Identifying core genes in sepsis by LASSO regression and SVM-RFE algorithm

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Abstract

Introduction: Sepsis is a major disease in intensive care units (ICU), with high morbidity and mortality. However, the core genes associated with the sepsis diagnosis remain unclear.

Material and methods: By merging five datasets, gene expression profiles were obtained: GSE28750, GSE57065, GSE64457, GSE65682 and GSE95233. Differentially expressed genes (DEGs) were identified using the Limma package in R. To examine the enriched functions, both Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) were employed. Subsequently, the protein-protein interaction network (PPI) was constructed, and module analysis was carried out using STRING and Cytoscape. Furthermore, core genes were identified using support vector machine recursive feature elimination (SVM-RFE) analysis and the least absolute shrinkage and selection operator (LASSO) model. To verify the diagnostic significance of these essential genes, we conducted an analysis of the receiver operating characteristic curve (ROC).

Results: We analyzed 230 DEGs, consisting of 183 upregulated DEGs and 47 downregulated DEGs. The GO and KEGG analyses revealed that the DEGs were enriched in immune-related pathways and functions. The DEGs formed a PPI network consisting of 180 protein nodes and 351 interaction edges. Ultimately, we identified the five critical core genes (C3AR1, CHPT1, RAB32, SLC22A4, and SRPK1) common between both algorithms. The analysis of the ROC curve demonstrated that the AUC values for the five fundamental genes were as follows: 0.881, 0.876, 0.946, 0.927, and 0.931, respectively.

Conclusions: The five core genes screened in this study will help us to interpret the underlying molecular mechanism of sepsis and hopefully become potential diagnostic targets.

Key words: sepsis, LASSO regression, support vector machine recursive feature elimination (SVM-RFE) algorithm, bioinformatics analysis, functional analysis.

Introduction

Sepsis is a systemic inflammatory response syndrome (SIRS) with physiological, pathological and biochemical abnormalities caused by maladjustment of the response to infection, with high morbidity and mortality [1, 2]. The complex inflammatory responses during sepsis have not been fully elucidated. Every year, the number of new cases in the world continues to rise. It is reported that there are 6 million deaths due to sepsis every year, and it is the main cause of death of patients in

intensive care units (ICU) [3]. Although medical science has made progress in identifying early diagnostic markers for sepsis, such as interleukin-6 (IL-6), C-reactive protein (CRP) and procalcitonin (PCT), their sensitivity and specificity for early detection are still unknown [4]. Blood-based non-invasive biomarkers may be vital to individualized treatment of sepsis, and patients receive specific treatment because of their recognizable molecular characteristics [5]. Clinically, blood culture analysis and drug sensitivity results are still the main ways to diagnose and treat sepsis, while molecular diagnosis is still used for auxiliary diagnosis [6]. So, it is urgent to find new potential biomarkers to help clinicians diagnose early sepsis quickly.

High-throughput sequencing technology displays great potential in exploring the genomic changes of sepsis [7, 8]. Bioinformatics has been developed to analyze and manage the growing biological data [9]. With the introduction of a comprehensive database of gene expression (Gene Expression Omnibus – GEO) and the rapid development of genetic knowledge in the last decade, bioinformatics analysis based on the database not only reveals the whole picture of genome changes related to sepsis, but also lays a foundation for the research of immunotherapy related to sepsis [10, 11].

The biomarkers and potential molecular mechanisms of sepsis were investigated in this study. We downloaded the gene expression matrix from GSE28750, GSE57065, GSE64457, GSE65682 and GSE95233 for analysis. Then, we examined genes that were expressed differentially (DEGs) and constructed a protein-protein interaction (PPI) network. The LASSO regression algorithm and SVM-RFE algorithm are efficient feature selection techniques, which have shown their power in many applications. The SVM-RFE algorithm removes sequences and reorders features according to SVM-based recursive features, which is particularly suitable for feature gene screening. Therefore, the least absolute shrinkage and selection operator (LASSO) combined with support vector machine-recursive feature elimination (SVM-RFE) analysis was used to select potential key genes to improve the accuracy of feature genes. Lastly, the chosen core genes were verified using receiver operating characteristic curve (ROC) analysis. This study aimed to identify the characteristic genes of sepsis by LASSO regression and the SVM-RFE algorithm, and the results can provide a reference for the diagnosis, treatment and prognostic evaluation of sepsis.

Material and methods

Data source

The gene expression profiles were downloaded from GEO (http://www.ncbi.nlm.nih.gov/geo/). The integrated gene expression matrix from the five GEO datasets consisted of 875 sepsis patients and 117 normal subjects, obtained by gene sequencing of human blood samples after centrifugation. Among them, GSE28750 included 21 cases of sepsis and 20 normal cases; GSE57065 included 28 cases of sepsis and 25 normal cases; GSE64457 included 15 cases of sepsis and 8 normal cases; GSE65682 included 760 cases of sepsis and 42 normal cases; GSE95233 included 51 cases of sepsis and 22 normal cases.

