Identification of potential biomarkers and therapeutic targets in the chronic obstructive pulmonary disease and acute myocardial infarction

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Research Article

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) and acute myocardial infarction (AMI) have a strong association. We aimed to study the relationships between COPD and AMI, and reveal potential therapeutic targets and biomarkers. ,

Methods

The dataset GSE38974 and GSE60993 were downloaded from the Gene Expression Omnibus (GEO) database to analyze the intersections among differentially expressed genes (DEGs). Common DEGs were identified and performed functional enrichment analyses. The hub genes were obtained based on the protein-protein interaction (PPI) network by cytoHubba in Cytoscape software. The receiver operator characteristic (ROC) curve analysis was applied to identify the diagnosis efficacy of hub genes. The relationship between hub genes and these two diseases in the CTD database were validated. Finally, the transcription factors (TFs) corresponding to hub genes were also analyzed.

Results

In our study, sixty-five common DEGs were obtained in COPD and AMI. GO enrichment analysis indicated that inflammation or apoptotic biological processes are significant enriched biological processes. Common DEGs were mostly enriched in pathways including apoptosis, HIF-1 signaling pathway, TNF signaling pathway, and cytokine-cytokine receptor interaction. MMP9, SOCS3, MCL1, ERBB2 and S100A12 were identified as the hub genes. Furthermore, we found that the expression of hub genes was significantly associated with a diagnosis efficacy of COPD and AMI. We also validated the relationship between the hub genes and these two diseases in the CTD database. We also found that ELK1, ETV4, STAT3 and TFAP2A were significant TFs, which interacted with the hub genes.

Conclusions

In conclusion, our study revealed the communal DEGs and related mechanisms between the pathophysiology of COPD and AMI. MMP9, SOCS3, MCL1, ERBB2 and S100A12 were identified as the hub genes that are associated with COPD and AMI. Our study provides new ideas and evidence for further exploration of the mechanisms and treatment of COPD and AMI.

Introduction

Chronic obstructive pulmonary disease (COPD) is an irreversible or partially reversible disorder with slow progress, characterized by progressive airflow obstruction[1]. COPD is one of the leading cause of

morbidity and mortality all over the world[2]. The exact pathogenesis of COPD has yet to be fully explained and cigarette smoke (CS) is the predominant risk factor of this complicated process[3]. Acute myocardial infarction (AMI), is a significant area of interest within the field of cardiovascular diseases (CVDs), which is the multifactorial injury event[4]. AMI is a common disorder characterised by the partial or complete occlusion of the coronary artery and is the multifactorial injury event [5]. Data from several studies suggest that smoking, hypertension, diabetes, hypercholesterolemia and dyslipidaemia are the main cause of AMI[6, 7]. However, the potential mechanisms concerning relationship between COPD and AMI remains unclarified.

Accumulating evidence have emphasized a strong association between COPD and AMI[8]. Patients with COPD were more likely to be diagnosed with different cardiovascular disease, including MI [9]. In a UK registry among those 29870 patients who had COPD attending primary care facilities, the relative risk estimates of developing an incident diagnosis of MI also tended to be increased for patients with COPD as compared to COPD-free population [10]. The prevalence of COPD was as much as 30% in patients with coronary artery disease based on previous literatures[11]. Several pathological mechanisms underlie the relationship between the two diseases. For example, smoking and increasing age are most important common risk factors shared by COPD and ischaemic heart disease[12]. The increased platelet reactivity and count, which caused the higher risk of thrombotic events, was induced by systemic inflammation in patients with COPD [13]. COPD-related hypoxia induced the activation of the renin–angiotensin system, further reduced peripheral vasoconstriction and renal blood flow and increased oxidative stress, which eventually increased the risk of AMI[8].

Common differentially expressed genes (DEGs) may provide further insight into the shared biological mechanisms in COPD and AMI. DEGs between disease samples and healthy controls in COPD and AMI gene expression profile from the Gene Expression Omnibus (GEO) database were analysed. In the present study, the identified hub genes, the obtained molecular mechanisms and signal pathways may also help to explain the relationships between COPD and AMI.

Methods

Microarray data collection

GSE38974[14] and GSE60993[15] datasets were downloaded from Gene Expression Omnibus (GEO) database and expression arrays were generated using GPL4133 Agilent-014850 Whole Human Genome Microarray 4x44K G4112F(Feature Number version) and GPL6884 Illumina HumanWG-6 v3.0 expression bead chip, respectively. Additionally, GSE38974 included a total of 32 lung samples from 23 patients with COPD and 9 healthy controls (control, n = 9). GSE60993 consisted of 24 whole blood samples from seventeen patients with AMI (AMI, n = 17), and seven healthy controls (control, n = 7).

Screening of DEGs

GEO2R is an online useful tool for analyzing DEGs in the GEO platform[16]. The selected criteria in the AMI dataset were set as *p*-value < 0.05 and |log2 FC| >0.5, while in the COPD dataset, the cut-off values were *p*-value < 0.05 and |log2 FC| >1. The intersection DEGs of two datasets were obtained from the 2 datasets into an online analysis tool Venn. The common DEGs were used for subsequent analysis.

Functional enrichment analyses for common DEGs

The Gene Ontology (GO) functional and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were analyzed by Metascape. $p < 0.05$ were defined as statistically significant.

Protein–protein interaction network construction

A protein–protein interaction (PPI) network for the enriched DEGs of KEGG analysis was conducted by the STRING database. An interaction score with median confidence of 0.4 was the standard cutoff criteria. The network was visualized using the Cytoscape software platform based on functional analysis information. In Cytoscape, cytoHubba was used to identify hub genes.

Diagnostic analysis of hub genes

The usefulness of these hub genes in predicting AMI or COPD were determined by the receiver operator characteristic (ROC) curve analysis. The statistical analysis was conducted using the SPSS software (version 21.0; IBM; New York; America). $p < 0.05$ were defined as statistically significant.

Identification of common DEGs associated with cardiovascular or respiratory tract diseases

The comparative toxicogenomic database was used to predict the correlation between

diseases and genes. The data obtained from CTD were used to analyze association between cardiovascular or respiratory tract diseases and gene products.

Transcription factors (TFs) analysis of hub DEGs

By submitted common DEGs to the Tfacts database (http://www.tfacts.org/), we predicted the TFs regulating common DEGs by false discovery rate, E value, q value, and *p* value. To obtain reliable TFs, false discovery rate, E value, *q* value, and *p* value should be all less than 0.05. The TFs of common DEGs were counted.

Results

Identification of DEGs

The COPD related dataset (GSE38974) was enrolled in the study, the dataset contained 23 COPD patient samples and 9 control samples. A total 937 DEGs were identified in lung tissues of COPD patients compare with the healthy controls. In the AMI dataset GSE60993, 1079 DEGs were screened out when we

compared the 17 AMI samples with 7 normal controls. The volcano plot demonstrating the gene expression profiles of DEGs are presented in Fig. 1A-B. The detailed information about DEGs is listed in Supplementary Table S1–2. Furthermore, we obtained 65 overlapping common genes of 2 datasets and are shown in Fig. 2. The common genes are shown in the Supplementary Table S3.

GO Enrichment and KEGG pathway analyses

The GO and KEGG analysis of 65 common DGEs were performed by metascape. Common DEGs were mostly enriched in GO biological processes (BP) including T cell activation, leukocyte activation involved in immune response, regulation of inflammatory response, intrinsic apoptotic signaling pathway, regulation of MAP kinase activity, immune response-regulating signaling pathway and interleukin-1-mediated signaling pathway, shown in Fig. 3A. In particular, common DEGs were mostly enriched in in the KEGG pathway including apoptosis, HIF-1 signaling pathway, TNF signaling pathway, cytokine-cytokine receptor interaction, Ribosome and MAPK signaling pathway, which are illustrated in Fig. 3B.

