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Original Article

A bioinformatics approach to identifying the biomarkers and pathogenesis of major depressive disorder combined with acute myocardial infarction

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Abstract: This study investigated the pathogenesis of major depressive disorder (MDD) and acute myocardial infarction (AMI) using bioinformatics. We analyzed MDD and AMI (MDD-AMI) datasets provided by the Gene Expression Omnibus (GEO) database for genes common to MDD and AMI using GEO2R and weighted gene co-expression network analysis (WGCNA). We also performed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, and we used Disease Ontology (DO) analysis to identify a) the pathways through which genes function and b) comorbidities. We also created a protein-protein interaction (PPI) network using the STRING database to identify the hub genes and biomarkers. NetworkAnalyst 3.0 was used to construct a transcription factor (TF) gene regulatory network. We also identified relevant complications and potential drug candidates. The 27 genes common to MDD and AMI were enriched in the pathways regulating TFs and mediating immunity and inflammation. The hub genes in the PPI network included TLR2, HP, ICAM1, LCN2, LTF, VCAN, S100A9 and NFKBIA. Key TFs were KLF9, KLF11, ZNF24, and ZNF580. Cardiovascular, pancreatic, and skeletal diseases were common complications. Hydrocortisone, simvastatin, and estradiol were candidate treatment drugs. Identification of these genes and their pathways may provide new targets for further research on the pathogenesis, biomarkers, and treatment of MDD-AMI. Together our results suggested that TLR2 and VCAN might be the key genes associated with MDD complicated by AMI.

Keywords: Major depression disorder, acute myocardial infarction, biomarkers, pathogenesis, bioinformatics analysis

Introduction

Major depressive disorder (MDD) is a serious psychiatric health complication and a leading cause of suicide. The World Health Organization indicates that by 2030 depression will comprise the major worldwide disease burden [1]. Acute myocardial infarction (AMI) has declined significantly with the use of evidence-based medicine; however, AMI is still a major contributor to global morbidity and mortality, affecting approximately seven million people worldwide anually [2]. MDD and AMI are closely related, and MDD increases the morbidity and mortality of individuals with cardiovascular disease, especially AMI [3]. For individuals with depression, after AMI, the all-cause mortality increases 2.25-fold, the risk of cardiac death increases by 2.71-fold, and the new cardiac risk increases by 1.59-fold [4]. Additionally, the incidence of one-year MDD was 13.8% higher in patients with AMI than in the healthy population [5, 6].

Therefore, early diagnosis of MDD in AMI patients is critical for reducing morbidity and mortality.

MDD and AMI interacts via the neuroendocrine system that regulates the electrical activity of the heart. Patients with depression have a dysfunctional autonomic nervous system, which is manifested by an increased sympathetic tone and decreased vagal tone, thereby affecting cardiac function [7]. Also, patients with MDD have abnormal serotonin levels in the central nervous system, and the receptors for serotonin on platelets are similar to those in the central nervous system. Therefore, increased platelet activation and aggregation are potential mechanisms for the interaction between MDD and AMI [8]. Moreover, the onset and progression of MDD are associated with the activation of the immune system [9], with increased expression of inflammatory factors such as interleukin 6 (IL-6), tumor necrosis factor (TNF), and C-reactive protein (CRP) [10]. Increased TNF has been shown to be associated with depression after myocardial infarction [11]. Although the exact pathogenic mechanisms are unknown, genetic factors contribute to the onset and progression of depression [12]; *GPR18*, *PDK4*, *NRG1*, and *EPHB2* are diagnostic markers for depression [13]. Similarly, *IL1R2*, *IRAK3*, and *THBD* are diagnostic markers for AMI [14]. However, no genetic studies yet explain the mechanisms underlying MDD-AMI.

We used high-throughput microarrays, an important tool for large-scale gene expression analysis [15], to screen for potential diagnostic markers of MDD-AMI. We used GEO2R and weighted gene co-expression network analysis (WGCNA) with the GSE98793 and GSE66360 datasets from the Gene Expression Omnibus (GEO) database to screen for genes commonly associated with both MDD and AMI. We also performed gene enrichment analysis to identify the gene regulatory mechanisms underlying MDD-AMI. Further, we created a protein-protein interaction (PPI) network to identify hub genes with a role in MDD-AMI. We also constructed a transcription factor (TF)-gene regulatory network and screened for drugs targeting the network. This study is the first to use a bioinformatics approach to explore the pathogenesis and biological markers characteristic of MDD-AMI.

Material and methods

Dataset acquisition and data preprocessing

We screened humans in the GEO database [16] and obtained two datasets, GSE98793 [17] and GSE66360 [18], corresponding to MDD and AMI, respectively (> 30 samples in each gene set). The dataset GSE98793 contains the whole blood data for 128 patients with MDD and 64 healthy controls, contributed by Kelly et al. [17] on platform GPL570, and GSE66360 contains the whole blood data for 49 patients with AMI and 50 healthy controls uploaded by Kramer ER et al. [18] using the GPL570 platform.

Screening for hub biomarkers

GEO2R is an online GEO tool to identify differentially expressed genes (DEGs) for two or more sets of samples. GEO2R includes the limma and GEOquery packages for data reading, ID conversion, forced normalization, and DEG acquisition. Our screening thresholds for DEGs between GSE98793 and GSE66360 were set to the absolute value of Log2 Fold Change ≥ 0.5 and $P < 0.05$.

The systems biology algorithm WGCNA identifies co-expression network modules to determine the relationship between these networks and phenotypic traits, generates gene regulatory networks, and identifies hub network module genes [19]. The gene co-expression network and adjacency matrix were constructed by removing outlier samples through dynamic shear tree clustering and filtering appropriate soft thresholds using the ickSoftThreshold function (package WGCNA), which was converted into a network topology matrix using appropriate β values [20]. Then, we set the minimum value of the network module to 80, obtained the gene regulatory network module, and determined the correlation between network modules and diseases using a Pearson correlation analysis. Genes within the network were analyzed to identify hub genes. We use the Venn package (version R 4.1.0) with the set of the DEGs obtained using GEO2R and the set of hub module genes analyzed by WGCNA to identify genes common to both sets for subsequent bioinformatics analysis.

Functional enrichment analysis

We analyzed molecular pathways associated with MDD-AMI using Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Disease Ontology (DO) enrichment analyses, and we screened the genes common to MDD and AMI for functional enrichment analysis and disease prediction [21]. GO enrichment analysis identifies the pathways related to cellular components (CCs), molecular functions (MFs), and biological processes (BPs) in the gene set [22]. The specific actions and metabolic pathways of genes common to MDD and AMI were identified by KEGG analysis [23]. We used the R package org.Hs.eg.db to transform the gene names to gene IDs and carried out the GO, KEGG, and DO enrichment analyses using the R packages ClusterProfiler [24] and Disease Ontology Semantic and Enrichment analysis (DOSE) [25]. We considered $P < 0.05$ as indicating a significant enrichment and the enrichment results were visualized using ggplot2 (version R 4.1.0).