Identification of DEGs

The probe matrix of the expression array in the five GEO datasets is converted to a gene matrix using the platform information file, then the processed gene matrix files are run through the impulse and limma packages of the R software. The data are subjected to missing value estimation and log transformation to obtain standardized data. The screening criteria for DEGs are a fold change (FC) > 2 and $p < 0.05$.

Functional enrichment analysis

In order to analyze the molecular mechanism of DEGs in sepsis, we annotated and described the gene functions in detail. Through the functional annotation of Gene Ontology (GO, http://www.geneontology.org), it covers three aspects of biology: cell composition (CC), molecular function (MF) and biological process (BP). The possible mechanism of DEGs was discussed through the enrichment analysis of Kyoto Encyclopedia of genes and genomes (KEGG, http://www.genome.jp/kegg/). The analysis and drawing requirements were based on the R language package clusterprofiler.

PPI network construction of DEGs

STRING is an online search tool, which can analyze and predict PPI, including physical and functional association, and is used to search among known proteins and predict the interaction between proteins [12]. We used it to establish a PPI network of DEGs, requiring a confidence score of the connections in this network > 0.15 and excluding the disconnected nodes in the network.

Screening core genes via LASSO regression and SVM-RFE model

To predict sepsis status, we used two machine learning algorithms to identify key prognostic variables and select sepsis characteristic genes. We then created an absolute contraction and selection operator (LASSO) Cox regression model using the glmnet package in R software to increase the model's plasticity and prevent over-fitting

while selecting core genes [13–15]. We excluded any subjectively scored genes that were associated with the difference between normal and sepsis samples, unless clearly labelled as such. When classifying diseases, we used the support vector machine (SVM) approach, a supervised machine learning technique that generates a decision boundary between two categories and allows predictions of labels from one or more feature vectors. We ensured a clear and concise explanation of all technical abbreviations used [16]. SVM recursive feature elimination (SVM-RFE) could select the most important genes according to the weight of the classifier [17]. SVM-RFE has been widely used in the screening of tumor-related core genes (such as skin cancer [18], colon cancer [19], and gastric cancer [20]), but little research has been done in relation to sepsis [21]. Finally, we defined the common genes screened by LASSO regression and SVM-RFE as the core genes specific to sepsis patients.

Diagnostic values of core genes

A ROC curve was constructed using the mRNA expression data of the core genes to assess the predicted values of the markers and to evaluate the reliability of the model. To determine the diagnostic efficacy of the core gene screening, the area under the ROC curve was analyzed.

Results

Identification of DEGs in sepsis

The scatterplot was used to identify DEGs in the GSE28750, GSE57065, GSE64457, GSE65682 and GSE95233 database (Supplementary Figure S1). We used the screening criteria of $p < 0.01$ and fold change (FC) > 2 to identify differentially expressed genes (DEGs). We identified a total of 230 DEGs, comprising 183 upregulated genes and 47 downregulated genes. The top 20 genes with upregulation and downregulation were displayed as a heatmap (Figure 1).

Functional enrichment analysis of DEGs in sepsis

GO functional enrichment analysis of DEGs was found to be largely focused on neutrophil activation, neutrophil degranulation, neutrophil activation involved in the immune response, neutrophil-mediated immunity, T-cell activation, T-cell differentiation and lymphocyte differentiation (Figure 2 A) to better elucidate the mechanisms by which DEGs affect sepsis characteristics. The

