes in the intersection were considered as hub genes.

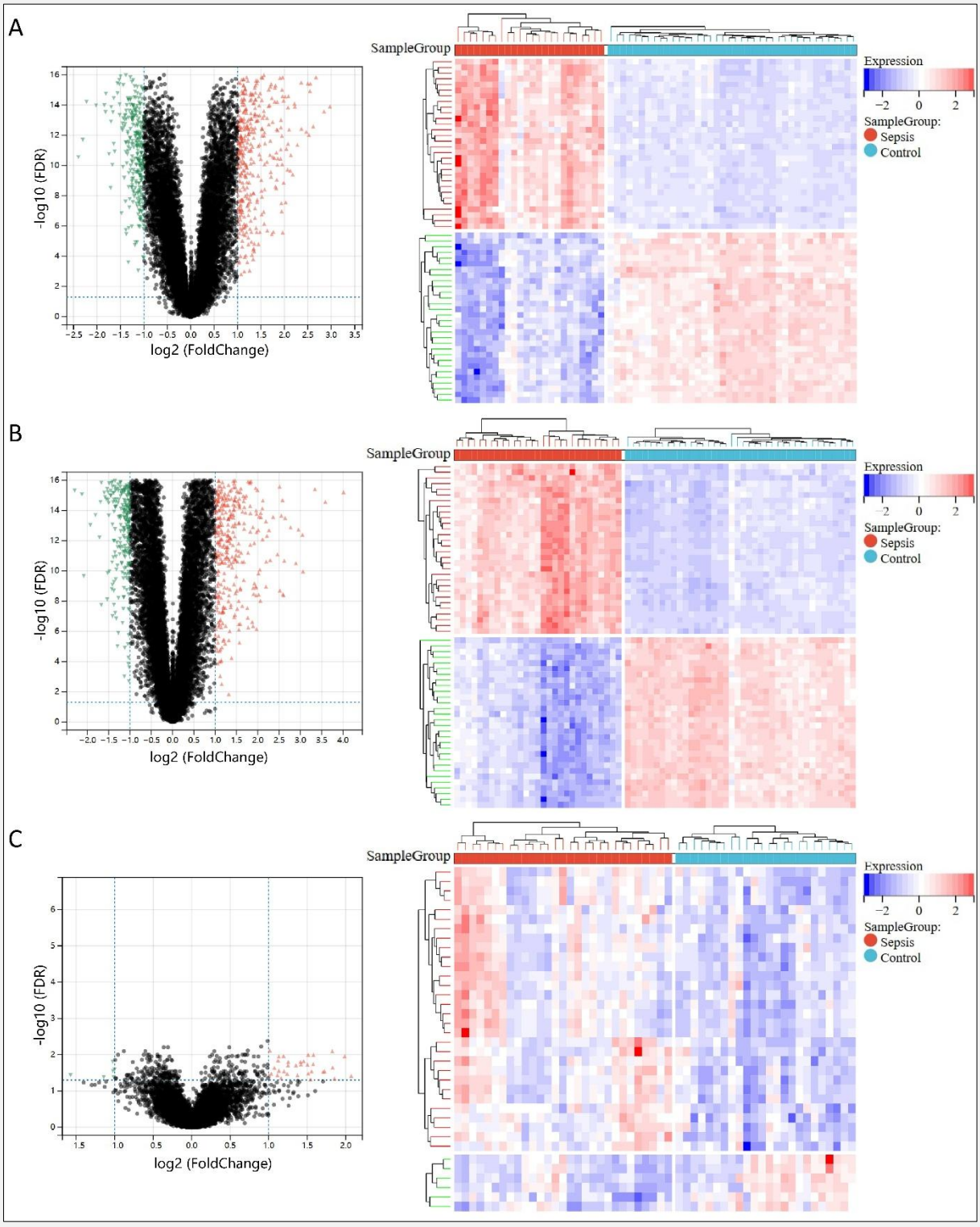

Figure 1. Volcano plot showing DEGs and heatmap of the top 30 DEGs of A: sepsis and healthy control samples, B: septic shock and healthy control samples, C: septic shock and sepsis samples.