PPI network construction for common DEGs and selection of hub genes

The PPI network of common DEGs was constructed to distinguish the hub DEGs from the common DEGs (Fig. 4). The 5 genes with the highest degrees, matrix metallopeptidase 9(MMP9), suppressor of cytokine signaling 3(SOCS3), BCL2 family apoptosis regulator (MCL1), erb-b2 receptor tyrosine kinase 2(ERBB2) and S100 calcium binding protein A12(S100A12), were selected as the hub genes in the PPI network of 65 common genes in AMI and COPD using the degree method in cytoHubba. Furthermore,function annotations of the 5 hub genes were performed to verify the identified biological processes shared between AMI and COPD. The results demonstrated that 5 hub genes were enriched in several biological processes. For example, MMP9 and S100A12 were enriched in leukocyte activation involved in immune response (Fig. 5A). The function annotations of the 5 hub genes were similar to the results of all 65 common DEGs. The results of our study highlighted KEGG terms in which the hub genes were involved (Fig. 5B). For example, MMP9 and SOCS3 were involved in TNF signaling pathway. ERBB2 was involved in HIF-1 signaling pathway, TNF signaling pathway and MAPK signaling pathway. Summaries for 5 hub genes are shown in Table 1–2.

Table 1
5 hub DEGs in GSE60993 and GSE38974 datasets

	GSE38974			GSE60993		
Gene symbol	logFC	*P*-value	Up/Down	logFC	*P*-value	Up/ Down
MMP9	1.7673041	0.000447	Up	2.33552668	0.00132	Up
SOCS3	1.264646	0.0106	Up	0.78445416	0.0174	UP
MCL1	1.1121676	0.0000000376	Up	0.63065429	0.0258	UP
S100A12	1.5003103	0.0206	Up	1.43428615	0.00171	UP
ERBB2	-1.1977155	0.000000000312	Down	-0.66181458	0.00617	Down

Table 2
Review of the hub genes involvement in AMI and COPD

No	Gene symbol	Full name	AMI	COPD
1	MMP9	matrix metallopeptidase 9	MMP9, as one inflammationassociated gene, was found to be significantly elevated in the AMI patients when compared to the normal controls subjects[17].	MMP-9 levels were higher in patients with COPD compared with controls[18].
2	SOCS3	suppressor of cytokine signaling 3	The mRNA expression levels of the SOCS3 gene in peripheral blood cells of AMI patients was 1.33-fold higher than that in the stable coronary artery disease (SCAD) patients[19].	Emerging data on SOCS-3 activation in the lungs during inflammation suggests that SOCS3 can be potential targets for regulating pulmonary inflammatory responses in COPD[20].
3	MCL1	anti-apoptotic Bcl-2 family member myeloid cell leukemia-1	MCL1 gene was up-regulated in the early stage of rat myocardial infarction[21].	Unstimulated neutrophils from COPD patients had significantly lower Bak mRNA expression and higher expressions of Bcl-xl and Mcl-1 mRNA than cells from healthy controls[22].
4	S100A12	S100 calcium binding protein A12	A gene-by-gene analysis of the platelet gene expression identified that S100A12 increased in the AMI patients when compared to the normal controls subjects[23].	S100A12 was identified to mediate inflammation and injury of the lung, and play critical roles in the pathogenesis of COPD[24].
5	ERBB2	erb-b2 receptor tyrosine kinase 2	Expression of ErbB2 and ErbB4 receptors mRNA is down-regulated in myocardial infarction, which may result from the hypoxia, deprivation of nutrients and cytokines[25].	ERBB2 was activated in whole lung, as well as isolated epithelial cells, from smokers, and that acute cigarette smoke exposure resulted in ERBB2 activation in cultured bronchial epithelial cells[26].

Validation of diagnostic value of hub genes

we constructed ROC curves to calculate the corresponding area under the curve (AUC) of these gene expression levels in the COPD and AMI datasets and to validate the diagnostic value of the 5 hub genes obtained from the above analysis. The expression of MMP9, SOCS3, MCL1, ERBB2 and S100A12 were also significantly associated with a diagnosis value of COPD (MMP9: AUC = 0.8502, $p = 0.0024$; SOCS3: AUC = 0.7633, $p = 0.0224$; MCL1: AUC = 0.9758, $p < 0.0001$; ERBB2: AUC = 0.9952, $p < 0.0001$; S100A12: AUC = 0.7633, $p = 0.0224$). The results were shown in Table 3 and Fig. 6. The expression of MMP9,

SOCS3, MCL1, ERBB2 and S100A12 were significantly associated with a diagnosis value of AMI (MMP9: AUC = 0.8824, $p = 0.0039$; SOCS3: AUC = 0.8403, $p = 0.0101$; MCL1: AUC = 0.7983, $p = 0.0242$; ERBB2: AUC = 0.8235, $p = 0.0145$; S100A12: AUC = 0.8992, $p = 0.0026$). The results were shown in Table 4 and Fig. 7.

Table 3
Receiver operator characteristic curve analysis of hub gene expression for COPD.

gene	p-value	AUC	95%CI
MMP9	0.0024	0.8502	0.7167–0.9837
SOCS3	0.0224	0.7633	0.546–0.9806
MCL1	< 0.0001	0.9758	0.9304–1.021
S100A12	0.0224	0.7633	0.5835–0.943
ERBB2	< 0.0001	0.9952	0.9796–1.011

Table 4
Receiver operator characteristic curve analysis of hub gene expression for AMI.

gene	p-value	AUC	95%CI
MMP9	0.0039	0.8824	0.7432–1.021
SOCS3	0.0101	0.8403	0.6772–1.003
MCL1	0.0242	0.7983	0.6155–0.9811
S100A12	0.0026	0.8992	0.7697–1.029
ERBB2	0.0145	0.8235	0.6525–0.9946

Identification of hub genes in the CTD database

The CTD database showed that MMP9, SOCS3, MCL1, ERBB2 and S100A12 targeted several respiratory tract diseases including COPD (MMP9: inference score 57.44; SOCS3: inference score 37.82; MCL1: inference score 23.72; ERBB2: inference score 16.39; S100A12: inference score 22.48) and several cardiovascular diseases including AMI (MMP9: inference score 227.15; SOCS3: inference score 101.21; MCL1: inference score 101.13; ERBB2: inference score 89.55; S100A12: inference score 14.89). The results are shown in Fig. 8–9.

TFs analysis of hub genes in AMI and COPD

We further analyzed the TFs corresponding to hub genes in AMI and COPD. 4 TFs including ELK1(ETS TF ELK1), STAT3(signal transducer and activator of transcription 3), ETV4(ETS variant TF 4) and TFAP2A (TF AP-2α), with 8 interactions obtained. For example,STAT3 had a strong regulatory effect on MCL1 and SOSC3. ETV4 could regulate MMP9 and ERBB2 (Fig. 10).

Discussion

In the present study, through analysing the COPD dataset (GSE38974) and the AMI dataset (GSE60993) from GEO, we found 65 common DEGs between these diseases. GO enrichment and KEGG pathway enrichment analyses were performed on the Metascape, and a PPI network was constructed to identify the top 5 hub genes from among the 65 common DEGs. These 5 genes may have important regulatory roles in COPD and AMI. The results of the present study may be beneficial for understanding the relationship between COPD and AMI.

