JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Identification of lipid metabolism-related biomarkers and prognostic analysis in geriatric patients with sepsis

Yeping Bian[1], Jian Xu[1], Xiaojing Deng[1], Suming Zhou[2], Jiayi Tong[3,4]

[1] *Department of Intensive Care Unit, Geriatric Hospital of Nanjing Medical University, Nanjing, China*
[2] *Department of Geriatrics Intensive Care Unit, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China*
[3] *Cardiovascular Institute, Southeast University, Nanjing, China*
[4] *Department of Cardiology, Zhongda Hospital Affiliated to Southeast University, Nanjing, China*

Abstract

Introduction: This study aimed to find the lipid metabolism-associated biomarkers in geriatric patients with sepsis.

Methodology: The gene expression profiles of specimens from geriatric patients with sepsis were retrieved from the Gene Expression Omnibus database. Differentially expressed genes were obtained *via* "limma" R package, and modules and genes highly associated with geriatric patients with sepsis were screened *via* "WGCNA" R package. The study also involved conducting enrichment analyses using Gene Ontology and Kyoto Encyclopedia of Genes and Genomes, as well as analyzing protein-protein interaction networks. The receiver operating characteristic curves were employed to determine the diagnostic values of hub genes.

Results: A total of 73 differentially expressed lipid metabolism-related genes (DELRGs) were retained from the 1,317 differentially expressed genes, 8,335 module genes, and 1,045 lipid metabolism-related genes. The Gene Ontology and Kyoto Encyclopedia of Genes and Genomes results showed that DELRGs were mostly related to lipid metabolism. We identified ten hub genes from the protein-protein interaction network of DELRGs. The result of receiver operating characteristic validation indicated that seven hub genes (PPARG, ACSL1, IRS2, PLA2G4A, ALOX5, SPTLC1, and JAK2) worked as the biomarkers of geriatric patients with sepsis. The prognostic nomogram suggested that the set of seven hub genes can be utilized to evaluate the mortality risk.

Conclusions: We screened seven lipid metabolism-related hub genes with diagnostic values. These molecules may exert a pivotal influence on the progression of sepsis in geriatric patients, as potential biomarkers and therapeutic targets.

Key words: Geriatric; sepsis; lipid metabolism; biomarkers; enrichment analysis; prognosis.

J Infect Dev Ctries 2024; 18(10):1502-1511. doi:10.3855/jidc.19014

(Received 07 August 2023 – Accepted 27 March 2024)

Introduction

Sepsis is a serious pathological state marked by a dysregulated response of hosts to an infection, resulting in organ dysfunction. It is often caused by bacterial, fungal, or viral infections. The common pathogens causing sepsis include *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus* [1]. Sepsis has been recognized as a major public health concern worldwide owing to the elevated rates of mortality and morbidity [2]. In the aging population, the incidence and mortality rates of sepsis are particularly high [3]. These phenomena are attributable to various factors, including pre-existing comorbidities, reduced functional reserves, and immune system impairment [4]. Furthermore, geriatric patients often do not manifest the typical signs. Therefore, the timely identification of geriatric patients with increased susceptibility to the adverse outcomes of sepsis and the use of highly sensitive and specific diagnostic markers can help perform appropriate treatment and possibly improve the outcomes.

The pathogenesis of sepsis involves several mechanisms, including endoplasmic reticulum stress, dysregulated inflammation, impaired immunity, impaired autophagy, coagulation derangement, abnormalities in the neuroendocrine-immune axis, and mitochondrial dysfunction [5]. However, lipoproteins have also been identified as significant factors in the disease process [6]. High-density lipoprotein and low-density lipoprotein cholesterol play vital roles in sepsis, such as clearing bacterial toxins, preventing excessive inflammatory cell migration, protecting endothelial cells, and aiding in steroid synthesis. Previous studies have demonstrated an association between lower lipid levels and worse outcomes during sepsis [7-9].

Until now, the changes in lipid metabolism-related gene expression, especially those in the geriatric population, remain largely unknown. Aging has been

associated with alterations in lipid metabolism, and interventions targeting lipid metabolism influence age-related diseases in various models [10]. Therefore, we conducted this study to find the gene markers related to lipid metabolism in geriatric patients with sepsis.

Methodology

Data source

We obtained the clinical information and gene expression profile data of septic elderly patients from the Gene Expression Omnibus database. All data were obtained from public databases and therefore did not require ethical approval. The GSE95233 dataset (GPL570 platform) was used as a training set, including blood samples from the sepsis patients aged ≥ 60 on day 1 after shock (n = 31) and healthy volunteers aged ≥ 60 (n = 8). The GSE112100 dataset (GPL17586 platform) was used as a validation set, including urine samples from the sepsis patients aged ≥ 60 on septic day 1 (n = 83) and control samples aged ≥ 60 undergoing vascular surgery (n = 29). The 1,045 lipid metabolism-related genes were from the study of Li *et al.* [11].

Identification of differentially expressed genes (DEGs) on geriatric patients with sepsis

The mRNA expression data of the training set were subjected to normalization and base-2 logarithm conversion by the "limma" package in R [12] The expression values were transformed to obtain DEGs, and genes were ranked based on their $\log_2$fold-change (logFC) values. The criterion for screening DEGs was that the adjusted *p* value (adj. *p*) < 0.05 and |logFC| > 1.