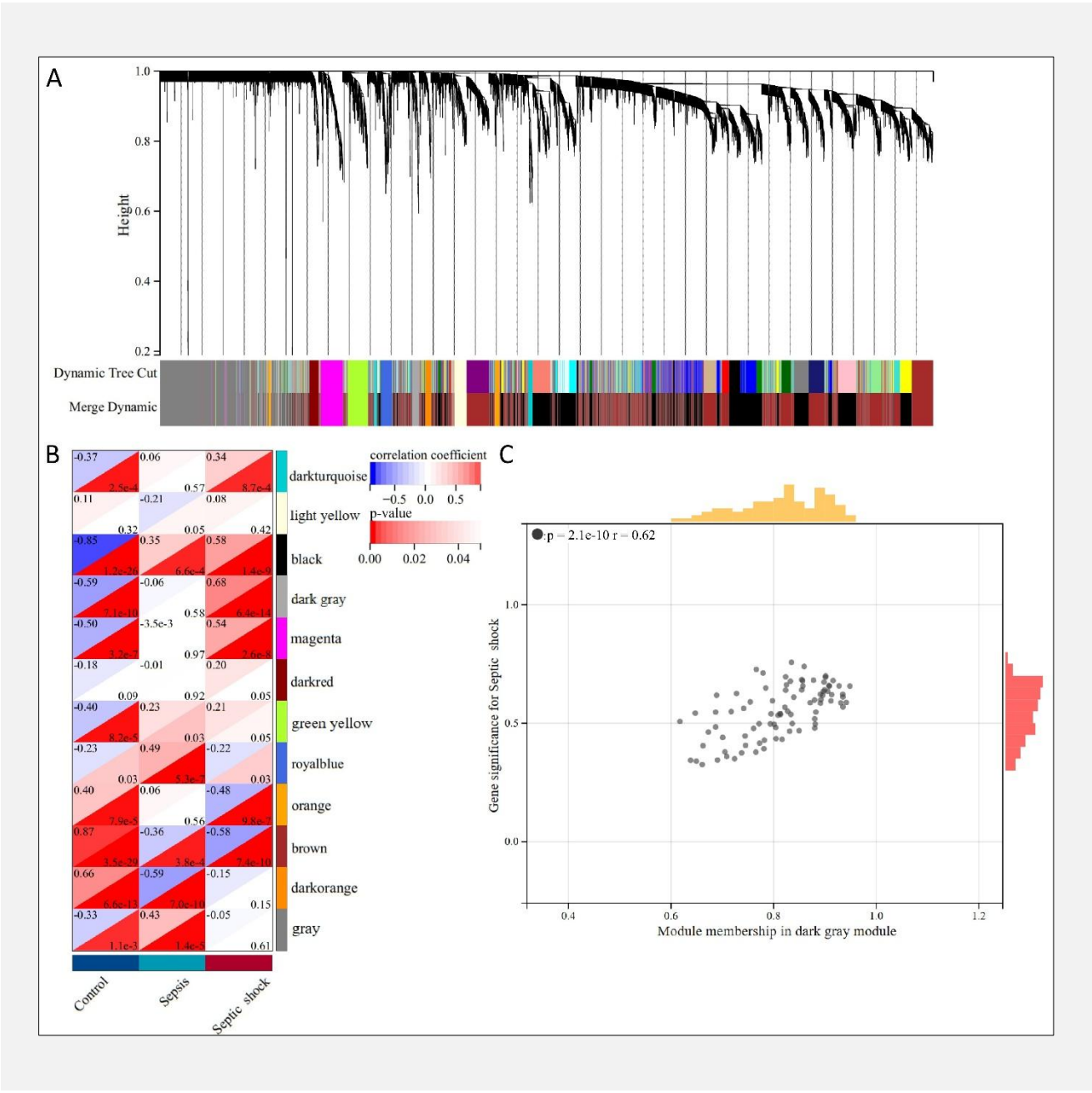

Figure 2. Results of the WGCNA. A: Cluster dendrogram of genes. B: Correlations between different modules and phenotypes. C: Correlation of module membership and gene significance for septic shock in the dark gray module.

Functional enrichment analysis on hub genes was then performed using the clusterProfiler package, based on the GO annotations in the org.Hs.eg.db package. GO terms with an FDR < 0.01 were considered statistically significant.

Expression difference and GSEA of each hub gene

To further elucidate the role of each gene in the development of sepsis, expression differences of each hub gene among healthy control, sepsis, and septic shock samples were visualized using violin plots. GSEA of each hub gene was performed via GSEA software (version 3.0) based on Reactome subset downloaded from the Molecular Signatures Database (http://www.gsea-msigdb.org/gsea/downloads.jsp), in order to further investigate their functions. The GSE154918 dataset was divided into two groups based on median values of hub gene expression, and pathways with a nominal p-value < 0.05 and |NES| > 1 were considered statistically significant.

