

Research Article

Analysis and Validation of Autophagy Related Genes in Septic Acute Kidney Injury

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Abstract

Background: The pathogenesis of acute kidney injury (AKI) in sepsis involves inflammatory response. Autophagy has been shown to regulate inflammatory response, but the role of autophagy-related genes (ARGs) in the regulation of inflammation in septic AKI requires further investigation. **Methods:** Initially, the dataset GSE57065 was downloaded and utilized in the R language to investigate differentially expressed autophagy-related genes (DEARGs) associated with septic shock. Subsequently, DEARGs enrichment analysis and protein-protein interactions (PPIs) were conducted. Hub genes were identified through PPIs, and their diagnostic value was evaluated using ROC analyses with the external dataset GSE65682. Additionally, the septic AKI animal model was established to validate hub genes through qRT-PCR. Finally, immune cell infiltration in the septic AKI and control group was analyzed. Furthermore, we examined the correlation between immune cell infiltration and the validated hub genes, and predicted the miRNA-mRNA network. **Results:** In the GSE57065 dataset, we have identified 22 differentially expressed genes (DEGs) primarily involved in autophagy. The receiver operating characteristic (ROC) analysis suggested that the top ten hub genes may have diagnostic value. In our animal experiment, qRT-PCR results demonstrated elevated expressions of TP53, MYC, FOXO1, CXCR4, and BCL-2, while PARP1 and PTEN exhibited reduced expressions in septic AKI. The CIBERSORT analysis revealed immune infiltration, and the validated hub genes were associated with immune cell infiltration in septic AKI. Lastly, we have discovered potential regulatory miRNAs through the miRNA-mRNA network. **Conclusions:** The potential diagnostic and therapeutic targets, namely TP53, MYC, FOXO1, CXCR4, BCL-2, PARP1, and PTEN, have been identified as potentially influential factors in the infiltration of immune cells in acute kidney injury associated with sepsis.

Keywords

Autophagy, Immune Infiltration, Inflammation, Sepsis, Acute Kidney Injury, Bioinformatics Analysis

1. Introduction

When sepsis induces systemic inflammatory response, the kidney emerges as the organ most susceptible to damage [1, 2], with septic acute kidney injury (AKI) being particularly prone to manifest in cases of septic shock [3, 4]. In sepsis, the mortality rate is significantly elevated in the presence of AKI

compared to its absence [5, 6]. A pathological anatomical examination of 19 deceased sepsis patients with AKI revealed a notable prevalence (42%) of extensive infiltration of mononuclear cells and multinucleated cells within the renal interstitium [7]. The pivotal role of excessive inflammatory re-

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Received: 24 July 2025; **Accepted:** 5 August 2025; **Published:** 26 August 2025



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sponse in septic AKI is undeniable, and while immunotherapy holds promise, multiple randomized controlled trials pertaining to immunomodulatory therapy have yielded unsuccessful outcomes [8].

In recent times, there has been a growing interest in understanding the role of autophagy in sepsis. Numerous research studies have provided evidence that autophagy plays a significant role in influencing both the innate and acquired immune systems, thereby regulating inflammation [9]. Autophagy exhibits dual effects, acting as both a pro-inflammatory and anti-inflammatory mechanism, which ultimately inhibits the occurrence of acute kidney injury caused by inflammatory responses [10]. Additionally, autophagy counteracts immune suppression by enhancing the survival rate of immune cells, although excessive autophagy can trigger programmed cell death in immune cells [11].

The role of autophagy related genes (ARGs) in septic acute kidney injury (AKI) remains uncertain, despite the significance of autophagy in immune regulation related to inflammation. To address this gap in knowledge, we employed bioinformatics and animal experiments to identify and validate ARGs in septic AKI. Specifically, we obtained the dataset GSE57065 and utilized the R language to investigate DEARGs associated with septic shock. Subsequently, enrichment analysis was conducted on DEARGs, followed by the construction of PPIs to identify hub genes. The diagnostic significance of these hub genes in patients with septic shock was assessed using the exogenous dataset GSE65682. Furthermore, the expression levels of the hub genes were validated by constructing the septic AKI animal model. Subsequently, immune cell infiltration and the correlation between immune cells and the validated hub genes were analyzed, and a miRNA-mRNA network was predicted.

2. Materials and Methods

2.1. Microarray Data and Autophagy Related Dataset

Using "sepsis, mRNA" as the search term, datasets containing samples of human peripheral blood in septic shock were found, including GSE57065 and GSE65682, and the mRNA expression datasets were downloaded from GEO (<http://www.ncbi.nlm.nih.gov/geo/>) [12]. The platform of two datasets was GPL570 (HG-U133_Plus_2) Affymetrix Human Genome U133 Plus 2.0 Array. GSE57065 included 28 septic shock patients and 25 healthy control groups. GSE65682 covered 686 patients with sepsis and 42 healthy controls. In the Human Autophagy Database (<http://www.autophagy.lu/index.html>), autophagy-related genes were identified.

2.2. Detection of DEARGs

A principal component analysis (PCA) was conducted on GSE57065 data in order to verify the repeatability of data in GSE57065 [13]. DEGs were defined as genes with $\log_{2}FC > 1$ and $p\text{-adj} < 0.05$ by the "limma" package of the R software [14]. To draw heat map and box diagram, R software's "heatmap" and "ggplot2" packages were used. The ARGs and DEGs were intersected to obtain DEARGs, using R software's "ggplot2" software package to map Wayne.

2.3. DEARGs Associated with GO and KEGG Pathways

The software package "GO plot" [15] was used for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis in the R software.

2.4. DEARGs by PPIs

The PPIs analysis was performed on DEARGs, which was analyzed by the STRING database (<https://string-db.org/>) [16] and Cytoscape software (<https://cytoscape.org/>) [17]. Using multiscale curvature classification (MCC) algorithms, the top 10 genes were identified using cytohubba as the hub genes.

2.5. An Analysis of ROC Data to Verify Hub Genes

The hub genes from an independent external dataset GSE65682 were evaluated for diagnostic value using receiver operating characteristic (ROC) analysis [18]. $AUC > 0.8$ and $P < 0.05$ were cut-off criteria for ROC analysis in RStudio.

