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ORIGINAL RESEARCH

PTGDS: As a Specific Biomarker for Septic Cardiomyopathy

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Purpose: Screening specific biomarkers for Septic Cardiomyopathy (SCM) to provide research targets for early identification and prognosis assessment.

Methods: Peripheral blood samples from 20 sepsis patients and 10 healthy volunteers were collected for RNA sequencing. Subsequently, an intersection was taken between the differentially expressed genes in sepsis and the heart-specific expressed genes. This intersecting gene set was subjected to PPI analysis, GO enrichment, and KEGG pathway analysis. Survival analysis was employed to screen for potential hub gene and assess the relationship between the gene and prognosis. ROC curve was used to determine the diagnostic value of the hub target. Single-cell RNA sequencing was utilized to identify the cellular localization of the core gene, aiding in the selection of reliable cell lines for experimental validation.

Results: The sepsis differential gene intersected with 1000 heart-specific genes for 40 targets. Survival analysis identified PTGDS as a potential core gene, with its expression levels positively correlating with the prognosis of sepsis patients. Notably, PTGDS emerged as a promising candidate, achieving an AUC of 0.898 in ROC curve analysis for diagnosing sepsis. It is important to note that these findings are based on an initial, proof-of-principle cohort with a limited sample size. Single-cell RNA sequencing demonstrated that PTGDS is primarily expressed in NK cells and T cells. A violin plot showed that the expression of PTGDS was lower in the sepsis group compared to the normal group.

Conclusion: Our study identifies PTGDS as a novel diagnostic biomarker for sepsis with potential involvement in SCM. These results highlight the potential of PTGDS as a target for future diagnostic development and mechanistic research, paving the way for improved clinical stratification of septic patients at risk of cardiac complications.

Keywords: septic cardiomyopathy, RNA sequencing, diagnosis, prognosis, PTGDS

Introduction

Sepsis is a life-threatening condition arising from a dysregulated host response to infection, characterized by a systemic inflammatory response that can lead to multi-organ dysfunction and a high mortality rate.[1] Among the numerous complications induced by sepsis, cardiac injury and functional impairment occur frequently.[2] Septic cardiomyopathy (SCM), also known as Sepsis-induced cardiomyopathy (SICM), can precipitate symptoms of acute cardiac decompensation in patients, including dyspnea, chest pain, fatigue, and syncope, and significantly increases the mortality rate.[3] Despite extensive research into the clinical presentation, pathophysiology, and diagnostic criteria of SCM, its definitive definition remains elusive.[4] Although SCM was historically considered a reversible condition, emerging evidence indicates that cardiac dysfunction persists in a substantial subset of survivors, which is associated with worse long-term outcomes. Nevertheless, even transient SCM significantly elevates the in-hospital mortality risk in septic patients by an alarming 70% to 90%.[5] This underscores the imperative for prompt recognition and intervention. The pathogenesis of SCM is intricate, encompassing inflammation-induced myocardial injury, microcirculatory dysfunction, mitochondrial damage, and hyperactivation of the sympathetic nervous system.[6] The diagnosis of SCM is challenging due to a lack of

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specific clinical manifestations and definitive diagnostic criteria. Its identification largely hinges on a comprehensive evaluation combining echocardiography, biomarker analysis, and hemodynamic monitoring.[4] The complex pathogenesis coupled with non-uniform diagnostic standards significantly heighten the challenges in recognizing SCM in clinical practice.

Currently, the diagnosis of cardiac involvement in sepsis relies heavily on established biomarkers such as cardiac troponins (cTnI/cTnT) and B-type natriuretic peptides (BNP/NT-proBNP). Troponins are highly specific markers of cardiomyocyte injury, while BNP reflects myocardial wall stress and volume overload. However, in the complex setting of sepsis, the elevation of these markers can be non-specific, being influenced by renal dysfunction, generalized systemic inflammation, and non-cardiac critical illness, which complicates their interpretation for specifically diagnosing SCM. Therefore, while indispensable, these markers primarily indicate ongoing damage or stress after it has occurred. Our study aims to identify biomarkers that might be involved in the earlier pathogenic processes of SCM, such as dysregulated inflammation and immune responses. The identification of PTGDS, a gene involved in prostaglandin synthesis and highly expressed in immune cells, offers a complementary perspective. It represents a different biological axis—linking systemic inflammation directly to potential cardiac dysfunction—and may potentially aid in earlier risk stratification or provide insights into a distinct aspect of SCM pathophysiology that is not captured by troponins or BNP.[7,8]

Specific treatment guidelines for SCM are notably absent. Presently, the therapeutic approach for SCM primarily centers on acute interventions, closely mirroring the management of sepsis. Among these, hemodynamic monitoring is a cornerstone endorsed by international guidelines for sepsis treatment. However, the efficacy and safety of treatment protocols for SCM remain subjects of ongoing research, warranting further investigation.[9,10] Hence, the pursuit of specific diagnostic markers and personalized targeted therapies for SCM is of paramount necessity. With the widespread adoption and advancement of RNA sequencing technologies, we can screen for differentially expressed genes (DEGs) in sepsis patients directly,[11] facilitating a deeper exploration of disease pathogenesis and the identification of specific therapeutic targets. Building upon this technology, our research integrates RNA sequencing with bioinformatics techniques to elucidate the pathogenic mechanisms of SCM and identify biomarkers that facilitate early diagnosis of SCM, thereby providing a theoretical basis for subsequent targeted therapy research on this condition. The procedures of this experiment are illustrated in Figure 1.

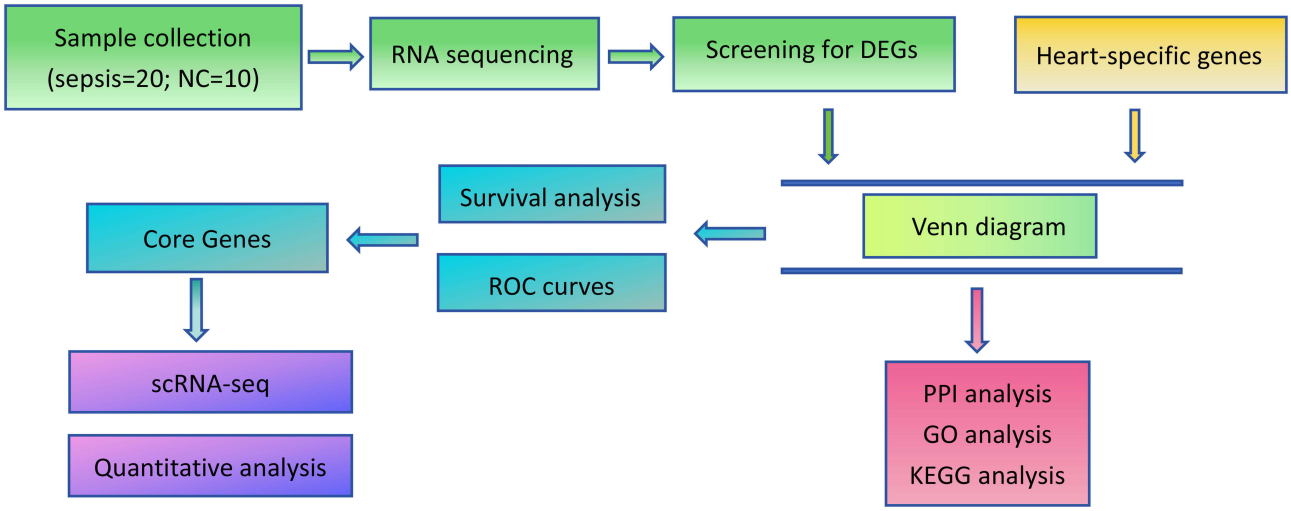

Figure 1 Flowchart. Blood samples were collected from 20 patients diagnosed with sepsis and 10 healthy volunteers for RNA sequencing and differential expression analysis. Cardiac-specific expressed genes were downloaded from the GTEx database. An intersection was taken between sepsis-differential genes and cardiac-specific expressed genes, and the intersected genes were subjected to PPI, GO, and KEGG pathway analyses. Survival analysis was employed to evaluate the relationship between genes and prognosis. ROC curve was utilized to ascertain the diagnostic value of core genes. Single-cell RNA sequencing was applied to clarify the cellular localization of these core genes.

