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Bioinformatics and system biology approach to identify potential common pathogenesis for COVID-19 infection and sarcopenia

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Sarcopenia is a condition characterized by age-related loss of muscle mass and strength. Increasing evidence suggests that patients with sarcopenia have higher rates of coronavirus 2019 (COVID-19) infection and poorer post-infection outcomes. However, the exact mechanism and connections between the two is unknown. In this study, we used high-throughput data from the GEO database for sarcopenia (GSE111016) and COVID-19 (GSE171110) to identify common differentially expressed genes (DEGs). We conducted GO and KEGG pathway analyses, as well as PPI network analysis on these DEGs. Using seven algorithms from the Cytoscape plug-in cytoHubba, we identified 15 common hub genes. Further analyses included enrichment, PPI interaction, TF-gene and miRNA-gene regulatory networks, gene-disease associations, and drug prediction. Additionally, we evaluated immune cell infiltration with CIBERSORT and assessed the diagnostic accuracy of hub genes for sarcopenia and COVID-19 using ROC curves. In total, we identified 66 DEGs (34 up-regulated and 32 down-regulated) and 15 hub genes associated with sarcopenia and COVID-19. GO and KEGG analyses revealed functions and pathways between the two diseases. TF-genes and TF-miRNA regulatory network suggest that FOXO1 and hsa-mir-155-5p may be identified as key regulators, while gene-disease analysis showed strong correlations with hub genes in schizophrenia and bipolar disorder. Immune infiltration showed a correlation between the degree of immune infiltration and the level of infiltration of different immune cell subpopulations of hub genes in different datasets. The ROC curves for ALDH1L2 and KLF5 genes demonstrated their potential as diagnostic markers for both sarcopenia and COVID-19. This study suggests that sarcopenia and COVID-19 may share pathogenic pathways, and these pathways and hub genes offer new targets and strategies for early diagnosis, effective treatment, and tailored therapies for sarcopenia patients with COVID-19.

KEYWORDS

sarcopenia, COVID-19, bioinformatics, pathogenesis, biomarkers

Introduction

Sarcopenia is a progressive and systemic disease of extreme skeletal muscle dysfunction (1) characterized by reduced muscle mass/quantity and muscle strength that is observed in both physiological and pathological processes (2, 3). According to the most recent guidelines from the European Working Group on Sarcopenia in the Elderly (EWGSOP), the primary diagnostic criteria for sarcopenia have shifted to include diminished muscle strength and function, rather than solely the loss of muscle mass. Additionally, impaired physical performance is now recognized as a key marker of advanced sarcopenia (4, 5). Studies have shown that sarcopenia occurs with age and the effects of many long-term conditions (2, 5), and is associated with decreased mobility, increased morbidity and increased mortality (6). Currently, sarcopenia affects over 50 million people and this number is expected to reach 500 million by 2050 (7, 8). Sarcopenia is estimated to affect 10–16% of older adults worldwide (9). One study reported that the prevalence of sarcopenia patients (EWGSOP definition) ranged from 8 to 36% in those aged <60 years and from 10 to 27% in those aged ≥60 years (10). The pathogenesis of sarcopenia is complex, with high morbidity and mortality, and it is currently believed that the pathogenesis of sarcopenia may be related to factors such as reduced satellite cell numbers and aging (11, 12), mitochondrial dysfunction (13), loss of motor neurons, decreased activity of neuromuscular junctions (14), endocrine alterations (15), and weight loss with decreased appetite (16), or a combination of these factors (17).

COVID-19 is a multi-organ infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2), particularly severe pneumonia and acute respiratory distress syndrome (18). As of September 7, 2023, the World Health Organization reported 770,437,327 confirmed cases, including 6,956,900 deaths.¹ COVID-19 can pose a serious health burden individuals, especially the elderly and those with underlying medical conditions such as advanced age (19), chronic kidney disease, diabetes mellitus, hypertension (20), and cancer (21, 22) are risk factors that have been widely documented to be responsible for COVID-19 infections and deaths. COVID-19 is characterized by severe inflammation and a highly muscle catabolic state, which affects the body's metabolic stress and profound changes in body composition. Researchers have attempted to prevent and treat COVID-19 by investigating drugs and developing vaccines, but its intervention in adverse body states (e.g., sarcopenia) may facilitate the treatment of COVID-19 (23, 24).

A study indicated that patients with sarcopenia experienced a higher prevalence of infection and poorer prognosis during the COVID-19 pandemic (23). Patients with sarcopenia have impaired immune cells (e.g., peripheral monocytes, neutrophils, and natural killer lymphocytes) (25), which result in the production of aberrant myofactors such as IL-6, IL-7, IL-15, or LIF (26), which ultimately lead to muscle catabolism and immune senescence (24, 25). However, the onset and progression of sarcopenia is accelerated during COVID-19 infection due to increased muscle atrophy and inhibition of muscle synthesis caused by severe inflammatory response and metabolic

stress (27), decreased physical activity and inadequate nutrient intake (28). Hospitalization, protein deficiency, and corticosteroid therapy during COVID-19 infection have been reported in several studies that often lead to the rapid progression of sarcopenia in patients with severe COVID-19 infection (29, 30). Skeletal muscle regulates immune system function through myokine signaling and expression of immunoregulatory surface molecules. Immune cells in turn severely affect muscle mass and function (25). This indicates that the interaction between sarcopenia and COVID-19 may be bidirectional, potentially creating a vicious cycle.

An increasing number of studies indicate a strong relationship between sarcopenia and COVID-19 infection; however, the mechanisms have not been fully elucidated. This study utilizes bioinformatics, R software, and several large databases to analyze the common DEGs and hub genes of sarcopenia and COVID-19 in terms of expression differences, functional enrichment, regulatory networks, disease drug prediction, and immune infiltration. This analysis will help further understand the potential co-pathogenesis of sarcopenia and COVID-19 and to screen for biomarkers and drug candidates.

Materials and methods

Data collection

RNA-seq data for patients with sarcopenia (GSE111016) and COVID-19 infections (GSE171110) were obtained from the GEO database.² GEO is one of the largest public database that includes microarray data and high-throughput gene expression data submitted by research institutions around the world (31). Both datasets used the GPL 16791 (Illumina NextSeq 500) high-throughput sequencing platform to extract RNA sequences. The GSE111016 dataset includes 20 muscle biopsies from healthy testers and 20 muscle biopsies from patients with sarcopenia (32). The GSE171110 dataset includes 44 COVID-19 patients and 10 healthy donors with whole blood gene expression profiling data (33).

Identification of common DEGs between sarcopenia and COVID-19

The “limma” package (version 4.3.1) of the R software (version 4.3.1) was used to select DEGs between COVID-19 and non-COVID-19 and between sarcopenia and non-sarcopenia. Because of the differences in sample size and data quality, different difference multiples criteria were selected to ensure statistical significance and biological relevance of the results. In the sarcopenia dataset, genes with $p < 0.05$ and a fold change > 1.2 were identified as DEGs; for COVID-19, genes with $p < 0.05$ and a fold change > 2 were identified as DEGs. In the sarcopenia dataset, the DEG of $\log_2FC < -0.263$ was considered down-regulated, whereas $\log_2FC > 0.263$ was considered up-regulated. For COVID-19, the DEG of $\log_2FC < -1$ was considered

¹ <https://covid19.who.int/>

² <https://www.ncbi.nlm.nih.gov/geo/>

down-regulated, whereas $\log_2FC > 1$ was considered up-regulated. The “Pheatmap” (version 1.0.12), “EnhancedVolcano” and “ggplot2” packages of the R software were applied to generate the heatmaps and volcano maps. Common DEGs for GSE111016 and GSE171110 were then obtained using the online VENN analysis tool.³

Enrichment analysis of gene ontology and pathways

Enrichr⁴ is a comprehensive resource for analyzing gene sets generated from genome-wide experiments, containing a total of 180,184 annotated gene sets from 102 gene set libraries (34). GO and pathway enrichment analyses were performed using EnrichR online tools [the Kyoto Encyclopedia of Genes and Genomes (KEGG)] to specify shared functions and pathways between sarcopenia and COVID-19. The GO terminology consists of three categories: biological process (BP), cellular component (CC), and molecular function (MF). A p -values < 0.05 was considered significantly enriched.

PPI network construction

STRING⁵ (version 12.0) is a database for studying protein–protein association networks, with an expanded information coverage of more than 12,535 species, 59.3 million proteins, and 20 billion interactions, integrating experimental interaction evidence and computational interaction prediction information, with the goal of realizing a comprehensive and objective global network (35). We performed PPI network analysis of the common DEG using the STRING database to construct differentially expressed and potential interactions of genes with interaction scores > 0.15 . The protein–protein interaction networks constructed in the String database were then imported into Cytoscape (version: 3.9.1) software for visualization (36, 37).

Identification and analysis of hub genes

In a PPI consisting of nodes, edges and their connections, the most entangled nodes were considered hub gene. Cytohubba⁶ is a novel plugin for Cytoscape that provides 11 topological analysis methods to rank nodes in a network (38). We applied seven algorithms (Closeness, MCC, Degree, MNC, Radality, Stress and EPC) to finally intersect them to select hub gene.

GeneMANIA⁷ is a flexible and user-friendly website that uses large amounts of genomics and proteomics data to generate hypotheses about gene function, analyze gene lists and prioritize genes

for functional analysis (39). We used it to construct co-expression networks of identified central genes.

