Bioinformatics approach to identify the influences of SARS-COV2 infections on atherosclerosis

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KEYWORDS
COVID-19, atherosclerosis, C1q, SARS-CoV-2, immune

Introduction

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been a global pandemic since early 2020. According to the WHO, until March 9, 2022, the number of confirmed cases worldwide was 448,313,293, including 6,011,482 deaths (1). In response to the COVID-19 pandemic, a global effort is in progress to develop a vaccine against SARS-CoV-2. Vaccination can help control SARS-CoV-2 outbreaks by preventing infection, reducing disease severity, and blocking transmission (2). COVID-19 is typically characterized by upper respiratory symptoms, including fever, cough, and fatigue, and it is often accompanied by pulmonary infection (3). In addition to typical symptoms, some patients have serious cardiovascular damage, or even the first symptoms. (4) Except for the traditional established risk factors for atherosclerosis, such as age, smoking, hyperlipidemia, and hypertension, viral infection has been supposed to be a potential implication in atherosclerosis (5). SARS-CoV-2 binds to ACE2 to gain intracellular entry, leading to endothelial dysfunction (6). SARS-CoV-2...
also promotes the accumulation of perivascular adipose tissue (7). These may exacerbate the underlying pathology of cardiovascular disease, leading to accelerated progression of atherosclerosis.

The purpose of this study was to explore the pathophysiological association between SARS-CoV-2 and atherosclerosis, and to better understand the underlying mechanisms, so as to facilitate early detection and prevention of atherosclerosis. Two gene expression datasets (GSE152418 and GSE100927) were downloaded from Gene Expression Omnibus (GEO) database. We used bioinformatics and enrichment analysis to determine the common DEGs and their functions for COVID-19 and atherosclerosis. In addition, protein protein interaction (PPI) networks were established to reveal hub genes. These data can better understand the potential link between the two diseases and provide evidence for therapeutic targets.

Materials and methods

Microarray data

The GSE152418 and GSE100927 gene expression profile were obtained from the GEO database (https://www.ncbi.nlm.nih.gov/geo) [Illumina NovaSeq 6000 (Homo sapiens)] platform was used for the GSE152418 dataset where samples were got from seventeen COVID-19 patients, and seventeen healthy people. On the contrary, for the GSE100927 dataset, GPL17077 [Agilent-039494 SurePrint G3 Human GE v2 8x60K Microarray 039381 (Probe Name version)] platform was adopted where samples were collected from sixty-nine atherosclerotic patients and thirty-five control subjects (Table 1).

Disease ontology (DO) analysis

Firstly, the “edgeR” package was applied to screen Differentially Expressed Genes (DEGs) from the GSE152418 dataset where samples were got from seventeen COVID-19 patients, and seventeen healthy people. On the contrary, for the GSE100927 dataset, GPL17077 [Agilent-039494 SurePrint G3 Human GE v2 8x60K Microarray 039381 (Probe Name version)] platform was adopted where samples were collected from sixty-nine atherosclerotic patients and thirty-five control subjects (Table 1).

Acquisition of common genes

The LIMMA package was used to detect the DEGs between atherosclerotic patients and healthy control from the GSE100927 dataset, and the adjusted P-value and |log2FC| were calculated. Genes that met the cutoff criteria, adjusted $P < 0.05$ and |log2FC| more than or equal to 1.0, were considered as DEGs. Then the common genes of the GSE152418 and GSE100927 sets were identified by using the Venn diagram webtool (bioinformatics.psb.ugent.be/webtools/Venn/).

Enrichment analysis of common genes

To further analyze biological processes of common DEGs, GO annotation analysis and KEGG pathway enrichment analysis were carried out through the Database for Annotation, Visualization and Integrated Discovery [DAVID (2021 Update), https://david.ncifcrf.gov/]. P-Value <0.05 was used as the enrichment screening condition.

Construction PPI network and selection hub genes

The PPI network was predicted using Search Tool for the Retrieval of Interacting Genes (STRING, version 11.5, http://string-db.org/) online database. The PPI pairs were extracted with a interaction score more than or equal to 0.15, and then the PPI network was visualized by Cytoscape software (www.cytoscape.org/). Here, we used Degree to evaluate and select hub genes.

