Identification and analysis of co-disease genes between COVID-19 and osteoarthritis

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Research Article

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Identification and analysis of co-disease genes between COVID-19 and osteoarthritis

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Abstract

Background: The molecular mechanisms of corona virus disease 2019 (COVID-19) and osteoarthritis (OA) are unclear, and there is an urgent need to identify new biomarkers and explore their potential molecular mechanisms in COVID-19 and OA.

Methods: The GSE57218, GSE157103 training sets and the GSE82107, GSE171110 validation sets were acquired via gene expression omnibus (GEO) database. First, differentially expressed genes (DEGs) between disease and normal samples in the GSE57218 and GSE157103 training sets were respectively sifted out by differential expression analysis. The modules with the highest correlation with OA and normal, COVID-19 and non COVID-19 were gained by weighted gene co-expression network analysis (WGCNA), individually. Then, OA-DEGs were intersected with the module genes that had significant correlation with OA, and COVID-19-DEGs were intersected with the module genes which were dramatically correlated with COVID-19 to yield OA-intersected genes and COVID-19 intersected genes, respectively. The OA-intersected genes and COVID-19 intersected genes were intersected to yield candidate genes, and they were analyzed for function enrichment analysis. Next, the seven algorithms (Closeness, MCC, Degree, MNC, Radality, Stress and EPC) were performed on candidate genes to sift out biomarkers. Finally, we constructed the competing endogenous RNA (ceRNA), transcription factor (TF)/miRNA-mRNA and drug-target regulatory networks.

Results: There were 1135 OA-DEGs and 4336 COVID-19-DEGs between disease and normal samples in the GSE57218 and GSE157103 training sets, respectively. The pink, blue and brown modules had...
significant correlations with OA in the GSE57218 training set, while in the GSE157103 training set, the pink and brown modules were notably correlated with COVID-19. We finally yield 715 OA-intersected genes and 2282 COVID-19-intersected genes. After intersecting the above two intersected genes, we gained 106 candidate genes, and they were involved in ADP metabolic process, nucleoside diphosphate phosphorylation, etc.. The 7 biomarkers, namely AK1, APP, ENO1, TPI1, HSP90B1, HSPB1 and ESR1, were acquired based on seven algorithms. Finally, we successfully constructed the ceRNA, TF/miRNA-mRNA and drug-target networks.

**Conclusion:** Through bioinformatic methods, we explored the biomarkers (AK1, APP, ENO1, TPI1, HSP90B1, HSPB1 and ESR1) of COVID-19 combined OA, providing new ideas for studies related to molecular mechanisms and treatment of comorbidity.