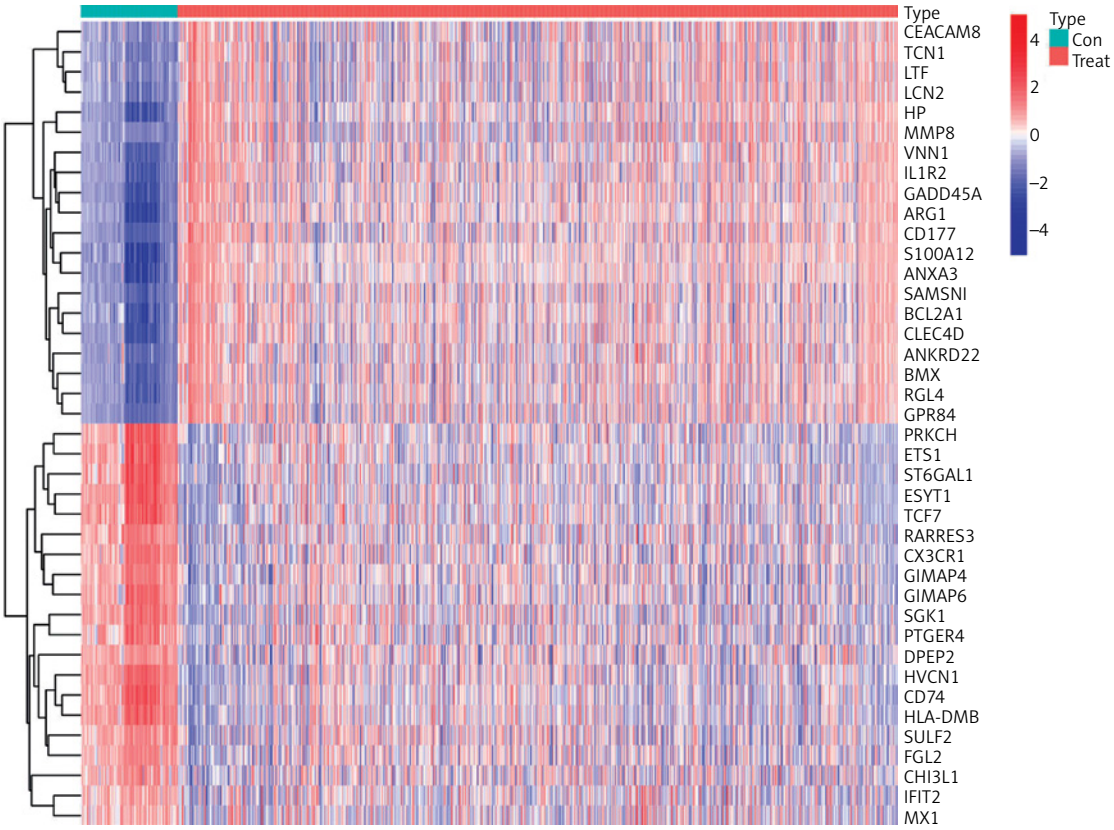

Figure 1. Heatmap of top 20 genes with upregulated and downregulated DEGs. Red represents gene upregulation and blue represents gene upregulation

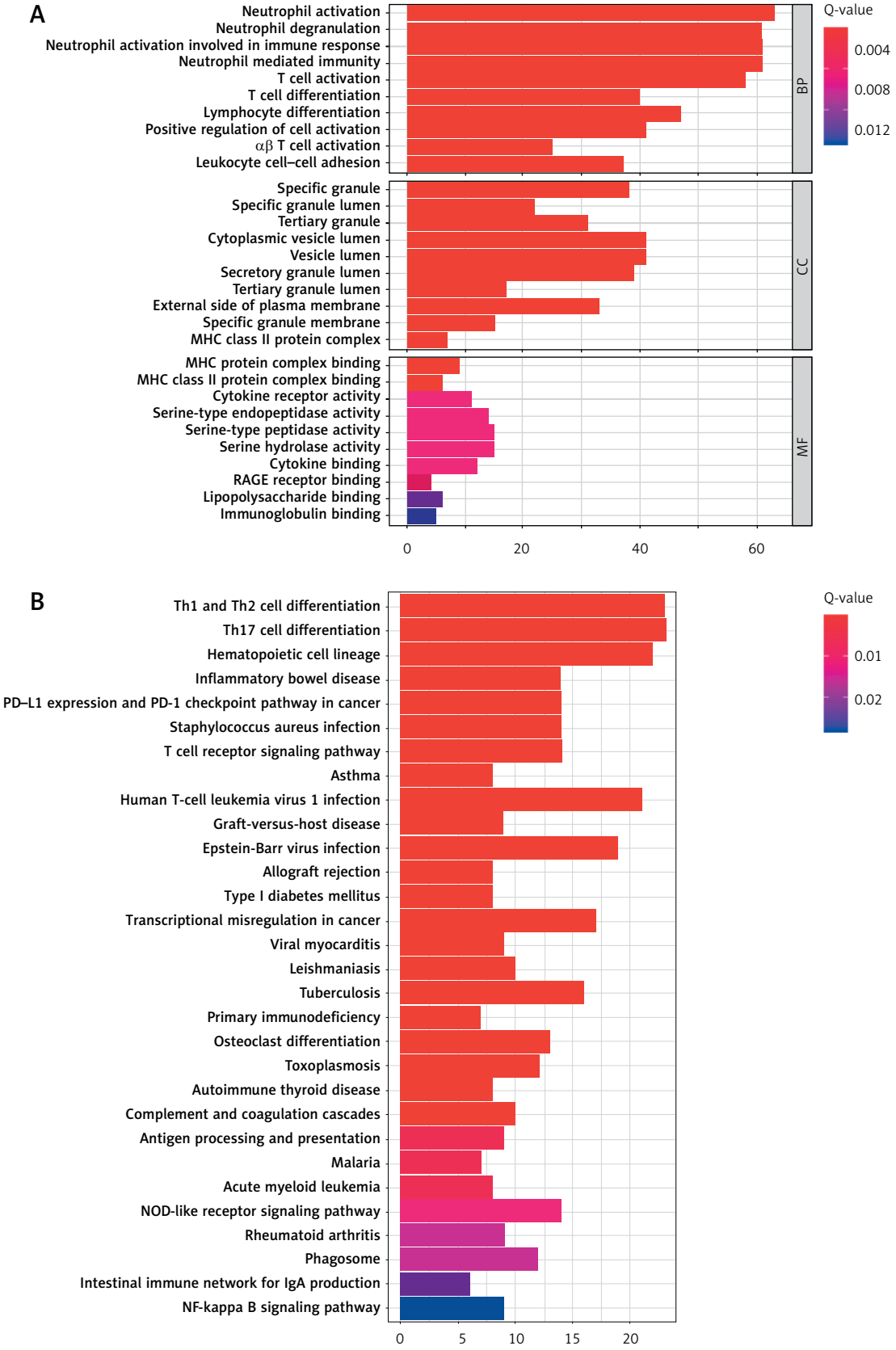

Figure 2. Functional enrichment analysis of DEGs. **A** – GO functional enrichment analysis. **B** – KEGG pathways analysis. In panel **A**, the bar is colored from red to blue, representing the gradual increase of q-value (range: 0.004–o 0.012). The colored bars in panel **B**, from red to blue, represent a progressive increase in the q-value (range: 0.01–0.02)