2.6. Immune Infiltration and Correlation Analysis

CIBERSORT algorithm was used to predict the infiltration of 22 kinds of immune cells in septic shock samples and control samples in GSE57065 [19]. Boxplots are used to show the proportion of different immune cells in two groups. At the same time, the Sangbox platform is used to display the correlation heatmap of immune cells. The relationship between validated hub genes and immune cells were analyzed with Spearman's rank correlation analysis and "ggplot2" package was used for data visualization. $P < 0.05$ was as a statistically significant criterion.

2.7. Animal Experiments

Three Gorges Hospital affiliated with Chongqing University approved the experiment and procedure. The male mouse C57BL6/J (age = 10-12w, weight = 20 ± 2 g, $n = 10$) was

purchased from Chongqing Enville Biotechnology Co., Ltd. To establish the septic AKI model, 10 mg/kg LPS was intraperitoneally injected into the AKI group (n=5), while saline was administered to the control group (n=5). And the mice were anesthetized with ketamine hydrochloride after 24 h, and all serum and kidney samples were collected for further analysis. Urea nitrogen and creatinine in blood were measured by an automated biochemical analyzer (Hitachi Co., Ltd., Tokyo, Japan).

2.8. RNA Extraction and Quantitative Real-time Polymerase Chain Reaction (qRT-PCR)

An appropriate amount of mouse kidney tissue was cut, with 5 samples in the normal group and 5 samples in the experimental group respectively. Total RNA was extracted by the traditional TRIZOL (Invitrogen) method, then the ex-

tracted mRNA was reversetranscribed into cDNA which was for real-time RT-PCR by PrimeScript RT reagent Kit (Takara, Dalian, China), and the relative mRNA expression levels were calculated by $2^{-\Delta\Delta Ct}$ method. We synthesized the Primers (see supplementary table 1) using Primer Blast (<http://www.ncbi.nlm.nih.gov>).

2.9. miRNA-Hub Gene

The miRNet database (<https://www.mirnet.ca/>) was used to predict miRNAs which were upstream of hub genes.

2.10. Statistical Analysis

GraphPad Prism 9 was to compare data from the two groups by a t-test of unpaired two-tailed students.

3. Results

3.1. Differences in the Expression of ARGs in Septic Shock

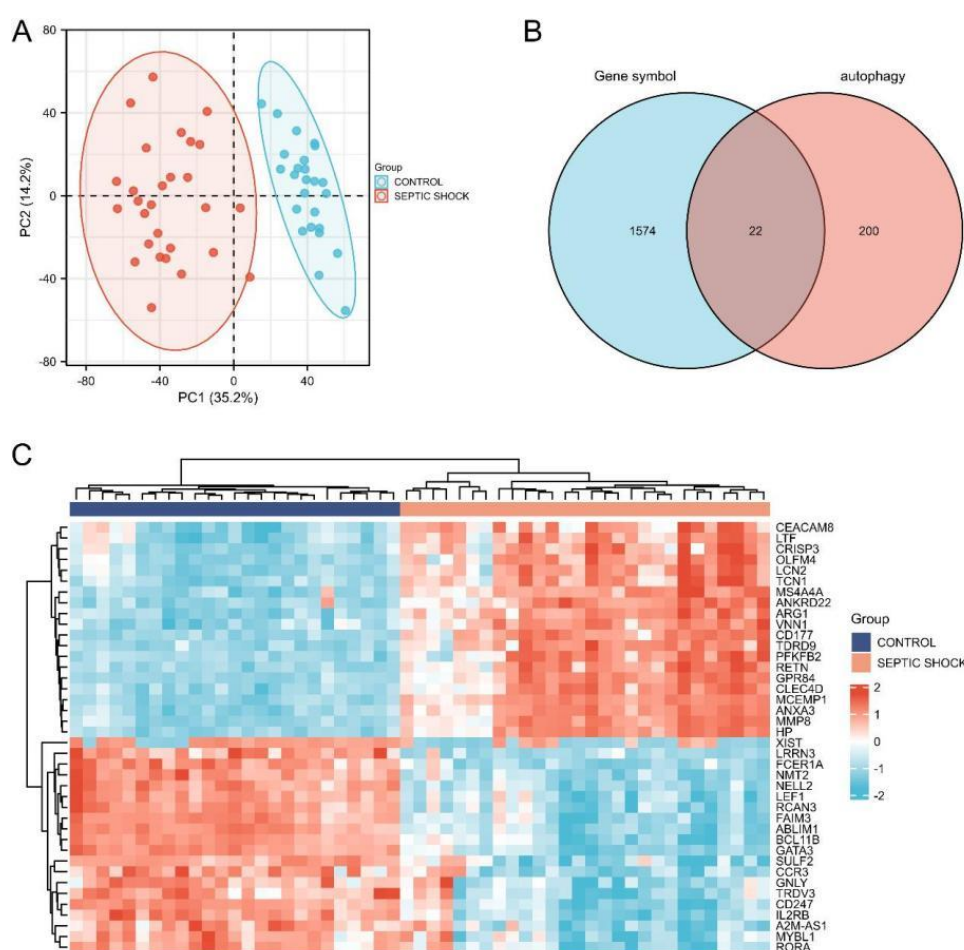


Figure 1. DEGs in septic shock group and control group. *a* Principal component analysis for GSE57065. *b* Venn diagram of intersecting genes between Human Autophagy Database and GSE57065. *c* Heatmap of the 20 up-regulated and down-regulated expressed genes in GSE57065.