Methods

Recruitment and Blood Sampling

Twenty patients with sepsis (sepsis group) admitted to the EICU of the Affiliated Hospital of Southwest Medical University from January 2019 to December 2020, and ten healthy volunteers (normal control group) from the same period, were enrolled in this study. Blood samples were collected within the first 24 hours of hospital admission. The study was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (Ethical Approval No.: ky2018029), and registered under the clinical trial registration number ChiCTR1900021261. The inclusion criteria for the sepsis group were: (1) compliance with the diagnostic criteria for Sepsis 3.0 jointly released by the American and European Societies of Critical Care Medicine in 2016, infection plus organ dysfunction (SOFA score ≥ 2);[12] (2) age ≥ 18 years; (3) patients or their legal representatives willing to participate in the study and sign the informed consent. Exclusion criteria were: (1) pregnant or lactating women; (2) patients with mental illness; (3) immunodeficiency or HIV-positive; (4) history of severe organ failure. The inclusion criteria for the normal control group were: (1) age ≥ 18 years; (2) no history of severe heart, liver, kidney, digestive, neurological, or immune system diseases; (3) negative serum hCG test for female volunteers of childbearing age; (4) voluntary participation in the study and signing of informed consent. The exclusion criteria were: (1) history of hemophobia, needle phobia, or severe anemia; (2) history of clinically severe diseases; (3) patients who have undergone surgery within the past 4 weeks; (4) history of drug abuse within the last year. All methods were performed in accordance with the relevant guidelines and regulations.

Blood Collection and Processing

The PAXgene tubes effectively collect whole blood, stabilize nucleic acids, and significantly reduce RNA degradation, enhancing the accuracy of transcriptomic analysis. Prior to use, ensure that the PAXgene tubes are at a temperature of 18°C to 25°C and are accurately labeled with patient information. Each patient requires two blood samples to be drawn. In the blood collection process, start by priming with a regular blood collection tube before switching to the PAXgene tube to complete the sample collection. After blood collection, gently shake the tube 8–10 times, followed by a 2-hour rest at room temperature. Subsequently, the PAXgene tubes will undergo 24-hour pre-freezing at −20°C and will eventually be stored at −80°C.

RNA Extraction and Sequencing

Using the Trizol kits, following the specialized protocol outlined by BGI Shenzhen, we meticulously processed peripheral blood samples to isolate and quantify total RNA. Amidst the diverse pool of total RNA, we employed sophisticated selection methods to exclusively capture mRNA molecules while effectively removing contaminating elements like small oligonucleotides and ribosomal RNA. The purified mRNA was then conserved for subsequent deep sequencing analysis.

Screening of DEGs

iDEP (Integrated Differential Expression and Pathway Analysis) is a web tool designed for analyzing RNA-seq datasets. By integrating comprehensive analytical functions with extensive annotation databases, it empowers biologists to effortlessly translate transcriptomics and proteomics data into actionable insights.[13] For this study, the online platform iDEP 2.01 was utilized for initial quality control and log transformation of the RNA sequencing data. Quality control measures included generating density plots and boxplots to assess the homogeneity and comparability of normalized data, enabling the exclusion of outlier samples. To ensure the robustness of our findings despite the sample size, we applied stringent false discovery rate (FDR) corrections during differential expression analysis and focused on genes with large effect sizes and high statistical significance ($FDR < 0.05$, $|FC| \geq 4.0$). This approach increases our confidence that the identified DEGs, including PTGDS, represent biologically relevant signals.

Screening of Heart-Specific Expression Genes

The Genotype-Tissue Expression (GTEx) database (https://xenabrowser.net/datapages/?cohort=GTEX&removeHub=https%3A%2F%2Fxena.treehouse.gi.ucsc.edu%3A443) is utilized to investigate the relationship between genetic variations and gene expression across human tissues.[14] Comprising DNA data from 838 deceased donors who were healthy prior to death, covering 54 distinct tissue types with a total of 17,382 RNA-seq records. Within the GTEx database, selecting "tpm" format and focusing on the primary tissue source of "Heart" allows us to identify the top 1000 genes highly enriched in cardiac tissue. Utilizing Venny2.1 (https://bioinfogp.cnb.csic.es/tools/venny/index.html), the intersection targets between sepsis-related DEGs and heart-specific genes can be determined, pinpointing key genes potentially implicated in both conditions.

PPI Analysis

Protein-Protein Interaction (PPI) Networks are constituted by proteins interacting with each other to engage in various life processes encompassing biological signal transduction, regulation of gene expression, energy and substance metabolism, as well as cell cycle control. Systematic analysis of large-scale protein interactions within biological systems is vital for comprehending how proteins function within these systems, elucidating the mechanisms of biological signals and metabolic responses under disease states, and understanding functional associations among proteins. The STRING database (https://cn.string-db.org/) is a resource dedicated to exploring functional associations among proteins.[15] Spanning 2031 organisms, this database encompasses over 9.6 million proteins and 13.8 million interactions between them. In the STRING database, set the minimum required interaction confidence score between any two proteins to 0.15. Removed unconnected nodes from the network, and highlighted the main cellular components and tissue distributions of these proteins.

GO Analysis

Gene Ontology (GO) enrichment analysis serves as a comprehensive resource pertaining to the functions of genes and their products, categorized into three principal domains: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF).[16] BP delineates the involvement of a gene in specific biological pathways; CC identifies its location within the cell; and MF elucidates its role at the molecular level. In this study, Omicshare (https://www.omicshare.com/) was employed to conduct GO enrichment analyses, providing an overarching perspective on the functional attributes of the intersecting genes. Specifically, the analysis focused on enriching the top 20 gene sets for BP, CC, and MF categories respectively, culminating in the creation of interactive visual representations.

KEGG Analysis

The Kyoto Encyclopedia of Genes and Genomes (KEGG) stands as a widely-utilized pathway database for understanding and simulating higher-order functional behaviors of cells or organisms based on genomic information.[17] KEGG integrates databases containing genomic, chemical, and systemic functional information, encompassing such diverse areas as metabolic pathways, hierarchical classifications, genes, and genomes. The objective of KEGG analysis is to identify genes within a given set that correlate with particular metabolic pathways, thereby revealing the biological significance of the gene ensemble. KEGG enrichment analysis of the intersecting genes was performed on the Omicshare website, aimed at pinpointing the top 20 pathways significantly enriched within the context of the entire genome. A p-value < 0.05 was designated as indicative of statistical significance.

Survival Analysis

Clinical data forms the cornerstone of scientific research, serving as a critical tool for investigating the correlation between genes and prognosis. In our study, survival analysis was carried out utilizing the GSE65682 dataset[18] from the GEO public database, with Log rank test selected as the statistical method. GSE65682 is a widely used and stable sepsis gene dataset based on the GPL13667 platform of peripheral blood RNA sequencing dataset of sepsis patients and healthy subjects, which contains 479 sepsis patients, alongside their respective gene expression values and clinical prognosis information.

ROC Curve

The Receiver Operating Characteristic curve (ROC curve) is a statistical tool used to assess the discriminative power of binary diagnostic tests.[19] It is frequently employed to gauge the diagnostic efficiency of diseases, where the Area Under the Curve (AUC) serves as a measure of diagnostic performance. When the AUC > 0.5, its proximity to 1 correlates with an enhanced diagnostic performance. Specifically, an AUC within the range of 0.5 to 0.7 indicates lower accuracy, whereas an AUC between 0.7 and 0.9 suggests moderate accuracy. An AUC > 0.9 denotes high accuracy. Conversely, an AUC of 0.5 implies that the diagnostic method lacks efficacy, rendering it diagnostically ineffectual. To evaluate the precision of core genes in diagnosing sepsis, we conducted ROC curve analysis using the GSE95233 dataset[20] retrieved from the GEO database. This dataset incorporates RNA-seq data obtained from blood samples of 51 sepsis patients and 22 healthy volunteers.