Identification of significant modules related to geriatric patients with sepsis using WGCNA

The "WGCNA" package [13] was utilized to build a co-expression network for the training set. First, we performed a cluster analysis to identify outliers and then computed the Pearson correlation coefficient matrices for pair-wise gene comparisons. We chose a suitable soft threshold power (β) by the pickSoftThreshold function to ensure a scale-free network. The power function was utilized to construct the adjacency matrix, followed by the construction of the topological overlap matrix using the adjacency function. Finally, the genes were grouped into modules based on their expression similarities, using the dynamic tree-cutting method and a dissimilarity measure computed from the topological overlap matrix.

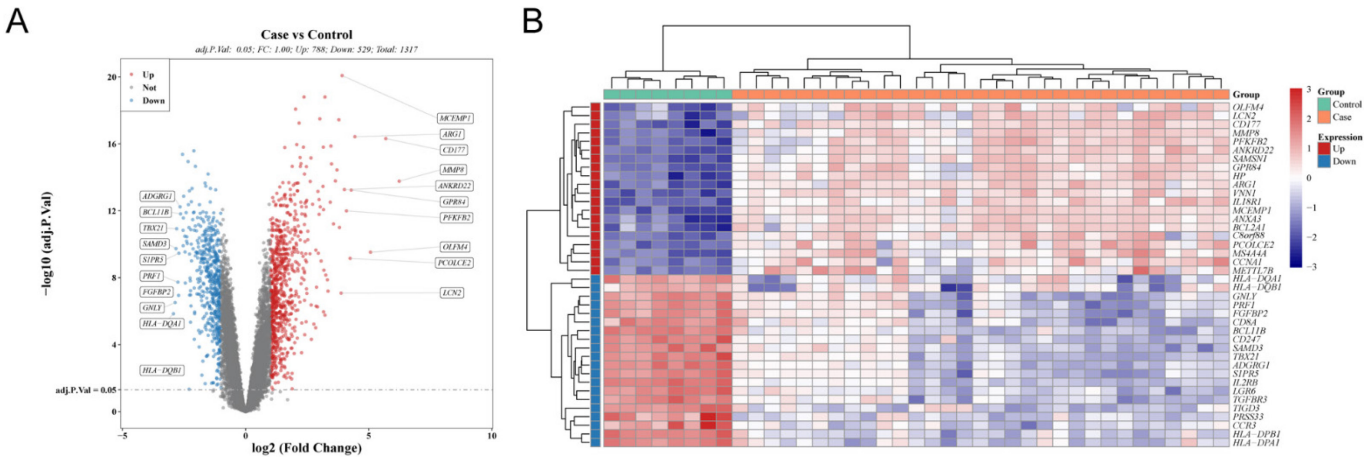
Functional enrichment of differentially expressed lipid metabolism-related genes (DELRGs)

The overlapping genes from the DEGs, module genes, and lipid metabolism-related genes were used as DELRGs of geriatric patients with sepsis. To reveal the functions of DELRGs, we implemented Gene Ontology (GO) annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses through the "clusterProfiler" package in R [14]. GO enrichment analysis was performed on three domains: biological processes (BP), cell component (CC), and molecular function (MF). Statistical significance was set at an adj. A *p* value of less than 0.05.

Construction of protein-protein interaction (PPI) network and identification of hub genes

We created a PPI network for DELRGs with the Search Tool for the Retrieval of Interacting Genes online database [15], and then imported it into Cytoscape. The CytoHubba plug-in of Cytoscape [16] was utilized to acquire hub genes in these DELRGs.

Figure 1. Identification of DEGs in geriatric patients with sepsis. (A) Volcano map of DEGs. (B) Heatmap of DEGs. DEGs: differentially expressed gene.



The top ten genes were acquired by the Maximal Clique Centrality (MCC) algorithm and chosen as the hub genes for subsequent research.

Receiver operating characteristic (ROC) analysis of hub genes

The ROC curves were plotted to detect the biomarkers with high sensitivity and specificity for geriatric patients with sepsis diagnosis. The area under curve (AUC) of each hub gene was computed using the "pROC" package in R [17]. An AUC greater than 0.7 was considered effective gene discrimination. With the help of "corrplot" package [18], we drew the correlation map which showed the expression correlation values between hub genes.