KEGG pathways of DEGs were mainly enriched in Th1 and Th2 cell differentiation, Th17 cell differentiation, hematopoietic cell lineage, inflammatory bowel disease, PD-L1 expression and PD-1 checkpoint pathway in cancer, *Staphylococcus aureus* infection, and T cell receptor signaling pathway (Figure 2 B). Disease Ontology (DO) analysis indicated hepatitis, tuberculosis, primary bacterial infectious disease, arteriosclerosis, atherosclerosis, arteriosclerosis cardiovascular disease, multiple sclerosis, hematopoietic system disease, demyelinating disease, and bacterial infectious disease (Figure 3).

Construction of PPI network

The identified DEGs were utilized to generate the PPI network using the STRING database, resulting in a network consisting of 180 nodes and 351 edges (Supplementary Figure S2). Subsequently, the MCODE plug-in in Cytoscape was employed to investigate the functional modules within the PPI network. The results illustrated that the PPI network includes many genes that were not included in the model and four models, among which models 1-4 are named, in which model 1 includes 20 nodes and 63 edges, model 2 includes 4 nodes and 6 edges, model 3 includes 13 nodes and 22 edges, and model 4 includes 6 nodes and 7 edges.

Screening core genes by LASSO regression and SVM-RFE algorithm

In order to analyze the core genes in the PPI network made up of DEGs objectively, we applied two distinct algorithms to filter underlying markers. The DEGs were reduced using the LASSO regression algorithm, which confirmed 69 genes as diagnostic biomarkers (Figure 4 A). Furthermore, 16 characteristics among the DEGs were identified with the SVM-RFE algorithm (Figure 4 B). Five overlapping genes (C3AR1, CHPT1, RAB32, SLC22A4, and SRPK1) were selected between the two algorithms, as shown (Figure 4 C).

Core gene verification

To elucidate the involvement of core genes in sepsis patients, 875 blood specimens from sepsis patients and 117 specimens from healthy individuals were analyzed for mRNA expression. The analysis of GEO databases revealed that patients with sepsis exhibited higher expression levels of C3AR1, CHPT1, RAB32, SLC22A4, and SRPK1 in comparison to healthy individuals (Figures 5 A–E, $p < 0.001$). An ROC curve, representing the true positive rate and false positive rate with sensitivity at different boundary points as the ordinate and 1-specificity as the abscissa, was also produced. The accuracy of the test increases as the area under the ROC curve grows. The predictive

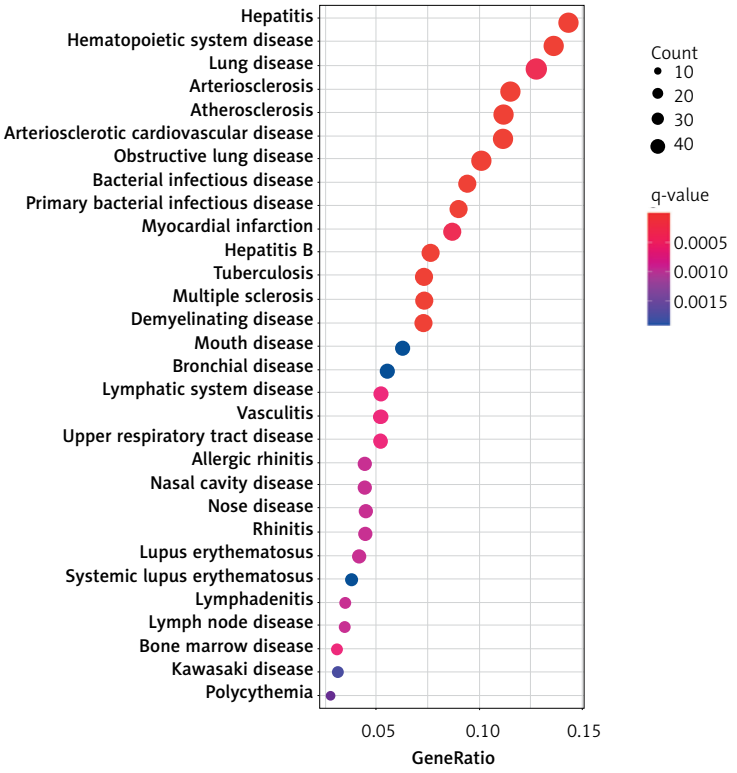

Figure 3. Disease Ontology (DO) analysis of DEGs. The size of the dot is the size of the count value, and the order from large to small is: 10, 20, 30 and 40. Bars are colored, with q-value ascending from red to blue (range: 0.0005–0.0015)