Single-Cell RNA Sequencing

To precisely determine the cellular origin of the core genes, we subjected five peripheral blood samples to 10× single-cell RNA sequencing studies, including 2 healthy controls, 1 SIRS patient, and 2 sepsis patients. The five peripheral blood mononuclear cell (PBMC) samples subjected to single-cell RNA sequencing were a subset of the same sepsis patients included in the bulk RNA-seq discovery cohort. This design allows for direct comparison and cell-type-specific interpretation of the bulk sequencing signals. Initially, we conducted a comprehensive quality control check on the raw data acquired. Subsequently, the data were aligned to the reference genome with high precision, ensuring both reliability and accuracy of the data. During the in-depth quality assurance phase, we meticulously filtered out all low-quality samples including doublets, multiplets, and dead cells. Following this, Principal Component Analysis (PCA) was applied to perform linear dimensionality reduction on the gene expression metrics. Ultimately, the tSNE algorithm was deployed to represent the results of PCA in a two-dimensional map visually, clearly illustrating the distribution of core targets among different cell lineages.

Quantitative Analysis

RNA sequencing data from blood samples of 20 sepsis patients and 10 normal controls were collected for comparative multi-dimensional analysis, illustrated through violin plots. Statistical analysis was executed using the R programming language. Depending on the characteristics of the data format, non-parametric testing was chosen, specifically the Wilcoxon rank sum test (utilizing the "stats" and "car" packages). Visualization of the data was achieved through the "ggplot2" package.

Results

Clinical Characteristics and DEGs

This study enrolled 20 patients diagnosed with sepsis and 10 healthy volunteers as controls. Clinical characteristics and laboratory parameters—including gender, age, white blood cell count, neutrophil count, monocyte count, lymphocyte count, direct bilirubin, total bilirubin, urea, and creatinine—were collected and statistically summarized as mean values (Table 1). Compared with the healthy control group, sepsis patients showed significantly elevated levels of inflammatory and organ injury biomarkers. The marked increase in WBC and neutrophil counts upon admission confirmed a systemic hyperinflammatory state, consistent with the clinical profile of sepsis. Density distribution plots revealed no outlier samples in either the sepsis group or the normal control group (Figure 2A), while boxplots indicated good homogeneity among samples in both groups, establishing comparability (Figure 2B). Differential expression analysis was conducted between the two groups using thresholds of $|FC| \geq 4.0$ and FDR < 0.05, yielding a total of 1000 DEGs. Among these, red dots represented 698 upregulated genes in the sepsis group, blue dots indicated 302 downregulated genes in the sepsis group, and gray dots signified genes without differential expression (Figures 2C and D). After removing irregular gene names, a final count of 960 differentially expressed genes was obtained.

Table 1 Comparison of Clinical Characteristics Between Sepsis and Control Groups

Parameter	Sepsis Group	Control Group	P value
Gender (Male/Female)	15/5	6/4	–
Age (years)	58.05±15.66	51.70±11.65	0.2675 ns
White blood cells (10^9/L)	12.30±6.517	6.364±1.747	0.0090 **
Neutrophils (10^9/L)	13.21±13.50	3.819±1.348	0.0381 *
Monocytes (10^9/L)	0.8970±1.117	0.3580±0.08417	0.1421 ns
Lymphocytes (10^9/L)	1.233±1.618	1.918±0.4858	0.2044 ns
Direct bilirubin (μmol/L)	15.37±15.29	4.460±1.623	0.0340 *
Total bilirubin (μmol/L)	31.30±40.43	14.30±4.531	0.1995 ns
Urea (mmol/L)	13.14±14.77	5.304±1.552	0.1082 ns
Creatinine (μmol/L)	122.3±135.4	67.67±12.15	0.2172 ns

Notes: Data are presented as mean ± SD. *p < 0.05; *p < 0.01.
Abbreviation: ns, not significant.

Screening of Heart-Specific Expression Genes

Heart-specific expression genes were downloaded from the GTEx database, and the top 1000 genes highly enriched in heart tissue were selected for subsequent analysis. Intersection of these 1000 heart-specific genes with the 960 DEGs in sepsis yielded 40 potential target genes associated with SCM (Figure 3A). Heatmaps based on transcriptomic mRNA sequencing data showed that genes such as NNMT, SMARCD3, COX7B, TIMP3, etc, were highly expressed in the sepsis group, whereas DKK3, PTGDS, COL6A2, AEBP1 had low expression in the same group, with differences being statistically significant ($p<0.05$) (Figure 3B).

PPI Analysis

The PPI network consisted of 40 nodes interconnected by 196 edges, featuring an average node degree of 9.8 and an average local clustering coefficient of 0.486. The enrichment p-value of PPI was < 1.0e-16. Each bubble in the network was color-coded according to distinct biological functions: red represented Extracellular region, yellow indicated Vesicle, pink denoted Mitochondrion, green stood for Viscus, and purple bubbles symbolized Cellular anatomical entity (Figure 4).

GO Analysis

The most significantly enriched top 20 gene sets in GO enrichment analysis included 7 BP and 13 CC (Figure 5A). When analyzing the top 20 gene sets separately enriched in BP, CC, and MF, it was observed that the intersecting genes primarily participated in biological processes such as aerobic respiration, ATP synthesis coupled electron transport, oxidative phosphorylation, and positive regulation of the apoptotic process (Figure 5B). They were predominantly located in the extracellular matrix, extracellular Vesicel, and respiratory chain complex and other cellular components (Figure 5C). These genes mainly engaged in molecular functions such as oxidoreduction-driven active transmembrane transporter activity, collagen binding, calcium-dependent protein binding, and electron transfer activity (Figure 5D).

KEGG Analysis

The top 20 most significantly enriched gene sets in the KEGG pathway analysis encompassed 3 pathways in Metabolism, 1 pathway in Environmental information Processing, 2 pathways in Cellular Processes, 4 pathways in Organismal Systems, and 10 pathways classified under Human Diseases (Figure 6A). These genes prominently featured in pathways such as Cardiac muscle contraction, Diabetic cardiomyopathy, Chemical carcinogenesis-reactive oxygen species, and Thermogenesis (Figure 6B).

