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Exploratory transcriptomic analysis of 7-day outcomes in patients receiving extracorporeal membrane oxygenation for cardiogenic shock after acute myocardial infarction

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Abstract

Background: We performed an exploratory secondary analysis of a public transcriptomic dataset to identify gene-expression patterns associated with 7-day outcome among 14 patients receiving ECMO for cardiogenic shock after acute myocardial infarction.

Methods: The microarray dataset (GSE93101, n = 14) was retrieved from the Gene Expression Omnibus online database. Differential expression, weighted gene co-expression network analyses (WGCNA), Gene Ontology, and Kyoto Encyclopedia of Genes and Genomes enrichment analyses were performed. To identify the top five hub genes, we used the mutual construction of the protein–protein interaction network and the Cytoscape software. Subsequently, a gene–microRNA (miRNA) network was established to identify the miRNAs that potentially regulate these hub genes.

Results: Ten genes were obtained when those in the two highest correlation modules of WGCNA were intersected with the differentially expressed genes. A total of 104 differentially expressed genes were found to be associated with oxidoreductase activity and metabolic pathways. We found the top five hub genes using the Cytoscape software: CD68, C8A, NR1H4, and ADGRE1 genes were downregulated, while TMPRSS6 was upregulated. TMPRSS6 had the highest degree of affinity and was regulated by 29 miRNAs, while CD68, NR1H4, CD163, and C8A were regulated by 18, 14, 14, and 2 miRNAs, respectively. Although CD163 was not in the top five hub genes, it is regulated by more miRNAs.

Conclusion: Through comprehensive analysis, CD68, which was regulated by 18 miRNAs, emerged as a promising prognostic biomarker for ECMO after AMI, and the mechanism may reflect macrophage activation and differentiation, thereby modulating postinfarction inflammatory responses and tissue repair.

Keywords: Acute myocardial infarction, Bioinformatics analysis, Extracorporeal membrane oxygenation, Hub gene, miRNA, WGCNA

Introduction

Acute myocardial infarction (AMI) is localized necrosis caused by myocardial ischemia and hypoxia due to coronary artery occlusion, resulting in a sharp reduction or even interruption of blood supply.[1] AMI complicated by cardiogenic shock is characterized by insufficient perfusion of peripheral organs and tissues and damage to vital organs due to ischemia and hypoxia. The main reason is cardiac dysfunction, and the global incidence is about 3%–13%.[2] Effective resuscitation of the patient's hemodynamic status is the premise and key to the successful application of emergency percutaneous coronary intervention, which can greatly improve the patient's prognosis.[3] Extracorporeal membrane oxygenation (ECMO) is a recent technology that can replace the pumping function of the heart, maintain blood circulation, and provide effective respiratory and circulatory support.[4] Although ECMO plays an important role in rescuing patients with cardiogenic shock after AMI, the mortality rate remains high. Therefore, it is of great significance to explore the molecular markers and targets that can affect the prognosis of ECMO treatment of cardiogenic shock after AMI.

Currently, high-throughput experimental methods such as microarray analysis have been widely used in differentially expressed gene (DEG) analysis.[5, 6] A large amount of microarray data has been stored in public databases. The GEO (http://www.ncbi.nlm.nih.gov/geo/) is an international public repository of high-throughput microarray data submitted by researchers and next-generation sequence-functional genomic datasets created by the National Center for Biotechnology Information of the National Library of Medicine in 2000. This resource archives raw and processed data or metadata that can be indexed, cross-linked, and searched. The GEO Repository archives and freely distributes microarray, next-generation sequencing, and other

The datasets generated during and/or analyzed during the current study are available in the Gene Expression Omnibus under accession GSE93101.

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forms of high-throughput functional genomic data, which are currently available in the public domain for over 1 million samples.

Because of the high mortality rate and the need for more personalized therapeutic targets, it is essential to explore the underlying molecular mechanisms and prognostic biomarkers associated with ECMO outcomes in this specific patient cohort. Therefore, this study was designed as a retrospective secondary bioinformatics analysis of the publicly available gene expression dataset GSE93101. Our hypothesis is that specific gene expression profiles and their associated molecular processes are significantly correlated with the clinical prognosis (successful vs. failure) of patients with cardiogenic shock after AMI treated with ECMO.