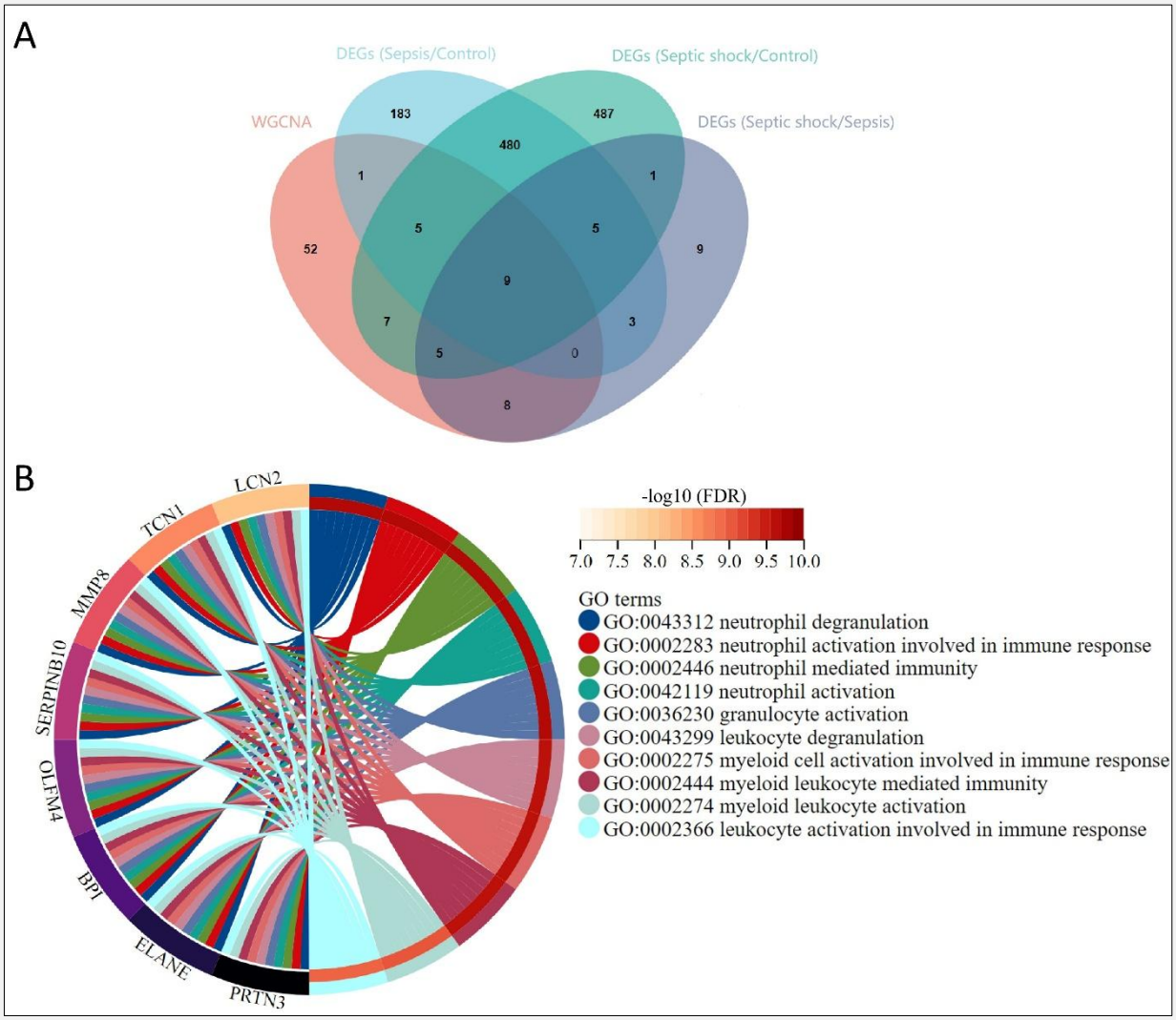

Figure 3. Hub genes and GO analysis. A: 9 hub genes screened by taking the intersections of 3 groups of DEGs and genes in dark gray module of the WGCNA. B: Biological processes of GO terms in which the hub genes were highly enriched.

Identification of biomarkers, construction of predictive models, and validation

Stepwise regression analysis was performed on sepsis and healthy control samples of GSE154918 to eliminate hub genes that were not significant for sepsis prediction, while retaining the significant hub genes as sepsis biomarkers. The same analysis was also performed on septic shock and sepsis samples, and biomarkers for differentiating septic shock from sepsis were obtained. Based on the two groups of biomarkers, logistic regression models for sepsis and septic shock were constructed. The diagnostic efficacy of these two models was then evaluated using receiver operating characteristic curves (ROCs). The constructed models were further validated with GSE131411 and GSE185263 datasets. The analyses mentioned above were performed using the "stats" and "pROC" packages in R software.