Results

DO analysis

Based on the cut-off criteria of adjusted $P < 0.05$ and |log2FC| more than or equal to 1, a total of 2080 DEGs were identified from GSE152418, including 1905 upregulated genes and 175 downregulated genes. we adjust $<0.05$ and gene counts more than or equal to 20 were used as the DO screening condition. Figure 1 shows the top ten most significantly enriched diseases, coronary artery disease, atherosclerosis, arteriosclerotic cardiovascular disease, arteriosclerosis, myocardial infarction, congestive heart failure, acute myocardial infarction, pulmonary hypertension, focal epilepsy and temporal lobe epilepsy. The enrichment results of other diseases by DO analysis are shown in Table 2.

Identification of common DEGs

From GSE100927, 418 DEGs including 295 upregulated genes and 123 downregulated genes were identified. We analyzed the intersection of the DEG profiles using Venn
TABLE 1  Basic information of the two microarray databases derived from the GEO database.

| Disease name      | Dataset ID   | Subjects                                   | GEO platform | Number of samples(control/disease) |
|-------------------|--------------|--------------------------------------------|--------------|------------------------------------|
| COVID-19          | GSE152418    | Peripheral blood mononuclear cell          | GPL24676     | 17/17                              |
| Atherosclerosis   | GSE100927    | Carotid, femoral and infra-popliteal arteries | GPL17077     | 35/69                              |

GEO, Gene Expression Omnibus; COVID-19, Coronavirus Disease 2019.