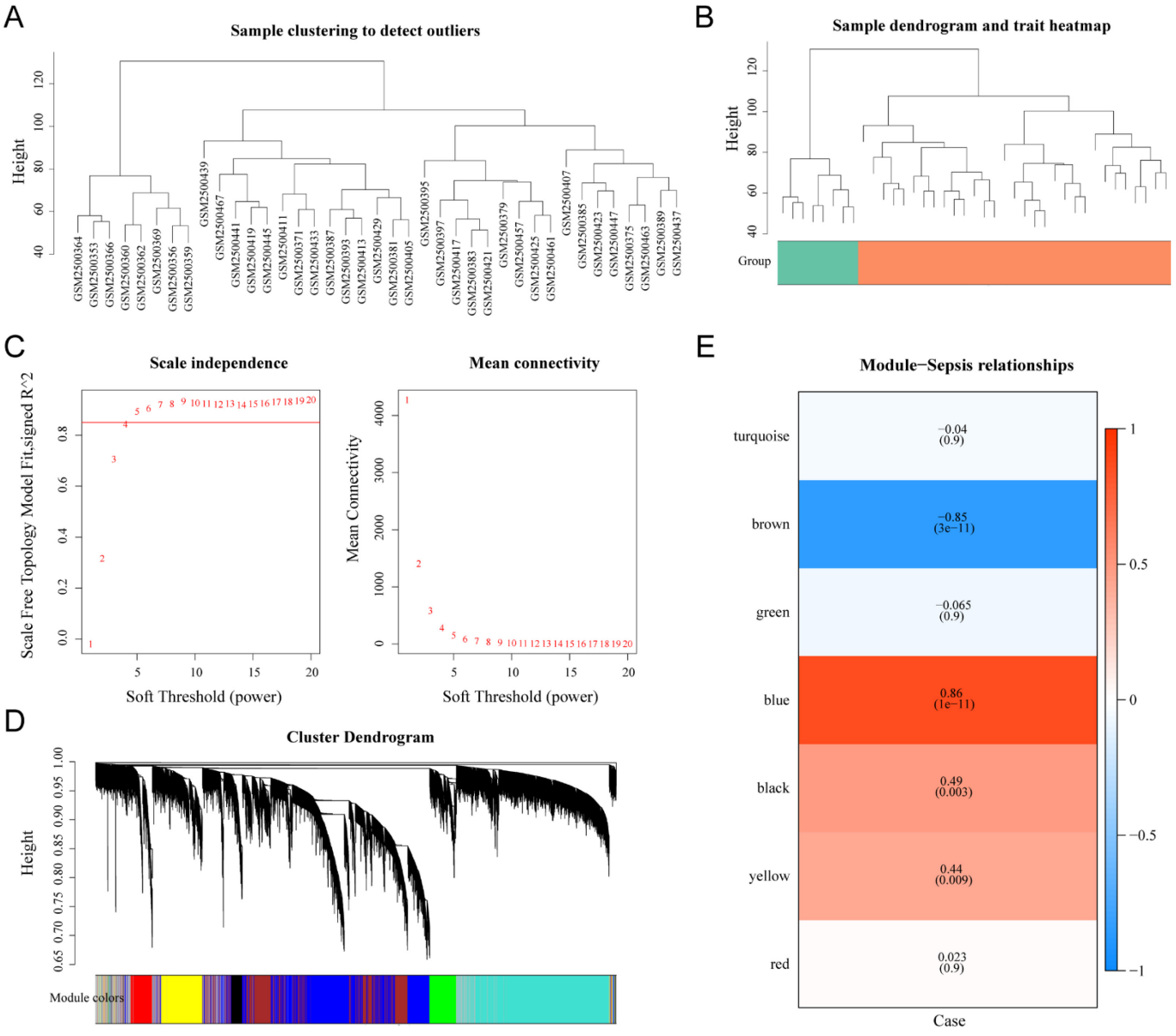
Drug-hub gene interaction

Promising drug targets were identified based on the hub genes using the Drug-Gene Interaction Database [19] for treating geriatric patients. We utilized the Cytoscape software to build an interaction network linking the identified drugs with the hub genes.

Nomogram

We implemented logistic regression analysis to assess the link between hub genes and the prognosis of geriatric patients with sepsis. The prognostic

Figure 2. Weighted co-expression network construction and identification of key modules. (A and B) No outliers in the sample. (C) Setting to β 5 created a scale-free network. (D) Heatmap of cluster tree. (E) Heat map of correlation.



nomogram was obtained, and its predictive accuracy was assessed using calibration curves.

Results

Identification of DEGs in geriatric patients with sepsis

After data preprocessing and gene differential expression analysis, 1,317 DEGs were obtained, with 788 genes significantly up-regulated and 529 genes down-regulated in geriatric patients with sepsis (Figure 1A). Figure 1B displays the cluster heatmap of the top 20 up-regulated and top 20 down-regulated DEGs with logFC.