In our study, GO enrichment analysis showed that common DEGs were mostly enriched in inflammation or apoptotic biological processes, such as intrinsic apoptotic signaling pathway, regulation of inflammatory response and immune response-regulating signaling pathway. Common DEGs in the KEGG pathway were mostly enriched in apoptosis, cytokine-cytokine receptor interaction, TNF signaling pathway, MAPK signaling pathway and HIF-1 signaling pathway. The results implied that above biological processes and pathways might acted important roles in COPD and AMI. Chronic inflammation affected predominantly the lung parenchyma and peripheral airways that resulted in largely irreversible and progressive airflow limitation during the process of COPD[27]. Inflammation is significant in the pathophysiology of atherosclerosis and of acute coronary syndromes and inflammatory activity in the vessel wall act important roles in plaque instability in AMI[28]. Therapeutic interventions in vivo implied that targeted inhibition of specific inflammatory signals protected the heart from acute infarcted injury and prevented adverse remodelling following MI[29]. Bronchial epithelial cells apoptosis is increased in COPD and contributed to the pathogenesis of COPD[30]. Ischemia hypoxia induces cardiomyocyte (CM) apoptosis in the process of AMI[31]. It has been reported that cytokine-cytokine receptor interaction was a significant pathway in COPD and AMI[24, 32]. Compared with healthy controls, TNF-α level was increased in COPD patients and higher TNF-α levels were induced by illness progression [33]. Inhibiting the inflammatory response by targeting TNF-α might be a potential therapeutic target for COPD[34]. TNF-α is a major predictor of mortality and new-onset heart failure in patients with AMI[35]. TNF-α antagonism ameliorates myocardial ischemia-reperfusion(I/R) injury in mice[36]. Compared with treatment with topical agents, use of TNF inhibitors for psoriasis was associated with a significant reduction in MI incident rate and risk [37]. Convincing evidence confirms a central role of HIF-1 in mammalian oxygen homeostasis[38]. With regard to the HIF-1 signaling pathway in COPD, increased expression of HIF-1, VEGF and VEGFR2 reflected the disease severity of COPD[39]. HIF-1 attenuated progression of cardiac dysfunction after MI and reduced infarction in the mouse[40]. Suppression of PHD2/HIF-1α/MAPK signaling pathway with NaHS may prevent emphysema, and subsequently inflammation, epithelial cell injury and apoptosis, and may be a novel strategy for the treatment of COPD[41]. AMI was accompanied by endoplasmic reticulum stress, probably involving the MAPK signaling pathway and SB203580, a specific inhibitor of the MAPK signaling pathway, could relieve CM apoptosis and protect the myocardium by suppressing such stress[42]. Our results were in accordance with previous studies.

In the PPI network of 65 overlapping DEGs in AMI and COPD, MMP9, SOCS3, MCL1, ERBB2 and S100A12 were identified as the hub genes using the degree method in cytoHubba. In addition, function annotations

of the 5 hub genes were performed and were similar to the enrichment results of all 65 common DEGs. MMPs, also called matrixins, are zinc-dependent endopeptidases known for their ability to cleave one or several extracellular matrix (ECM) constituents[43]. MMP9, one of the most complex forms of matrix metalloproteinases, has the ability to degrade the ECM components and has significant role in the pathophysiological functions[44]. MMP9 uniquely mediates pulmonary inflammation through augmentation of inflammation, neutrophil chemotaxis, and extracellular matrix degradation [45]. In the sever or very severe COPD patients, the mRNA levels of MMP9 increased compared to non-COPD smokers or moderate COPD patients[46]. Serum MMP9 is elevated in men with a history of MI and increased serum MMP9 may reflect inflammatory pathologic processes that are involved in the progression of atherosclerosis[47]. The SOCS family are responsible for preventing excessive cytokine signaling, including a group of eight proteins [48]. Among the different SOCS proteins, SOCS3 has received special attention and its dysfunction may be related with several diseases, including vascular inflammatory diseases, inflammatory bowel disease, cancers[49]. SOCS3 played important roles in COPD and was involved in JAK/STAT signaling pathway[50]. SOCS3 was significantly decreased in COPD at the transcriptional level and inhibition of SOCS3 mRNA expression may be associated with the dysbalance of cytokine signaling in COPD[51]. SOCS3 has also been identified as a key gene in AMI according to previous studies[52, 53]. SOCS3 increased in the vast majority of patients in the first days of MI [54]. The mRNA expression levels of the SOCS3 gene in AMI patients was 1.33-fold higher than that in the stable coronary artery disease patients, and the level of the SOCS3 protein was 1.25-fold higher[19]. B-cell lymphoma-2 (BCL2) family proteins, comprising proapoptotic proteins (Bax and Bak), antiapoptotic proteins (BCL2, BCL-XL, BCL-w, MCL1, and A1) and BCL-2 homology domain 3 (BH3)-only proteins (Bid, Noxa, and Puma), have long been identified as pivotal apoptosis regulators[55]. MCL1 is a crucial antiapoptotic member of the BCL-2 family and plays a key role in promoting cell survival[56]. Unstimulated neutrophils from COPD patients had significantly higher expressions of MCL1 mRNA than cells from healthy controls and MCL1 mRNA expressions were significantly negatively correlated with the FEV1/FVC ratio and predicted FEV1 [22]. A recent study demonstrated that chronic adaption to oxidative stress and up-regulation of MCL1 altered microbicidal function and mitochondrial metabolism, reducing the delayed phase of intracellular bacterial clearance in COPD[57]. Animal experiments showed that MCL1 was up-regulated in the early stage of rat MI[21]. miR-302 mediates hypoxia-reoxygenation-induced CM death by regulating MCL1 expression[58]. In SOCS3-CKO mice, myocardial apoptosis was prevented and the expression of MCL1 was augmented in myocardial efficacy injury[59]. ERBB2, also known as HER2 (Human Epidermal Growth Factor Receptor 2), CD340, and Neu protooncogene, is a member of the epidermal growth factor receptor (EGRF) family[60]. It has been reported that ERBB2 was activated in smokers and patients with COPD suggests that targeting ERBB2 with currently available inhibitors might be beneficial in reducing epithelial injury and pulmonary dysfunction caused by CS[26]. The mRNA expression of ERBB2 receptors was significantly down-regulated in the left ventricle of MI compared with the normal left ventricle[25]. PTP-PEST contributed to part of the damages resulting from myocardial I/R and Auranofin, potentially acting through the PTP-PEST- ERBB2 signalling axis, reduced myocardial I/R injury[61]. S100 proteins are Ca^2+-binding proteins exclusively expressed in vertebrates in a cell-specific manner and they might regulate a variety of functions acting as intracellular Ca^2 + sensors transducing

the Ca^{2+} signal and extracellular factors affecting cellular activity via ligation of a battery of membrane receptors[62]. Expression of S100A12 by monocytes/macrophages and neutrophils induces proinflammatory responses via ligation with the receptor for advanced glycation end-products (RAGE) and subsequent activation of intracellular signal transduction pathways [63]. S100A12 was identified to regulate injury and inflammation of the lung, and play key roles in the pathogenesis of COPD[24]. S100A12 activated airway epithelial cells to produce MUC5AC, which was known to contribute to severe muco-obstructive lung diseases worsening COPD pathogenesis [64, 65]. S100A12 is also involved in inflammatory cardiovascular disease and could be a novel biomarker for predicting cardiovascular events [66]. A gene-by-gene analysis of the platelet gene expression identified that S100A12 increased in the AMI patients when compared to the healthy controls[23]. These studies illustrated that MMP9, SOCS3, MCL1, ERBB2 and S100A12 played import roles in both COPD and AMI. Furthermore, we found that the expression of MMP9, SOCS3, MCL1, ERBB2 and S100A12 were significantly associated with a diagnosis efficacy of COPD and AMI using the area under the ROC curve (AUC). We also validated the relationship between the five hub genes and these two diseases in the CTD database.