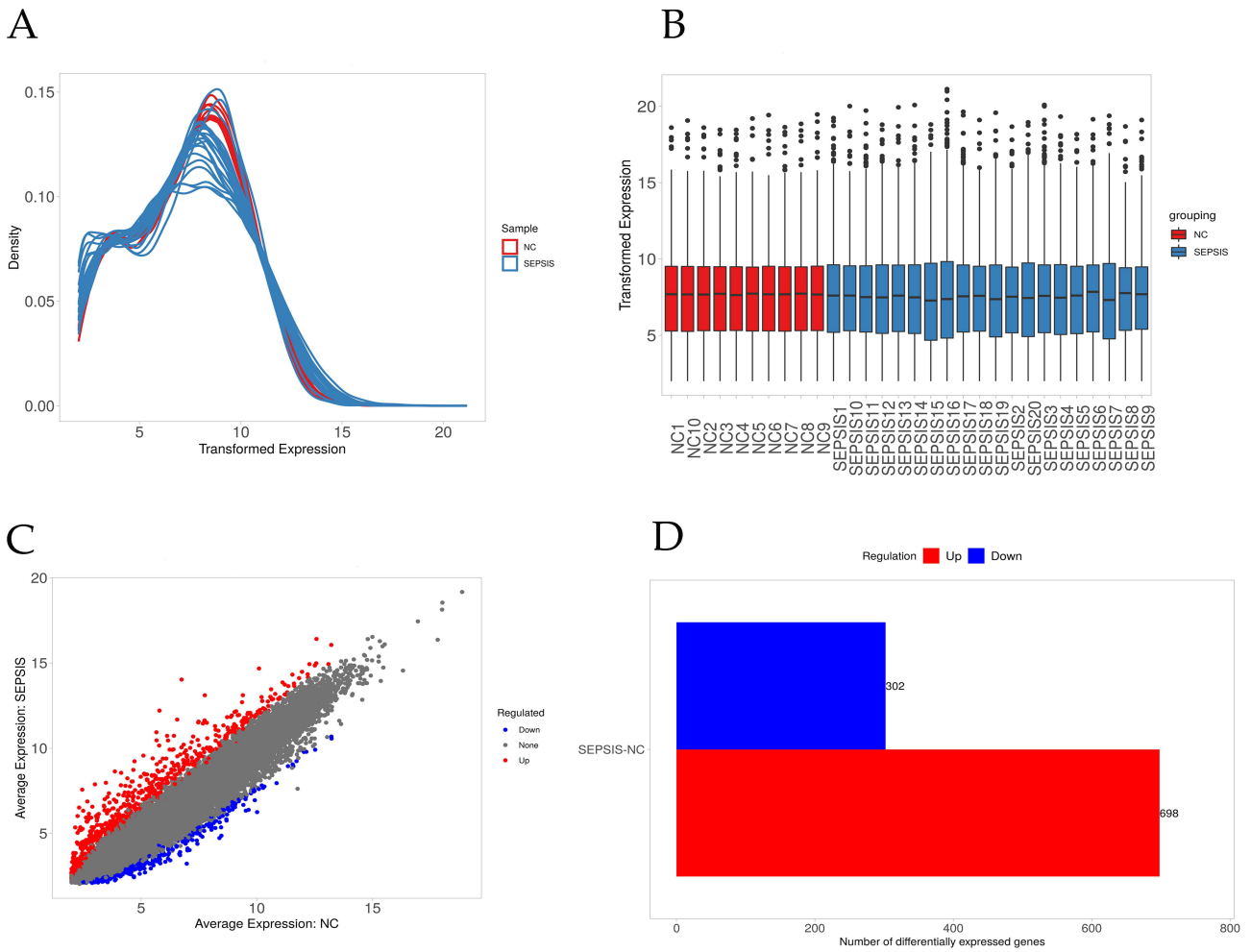

Figure 2 Data quality control and DEGs screening. (**A**) Density distribution plots indicated no outlier samples observed between the sepsis group and normal control group, demonstrating comparable data quality across all samples. (**B**) Boxplots showed that each sample's data was normalized to be on the same scale following preprocessing steps, ensuring comparability among different samples. (**C** and **A**) volcano plot depicted DEGs identified by analysis, with red representing upregulated genes and blue denoting downregulated genes in the sepsis group compared to controls. The x-axis represented the gene expression level in the normal control group, while the y-axis displayed the gene expression level in the sepsis group. (**D**) In the bar chart, red signified the 698 genes upregulated in the sepsis group, and blue indicated the 302 genes downregulated in the sepsis group.

Survival Analysis

Survival curves derived from clinical prognostic data contained in the GSE65682 dataset revealed that patients with higher expression of PTGDS exhibited better survival rates at 28 days compared to those with lower PTGDS expression, with the difference reaching statistical significance ($P < 0.05$). These findings suggest a positive correlation between PTGDS expression and prognosis in sepsis patients, indicating that elevated PTGDS expression could contribute to improved outcomes in individuals suffering from sepsis. This insight positions PTGDS as a potentially novel therapeutic target for sepsis research (Figure 7A).

ROC Curve Analysis

The ROC curve features false positive rate (1-specificity) on the horizontal axis and true positive rate (sensitivity) on the vertical axis. As illustrated, the AUC for PTGDS stands at 0.898, signifying certain diagnostic utility (Figure 7B). This finding underscores the high sensitivity and specificity of PTGDS in detecting sepsis, thereby introducing a promising new biomarker candidate for sepsis diagnosis.

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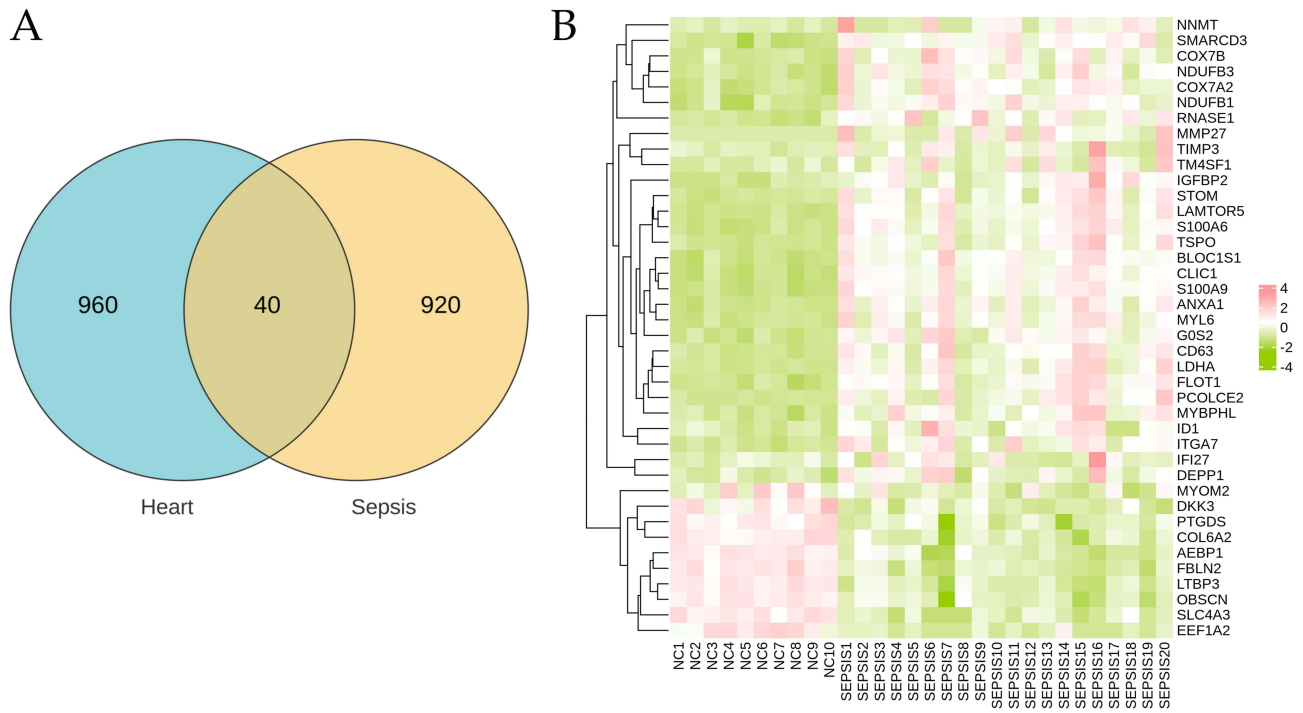

Figure 3 Selection of genes associated with SCM. (**A**) A Venn diagram illustrated the overlap of 1000 cardiac-specific genes with 960 sepsis-differential genes, revealing 40 intersecting target genes that are potentially linked to SCM. (**B**) Heatmap demonstrated differential expression patterns where 31 genes exhibited higher expression levels in the sepsis group, whereas 9 genes showed lower expression levels in comparison to the control group.

Single-Cell RNA Sequencing

To ensure data quality and integration, standard scRNA-seq preprocessing pipelines were applied, which included the removal of low-quality cells and doublets. Batch effects were assessed using visual inspection of UMAP projections and were found to be minimal across the five samples, thus no explicit batch-effect correction was applied for the integrated analysis presented here. Following marker gene identification and dimensionality reduction clustering, nine distinct cell populations were delineated. Among these, clusters 3 and 5 represented monocytes, cluster 4 denoted NK cells, whereas clusters 1, 2, 6, and 8 were attributed to T cells, cluster 7 corresponded to B cells, and cluster 9 indicated platelets (Figures 8A and B). Of particular note, PTGDS displayed predominant expression in cell clusters 2, 4, and 8, corresponding to NK cells and T cells (Figures 8C and D).

Quantitative Analysis

A quantitative analysis utilizing transcriptome RNA sequencing data was performed, with the Shapiro–Wilk normality test employed to evaluate the normality of the data distribution. Statistical analysis was conducted using the Wilcoxon rank-sum test, a non-parametric method. Analysis revealed that PTGDS was expressed at lower levels in the sepsis group compared to the normal control group, with the differences being statistically significant ($p < 0.001$) (Figure 8E).