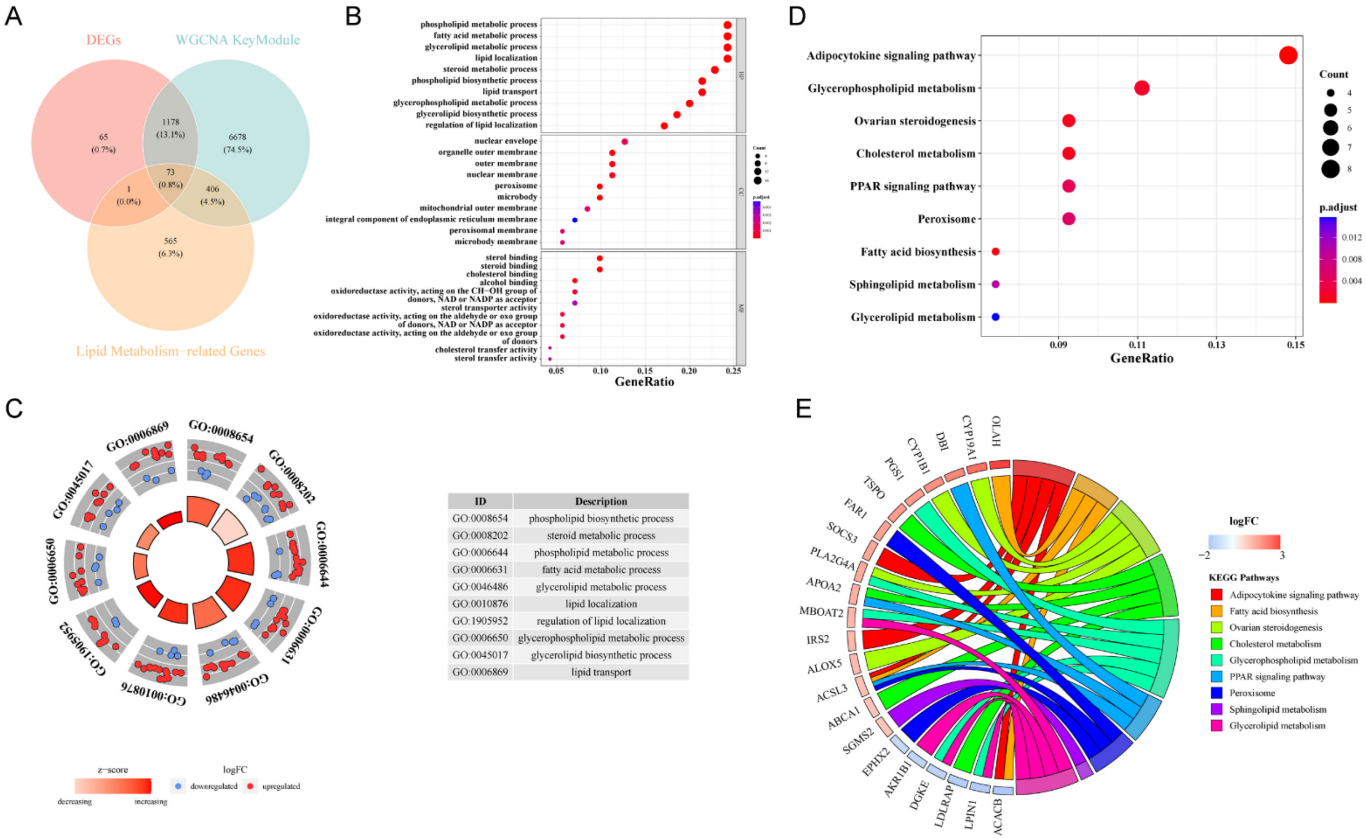
Weighted co-expression network construction and identification of key modules

We employed WGCNA to build a network based on the expression matrix of all genes from the samples of geriatric patients with sepsis. To assess the data quality, we implemented cluster analysis and determined that all 39 samples were within the cut-off value, and no outliers were detectable (Figure 2A and B). A scale-free network was established by setting β to 5, independence degree to 0.85, and mean connectivity to near 0 (Figure 2C). The genes with similar expression patterns were grouped into seven co-expression modules: black, blue, brown, green, red, turquoise, and yellow, excluding the grey module cluster to which it was assigned (Figure 2D). The eigengenes of the blue module exhibited a robust positive correlation with geriatric patients with sepsis (cor = 0.86, p = 1e-11), whereas those of the brown showed a strong negative correlation with geriatric patients with sepsis (cor = -0.85, p = 3e-11) (Figure 2E). Therefore, the blue and brown modules were used for the next analysis.

Identification and functional enrichment of DELRGs

The 73 overlapping genes from the DEGs, module genes, and lipid metabolism-related genes were retained as DELRGs for subsequent analysis (Figure 3A). To gain a more comprehensive understanding of the biological roles of these DELRGs, we utilized "clusterProfiler" package in R to implement GO annotation and KEGG pathway enrichment analyses. Figure 3B and C show that DELRGs are enriched in the lipid metabolism-related terms, such as "fatty acid metabolic process (BP)", "phospholipid metabolic process (BP)," "nuclear envelope (CC)," "organelle outer membrane (CC)," "sterol binding (MF)," and

Figure 3. Identification and functional enrichment of DELRGs. (A) Venn plot of DELRGs. (B and C) GO analysis of DELRGs. (D and E) KEGG analysis of DELRGs. DELRGs: differentially expressed lipid metabolism-related genes; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes.



"steroid binding (MF)". For KEGG enrichment analysis, the signaling pathways with strong association were lipid metabolism-related pathways, such as "adipocytokine signaling pathway" and "glycerophospholipid metabolism" (Figure 3D and E).

PPI network establishment and hub gene identification

DELRGs were analyzed to generate a PPI network by the Search Tool for the Retrieval of Interacting Genes online database (Figure 4A). The top ten hub genes were identified from the PPI network with the MCC algorithm in the CytoHubba plug-in of Cytoscape software (Figure 4B). Based on their MCC algorithm scores, the top ten hub genes were ranked, i.e., PPARG, ABCA1, ACSL1, SMARCD3, IRS2, PLA2G4A, LPIN1, ALOX5, SPTLC1, and JAK2.