PPI network construction

PPI networks are involved in biological signaling, energy, and material metabolism, as well as gene expression and cell cycle regulation. We constructed and analyzed a PPI network to search for hub regulatory genes [26-28]. The STRING 11.0 (Version 11.0) [28] database was used to identify genes common to MDD and AMI and construct a PPI network, which was imported into Cytoscape for visualization. The Molecular Complex Detection algorithm (MCODE) plug-in in Cytoscape was used to analyze the identified genes to acquire gene modules with the following reference thresholds: setting parameters as degree cutoff = 2, node score = 0.2, k-core = 2, and maximum depth = 100 [29]. Cytoscape's cytohubba plug-in was used to screen the hub genes using eight algorithms, including Degree, EcCentricity, BottleNeck, Density of Maximum Neighborhood Component (DMNC), Maximal Clique Centrality (MCC), Closeness, and Betweenness, which were displayed using an UpSet plot (a type of Venn diagram).

Construction of a TF-gene regulatory network

TFs are DNA-binding proteins that interact with specific genes to activate or inhibit transcription. A TF-gene regulatory network can identify the pathways by which TFs affect gene expression [30]. We applied the Encyclopedia of DNA Elements (ENCODE) database [31] from the web-based tool NetworkAnalyst 3.0 for analyzing gene expression to develop the TF-gene regulatory network.

Identification of drug candidates

Because there are no drugs to treat MDD-AMI and alleviate the psychological and physical burden on patients, we used bioinformatics to identify potential new drugs for clinical use in a shorter time and with less cost than typical drug development. The Drug Signature Database (DSigDB), which is hosted on the Enrichr web platform, associates drugs with their target genes [32]. We entered genes common to MDD and AMI into the Enrichr platform (https://amp. pharm.mssm.edu/enrichr/) to screen for drug candidates associated with these common genes in the DSigDB database.

Verify hub gene

To verify the validity of a hub gene, we analyzed the differences between the hub gene expression in the MDD dataset GSE38206 and the AMI dataset GSE60993. The GSE38206 dataset was obtained from the study by Belzeaux et al. [33] based on the GPL13607 platform, which analyzed peripheral blood samples from 18 healthy and 18 MDD groups. The GSE60993 dataset comprises data on blood samples uploaded by Park et al. [34] based on the GPL6884 platform for assessing and diagnosing biomarkers of ST-segment elevation myocardial infarction. We analyzed the difference between seven ST-segment elevation myocardial infarction samples, 10 non-ST-segment elevation myocardial infarction samples, and seven healthy controls. For the GSE60993 and the GSE38206 datasets, we used the limma R package to identify DEGs ($|\log2\ FC| \geq 0.5$, $P < 0.05$), the limma package of R software for difference analysis, the normalizeBetweenArrays function for mandatory normalization of the data, and the ggplot2 package for hierarchical clustering analysis of DEGs. The Venn package was used to identify the intersection of DEGs between the validation data sets GSE38206 and GSE60993.

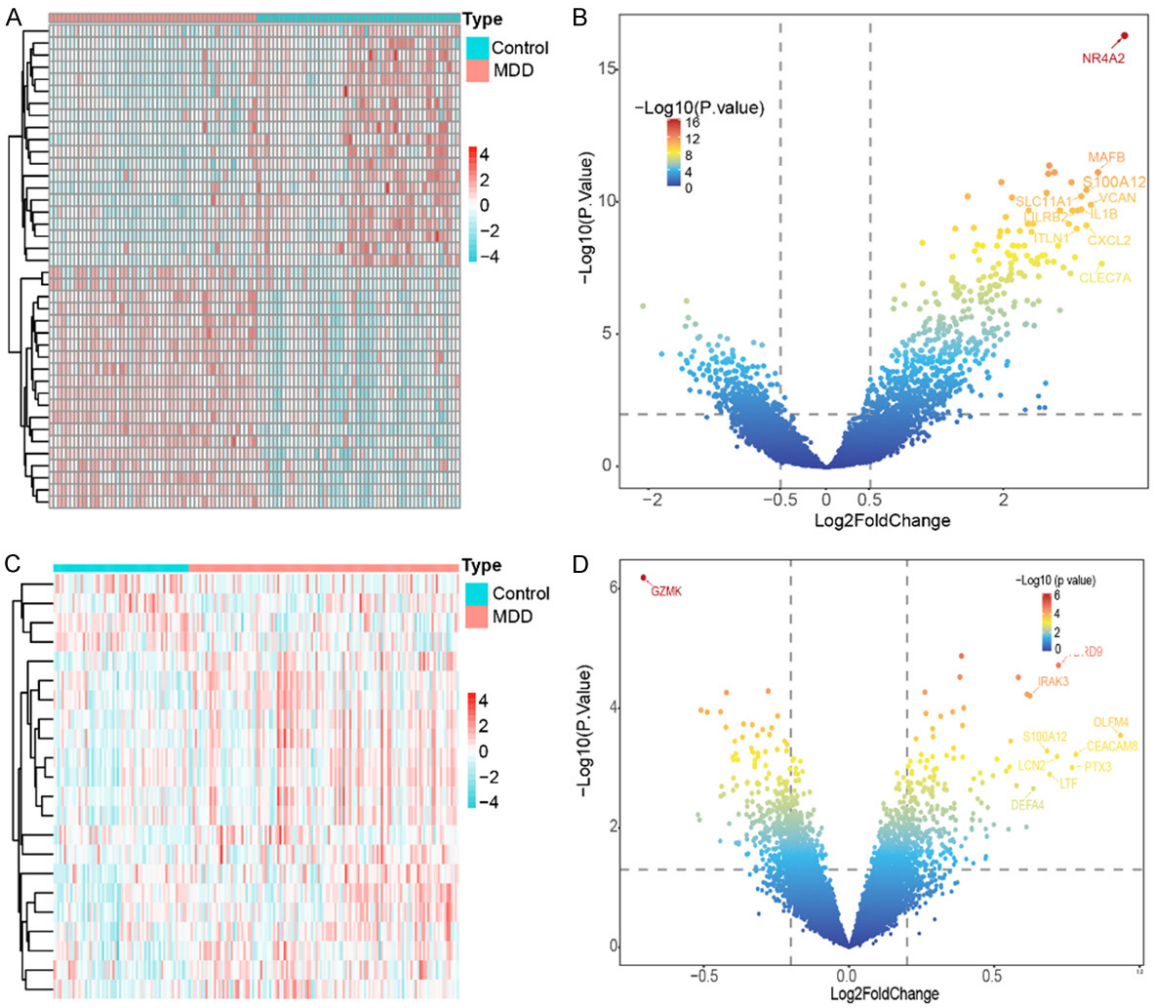

Figure 1. Identification of differentially expressed genes (DEGs) between GSE66360 and GSE98793. A. Heatmap of DEGs in GSE66360 (n = 99, adj. P < 0.05, |log2 fold change (FC)| > 0.5). B. Volcano plot of DEGs in GSE66360. C. Heatmap of DEGs in GSE98793 (n = 186, adj. P < 0.05, |log2 fold change (FC)| > 0.5). D. Volcano plot of DEGs in GSE98793.

Statistical analysis

Differential analysis, WGCNA, and enrichment analysis between the two groups were performed using the R software (v.4.1.0). We did the enrichment analysis with hypergeometric tests, and paired data comparisons were made using the Wilcoxon test. Detailed statistical strategies used in processing the transcriptomic data are presented in the Materials and Methodology section. P < 0.05 indicated a significant difference.