FIGURE 1  Disease Ontology (DO) analysis of the DEGs from the GSE152418 dataset. The size of the circle represents the number of genes involved, and the abscissa represents the frequency of the genes involved in the term total genes.
| DO ID    | Description                                         | Count | P-Value   | P-Adjust   |
|----------|-----------------------------------------------------|-------|-----------|------------|
| DOID:3393 | Coronary artery disease                           | 85    | 6.97E-09  | 5.83E-06   |
| DOID:5944 | Myocardial infarction                              | 71    | 2.17E-08  | 9.07E-06   |
| DOID:2234 | Focal epilepsy                                     | 24    | 1.52E-07  | 4.24E-05   |
| DOID:6000 | Congestive heart failure                           | 59    | 2.20E-07  | 4.59E-05   |
| DOID:3328 | Temporal lobe epilepsy                             | 21    | 3.18E-07  | 5.32E-05   |
| DOID:1936 | Atherosclerosis                                    | 79    | 3.97E-07  | 5.38E-05   |
| DOID:2348 | Arteriosclerotic cardiovascular disease            | 79    | 4.50E-07  | 5.38E-05   |
| DOID:6432 | Pulmonary hypertension                             | 27    | 9.09E-07  | 9.50E-05   |
| DOID:9408 | Acute myocardial infarction                        | 30    | 1.34E-06  | 0.000124898|
| DOID:2349 | Arteriosclerosis                                   | 79    | 1.70E-06  | 0.000142212|
| DOID:5679 | Retinal disease                                    | 77    | 7.92E-06  | 0.000601666|
| DOID:1168 | Familial hyperlipidemia                            | 26    | 1.20E-05  | 0.000834368|
| DOID:3146 | Lipid metabolism disorder                         | 28    | 1.34E-05  | 0.00085861 |
| DOID:1793 | Pancreatic cancer                                  | 69    | 1.94E-05  | 0.00115929 |
| DOID:850  | Lung disease                                       | 98    | 2.75E-05  | 0.001532539|
| DOID:4450 | Renal cell carcinoma                               | 72    | 3.34E-05  | 0.001746893|
| DOID:8466 | Retinal degeneration                               | 58    | 3.98E-05  | 0.001958846|
| DOID:6364 | Migraine                                           | 23    | 4.23E-05  | 0.00196426 |
| DOID:3324 | Mood disorder                                      | 45    | 5.17E-05  | 0.00227529 |
| DOID:080000 | Muscular disease                                 | 82    | 5.54E-05  | 0.002316532|
| DOID:263  | Kidney cancer                                      | 86    | 8.04E-05  | 0.003053437|
| DOID:3459 | Breast carcinoma                                   | 77    | 9.26E-05  | 0.003364892|
| DOID:060037 | Developmental disorder of mental health           | 75    | 0.000113602| 0.003794572|
| DOID:1826 | Epilepsy syndrome                                  | 46    | 0.000118977| 0.003794572|
| DOID:4451 | Renal carcinoma                                    | 76    | 0.000122552| 0.003794572|
| DOID:1686 | Glaucoma                                           | 29    | 0.00014554 | 0.004217764|
| DOID:2355 | Anemia                                             | 53    | 0.0001587 | 0.004416723|
| DOID:2742 | Auditory system disease                            | 27    | 0.000187263| 0.00470284 |
| DOID:936  | Brain disease                                      | 87    | 0.000192221| 0.00470284 |
| DOID:15   | Reproductive system disease                        | 76    | 0.000205883| 0.00470284 |
| DOID:120  | Female reproductive organ cancer                   | 87    | 0.000207772| 0.00470284 |
| DOID:74   | Hematopoietic system disease                       | 90    | 0.00020814 | 0.00470284 |
| DOID:3996 | Urinary system cancer                              | 94    | 0.000217288| 0.00473576 |
| DOID:4074 | Pancreas adenocarcinoma                            | 38    | 0.000234928| 0.00473576 |
| DOID:060040 | Pervasive developmental disorder                   | 45    | 0.000239673| 0.00473576 |
| DOID:060116 | Sensory system cancer                             | 34    | 0.000241385| 0.00473576 |
| DOID:2174 | Ocular cancer                                      | 34    | 0.000241385| 0.00473576 |
| DOID:060041 | Autism spectrum disorder                          | 43    | 0.000254915| 0.00473576 |
| DOID:12849 | Autistic disorder                                 | 43    | 0.000254915| 0.00473576 |
| DOID:18   | Urinary system disease                             | 90    | 0.000280864| 0.005097229|
| DOID:3083 | Chronic obstructive pulmonary disease              | 48    | 0.000286567| 0.005097229|
| DOID:423  | Myopathy                                           | 77    | 0.000303999| 0.005647089|
| DOID:66   | Muscle tissue disease                              | 77    | 0.000303999| 0.005647089|
| DOID:374  | Nutrition disease                                  | 67    | 0.000399054| 0.006672186|
| DOID:0050700 | Cardiomyopathy                               | 35    | 0.000449318| 0.007240401|
| DOID:6713 | Cerebrovascular disease                            | 29    | 0.000459021| 0.007240401|
| DOID:654  | Overnutrition                                      | 64    | 0.000496562| 0.007574304|
| DOID:4905 | Pancreatic carcinoma                               | 50    | 0.000498309| 0.007574304|