Construction of TF-gene and miRNA-gene regulatory network

TFs are proteins that control the transcription of DNA into RNA by attaching to specific DNA sequences. miRNAs are mainly involved in the regulation of protein expression by binding to target sites on mRNA transcripts and inhibiting their translation, making them essential for regulating biomolecules (40, 41). We visualized the co-regulatory network of hub genes through the NetworkAnalyst platform, which has been widely used as a bioinformatics tool (42). We used NetworkAnalyst to extract microRNAs interacting with hub genes from the miRTarBase database (43) and construct a DEG-microRNA (miRNA) interaction network, and then localized TFs binding to hub genes through the JASPAR database (44) and constructed a DEG-transcription factor interaction network. We performed GRN analysis using hub-DEG to reveal transcription elements and miRNAs that regulate DEG at the post-transcriptional level.

Gene-disease association analysis

DisGeNET is a comprehensive knowledge management platform that integrates and normalizes data on disease-associated genes and variants from multiple sources, including the scientific literature, and can be used to study the molecular basis of specific human diseases and their complications, to analyze the characterization of disease genes and to validate the performance of computationally predicted disease genes (45). It currently covers more than 24,000 diseases and traits, 17,000 genes and 117,000 genomic variants (46). We examined gene-disease relationships using the DisGeNET database through NetworkAnalyst to reveal diseases and their complications associated with central genes.

Correlation analysis of hub gene expression with immune infiltration

To explore the immune infiltration of multiple immune cells including T cells, B cells, NK cells, monocytes, macrophages, neutrophils, and dendritic cells in GSE111016 and GSE171110 peripheral blood (47), single-sample gene set enrichment analysis (ssGSEA) (48) of 28 immune gene sets was performed using the “GSVA” R package, assessing the immunological characteristics of the samples. The Vioplot and pheatmap R packages were used for visualization. Finally, the Pearson correlation coefficient determined the correlation between hub genes and different immune infiltrating cells, visualized through the ggplot2 package.

Target drugs analysis

The DSigDB database is a new gene set resource that links drugs/compounds to their target genes. It currently has 22,527 gene sets

3 <http://jvenn.toulouse.inra.fr/app/example.html>

4 <https://maayanlab.cloud/Enrichr/>

5 <http://string-db.org>

6 <http://apps.cytoscape.org/apps/cytohubba>

7 <https://genemania.org>

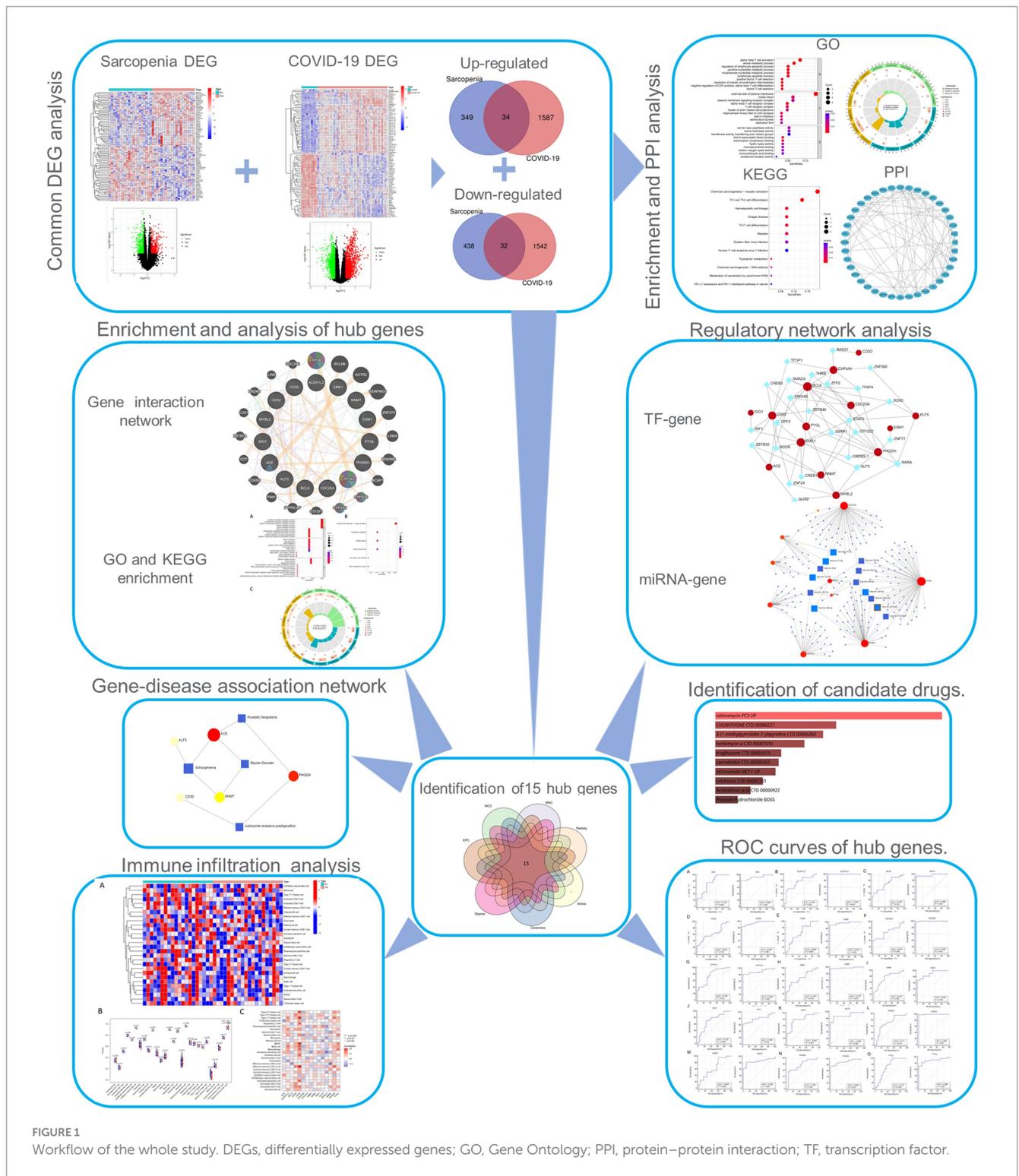


FIGURE 1 Workflow of the whole study. DEGs, differentially expressed genes; GO, Gene Ontology; PPI, protein–protein interaction; TF, transcription factor.

consisting of 17,389 unique compounds, covering 19,531 genes (49). We detected 15 drug molecules identified based on hub genes from the DSIgDB database on the Enrichr⁸ platform. These drugs

represent possible common drugs used for sarcopenia and COVID-19.

ROC curves of hub genes

The receiver operating characteristic (ROC) curve is a useful tool for evaluating classifiers in biomedical and bioinformatics applications. In