Materials and methods

Microarray data sourcing and processing

This study was a retrospective secondary bioinformatics analysis utilizing publicly available gene expression data. The microarray dataset GSE93101 was retrieved from the Gene Expression Omnibus (GEO) database (National Center for Biotechnology Information). There were 33 peripheral blood mononuclear cell samples collected at the time of ECMO initiation from patients with successful or failed ECMO outcomes, including 14 patients with AMI, 6 with acute myocarditis, 6 with dilated cardiomyopathy, 3 with congestive heart failure, 2 with arrhythmia, and 2 with aortic dissection. We screened 14 patients with post-myocardial infarction (MI) cardiogenic shock from the dataset, of whom 7 had successful outcomes (survived for more than 7 days after ECMO), and 7 had failed outcomes (death or multiple organ failure within 7 days after ECMO). This dataset was generated using the platform GPL570 ([HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array). Sangerbox[7] (http://www.sangerbox.com/tool) was employed to screen differentially expressed genes (DEGs) between successful ECMO and failed ECMO samples. In the present study, genes with a nominal $P < 0.05$ and $|\log_2 (\text{fold change})| > 0.6$ were considered DEGs. To mitigate the risk of false positives inherent in these thresholds, a subsequent two-step filtering strategy was implemented by combining this initial DEG list with a system-level co-expression network analysis (WGCNA), which enabled network construction, gene module identification, and cluster analysis. The co-expression modules were matched with the clinical traits, gene significance (GS), module significance, and module membership were calculated. The association between co-expression modules and treatment outcomes was analyzed to determine highly correlated modules for subsequent analysis (Sangerbox Tool; Soft-thresholding power = 6; Network type was an unsigned weighted network; Min module size = 30; Module merging threshold = 0.35; Hub gene screening: module membership threshold = 0.8, GS threshold = 0.1, weighting threshold = 0.1).

Functional enrichment analyses of the differentially expressed genes

Database for Annotation, Visualization, and Integrated Discovery (DAVID), version 6.8 (http://davidbioinformatics.nih.gov/), an online tool, was applied to evaluate the biological significance of the DEGs. Both Gene Ontology (GO) term enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were performed. Gene functions were categorized into biological processes, molecular functions, and cellular components. According to the hypergeometric distribution test, GO enrichment was considered statistically significant at an FDR <0.05, whereas KEGG pathway enrichment was considered significant at a P value <0.05.

Protein–protein interaction network construction and identification of hub genes

The potential protein–protein interaction (PPI) network of DEGs was constructed using the Search Tool for the Retrieval of Interacting Genes (STRING) database (http://string-db.org/, Confidence score >0.7 as cutoff parameter), which offers integrated associations for protein networks. The PPI network was extracted and subsequently visualized using Cytoscape 3.7.1 (http://www.cytoscape.org). CytoHubba, a plugin of Cytoscape, was employed for calculating the degree of connectivity of protein nodes, and the top five highly connected genes were regarded as hub genes.

Target gene–microRNA network construction

The interactions between DEGs and microRNAs (miRNAs) were predicted using the NetworkAnalyst (http://www.networkanalyst.ca/) tool, a web-based tool integrating miRNA databases such as miRTarBase (https://ngdc.cncb.ac.cn/databasecommons/database/id/167) and TarBase (http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=tarbase/index). A target gene–miRNA network was constructed based on the meta-analysis results of the expression data (miRTarBase was selected in the network construction, and other parameters were based on the site's default).

Results

The GSE93101 dataset, comprising post-MI cardiogenic shock cases, was used, and the cases were categorized into successful and failed groups for differential gene expression analysis. The results showed that there were 104 DEGs, including 37 upregulated genes and 67 downregulated genes (Fig. 1). A total of 23 modules were identified by constructing the weighted gene co-expression network (Fig. 2A). Cluster analysis was performed on the 23 modules. The brown4 and darkolivegreen modules showed the highest absolute correlations with treatment outcome, although these associations did not reach statistical significance ($P > 0.05$). Given their relatively stronger correlations compared with the remaining modules, these two modules were selected for subsequent exploratory analyses (Fig. 2B, C). The genes in these two modules were intersected with the DEGs to identify 10 genes that were highly correlated with prognosis (Fig. 2D, Table 1). To enhance statistical reliability and identify genes most relevant to the prognostic phenotype, we utilized the above-mentioned two-step filtering approach: the identified 104 DEGs with the genes from the two WGCNA modules (brown4 and darkolivegreen) that showed the highest correlation with the clinical outcome. Neither of the two strongest module–outcome correlations reached statistical significance. WGCNA findings were therefore treated as descriptive and hypothesis-generating and were not considered independent validation of the differential-expression results.