(Continued)
TABLE 2 Continued

| DO ID     | Description                     | Count | P-Value     | P-Adjust      |
|-----------|---------------------------------|-------|-------------|---------------|
| DOID:557  | Kidney disease                  | 86    | 0.00522392  | 0.00798559    |
| DOID:4845 | Retinal cancer                  | 29    | 0.00620866  | 0.00865072    |
| DOID:9970 | Obesity                         | 62    | 0.00663498  | 0.00894652    |
| DOID:1115 | Sarcoma                         | 42    | 0.00711231  | 0.00914753    |
| DOID:229  | Female reproductive system disease | 42  | 0.00711231  | 0.00914753    |
| DOID:2320 | Obstructive lung disease        | 61    | 0.00734442  | 0.00930292    |
| DOID:10534| Stomach cancer                  | 55    | 0.00959048  | 0.01151851    |
| DOID:768  | Retinoblastoma                  | 28    | 0.01033977  | 0.01213846    |
| DOID:771  | Retinal cell cancer             | 28    | 0.01033977  | 0.01213846    |
| DOID:3312 | Bipolar disorder                | 35    | 0.01091638  | 0.01250150    |
| DOID:9352 | Type 2 diabetes mellitus        | 45    | 0.01110794  | 0.01254896    |
| DOID:5041 | Esophageal cancer               | 33    | 0.01158125  | 0.01290923    |
| DOID:3770 | Pulmonary fibrosis              | 29    | 0.01261354  | 0.01351912    |
| DOID:403  | Mouth disease                   | 40    | 0.01484673  | 0.01531642    |
| DOID:26   | Pancreas disease                | 37    | 0.01650415  | 0.01597706    |
| DOID:633  | Myositis                        | 21    | 0.01648237  | 0.01621089    |
| DOID:0060085| Organ system benign neoplasm | 52    | 0.0167946   | 0.01632591    |
| DOID:4607 | Biliary tract cancer            | 38    | 0.01807765  | 0.01737116    |
| DOID:0060084| Cell type benign neoplasm      | 85    | 0.02061029  | 0.01959779    |
| DOID:657  | Adenoma                         | 64    | 0.02109774  | 0.01959745    |
| DOID:1074 | Kidney failure                  | 34    | 0.02145424  | 0.01970961    |
| DOID:48   | Male reproductive system disease| 30   | 0.0220606   | 0.01996808    |
| DOID:865  | Vasculitis                      | 28    | 0.02325292  | 0.02090475    |
| DOID:8398 | Osteoarthritis                  | 39    | 0.02473537  | 0.02199869    |
| DOID:0060100| Musculoskeletal system cancer  | 79    | 0.02508247  | 0.02203954    |
| DOID:299  | Adenocarcinoma                  | 34    | 0.02676763  | 0.02217729    |
| DOID:5223 | Infertility                     | 42    | 0.02695257  | 0.02217729    |
| DOID:3082 | Interstitial lung disease       | 36    | 0.0271993  | 0.02217729    |
| DOID:1575 | Rheumatic disease               | 39    | 0.02732367  | 0.02217729    |
| DOID:418  | Systemic sclerosis              | 39    | 0.02732367  | 0.02217729    |
| DOID:419  | Scleroderma                     | 39    | 0.02732367  | 0.02217729    |
| DOID:2394 | Ovarian cancer                  | 59    | 0.02780859  | 0.02233176    |
| DOID:201  | Connective tissue cancer        | 68    | 0.02894952  | 0.02233176    |
| DOID:10952| Nephritis                       | 32    | 0.02911676  | 0.02233176    |
| DOID:3620 | Central nervous system cancer   | 28    | 0.02988188  | 0.02250563    |
| DOID:0800015| Physical disorder              | 30    | 0.03147388  | 0.02328509    |
| DOID:4960 | Bone marrow cancer              | 61    | 0.03537522  | 0.02549457    |
| DOID:0070004| Myeloma                       | 60    | 0.03590591  | 0.02626496    |
| DOID:2621 | Autonomic nervous system neoplasm| 68 | 0.04049339  | 0.02626496    |
| DOID:769  | Neuroblastoma                   | 68    | 0.04049339  | 0.02626496    |
| DOID:1091 | Tooth disease                   | 34    | 0.04084239  | 0.02626496    |
| DOID:10825| Essential hypertension          | 27    | 0.04075812  | 0.02881255    |
| DOID:289  | Endometriosis                   | 21    | 0.04883272  | 0.02927647    |
| DOID:854  | Collagen disease                | 40    | 0.05216331  | 0.03128014    |
| DOID:1107 | Esophageal carcinoma            | 27    | 0.05290025  | 0.03136497    |
| DOID:0050737| Autosomal recessive disease    | 61    | 0.05365584  | 0.03158893    |
| DOID:0060036| Intrinsic cardiomyopathy       | 29    | 0.0544447  | 0.03160817    |
| DOID:127  | Leiomyoma                       | 22    | 0.05828457  | 0.03292290    |