8 <https://amp.Pharm.mssm.Edu/Enrichr/>

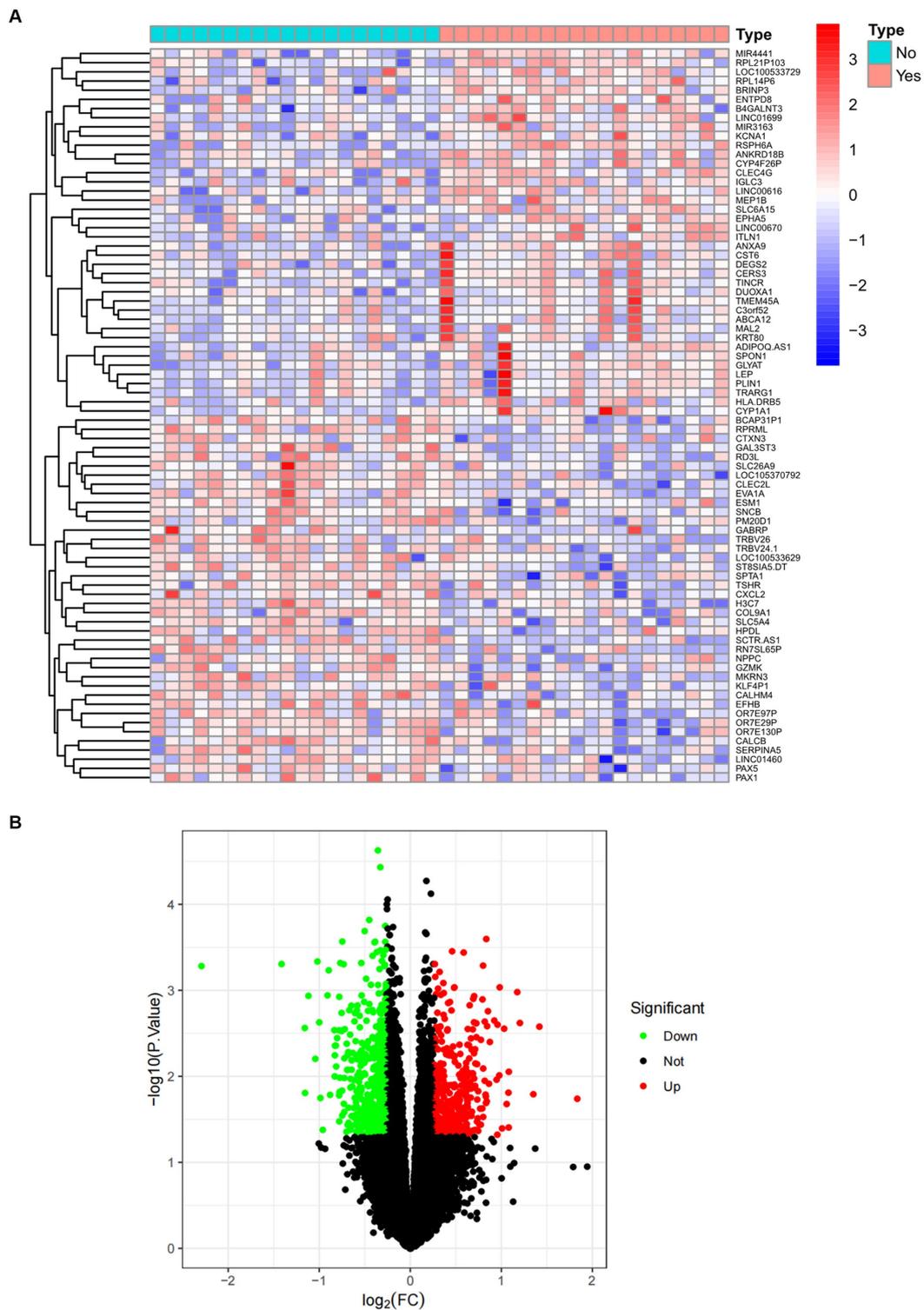


FIGURE 2 Expression characteristics of DEGs in sarcopenia. **(A)** Heat map and **(B)** volcano plot present the DEGs identified between sarcopenia patients and normal controls ($|\log_2FC| > 0.263$ defined as the screening criterion to obtain DEGs in sarcopenia). Blue color indicates low expression values and red color indicates high expression values.

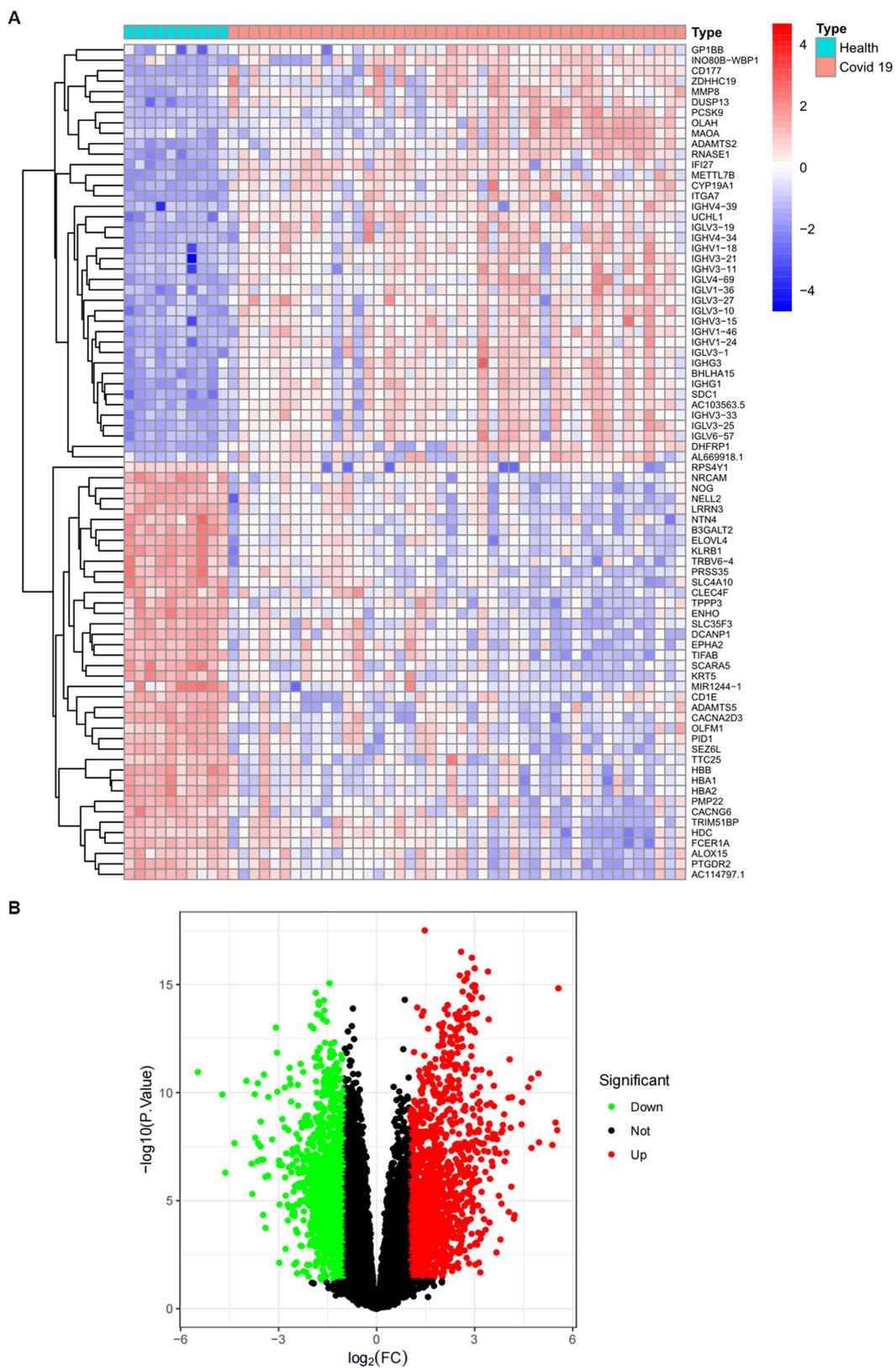


FIGURE 3 Expression characteristics of DEGs in COVID-19 patients. **(A)** Heat map and **(B)** volcano plot present the DEGs identified between COVID-19 patients and normal controls ($|\log_2FC| > 1.0$ is defined as a screening criterion to obtain a DEG for COVID-19). Blue indicates a low expression value and red indicates high expression value.

this study, R was established by “pROC” based on the expression profile data of hub genes (50). The area under the ROC curve (AUC) was used to evaluate the diagnostic value of candidate hub genes separately.

Results

Identification of DEGs and shared genes between sarcopenia and diabetes

The overall flowchart of this study is shown in Figure 1A. A total of 853 differential genes (DEGs) were identified based on the sarcopenia dataset GSE111016 using the limma R software package, of which 383 were upregulated and 470 were downregulated. The heatmap plot shows the identified DEGs (Figure 2A), and the heat map shows the distribution of the top 25 DEGs for up- and down-regulation in sarcopenia patients and non-sarcopenia patients, respectively (Figure 2B). In addition, a total of 3,195 DEGs were obtained from the COVID-19 dataset GSE171110, of which 1,621 genes were up-regulated and 1,574 genes were down-regulated. The top 25 DEG heat maps of up- and down-regulation and the volcano

map of DEG are shown in Figures 3A,B. The intersection of DEGs from the GSE111016 and GSE171110 datasets was visualized by a Wayne’s diagram. In total, 34 common up-regulated DEGs and 32 common down-regulated DEGs are shown (Figures 4A,B).

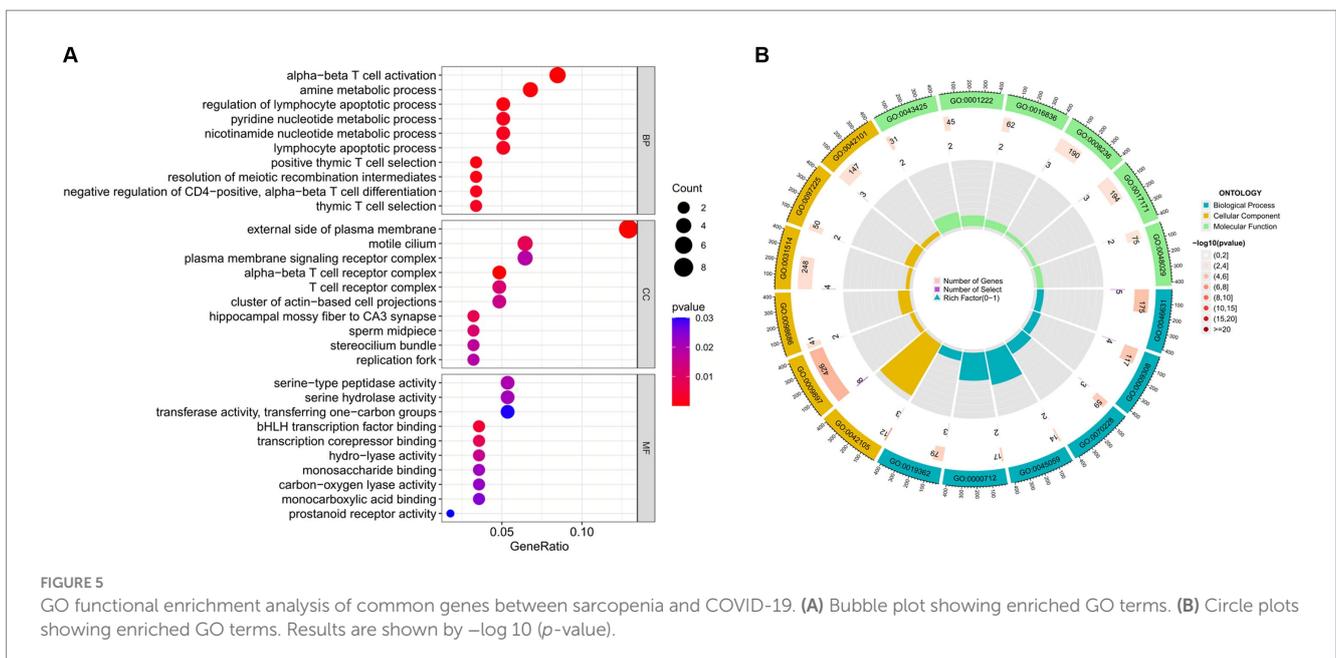
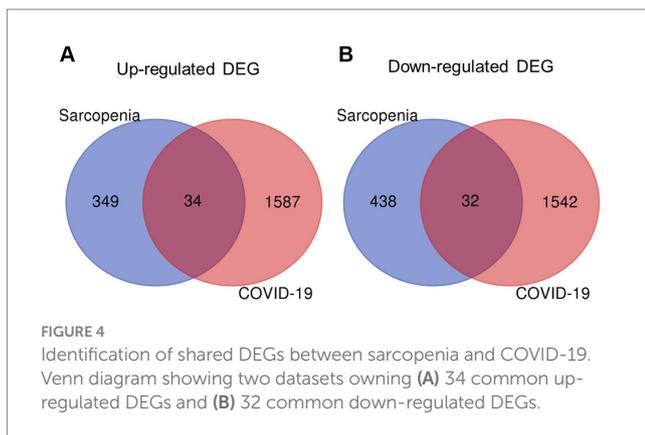
Gene ontology and pathway enrichment analysis

