Identification of Key Genes and Signaling Pathways Involved in Acute Myocardial Infarction and Potential Biomarkers of Its Consequent Heart Failure Based On Bioinformatics Analysis

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Research

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Abstract

Backgrounds

: Acute myocardial infarction (AMI) is the predominant cause of cardiac death and ischemic heart failure (IHF) worldwide in coronary artery disease (CAD). Although it results from coronary acute occlusion, we in the study explored some key genes involved in the development of AMI and consequent IHF using bioinformatics analysis.

Methods

Utilizing expression data of 52 patients with AMI and 53 controls from GSE66360 and GSE97320 datasets, we screened shared differentially expressed genes (DEGs) in the independent datasets. Functional enrichment analysis and protein-protein interaction (PPI) network were employed. GSE58967 of 111 AMI patients and 46 controls was used to validate the shared DEGs and further analyzed to identify the DEGs in AMI patients with and without heart failure (HF) with the dynamic changes also being evaluated. The receiver operating characteristic (ROC) curves and area under the curve (AUC) were used to validate the diagnostic efficiency.

Results

In the comparison of AMI patients with controls, we identified 105 shared DEGs. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis showed the shared DEGs mainly enriched in immune-related inflammation process and pathways. Filtered with PPI network, 5 genes of *CXCL8*, *CXCL1*, *MMP9*, *FPR1* and *TLR2* were considered as hub genes, which were further validated in GSE59867. Compared with the genes in AMI patients without HF, those of *TNFAIP6*, *ADM*, *TRIB1*, *AQP9* and *IL1R2* associated with ventricular remodeling were found to be significantly high expressed in patients with HF on admission with the AUC of ROC curves was 0.792–0.847 (all $p < 0.05$), which can be used as the potential biomarkers for early prediction of HF after AMI.

Conclusions

These findings based on integrated bioinformatic analysis provide new insights into the important roles of genes to play in the patients with AMI and consequent HF.

Background

Acute myocardial infarction (AMI) remains predominant cause of cardiac death and ischemic heart failure (HF) in coronary heart disease all over the world (1). In 2015, there was an estimated 7.29 million AMI worldwide (2), making it a globally economic burden. Additionally, population-based studies have

found 1–2% of population living with HF, causing large numbers of deaths and huge economic and social costs (3). Although AMI is directly caused by coronary thrombotic acute obstruction based on vulnerable atherosclerotic plaque, the genetic roles to play after AMI are still uncertain. Fortunately, with newly developed gene chip approach, microarray analysis was widely used in cardiovascular study to provide a novel and effective approach for profiling the gene expression and identifying the possible genes and signaling pathways related to AMI and the consequent HF. Therefore, in the present study, we aimed at screening out key genes and pathways involved in the development of AMI and the consequent HF.

Methods

Source of Microarray Data

GSE66360 (49 AMI patients and 50 controls; endothelial cell samples), GSE97320 (3 AMI patients and 3 controls; peripheral blood samples) and GSE59867 (111 AMI patients and 46 controls; peripheral blood samples), were downloaded from Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/) database. GSE66360 and GSE97320 were based on the platform of GPL570 Affymetrix Human Genome U133 Plus 2.0 Array, and GSE59867 was based on the platform of GPL6244 Affymetrix Human Gene 1.0 ST Array. Blood samples in GSE59867 were collected at four time points (admission, discharge, 1 month and 6 months after AMI). In AMI patients of GSE59867, details of the HF development during 6-month follow-up were recorded, containing nine with HF and eight without HF patients. The blood samples at four different time points were used for further analysis of biomarkers for diagnosis of HF after AMI. The flowchart of the study was shown in Fig. 1A.

The screening of DEGs

Raw microarray data were background corrected and normalized by Limma package (4) in R software (version 4.0.1). The DEGs between AMI and controls were also screened out by Limma package under the threshold of |log2(foldchange)| >1 and $p < 0.05$ in GSE66360 and GSE97320, and in GSE59867 the threshold was set at |log2(foldchange)| >0.5 and $p < 0.05$. The differences were visualized in Heatmap and Volcano Plot via pheatmap (5) and ggplot2 (6). To visualize the shared DEGs in GSE66360 and GSE97320, a Venn Diagram online tool (http://bioinformatics.psb.ugent.be/webtools/Venn/) was used to draw a Venn diagram.

Functional enrichment analyses

Biological functions of DEGs obtained from microarray data were explored with GO analysis and KEGG pathway analysis by using Clusterprofiler (7). The cut-off value for significance was set at $p < 0.05$.