**Key words:** Corona virus disease 2019; osteoarthritis; GEO; Bioinformatic

1. Introduction

Coronavirus (CoV) is the largest group of Nestoviruses. In the past 20 years, CoV has caused three global outbreaks, with coronavirus disease (COVID-19) being the latest in 2019 in Wuhan, China[1]. A group of patients developed atypical pneumonia-like respiratory symptoms and shared a history of visiting the Wuhan seafood market[2]. Initially, the virus was considered a new type of CoV and labeled 2019 New CoV (2019 nCoV). The World Health Organization (WHO) declared the epidemic a public health emergency on January 30, 2020 and was declared a global pandemic on March 11, 2020[3]. As the number of COVID-19 cases continues to increase globally, its confirmed cases now exceed 486.8 million, and the number of deaths exceeds 6.1 million, having a significant impact on the world[4]. The main transmission routes include direct contact, droplet inhalation, or contact with the oral cavity and nasal cavity. Typical clinical symptoms include fever, dry cough, myalgia, and pneumonia[5,6]. Severe cases can lead to respiratory failure[7]. Currently, most countries' targeted vaccine research and development for COVID-19 have problems such as complex processes, relatively high market prices, and difficulty to find targets. These restrictions prevent routine vaccination for COVID-19 patients[8]. In addition, COVID-19 can cause multiple complications, leading to poor prognosis in COVID-19 patients[9]. Therefore, identifying new biomarkers and exploring their potential molecular mechanisms is crucial for the targeted treatment of COVID-19.
Osteoarthritis is a common chronic degenerative joint disease. The definition of OA by the International Association for the Study of Osteoarthritis is: "This disease first manifests itself as a molecular disorder (abnormal metabolism of joint tissue), and/or a physiological disorder (characterized by cartilage degradation, bone remodeling, etc.)." Leading to osteophyte formation, joint inflammation, and loss of normal joint function, ultimately leading to disease\(^{[10]}\). Its pathogenesis is complex and unclear. The main pathological changes are apoptosis and dysfunction of chondrocytes\(^{[11]}\). It is estimated that 240 million people worldwide suffer from OA with symptoms and limited activity\(^{[12]}\). Almost 30% of patients over the age of 45 have radiographic evidence of knee osteoarthritis, and approximately half have knee symptoms\(^{[10]}\). The prevalence of symptomatic radiographic hip osteoarthritis is approximately 10%\(^{[10]}\). Because of the age characteristics of the disease, it is usually accompanied by primary chronic diseases such as cardiovascular disease/diabetes, which not only brings economic burden to patients and society, but also is more vulnerable to COVID-19\(^{[13]}\). Moreover, COVID-19 can affect the treatment strategy of OA. The use of non steroidal anti-inflammatory drugs, paracetamol, and other drugs to relieve pain in the early stage of OA may increase the incidence of secondary infection or complications of COVID-19, and the late stage of OA may affect joint replacement surgery\(^{[14]}\). In order to develop effective treatment strategies, it is necessary to study the underlying mechanisms of the development of osteoarthritis.

Biomarkers refer to biochemical indicators that can mark changes or possible changes in the structure or function of systems, organs, tissues, cells, and subcellular cells, and have a very wide range of uses\(^{[15]}\). Biomarkers can be used to diagnose diseases, determine disease stages, or evaluate the safety and effectiveness of new drugs or therapies in target populations\(^{[16]}\).

In this study, we obtained the relevant data sets of osteoarthritis and COVID-19 from GEO database, and the biomarkers of osteoarthritis complicated with novel coronavirus using weighted gene co expression network analysis (WGCNA), differential gene expression analysis, construction of PPI network and other methods. We have also constructed ceRNA, TF/miRNA-mRNA, and drug target regulatory networks based on biomarkers. Exploring the mechanism of biomarkers in the pathogenesis of OA complicated with COVID-19 infection is of great significance for the diagnosis and treatment of complications.
2. Materials and methods

2.1 Source of data


2.2 Differential expression analysis and weighted gene co-expression network analysis (WGCNA)

In this study, the differentially expressed genes (DEGs) between disease and normal samples in the GSE57218 and GSE157103 training sets were sifted out by limma package (version 3.42.2) [PMID: 34977039] and DESeq2 package (version 1.34.0) [PMID: 34605806] setting \( P < 0.05 \) and \(|\log_{2}\text{fold change (FC)}| > 0.5\), respectively. In the GSE57218 and GSE157103 training sets, we utilized the WGCNA package (version 1.69) [PMID: 19114008] for outlier detection and respectively screened out the modules with the highest correlations with OA and normal, COVID-19 and non COVID-19 by constructing co-expression networks \(|\text{cor}| > 0.3 \) and \( P < 0.05 \).

2.3 Acquisition of candidate genes

First, the OA-DEGs were intersected with the module genes that had significant correlation with OA, and COVID-19-DEGs were intersected with the module genes which were dramatically correlated with COVID-19 to yield OA-intersected genes and COVID-19 intersected genes, respectively. Then, OA-intersected genes and COVID-19 intersected genes were intersected to acquire candidate genes, and they were analyzed for gene ontology (GO) and kyoto encyclopedia of genes and genomes (KEGG) functional enrichment by clusterProfiler package (version 3.18.0) [PMID: 22455463].

2.4 Construction of protein protein interaction (PPI) network

In order to explore the existence of reciprocal relationships among candidate genes, we constructed a PPI network via STRING database (medium confidence=0.4, removing discrete proteins) (https://string-db.org). Secondly, the seven algorithms (Closeness, MCC, Degree, MNC, Radality, Stress, and EPC) from cytoscape software's cytohubba plug-in were applied to candidate genes, and the
top 15 genes gained from seven algorithms were intersected to sift out biomarkers. Furthermore, the expression levels of biomarkers between disease and normal samples in the GSE57218, GSE157103 training sets, and GSE82107, GSE171110 validation sets were analyzed through wilcox.test, and we plotted the receiver operating characteristic (ROC) curves of biomarkers by pROC package (version 1.17.0.1) [PMID: 21414208].