Results

Screening of DEGs

The GSE66360 and GSE98793 datasets were analyzed using the limma and GEOquery packages of the GEO2R web tool. We identified 986 DEGs from the GSE66360 dataset, including 662 upregulated and 324 downregulated genes. The heat map of GSE66360 (**Figure 1A**) and gradient volcano map (**Figure 1B**) show the expression levels and distribution sites of these DEGs. In addition, we identified 496 DEGs from the GSE98793 dataset, including 250 upregulated genes and 246 downregulated genes. The heat map of GSE98793 (**Figure 1C**) and gradient volcano map (**Figure 1D**) show the expression levels and distribution sites of these DEGs.

WGCNA

We used WGCNA to identify the links between relevant phenotypes and hub genes. Initially,

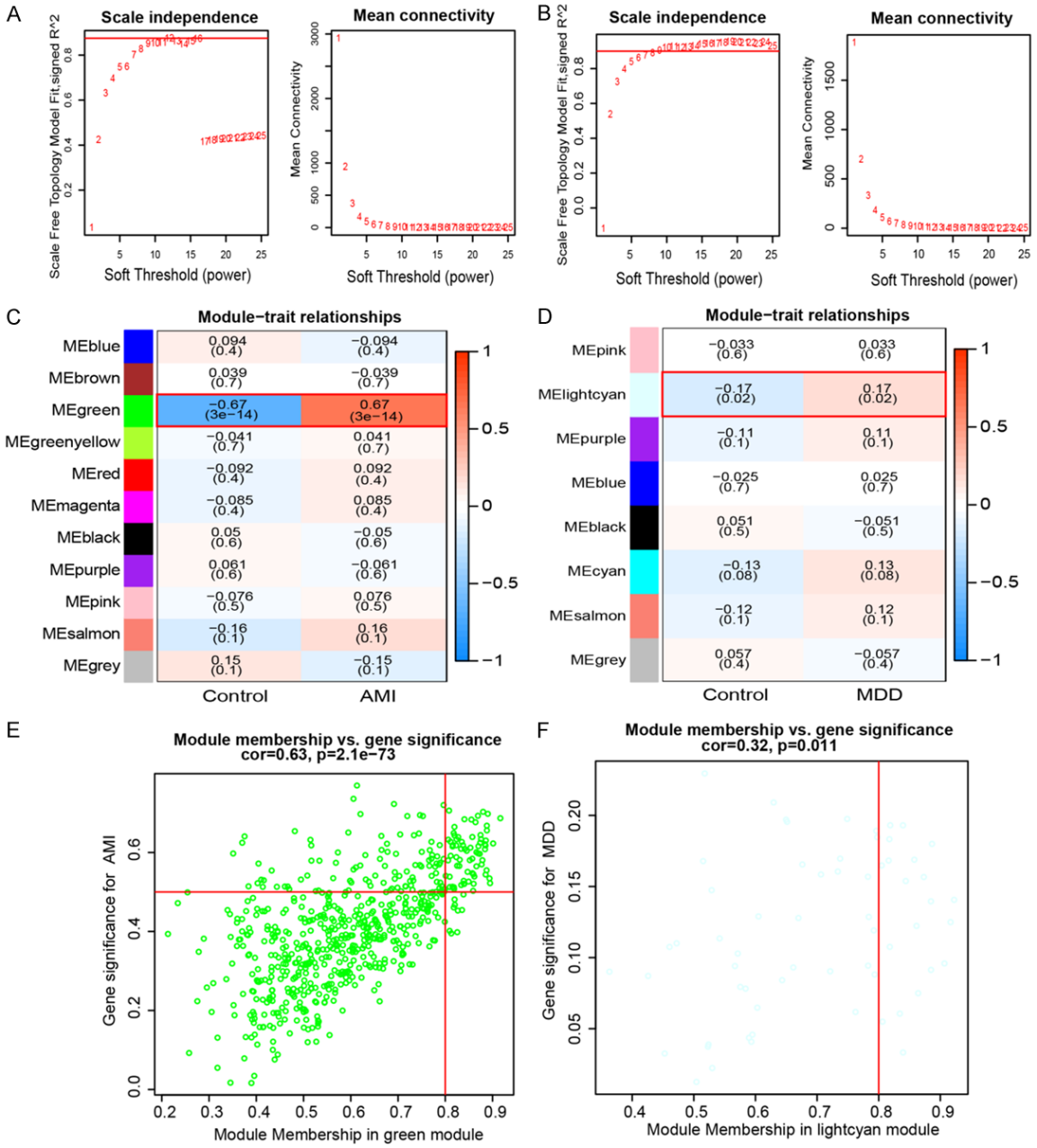

Figure 2. Weighted gene co-expression network analysis (WGCNA) of GSE66360 and GSE98793. A. Determination of soft thresholding power for GSE66360. B. Determination of soft-thresholding power for GSE98793. C. Heatmap of the correlation between module eigengenes and the occurrence of acute myocardial infarction (AMI). D. Heatmap of the correlation between module eigengenes and the occurrence of major depressive disorder (MDD). E. Module membership in green module vs. gene significance for AMI. F. Module membership in light cyan module vs. Gene significance for MDD.

we applied the dynamic shear tree method to eliminate one outlier sample in GSE98793 when the shear line was 130, and there were no outlier samples in GSE66360. Then, the two datasets were analyzed separately by WGCNA. The optimal soft threshold for GSE66360 was β = 12 (**Figure 2A**), yielding 11 network modules (**Figure 2C**), and for GSE98793, it was β = 9 (**Figure 2B**), yielding 11 network modules (**Figure 2D**). Then, we determined the link between network modules and clinical features. In the GSE66360 database, the green

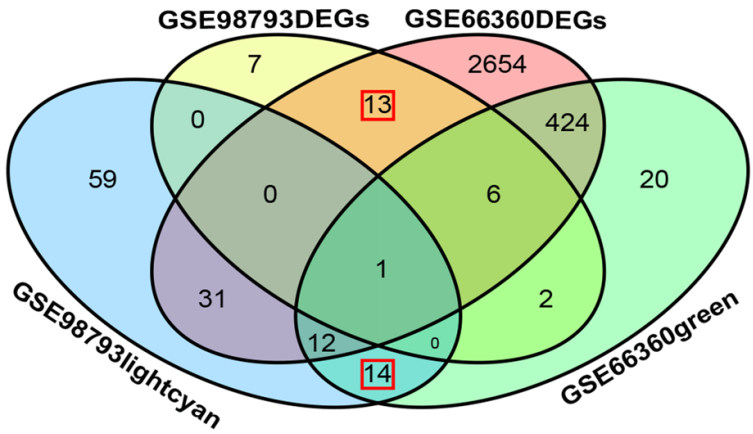

Figure 3. Venn diagram of MDD and AMI common genes. There were 27 genes common to MDD and AMI. Among them, 13 DEGs were obtained by differential analysis and 14 typical modular genes were obtained by WGCNA. Acute Myocardial Infarction (AMI), Major Depressive Disorder (MDD), Weighted Gene Co-expression Network Analysis (WGCNA).

module had the strongest positive link with AMI ($r = 0.67$, $P < 0.05$), and module membership and gene significance were closely correlated (cor = 0.63, P = 2.1e-73) (**Figure 2E**). In the GSE98793 dataset, light cyan modules were statistically significant ($r = 0.17$, $P < 0.05$), where module membership and gene significance were closely correlated (cor = 0.32, P = 0.011) (**Figure 2F**).