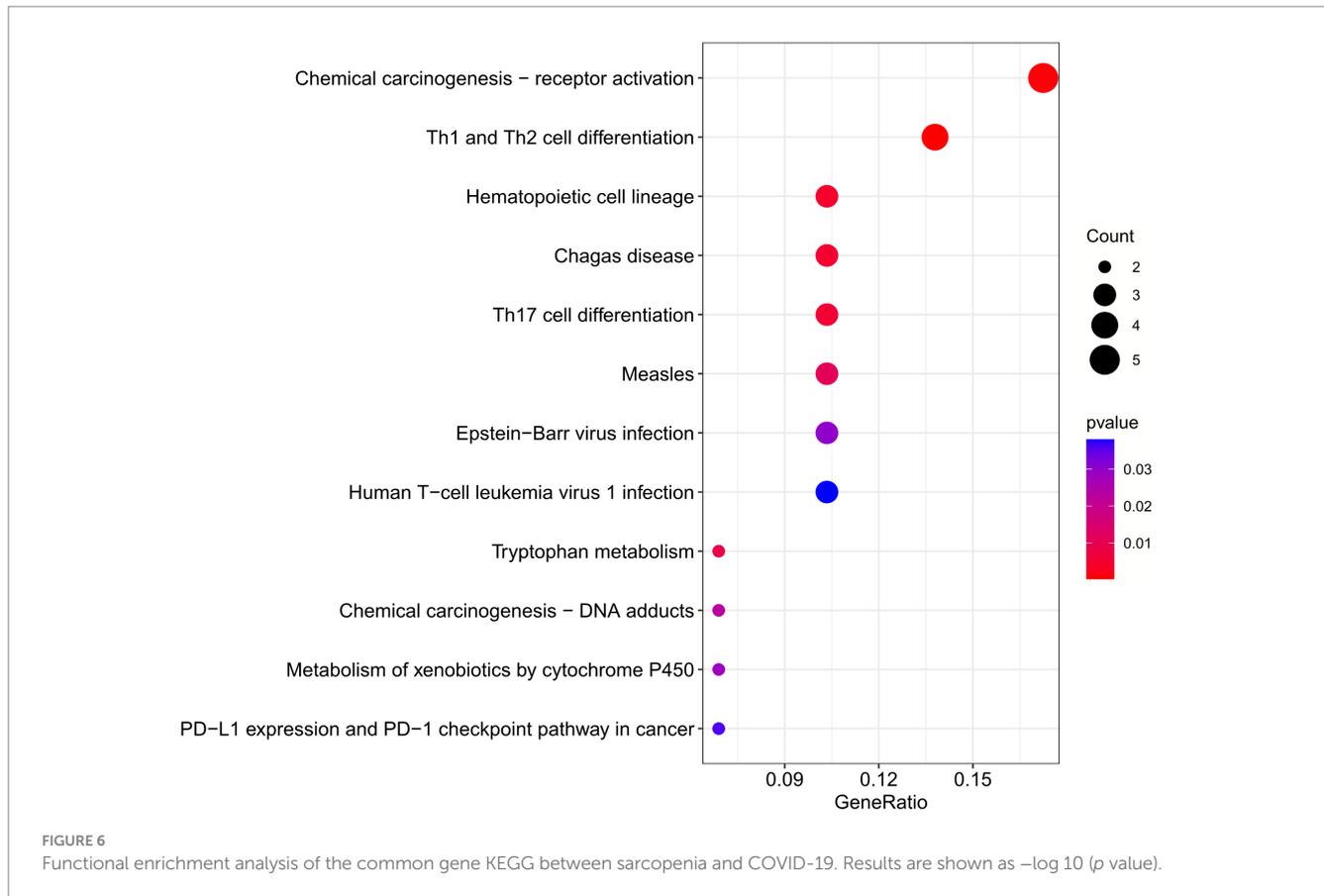
Enrichment analysis aids in further understanding the biological functions of genes shared between COVID-19 and sarcopenia patients. By analyzing Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG), we predicted the functions of DEGs and their common differential genes in COVID-19 and sarcopenia. GO analysis predicted gene functions in three categories: biological processes, cellular components, and molecular functions. Results indicated that key biological processes include alpha-beta T cell activation, amine metabolic processes, and the regulation of lymphocyte apoptotic processes. Primary cellular components involved are the alpha-beta T cell receptor complex, the external side of the plasma membrane, and the hippocampal mossy fiber to CA3 synapse. Predominant molecular functions include binding of bHLH transcription factors, transcription corepressor binding, and hydro-lyase activity (Figure 5; Supplementary Figure S2).

The enrichment pathways of common DEGs between COVID-19 and sarcopenia were collected from the KEGG database and visualized in Figure 6. KEGG enrichment analysis showed that common genes were mostly enriched in the Th1 and Th2 cell differentiation, chemical carcinogenesis – receptor activation, and hematopoietic cell lineage pathways (Figure 6).

PPI network analysis

We utilized the STRING database to construct a Protein–Protein Interaction (PPI) network analysis of the shared genes, aiming to





predict interactions and adhesion pathways among common DEGs. The network was then imported into Cytoscape for visualization to explore their potential interactions. As expected (Supplementary Figure S3), the PPI network of shared DEGs comprises 40 nodes and 82 edges, and it was subsequently used in subsequent steps for identifying hub genes and detecting drug molecules for both COVID-19 and sarcopenia.

Identification of hub genes

From the PPI network in CytoHubba, a plugin for Cytoscape software, we selected the top 23 hub genes using seven algorithms. Through intersection using a Venn diagram, we ultimately identified 15 common hub genes, including ACE, ALDH1L, CYP1A1, PYGL, KLF5, NNMT, PHGDH, IDO1, EME1, CD52, MYBL2, CDC25A, BCL6, CD3D, and ESM1 (Figure 7). These hub genes may be potential biomarkers and common molecular mechanisms of pathogenesis in patients with sarcopenia and COVID-19, which may guide new therapeutic strategies for disease research.

Functional enrichment analysis of hub genes

Based on GeneMANIA database, we constructed an interaction network of common hub genes and their related genes to decipher the biological functions and predictive values of these hub genes, with

Co-expression of 65.97%, Co-localization of 19.71%, Predicted of 12.57%, and Genetic Interactions was 1.75%. The GeneMANIA results also indicated that the functions of common hub genes and their related genes (CYP1B1, BCL6B, AGTR2, SERPING1, ZNF274 LIN54, BDKRB2, ACAP1, CYP2D6, etc.) were mainly related to the metabolic process of retinoids, steroid hydroxylase activity, protol metabolic processes, hormone metabolic processes, long-chain fatty acid metabolic processes, cytokinetic hormone metabolic processes, and monooxygenase activity (Figure 8).