RESULTS

Screening of DEGs

Based on the RNA-Seq data from the GSE154918 dataset, a total of 686 DEGs were identified in the differential expression analysis between sepsis and healthy control samples, while 1183 DEGs were identified in the analysis comparing septic shock with healthy control samples. In the analysis of septic shock versus sepsis

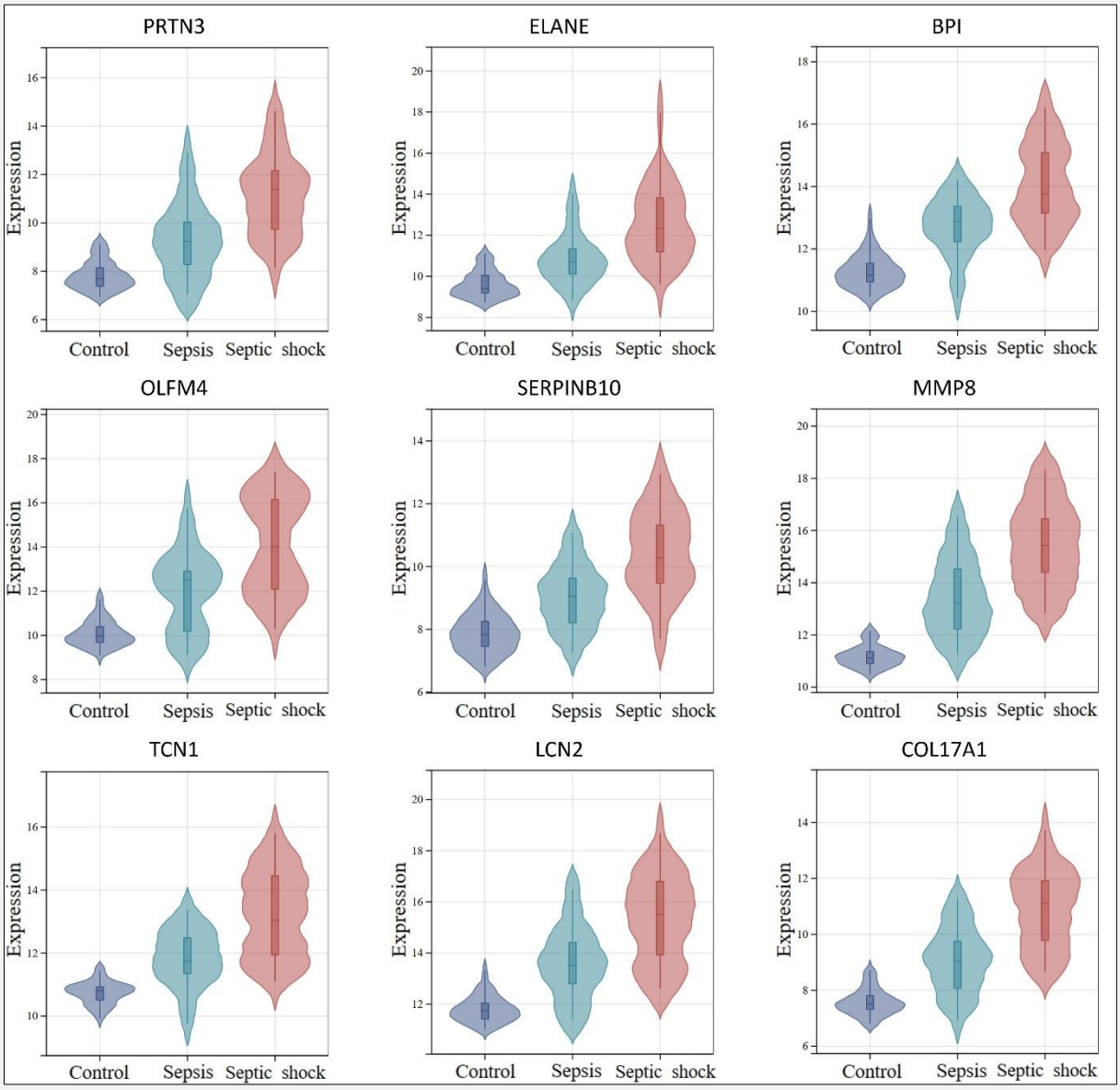

Figure 4. Expression of the 9 hub genes in samples of health control, sepsis, and septic shock, respectively.

samples, 40 DEGs were screened. These DEGs were visualized using volcano plots for each differential expression analysis and heatmaps were created for the top 30 DEGs of each analysis (Figures 1).