Gene enrichment analysis of the DEGs in the success and failure groups was performed. GO analysis results revealed that the majority of DEGs were enriched in molecular functions terms, including oxidoreductase activity, aldehyde dehydrogenase [NAD(P)+] activity, aldehyde dehydrogenase (NAD)

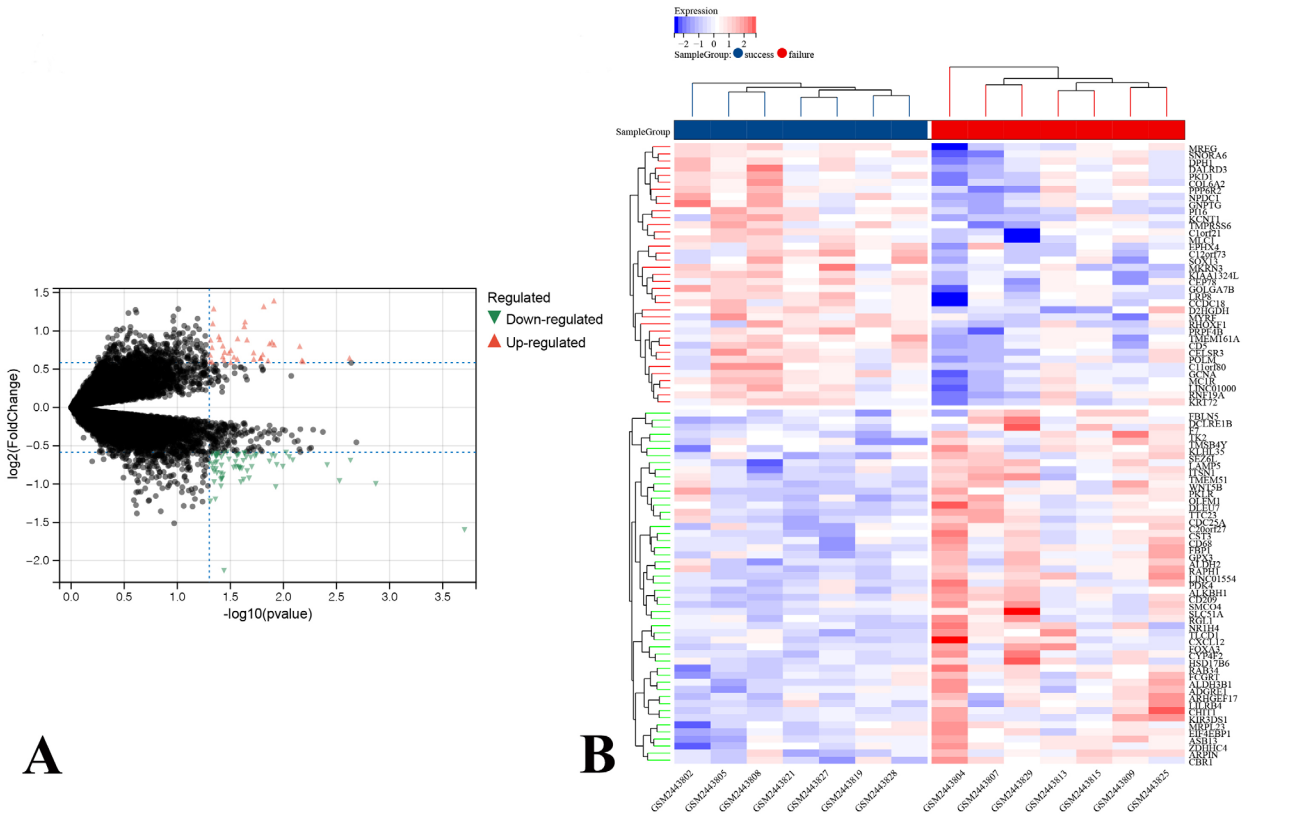


Figure 1. Differential gene expression analysis of the postmyocardial infarction shock success group and the failure group in the GSE93101 dataset. (A) Volcano plot. (B) Cluster analysis of the differentially expressed genes (DEGs). DEGs, differentially expressed genes.

activity, IgG binding, Ral GTPase binding, immunoglobulin binding, acting on the aldehyde or oxo group of donors, NAD or NADP as acceptor, UDP-*N*-acetylglucosamine-lysosomal-enzyme *N*-acetylglucosaminephosphotransferase activity, arginine–tRNA ligase activity, and melanocyte-stimulating hormone receptor activity (Fig. 3A). KEGG pathway analysis demonstrated that DEGs were chiefly enriched in metabolic pathways, including glycolysis/gluconeogenesis, histidine metabolism, beta-alanine metabolism, arachidonic acid metabolism, insulin signaling pathway, cellular senescence, maturity-onset diabetes of the young, pyruvate metabolism, and arginine and proline metabolism (Fig. 3B). These enriched pathways are mainly involved in metabolic regulation, inflammatory signaling, and cellular stress responses, suggesting that metabolic remodeling and inflammation may contribute to the prognosis of patients with cardiogenic shock receiving ECMO support.