To further explore the biological functions and signaling pathways associated with the hub genes involved in sarcopenia and COVID-19, we performed gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses. GO analysis predicted the functional roles of the genes in terms of biological processes, cellular components and molecular functions, and the results showed (Figures 9A,C) that hub genes were enriched in several biological processes (BP), including pyridine nucleotide metabolism, nicotinamide nucleotide metabolism, pyridine compounds metabolism, vitamins metabolism, amine metabolism, and NAD biosynthesis; with regard to cellular component (CC), hub genes are mainly associated with sperm midpiece, replication fork, sperm flagellum, actin-based cell protrusion, active cilia, and T cell receptor complex. In MF it mainly includes electron transfer activity, heme binding, tetrapyrrole binding, hydroxymethyl-formyl- and related transferase activity, DNA endonuclease activity and bile acid binding. As shown in Figures 6, 9B KEGG pathways were significantly associated with sarcopenia and COVID-19 common

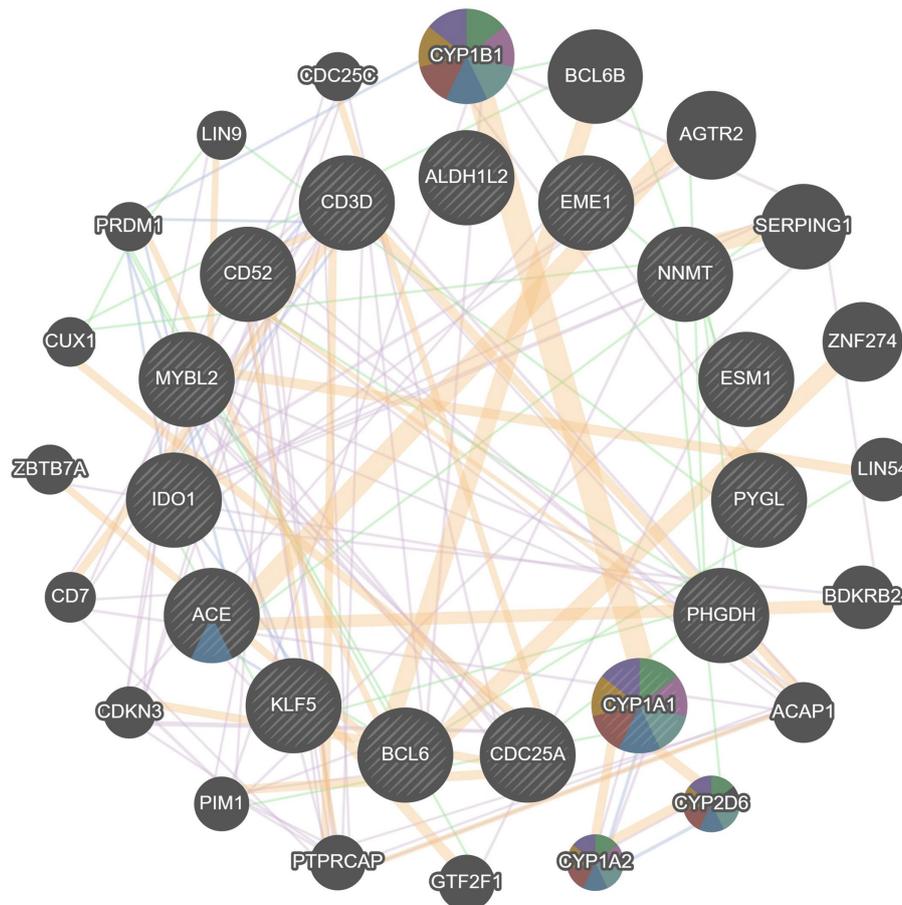


FIGURE 8 Analyze hub genes and their co-expressed genes by GeneMANIA.

analysis was performed on the sarcopenia and COVID-19 datasets. Figures A and B show the degree of infiltration of different immune cells in the sarcopenia dataset. The relationship between common key genes and immune cells was analyzed and visualized in Figure 13C. The sarcopenia group had lower expression scores of Activated.CD8.T.cell ($p = 0.018$) and Type.17.T.helper.cell ($p = 0.015$) compared to healthy controls, however, the proportion of other immune cell subsets did not differ significantly between the two groups. Subsequently, we evaluated the correlation between the expression of common hub genes and the level of infiltration of different cell subpopulations, and showed that CD52 had a strong positive correlation with Type.2.T.helper.cell, Type.1.T.helper.cell, MDSC, and Effector.memory.CD4.T.cell cells ($p < 0.0001$), whereas PHGDH had a strong correlation with Effector.memory.CD4.T.cell and Type.1.T.helper.cell cells ($p < 0.001$). In contrast, MYBL2 was negatively correlated with Plasmacytoid.dendritic.cell, Monocyte and Immature.dendritic.cell ($p < 0.01$). Similarly, the immunoinfiltration results of the COVID-19 dataset are shown in Supplementary Figure S1.

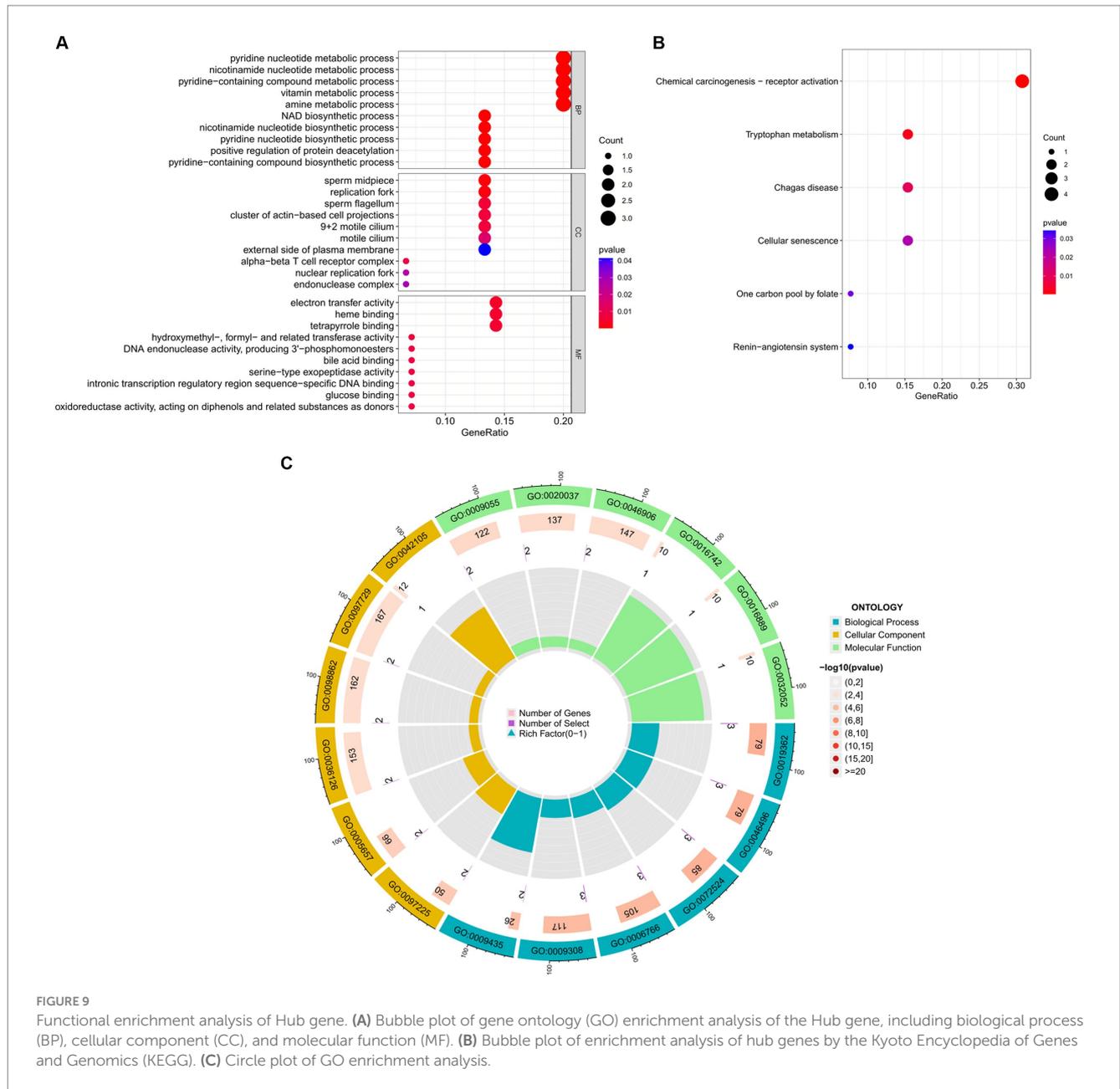
Identification of candidate drugs

Ten potential therapeutic small molecule drugs were identified using Enrichr based on transcriptional characterization of the DSigDB

database, which represent possible common drugs used for sarcopenia and COVID-19. The results of potential small molecules were generated based on their p -values to indicate the proximity between the small molecule and the gene. Figure 14 show the top 10 enriched drugs (valinomycin PC3 UP, LUCANTHONE CTD 00006227, 3-(1-methylpyrrolidin-2-yl) pyridine CTD 00006393, herbimycin a CTD 00001010, troglitazone CTD 00002415, cannabidiol CTD 00005567, niclosamide MCF7 UP, colchicine CTD 00005701, Arsenenous acid CTD 00000922, Prazosin hydrochloride BOSS).

ROC curves of hub genes

ROC curves were plotted to assess the diagnostic efficacy of 15 key genes (Figure 15). ACE (AUC: 0.923), CYP1A1 (AUC: 0.902), EME1 (AUC: 0.977), CD52 (AUC: 0.970), MYBL2 (AUC: 0.995), CDC25A (AUC: 0.998), BCL6 (AUC: 0.966) and CD3D (AUC: 0.955) showed relatively good diagnostic efficiency in distinguishing COVID-19 patients from healthy controls. While in the sarcopenia dataset, ACE (AUC: 0.742), ALDH1L2 (AUC: 0.748), CYP1A1 (AUC: 0.765), PYGL (AUC: 0.73), KLF5 (AUC: 0.803), PHGDH (AUC: 0.76), IDO1 (AUC: 0.72), EME1 (AUC: 0.703), MYBL2 (AUC: 0.711), BCL6 (AUC: 0.705), and ESM1 (AUC: 0.746) demonstrated better diagnostic performance for distinguishing sarcopenia from healthy individuals.