Gene co-expression network construction and key module selection

A total of 9,053 genes were screened for WGCNA analysis, and no samples were removed. The soft threshold power was chosen to be 14, with scale independence reaching 0.86 and an average connection value of 36.42. After setting the cut height to 0.30 and the minimum module size to 50, 12 co-expression modules were ultimately identified (Figure 2A). Correlations between modules and phenotypes of different groups were then analyzed (Figure 2B). The dark gray module, containing 87 genes, exhibited the highest positive correlation with septic shock ($r = 0.68$, $p = 6.4e\text{-}14$) and was selected for further analysis. Additional correlation analysis between gene significance for septic shock and module membership in the dark gray module, as shown in the dot plot (Figure 2C), indicated that these genes were closely cor-

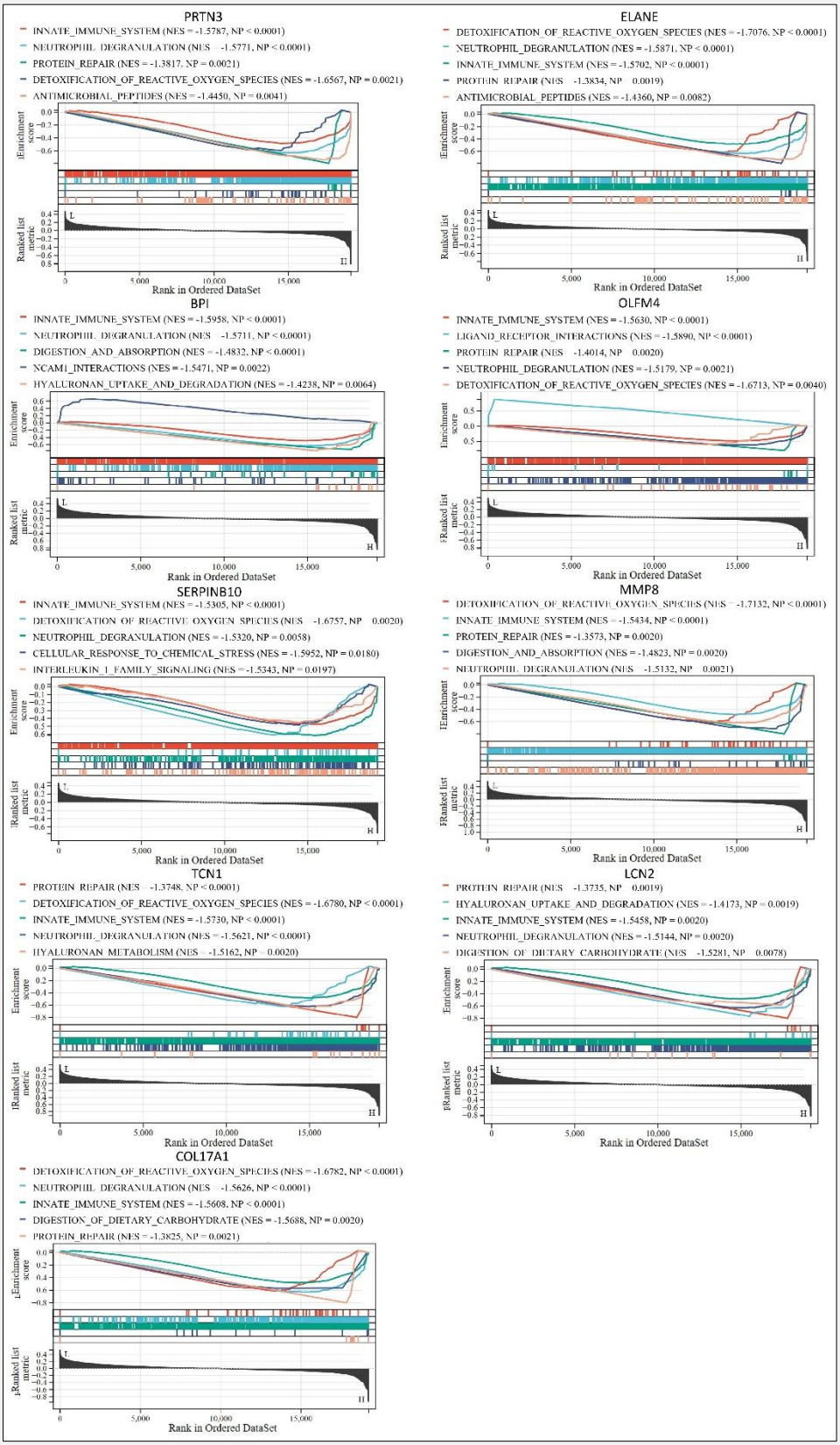

Figure 5. GSEA revealed the enriched pathways of the 9 hub genes.