(Continued)
TABLE 2  Continued

| DO ID  | Description                          | Count | P-Value       | P-Adjust       |
|--------|--------------------------------------|-------|---------------|---------------|
| DOID:37 | Skin disease                         | 63    | 0.00656053    | 0.03584707    |
| DOID:1192 | Peripheral nervous system neoplasm | 70    | 0.00679009    | 0.03626181    |
| DOID:552 | Pneumonia                            | 24    | 0.007057917   | 0.03782319    |
| DOID:4766 | Embryoma                            | 63    | 0.007450764   | 0.03942302    |
| DOID:3388 | Periodontal disease                 | 29    | 0.00830314    | 0.04322301    |
| DOID:16  | Integumentary system disease         | 69    | 0.008758512   | 0.04410913    |
| DOID:0060038 | Specific developmental disorder  | 42    | 0.009006264   | 0.04481688    |
| DOID:12930 | Dilated cardiomyopathy              | 21    | 0.009380129   | 0.04640111    |
| DOID:230 | Lateral sclerosis                    | 24    | 0.009987727   | 0.047987012   |

DEG, Differentially Expressed Gene; DO, Disease Ontology; ID, Identity Document.

(Figure 2). Ultimately, 34 DEGs were significantly differentially expressed in two datasets, of which 33 were significantly upregulated genes and 1 was downregulated gene.

Gene ontology and pathway enrichment analysis

GO and KEGG pathway analyses for DEGs were performed using the DAVID. The biological processes of DEGs were primarily associated with synapse disassembly, complement activation and innate immune response. For the cellular component, the DEGs were enriched in extracellular region, blood microparticle, hemoglobin complex, collagen trimer, and so on. Molecular functions analysis showed that the DEGs were significantly enriched in oxygen transporter activity, oxygen binding, scavenger receptor activity, voltage-gated potassium channel activity involved in atrial cardiac muscle cell action potential repolarization, phosphatidylincholine-sterol O-acyltransferase activator activity, haptoglobin binding, organic acid binding and heme binding (Table 3). In addition, the KEGG pathway analysis showed that the DEGs were significantly enriched in Complement and coagulation cascades, Pertussis, Coronavirus disease—COVID-19, Staphylococcus aureus infection, Chagas disease, Systemic lupus erythematosus and Alcoholic liver disease (Table 4).

PPI network construction and hub gene identification

Using STRING tools, we predicted protein interactions among DEGs. The PPI network presented in Figure 3 consists of 34 nodes and 209 edges. Based on the PPI network, we identified 10 genes with the highest connectivity degree (Table 5). The results showed that C1QA was the most outstanding gene with
TABLE 3  Significantly enriched GO terms of DEGs.