Discussion

SCM, manifesting as cardiac dysfunction precipitated by sepsis, ranks prominently among the factors escalating mortality rates amongst patients grappling with severe forms of sepsis.[21,22] SCM is characterized by impaired contractile and relaxant functions impacting both the left and right ventricles, coupled with sinus tachycardia.[23] Despite leading to a severely clinically poor prognosis, SCM lacks a universally accepted definition, leading to variations in reported incidence rates, prognosis, and overall clinical relevance.[24] The complex etiology intertwined with ambiguities surrounding diagnostic criteria collectively pose challenges for early recognition and tailored treatment approaches in SCM, potentially delaying critical care interventions and resulting in poor patient outcomes or heightened fatality rates. Thus,

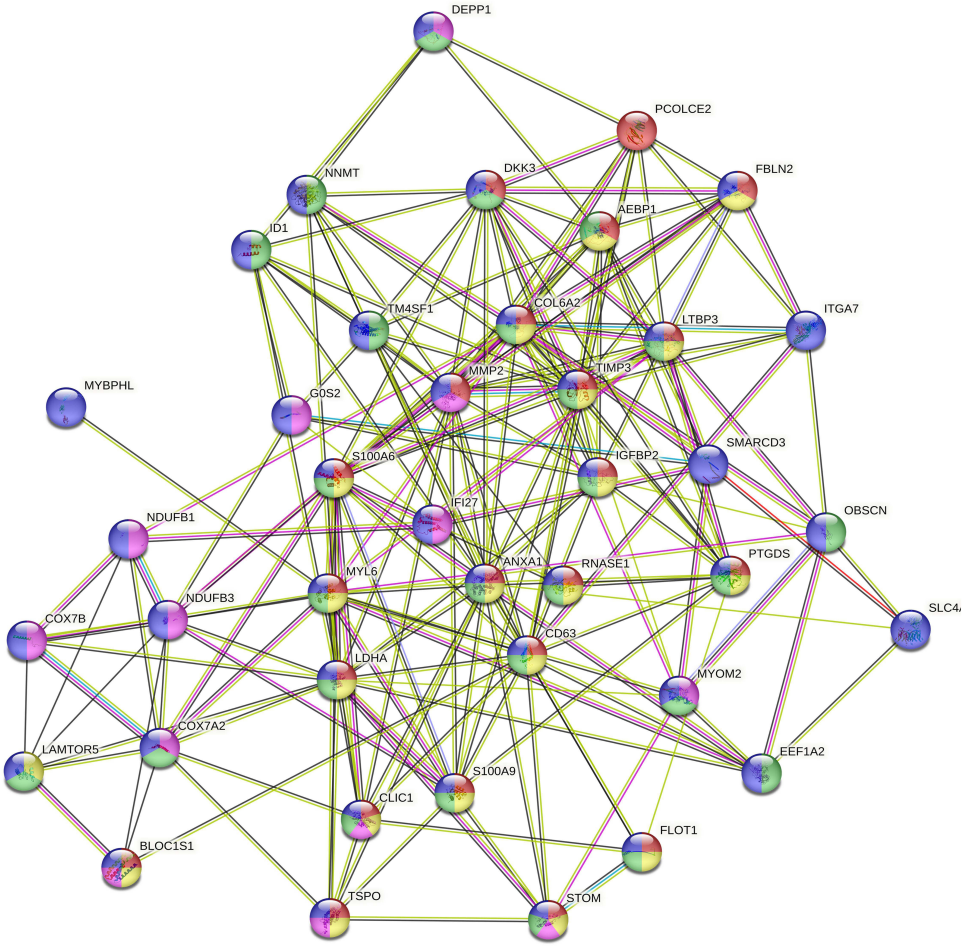

Figure 4 PPI network. The PPI network consisted of 40 nodes connected by 196 edges. Each bubble was color-coded according to distinct biological functionalities. Red corresponded to Extracellular region, yellow signified Vesicle, pink marked out the Mitochondrion, green represented Viscus, and purple delineated Cellular anatomical entity.

the quest for specific biomarkers indicative of SCM becomes imperative, paving the way for prompt diagnostics and targeted therapies that address the disease's core mechanisms.

The sample size for this initial discovery cohort (N=20 sepsis, N=10 control) was determined based on practical considerations for pilot-scale, high-throughput transcriptomic studies. While this limits the power to detect genes with small effect sizes, it is sufficient to identify large and consistent expression differences, which is the primary objective of this exploratory phase. To ensure the robustness of our findings, we employed stringent false discovery rate (FDR) corrections to minimize false positives. Utilizing an integrative approach combining RNA sequencing technology with bioinformatics analyses, we successfully identified 302 genes significantly downregulated and 698 genes upregulated under septic conditions. Among these DEGs, we delved deeper to investigate their overlap with heart-specific genes, uncovering 40 pivotal targets. These key targets play central roles in extracellular region, aerobic electron transport chain, cellular respiration, positive regulation of apoptotic process, and cardiac muscle contraction. Collectively, they offer novel insights into the molecular mechanisms underlying the impact of sepsis on cardiac function. Notably, PTGDS emerges as a promising candidate, achieving an AUC of 0.898 in ROC curve for diagnosing sepsis. This high diagnostic value underscores its potential as a powerful tool for early diagnosis and monitoring of disease progression in clinical settings. Furthermore, leveraging single-cell RNA sequencing techniques, we pinpointed the expression landscape of PTGDS within various cells. It was predominantly expressed in cell clusters 2, 4, and 8, corresponding to NK cells and T cells, revealing intricate interactions between inflammation, immunity, and cardiomyocyte homeostasis.

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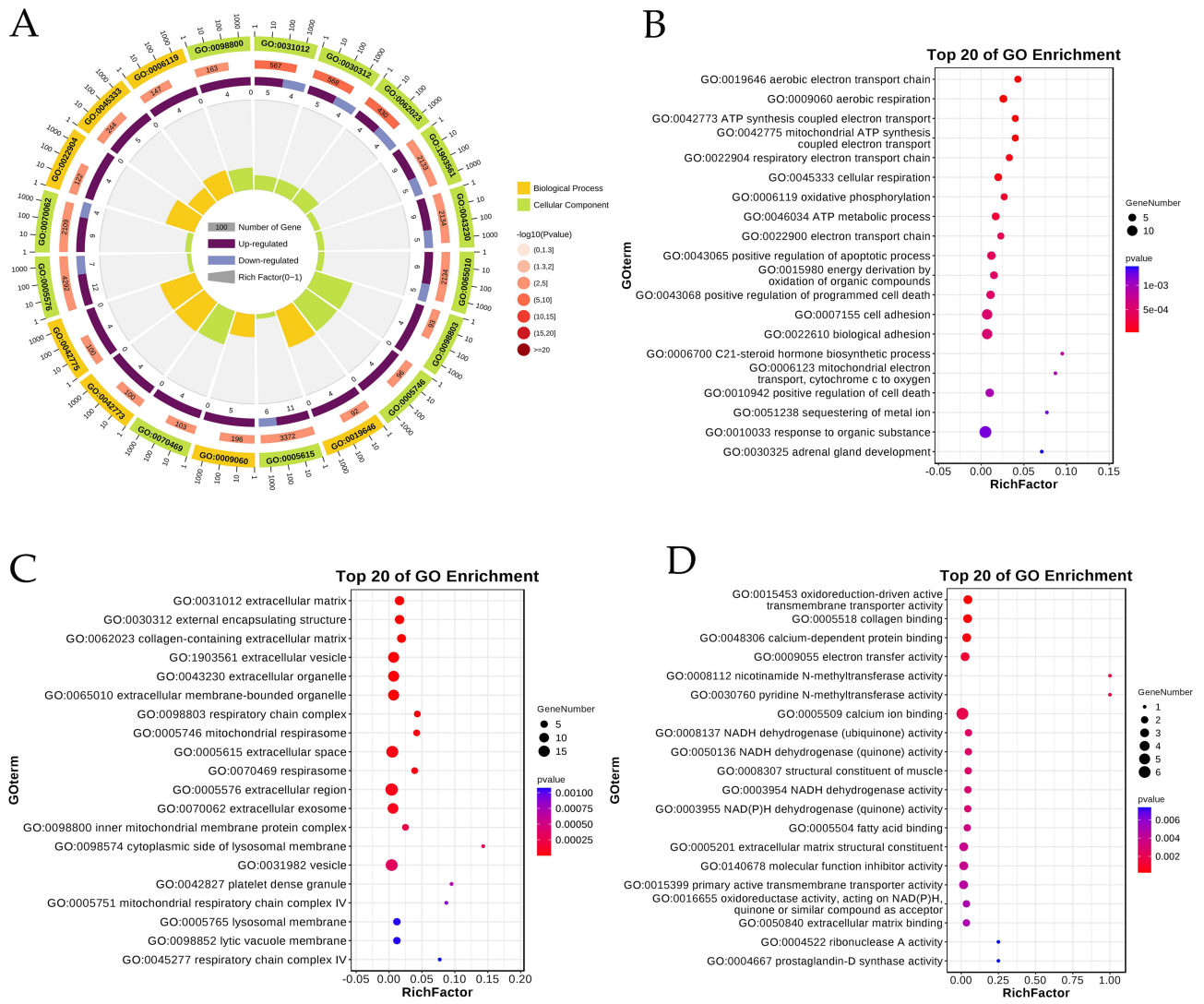

Figure 5 GO analysis. (**A**) The top 20 most significantly enriched gene sets resulting from GO analysis included 7 BP and 13 CC. (**B**–**D**) The top 20 enriched BP, CC and MF of the intersected genes, respectively.