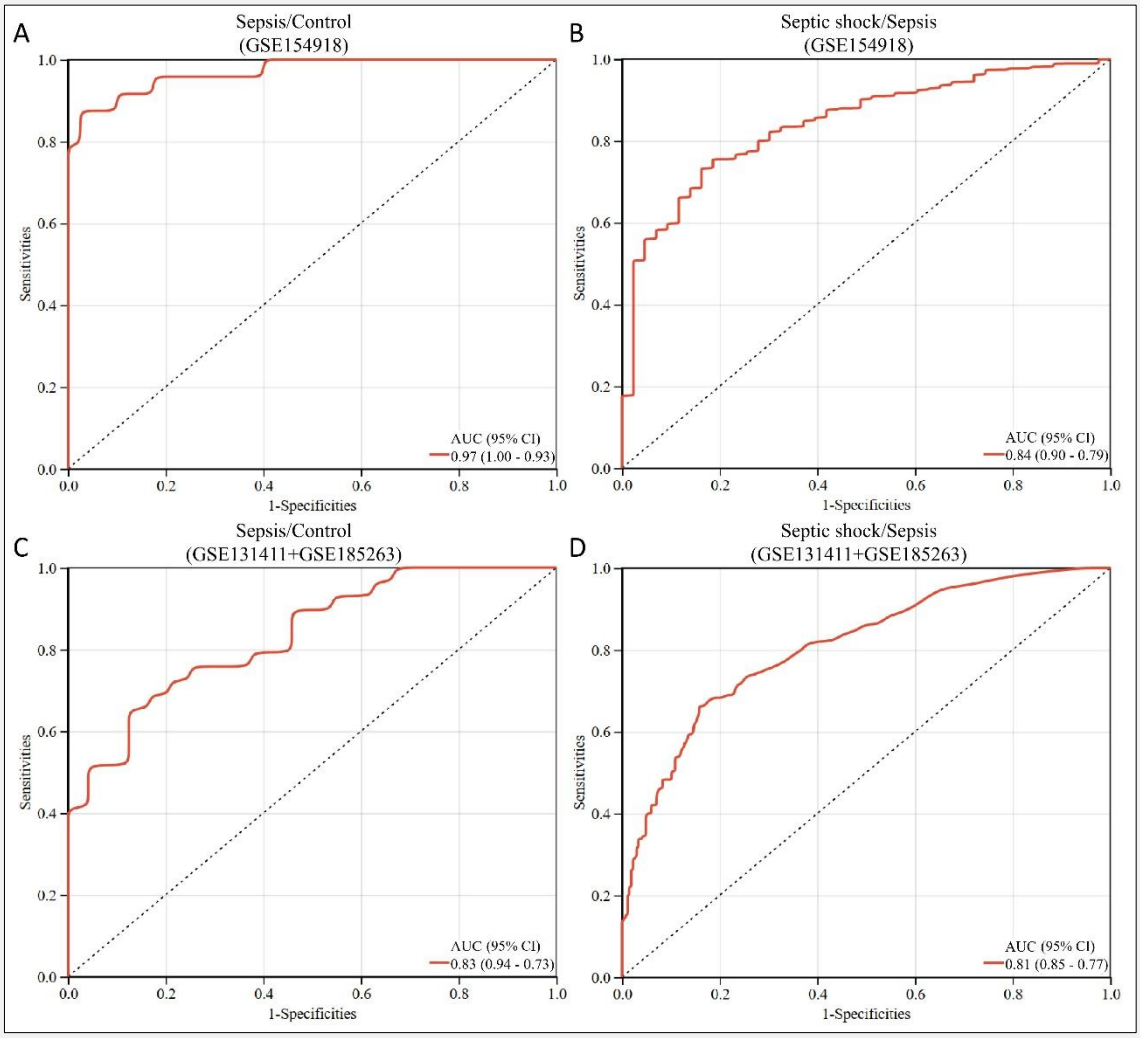

Figure 6. ROC curves and corresponding AUC values for the predictive models. A: The model for sepsis based on GSE154918. B: The model for septic shock based on GSE154918. C: Validation of the model for sepsis with GSE131411 and GSE185263. D: Validation of the model for septic shock with GSE131411 and GSE185263.

related with both the phenotype of the group and the module (r = 0.62, p = 2.1e-10).

Identification and GO analysis of hub genes

Nine hub genes were identified by taking the intersections of DEGs of sepsis and healthy control samples, septic shock and healthy control samples, septic shock and sepsis samples, and genes in the dark gray module identified via WGCNA (Figure 3A). Subsequent GO analysis of the hub genes revealed that 8 of them were highly enriched in biological processes related to degranulation and activation of different types of leukocytes involved in immune response, including myeloid leukocytes, granulocytes and neutrophils (Figure 3B).