| GO ID           | Description                                                                 | Count | P-Value | Genes                                      |
|-----------------|------------------------------------------------------------------------------|-------|---------|--------------------------------------------|
| Biological process |                                                                              |       |         |                                            |
| GO:0098883      | Synapse disassembly                                                         | 3     | 6.04E−05| C1QB, C1QA, C1QC                           |
| GO:0006958      | Complement activation, classical pathway                                      | 5     | 8.67E−05| C1QB, C1QA, IGLL5, IGLL1, C1QC             |
| GO:0045087      | Innate immune response                                                       | 7     | 2.32E−04| C1QB, C1QA, IGLL5, VNN1, IGLL1, C1QC, OASL |
| GO:0008998      | Receptor-mediated endocytosis                                                | 4     | 0.001825851| CD163, STAB1, HBA2, APOE                    |
| GO:0006954      | Inflammatory response                                                        | 5     | 0.002915761| CCR1, VNN1, STAB1, SPP1, SIGLEC1           |
| GO:0098869      | Cellular oxidant detoxification                                               | 3     | 0.00591978| HBA2, HBD, APOE                            |
| GO:0042159      | Lipoprotein catabolic process                                                | 2     | 0.007472267| APOE, CTSD                                 |
| GO:0098914      | Membrane repolarization during atrial cardiac muscle cell action potential   | 2     | 0.007472267| KCNJ5, KCNA5                               |
| GO:0008956      | Complement activation                                                        | 3     | 0.008884327| C1QB, C1QA, C1QC                           |
| GO:0034447      | Very-low-density lipoprotein particle clearance                              | 2     | 0.008960238| APOC1, APOE                                |
| GO:0034382      | Chylomicron remnant clearance                                                | 2     | 0.010446055| APOC1, APOE                                |
| GO:0030449      | Regulation of complement activation                                          | 3     | 0.012175792| C1QB, C1QA, C1QC                           |
| GO:0010873      | Positive regulation of cholesterol esterification                            | 2     | 0.013411239| APOC1, APOE                                |
| GO:0033700      | Phospholipid efflux                                                          | 2     | 0.017842935| APOC1, APOE                                |
| GO:0044267      | Cellular protein metabolic process                                           | 3     | 0.021136392| MMP1, SPP1, APOE                           |
| GO:0015671      | Oxygen transport                                                             | 2     | 0.022255408| HBA2, HBD                                 |
| GO:0015909      | Long-chain fatty acid transport                                              | 2     | 0.025186416| FABP5, APOE                                |
| GO:0034375      | High-density lipoprotein particle remodeling                                 | 2     | 0.026648738| APOC1, APOE                                |
| GO:0021457      | Lipoprotein metabolic process                                                | 2     | 0.032476871| APOC1, APOE                                |
| GO:0033344      | Cholesterol efflux                                                           | 2     | 0.036825845| APOC1, APOE                                |
| GO:0045671      | Negative regulation of osteoclast differentiation                            | 2     | 0.039714668| MABF, LILRB4                               |
| GO:0032703      | Negative regulation of interleukin-2 production                              | 2     | 0.041159541| VSG4, LILRB4                               |
| GO:0042744      | Hydrogen peroxide catabolic process                                          | 2     | 0.041159541| HBA2, HBD                                 |
| GO:0010033      | Response to organic substance                                                | 2     | 0.042595125| AQP9, KCNA5                                |
| GO:0007267      | Cell-cell signaling                                                          | 3     | 0.049927718| CCR1, C1QA, STAB1                         |
| GO:0002474      | Defense response to bacterium                                                | 3     | 0.046288292| IGLL5, IGLL1, STAB1                       |
| Cellular component |                                                                              |       |         |                                            |
| GO:0005576      | Extracellular region                                                         | 17    | 2.40E−08| C1QB, C1QA, CD163, CD163L1, MMP1, HBA2, VNN1, ENDIC1, FABP5, IGLL1, APOC1, SPP1, PLBD1, SIGLEC1, APOE, CTSD, C1QC |
| GO:0072562      | Blood microparticle                                                          | 5     | 7.68E−05| C1QB, HBA2, HBD, APOE, C1QC                |
| GO:0005833      | Hemoglobin complex                                                           | 3     | 2.19E−04| HBA2, HBD                                 |
| GO:0005851      | Collagen trimer                                                              | 4     | 4.28E−04| C1QB, C1QA, MMP1, C1QC                    |
| GO:0009897      | External side of plasma membrane                                            | 6     | 6.43E−04| CCR1, KCNJ5, IGLL5, CD163, CD163L1, IGLL1 |
| GO:0005602      | Complement component C1 complex                                              | 2     | 0.003171533| C1QB, C1QA                                |
| GO:0098794      | Postsynapse                                                                  | 3     | 0.012921039| C1QB, C1QA, C1QC                          |
| GO:0031838      | Haptoglobin-hemoglobin complex                                               | 2     | 0.017323254| HBA2, HBD                                 |
| GO:0042627      | Chylomicron                                                                  | 2     | 0.021990795| APOC1, APOE                                |
| GO:0071682      | Endocytic vesicle lumen                                                       | 2     | 0.028193596| HBA2, APOE                                 |
| GO:0016021      | Integral component of membrane                                               | 15    | 0.028427769| PTCRA, CCR1, KCNJ5, CD163, CD163L1, AQP9, KCNA5, HBD, LILRB4, MSA4A4, VNN1, SLC02B1, STAB1, SIGLEC1, VSG4 |

(Continued)
TABLE 3  Continued

| GO ID    | Description                                                                 | Count | P-Value    | Genes       |
|----------|-----------------------------------------------------------------------------|-------|------------|-------------|
| GO:0034361 | Very-low-density lipoprotein particle                                       | 2     | 0.03281913 | APOC1, APOE |
| GO:0045202 | Synapse                                                                      | 4     | 0.041387143| C1QB, C1QA, FABP5, C1QC |
| GO:0034364 | High-density lipoprotein particle                                           | 2     | 0.042002749| APOC1, APOE |