Protein-protein interaction (PPI) network construction

A PPI network of shared DEGs was constructed with STRING database (version 11.0; www.string-db.org), and a combined score of > 0.4 was defined as cut-off value. Cytoscape 3.7.1 (www.cytoscape.org) was

applied to visualize PPI network. The hub genes were identified by cytoHubba plug-in according to degrees. The Molecular Complex Detection (MCODE) plugin was used to identify module clusters with the following parameters: Degree Cutoff = 2, Node Score Cutoff = 0.2, K-Core = 2, Max.Depth = 100. The significant module was defined as MCODE score > 5.

Construction of ROC curves and AUC

We constructed ROC curves and calculated the AUC of potential biomarkers of HF via SPSS 23.0 to test the diagnostic efficiency. The statistical significance was set at $p < 0.05$.

Results

Identification of shared DEGs in AMI

To identify key genes involved in AMI, comparisons between patients with AMI and controls were performed in GSE66360 and GSE97320. A total of 432 DEGs were identified in GSE66360, consisting of 93 downregulated and 339 upregulated genes, while a total of 840 DEGs were screened in GSE97320 with 318 downregulated and 522 upregulated genes. Heatmap and volcano plot showed that DEGs in the datasets can easily distinguish patients with AMI from controls (Fig. 1B-1E.). Using Venn Diagram online tool, 105 shared DEGs were obtained, containing 4 downregulated and 101 upregulated genes (Fig. 2A.). The details of the shared DEGs are listed in **Supplementary Table 1**. These shared genes may play an important role in the development of AMI.

GO and KEGG enrichment analyses

To analyze biological classification of the shared DEGs, functional and pathway enrichment analyses were performed. The top 10 GO analysis results (Fig. 2B.) exhibited the changes in biological process (BP), cellular component (CC) and molecular function (MF). BP were significantly enriched in immune response (such as neutrophil activation involved in immune response, response to lipopolysaccharide), CC revealed the DEGs mainly existed in granule membrane or lumen, and MF were mainly enriched in immunoglobulin binding and immune receptor activity. The top 10 KEGG pathways (Fig. 2C.) were mostly enriched in several immune system diseases (tuberculosis, leishmaniasis, amoebiasis), immune-related pathways (IL-17, NF-kappa B and TNF signaling pathway), osteoclast differentiation, and transcriptional mis-regulation in cancer.

PPI network was employed to investigate the interaction between proteins encoded by the shared DEGs. Based on STRING, a total of 105 shared DEGs were filtered into the PPI network, with 103 nodes and 294 edges (Fig. 3A.). By calculating degrees (**Supplementary Fig. 1**) via cytoHubba plug-in, the top 5 highest degree genes, including *CXCL8* (degree = 30), *TLR2* (degree = 29), *MMP9* (degree = 25), *CXCL1* (degree = 24) and *FPR1* (degree = 20) were screened out to be hub genes (Fig. 3A.). The MCODE analysis was used to perform analysis from another perspective. After calculation, the significant module (Fig. 3B.) involved 18 genes including *CXCL1, MMP9, CH13L1, SLPI, MNDA, NCF2, CST3, CXCL16, IL1R2, FCGR2A, P2RY13, HCAR3, CDA, S100A9, HCK, VNN2, AQP9, FCGR3B* and included 2 hub genes, and it was enriched in

immune related response (such as neutrophil and leukocyte related response) as well as IL-17 and chemokine signaling pathway (Table 1**).**

Table 1
The biological process and KEGG pathway enrichment analysis of the cluster genes from the module.

Category	Term	*p* value	Count
BP	GO:0043312 ~ neutrophil degranulation	4.6368E-12	10
BP	GO:0002283 ~ neutrophil activation involved in immune response	4.9286E-12	10
BP	GO:0042119 ~ neutrophil activation	6.0243E-12	10
BP	GO:0002446 ~ neutrophil mediated immunity	6.1450E-12	10
BP	GO:0019730 ~ antimicrobial humoral response	2.0677E-04	3
BP	GO:0045861 ~ negative regulation of proteolysis	3.2880E-04	4
BP	GO:0050727 ~ regulation of inflammatory response	3.8815E-04	4
BP	GO:0045730 ~ respiratory burst	5.7312E-04	2
BP	GO:0052548 ~ regulation of endopeptidase activity	6.2880E-04	4
BP	GO:0052547 ~ regulation of peptidase activity	7.9211E-04	4
BP	GO:0030574 ~ collagen catabolic process	9.2495E-04	2
BP	GO:0006968 ~ cellular defense response	1.1314E-03	2
BP	GO:0050900 ~ leukocyte migration	1.1450E-03	4
BP	GO:0030595 ~ leukocyte chemotaxis	1.2172E-03	3
KEGG	hsa05140 ~ Leishmaniasis	3.5455E-04	3
KEGG	hsa04666 ~ Fc gamma R-mediated phagocytosis	6.1776E-04	3
KEGG	hsa04657 ~ IL-17 signaling pathway	6.3740E-04	3
KEGG	hsa04380 ~ Osteoclast differentiation	1.5624E-03	3
KEGG	hsa05418 ~ Fluid shear stress and atherosclerosis	1.9800E-03	3
KEGG	hsa04145 ~ Phagosome	2.5563E-03	3
KEGG	hsa04062 ~ Chemokine signaling pathway	4.7323E-03	3