Expression and diagnostic value validation of hub genes

In the training set GSE95233, PPARG, ABCA1, ACSL1, SMARCD3, IRS2, PLA2G4A, ALOX5, SPTLC1 and JAK2 were up-regulated and LPIN1 was down-regulated in geriatric patients with sepsis (Figure 5A). All the ten hub genes showed the AUC values of > 0.9 (Figure 5B). Furthermore, the validation set GSE112100 exhibited significant differences in the expressions of 8 hub genes between the two groups, i.e., PPARG, ABCA1, ACSL1, IRS2, PLA2G4A, ALOX5, SPTLC1, and JAK2, which had the same expression trend in training and validation sets (Figure 5C). The AUCs of PPARG, ACSL1, IRS2, PLA2G4A, ALOX5, SPTLC1, and JAK2 were greater than 0.7 (Figure 5D). Seven hub genes (PPARG, ACSL1, IRS2, PLA2G4A, ALOX5, SPTLC1, and JAK2) were successfully validated according to the results of gene expression and ROC curve. All the seven hub genes exhibited a positive correlation with one another ($p < 0.05$), and ACSL1 and ALOX5 had the highest correlation (cor = 0.88) (Figure 5E).

Potential drugs identification of hub genes

In the Drug-Gene Interaction Database, we identified 220 pairs of drug-gene interactions involving 212 drugs and five hub genes (PPARG, JAK2, ALOX5, PLA2G4A, and IRS2) (Figure 6). PPARG had the highest degree and was targeted by 121 small molecules or drugs, followed by JAK2 (degree = 62), ALOX5 (degree = 25), PLA2G4A (degree = 9), and IRS2 (degree = 3). The majority of potential drugs may interact with the hub genes in unknown ways or as inhibitors, agonists, or modulators. This result may help develop new targets for treating geriatric patients with sepsis.

Figure 4. PPI network establishment and hub gene identification. (A) PPI network of DELRGs. (B) PPI network of the top ten hub genes. DELRGs: differentially expressed lipid metabolism-related genes; PPI: protein-protein interaction.

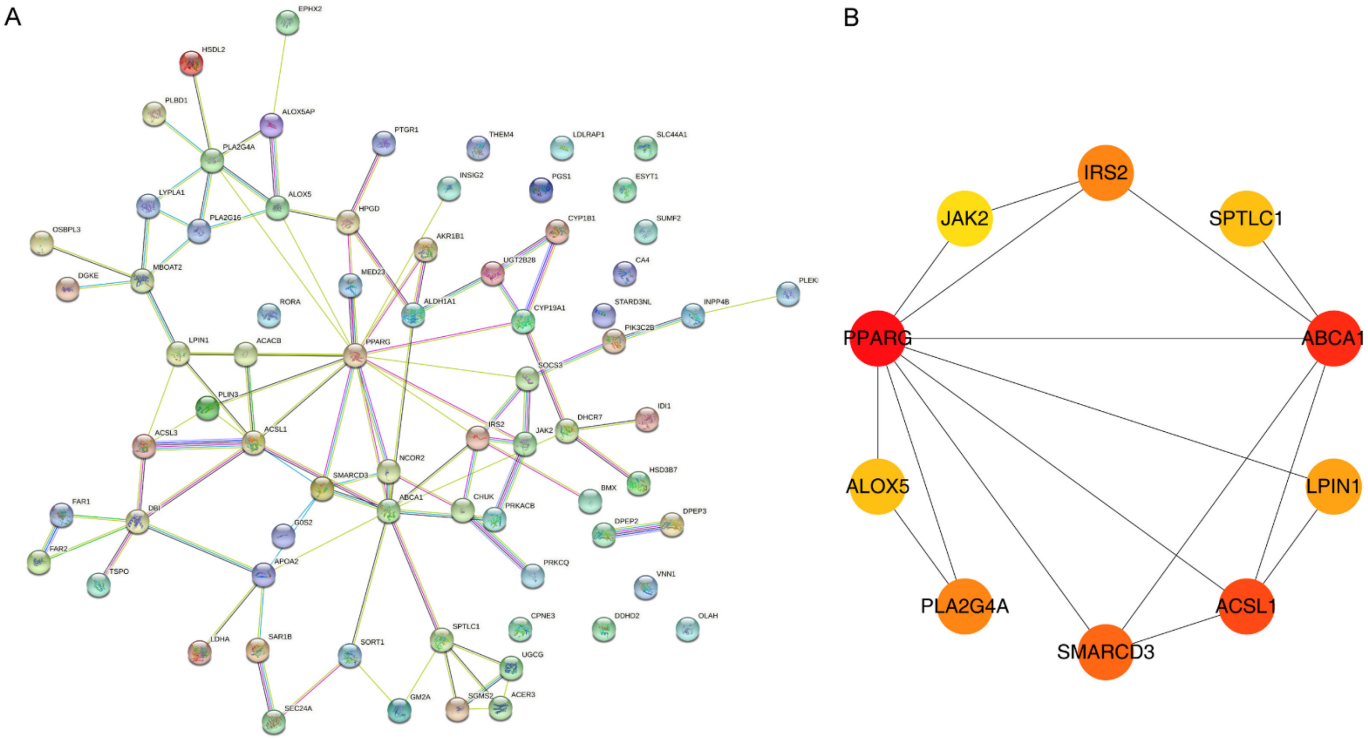


Figure 5. Expression and diagnostic value validation of hub genes. (A and B) Boxplots of hub genes expression in the training and validation sets. (C and D) ROC curves of hub genes in the training and validation sets. (E) Heatmap of correlation of hub genes. ROC, receiver operating characteristic.