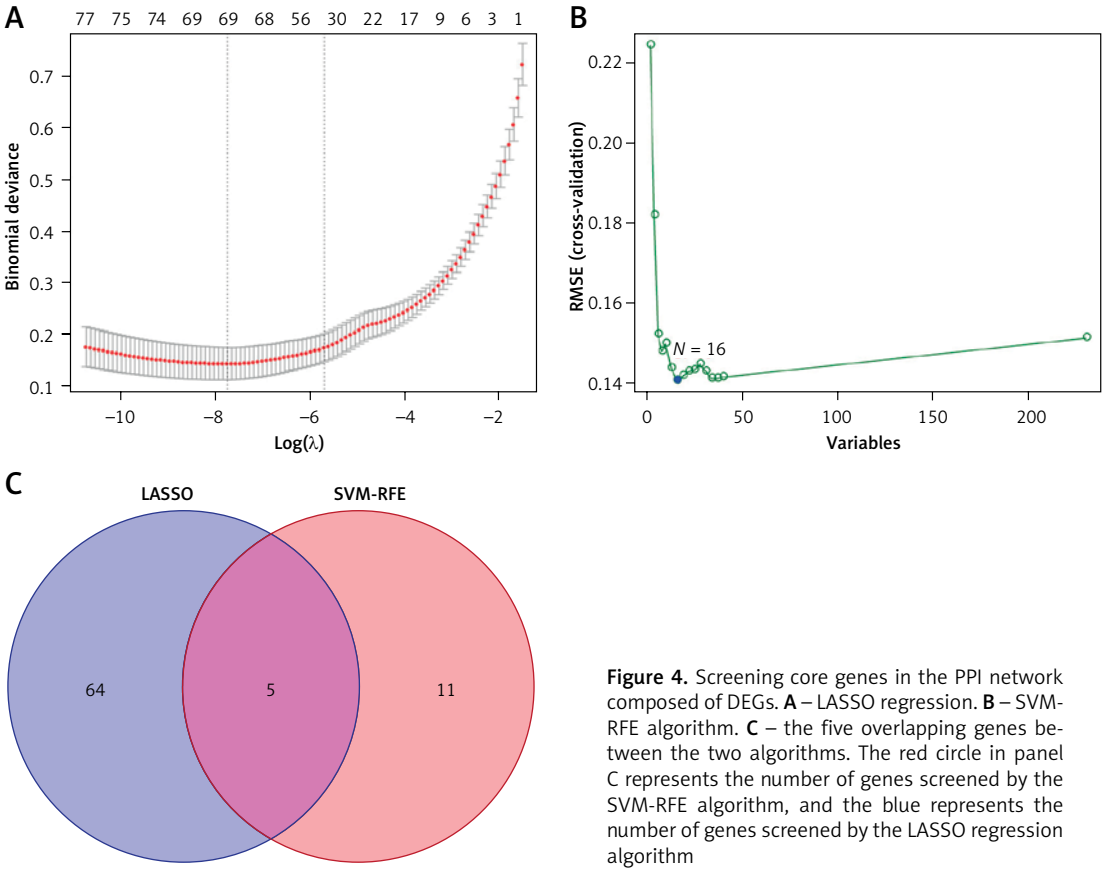

Figure 4. Screening core genes in the PPI network composed of DEGs. **A** – LASSO regression. **B** – SVM-RFE algorithm. **C** – the five overlapping genes between the two algorithms. The red circle in panel C represents the number of genes screened by the SVM-RFE algorithm, and the blue represents the number of genes screened by the LASSO regression algorithm

efficacy of C3AR1, CHPT1, RAB32, SLC22A4, and SRPK1 in sepsis patients was evaluated using ROC curves. The respective areas under the curve (AUCs) for C3AR1, CHPT1, RAB32, SLC22A4, and SRPK1 were 0.881, 0.876, 0.946, 0.927, and 0.931 (Figures 6 A–E).

Co-expression analysis of core genes

In order to further explore the co-expression relationship of the above five core genes (C3AR1, CHPT1, RAB32, SLC22A4 and SRPK1), the co-expression analysis of blood samples from sepsis patients and healthy controls was performed, and the results are shown in Figure 7. There was a positive correlation between SPPK1 and SLC22A4 in the Con group, and the expression of SPPK1 and SLC22A4 was significantly different ($p < 0.05$). However, in the Treat group, there was a positive feedback regulatory relationship between SLC22A4 and C3AR1, and the gene expression was significantly different ($p < 0.05$). The gene expression between RAB32 and CHPT1 was also different and positively correlated. The results suggest that the regulatory relationship between SPK1 and SLC22A4 plays an important role in healthy normal people. However, the abnormal expression of SLC22A4, C3AR1, RAB32 and CHPT1 may be related to the abnormal expression of sepsis.