Using the STRING database, a PPI network of the DEGs was built. The DEGs were evaluated on account of the degree of connectivity in the network (Fig. 4A). The top five highly connected genes were identified as hub genes (Fig. 4B). The results revealed that TMPRSS6 had the highest connectivity, followed by CD68, C8A, NR1H4, and ADGRE1. CD68, C8A, NR1H4, and ADGRE1 were downregulated while TMPRSS6 was upregulated. CD68 and ADGRE1 were among the 10 genes listed in Table 1. CD68, CD163, and the other network-prioritized genes should be regarded as candidate outcome-associated genes generated from the same discovery dataset. They have not been externally validated as prognostic biomarkers.

Potential miRNAs that closely interacted with the DEGs were recognized on the basis of expression data. Results also indicated that TMPRSS6 had the highest degree of affinity and was regulated by 29 miRNAs, while CD68, NR1H4, CD163, and C8A were regulated by 18, 14, 14, and 2 miRNAs, respectively (Fig. 5). Although CD163 was not among the top five hub genes, it is regulated by more miRNAs.

Discussion

In the current study, differential expression and WGCNA analyses were performed on the expression profile microarray data of peripheral blood mononuclear cells from patients with cardiogenic shock after AMI treated with ECMO, and a total of 104 DEGs were identified, including 37 upregulated and 67 downregulated genes. GO enrichment analysis showed that the identified genes were mainly associated with oxidoreductase activity, representing one of the most significantly enriched functional categories, while KEGG enrichment analysis showed that they were associated with metabolic pathways. Using the PPI network, we identified the top five hub genes using the Cytoscape software and then constructed a gene–miRNA network, providing a theoretical basis for further research.

In AMI complicated by cardiogenic shock, the mortality rate is as high as 60%–80% even with high-dose vasoactive drugs or an intra-aortic balloon pump.[8] Cardiac assist devices can stabilize the hemodynamics of such patients, creating an opportunity for surgery to obtain a higher survival rate. Ventricular assistance has developed rapidly in recent years.[9] After 40 years of development, more clinical experience has been accumulated, treatment has significantly improved, the scope of application