2.5 Construction of competing endogenous RNA (ceRNA), transcription factor (TF)/miRNA-mRNA and drug-target regulatory networks

Our study utilized miRWalk database (Score=0.95, bindingp ≥ 1, Position: 3UTR) (http://mirwalk.umm.uni-heidelberg.de/) and miRNA target prediction and functional annotations database (miRDB) (Target Score ≥ 80) (https://mirdb.org/mirdb/index.html) to predict target miRNAs for biomarkers, separately. After that, the miRNAs predicted by these two databases were intersected to acquire intersected miRNAs. Then, the starbase (https://starbase.sysu.edu.cn/starbase2/) and miRNet (https://www.mirnet.ca/miRNet/home.xhtml) databases were applied to predict the lncRNAs which had interactions with intersected miRNAs, respectively. The lncRNAs gained from above two databases were intersected to yield intersected lncRNAs. Finally, the mRNA-miRNA-lncRNA regulatory network was mapped via cytoscape software (version 3.6.1). Moreover, we predicted the TFs of biomarkers by utilizing transcriptional regulatory relationships unravelled by sentence-based text-mining (TRRUST) (www.grnpedia.org/trrust) database, and constructed the TF/miRNA-mRNA network. The potential therapeutic drugs of biomarkers were predicted via drug-gene interaction database (DGIdb) (DGIdb, www.dgidb.org).

3. Results

3.1 Identification of DEGs and gene modules

There were 1135 OA-DEGs and 4336 COVID-19-DEGs between disease and normal samples in the GSE57218 and GSE157103 training sets, respectively (Figure 1A), the heat maps illustrated the top50 up- and down-regulated DEGs (Figure 1B). From Figure S1, we could see that there were 1 (GSM1380887) and 2 (GSM4753070 and GSM4753146) outlier samples in the GSE57218 and GSE157103 training sets, individually, thus, they were eliminated (Figures 1C). According to the positions of red lines in Figure 1D, the power thresholds of the GSE57218 and GSE157103 training sets were separately determined to be 4 and 8. Based on the GSE57218 and GSE157103 training sets,
the co-expression matrices were constructed to yield 9 and 6 gene modules, respectively (Figure 1E). The pink, blue and brown modules were remarkably correlated with OA in the GSE57218 training set (Figure 1F), while the pink and brown modules had high correlation with COVID-19 in the GSE157103 training set (Figure 1G).

### 3.2 Functional annotation analysis of candidate genes

The OA-DEGs were intersected with module genes that were strongly correlated with OA, and the COVID-19-DEGs were intersected with module genes which were significantly correlated with COVID-19 to acquire 715 OA-intersected genes and 2282 COVID-19-intersected genes, respectively (Figure 2A). We took intersection of above intersected genes to yield 106 candidate genes (Figure 2B), and they were involved in GO functional entries such as ADP metabolic process, nucleoside diphosphate phosphorylation, platelet alpha granule lumen, secretory granule lumen, cytoplasmic vesicle lumen. Figure 2C demonstrated the top5 GO entries.

### 3.3 Characterization of biomarkers

A total of 57 nodes and 69 edges formed the PPI network, which included NOXA1-CYBA, TPI1-ENO1, HSP90B1-HSPB1 and other reciprocal relationship pairs (Figure 3A). The seven biomarkers, namely AK1, APP, ENO1, TPI1, HSP90B1, HSPB1 and ESR1, were gained by intersecting the top 15 genes obtained from seven algorithms (Figure 3B). The expression levels of biomarkers were notably different between disease and normal samples in both the GSE57218 and GSE157103 training sets (Figure 3C). The AUC values of biomarkers were all greater than 0.7 in both the GSE57218 and GSE157103 training sets, indicating that they had a good predictive ability (Figure 3D). The expression trends of biomarkers between OA and normal samples in the GSE82107 validation set were identical to those in the GSE57218 training set (Figure S2). The expression of APP, ESR1, HSP90B1, and AK1 were all significantly different between COVID-19 and healthy samples in both the GSE157103 training set and GSE171110 validation set, and expression trends of them were consistent in these two datasets (Figure S2).