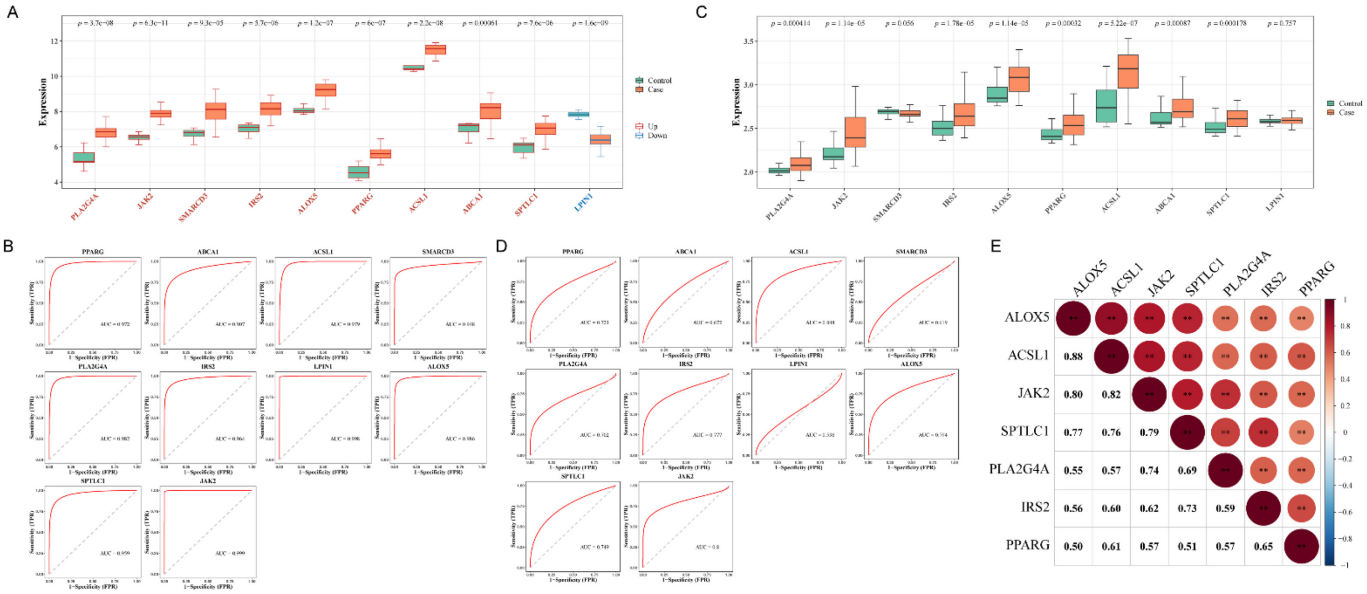
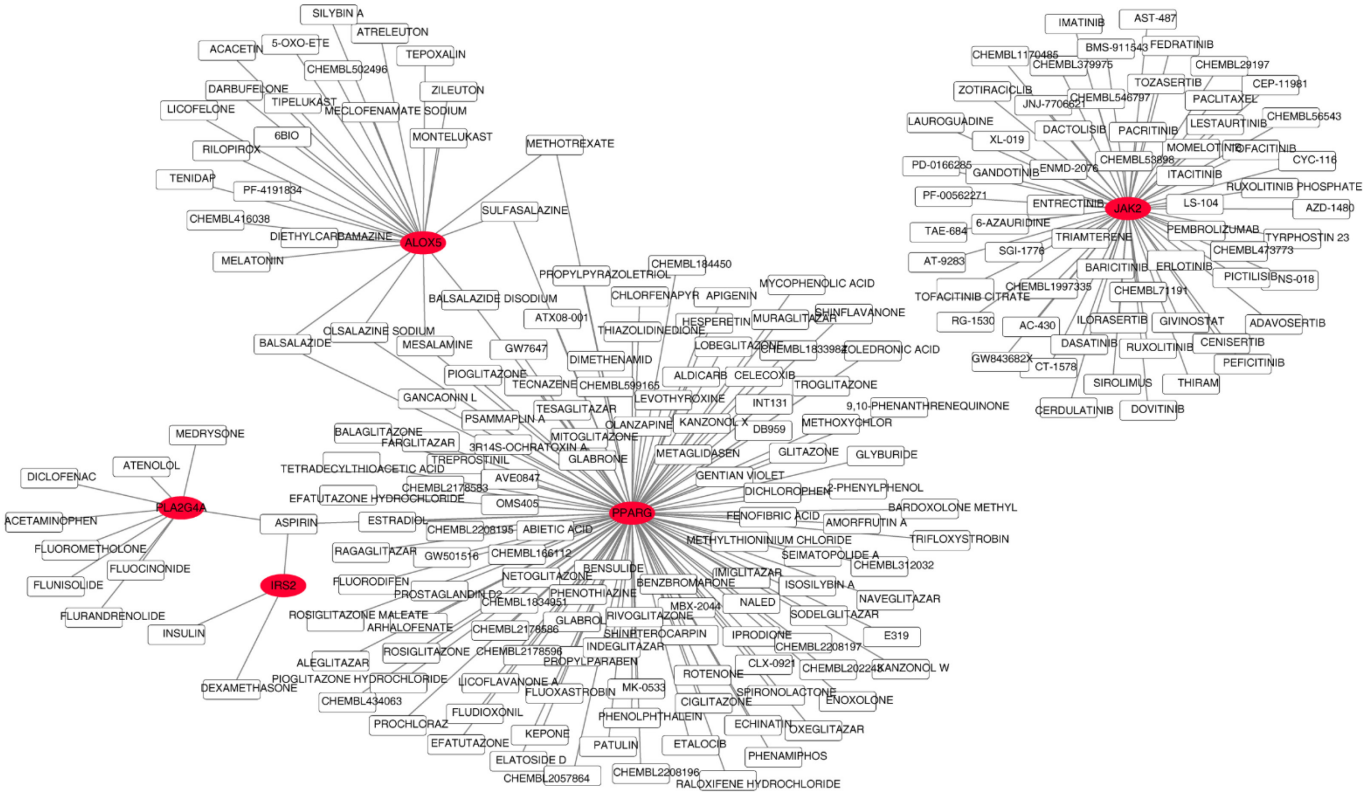