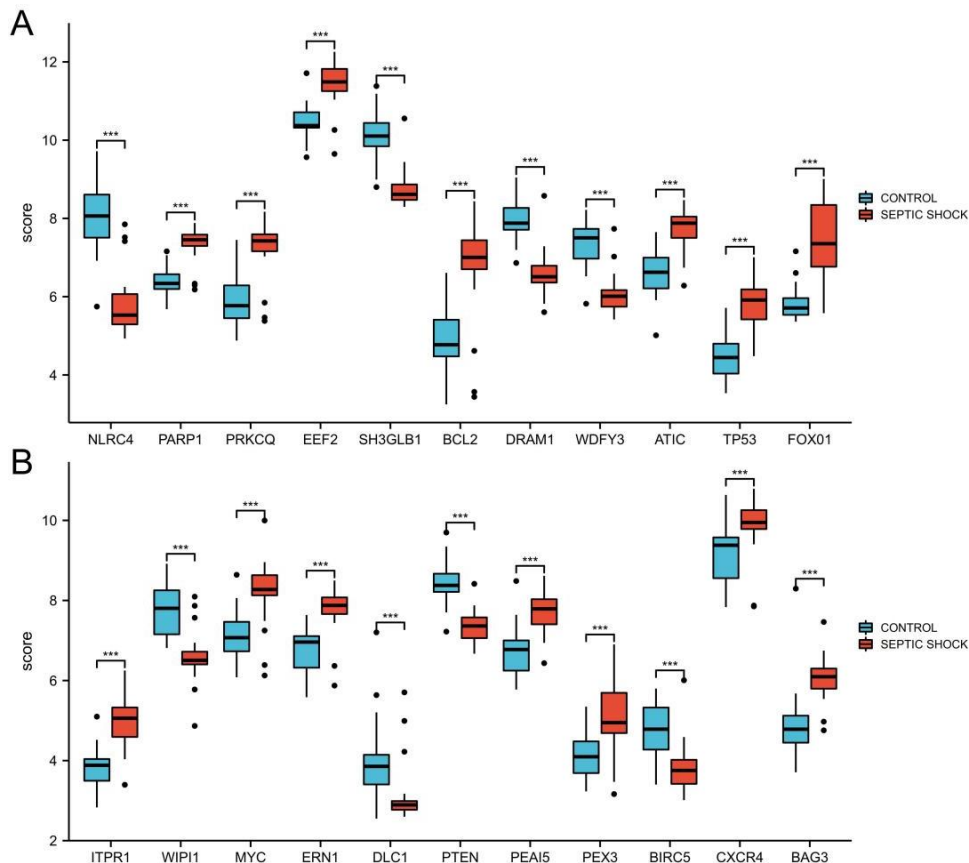


Figure 2. The boxplot of 22 DEARGs in septic shock group and control group. *a* The boxplot of top 11 DEARGs. *b* The boxplot of last 11 DEARGs. *** $P<0.005$.

PCA of GSE57065 dataset was performed to check whether the datas were repeatable with acceptable results (Figure 1A). Next, we analyzed the DEGs in GSE57065 and used a heat map to describe the first 20 genes of up-regulated and

down-regulated (Figure 1C). ARGs and septic shock DEGs were intersected to get 22 DEARGs (Figure 1B). The boxplot showed 22 DEARGs in septic shock group and control group (Figure 2).

3.2. DEARGs Associated with GO and KEGG Pathways

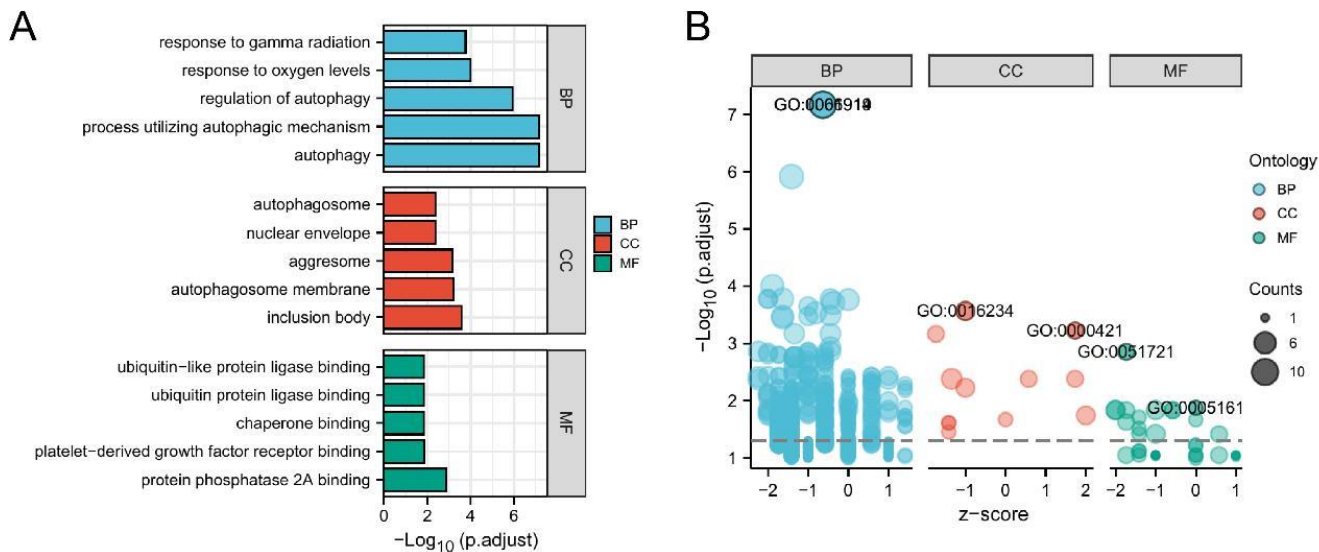


Figure 3. Gene Ontology (GO) enrichment analysis for autophagy related DEGs. *a* Barplot; *b* Dotplot.