In SCM, a plethora of inflammatory mediators contribute to myocardial injury and functional impairment through various pathways, such as the damaging of macrophages, triggering of inflammatory cascades, inhibition of calcium handling, impairing mitochondrial function, stimulation of nitric oxide (NO) production, and activation of myocyte hydrolases.[21,25] Mitochondrial dysfunction plays a crucial role in the pathophysiology of SCM, potentially leading to inadequate energy supply and enhanced oxidative stress in myocardial cells.[26,27]

Prostaglandin D2 synthase (PTGDS) is an enzyme that catalyzes the conversion of prostaglandin H2 (PGH2) to prostaglandin D2 (PGD2).[28] PGD2 interacts with DP1 and DP2 receptors, playing a critical role in modulating inflammatory responses. There exists a close association between PTGDS and inflammation. PTGDS participates in the initiation and progression of inflammatory processes through the synthesis of PGD2. Research has highlighted the significance of PTGDS in various types of cancer, demonstrating tissue-specific roles.[29] Moreover, PTGDS exhibits a strong correlation with alterations in synovial inflammation in osteoarthritis (OA), influencing disease pathology.[30] Additionally, it has been shown to affect the anti-inflammatory functions of astrocytes mediated by DJ-1 gene regulation in Parkinson's disease contexts.[31]

Studies have demonstrated that hydrogen gas (H2) mitigates brain injury in septic mice by modulating protein expression levels including that of PTGDS.[32] Similarly, memantine (MEM) treats neonatal mice suffering from sepsis

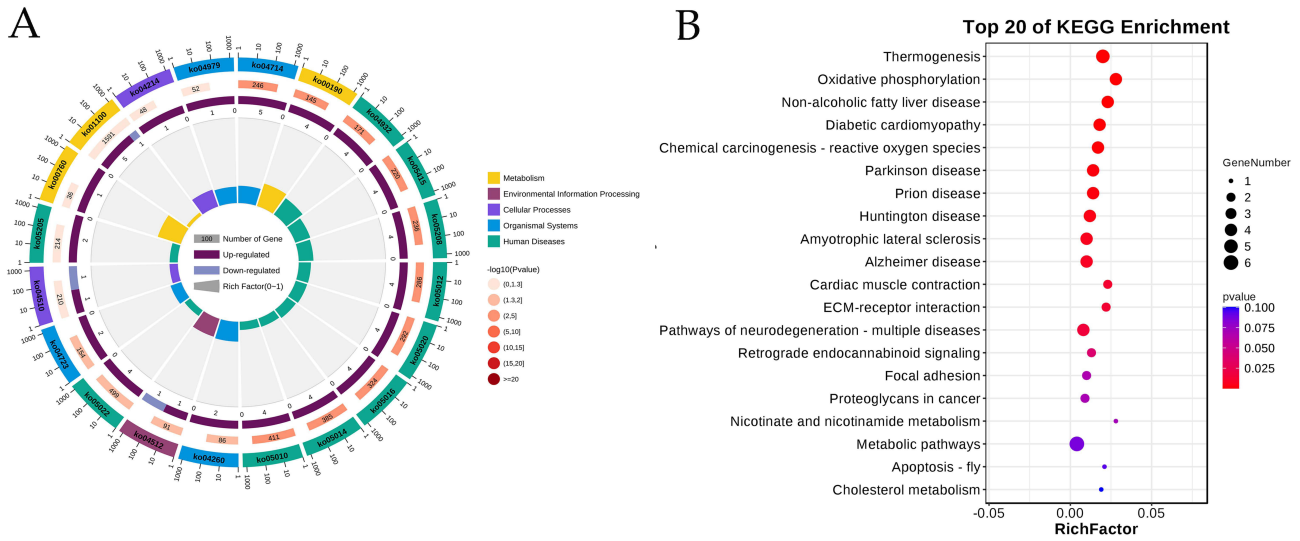

Figure 6 KEGG analysis. (**A**) Among the top 20 gene sets identified as significantly enriched through KEGG pathway analysis, three pathways were related to metabolism, one pathway pertained to environmental information processing, two pathways were associated with cellular processes, four pathways were linked to organismal systems, and ten pathways were categorized under human diseases. (**B**) The top 20 signaling pathways enriched by the intersected genes.

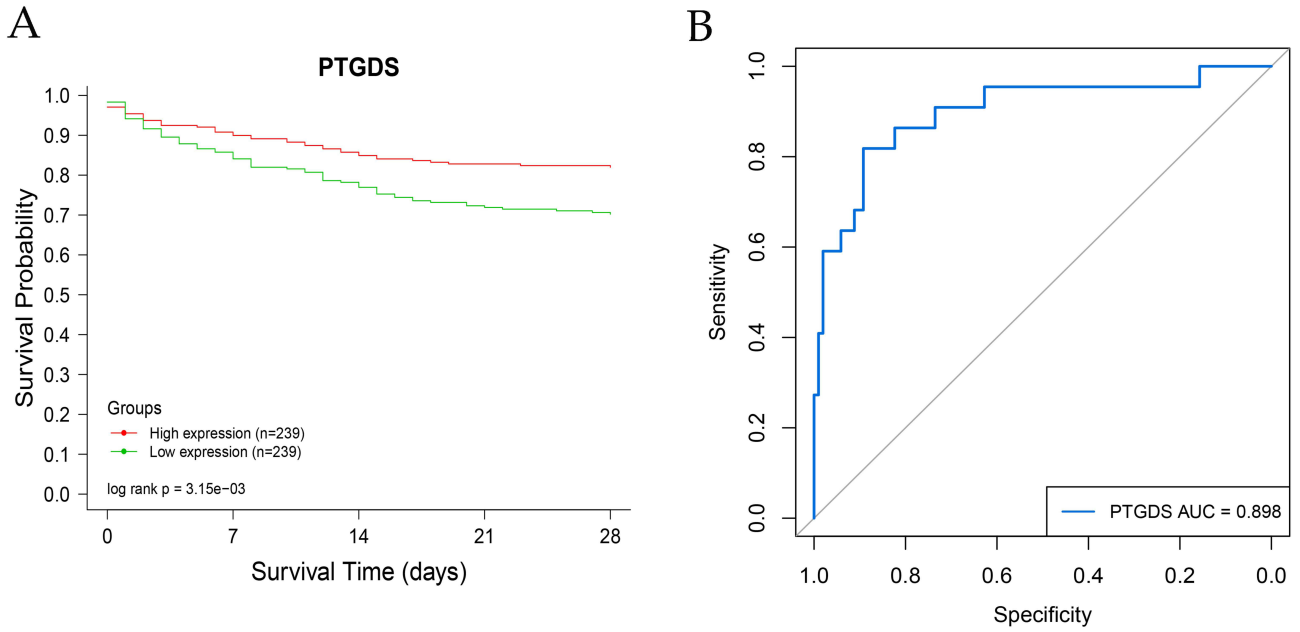

Figure 7 Diagnostic and prognostic analysis. (**A**) The 28-day survival curve of PTGDS in sepsis patients revealed that patients with high PTGDS expression exhibited a better survival rate than those with low expression. The X-axis represented days survived, while the Y-axis showed the survival probability. This difference in survival rates was statistically significant ($p < 0.05$). (**B**) With an AUC value of 0.898, the findings indicated a certain diagnostic accuracy of PTGDS in the context of SCM.

and meningitis by significantly upregulating anti-inflammatory factors such as PTGDS.[33] Given our research findings corroborated by previous studies, we propose that PTGDS along with its metabolite PGD2 may exert significant influence during the pathophysiological course of SCM. Our data suggest that PTGDS holds potential as a target gene for evaluating the severity and prognosis of sepsis.