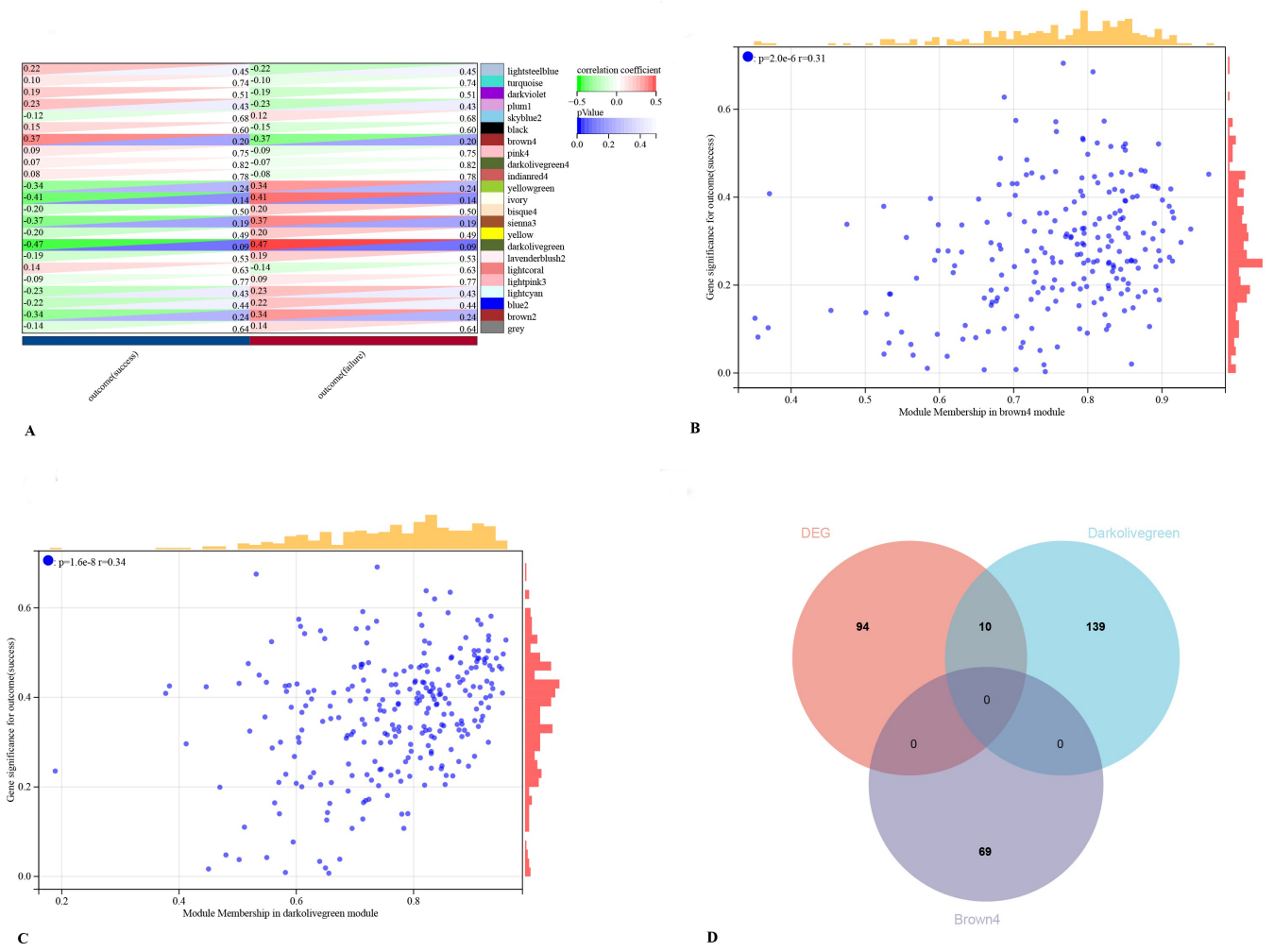


Figure 2. Co-expression network construction performed by WGCNA. (A) Heatmap of correlation between prognosis and module features. (B) Scatter plot of the brown4 module and the outcome. (C) Scatter plot of darkolivegreen module and outcome. (D) Venn diagram of two modules intersected with the DEGs. WGCNA, weighted gene co-expression network analysis.

has greatly expanded, and several patients have been rescued. However, complexity, high cost, and other factors limit its development and use. ECMO is an improved artificial heart–lung machine that can be quickly set up after percutaneous vascular puncture at the bedside and provides circulatory assistance and gas exchange, which is close to full cardiac output, improves the rate of successful electrical defibrillation, and prevents re-cardiac arrest after resuscitation.[10] It can also create favorable conditions for percutaneous coronary intervention[11] and can be used as an alternative to rescue cardiopulmonary resuscitation in patients with ineffective cardiac arrest, known as extracorporeal cardiopulmonary resuscitation.[12] Therefore, the current study aimed to provide a theoretical basis for applying ECMO to more patients with cardiogenic shock after AMI.

To our knowledge, few studies have investigated the genes and molecular processes associated with the prognosis of cardiogenic shock after AMI treated with ECMO. In the present study, we identified several candidate hub genes and pathways that may contribute to prognostic prediction in this patient population. To improve the selection of prognosis-associated genes, we intersected the DEGs and those from the WGCNA-related modules, and then listed the top five genes related to the prognosis using PPI network construction and the Cytoscape software. Among these, CD68 exhibited a high correlation with prognosis.

Transmembrane serine protease 6 (TMPRSS6), the hub gene with the highest connectivity identified in the current study, is a negative regulator of the liver antibacterial polypeptide (hepcidin),

Table 1

Ten Genes Highly Correlated With Prognosis by Venn Diagram

Genes	logFC	*P*
RAB34	−0.961	0.003
GPX3	−1.039	0.012
CST3	−0.625	0.013
ALDH2	−0.653	0.020
SMCO4	−0.779	0.026
RGL1	−0.930	0.038
CD68	−0.650	0.038
ADGRE1	−1.030	0.039
BATF3	−0.857	0.042
RRAS	−0.647	0.043

log2 fold change was calculated as log2(expression in the 7-day survival/success group ÷ expression in the failure group); positive values therefore indicate higher expression in the survival/success group.