Validation and identification of potential genes related to HF

GSE59867 contained gene expression profiles of AMI and HF at four different time points. Comparison between AMI at admission and control (Comparison 1) in GSE59867 revealed 142 DEGs, whereas comparison of samples collected on admission between HF and non-HF patients post AMI (Comparison 2) exhibited 205 DEGs (**Supplementary Fig. 2**). To validate the genes involved in the development of AMI, we overlapped the 105 shared DEGs with Comparison 1. A total of 17 shared genes including *FPR1* were found and the expression change trends were consistent in three datasets (**Supplementary Table 2)**, which indicates that they are important in the development of AMI.

After AMI, a patient may develop left ventricular dysfunction, cardiac remodeling and HF. Through comparing blood samples on admission in AMI patients with and without HF, we found novel genetic biomarkers to predict whether patients would develop HF post AMI in the follow-up. We overlapped the 17 shared genes gotten in above validation analysis with Comparison 2 and identified five DEGs of *TNFAIP6*, *ADM*, *TRIB1*, *AQP9* and *IL1R2*. To validate the diagnostic value of 5 genes, we constructed ROC curves and calculated the AUC of these gene expression levels in GSE59867 (Fig. 4A-4B.). The AUC for *ADM*, *TRIB1*, *TNFAIP6*, *AQP9* and *IL1R2* were 0.833 (95% CI, 0.623-1.000; $p = 0.021$), 0.792 (95%CI, 0.554-1.000; $p = 0.043$), 0.792 (95%CI, 0.546-1.000; $p = 0.043$), 0.792 (95%CI, 0.554-1.000; $p = 0.043$), 0.847 (95%CI, 0.634-1.000; $p = 0.016$) respectively, indicating a good diagnostic value of the genes chosen. Moreover, the expression changes of these five genes were separately compared at four time points after AMI in HF and non-HF group (Fig. 4C-4G.). The five genes were significantly elevated on admission in HF group while in the following time points we observed a gradual decrease in expression between discharge and 1 month, and came to stabilization in 6 months, making them potentially genetic biomarkers for predicting HF post AMI at an early stage.

Discussion

In present study, we identified 5 immune-related hub genes of *CXCL8*, *TLR2*, *MMP9*, *CXCL1* and *FPR1* and immune-related pathways in patients with AMI. In addition, we also identified other 5 DEGs of *TNFAIP6*, *ADM*, *TRIB1*, *AQP9* and *IL1R2* relative to ventricular remodeling in AMI patients complicating HF, which are potential genetic biomarkers for predicting HF at post-MI follow-up.

Based on integrated bioinformatic analysis, we screened out five hub genes and found that they are key in immune response after AMI, which is essential in the dissolution, absorption and reparative process of necrotic myocardium. C-X-C motif chemokine ligand (CXCL) is important in chemotactic recruitment of neutrophils to necrotic myocardium post AMI. *CXCL8*, also known as *IL-8*, got the highest degree in above PPI analysis. Its level upregulated in the infarcted area (8) and is reported to be the major mediator of inflammatory response and may induce neutrophils infiltration after ischemic injury (9). Moreover, higher plasma *IL-8* levels were associated with larger infarct size and adverse outcome in patients with AMI undergoing percutaneous coronary intervention (10). *CXCL1* is also important in inflammation and act as a chemoattractant for neutrophils (11). As different researches reported, the plasma levels of *CXCL1* chemokine in AMI patients were notably higher than in healthy participants (12, 13), suggesting an increased mobilization and recruitment of neutrophils in AMI patients. Matrix metalloproteinases (MMPs)