Specifically, ALDH1L2 (AUC: 1) showed the best diagnostic efficiency for differentiation in the COVID-19 dataset, whereas KLF5 (AUC: 0.803) demonstrated the best discriminatory ability in the sarcopenia dataset.

Discussion

There is evidence that patients with sarcopenia have a higher prevalence and worse prognosis after COVID-19 infection (23). COVID-19 infection can cause pathologic changes in multiple organs, including the musculoskeletal system (51), which may be associated with certain mechanisms of inflammation, immune response, and metabolic stress (52). Therefore, we sought to explore the common functions and pathways between COVID-19 and sarcopenia and to determine the interrelationship between COVID-19 and sarcopenia.

In this study, 66 common DEGs and 15 key genes (ACE, ALDH1L, CYP1A1, PYGL, KLF5, NNMT, PHGDH, IDO1, EME1, CD52, MYBL2, CDC25A, BCL6, CD3D, and ESM1) have been identified.

Four of these genes (ACE, KLF5, IDO1, and CDC25A) have been reported to be associated with the pathological mechanisms of COVID-19 and sarcopenia. Angiotensin-converting enzyme (ACE) is a chloride- and zinc-dependent peptidyl-carboxypeptidase that hydrolyzes AngI (angiotensin I) to AngII and serves as a biologically active component of the renin-angiotensin system (RAS) and the kinin-releasing enzyme-kinin system (KKS) (53, 54). ACE has been a drug target for screening against cardiovascular diseases such as hypertension and heart failure (55), and inhibition of ACE activity can prevent mitochondrial decline, improves endothelial function and muscle metabolism, and thus plays an important role in water-electrolyte homeostasis, blood pressure regulation, cardiovascular system development and vascular remodeling (53, 56). Meanwhile, it

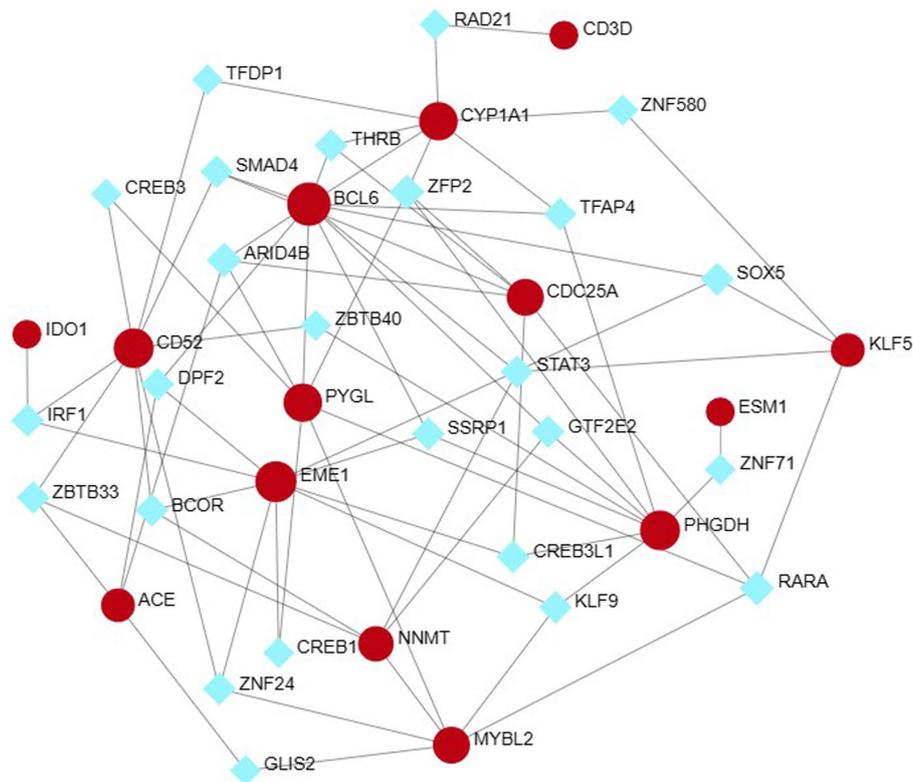
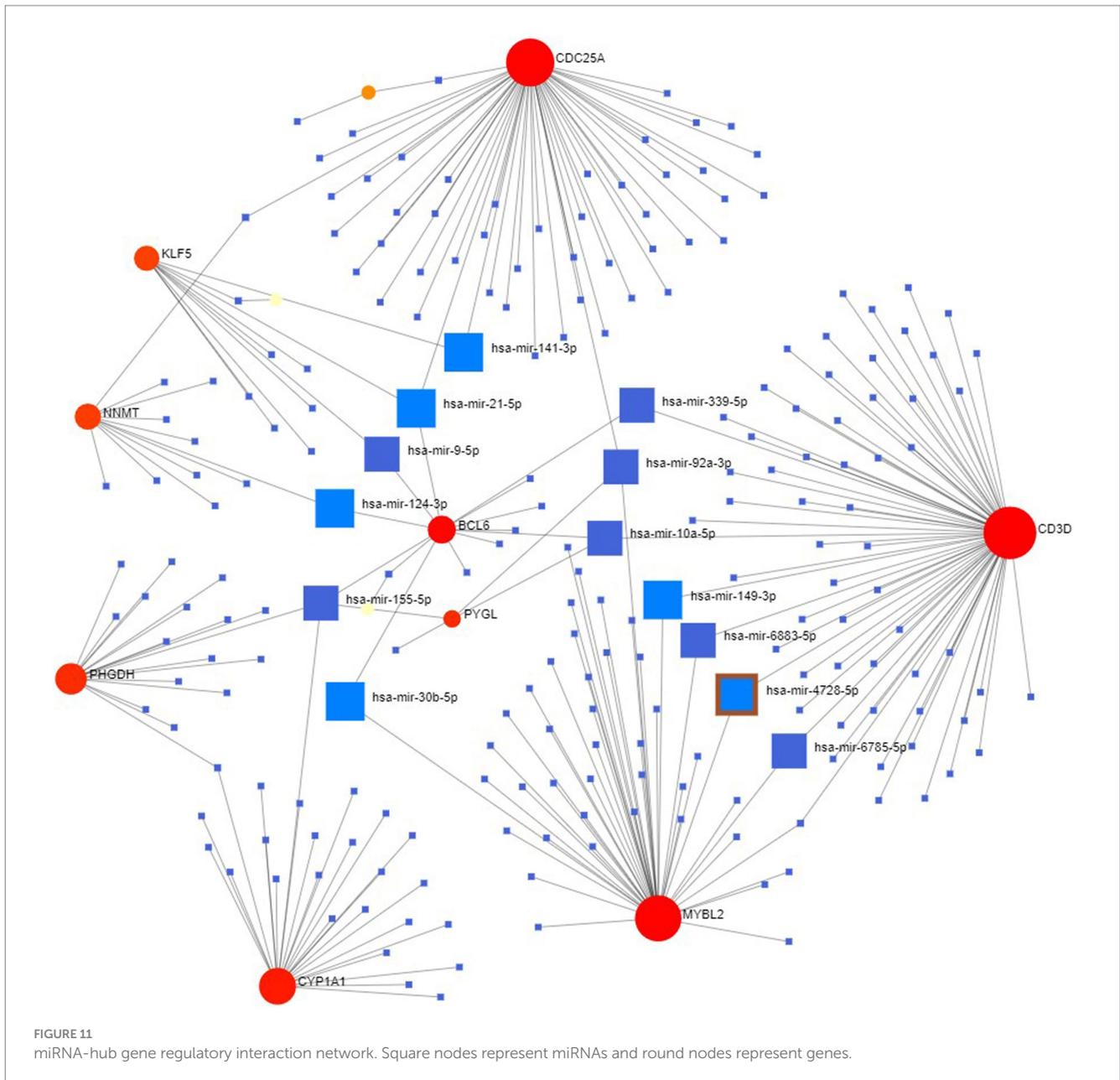


FIGURE 10
Hub-TF gene regulatory interaction network. Square nodes represent TF and round nodes represent genes.

has been reported that SARS-CoV-2 virus has a strong affinity for angiotensin-converting enzyme-2 (ACE2) receptor (57). The coronavirus type 2 spiking proteins bind to cells via angiotensin-converting enzyme 2 (ACE2) receptors, leading to fusion of the viral envelope with the cell membrane and allowing viral genetic material to enter the cell where ACE2 receptors are prevalent throughout the body, leading to a wide range of tissue damage (58). KLF5 is a key zinc finger transcriptional regulator mediating muscle atrophy and is upregulated in atrophied myotubes (59, 60). It can play a key role in the development of muscle atrophy *in vitro* and *in vivo* by controlling lipid metabolism in mature skeletal muscle (61) and regulating muscle differentiation in adult myoblasts (62). It has been reported that KLF5 can also physically interact with the transcription factor Foxo1 and cooperates with it to control the transcription of Fbxo32 (63). IDO1 (indoleamine-2,3-dioxygenase) is a cofactor-binding, redox-sensitive protein that converts tryptophan to kynurenine (Kyn) (64). Some studies have reported that inflammatory cytokines such as interferon-gamma induce IDO1 production, which leads to catabolism to produce kynurenine. Kyn levels increase with age, which can lead to muscle atrophy and bone marrow stem cells aging, and are closely associated with diseases such as sarcopenia and osteoporosis (65). Meanwhile, IDO1, as an immunomodulatory enzyme that enhances cellular immune escape, has also been significantly associated with inflammatory neointima formation (66). Coronaviruses (CoV) can activate AhR and establish infection through the IDO1-kynurenine-AhR signaling pathway (67). Recent histologic studies have shown that indoleamine 2,3-dioxygenase (IDO) is differentially expressed in the pulmonary vasculature in patients with COVID-19,