In addition, we further analyzed the TFs corresponding to hub genes in AMI and COPD. We found that ELK1, ETV4, STAT3 and TFAP2A were significant TFs, which interacted with the hub genes. TF ELK1 has been found to act a carcinogenic role in human cancers, like hepatocellular carcinoma, thyroid cancer, breast cancer[67]. Jennifer T Cairns etal. have proved that human lung epithelial cells and murine lung slices to CS extract demonstrated reduction of ELK1[68]. Endothelial cells (ECs) apoptosis contributes the initiation and progression of atherosclerosis, which involves the development of AMI[8]. miR-150 expression was substantially up-regulated during the oxidized low-density lipoprotein-induced apoptosis in ECs via targeting ELK1[69]. It has been reported that ELK1 knockdown was sufficient to block ascites-induced MCL1 expression in ovarian cancer cells[70]. ETV4 belongs to the E26 transformation-specific (ETS) family and has been found to be overexpressed in multiple cancers[71]. Overexpression of NRP2 induced expression of the TF ETV4 and ERK MAP kinase, leading to enhanced MMP2 and MMP9 activity and suppression of E-cadherin in oesophageal squamous cell carcinoma (ESCC)[72]. STAT3 is one of the crucial transcription factors, responsible for regulating immune activation, angiogenesis, inflammatory response, programmed cell death, cellular differentiation, migration, and cellular proliferation [73]. STAT3 participates in the signaling pathways for many cytokines in various cells and organs that are regulated by the suppressor of SOCS3 and the activation and function of STAT3 and SOCS3 in the lung during the acute inflammatory response are emerging[74]. Cardiac-specific SOCS3 deletion enhanced multiple cardioprotective signaling pathways including extracellular signal-regulated kinase (ERK)-1/2, AKT and STAT3[75]. As one member of the activator protein 2 (AP-2) TF family, TFAP2A is important for the regulation of gene expression during early development as well as carcinogenesis process[76]. High ERBB2 expression may result either from gene amplification or from increased TFAP2A levels in breast tumours[77]. However, the roles of four TFs, ELK1, ETV4, STAT3 and TFAP2A in COPD and AMI, and the four TFs interactions with hub genes, are still need further exploration.

However, there are several limitations in our study. First,our study is a microarray analysis that all the results based on gene expression value. The sample sizes were relatively small, and larger-sample, multicenter research is needed. Second, the DEGs screened in our study are associated with COPD and AMI, and external validation in vivo and in vitro experiments and with clinical cases is needed to consolidate our results. Additionally, it is necessary to perform functional studies to confirm the roles of the DEGs in COPD and AMI.

Conclusion

our study revealed the communal DEGs and related mechanisms between the pathophysiology of COPD and AMI. MMP9, SOCS3, MCL1, ERBB2 and S100A12 were identified as the hub genes that are associated with COPD and AMI. Our study provides new ideas and evidence for further research of the mechanisms and treatment of COPD and AMI.

Declarations

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Data Availability Statement

GSE38974[14] and GSE60993[15] datasets were downloaded from Gene Expression Omnibus (GEO) database. Other datasets supporting the conclusions of this article are included within the article and Supplementary Material.

Authors' contributions

FSC, HJH and BT: takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation, drafting the article. FSC, BT, DW, HJH and JH: takes responsibility for statistical analyses, and interpretation of data. BT, HJH and JH: takes responsibility for full text evaluation and guidance, final approval of the version to be submitted. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable

Ethics approval and consent to participate

Not applicable.

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Figures

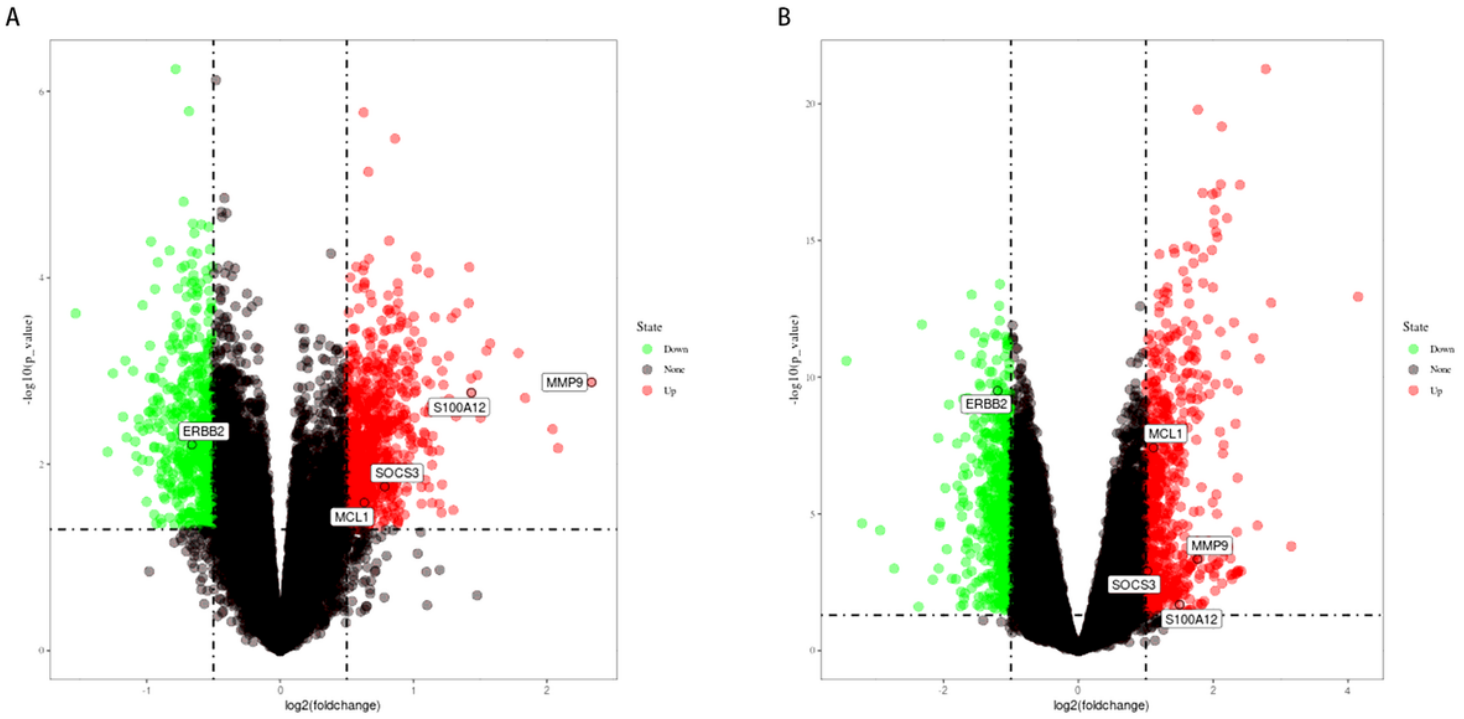

Figure 1

DEGs in the COPD dataset GSE38974 and the AMI dataset GSE60993. Volcano plot of DEGs in GSE38974 (A) and GSE60993 (B). The red and blue points symbolize the upregulated and downregulated DEGs with statistical significance.