**Molecular function**

| GO ID    | Description                                                                 | Count | P-Value    | Genes       |
|----------|-----------------------------------------------------------------------------|-------|------------|-------------|
| GO:0005344 | Oxygen transporter activity                                                  | 3     | 3.12E−04   | HBA2, HBD   |
| GO:0019825 | Oxygen binding                                                              | 3     | 0.001605913| HBA2, HBD   |
| GO:0005404 | Scavenger receptor activity                                                  | 3     | 0.002957949| CD163, CD163L1, STAB1 |
| GO:008689 | Voltage–gated potassium channel activity involved in atrial cardiac muscle cell action potential repolarization | 2     | 0.006590464| KCNJ5, KCNAs |
| GO:0060228 | Phosphatidylcholine-sterol O-acyltransferase activator activity             | 2     | 0.009869914| APOC1, APOE |
| GO:0031720 | Haptoglobin binding                                                         | 2     | 0.016397412| HBA2, HBD   |
| GO:0043177 | Organic acid binding                                                        | 2     | 0.018022768| HBA2, HBD   |
| GO:0020037 | Heme binding                                                                | 3     | 0.02566884 | HBA2, HBD   |

**Table 4  Significantly enriched KEGG terms of DEGs.**

| KEGG ID    | Description                                           | Count | P-Value    | Genes       |
|------------|-------------------------------------------------------|-------|------------|-------------|
| hsa04610 | Complement and coagulation cascades                   | 4     | 0.001112855| C1QB, C1QA, VSIG4, C1QC |
| hsa05133 | Pertussis                                              | 3     | 0.014775214| C1QB, C1QA, C1QC |
| hsa05171 | Coronavirus disease—COVID-19                          | 4     | 0.018374812| C1QB, C1QA, MMP1, C1QC |
| hsa05150 | Staphylococcus aureus infection                        | 3     | 0.02298086 | C1QB, C1QA, C1QC |
| hsa05142 | Chagas disease                                         | 3     | 0.02567277 | C1QB, C1QA, C1QC |
| hsa05322 | Systemic lupus erythematosus                           | 3     | 0.043532485| C1QB, C1QA, C1QC |
| hsa04936 | Alcoholic liver disease                                | 3     | 0.047059029| C1QB, C1QA, C1QC |

DEG, Differentially Expressed Gene; GO, Gene Ontology; ID, Identity Document.

Discussion

Some diseases, thought to be unrelated, share the same biological processes (10). We conducted the DO analysis on the GSE152418 dataset to find the similarity between diseases and COVID-19, and found that COVID-19 was most significantly associated with atherosclerosis among various diseases. Our results suggest that COVID-19 will lead to faster atherosclerosis. Then, we took the intersection of two datasets, GSE152418 and GSE100927, to identify common genes between COVID-19 and atherosclerosis. After obtaining 34 common genes, the GO, pathway, PPI networks were further analyzed.