participated in numerous disease process including cardiovascular disease, while *MMP9* played an important role in regulation of inflammatory response and scar formation post AMI (14). In response to infarction, infiltrating neutrophils and macrophages produce cytokines and chemokines that stimulate production and release of *MMP-9*(15). In turn, *MMP9* regulates the inflammatory response via activating related inflammatory molecules (16), influencing the fibrotic healing process of infarcted myocardium at different stage post-AMI. As a member of Toll-like receptors (TLRs) family, *TLR2* is vital in activating innate immunity and the upregulated level of *TLR2* in circulating inflammatory cells have been reported to be associated with increased infarct size post AMI (17). Besides, anti-*TLR2* therapy exerted cardioprotective effects via reducing leukocyte influx, cytokine production and proapoptotic signaling (18). In our study, we discovered *TLR2* to be a crucial DEG in AMI which is enriched in immune response, suggesting that TLR2 might be tightly associated with dissolution and absorption of necrotic myocardium. Formyl peptide receptors 1 (*FPR1*) is key in regulating inflammation level, cardiomyocyte apoptosis and ventricular remodeling (19). Furthermore, Qin *et al.* revealed that targeting *FPR1* have cardioprotective effects, making it a potential novel target in AMI treatment (20).

Further analysis of the significant module revealed that BP and KEGG pathways mainly enriched in immune responses and pathways, especially IL-17 and chemokine signaling pathway. As is known, massive of cardiomyocytes are lost and a large number of inflammatory cytokines including IL-17 are released post AMI. In turn, IL-17 aggravate cardiomyocytes apoptosis (21) and promotes leukocytes (22) and neutrophils (23) accumulation. Besides, IL-17 could induce macrophages infiltration and activate Nod-like receptor protein 3 inflammasome contributing to aggravating inflammatory response during AMI (24). Moreover, the enhancement of IL-17 signaling contributes to ventricular remodeling in infarcted heart (25, 26), making it a key part in the development of AMI and a novel therapeutic target. On the other hand, chemokines are essential in regulating leukocytes infiltration and modulating infarct angiogenesis as well as fibrous tissue deposition post AMI, among which CXC chemokines and CC chemokines are two major subfamilies. Timely and effective suppression of chemokine signaling may contribute to regulating inflammatory response and preventing heart from adverse remodeling (27). Therefore, the five hub genes and the two signaling pathways were involved in immunomodulation and inflammatory response to different degree, and played central roles in the process of dissolution, removal and repair of necrotic myocardium after AMI.

By further overlapping analysis, we identified *TNFAIP6*, *ADM*, *TRIB1*, *AQP9* and *IL1R2* were related to HF. They have already been reported to be associated with HF and immune response, making them potential biomarkers for predicting HF at an early stage after AMI. Due to AMI, sudden loss of massive cardiomyocytes triggers an intense immune response, inducing the expression of proinflammatory cytokines and chemokines (28). But prolonged or exaggerated inflammation, or improper suppression of inflammation contribute to worsen tissue damage, adverse remodeling, chamber dilation and HF (29). A better understanding of specific immune-related molecules or signaling pathways associated with adverse remodeling and HF post AMI might help to diagnose HF at an early stage and provide novel therapeutic targets (30, 31). The increased level of adrenomedullin (*ADM*) have been confirmed to be correlated with adverse cardiovascular outcomes in patients with AMI and complicating HF in several

different studies (32). Matthew *et al.* found that one nmol/l increase in midregional proadrenomedullin was associated with hazard ratio ranging from 1.77 to 2.79 for death in patients with HF, making it a prognostic biomarker for patients with AMI and HF (33). Aquaporins (AQP) is of great importance in participating in inflammatory process (34), among which *AQP9* is one important member. After AMI, the level of *AQP9* in peripheral blood were notably elevated and *AQP9* gene silencing in rats could significantly attenuate myocardial inflammatory response and improve cardiac function, making it an important target in the treatment of AMI (35). Furthermore, overexpression of miR-212 inhibited *AQP9* and alleviated ventricular remodeling post AMI (36). Dysregulated interleukin 1 (IL-1) signaling following MI can disturb infarct healing and cause collateral damage as well as contributing to maladaptive left ventricular remodeling, while IL-1 activity is tightly regulated at the receptor level (37). Interleukin 1 receptor type 2 (*IL1R2*) can act as a decoy receptor to avoid excessive inflammatory response. Levels of *IL1R2* remained elevated in acute and chronic phase post AMI and it was associated with development of left ventricular remodeling (38), making it a possible biomarker for predicting HF after AMI. However, further studies are needed to confirm the association between TNF Alpha Induced Protein 6 (*TNFAIP6)* and Tribbles pseudokinase 1 (*TRIB1*) with HF. *TNFAIP6* is expressed by many different cell types in response to proinflammatory cytokines and participate in the protection of tissues from the damaging consequences of acute inflammation (39). Plasma *TNFAIP6* levels were significantly higher in a comparison between 135 patients with coronary artery disease (CAD) and 47 patients controls (40). *TRIB1* is correlated with diverse human pathologies, and it is overexpressed in human atherosclerotic arteries and reported to control smooth muscle cell proliferation and chemotaxis in the arterial intima (41). Utilizing the results from > 71000 individuals, Anette *et al.* revealed that *TRIB1* was associated with increased risk of ischemic heart disease and MI in general population (42). The ROC analysis further confirmed that *TNFAIP6*, *ADM*, *TRIB1*, *AQP9* and *IL1R2* are likely to be genetic biomarkers for predicting whether the patients would develop the symptom of HF post AMI during 6 months follow-up.