and that IDO1 is predominantly present in lung tissues of patients with early/mild pneumonitis and those suffering from prolonged pneumonia (68). CDC25A (Cell Division Cycle-25A) plays a crucial role in the cell cycle and apoptosis by dephosphorylating its substrates (69). mRNA expression of CDC25A has been reported to be down-regulated in aging skeletal muscle (70) and up-regulated in COVID-19 (71). In COVID-19, CDC25A has been found to be closely associated with immune cell infiltration such as plasma cells, macrophages, T cells, dendritic cells and NK cells, and plays an important role in disease progression as a biomarker for COVID-19 diagnosis (71, 72). It has been demonstrated that MYBL2 and BCL6 are significantly upregulated in SARS-CoV-2 infected patients (73, 74). CYP1A1 is a key enzyme mediating the metabolism of broad-spectrum xenobiotics and endogenous elements, and is expressed predominantly in the peripheral airway epithelium (75). CYP1A1 has been extensively studied in pneumonia, and an association between CYP1A1 polymorphisms and the risk of pneumonia has been reported (76). The role of the remaining eight key genes (ALDH1L, EME1, PYGL, NNMT, PHGDH, CD52, CD3D, and ESM1) in COVID-19 and sarcopenia has been less studied, emphasizing their importance in future research.

In our study, GO enrichment analysis revealed that these hub genes are mainly associated with biological processes involved in energy and nucleotide metabolism. This is consistent with earlier studies that dysfunctional mitochondria play a key role in the progression of sarcopenia (77), associated with decreased respiration and increased oxidative stress (78). KEGG analysis suggests that chemical oncogenic-receptor activation and tryptophan metabolic

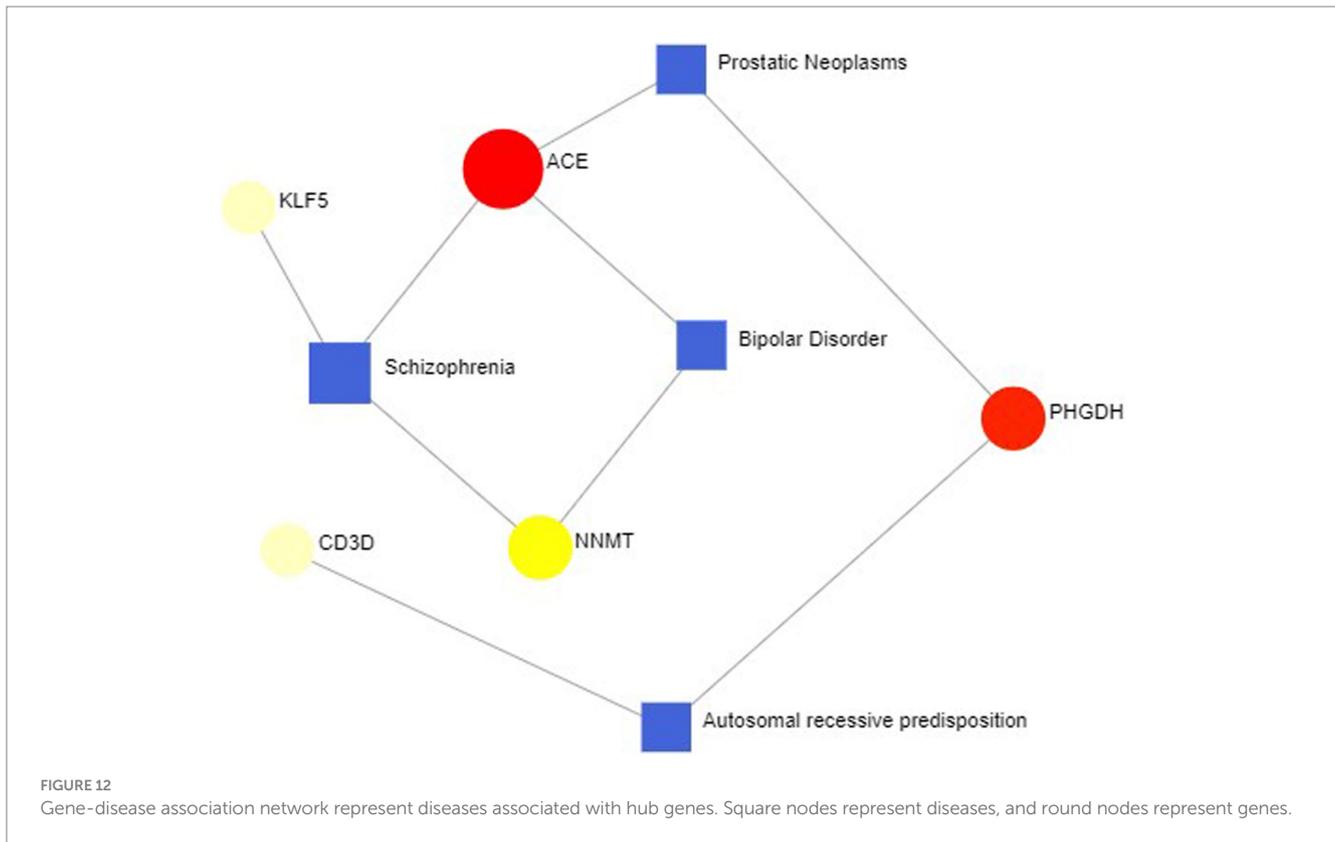


signaling pathways are common pathogenic mechanisms in COVID-19 and sarcopenia. Tryptophan uses two metabolic pathways in humans, kynurenine and serotonin, and the imbalance in the synthesis of itself and its metabolites can lead to the occurrence of various neuropsychiatric disorders (79). In our study, disease-gene association analysis confirmed that these 15 hub genes were most associated with schizophrenia, bipolar disorder, prostate tumors, and autosomal recessive susceptibility. This finding is consistent with previous evidence that dementia and depression have been significantly associated with sarcopenia (80).

TFs and miRNAs regulate gene expression in transcription and post-transcription, respectively, and the results suggest that the transcription factor FOXC1 and miRNA (hsa-mir-155-5p) may be common molecules that simultaneously regulate the expression of these hub genes. FOXC1 is an important member of the FOX family of transcription factors, and several studies have reported that it is an

important TF for COVID-19 (81, 82). And microRNA-155-5p is significantly upregulated in the acute phase of COVID-19, which promotes its immune-inflammatory response (83, 84), thus establishing its association with disease prognosis and playing an important role as a useful biomarker for monitoring and diagnosing COVID-19 disease (85). It suggests that in the future, we can intervene in its expression to regulate the gene and further study and control the disease.

In this study, we further analyzed the infiltration of immune cells in different diseases and the correlation between hub genes and immune factors. The results revealed that the sarcopenia group had lower expression scores of Activated.CD8.T.cells ($p = 0.018$) and Type.17.T.helper.cells ($p = 0.015$) compared with the healthy controls group. CD52 had a strong positive correlation ($p < 0.0001$) with Type.2.T.helper.cells, Type.1.T.helper. Cells and MDSC cells, whereas MYBL2 was negatively correlated with Plasmacytoid.dendritic.cell, Monocyte and Immature.dendritic.cell ($p < 0.01$). It was previously



proposed that the immune system regulates muscle regeneration and growth and plays an important role in the progression of sarcopenia (86). These immune cells, including lymphocytes, macrophages, neutrophils and other immune cells, work together to alter the condition of muscle fibers, leading to loss of muscle strength and muscle mass (87). It has also been found that aging of the immune system leads to a reduction in muscle stem cell populations, promoting their transition to a fibrotic phenotype, which regulates sarcopenia (88). This suggests the importance of different levels of immune cell infiltration for COVID-19 and sarcopenia. Several chemical agents and drugs have been used as potential therapeutic targets against COVID-19 or sarcopenia. However, to date, no drugs have been identified to treat individuals with both COVID-19 and sarcopenia. In our study, we explored 10 drugs that could be used as possible targets. The results showed that valinomycin PC3 UP is the best candidate for the treatment of sarcopenia and COVID-19.

Although some previous studies have reported the relationship between COVID-19 or sarcopenia and the hub gene, but the common molecular mechanisms between the two have not been explored by bioinformatics approaches. In this study, we explored and identified the common DEG and hub genes of COVID-19 and sarcopenia for the first time, which may help to further elucidate the common pathogenesis of both. However, there are some limitations of our study. First, the data were downloaded from public databases, and the amount of data and information was limited and unbalanced. In addition, even though differential and enrichment analyses were performed for sarcopenia and COVID-19, key genes driving disease progression may still be missed. Finally, the pathological causal mechanism of diseases caused by HUB gene and immune infiltration require external experiments to further validate our findings.