Figure 6. Potential drugs identification of hub genes.



Identification of prognostic genes

Using the logistic regression coefficient, we established a nomogram. The high expression levels of PPARG, PLA2G4A, IRS2, SPTLC1, and JAK2, along with the low expression levels of ACSL1 and ALOX5, were linked to an increased risk of mortality in geriatric patients with sepsis (Figure 7A). The calibration curve demonstrated the satisfactory performance of the nomogram versus the ideal model (Figure 7B). Hence, the seven hub genes may work as valuable predictors of mortality risk in geriatric patients with sepsis.

Discussion

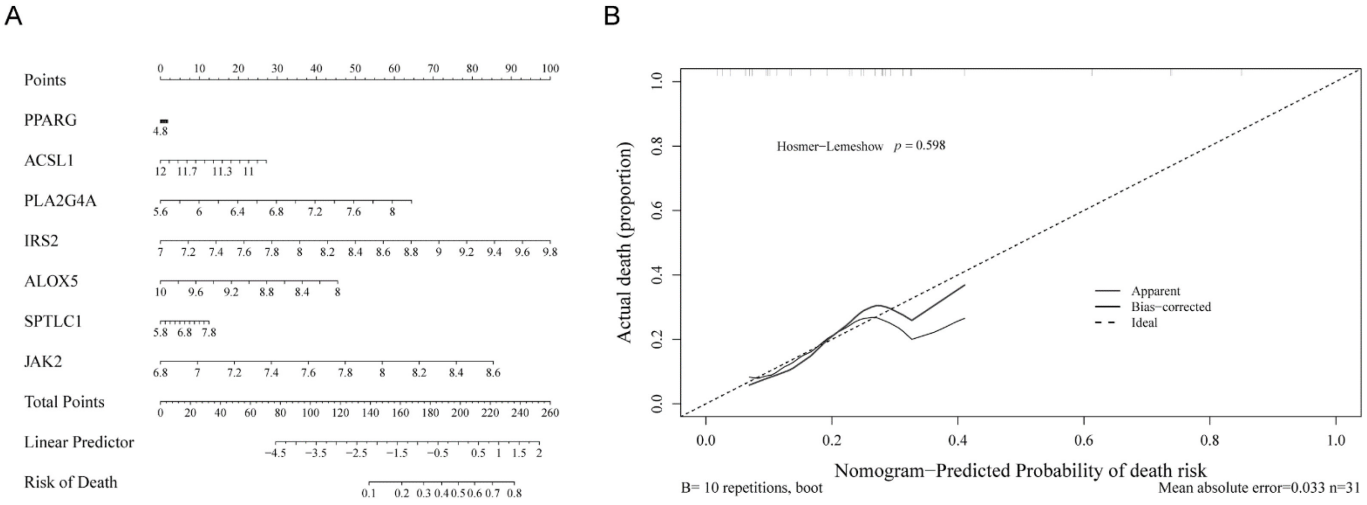
The timely identification of geriatric sepsis in high-risk individuals is crucial for effective treatment and favorable outcomes. This study aimed to elucidate the potential lipid metabolism-related biomarkers in geriatric septic patients by subjecting sepsis and lipid metabolism-related gene data to bioinformatics analysis. We identified 73 DELRGs, and further GO and KEGG results demonstrated their contribution to lipid metabolism. Furthermore, we identified ten hub genes from the PPI network of DELRGs. The result of ROC validation indicated that seven hub genes (PPARG, ACSL1, IRS2, PLA2G4A, ALOX5, SPTLC1, and JAK2) were the biomarkers of geriatric patients with sepsis. The prognostic nomogram suggested that the seven hub genes had the potential to predict the mortality risk in geriatric septic patients.

We found significant differences in the expressions of mRNAs related to lipid metabolism between geriatric patients with sepsis and control samples. GO enrichment analysis revealed DELRGs were related to lipid metabolisms, such as fatty acid metabolic process, phospholipid metabolic process, glycerolipid metabolic process, and lipid localization. The enrichment of DELRGs in the adipocytokine signaling pathway and other signaling pathways related to lipid metabolism was also revealed by KEGG enrichment analysis. These biological processes and signaling pathways may be crucial in the pathological process of geriatric septic patients.