However, there are some limitations of the present study. Firstly, the DEGs were identified by bioinformatic analysis, and there is a lack of *in vitro* and *in vivo* validation. Secondly, the sample size of patients with HF and non-HF post MI is relatively small, thus needing a larger and multi-center research. Despite these limitations, this study still provides novel insights into the important roles of genes to play in the healing process of inflammation, remodeling and development of AMI and HF.

Conclusions

In the present study, DEGs between samples obtained from AMI and controls were identified. Five DEGs of *CXCL8*, *TLR2*, *MMP9*, *CXCL1* and *FPR1* were found as key genes involved in AMI. Furthermore, IL-17 and chemokine signaling pathway were found to be important in the development of AMI. Further overlapping analysis of DEGs between HF and non-HF patients with AMI identified 5 other genes of *TNFAIP6*, *ADM*, *TRIB1*, *AQP9* and *IL1R2* to be potential genetic biomarkers in HF post AMI. Taken together, several genes associated with inflammation process and ventricular remodeling were found to be highly expressed in AMI patients and other five genes are considered as potential biomarkers for the prediction

of HF. These findings provide new insights into the key roles of genes to play in the healing process AMI and HF through regulating inflammation response and remodeling of infarcted myocardium.

List Of Abbreviations

AMI
Acute myocardial infarction; HF:heart failure; BP:biological process; CC:cellular component; MF:molecular function; CXCL:C-X-C motif chemokine ligand; MMP:matrix metalloproteinases; TLR:Toll-like receptor; FPR1:formyl peptide receptors 1; ADM:adrenomedullin; AQP:aquaporins; IL-1:interleukin 1; IL1R2:interleukin 1 receptor type 2; TNFAIP6:TNF Alpha Induced Protein 6; TRIB1:tribbles pseudokinase 1; CAD:coronary artery disease.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are openly available in GEO at https://www.ncbi.nlm.nih.gov/geo/, reference number (43-45).

Competing interests

The authors declare that they have no competing interests

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Author Contributions

Y.X. have substantial contributions to the conception and design of the study. YX contributed to data collection and analysis, and drafted the manuscript; Y.X. and Y.Y. contributed to the critical revision and final approval of the manuscript.