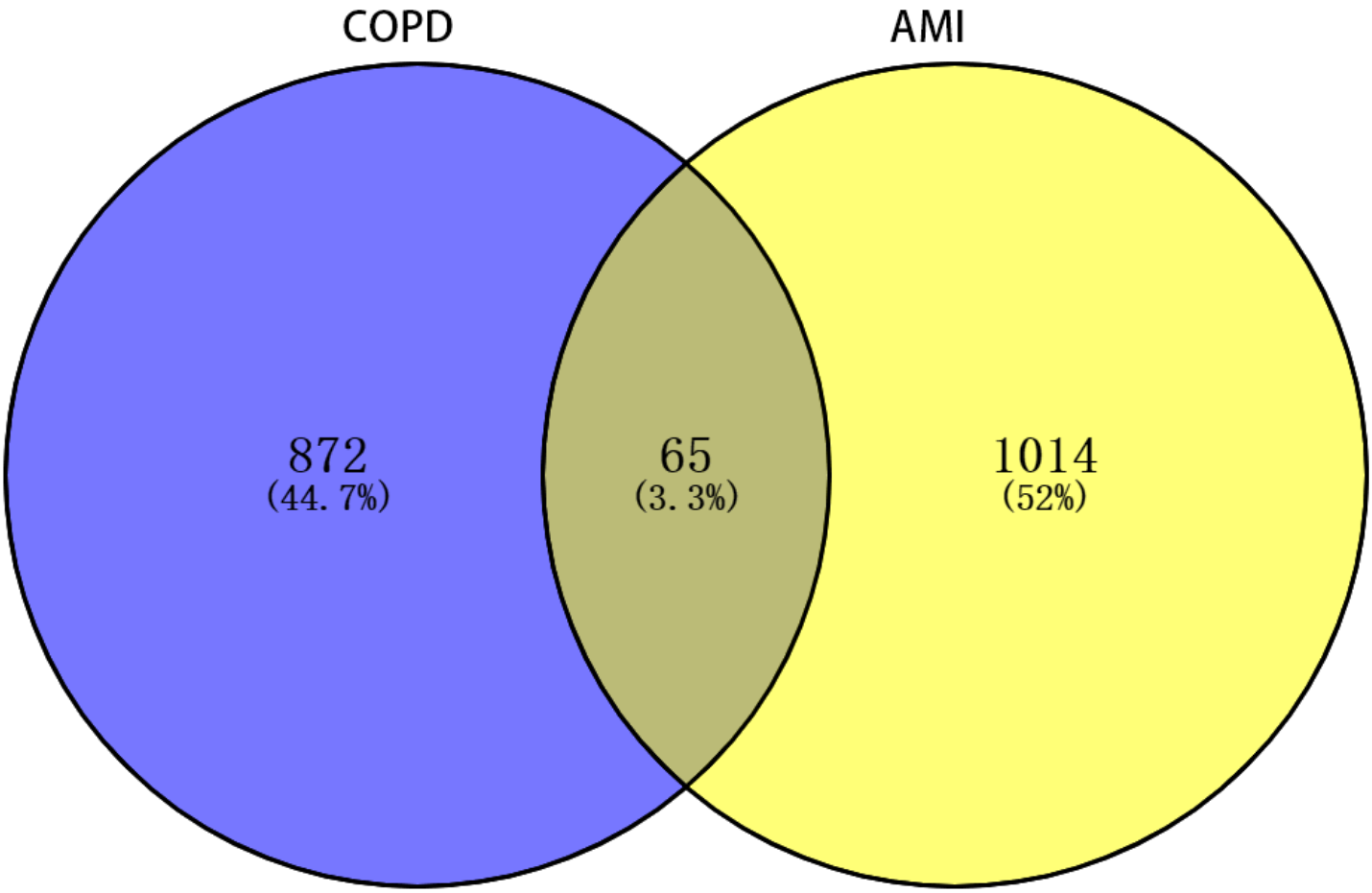

Figure 2

Venn graph of common DEGs in GSE38974 and GSE60993.

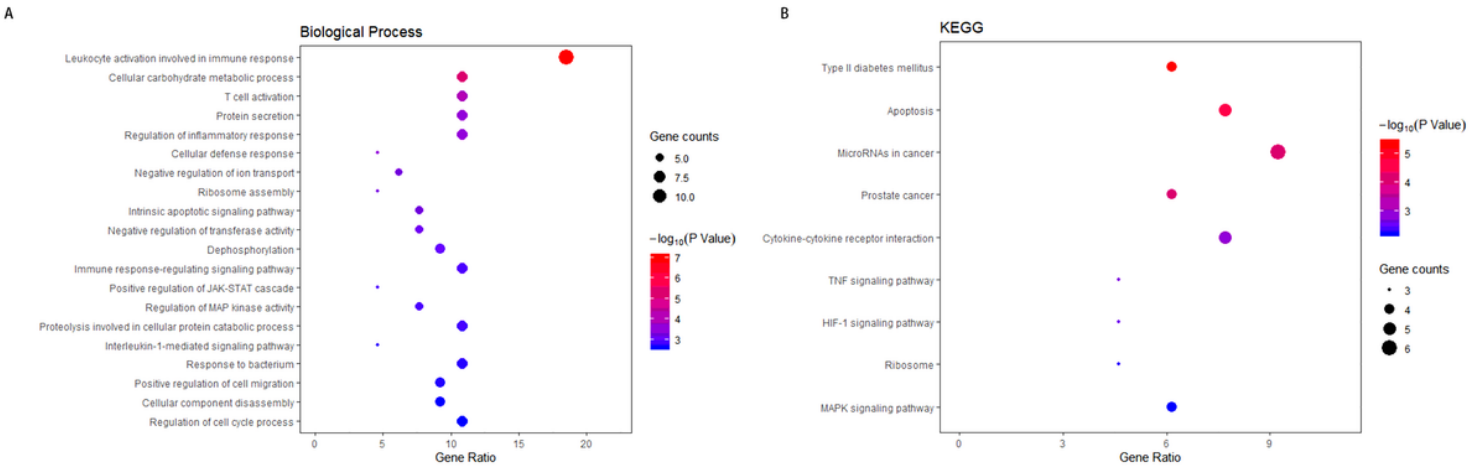

Figure 3

GO and KEGG pathway functional enrichment analysis of the common DEGs. (A) The representative significant GO terms. (B) The representative significant KEGG pathway terms.

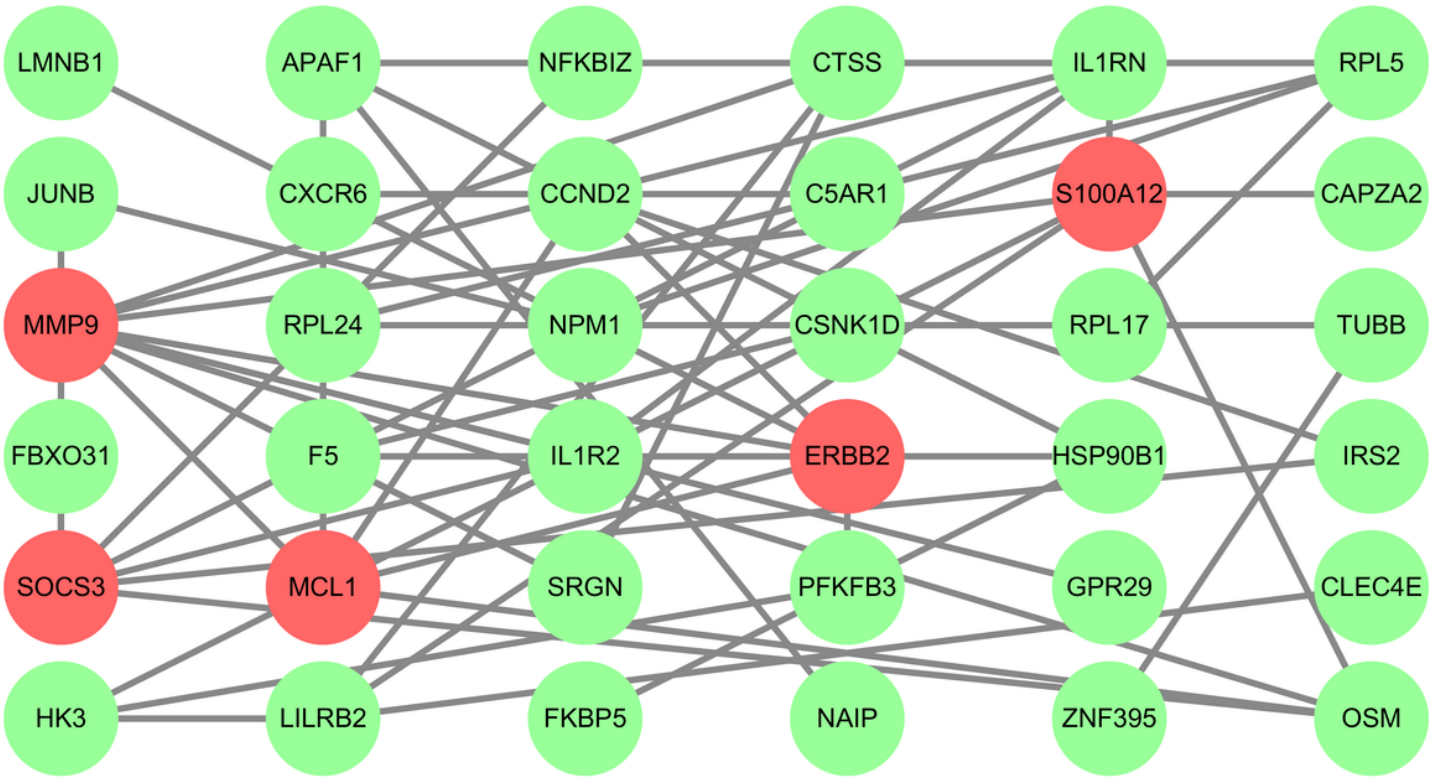

Figure 4

Protein–protein interaction network of the common DEGs. Red circle nodes had higher degree and were identified as hub genes.