We determined the intersection of the genes from the GEO2R differential analysis and WGCNA separately using the R package ggVennDiagram [35]. We identified 13 DEG intersections between GSE66360 and GSE98793 and 14 intersections for WGCNA, resulting in 27 genes common to MDD and AMI (**Figure 3**).

Enrichment analyses

The analysis results for the top 10 GO terms indicated that the genes common to MDD and AMI were primarily enriched in the regulation of TFs and responses to bacteria and fungi. CC was primarily related to cellular granules and their release. BF was primarily related to carbohydrates, toll-like receptors, and other mutual interactions (**Figure 4**; **Table 1**). The analysis results for the top 10 KEGG terms revealed that genes common to MDD and AMI were primarily related to immunity and inflammation (**Figure 5A**; **Table 2**). In addition, MDD-AMI was significantly associated with cardiovascular, pancreatic, and skeletal diseases (**Figure 5B**).

PPI network analysis

The interactions between proteins identified the pathways of interaction between genes common to MDD and AMI. A total of 26 hub targets (96 edges, an average number of nodes of 7.38, and an average clustering coefficient of 0.56) were obtained from the PPI network analysis with a confidence coefficient set to 0.15 (**Figure 6A**). Then, the PPI network was imported into Cytoscape and visualized by the MCODE and cytohubba plug-ins. In addition, eight of the plug-ins were selected for hub gene screening to obtain eight hub genes, including toll-like receptor (*TLR2*), haptoglobin (*HP*), intercellular adhesion molecule 1 (*ICAM1*), lipocalin 2 (*LCN2*), lactotransferrin (*LTF*), versican (*VCAN*), S100 calcium-binding protein A9 (*S100A9*), and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (*NFKBIA*) (**Figure 6B**).

Construction of the TF-mRNA regulatory network

We used the ENCODE database of NetworkAnalyst 3.0 to construct the TF-gene regulatory network. The interaction between TFs and hub genes is illustrated in **Figure 7**. The network contained seven hub targets, 161 nodes, and 220 edges. *ICAM1* was regulated by up to 71 TFs, whereas the TF Krüppel-like factor 9 (*KLF9*) regulated four core genes simultaneously.

Identification of drug candidates

The hub genes were entered into the DSigDB database of the Enrichr platform to screen for drugs targeting these genes (**Table 3**). The top 10 drug candidates were glycoprotein, potassium persulphate, maltotriose, iron, trimethoprim, isoguanine, hydrocortisone, sodium

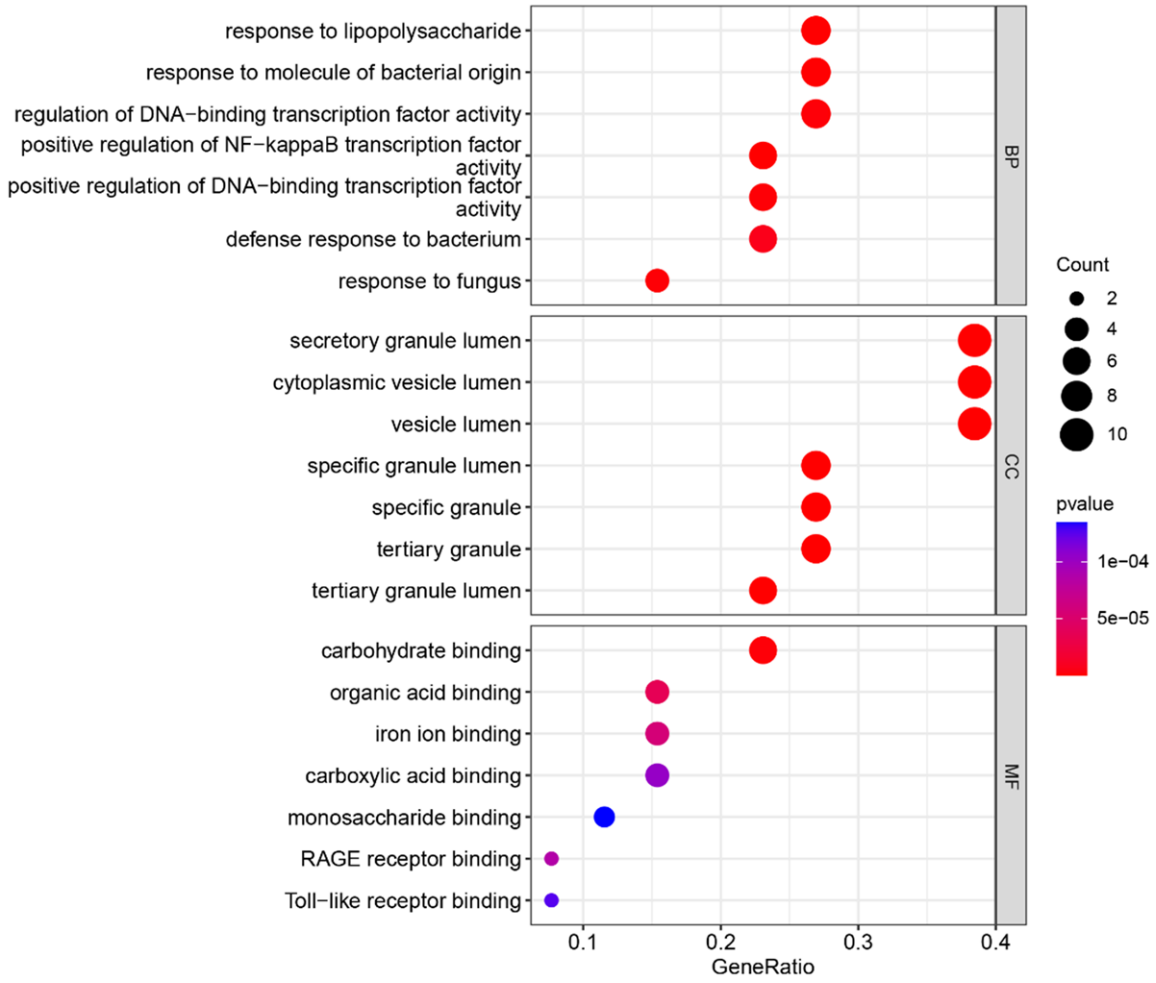

Figure 4. Gene Ontology (GO) enrichment analysis results for common genes.

dodecyl sulfate, simvastatin, and estradiol (**Table 4**).

Verification of hub genes

The MDD dataset GSE38206 and the AMI dataset GSE60993 were selected to verify hub genes. **Figure 8A** and **8B** shows the forced normalization of the two datasets, and **Figure 8C** and **8D** shows the hierarchical clustering heat maps of the DEGs in the two datasets. **Figure 8E** shows the common intersection of the DEGs between the two validation datasets, where hub genes *TLR2* and *VCAN* were screened as genes common to MDD and AMI.