Expression difference and GSEA of each hub gene

To further investigate the potential role of each hub gene in the development of sepsis, the expression levels of the nine hub genes across the three groups were visualized using violin plots (Figure 4). In conjunction with previous findings, the expression differences of hub genes among the groups were significant, exhibiting a gradient increase in expression levels from healthy control to sepsis and septic shock samples. GSEA of each hub gene based on Reactome subset revealed that all the hub genes were involved in pathways related to the innate immune system and neutrophil degranulation. Additionally, some of the hub genes were associated with detoxification of reactive oxygen species (ROS) and hyaluronan (hyaluronic acid, HA) metabolism (Figure 5).

Biomarkers, predictive models, and validation

Stepwise regression analysis was conducted on sepsis and healthy control samples from the GSE154918 dataset. MMP8, ELANE, and OLFM4 were found to be significant for sepsis prediction and were considered as sepsis biomarkers. Subsequent analysis on septic shock and sepsis samples revealed that COL17A1 could serve as a single biomarker for differentiating septic shock from sepsis. Logistic regression models for sepsis and septic shock based on these biomarkers were constructed, yielding AUCs of 0.97 and 0.84, respectively (Figure 6A, B). Further validation of the constructed models using samples from the GSE131411 and GSE185263 datasets demonstrated good diagnostic performance, with AUCs of 0.83 and 0.81, respectively (Figures 6C, D). These results underscore the significance and reliability of the identified biomarkers and the constructed models for diagnosing sepsis and differentiating septic shock from sepsis.

DISCUSSION

According to a recent study, approximately 48.9 million cases of sepsis occurred globally in 2017, with 11 million sepsis-related deaths, and the incidence of sepsis continues to exhibit an upward trend [8]. Septic shock, as a severe condition of sepsis with underlying cellular or metabolic abnormalities, is associated with even higher survival risk [2]. Early identification and treatment are essential to improve the prognosis of patients with sepsis. In this study, in order to identify proper biomarkers and construct predictive models, the hub genes in peripheral blood of patients with sepsis and septic shock were firstly screened through differential expression analysis and WGCNA of RNA-Seq data followed by the identification of their enriched functional pathways.

The expression levels of all nine hub genes in sepsis and septic shock samples displayed a gradient upward trend, and GSEA results demonstrated that they were all enriched in pathways related to the innate immune system and neutrophils. Immune cells play a pivotal role in the immune response. During sepsis, circulating immune cells including neutrophils and macrophages are recruited to eliminate pathogens and infected cells, rapidly activating the innate immune system [9]. Neutrophils, members of the myeloid leukocyte family, constitute over 50% of circulating leukocytes and play a crucial role in the body's defense against infection [10]. As the primary innate immune cells, neutrophils exhibit multiple effector functions, including phagocytosis, degranulation, and the release of extracellular traps. The massive release of active neutrophil mediators and proteolytic enzymes can lead to extensive tissue damage while eradicating pathogens. Due to the adhesion and infiltration of neutrophils, the function of endothelial cells is also affected, and the activation of circulating coagulation factors leads to extensive microvascular thrombosis [11]. These factors further exacerbate tissue hypoxia and organ dysfunction, potentially resulting in septic shock or multiple organ failure. Additionally, neutrophil-produced reactive oxygen species (ROS) play a pivotal role in organ dysfunction caused by sepsis [12]. In this study, GSEA results of hub genes also indicated their involvement in ROS metabolic processes. It has been reported that ROS released by the nicotinamide adenine dinucleotide phosphate oxidases (NOX) in neutrophils can form neutrophil trapping nets (NETs) by activating granzymes and stimulate TNF-α and macrophage inflammatory protein 2 (MIP-2) to enhance the antibacterial response of neutrophils [13]. Wang's study also found that the continuous production of ROS by neutrophils is related to septic cardiomyopathy, resulting the poorer prognosis of patients with sepsis [14]. Macrophages are also crucial components involved in the innate immune response. They perceive various toxins and pathogens through the pattern recognition receptors (PRR) on the cell membrane surface and participate in immune regulation through TLR4, MyD88, and NF-κB signaling pathways. Pathogens stimulate macrophages to produce excessive and sustained inflammatory responses that damage tissues and cause a series of cascade effects, resulting in adverse consequences for the body [15]. Research has shown that the continuous production of ROS in macrophages in septic animal models can lead to organ damage and increased inflammatory response [16]. Furthermore, another study demonstrated that macrophage-derived exosomes can mediate cellular damage in a state of tissue inflammation during sepsis [17].