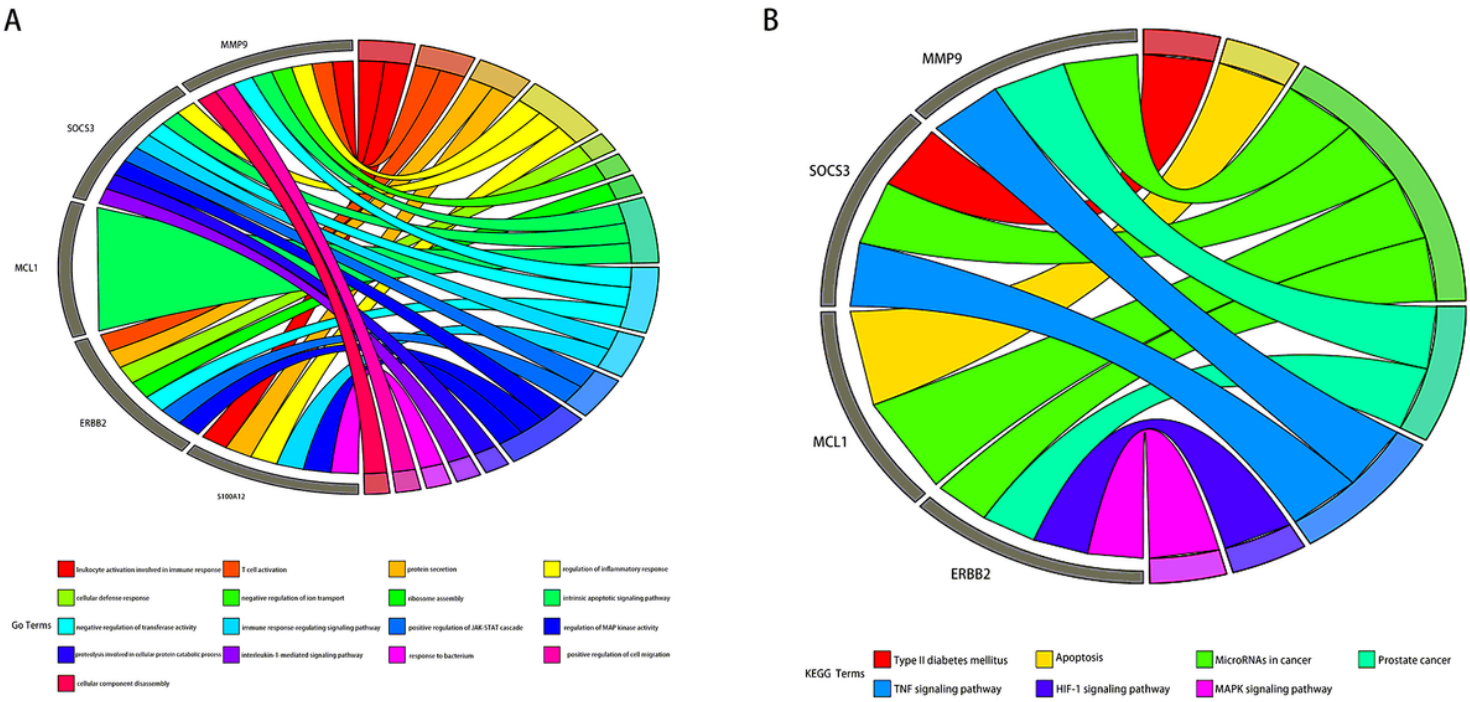

Figure 5

Functional annotation of the hub genes. (A) Circos plot of the GOs enriched by hub genes. (B) Circos plot of the KEGG pathway enriched by hub genes.

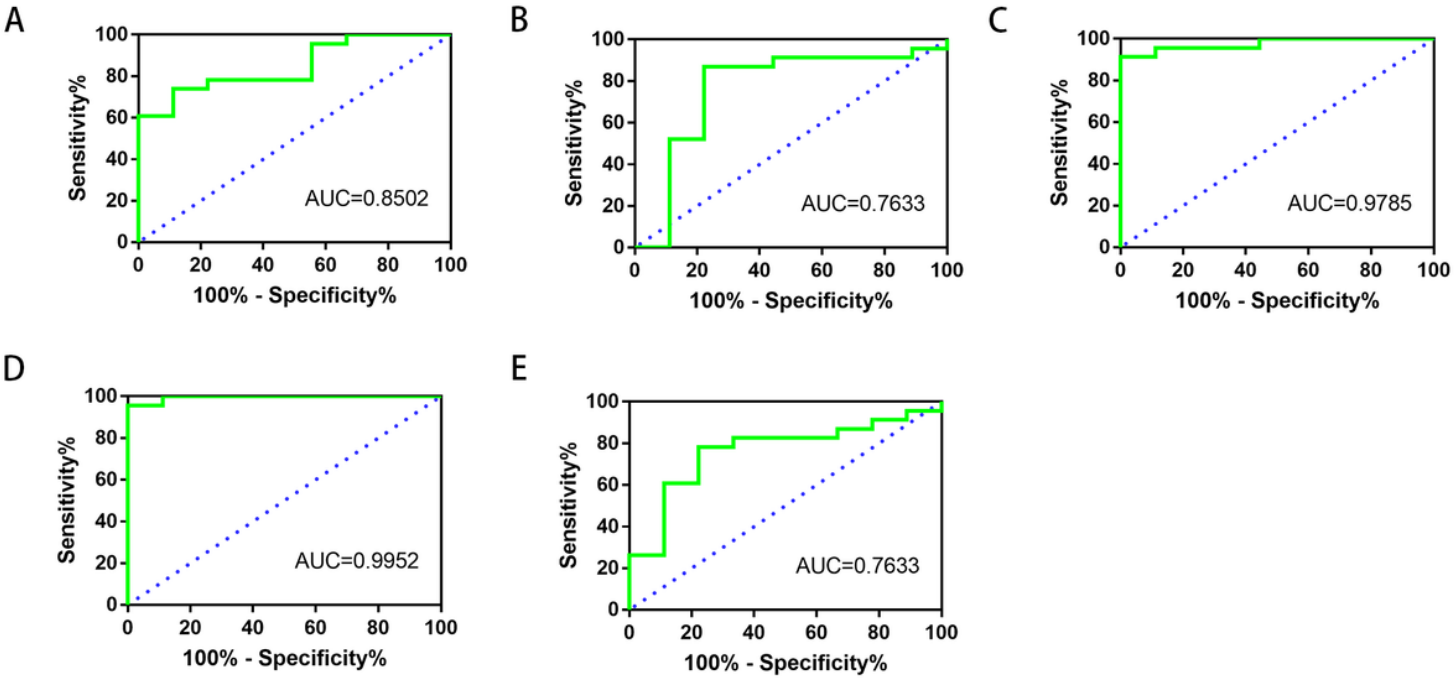

Figure 6

Diagnostic value of MMP9(A), SOCS3(B), MCL1(C), ERBB2(D) and S100A12(E) with ROC curves in COPD.