Discussion

In the past ten years, our understanding of the biology of mood disorders and cardiovascular diseases has advanced significantly. Several pathophysiological aspects of depressive disorders may contribute to susceptibility to coronary heart disease. A systems biology approach has been used to develop a map of the processes that link depression with cardiovascular diseases [36]. In addition, mathematical models have identified a link between the symptoms of depression and 12-month mortality after myocardial infarction [37]. Platelet coagulation cascade, the autonomic nervous system, heart rate variability, inflammation, endothelial progenitor cell accessibility, hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axis function, along with changes in vascular calcification, ventricular instability, oxidative stress, myocardial ischemia, and genetic factors may enhance the risk of coronary heart disease in depressed individuals. However, the

Table 1. Gene ontology (GO) category, GO ID, GO description, and their corresponding *P*-value

Category	ID	Description	*P*-value
BP	GO:0051092	positive regulation of NF-kappaB transcription factor activity	5.22E-08
BP	GO:0032496	response to lipopolysaccharide	3.18E-07
BP	GO:0002237	response to molecule of bacterial origin	4.65E-07
BP	GO:0051091	positive regulation of DNA-binding transcription factor activity	1.23E-06
BP	GO:0009620	response to fungus	1.35E-06
BP	GO:0051090	regulation of DNA-binding transcription factor activity	1.69E-06
BP	GO:0042742	defense response to bacterium	6.86E-06
BP	GO:0071222	cellular response to lipopolysaccharide	8.98E-06
BP	GO:0071219	cellular response to molecule of bacterial origin	1.18E-05
BP	GO:0071216	cellular response to biotic stimulus	1.97E-05
CC	GO:0035580	specific granule lumen	1.43E-12
CC	GO:0034774	secretory granule lumen	5.38E-12
CC	GO:0060205	cytoplasmic vesicle lumen	5.89E-12
CC	GO:0031983	vesicle lumen	6.26E-12
CC	GO:1904724	tertiary granule lumen	8.25E-11
CC	GO:0042581	specific granule	1.24E-09
CC	GO:0070820	tertiary granule	1.48E-09
CC	GO:0071682	endocytic vesicle lumen	0.000423
CC	GO:0030867	rough endoplasmic reticulum membrane	0.000501
CC	GO:0005791	rough endoplasmic reticulum	0.005291
MF	GO:0030246	carbohydrate binding	1.75E-06
MF	GO:0043177	organic acid binding	3.68E-05
MF	GO:0005506	iron ion binding	5.7E-05
MF	GO:0050786	RAGE receptor binding	8.61E-05
MF	GO:0031406	carboxylic acid binding	0.000103
MF	GO:0035325	Toll-like receptor binding	0.000126
MF	GO:0048029	monosaccharide binding	0.000135
MF	GO:0031418	L-ascorbic acid binding	0.00036
MF	GO:0001530	lipopolysaccharide binding	0.00099
MF	GO:0019842	vitamin binding	0.001163

mechanisms that associate MDD with AMI are unknown. This research intends to explore the mechanisms underlying MDD-AMI using bioinformatics.

We analyzed the gene sets GSE98793 and GSE66360 using WGCNA and GEO2R to identify genes common to MDD and AMI and performed enrichment analyses on these genes to identify the pathways in which the genes function. Then, STRING was applied to the genes common to MDD and AMI to construct the PPI network. Finally, eight hub genes (*TLR2*, *HP*, *ICAM1*, *LCN2*, *LTF*, *VCAN*, *S100A9*, and *NFKBIA*) were screened. After dataset verification, we found that *TLR2* and *VCAN* were common to MDD and AMI. Although there is no information on the genetic mechanisms that underlie MDD-AMI, the genes *HP*, *LCN2*, *NFKBIA*, *TLR2*, and *VCAN* that were associated with both diseases may play a role in the occurrence and progression of MDD-AMI. *SI00A9* has been studied in AMI; however, there are no studies on *SI00A9* related to MDD. Neither *LCAM1* nor *LTF* has been studied in the context of MDD-AMI, which needs further investigation.

Haptoglobin, encoded by *HP*, binds to free hemoglobin to reduce tissue damage from oxidative stress [38]. HP exists in three variant protein phenotypes, HP1-1, HP1-2, and HP2-2. HP2-2 was reportedlt to have lower antioxidant activity than the other variants, and myocardial infarction patients with HP2-2 have a poorer

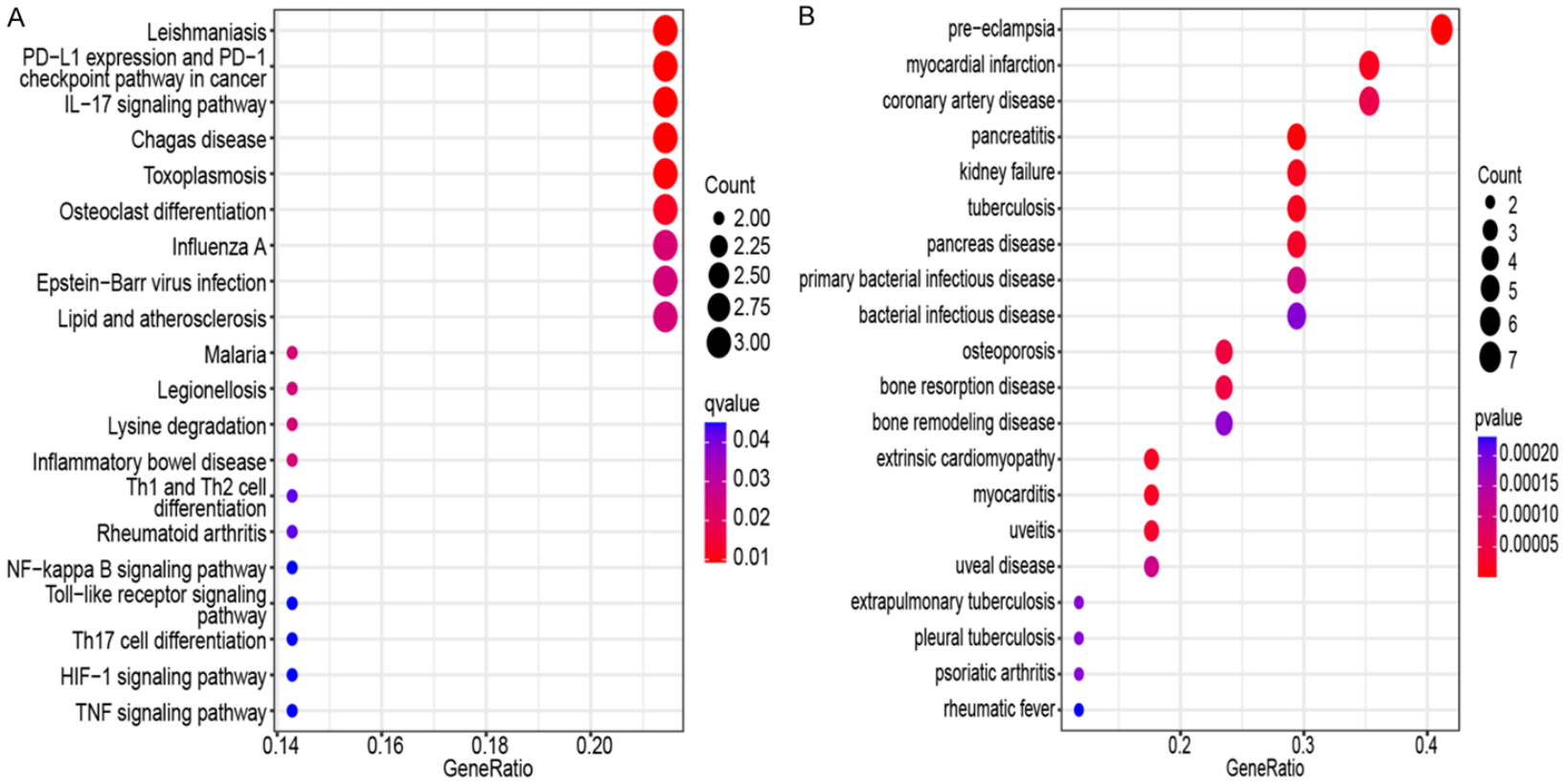

Figure 5. Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis and complication analysis of common genes. A. KEGG enrichment analysis results for 27 genes screened by WGCNA. B. Complications of myocardial infarction major depression derived from analysis of 27 genes screened by WGCNA. Weighted Gene Co-expression Network Analysis (WGCNA).