Placing PTGDS in the context of other emerging biomarkers for SCM helps to clarify its potential unique contribution. While recent studies have explored markers like soluble ST2 (reflecting myocardial stress and fibrosis), growth differentiation factor-15 (involved in inflammation and apoptosis), and microRNAs (eg, miR-21, miR-155 regulating hypertrophic and inflammatory pathways), our identification of PTGDS introduces a distinct element: a direct link to the prostaglandin synthesis pathway with

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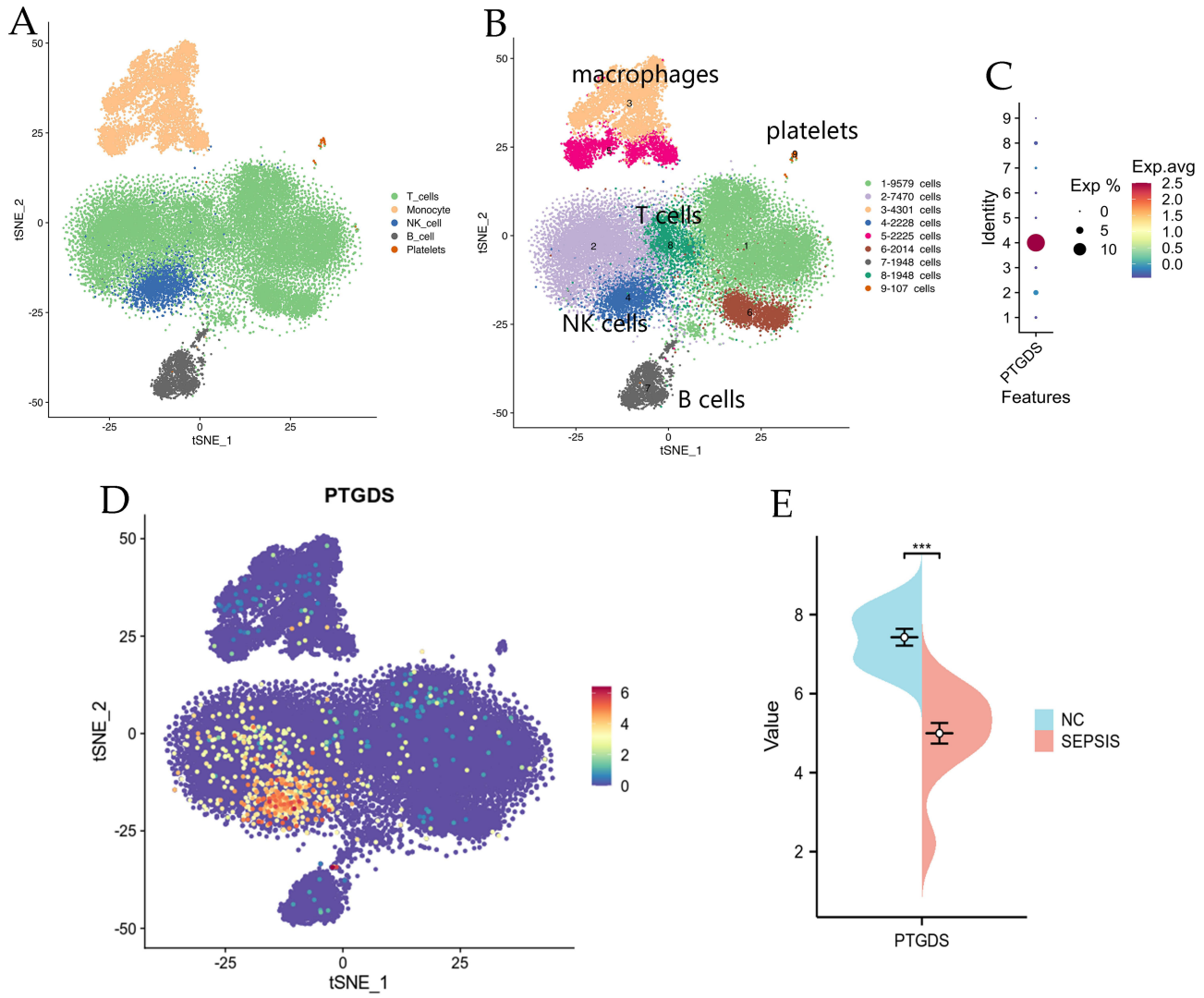

Figure 8 Single-cell RNA sequencing and quantitative analysis. (**A**) After identification via marker genes, the mixed cell population was primarily classified into T cells, monocytes, NK cells, B cells, and platelets. (**B**) Post dimensionality reduction and clustering, a total of nine distinct cell clusters were obtained. Specifically, clusters 3 and 5 were designated as monocytes, cluster 4 represented NK cells, clusters 1, 2, 6, and 8 are identified as T cells, cluster 7 corresponds to B cells, and cluster 9 comprised platelets. (**C**) PTGDS expression was predominantly observed in cell clusters 2, 4, and 8. (**D**) The expression of PTGDS was mainly observed in NK cells and T cells. (**E**) The expression level of PTGDS in the sepsis group was significantly lower than that in the normal group (***p < 0.001).

specific expression in immune cells. Unlike markers that primarily indicate downstream injury or stress, PTGDS may be involved in earlier regulatory processes at the immune-cardiac interface. This suggests that a multi-marker panel, combining established markers of injury (troponins), stress (BNP), and novel regulators of inflammation (PTGDS), could potentially offer a more comprehensive and earlier assessment of SCM risk and pathogenesis.

Despite the absence of literature explicitly connecting PTGDS with SCM in Pubmed searches, SCM's etiology encompasses a broad range encompassing inflammatory reactions, mitochondrial dysfunction, and apoptosis among others. Through GO and KEGG analyses, we unveiled PTGDS' associations with aerobic electron transport chain, cellular respiration, positive regulation of the apoptotic process, and cardiac muscle contraction. These functional pathways bear relevance to the pathogenesis of SCM, suggesting that PTGDS might indirectly influence the development of SCM by affecting one or multiple aspects of these physiological processes. For instance, PTGDS could potentially exert its effects by modulating the release of pro-inflammatory cytokines or by impacting metabolic pathways and signaling cascades in cardiomyocytes. Our identification of PTGDS as a key biomarker associated with sepsis and its potential role in SCM opens up promising avenues for novel therapeutic strategies. Given that PTGDS catalyzes the production of PGD2, which signals through DP1 and DP2 receptors, our findings suggest that the PTGDS/PGD2 axis could be a viable target for drug intervention. For instance, the

development of specific PTGDS inhibitors or receptor antagonists could be explored to mitigate the detrimental inflammatory and metabolic effects on the heart during sepsis. Conversely, if further research confirms a cardioprotective role under certain conditions, modulating this pathway with receptor agonists might be beneficial. The high diagnostic AUC value of PTGDS also highlights its utility not just as a biomarker but as a potential companion diagnostic for stratifying patients who might benefit from such targeted therapies. While these possibilities are currently speculative, they are directly grounded in our bioinformatic evidence and the well-defined biology of the PGD2 pathway. Future studies utilizing SCM animal models with genetic or pharmacological manipulation of PTGDS will be crucial to validate these therapeutic hypotheses and translate our findings from bench to bedside. Despite the promising diagnostic performance of PTGDS in our discovery cohort (AUC = 0.898), a key limitation of this study is the lack of external validation. To unequivocally establish the clinical validity of PTGDS, our immediate next step is to validate its expression and diagnostic accuracy in a large, prospectively collected, independent cohort of sepsis patients with and without cardiac involvement. This will be essential to confirm its utility as a robust biomarker and to assess its generalizability across diverse patient populations.

Limitations

The primary limitation of this study is the relatively small sample size, which is inherent to the initial, proof-of-principle nature of this investigation. While this limits the broad statistical power and generalizability of our findings, it is a common starting point for exploratory biomarker discovery using high-throughput technologies.

Conclusions

PTGDS, predominantly expressed in NK cells and T cells, is identified as a novel and robust candidate biomarker for the early detection of sepsis and sepsis-associated cardiac impairment. This discovery also paves the way for a deeper understanding of the disease's underlying mechanisms, which may facilitate the development of novel therapeutic target and strategy.

Data Sharing Statement

RNA sequencing data from 20 sepsis patients and 10 healthy volunteers are available in the China National GeneBank Database (CNGBdb) with https://db.cngb.org/, accession number: CNP0002611.