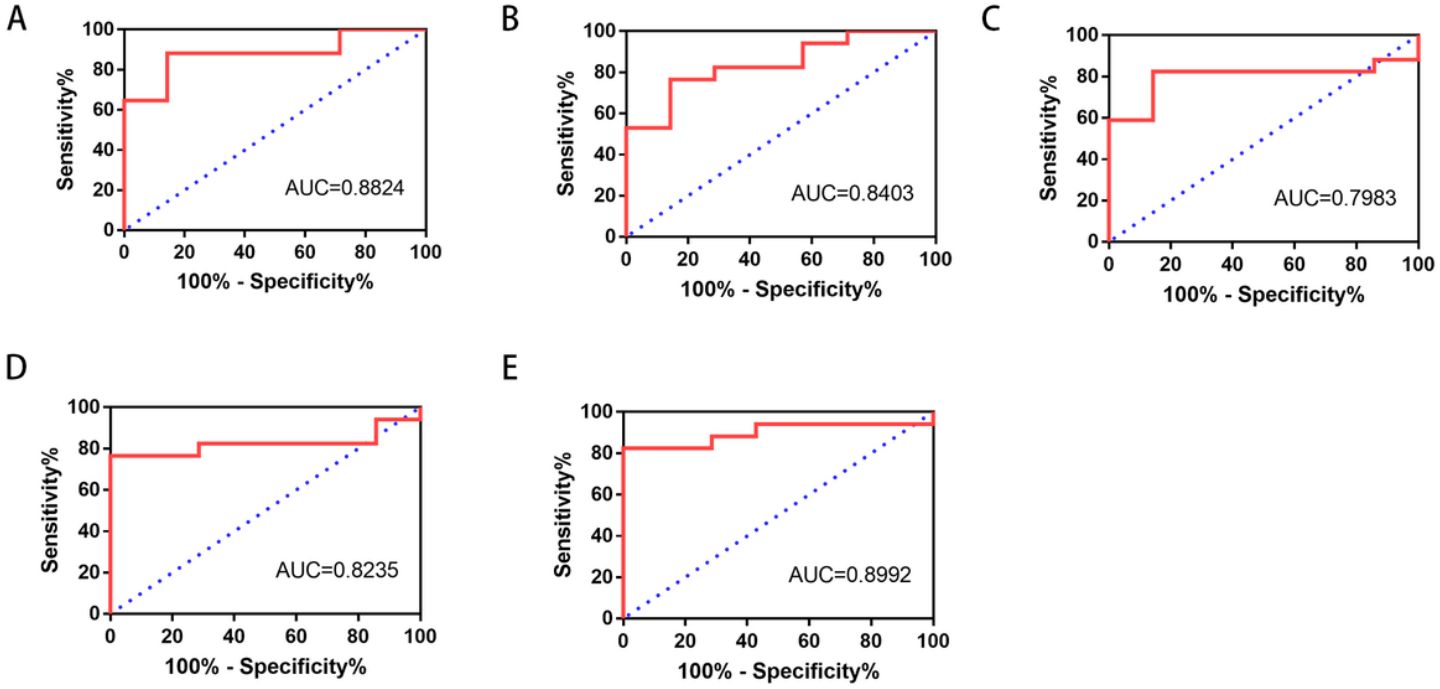

Figure 7

Diagnostic value of MMP9(A), SOCS3(B), MCL1(C), ERBB2(D) and S100A12(E) with ROC curves in AMI.

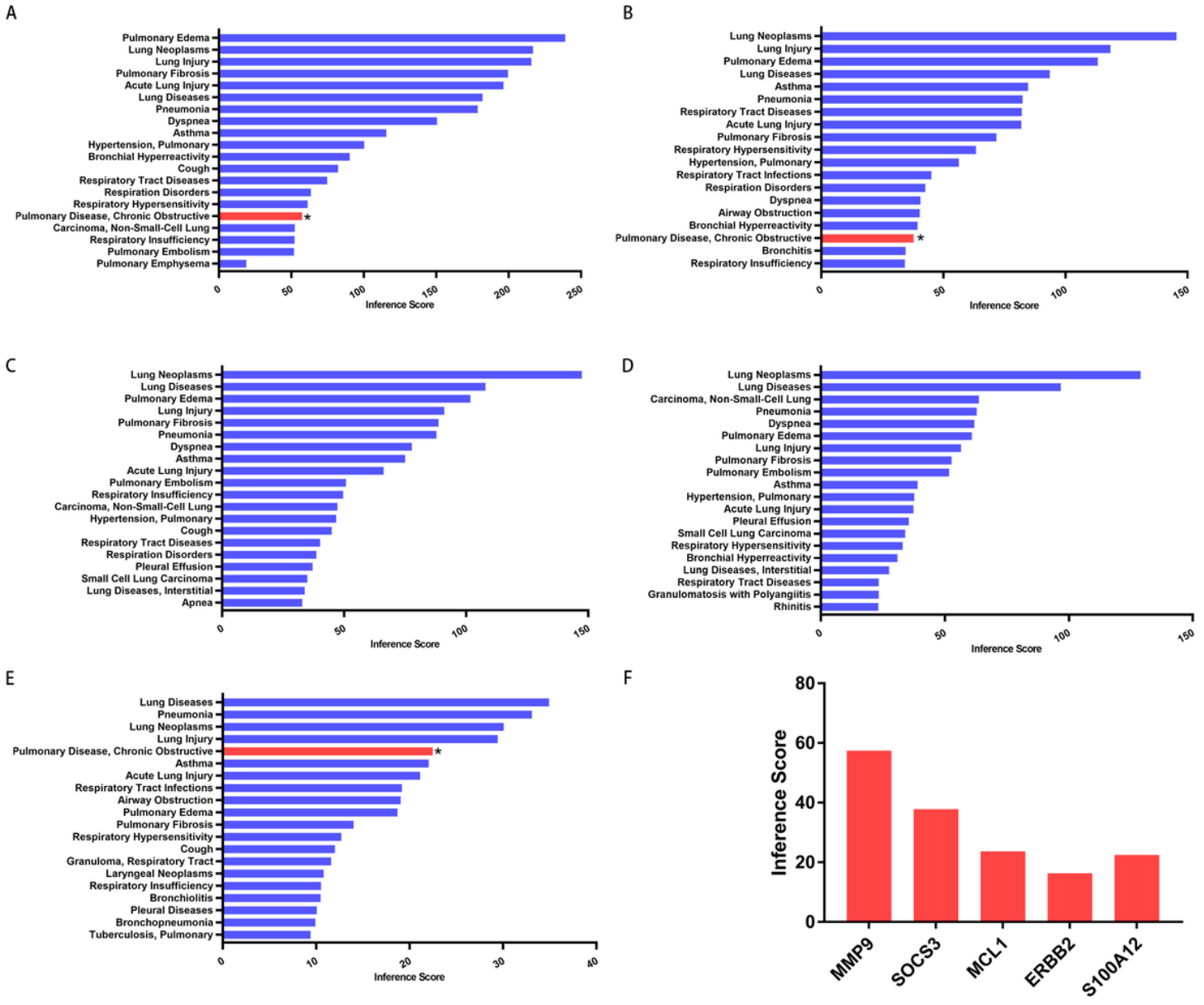

Figure 8

Identification of hub genes with respiratory tract diseases in the CTD database. Top 20 relationship to respiratory tract diseases related to MMP9(A), SOCS3(B), MCL1(C), ERBB2(D) and S100A12(E) based on the CTD database. * relationship to COPD. (F) Identification of hub genes with COPD in the CTD database.