Discussion

Sepsis is a serious infectious disease involving multiple factors. Early diagnosis is important, and bioinformatics analyses provide new ideas and technical tools. Genomics, proteomics and metabolomics can reveal molecular mechanisms, risk factors, potential therapeutic targets and drugs. These findings help to understand the developmental process, establish early diagnosis, find therapeutic targets and improve efficacy.

In this study, after analyzing five GEO datasets (GSE28750, GSE57065, GSE64457, GSE65682, and GSE95233) with sepsis gene expression sequences, 230 DEGs, including 183 up-regulated genes and 47 down-regulated genes, were obtained between sepsis and control groups. The GO function enrichment of DEGs was mainly in the areas of neutrophil granulocyte activation, degranulation, immune response, T-cell activation, differentiation and lymphocyte differentiation. KEGG pathway enrichment of DEGs was in Th1 and Th2 cell differentiation, Th17 cell differentiation, hematopoietic cell lineage, PD-1 checkpoint pathway, *Staphylococcus aureus* infection, and T-cell receptor signaling pathway.

Srisawat *et al.* [22] assessed neutrophil function by neutrophil chemotactic activity and CD-11b expression; they found that survivors had significantly higher neutrophil chemotactic activ-

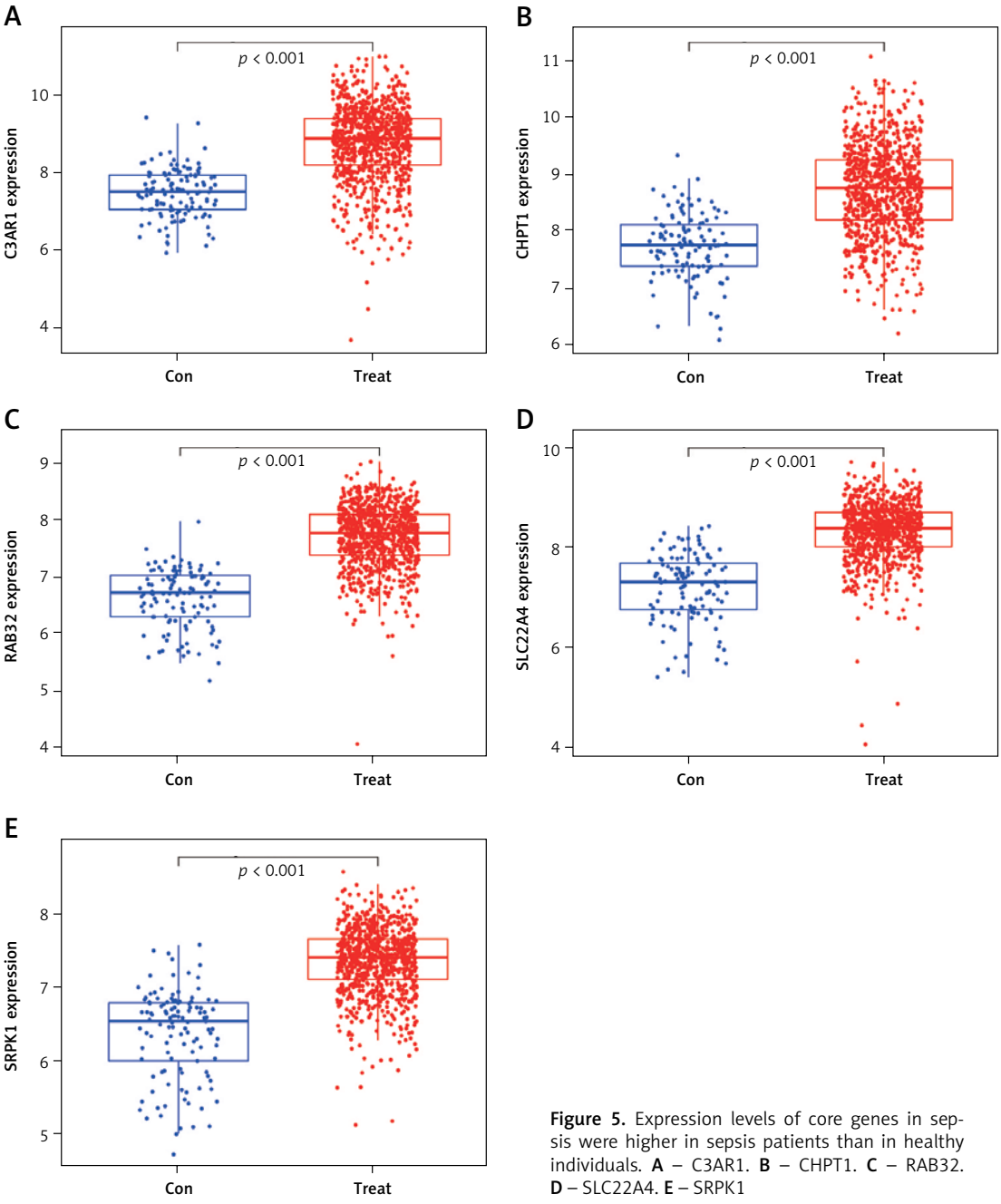

Figure 5. Expression levels of core genes in sepsis were higher in sepsis patients than in healthy individuals. **A** – C3AR1. **B** – CHPT1. **C** – RAB32. **D** – SLC22A4. **E** – SRPK1