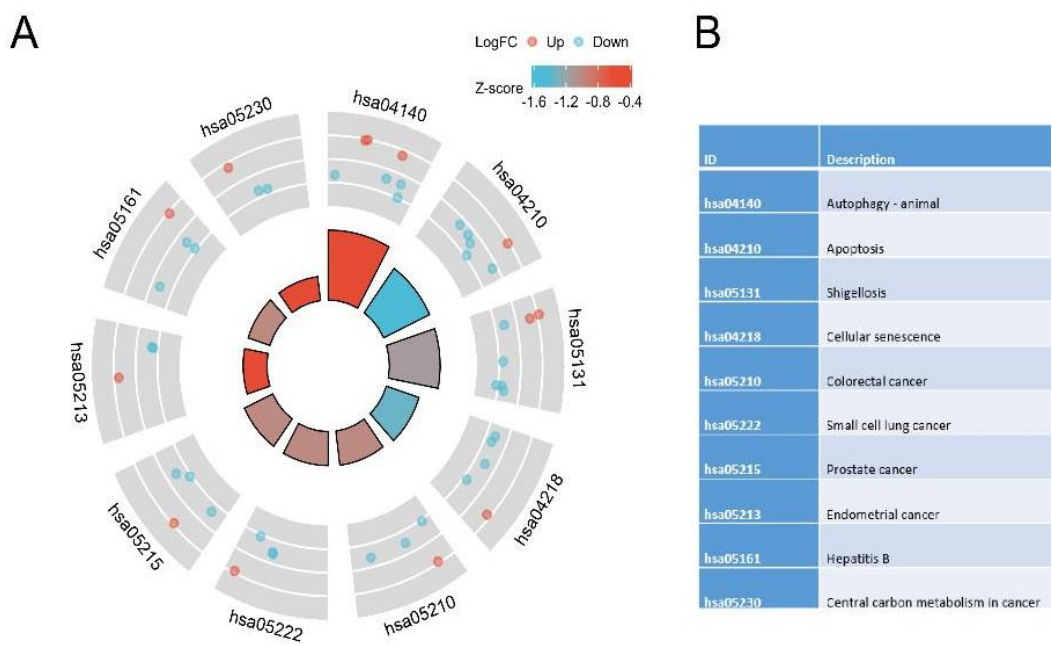


Figure 4. KEGG analysis of DEARGs.

To analyze the potential biological functions of DEARGs, we used R software to conduct GO and KEGG enrichment analyses. The results showed that the biological process (BP) were mainly enriched in reaction to oxygen levels, regulation of autophagy, and the process of utilizing autophagy mechanism; the cell components (CC) were mainly enriched in autophagosome, nuclear envelope, aggresome, autophagosome membrane, inclusion, the molecular function (MF) were mainly enriched in Ubiquitin-like protein ligase binding, chaperone binding, platelet-derived growth factor receptor binding, and protein phosphatase 2A (Figure 3). In the KEGG enrichment analysis, the DEARGs were mainly involved in autophagy and apoptosis (Figure 4).

3.3. PPI Network and Correlation Analysis of Gene Difference Expression Associated with Autophagy

To determine the interaction between DEARGs expressed in the dataset GSE57065, we performed a PPI analysis. Results showed interactions between these DEARGs and the number of these between each gene (Figure 5A). TP53, MYC, FOXO1, PTEN, PARP1, BIRC5, CXCR4, BCL2, EEF2 and ERN1 were selected as hub genes (Figure 5B).

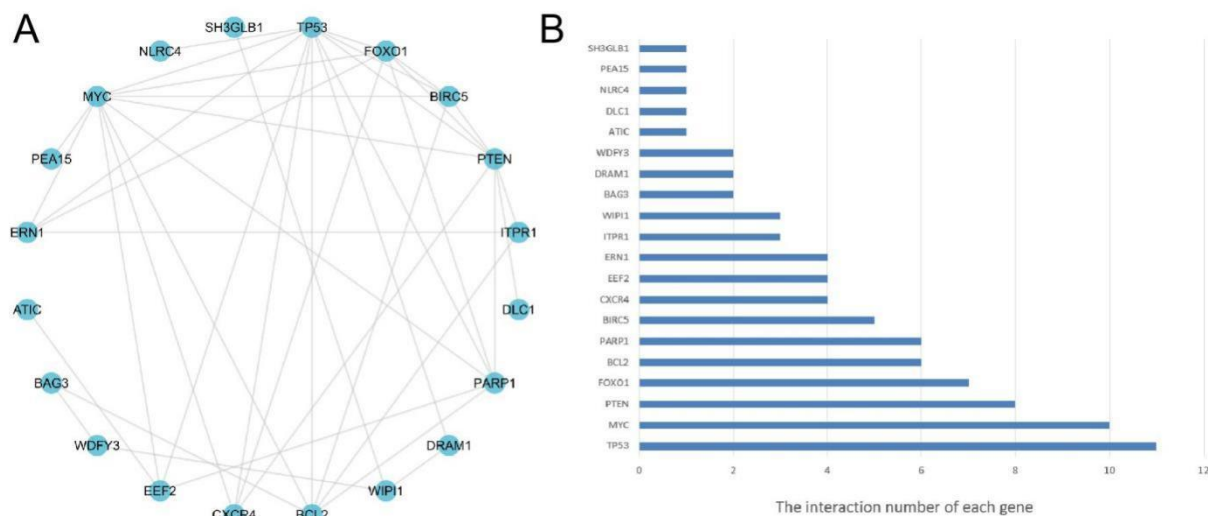


Figure 5. The PPI of the 22 DEARGs. a The PPI of the 22 DEARGs. b The interaction number of each DEARG.

3.4. ROC Curves for Hub Genes

Based on the external dataset GSE6568, ROC curves were generated for the hub genes (Figure 6). The results showed that TP53, MYC, FOXO1, PTEN, PARP1, CXCR4, and EEF2 have diagnostic value.

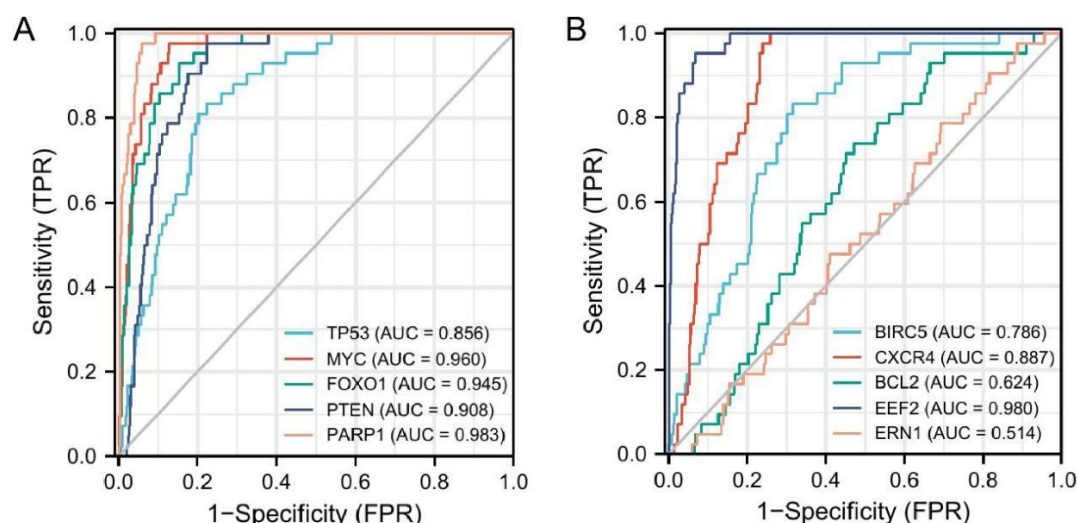


Figure 6. The ROCs of the hub genes. (A) TP53, MYC, FOXO1, PTEN, PARP1, (B) BIRC5, CXCR4, BCL2, EEF2, ERN1.