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Figures

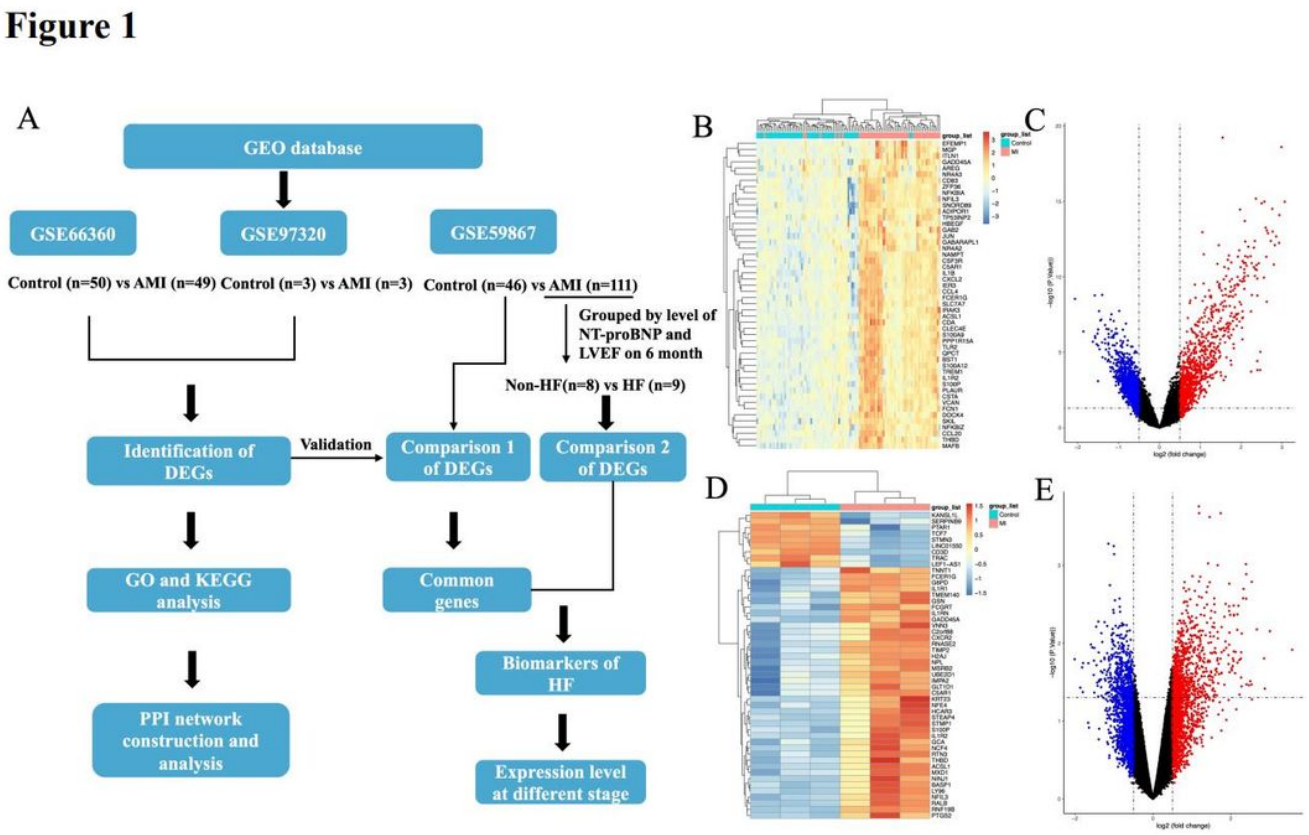


Figure 1

Design of the study and heatmap and volcano plot. A, Flowchart of study procedure; B-C, Heatmap and volcano plot exhibited the DEGs in GSE66360; D-E, Heatmap and volcano plot exhibited the DEGs in GSE97320.