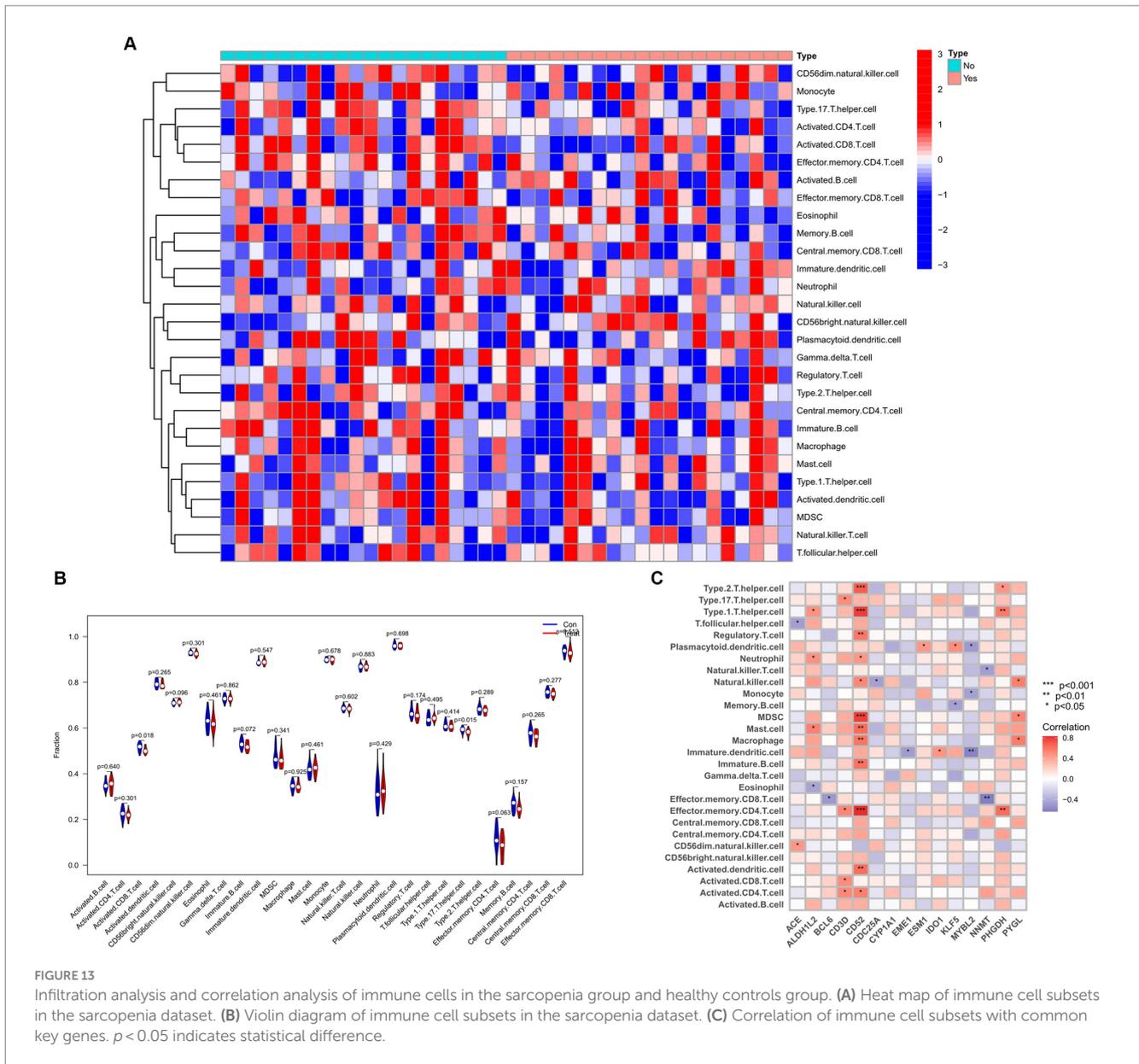
Overall, we explored the link between sarcopenia and COVID-19 using transcriptomic data analysis, further identified the common DEG and hub genes for sarcopenia and COVID-19, and performed several bioinformatics analyses based on them. It was found sarcopenia and COVID-19 share some common pathogenic mechanisms, which may be mediated by specific key genes. This study provides new biological targets and ideas for further investigation of molecular mechanisms, search for new drugs, and early diagnosis and effective treatment for patients with sarcopenia and COVID-19. However, the biological significance of these results needs to be further explored through *in vitro* and *in vivo* experiments.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: <https://www.ncbi.nlm.nih.gov/geo/>, GSE111016 and GSE171110.

Author contributions

JZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. HuY: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JY:



Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YD: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft. ZheL: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. XL: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Validation, Writing – original draft. HaY: Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – original draft. ZhW: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. ZiW: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. LJ: Conceptualization, Data curation, Software, Supervision,

Writing – original draft. ZR: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. HL: Data curation, Methodology, Project administration, Resources, Writing – original draft. ZhoL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. YL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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- valinomycin PC3 UP
- LUCANTHONE CTD 00006227
- 3-(1-methylpyrrolidin-2-yl)pyridine CTD 00006393
- herbimycin a CTD 00001010
- troglitazone CTD 00002415
- cannabidiol CTD 00005567
- niclosamide MCF7 UP
- colchicine CTD 00005701
- Arsenous acid CTD 00000922
- Prazosin hydrochloride BOSS

FIGURE 14
List of top 10 drugs recommended for COVID-19 and sarcopenia patients.

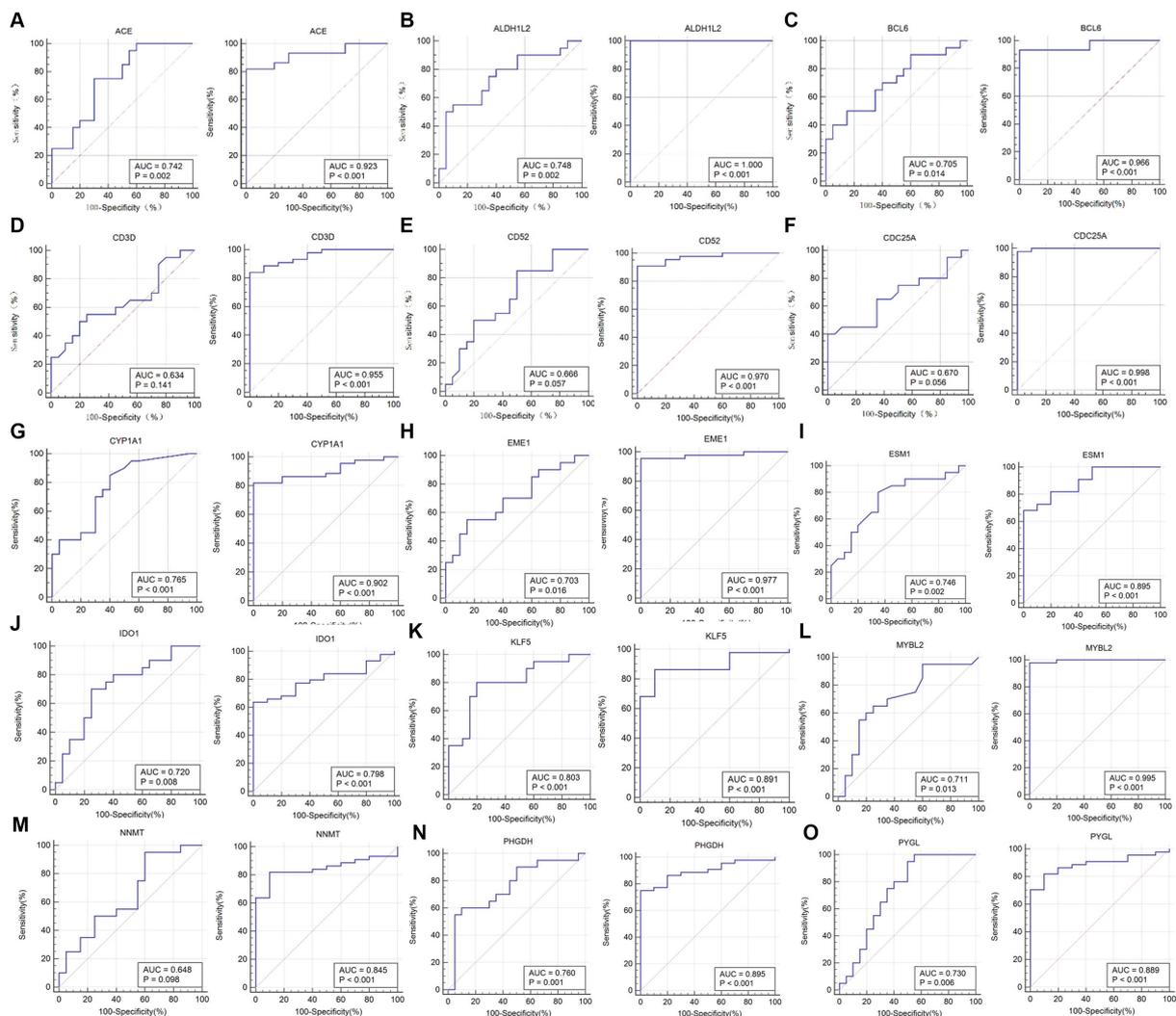


FIGURE 15
Validation of the common hub gene for diagnosis in the sarcopenia (GSE111016) dataset and the COVID-19 infected patient (GSE171110) dataset. (A) ACE, (B) ALDH1L2, (C) BCL6, (D) CD3D, (E) CD52, (F) CDC25A, (G) CYP1A1, (H) EME1, (I) ESM1, (J) IDO1, (K) KLF5, (L) MYBL2, (M) NNMT, (N) PHGDH, and (O) PYGL.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2024.1378846/full#supplementary-material>

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