3.5. The Validation of DEARGs in Animal Experiments

We successfully constructed an animal model of SA-AKI, and the detection of blood urea nitrogen (BUN) and creatinine suggested that the model group was significantly higher than

that of the control group, which was statistically significant (Figure 7A, 7B). qRT-PCR analysis revealed that TP53, MYC, FOXO1, CXCR4 and BCL-2 gene expression were up-regulated, and the expression of PARP1 and PTEN genes were down-regulated in septic AKI. EEF2, ERN1, and BIRC5 expression levels did not differ significantly (Figure 7C).

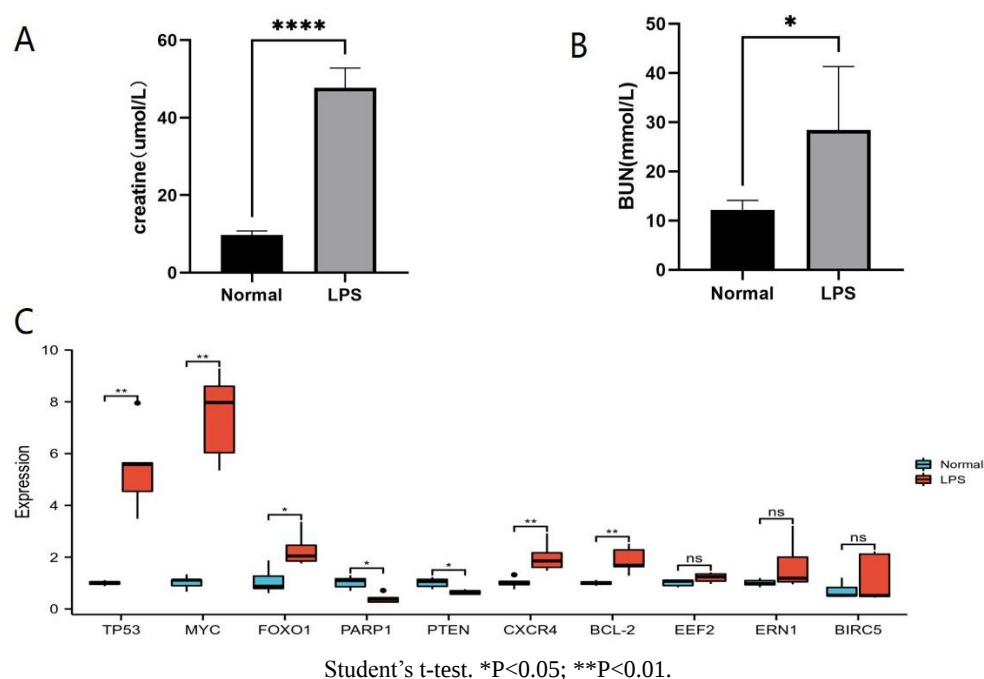
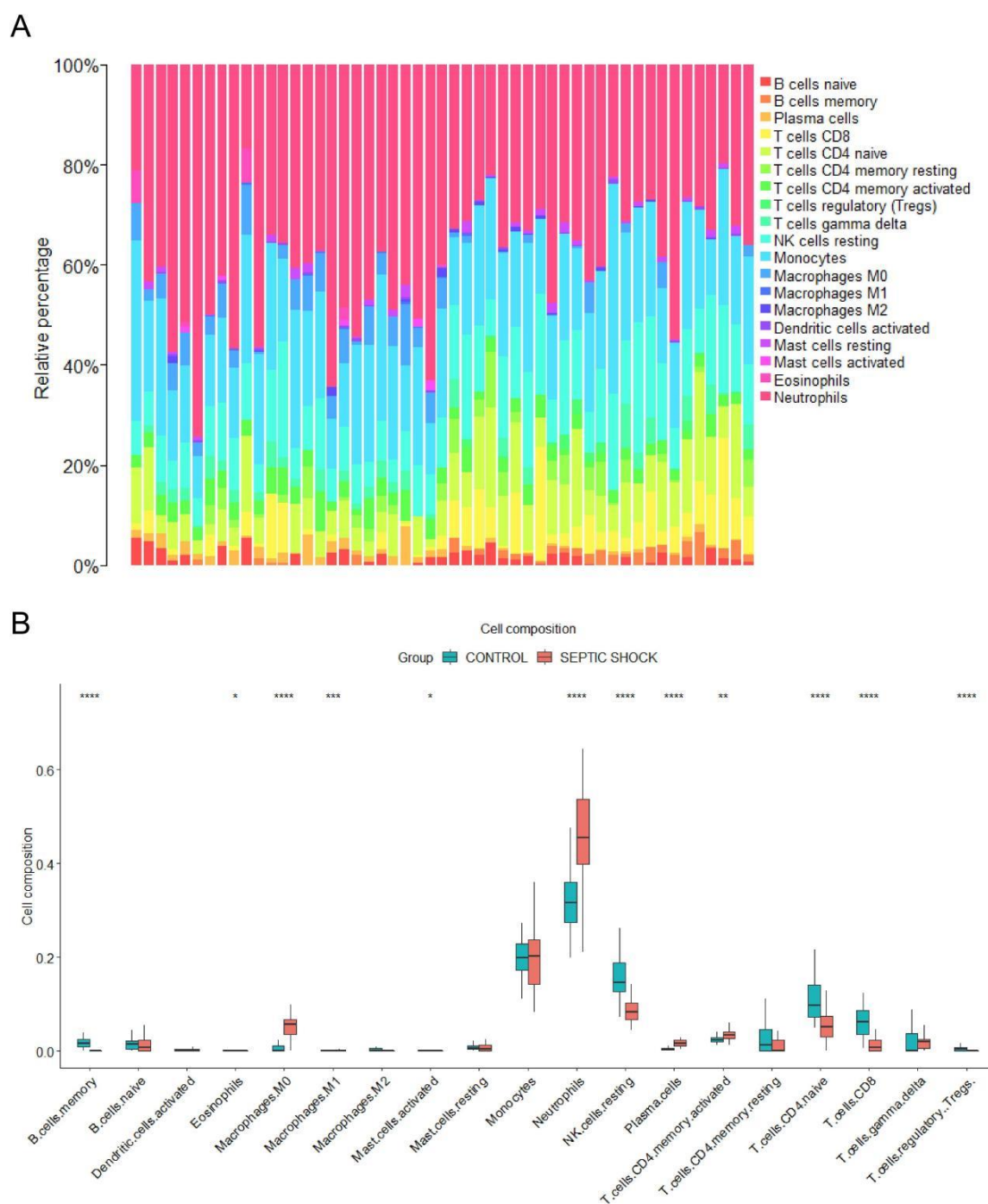