Table 2. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways ID and description and their corresponding *P*-value

ID	Description	*P*-value
hsa05140	Leishmaniasis	0.000274
hsa05235	PD-L1 expression and PD-1 checkpoint pathway in cancer	0.000421
hsa04657	IL-17 signaling pathway	0.000494
hsa05142	Chagas disease	0.000628
hsa05145	Toxoplasmosis	0.000825
hsa04380	Osteoclast differentiation	0.001215
hsa05164	Influenza A	0.00279
hsa05144	Malaria	0.003206
hsa05134	Legionellosis	0.004148
hsa05169	Epstein-Barr virus infection	0.004468

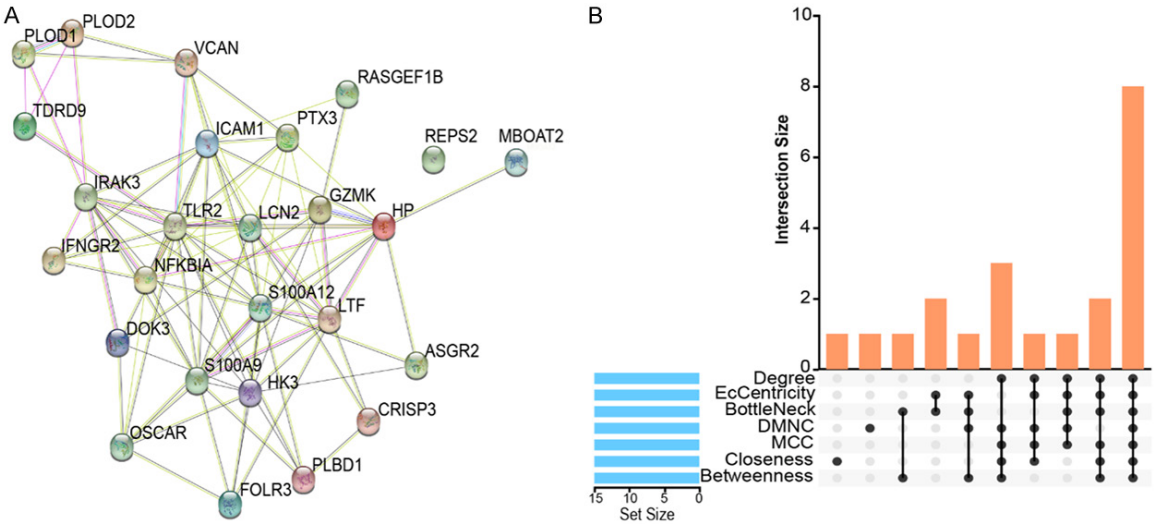

Figure 6. Protein-protein interaction network. A. Protein-protein interaction (PPI) network. Based on the STRING database, protein-protein interaction networks of the common genes in the AMI and MDD. B. Upset Venn showed the number of core genes screened for overlap with each other for the eight models in the PPI network. Acute Myocardial Infarction (AMI), Major Depressive Disorder (MDD).

prognosis [39]. HP plasma levels were considerably higher in individuals with MDD vs. healthy controls or mildly depressed individuals [40]. Therefore, oxidative stress may be a critical pathway for MDD-AMI, and HP may be an important mechanism through which MDD and AMI mutually increase the risk of morbidity. However, the impact of different *HP* gene variants on the prognosis of patients with MDD needs further exploration.

LCN2, also called neutrophil gelatinase-associated lipocalin (*NGAL*), encodes a cytokine secreted primarily by adipocytes. *LCN2* overexpression has anti-inflammatory and antioxidant cytoprotective effects that reduce cardiomyocyte death and remodeling [41, 42]. Low expression of *LCN2* in hippocampal neurons contributes to the onset of depression. In addition, *LCN2* may lead to the comorbidity between myocardial infarction and depression through inflammation [43].

The *NFKBIA*-encoded protein mediates the expression of pro-inflammatory genes that are critically involved in atherosclerosis-like diseases [44]. Expression of *NFKBIA*, a stress-related gene, is elevated in the hippocampal and amygdala regions of mice with posttraumatic stress disorder [45]. High expression of *NFKBIA* may

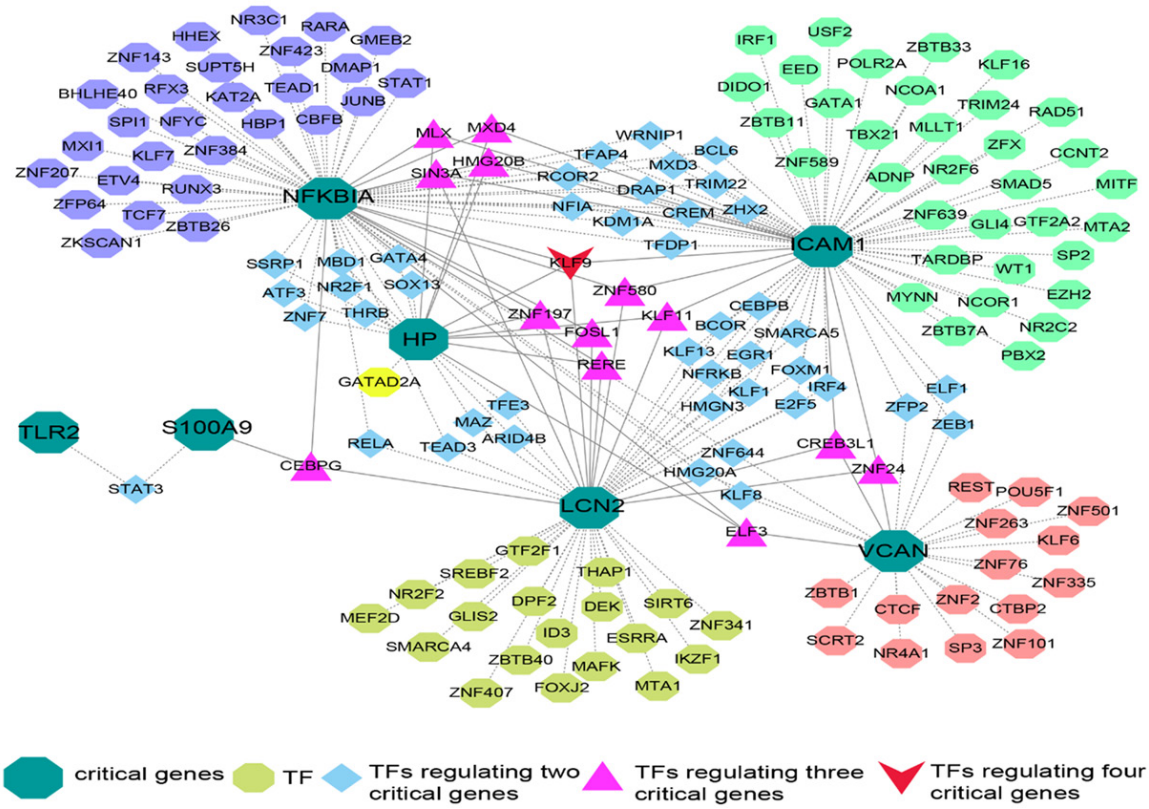

Figure 7. Transcription Factor (TF)-common gene regulatory network. The interrelationship between transcription factors and critical genes, dark green octagon represents critical genes, other color octagons represent TFs that can only regulate the corresponding core genes, sky blue quadrilateral represents TFs regulating two critical genes, the lavender triangle represents TFs regulating three critical genes, red quadrilateral represents TFs regulating four critical genes.