ity and that reduced neutrophil chemotactic activity correlated with 28-day mortality, confirming neutrophil chemotactic activity as a novel immune biomarker predicting clinical prognosis in patients with severe sepsis. Saito *et al.* [23] explored the trend of sepsis-induced T-cell exhaustion and the effect of IL-15 on it; the results showed that sepsis-induced T-cell exhaustion was significantly more severe in aged mice than in young mice, and was accompanied by a decrease in initial CD4 and CD8 T-cells, an increase in the expression of programmed death 1 on T-cells, and a decrease in regulatory T-cell populations; IL-15 significantly ameliorated sepsis-induced T cell failure, resulting in a significant increase in the number of natural killer cells and macrophages and a significant increase in phagocytic activity in aged septic mice. It has also been shown that immunosuppression and aberrant differentiation of splenic CD4 T cells in septic mice can contribute to the amelioration of sepsis-induced T-lymphocyte immunosuppression and acute organ dysfunction through the mediated NFAT signaling pathway. CD4 T cell apoptosis and dysfunction-mediated immunosuppression are key factors contributing to the progression of sepsis [24]. Lu *et al.* [25] reported that using an inhibitor of endoplasmic reticulum stress reduced apoptosis and maintained CD4 T cell function in

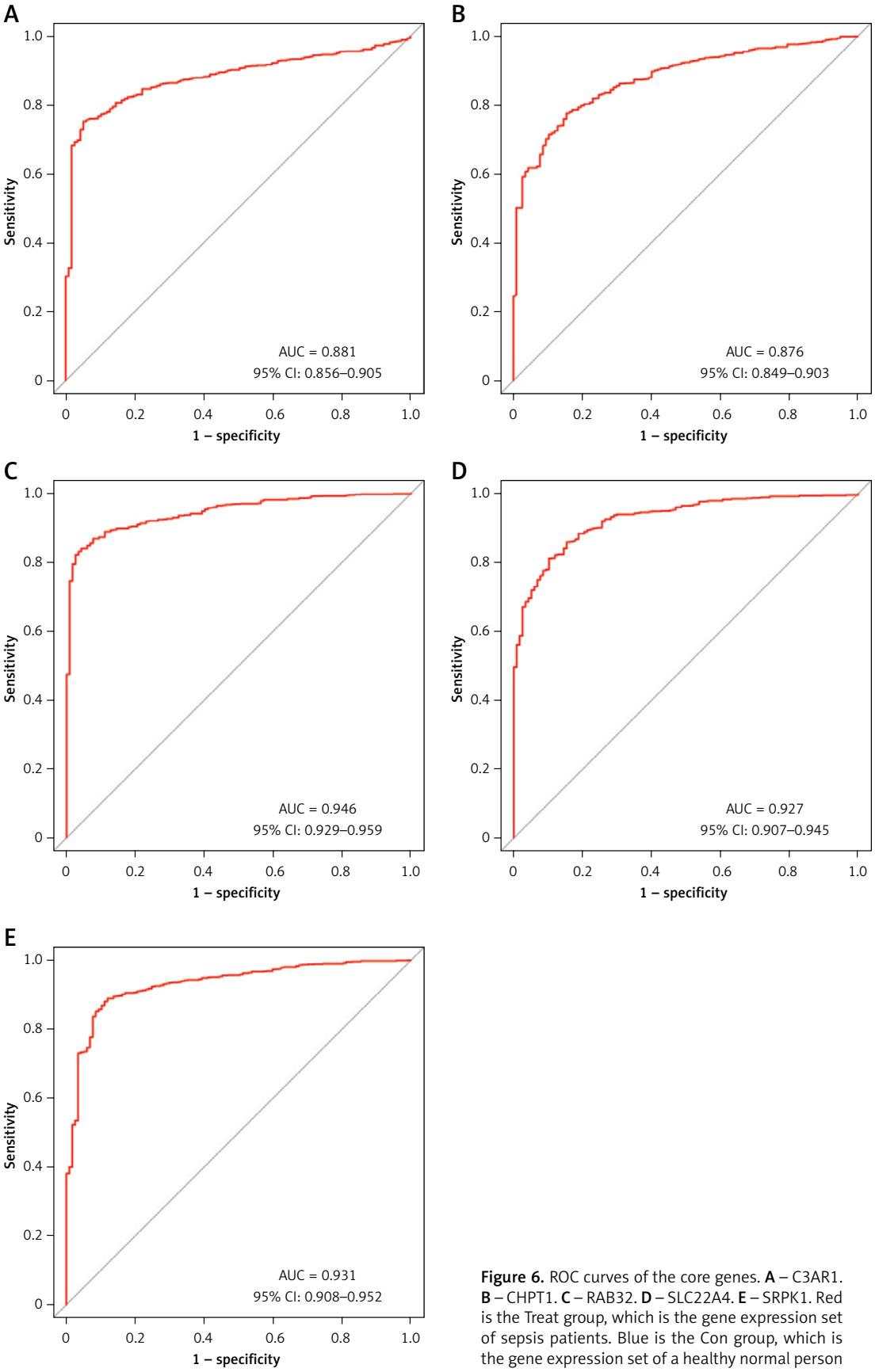

Figure 6. ROC curves of the core genes. **A** – C3AR1. **B** – CHPT1. **C** – RAB32. **D** – SLC22A4. **E** – SRPK1. Red is the Treat group, which is the gene expression set of sepsis patients. Blue is the Con group, which is the gene expression set of a healthy normal person