Figure 7. The validation of DEARGs in the animal experiment. (A) BUN and creatinine levels in mouse normal and LPS groups. (B) qRT-PCR analysis of the hub genes.

3.6. Characteristics of Immune Infiltration

Across all samples, immune cell distributions were represented using histograms. In comparison with healthy controls, the percentage of Macrophages M0, Neutrophils, T cells CD4 memory activated were higher in septic shock, while the fraction of T cells regulatory Tregs, T cells CD8, T cells CD4 naive, NK cells resting, Macrophages M1, Eosinophils, B cells naive,

B cells memory were relatively lower (Figure 8A, 8B). Correlation heat map of immune cells also revealed relationships between different immune cells (Figure 9). At the same time, it was found that the validated hub genes and immune cells included B cells memory, macrophages M0, macrophages M1, mast cells activated, neutrophils, NK cells resting, plasma cells, T cells CD4 memory activated, T cells CD4 naive, T cells CD8, T cells regulatory (Tregs) were related (Figure 10).



Student's t-test. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$; **** $P < 0.0001$.

Figure 8. Analysis results of 22 kinds of immune cell infiltration. (A) Distribution of 22 kinds of immune cells in septic shock group and control group. (B) The heat map showed differences in immune cell infiltration.

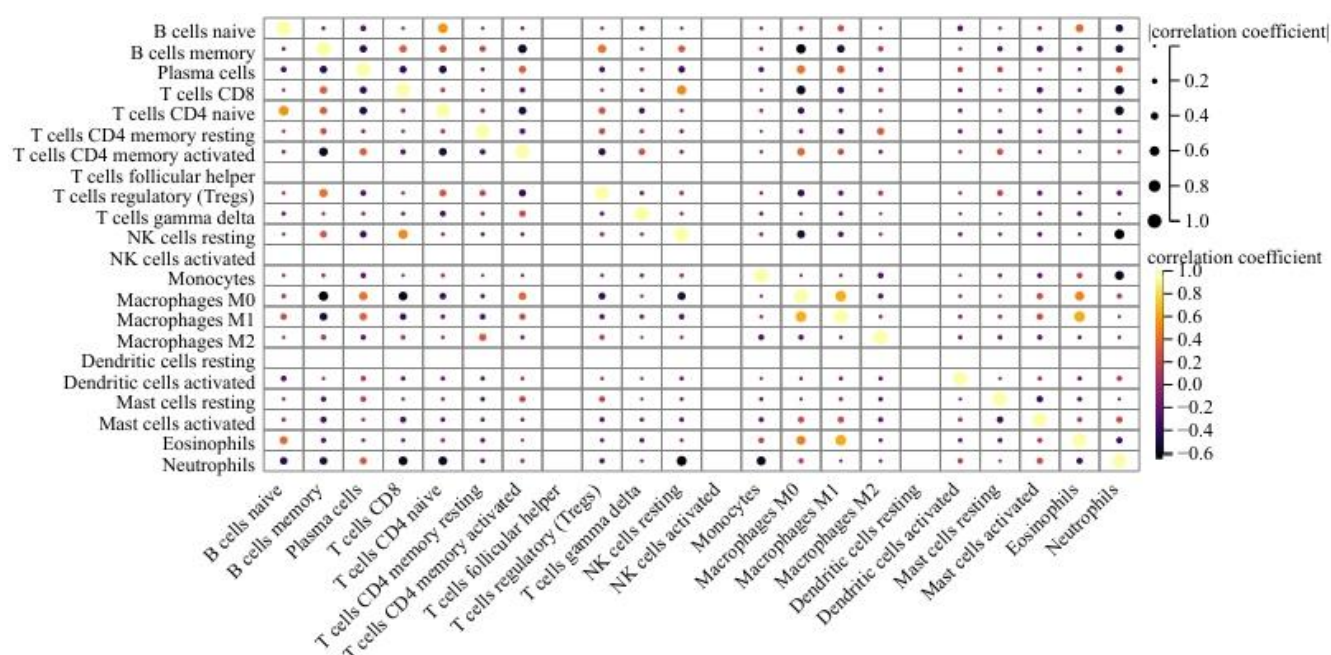


Figure 9. The heat map of immune cells. Blue and yellow indicated a negative and positive correlation between 22 immune cells, respectively. Dot size indicated closer ties.