Table 3. Acute myocardial infarction (AMI) and Major depressive disorder (MDD) gene-targeted drugs

Term	*P*-value	Combined Score	Genes
GLYCOPROTEIN BOSS	3.91E-09	3473.479	*HP*; *LCN2*; *TLR2*; *ICAM1*; *LTF*
POTASSIUM PERSULFATE CTD 00000451	6.45E-08	10443.16	*LCN2*; *S100A9*; *LTF*
maltotriose BOSS	4.51E-07	1626.416	*HP*; *TLR2*; *ICAM1*; *LTF*
IRON BOSS	4.82E-07	1592.053	*HP*; *LCN2*; *ICAM1*; *LTF*
trimethoprim BOSS	5.48E-07	1526.976	*LCN2*; *TLR2*; *ICAM1*; *LTF*
Isoguanine BOSS	5.59E-07	1516.576	*HP*; *TLR2*; *ICAM1*; *LTF*
hydrocortisone BOSS	6.32E-07	1456.666	*HP*; *TLR2*; *ICAM1*; *LTF*
Sodium dodecyl sulfate CTD 00006753	2.47E-06	2236.6	*S100A9*; *TLR2*; *ICAM1*
simvastatin CTD 00007319	3.49E-06	824.7797	*NFKBIA*; *S100A9*; *TLR2*; *ICAM1*
estradiol CTD 00005920	4.86E-06	1533239	*NFKBIA*; *VCAN*; *HP*; *LCN2*; *S100A9*; *TLR2*; *ICAM1*; *LTF*

contribute to suicidal behavior in depressed patients through the pathways of apoptosis, cell death, and inflammation [46]; thus, this gene may be involved in the mechanism by which AMI causing depression.

S100A9 is a potential genetic marker for AMI [47]. In AMI-related reperfusion injury, *S100A9* damages cardiomyocytes by inhibiting mitochondrial function, and *S100A9*-neutralizing antibodies significantly attenuate myocardial

Table 4. Detailed information on eight critical genes

Gene	Full name	Gene-related function
TLR2	Toll Like Receptor 2	Toll-like receptors (TLRs) are single transmembrane cell surface receptors that play a key role in the innate immune system.
HP	Haptoglobin	*Hp*, also known as haptoglobin, reduces tissue damage caused by oxidative stress by binding to free hemoglobin.
ICAM1	Intercellular Adhesion Molecule 1	*ICAM1* is a cell-surface glycoprotein that is involved in the binding of a cell to another cell or extracellular matrix. *ICAM1* is commonly expressed on endothelial and immune system cells and plays a role in cell proliferation, differentiation, locomotion, transportation, apoptosis and tissue construction.
LCN2	Lipocalin 2	*LCN2*, also known as neutrophil gelatinase-associated calcitonin (*NGAL*), is a cytokine mainly secreted by adipocytes. Overexpression of *LCN2* can exert cellular protective mechanisms through anti-inflammatory and antioxidant activities and reduce cardiac myocyte death and remodeling.
LTF	Lactotransferrin	*LTF*, a member of the transferrin gene family, has antimicrobial activity and is an important component of the non-specific immune system.
VCAN	Versican	*VCAN* is a large chondroitin sulfate proteoglycan that plays a role in intercellular signaling and in connecting cells to the extracellular matrix. It also plays a role in diseases such as wound healing and tissue remodeling.
S100A9	S100 Calcium Binding Protein A9	*S100A9* leads to myocardial cell damage by inhibiting mitochondrial function.
NFKBIA	NFKB Inhibitor Alpha	*NFKBIA* plays an important role in atherosclerotic diseases by regulating the expression of pro-inflammatory genes.

infarction-related reperfusion injury [48]. Additionally, higher *S100A9* levels during a myocardial infarction exacerbate the risk of heart failure [49]. The unexplored relationship between *S100A9* and MDD could be a new research direction.

Toll-like receptors (*TLR*s), a family of transmembrane proteins that bind primarily to microbial products, play a central role in innate immunity by recognizing pathogens and damage-related molecular patterns and are associated with a range of inflammatory and autoimmune diseases [50]. Damage to cardiomyocytes in mice with myocardial infarction is attenuated by the inhibition of *TLR2* [51]. A *TLR* profile can predict the response to antidepressant treatment. Elevated *TLR2* levels may contribute to suicide in patients with MDD [46], and the *TLR2* levels decrease in depressed patients after treatment [52]. Our GO analysis suggested that toll-like receptors are essential for the hub genes to function. KEGG analysis also revealed that immunity and inflammation are important pathways for MDD-AMI. Therefore, *TLR2* may be a key mechanism underlying MDD-AMI.

VCAN, encoding a large chondroitin sulfate proteoglycan, is involved in intercellular signaling and connecting cells to the extracellular matrix [53], as well as in wound healing and tissue remodeling. Elevated *VCAN* expression was observed in patients with AMI [54]. *VCAN* gene variants may contribute to the onset of depression through alterations in the microstructural integrity of brain white matter [55]. Here, we found that orthopedic disorders are a common complication of MDD-AMI; therefore, this gene may contribute to this complication.

LTF belongs to the family of transferrin genes, and the protein it encodes has anti-microbial activity, making it an essential component of the non-specific immune system. This transferrin regulates iron homeostasis, acts as a host defense against several microbial infections, has anti-inflammatory activity, regulates cell growth and differentiation, and protects against cancer progression and metastasis. LTF and its peptides have anti-microbial, anti-viral, anti-fungal, and anti-parasitic activities [56]. However, as it has not been associated with MDD-AMI, this could provide a new area for research.