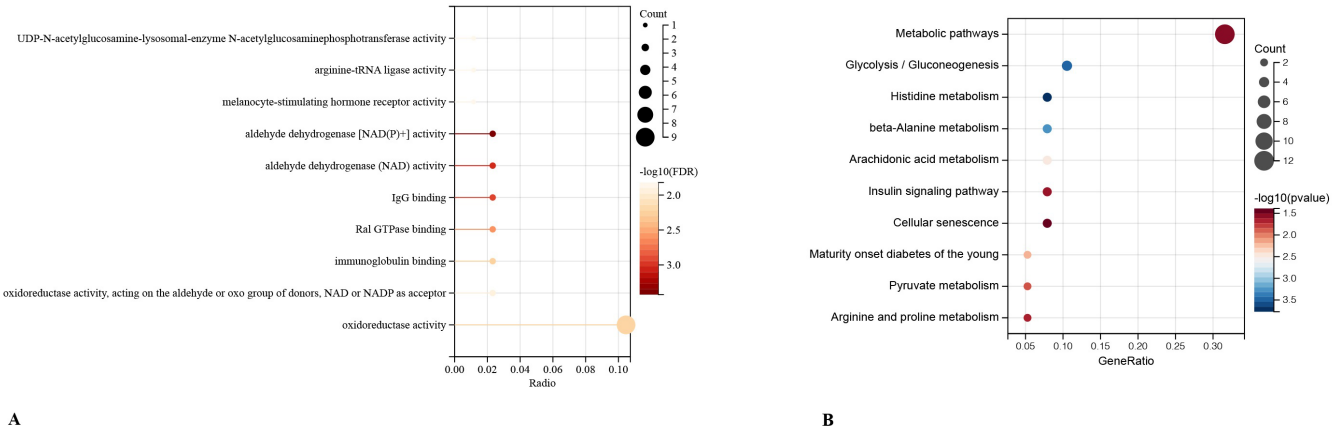


Figure 3. Gene enrichment analysis on all DEGs in the success and failure groups. (A) GO analysis on all DEGs in the success and failure groups. (B) KEGG pathway analysis on all DEGs in the success and failure groups. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

first reported by Du et al.[13] Hepcidin can inhibit intestinal iron absorption by inducing ferroportin degradation, thereby reducing systemic iron availability and impairing erythropoiesis.[14] Therefore, the normal expression of TMPRSS6 plays an important role in maintaining the body's iron homeostasis and erythropoiesis. Iron is involved in several physiological processes, such as oxygen transport, storage, and utilization, and ATP synthesis. Iron has a significant effect on respiration and energy metabolism.[15] TMPRSS6 regulates the body's iron homeostasis mainly by negatively regulating the liver antibacterial polypeptide (hepcidin).[16] A study[17] reported that hypoxia-inducible factor (HIF) may be an upstream regulator of TMPRSS6. As a key factor in the body's response to hypoxia, HIF-1α can induce the expression of various iron metabolism-related proteins, thereby affecting hematopoiesis and iron metabolism. This HIF-dependent regulatory pathway increases TMPRSS6 expression, promotes hemojuvelin (HJV) shedding on cell membranes, and reduces hepcidin expression in hepatocytes.[18] In a hypoxic environment, hepcidin expression can be inhibited by reducing the SMAD signaling in hepatocytes.[19] Based on our findings, we hypothesize that following MI, HIF-1α functions as an upstream regulator of TMPRSS6 expression. This regulation impacts the body's iron metabolism homeostasis, consequently affecting respiratory and energy balance. These changes, in turn, may influence the patient's prognosis. Our findings also indicated that 29 miRNAs regulate the expression of TMPRSS6, and further research on the mechanism is warranted.

CD68 is a type I hyperglycosylated transmembrane protein belonging to the lysosome-associated membrane protein family of glycoproteins.[20] It is widely used as a specific marker of mononuclear macrophages in diagnosis and research. Macrophages are a heterogeneous population of cells derived from monocytes,