The prediction model for sepsis consists of MMP8, ELANE, and OLFM4. MMP8 is an important inflammatory mediator that mediates leukocyte adhesion and was first discovered in neutrophils [18]. In line with the results of this study, previous studies also found high expression of MMP8 in the serum of patients with septic shock [19]. Research has reported that MMP8 plays a role in the development of sepsis through the p38-MAPK and ERK phosphorylation pathways [20]. Phosphorylation signals following activation of the p38-MAPK and ERK pathways are critical in neutrophil activation and functions such as phagocytosis, degranulation, and ROS generation [21]. Moreover, these processes also activate NF-κB transcription factors, enhancing the transcription of specific inflammation-related genes. ELANE encodes neutrophil elastase (NE), which is crucial in innate immunity including microbial defense. NE is one of the major causes of tissue destruction during inflammatory disorders and has been reported as a therapeutic target for inflammatory disease [22]. It has been documented that under pathological conditions, NE, as one of the components of NETs, is released uncontrollably during septic shock and has been proven to participate in promoting fibrinogenesis [23]. A study revealed that inhibition of NE synthesis can significantly improve the survival rate of septic rats [24], indicating the potential of ELANE as an important

therapeutic target for septic shock. In fact, recent studies have reported that ELANE is an essential signature related to the severity (SOFA score) and prognosis of sepsis patients [25,26]. OLFM4 is primarily expressed in neutrophils and plays key roles in innate immunity, inflammation, and carcinogenesis, promoting leukocyte-mediated migration, neutrophil activation, and degranulation. A study has shown that higher expression of OLFM4 in blood samples and a higher percentage of OLFM4+ neutrophils are associated with worse outcomes in patients with sepsis and septic shock [27]. Therefore, OLFM4 may be an indicator of a pathogenic neutrophil subset in patients with septic shock. OLFM4 is also a target gene of the NF-κB pathway and responds to a variety of microbial infections and is overexpressed during bacterial infections. A recent microarray analysis based on whole-blood samples found that OLFM4, as well as MMP8, were upregulated in septic shock patients [28]. Furthermore, OLFM4 expression pattern was shown to be a better biomarker than PCT and CRP [19]. Thus, OLFM4 shows potential as an ideal biomarker for the diagnosis and treatment of septic shock.

COL17A1, known to be a prognostic factor and overexpressed in several malignancies, as well as involved in cell proliferation and invasion [29], is the only component of the predictive model for septic shock. It has also been reported that COL17A1 is one of the components of activating the NF-κB pathway and participates in the immune process of infection [30]. COL17, also known as BP180, is a transmembrane protein encoded by COL17A1. Similar to the results of this analysis, previous studies have shown that COL17 mediates the degranulation of neutrophils and the metabolic process of ROS by participating in p38MAPK and ERK pathways [31]. Additionally, COL17 can be targeted by various proteases, including MMPs and NE [32], which are also involved in the predictive model for sepsis in this study. The above studies demonstrate that the identified biomarkers are involved in immune-related pathways in the development of sepsis and are associated with neutrophil-related processes, which is consistent with the results of this study. The prediction models based on these biomarkers have also been verified to have high diagnostic efficiency, providing a theoretical basis for subsequent research. However, due to the limited amount of data and the characteristics of transcriptomics, further molecular biology experiments are still needed to elucidate and confirm the pathogenic mechanisms of these biomarkers in sepsis.

CONCLUSION

In this study, 9 hub genes in whole blood samples of sepsis and septic shock patients were identified through the integration of differential expression analysis and WGCNA. The expression levels of all 9 hub genes in sepsis and septic shock samples exhibited a gradient upward trend, and GSEA results indicated that they were all enriched in pathways related to the innate immune system and neutrophils. Predictive models for sepsis (participating biomarkers: ELANE, OLFM4, and MMP8) and septic shock (participating biomarker: COL17A1) were constructed via stepwise regression and logistic regression analyses and were validated to possess good diagnostic efficacy. Nevertheless, due to the limited amount of data and the characteristics of transcriptomics, further experiments are still needed to elucidate and confirm the pathogenic mechanism of these biomarkers in sepsis.

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Availability of Data and Material:
The datasets generated or analyzed during this study are included in the GEO repository (GSE154918, GSE131 411 and GSE185263).

Ethics Approval and Consent to Participate:
No ethics approval is needed for this study.

Sources of Support:
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Declaration of Interest:
The authors declare that there are no conflict of interests.

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