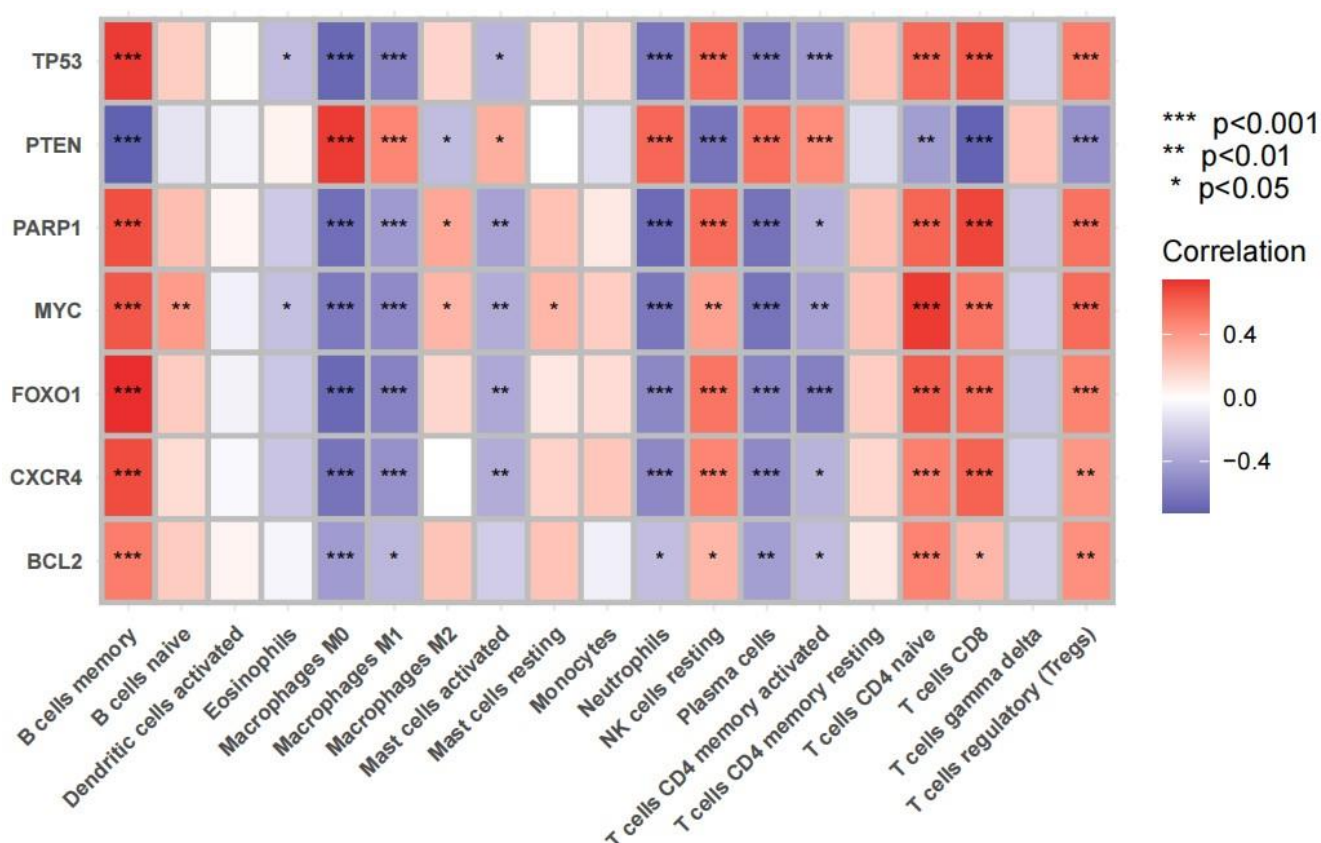


Figure 10. Correlation between TP53, PTEN, PARP1, MYC, FOXO1, CXCR4, BCL2 and immune cells.

3.7. miRNA-Hub Genes

The miRNet database was used to predict miRNAs of hub genes (Figure 11, supplementary table 2).

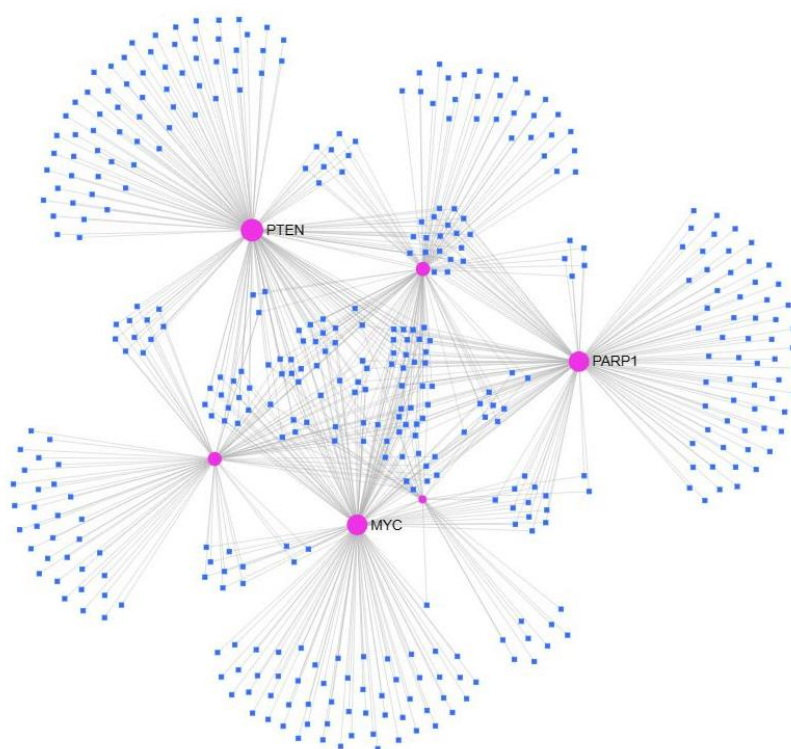


Figure 11. miRNA-hub genes network. Red represented hub genes, and blue represented miRNAs.

4. Discussion

In the pathophysiological mechanism of acute kidney injury in sepsis, the inflammation response is known to play a significant role [7, 20]. However, further exploration is needed to determine how inflammation can be regulated to protect the kidney. Previous studies have demonstrated the crucial role of autophagy in inflammation regulation. For instance, Kimura T et al. discovered that the autophagy pathway can inhibit septic AKI by regulating type I interferon and inflammasome [21]. Interestingly, it was also observed that the autophagy pathway can activate type I interferon production and promote the secretion of IL1B [22]. Therefore, autophagy can have both beneficial and detrimental effects in this context [23].