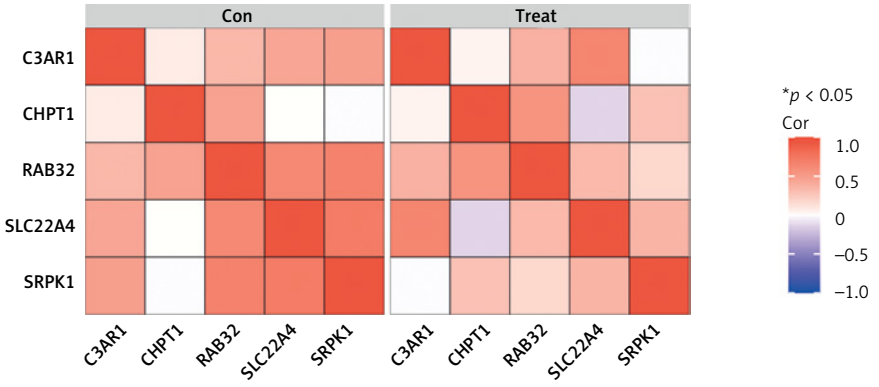

Figure 7. Results of co-expression analysis of core genes. The colored bars represent Cor values, which decrease from red to blue (1.0 to –1.0)

renal cells. It has been shown that PD-1, a conventional cancer checkpoint, is also able to play a significant role in sepsis through blockade, but has no therapeutic role in patients with previous malignancies combined with sepsis [26]. This is in general agreement with the results of the annotation/enrichment in this study.

C3AR1, CHPT1, RAB32, SLC22A4 and SRPK1 screened in this study are relevant to the mechanisms of sepsis onset and progression. Brennan *et al.* [27] found that C3AR1, the receptor for the complement activation product 3A, is involved in negatively regulating the response of neutrophils to tissue injury. The C3A/C3AR1 axis mediates neutrophil chemotactic signaling and indirectly acts as a negative regulator of the PI3K/AKT pathway through the involvement of C3AR1 in the increase of PTEN activity. It has been shown to be a therapeutic target for neutrophil mobilization/recruitment and the reduction of inflammatory pathology after tissue injury. The main function of the kidney is to excrete metabolic wastes, and loss of renal function can lead to significant changes in metabolites in vivo, which can result in dramatic changes in metabolites in the renal cortex, renal medulla, and plasma, e.g., CHPT1 is enriched for glycerophospholipid metabolism. The findings are in agreement with those of Cadenas *et al.* [28], who reported that changes in metabolism-related pathways in sepsis-triggered renal injury may be due to the fact that RAB32 may be associated with aberrant mitochondrial endocrine signaling (Golgi-Rab32 pathway), and defects in this pathway may be responsible for renal hypoplasia and sepsis [29]. SLC22A4, an isoform of the solute carrier transporter family (SLC22) of transporter proteins, is a key component of the renal proximal tubule in the elimination of endogenous metabolic wastes as well as water-soluble exogenous drugs and their metabolites [30]. The results are consistent with those of Gottier Nwafor *et al.* concerning exogenous drugs and their metabolites, and sepsis is often accompanied by signs of metabolic acidosis [31]. It has been shown that NH4Cl induces up-regulation of SLC22A4 mRNA expression to ameliorate metabolic acidosis; thus, it is clear that this target plays a key role in pharmacokinetics and waste metabolism. Guo *et al.* [32] demonstrated that SRPK1 could be used in the metabolism of endogenous drugs and their metabolites, and by using molecular biological experiments confirmed that SRPK1 regulates PI3K/AKT/FOXO3/NLRP3 signaling to inhibit sepsis-complicated acute lung injury; thus, SRPK1 is a potential biomarker for the treatment of sepsis complications.

In conclusion, the core genes screened through five data sets affecting the occurrence of sepsis are C3AR1, CHPT1, RAB32, SLC22A4 and SRPK1, which is supported by the existing theory. Further, through gene co-expression analysis, in normal healthy people, the regulatory relationship between SPK1 and SLC22A4 plays an important role. However, in the presence of abnormal conditions of sepsis, SLC22A4, C3AR1, RAB32, and CHPT1 may show aberrant expression. This suggests that abnormalities in these genes may be involved in the development of sepsis. Although this study uses a large amount of data for research and analysis and has theoretical proof, the limitation of sample size may affect the final analysis results, and further *in vivo* and *in vitro* experiments are needed for verification.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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