### 3.4 The ceRNA, TF/miRNA-mRNA and drug-target regulatory networks

The miRWalk and miRDB databases predicted 1541 and 178 miRNAs, respectively, and 95 intersected
miRNAs were gained after intersecting them (Figure 4A). The starbase and miRNet databases were separately utilized to predict 1092 and 401 IncRNAs, and 385 intersected IncRNAs were yielded after intersecting them (Figure 4B). A total of 435 nodes and 2411 edges formed the mRNA-miRNA-IncRNA regulatory network, including ENO1-hsa-miR-22-3p-NUTM2B-AS1, HSP90B1-hsa-miR-107-CASC19, APP-hsa-miR-302c-3p-KCNQ1OT1, etc.. (Figure 4C). The 41 nodes and 40 edges constructed a TF-mRNA regulatory network, containing ESR1-HSPB1, TWIST1-ESR1, CTCF-APP, etc.. (Figure 4D). We utilized 50 nodes and 85 edges to form a miRNA-mRNA regulatory network, which contained hsa-miR-106b-5p-AK1, hsa-miR-520f-3p-TPI1, hsa-miR-613-HSP90B1, etc.. (Figure 4E). Totally 256 nodes and 257 edges constituted the drug-target network, including Exemestane-ESR1, Methylinositol-APP, Apatersen-HSPB1, etc.. (Figure 4F).

4. Discussion

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), becoming one of the most deadly epidemics in human history[17]. The time from infection to symptoms usually ranges from 1 to 14 days. The first three days after the onset of symptoms are the most infectious. So far, various testing methods have been developed to diagnose the disease, and the relevant diagnostic standard is to detect viral nucleic acid by collecting oral, nasal, and pharyngeal swabs[18]. After symptoms appear, COVID-19 will attack everywhere in the body. It has been reported that COVID-19 will attack human organs, including joints[19]. Elderly people or patients with underlying diseases are at higher risk of developing severe symptoms. It is unclear whether patients with osteoarthritis infected with COVID-19 will aggravate the damage of cartilage and subchondral bone, and whether it will cause problems in the treatment of osteoarthritis. Therefore, it is particularly important to explore the comorbidity genes of the two diseases and formulate corresponding treatment plans.

There are precise definitions of biomarkers in many literature. The World Health Organization defines biomarkers as "any chemical substance, biological structure, or biological process that can be used to measure and predict possible outcomes or possible diseases"[20]. In a broader definition, biomarkers can also be used to measure the effectiveness of treatment or intervention, and even the results of environmental exposure (such as chemicals or intake of nutrients). In this study, we collected genes related to COVID-19 and osteoarthritis through GEO database, analyzed the similarities and
differences between the two from the perspective of bioinformatics, and obtained key genes to provide new treatment methods for patients with osteoarthritis infected with COVID-19.

We found the hub gene of osteoarthritis and COVID-19 through bioinformatics methods, and screened seven biomarkers, AK1, APP, ENO1, TPI1, HSP90B1, HSPB1 and ESR1. Adenylate kinase 1 (AK1) is an enzyme in the AK family that catalyzes nucleotide phosphorylation and regulates intracellular ATP concentration\[^{21}\]. AK transfers the phosphate group at the end of ATP to AMP, forming two ADP molecules that participate in nucleic acid synthesis and cell energy metabolism, and play an important role in regulating tumor cell metabolism, cell migration, and invasion\[^{22}\]. α- Alpha enolase (ENO1) is one of three subtypes of enolase, which exists in eukaryotic cells\[^{23}\]. ENO1 maintains cellular ATP levels through glycolysis. High expression of ENO1 produces more phosphoenolpyruvic acid under hypoxia, which is beneficial for tumor cells to progress towards nucleic acid synthesis\[^{24}\]. ENO1 can also play a role in skeletal muscle production as an important component of the plasminogen activation system\[^{25}\]. The glycolytic regulator trisaccharide phosphate isomerase 1 (TPI1) plays an important role in glycolysis and is essential for effective energy generation\[^{26}\]. It plays an important role in the progression of rheumatoid arthritis, and its overexpression usually indicates an enhanced immune environment in the body\[^{27}\]. The above three biomarkers regulate ADP metabolism, participate in glycolysis, tricarboxylic acid cycle, and platelet activation processes, thereby exerting biological functions.