Our concern lies in effectively regulating autophagy to prevent an excessive inflammatory response or immunosuppression, thereby avoiding acute kidney injury resulting from inflammation. The role of autophagy genes in regulating the inflammatory response of acute kidney injury in sepsis has been investigated in recent studies [10, 21].

The study has demonstrated that SIRT1 mitigates septic acute kidney injury by activating autophagy through Beclin1 deacetylation [24]. The impact of SW033291 on 15-hydroxyprostaglandin dehydrogenase inhibition was explored in this study, revealing its potential to enhance autophagy and mitigate oxidative stress, thereby alleviating LPS-induced acute kidney injury (AKI) in mice through

apoptosis modulation [25]. Nevertheless, the investigation of septic AKI in relation to bioinformatic analysis of ARGs remains limited.

By employing bioinformatics analysis, a total of 22 potential DEARGs were identified in both the septic shock and control group. Subsequently, a comprehensive examination of the functional enrichment of these DEARGs was conducted, revealing that the biological processes (BP) were primarily enriched in response to oxygen levels and autophagy regulation. Furthermore, the cellular components (CC) exhibited enrichment in autophagosomes and the nuclear envelope, while the molecular functions (MF) were enriched in Ubiquitin-like protein ligase binding and chaperone binding. Additionally, the signaling pathways were found to be enriched in NF- κ B and P53 signaling pathways.

Subsequently, Protein-Protein Interaction (PPI) analyses were conducted on DEARGs, leading to the identification of ten hub genes, namely TP53, MYC, FOXO1, PTEN, PARP1, BIRC5, CXCR4, BCL2, EEF2, and ERN1. To assess their diagnostic potential, ROC analyses were performed on these hub genes in conjunction with the external dataset obtained from GSE65682, revealing their significant diagnostic value.

In our septic AKI animal model, the expression levels of 10 DEARGs were further identified using qRT-PCR. Specifically, the genes TP53, MYC, FOXO1, CXCR4, and BCL-2 exhibited up-regulation, whereas PARP1 and PTEN showed down-regulation. On the other hand, EEF2, ERN1, and BIRC5 did not display differential expression. It was worth noting that septic AKI has been linked to some of these iden-

tified genes. Additionally, the FOXO1/NF- κ B signaling pathway has been found to protect mice from septic shock by inhibiting macrophage NLRP3 activation [12]. Deacetylation of p53 alleviates septic AKI by promoting autophagy [26]. PTEN promotes autophagy through the PI3K/Akt pathway, thus alleviating the inflammatory response of acute kidney injury in sepsis and protecting the kidney [27]. However, the specific mechanism by which these genes contribute to septic AKI remains largely unclear.

To gain a deeper understanding of immune cell infiltration in septic acute kidney injury (AKI) and the involvement of validated hub genes in the pathogenesis of septic AKI, we employed the cibersort method to quantify the proportions of immune cells. Our analysis revealed significant differences in the proportions of Macrophages M0, Neutrophils, T cells CD4 memory activated, T cells regulatory Tregs, T cells CD8, T cells CD4 naive, NK cells resting, Macrophages M1, Eosinophils, B cells naive, and B cells memory. Additionally, the heat map depicting immune cell distributions provided insights into the relationships between different immune cells. Simultaneously, it was discovered that the validated hub genes exhibited associations with certain immune cells. Finally, we conducted a prediction analysis on the upstream miRNAs of validated hub genes with the aim of finding potential miRNAs for regulatory hub genes.

Our study encountered several limitations. Firstly, the dataset utilized for our bioinformatics analysis consisted of patients with septic shock rather than septic AKI. Nevertheless, given the substantial prevalence of septic AKI within the septic shock population, it was deemed clinically justifiable to select this dataset. Secondly, our investigation solely entailed the validation of DEARG expression levels in animal samples, without conducting additional in vivo and in vitro experiments to elucidate the underlying mechanism. Thirdly, the absence of clinical samples hindered the analysis of its clinical significance.

5. Conclusions

In conclusion, our study employed bioinformatics techniques and in vivo experiments to identify a total of seven pivotal genes. By assessing the expression levels of these genes, we might effectively discern patients suffering from acute kidney injury with sepsis. Additionally, combined with CIBERPORT, these pivotal genes have the potential to modulate the inflammatory response associated with acute kidney injury in sepsis by regulating immune cell functionality. Consequently, our findings offer novel perspectives for the diagnosis and treatment of individuals afflicted with acute kidney injury in sepsis.

Abbreviations

AKI Acute Kidney Injury

ARGs	Utophagy-related Genes
DEARGs	Differentially Expressed Autophagy-related Genes
PPIs	Protein-Protein Interactions
DEGs	Differentially Expressed Genes
ROC	Receiver Operating Characteristic
PCA	Principal Component Analysis
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
MCC	Multiscale Curvature Classification
BP	Biological Process
CC	Cell Components
MF	Molecular Function
BUN	Blood Urea Nitrogen

Supplementary Material

The supplementary material can be accessed at <https://doi.org/10.11648/j.bs.20251102.11>

Author Contributions

Yang Pan: Wrote the original draft, Review and editing, Acquired funding, Collected resources, Project administration.

Si Chen: Designed the research, Revised the manuscript, Bioinformatics analyses, Data curation.

Ethics

All animal experiments in this study were strictly reported in accordance with the ARRIVE guidelines and conducted in strict compliance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals, the Chinese Ministry of Science and Technology's "Guideline on the Humane Treatment of Laboratory Animals," and the "Administrative Regulations on Laboratory Animals." The animal experiments were ethically reviewed, approved, regulated, and supervised by the Institutional Ethics Committee of Chongqing University Three Gorges Hospital (Approval No: 2023-016; Date: June 12, 2023). We are committed to minimizing the number of animals used, optimizing experimental design to alleviate pain and suffering, and providing animals with standard-compliant housing environments and care throughout the experimental process.

Availability of Data and Materials

Availability of data and materials Datasets including GSE57065, GSE65682 were downloaded from NCBI Gene Expression Omnibus database (GEO, <http://www.ncbi.nlm.nih.gov/geo>).

Funding

This study was supported by Wanzhou District Science and Health Joint Medical Research Project (wzstc-kw2022015).

Conflicts of Interest

The authors declare no conflicts of interest.

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