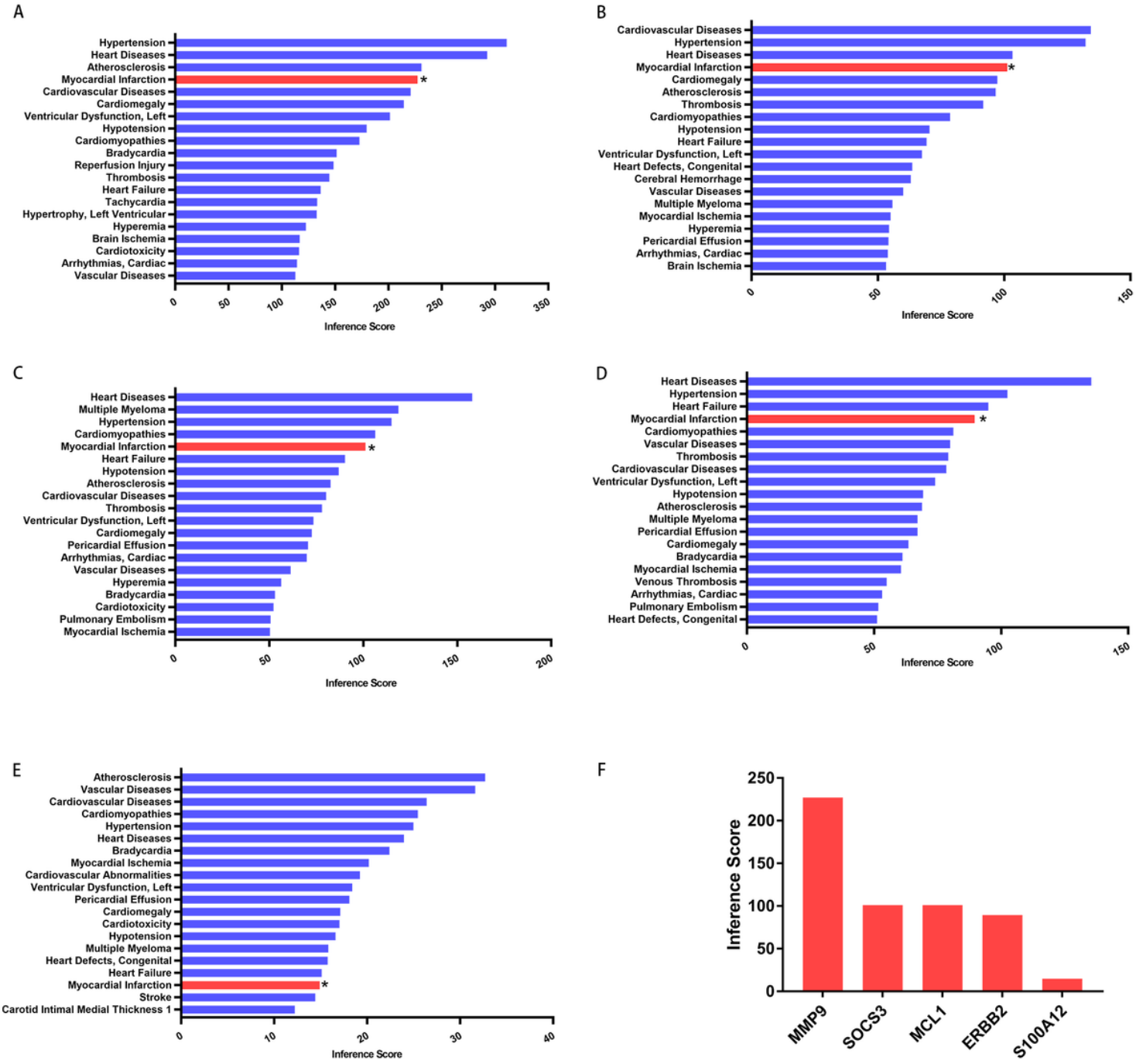

Figure 9

Identification of hub genes with cardiovascular diseases in the CTD database. Top 20 relationship to cardiovascular diseases related to MMP9(A), SOCS3(B), MCL1(C), ERBB2(D) and S100A12(E) based on the CTD database. * relationship to AMI. (F) Identification of hub genes with MI in the CTD database.

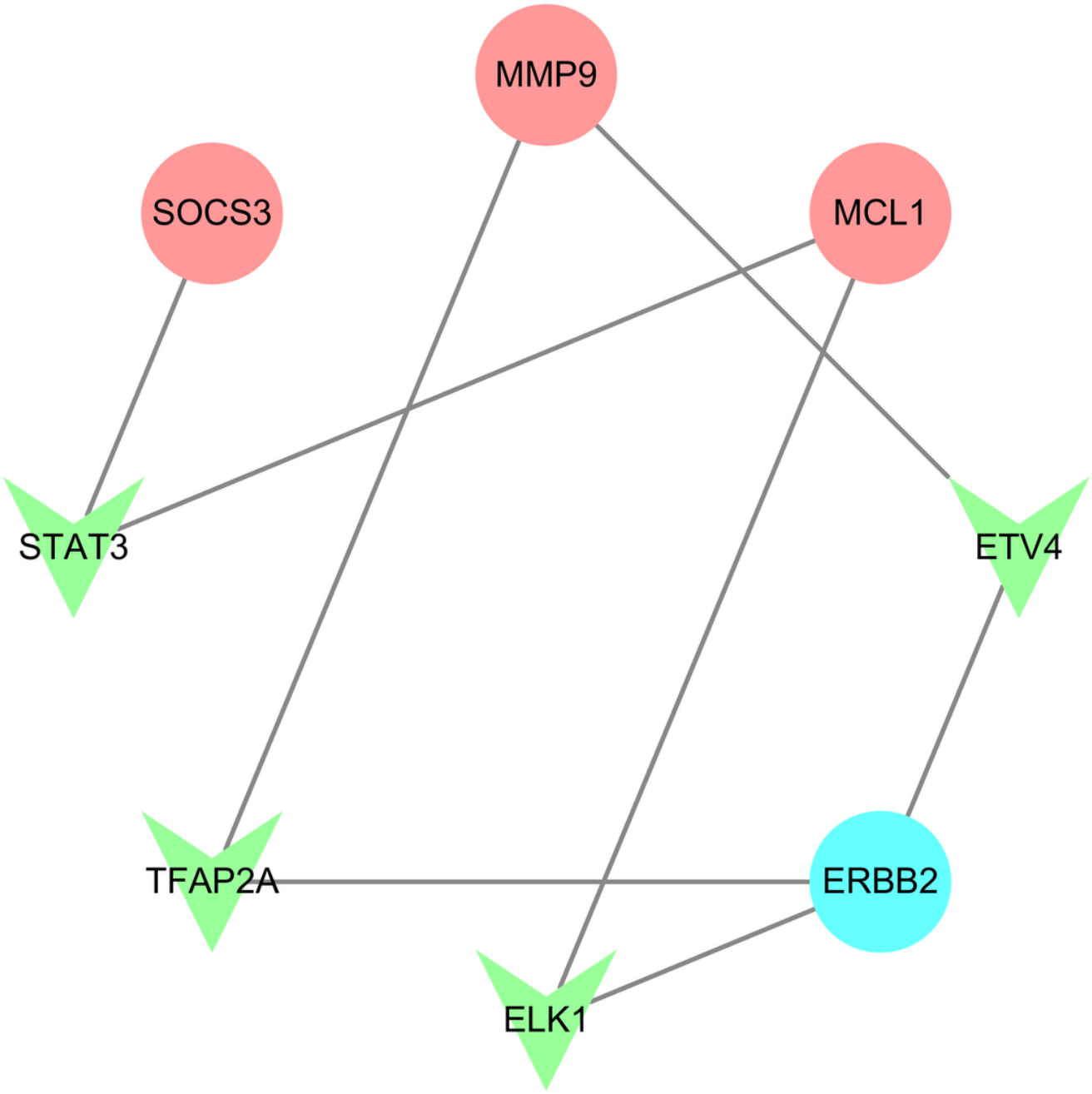

Figure 10

Transcription factor analysis network of hub genes in AMI and COPD. The shape of V indicates the TFs, while the red nodes indicate upregulated hub genes and the green nodes indicate downregulated hub genes.

Supplementary Files

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

- SupplementaryTableS1.xlsx

- SupplementaryTableS2.xlsx
- SupplementaryTableS3.xls