HSPs are one of the proteins that are highly expressed in organisms after stress, and their intracellular expression is relatively low under physiological conditions\[^{28}\]. HSP90 plays a role in viral genome replication, capsid assembly, and viral particle release, and can stabilize viral proteins. Inhibiting the activity of HSP90 can effectively reduce the generation of virus progeny. In vivo, there are various cell receptors (such as Akt, Apaf-1, HER-2/neu, Raf-1, CDK4, CDK6, etc.) involved in the regulation of cell cycle, cell transformation, cell survival, and apoptosis\[^{29}\]. The expression of these receptors is significantly increased in various tumor cells. HSP90 activates intracellular signal transduction pathways by binding to these receptors, thereby stimulating the abnormal proliferation of tumor cells. HSP90 can also bind to mutant p53 genes through changes in its own conformation, thereby promoting the unlimited proliferation of tumor cells and the further formation of tumors\[^{30}\]. HSPB1 is a member of the heat shock protein molecular family and is an ATP-independent protein molecular chaperone\[^{31}\]. It is mainly involved in the maintenance of cell homeostasis, inhibition of cell
Estrogen receptor α (Estrogen receptor, ESR) can be located in the cell membrane, cytoplasm, or nucleus. Its main function is to specifically bind to estrogen, regulate downstream gene transcription, and enable estrogen to exert biological functions in corresponding tissues and organs\(^{[32]}\). ESR α is mainly expressed in reproductive-related brain regions, thecal cells, and mammary ducts and lobules. It is crucial for female reproduction, breast development, and lactation. In bone tissue, ERα can regulate the growth of articular cartilage, subchondral bone, and joint synovium, and regulate the activity of osteoblasts and osteoclasts to regulate the bone cartilage surface\(^{[33]}\). When estrogen deficiency occurs in women, the homeostasis of secretion of synovial cells and changes in chondrocyte metabolism significantly weaken the protective effect on joints, accelerating the process of osteoarthritis.Amyloid precursor protein (APP) mRNA and protein are expressed in brain, thymus, heart, muscle, lung, kidney, adipose tissue, liver, spleen, skin, and intestinal tissues. It has the function of promoting the proliferation and differentiation of nerve cells, promoting the formation and growth of synapses, participating in learning and memory, and participating in insulin secretion\(^{[34,35]}\).