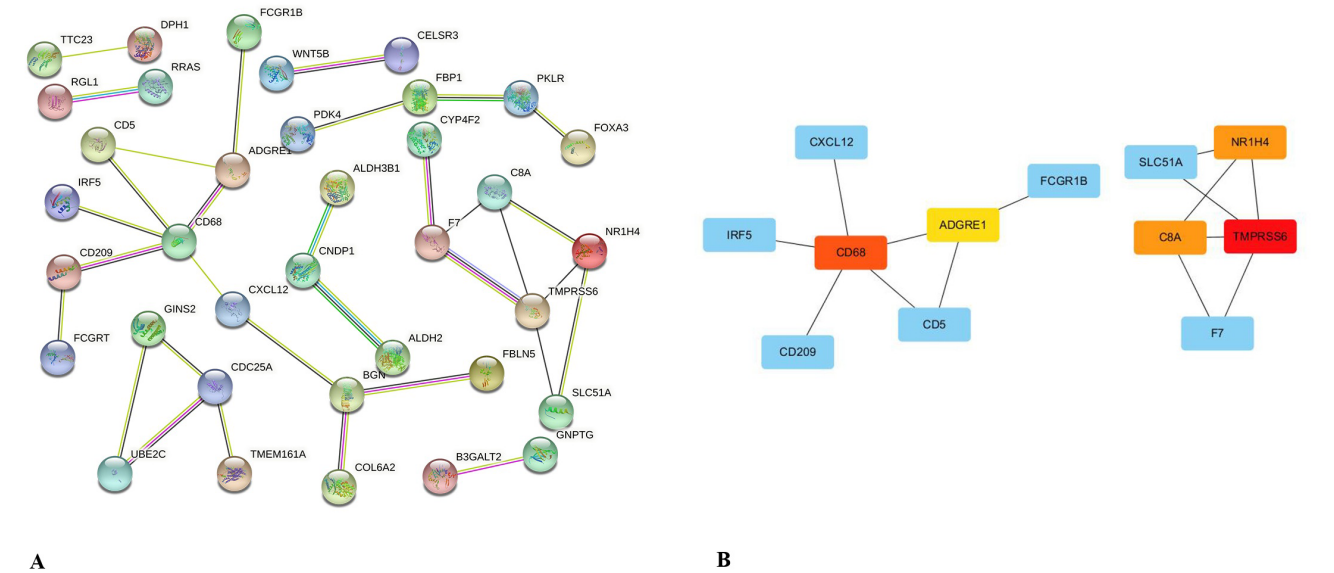


Figure 4. Protein–protein interaction (PPI) network for the DEGs. (A) PPI network evaluated by the String database. (B) The Top five genes were regarded as hub genes by Cytoscape 3.7.1.