Figure 2

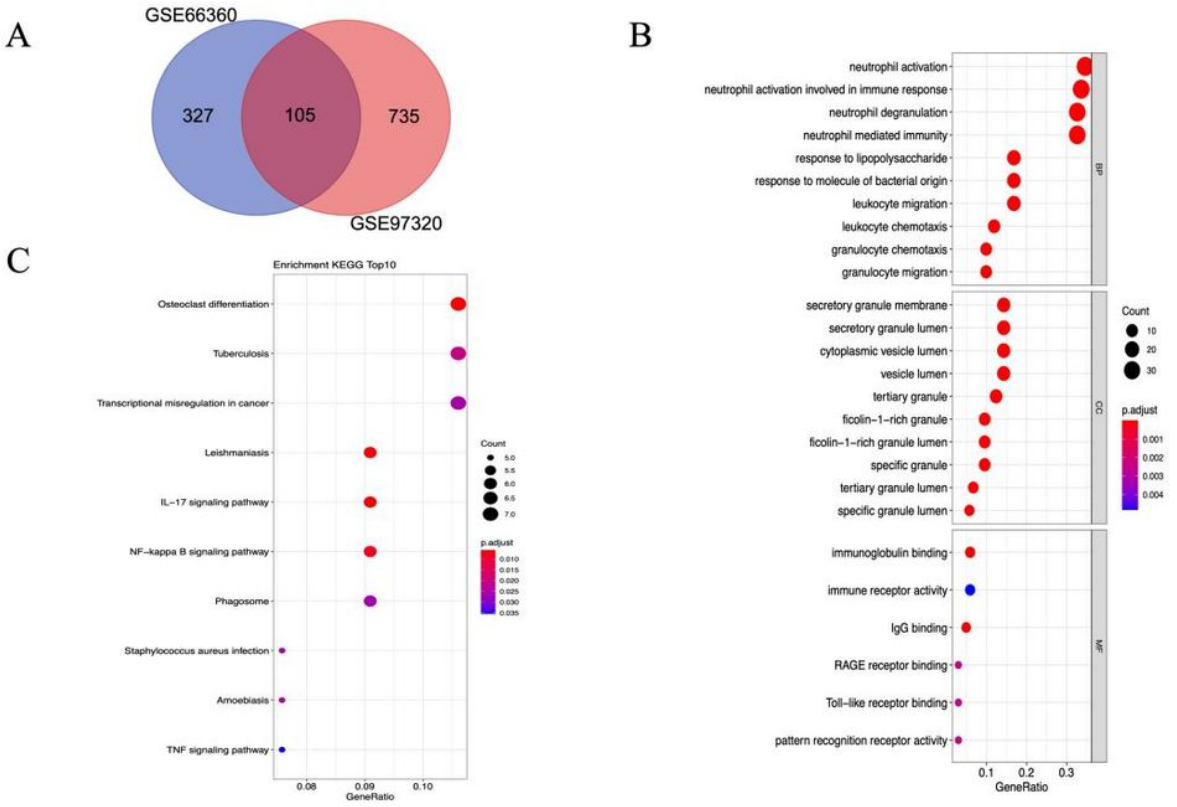


Figure 2

GO and KEGG enrichment of the shared DEGs. A, Venn Diagram showed the share DEGs in GSE6630 and GSE97320; B, Top 10 GO analysis results including BP, CC and MF; C, Top 10 enriched KEGG pathways.