Ethics Approval and Consent to Participate

The study was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (Ethical Approval No.: ky2018029), and registered under the clinical trial registration number ChiCTR1900021261. This study is in accordance with the Helsinki Declaration.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Hu D, Sheeja Prabhakaran H, Zhang YY, Luo G, He W, Liou YC. Mitochondrial dysfunction in sepsis: mechanisms and therapeutic perspectives. *Crit Care*. 2024;28(1):292. doi:10.1186/s13054-024-05069-w
2. Ni D, Lin X, Deng C, et al. Energy metabolism: from physiological changes to targets in sepsis-induced cardiomyopathy. *Hellenic J Cardiol*. 2024;80:96–106. doi:10.1016/j.hjc.2024.05.010
3. Fan D, Wu R. Mechanisms of the septic heart: from inflammatory response to myocardial edema. *J Mol Cell Cardiol*. 2024;195:73–82. doi:10.1016/j.yjmcc.2024.08.003
4. Hiraiwa H, Kasugai D, Okumura T, Murohara T. Clinical implications of septic cardiomyopathy: a narrative review. *Medicine*. 2024;103(17): e37940. doi:10.1097/MD.0000000000037940
5. Ravikumar N, Sayed MA, Poonsuph CJ, Sehgal R, Shirke MM, Harky A. Septic cardiomyopathy: from basics to management choices. *Curr Prob Cardiol*. 2021;46(4):100767. doi:10.1016/j.cpcardiol.2020.100767
6. Chen D, Wang LJ, Li HL, Feng F, Li JC, Liu L. Progress of heparanase in septic cardiomyopathy: a review. *Medicine*. 2024;103(33):e38901. doi:10.1097/MD.0000000000038901
7. Beesley SJ, Weber G, Sarge T, et al. Septic cardiomyopathy. *Crit Care Med*. 2018;46(4):625–634. doi:10.1097/CCM.0000000000002851
8. Zhao Z, Wang X, Tan F, et al. Exploration and validation of signature genes and immune associations in septic cardiomyopathy. *Ann Clin Exp Hypertens*. 2024;46(1):2302570. doi:10.1080/10641963.2024.2302570
9. Rhodes A, Le E, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45(3):486–552. doi:10.1097/CCM.0000000000002255
10. Sato R, Nasu M. A review of sepsis-induced cardiomyopathy. *J Intensive Care*. 2015; 3:48.
11. Deng Y, Leng L, Wang C, Yang Q, Hu Y. Analyzing the molecular mechanism of Scutellaria Radix in the treatment of sepsis using RNA sequencing. *BMC Infect Dis*. 2024;24(1):695. doi:10.1186/s12879-024-09589-2
12. Srzić I, Nesek Adam V, Tunjić Pejak D. SEPSIS definition: what's new in the treatment guidelines. *Acta Clinica Croatica*. 2022;61(Suppl 1):67–72. doi:10.20471/acc.2022.61.s1.11
13. Ge SX, Son EW, Yao R. iDEP: an integrated web application for differential expression and pathway analysis of RNA-Seq data. *BMC Bioinf*. 2018;19(1):534. doi:10.1186/s12859-018-2486-6
14. Lonsdale J, Thomas J, Salvatore M. The genotype-tissue expression (GTEx) project. *Nat Genet*. 2013;45(6):580–585. doi:10.1038/ng.2653
15. von Mering C, Huynen M, Jaeggi D, Schmidt S, Bork P, Snel B. STRING: a database of predicted functional associations between proteins. *Nucleic Acids Res*. 2003;31(1):258–261. doi:10.1093/nar/gkg034
16. Sa A, Balhoff J, Carbon S, et al. The gene ontology knowledgebase in 2023. *Genetics*. 2023;224(1). doi:10.1093/genetics/iyad031.
17. Kanehisa M. The KEGG database. *Novartis Found Symp*. 2002;247:91–101; discussion101–103,119–128,244–152.
18. Bp S, Klein KPM, van Vught LA, et al. A molecular biomarker to diagnose community-acquired pneumonia on intensive care unit admission. *Am J Respir Crit Care Med*. 2015;192(7):826–835. doi:10.1164/rccm.201502-0355OC
19. Martínez Pérez JA, Pérez Martin PS. [ROC curve]. *Med Familia-SEMERGEN*. 2023;49(1):101821. Indonesian. doi:10.1016/j.semerg.2022.101821
20. Tabone O, Mommert M, Jourdan C, et al. Endogenous retroviruses transcriptional modulation after severe infection, trauma and burn. *Front Immunol*. 2018;9:3091. doi:10.3389/fimmu.2018.03091
21. Song J, Fang X, Zhou K, Bao H, Li L. Sepsis-induced cardiac dysfunction and pathogenetic mechanisms (Review). *Mol Med Rep*. 2023;28(6). doi:10.3892/mmr.2023.13114
22. Ye H, Hu H, Zhou X, Dong M, Ren J. Targeting ferroptosis in the maintenance of mitochondrial homeostasis in the realm of septic cardiomyopathy. *Curr Opin Pharmacol*. 2024;74:102430. doi:10.1016/j.coph.2023.102430
23. Müller-Werdan U, Vogt A, Werdan K. [Septic cardiomyopathy-diagnosis and estimation of disease severity]. *Medizinische Klinik-Intensivmedizin Notfallmedizin*. 2025;120(3):185–191. German. doi:10.1007/s00063-024-01109-z
24. Han Z, Quan Z, Zeng S, Wen L, Wang H. Utilizing omics technologies in the investigation of sepsis-induced cardiomyopathy. *Int J Cardiol Heart Vasculature*. 2024;54:101477. doi:10.1016/j.ijcha.2024.101477
25. Bi CF, Liu J, Yang LS, Zhang JF. Research progress on the mechanism of sepsis induced myocardial injury. *J Inflamm Res*. 2022;15:4275–4290. doi:10.2147/JIR.S374117
26. Fang X, Wang J. [Role of mitochondrial dysfunction in the pathogenesis of septic cardiomyopathy]. *Zhonghua Wei zhong Bing Ji Jiu Yi Xue*. 2018;30(2):189–192. Dutch. doi:10.3760/cma.j.issn.2095-4352.2018.02.019
27. Neri M, Riezzo I, Pomara C, Schiavone S, Turillazzi E. Oxidative-nitrosative stress and myocardial dysfunctions in sepsis: evidence from the literature and postmortem observations. *Mediators Inflamm*. 2016;2016:3423450. doi:10.1155/2016/3423450
28. Munkholm K, Peijs L, Kessing LV, Vinberg M. Reduced mRNA expression of PTGDS in peripheral blood mononuclear cells of rapid-cycling bipolar disorder patients compared with healthy control subjects. *Int J Neuropsychopharmacol*. 2014;18(5). doi:10.1093/ijnp/pyu101
29. Pan J, Zhang L, Huang J. Prostaglandin D2 synthase/prostaglandin D2/TWIST2 signaling inhibits breast cancer proliferation. *Anti-Cancer Drugs*. 2021;32(10):1029–1037. doi:10.1097/CAD.0000000000001111
30. Tu B, Fang R, Zhu Z, Chen G, Peng C, Ning R. Comprehensive analysis of arachidonic acid metabolism-related genes in diagnosis and synovial immune in osteoarthritis: based on bulk and single-cell RNA sequencing data. *Inflammation Res*. 2023;72(5):955–970. doi:10.1007/s00011-023-01720-4
31. Lee K, Choi D, An J, Jou I, Park S, Joe E. A Parkinson's disease gene, DJ-1, regulates anti-inflammatory roles of astrocytes through prostaglandin D2 synthase expression. *IBRO Rep*. 2019;6:S124–s125. doi:10.1016/j.ibror.2019.07.396
32. Xie K, Lian N, Kan Y, et al. iTRAQ-based quantitative proteomic analysis of the therapeutic effects of 2% hydrogen gas inhalation on brain injury in septic mice. *Brain Res*. 2020;1746:147003. doi:10.1016/j.brainres.2020.147003
33. Yu JY, Zhang B, Peng L, et al. Repositioning of memantine as a potential novel therapeutic agent against meningitic E. coli-induced pathogenicities through disease-associated Alpha7 cholinergic pathway and RNA sequencing-based transcriptome analysis of host inflammatory responses. *PLoS One*. 2015;10(5):e0121911. doi:10.1371/journal.pone.0121911