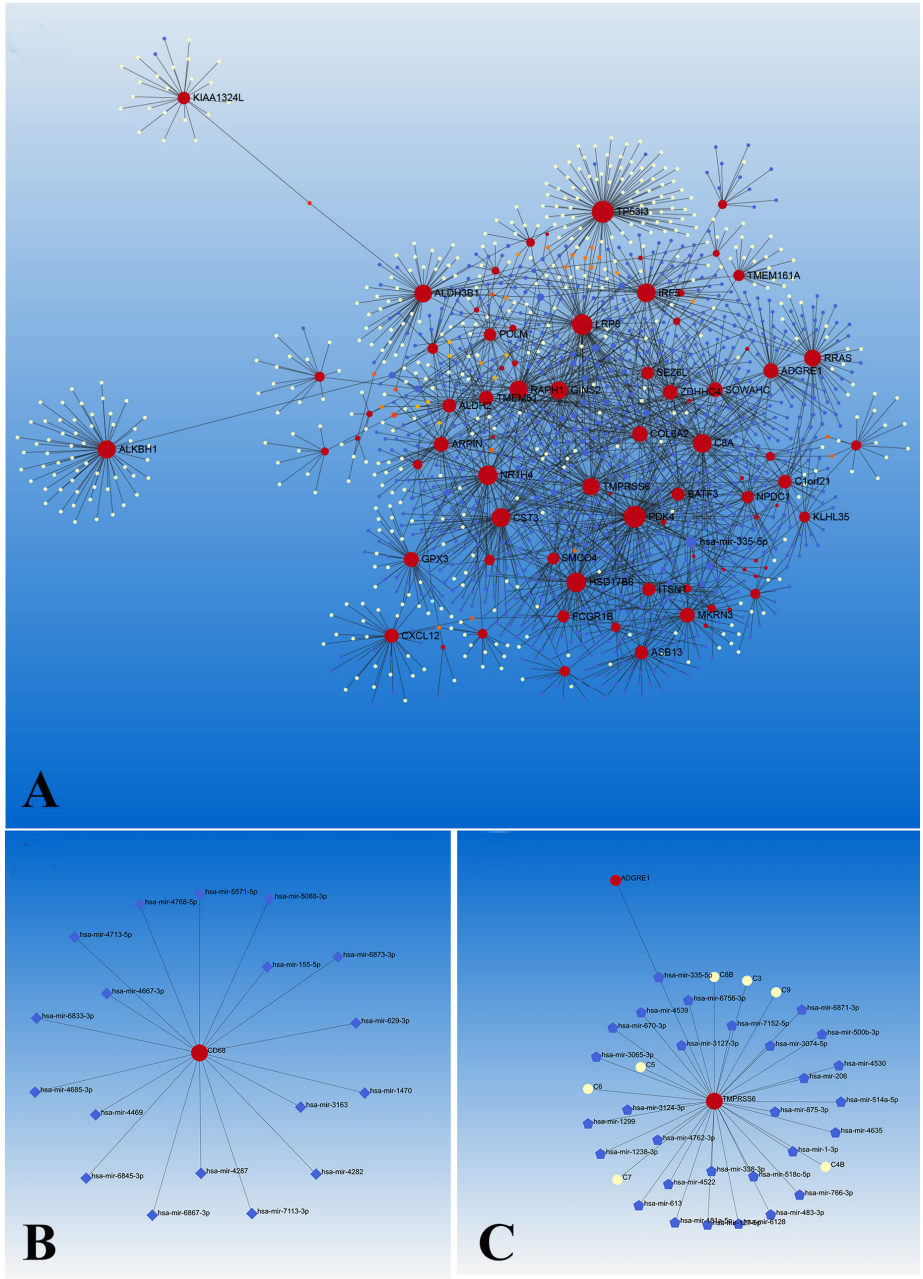


Figure 5. Target gene–miRNA network. (A) The network of the differentially expressed genes and associated miRNAs. (B) CD68 was regulated by 18 miRNAs. (C) TMPRSS6 was regulated by 29 miRNAs. miRNA, microRNA.

constitute an important cellular component of the innate immune system, and have a wide range of functions, including phagocytosis, antigen presentation, and secretion of growth factors, cytokines, and so on.[21] Cardiac remodeling after MI may lead to serious consequences such as heart failure and cardiac rupture. Inflammation and immune responses are the main responses after myocardial injury and play an important role in cardiac remodeling.[22] As important innate immune cells, macrophages play an important role in the inflammatory response and cardiac remodeling after MI through phagocytosis of necrotic cells and debris.[23] Macrophages can also directly secrete cytokines and growth factors to regulate fibroblasts and other cells. It is also reported[23] that monocytes in the peripheral blood migrate to the site of MI and can be activated into two types in different microenvironments: classically activated (M1 type) macrophages and alternatively-activated (M2 type) macrophages. M1 macrophages are induced by lipopolysaccharide, Th1-related cytokines, and chemokines, and they can secrete interleukins, nitrogen oxide, and so on. M1 macrophages also have a certain proinflammatory effect. M2 macrophages can suppress inflammation and promote cell proliferation and angiogenesis. In the present study, we found that CD68 might be one of the markers that indicate the prognosis after ECMO in shock after AMI. The underlying mechanism may be associated with macrophage differentiation. Additionally, CD68, as a marker for macrophages, its expression level can serve as an indicator for assessing the state of inflammation and tissue repair after MI, which may in turn affect the patient's prognosis.

Taken together, although TMPRSS6 demonstrated the highest network connectivity, CD68 was prioritized because it was consistently supported by multiple complementary analytical

approaches and possesses well-established biological functions in macrophage activation, inflammation, and myocardial repair. Therefore, CD68 may represent a more robust and biologically plausible candidate biomarker for prognostic evaluation in ECMO-treated cardiogenic shock after AMI.

Limitations

The present study has several limitations that should be acknowledged. First, the most significant limitation is the small sample size. Our analysis was based on a highly specific subset of patients (n = 14) with cardiogenic shock after AMI treated with ECMO, derived from the publicly available GSE93101 dataset. This small number may compromise the statistical power and robustness of our findings. Therefore, the results presented here should be interpreted with caution and regarded as purely hypothesis-generating rather than confirmatory or conclusive. Second, as a retrospective secondary bioinformatics analysis, we were unable to account for potential clinical confounding factors (eg, comorbidities, shock severity, or specific ECMO parameters) whose detailed data were not consistently available in the public repository, which could influence gene expression and prognosis. Finally, our findings from the regulatory network analysis (miRNA–gene) are purely predictive and lack in vitro or in vivo experimental validation. In addition, the use of relatively lenient statistical thresholds and the absence of multiple testing correction in some analyses may have increased the risk of false-positive findings. Future prospective studies with larger, multi-center cohorts are warranted to validate the identified hub genes and molecular pathways.

Conclusion

This retrospective bioinformatics analysis of the GSE93101 dataset identified prognostic molecular features in ECMO-treated cardiogenic shock patients after AMI. The DEGs were mainly associated with metabolic pathways and oxidoreductase activity. CD68 and TMPRSS6 were identified as the two most promising prognostic hub genes, suggesting potential mechanisms related to macrophage differentiation and iron metabolism. Based on the results of the Venn diagram (Table 1) and Cytoscape analysis, we believe that CD68 emerged as a promising prognostic biomarker for ECMO after AMI. The small sample size, nonsignificant module–outcome correlations, repeated use of the same discovery dataset, and absence of external validation preclude biomarker or causal claims. The findings require confirmation in larger, independent, clinically annotated cohorts.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Liu C contributed to study design, data analysis, and paper writing. Li W contributed to data acquisition and data analysis. Liu S contributed to the study design and reviewed the manuscript.

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Ethical approval of studies and informed consent

Not applicable.

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