We all know that transcription factors can bind directly to the promoter region of miRNA and regulate miRNA expression\(^{[36]}\). In the regulatory network formed by transcription factors and miRNAs, transcription factors and miRNAs share the same regulatory approach in transcriptional regulation. Transcription factors directly regulate miRNAs and target genes, while miRNAs can also regulate transcription factors and target genes, and transcription factors can also be regulated by both transcription factors and miRNAs. Transcription factors and miRNAs, as key factors in the regulation of transcriptional and post-transcriptional levels, play an important role in the regulation of gene expression in cells. Therefore, the regulatory network formed by the two can understand the regulatory mechanism and pathways at the system level. In this study, GO and KEGG enrichment analysis showed that candidate genes were involved in the metabolic process of ADP, its phosphorylation, and vesicular transport. Predict the transcription factors of 7 hub genes, and construct a regulatory network formed by transcription factors and miRNA. ESR1 is both a hub gene and a transcription factor of HSPB1. Therefore, we speculate that ESR1 is a key molecule of COVID-19 and osteoarthritis. The intracellular signal transduction patterns of estrogen include nuclear receptors and membrane receptors\(^{[37]}\). The estrogen-mediated genomic action pattern of nuclear receptors is divided into three steps: estrogen diffuses into cells or undergoes in situ synthesis within cells, binds to nuclear ER, activates to form ER
homologous or heterodimers, and then binds to DNA enhancer estrogen response elements (ERE) to form ER ERE complexes, promoting the formation of transcription initiation complexes and inducing transcription\[38\]. Estrogen-mediated membrane receptors can alter the electrophysiological properties of neurons within seconds, reducing the Ca\(^{2+}\) current of neurons that do not express nuclear receptors within minutes, leading to specific enhancement of gene expression, such as activation of MAPK pathway, PKA, CREB, and so on\[39\]. Estrogen can rapidly activate the second signaling system in cells through membrane ER, indirectly regulating a series of gene transcription, and rapidly exerting biological effects in various cell types. The known ER-mediated signal pathways include MAPK/ERK signal transduction pathway, PI3K/Akt signal transduction pathway, JNK signal transduction pathway, and so on\[40-42\]. PI3K/Akt signaling pathway has important significance for chondrocyte apoptosis. Its downstream factors, Bcl-2 and Bax, are the main factors that regulate apoptosis and are closely related to chondrocyte apoptosis in the process of knee osteoarthritis\[43\]. JNK is an amino-terminal kinase that plays an important role in the expression of genes related to cell inflammation and apoptosis. It has been reported that mitogen-activated protein kinases (MAPKS), including JNK, can regulate knee osteoarthritis\[44\]. Its signal role in cell differentiation, apoptosis, and proliferation can be regulated by three conservative enzyme cascades that activate transcription factors. Estrogen receptors can also regulate energy supply in vivo by participating in processes such as glucose transport, glycolysis, tricarboxylic acid cycle, and oxidative phosphorylation\[45\]. Heat shock proteins can bind to estrogen receptors to prevent their degradation\[46\]. However, how estrogen receptors affect the occurrence and development of osteoarthritis and COVID-19 infection still needs to be confirmed.

Exemestane (trade name: Aromasin) is an anti-estrogen drug for the treatment of breast cancer, belonging to the category of aromatase inhibitors\[47\]. Certain breast cancer cells have estrogen receptors (ER) that stimulate their growth, known as ER positive\[48\]. Aromatase is an enzyme that synthesizes estrogen, and its inhibitors can prevent the synthesis of estrogen to slow down the growth of tumors\[49\]. Methylinositol has been used in trials to study the treatment of dementia and Alzheimer's disease\[50\]. Apatorsen is a second-generation antisense drug, which can inhibit the production of heat shock protein 27 (Hsp27) in preclinical experiments\[51\]. This cell survival protein has been found to increase in many human cancers, including prostate cancer, lung cancer, breast cancer, ovarian cancer, bladder cancer, kidney cancer, pancreatic cancer, multiple cancer myeloma, and liver cancer. However, the above drugs have not been applied to the treatment of COVID-19 infection and osteoarthritis, and further drug
experiments are needed.

To summarize, we combined COVID-19 infection and osteoarthritis through the GEO database, explored key genes, and screened 7 candidate genes. Through the establishment of TF and miRNA regulatory networks, it was found that ESR1 is a key site in this study and is expected to be used as a biomarker in both diseases. The disadvantage of this study is that it did not validate the selected genes in vitro, nor did it validate the drugs and corresponding proteins. We will continue to focus on research related to biomarkers, novel coronavirus infection, and osteoarthritis.

Declarations

Ethical Approval
Not applicable

Competing interests
The authors declare that they have no competing interests, and all authors should confirm their accuracy.

Authors’ contributions
ZQ performed data analysis and drafted the manuscript. Ninghao Liu collected the data and arranged the figures. Dawei Li and Yingjie Zheng conceived and designed this study and revised the manuscript. All the authors read and approved the final manuscript.

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Availability of data and materials
The original contributions are contained in the article. Besides, further inquiries can be made to the corresponding authors. The data sets were downloaded from the GEO database (https://www.ncbi.nlm.nih.gov/gds).

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Figure 1A

Figure 1B
Figure 1G

Figure 2A
Figure 2B
COVID_19

OA

2176 (75.3%)
106 (3.7%)
609 (21.1%)

Figure 2C

Figure 3A
Figure S2
Figure 4A

Figure 4B
Figure 4C

Figure 4D