Intercellular cell adhesion molecule-1 (*LCAM1*), a cell surface glycoprotein that mediates the binding of cells to each other or the extracellu-

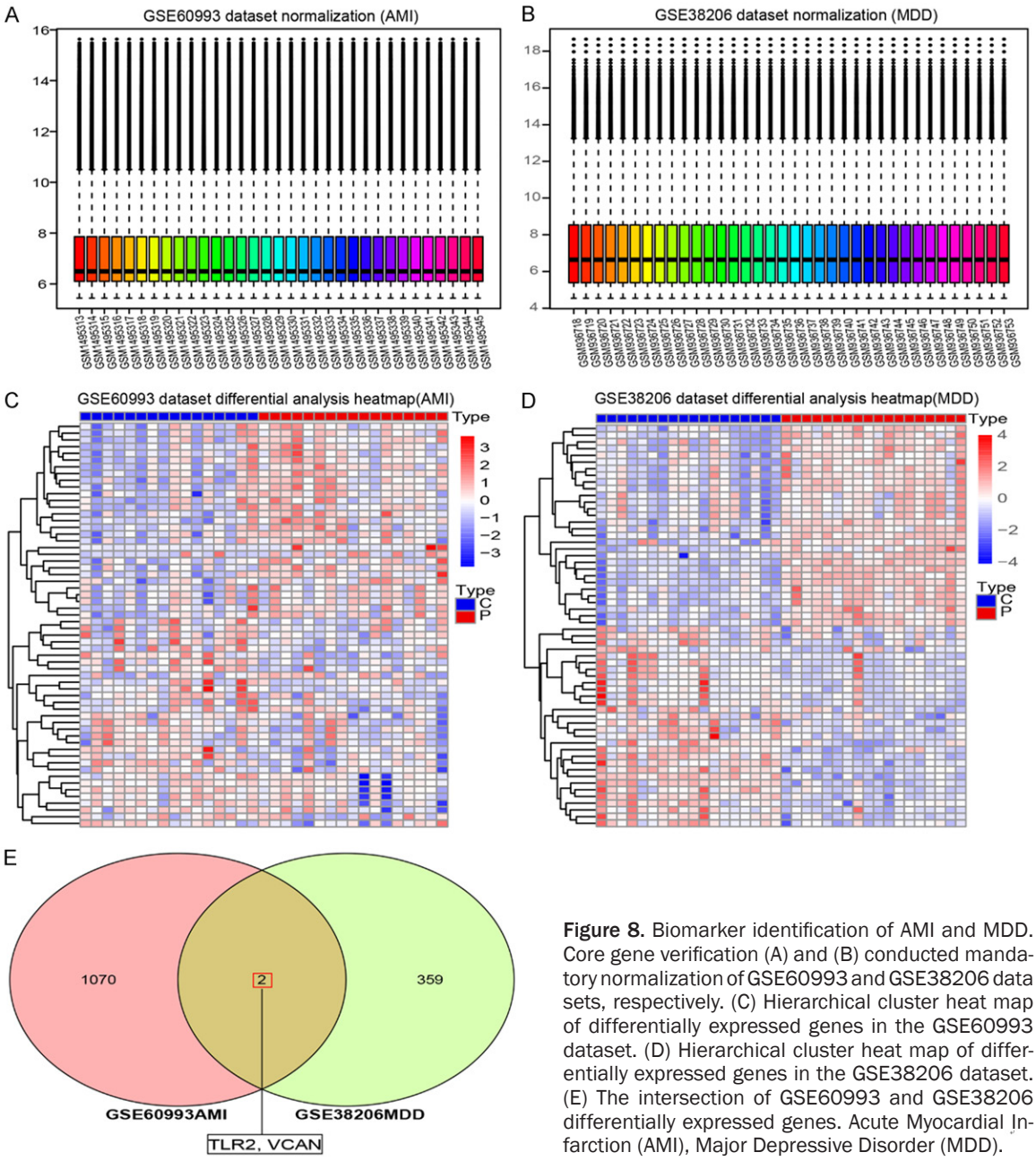

Figure 8. Biomarker identification of AMI and MDD. Core gene verification (A) and (B) conducted mandatory normalization of GSE60993 and GSE38206 data sets, respectively. (C) Hierarchical cluster heat map of differentially expressed genes in the GSE60993 dataset. (D) Hierarchical cluster heat map of differentially expressed genes in the GSE38206 dataset. (E) The intersection of GSE60993 and GSE38206 differentially expressed genes. Acute Myocardial Infarction (AMI), Major Depressive Disorder (MDD).

lar matrix, is commonly expressed on endothelial cells [57] and immune system cells [58]. It is critical for cell proliferation, differentiation, motility, transport, apoptosis, and tissue construction. Because MDD is closely related to immunity [13], it could increase the risk of AMI through an immune pathway that affects the function of endothelial cells. Currently, there is no information about the relationship between *LCAM1* and MDD-AMI.

Enrichment analyses revealed that the pathways of hub genes were primarily enriched in regulating TFs, suggesting that TFs are important for MDD-AMI. Krüppel-like factor 11 (*KLF11*) is a key regulator of MDD; the expression of *KLF11* increases by 44% in the postmortem cerebral cortex of patients with MDD compared with healthy subjects [59]. *KLF9*, a direct glucocorticoid receptor target gene induced by stress, mediates the action of glu-

cocorticoids on brain gene expression and neuronal structure [60]. Zinc finger protein 580 (*ZNF580*) regulates vascular endothelial proliferation and migration [61]. Zinc finger protein 24 (*ZNF24*) inhibits the platelet-derived growth factor receptor beta (PDGFR-β), thereby inhibiting the progression of atherosclerosis.

Comorbidity analysis suggested that MDD-AMI may be complicated by cardiovascular diseases such as preeclampsia, myocarditis, cardiomyopathy, coronary artery diseases, orthopedic diseases such as osteoporosis and bone resorption disease, pancreatic diseases such as pancreatitis, and various other diseases such as renal failure, tuberculosis, and uveitis. MDD accelerates aging and increases the incidence of cardiovascular diseases and osteoporosis [62]. MDD is seven times more prevalent in patients with pancreatic cancer than in the general population [63].

No drugs are available for MDD-AMI treatment, and new drug development is costly and time-consuming. Therefore, bioinformatics approaches to find drugs that target hub genes could greatly improve efficiency and reduce costs. We suggest that hydrocortisone, simvastatin, and estradiol might be effective in treating MDD-AMI. The dysregulation of the hypothalamic-pituitary-adrenal axis and abnormal levels of cortisol secretion leads to shorter telomeres and reduced stress capacity in patients with MDD [64]. Therefore, hydrocortisone may improve the symptoms of patients with MDD-AMI. Because inflammation may lead to depression, the anti-inflammatory drug simvastatin may effectively treat AMI and MDD, thereby exhibiting anti-atherosclerotic and antidepressant roles [65]. Estradiol activates stress circuits in the bilateral amygdala, hippocampus, and hypothalamus. Estradiol regulation is low in women with MDD resulting in improved MDD in women [66].

This study has certain limitations. GSE98793 and GSE66360 are the largest available datasets for MDD and AMI, however, their sample sizes are still relatively small. Therefore, further mining experiments will require larger sample sizes. Additionally, we lacked data on patients with MDD-AMI and relevant gene sets. Further validation is needed for the diagnostic markers identified in this study.

Conclusions

The pathogenesis of AMI combined with MDD may be related to the regulation of transcription factors and the modulation of immunity and inflammation by genes common to MDD and AMI. Bioinformatics analysis identified 27 genes common to MDD and AMI. Eight critical genes and biomarkers (*TLR2*, *HP*, *ICAM1*, *LCN2*, *LTF*, *VCAN*, *S100A9*, and *NFKBIA*) were identified, and a TF-gene regulatory network was constructed to find relevant transcription factors. Complications related to MDD and AMI and potential treatment drugs were identified, providing new information for the clinical diagnosis and treatment of MDD complicated with AMI. Through dataset validation, we identified *TLR2* and *VCAN* as possible biomarkers of MDD complicated with AMI.

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Disclosure of conflict of interest

None.

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