To explore the key lipid metabolism-related genes affecting geriatric patients with sepsis, we identified 10 hub genes by PPI network and evaluated and verified the diagnostic performance of these genes using ROC curves, among which seven genes (PPARG, ACSL1, IRS2, PLA2G4A, ALOX5, SPTLC1, and JAK2) had high diagnostic values. The results of prognostic nomogram and calibration curve showed that these genes had the potential to predict the mortality risk in geriatric septic patients.

PPARG is expressed in various immune cells and has potent anti-inflammatory effects. These effects include modulation of neutrophil migration and activation, enhancement of macrophage phagocytosis, regulation of inflammatory mediator production, and activation of oxygen/nitrogen species [20-22]. In septic patients, a decrease in the level of PPARG expression has been observed in mononuclear cells [23]. Additionally, the murine models of sepsis have decreased PPARG expression, particularly in the lungs [24]. In both *in vivo* and *in vitro* studies, PPARG agonists have been verified to suppress sepsis-triggered inflammatory responses [25], acute lung injury [26], and inflammation [27]. This suppression enhances the host's ability to eliminate pathogenic bacteria and to improve the prognosis. We herein found that PPARG had the highest degree and was targeted by 121 small

Figure 7. Identification of hub genes. (A) Nomogram of hub genes. (B) Calibration curve of nomogram.



molecules or drugs, suggesting that PPARG may be a promising target for treating geriatric septic patients.

The inhibition of fatty acid β-oxidation by the PPARG pathway is associated with high ACSL1 gene expression, raising the triglyceride level [28]. Several independent datasets have verified a notable increase in the ACSL1 transcript abundance during sepsis [29]. There is a close correlation between ACSL1 expression and both CHREBP in hyperglycemic settings and NF-κB in the presence of inflammation [30]. The exposure of bone marrow-derived macrophages to lipopolysaccharide to induce inflammation led to an increase in ACSL1 mRNA expression owing to the activation of transcription factor NF-κB, as demonstrated by Peña *et al*. [31]. Additionally, lipopolysaccharide treatment results in an increase in ACSL1 protein levels which is localized to the membrane, facilitating its function. JAK2 is a downstream effector of IL6, a pleiotropic cytokine produced by various immune cells to initiate inflammation and immune responses. The role of JAK2 in modulating innate immune responses during sepsis remains elusive, but it has recently been implicated in activating NF-κB in response to bacterial endotoxin. IRS2 functions as a pivotal regulator of insulin and insulin growth factor signaling. In addition, it plays a crucial role in mediating T helper 2 signaling and macrophage activation *via* type I interleukin-4 receptor [32]. PLA2G4A is an enzyme that catalyzes the hydrolysis of membrane phospholipids to release arachidonic acid, a precursor for the biosynthesis of various eicosanoids such as prostaglandins and leukotrienes. These lipid mediators are involved in regulating inflammatory responses, hemodynamics, and various intracellular pathways that participate in sepsis [33]. ALOX5 belongs to the lipoxygenase family that converts arachidonic acid into leukotrienes, potent mediators involved in various inflammatory and allergic conditions [34]. SPTLC1 is a crucial enzyme in sphingolipid biosynthesis, which converts L-serine and palmitoyl-CoA to 3-oxosphinganine with pyridoxal 5'-phosphate. Sphingolipids are pivotal components of cell membranes and bioactive molecules that regulate cell growth, differentiation, and death, and their metabolism may contribute to sepsis pathophysiology [35]. All these genes are critical in lipid metabolism and may also exert a vital effect on inflammatory responses, making them potential targets for the progression of sepsis.

For sepsis, there is no specific immunotherapy. Despite developments in the prevention and treatment of sepsis, the morbidity and mortality rates remain high. Based on the diagnostic genes, we screened the corresponding drugs. Many pharmacological agents have the potential to interact with hub genes either through unknown mechanisms or by acting as inhibitors, agonists, or modulators. For instance, aspirin is a non-selective inhibitor of cyclooxygenase and both act on PLA2G4A and IRS2. A meta-analysis of individual patient data from published observational studies examined the relationship between the pre-onset use of aspirin and mortality in hospitalized patients with sepsis [36]. *In-vitro*, animal, and human experiments have demonstrated several possible mechanisms, including the suppression of tumor necrosis factors, resolution of lipid mediators of inflammation, and inhibition of platelet activation [37].

Nevertheless, our study has limitations. Firstly, the gene data were sourced from a public database, and the sample size was relatively small, which may introduce bias into the results. Secondly, the lack of molecular validation experiments means that larger-scale clinical samples are required to confirm our findings. Thirdly, additional investigation is necessary to elucidate the mechanism of key genes associated with the pathogenesis and progression of sepsis in geriatric patients.

Conclusions

In conclusion, seven lipid metabolism-related hub genes may have important implications in understanding the sepsis pathogenesis in geriatric patients and have potential diagnostic and therapeutic applications. Further investigation is needed to elucidate the functions and mechanisms of these genes.

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Corresponding authors

Ms. Yeping Bian
No. 30 Luojia Road,
Geriatric Hospital of Nanjing Medical University,
Nanjing, China, 210024
Email: bianypghnmu@uic-edu.cn

Dr. Suming Zhou
No. 300, Guangzhou Road,
The First Affiliated Hospital of Nanjing Medical University,
Nanjing, China, 210029
Email: qiankangtou030@163.com

Conflict of interests: No conflict of interests is declared.