Figure 3

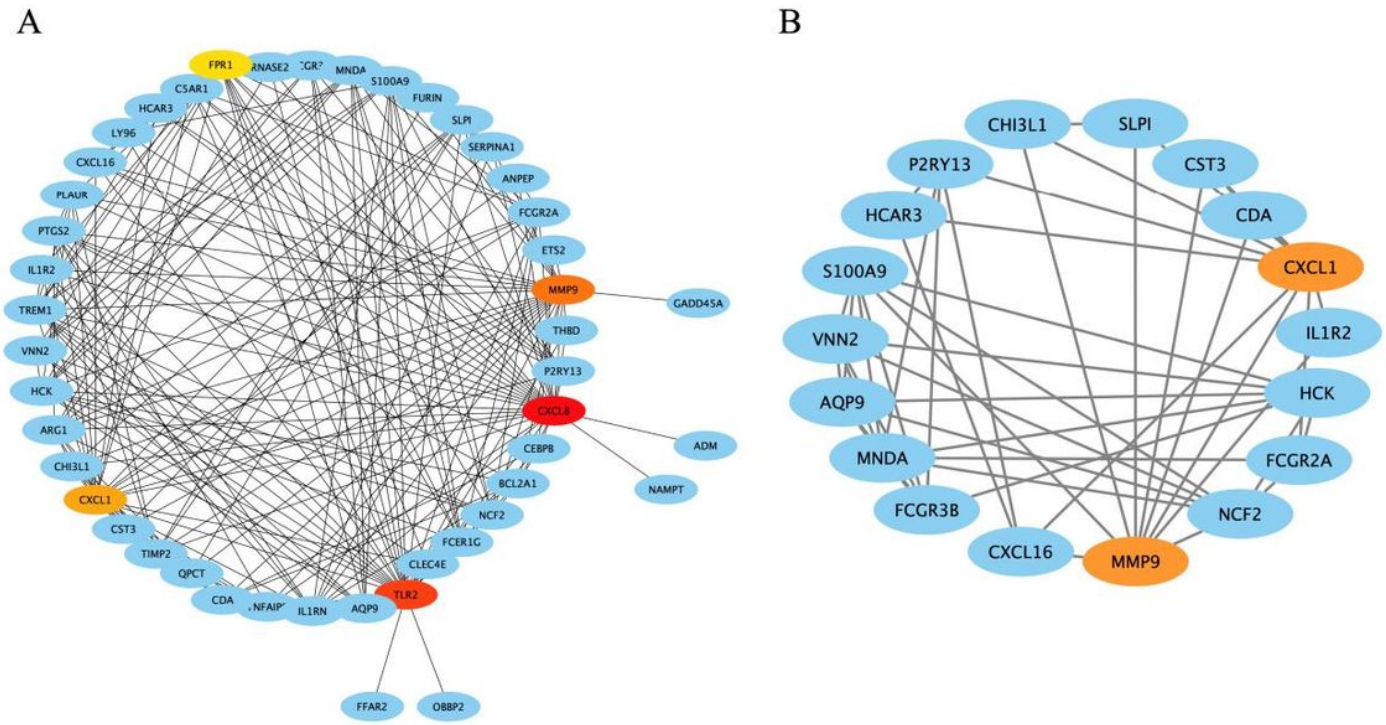
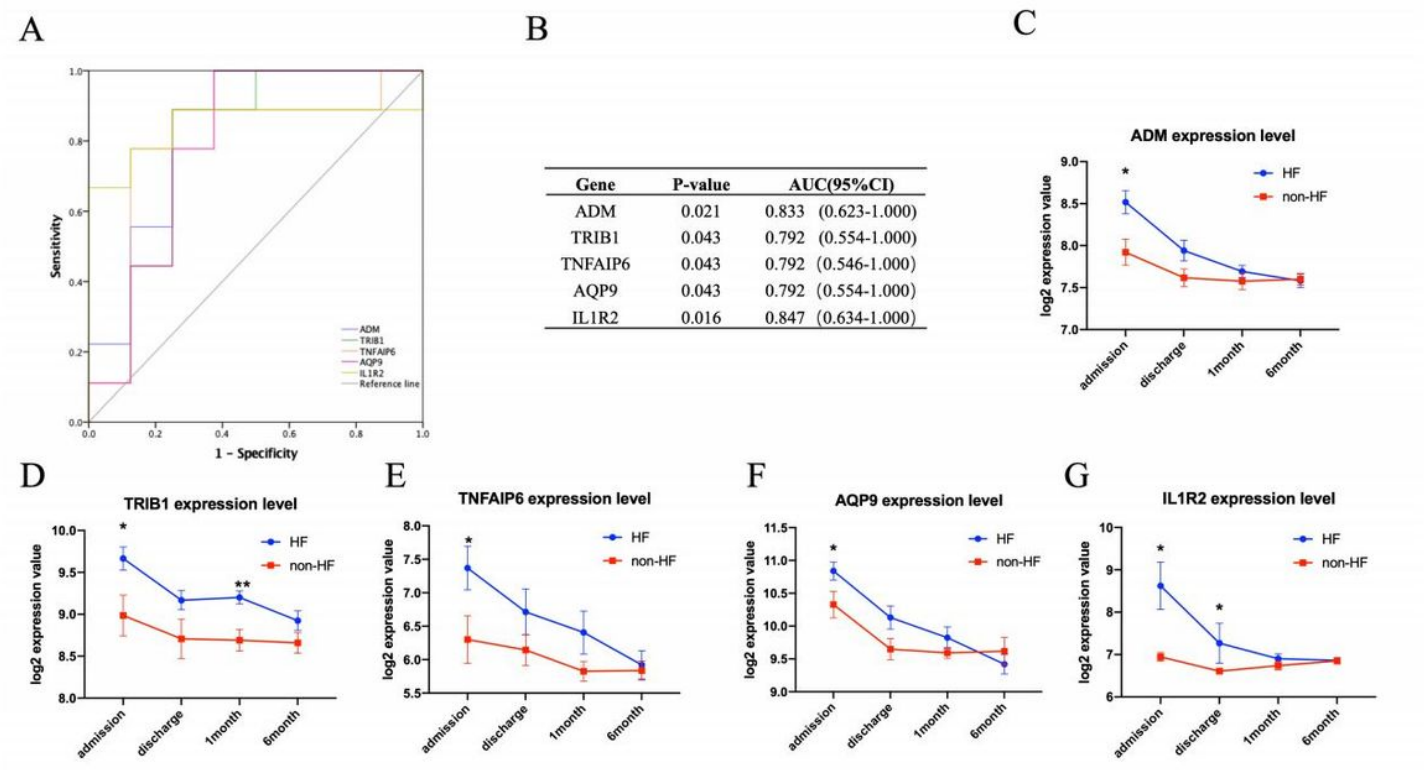


Figure 3

The interaction between the proteins encoded by the shared DEGs. A, PPI network of the shared DEGs and hub genes are listed in different color; B, PPI network of the significant module with two hub genes in different color.

Figure 4



Gene	P-value	AUC(95%CI)
ADM	0.021	0.833 (0.623-1.000)
TRIB1	0.043	0.792 (0.554-1.000)
TNFAIP6	0.043	0.792 (0.546-1.000)
AQP9	0.043	0.792 (0.554-1.000)
IL1R2	0.016	0.847 (0.634-1.000)

Figure 4

Diagnostic efficiency of five genes with ROC curves and AUC: A, ROC curves; B, detailed AUC values of the 5 genes; the expression changes of the five genes were separately compared at four time points after AMI: C, ADM expression level; D, TRIB1 expression level; E, TNFAIP6 expression level; F, AQP9 expression level; G, IL1R2 expression level. Data represent log2 expression value ± standard error. Statistical significance: *p <0.05; ** p <0.01.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.pdf