GO enrichment analysis showed that C1QA, C1QB, C1QC were significantly enriched in synapse disassembly, complement activation, and innate immune response. Complement 1q (C1q) is composed of six subunits, which form a molecule containing 18 polypeptide chains, while C1qA, C1qB, and C1qC genes encode three types of polypeptide chains, A, B, and C of the subunit of C1q, respectively (11). C1q is an important recognition molecule to initiate the classical pathway involved in the complement activation and function, playing a major role in the connection between innate and specific immunity. After identifying the complement binding site on the antibody Fc segment of the IgM or IgG immune complex, the complement cascade will be activated to clear the antigen-antibody complexes (14). Complement proteins specifically locate apoptotic, immature or weak developing synapses in the central nervous system (15). The number of those apoptotic markers in the synapse is equal to the localization of C1q, which promotes synaptic pruning (16). A study found that of 281 patients diagnosed with COVID-19, 21.1% had dementia and 8.9% had mild cognitive impairment (MCI) (17). Moreover, high activation of C1q leads to a large number of synaptic loss which is associated with the development of Alzheimer's disease.
Then, does the activation of complement system C1q cause cognitive impairment in COVID-19 patients? KEGG enrichment analysis is the best way to reflect the changes of pathways in organisms. Those results indicate that complement and coagulation cascades change most significantly in atherosclerosis and COVID-19. Macor et al. found positive lung C1q staining which suggests that the classical pathway is important for complement activation which may be triggered by IgG, antibodies widely distributed in patients’ lungs (19). In atherosclerosis plaques, C1q activates the classical complement pathway by recognizing oxidized low-density lipoprotein auto-antibodies or directly binding modified lipoprotein and cholesterol crystal (20). Endothelial dysfunction, an important mechanism for the formation and development of atherosclerosis, can be caused by the activation of the complement system can lead to (20). Gao et al. demonstrated that subsequent endothelial dysfunction persisted in COVID-19 survivors even 327 days after diagnosis (6). The activated fragments generated after the activation of the complement system may be closely related to the coagulation and fibrinolytic system and inflammation in COVID-19 patients, so additional studies on the changes in the number of fragments and tissue distribution are needed.

The 10 hub genes selected by PPI were C1QA, C1QB, C1QC, CD163, SIGLEC1, APOE, MS4A4A, VSIG4, CCR1, and STAB1. The C1QA, C1QB, and C1QC genes had the highest degree in the PPI networks. Then v-set and immunoglobulin domain containing 4 (VSIG4) is the receptor of complement component 3 fragments C3b and iC3b, which activates macrophage immunity through C3b/iC3b binding (21). VSIG4 may be involved in lung injury through induction of phagocytosis (22). VSIG4 activate macrophages, through induction of chemokines, promote the migration of inflammatory cells to the lesion area, and participate in the pathogenesis of arteriosclerosis.

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The increased expressions of C1QA, C1QB, C1QC, and VSIG4 all relate to enhanced complement system. CD163, a scavenger receptor, is a major component of inflammation and the immune response. Among plasmacytoid dendritic cells, type I interferon is induced with the appearance of CD163+ SIGLEC1+ macrophages with increased angiotensin converting enzyme 2 (ACE2) levels. Macrophages are highly enriched in the lungs of macaques at peak viremia and harbor the SARS-CoV-2 virus while also expressing an interferon-driven innate antiviral gene signature. CD163(+) macrophages promote angiogenesis, vascular permeability and inflammation in atherosclerosis via the CD163/HIF1α/VEGF-A pathway. The increased expression of CD163 was revealed in ruptured coronary plaques. There are three APOE isoforms, namely APOE epsilon2 (APOE2), APOE epsilon3 (APOE3) and APOE epsilon4 (APOE4) located on chromosome 19q13.2. APOE can function as an endogenous, concentration-dependent pulmonary signal that primes and activates the NLRP3 inflammasome in bronchoalveolar lavage fluid macrophages from asthmatic subjects to secrete IL-1β. A recent study in the UK Biobank Cohort, APOE4 has been shown to associate with increased susceptibility to SARS-CoV-2 infection and COVID-19 mortality. APOE is a therapeutic target for statins that inhibit inflammation in patients with atherosclerotic vascular disease. Statins possess antiviral, immunomodulatory, antithrombotic, and anti-inflammatory properties, which may improve short- and long-term outcomes in COVID-19 patients.

STAB1 encodes an unusual type of multifunctional scavenger receptor that causes increased lipid uptake and transient lipid depletion in virus-infected areas and is associated with poor prognosis for COVID-19. STAB1 expression may contribute to foam cell formation, monocyte adhesion/migration, and regulation of inflammation in atherosclerotic lesions. Lectins such as sialic acid-binding Ig-like lectin 1 (SIGLEC1/CD169) mediate the attachment of viruses to Antigen-presenting cells (APCs). SIGLEC1 expression is induced on APCs upon IFN-α or LPS exposure and increased in myeloid cells of COVID-19 patients. Inhibition of Siglec-1 prevents monocytes from adhering to vascular endothelial cells in the early stage of atherosclerosis, and reduces lipid phagocytosis and chemokine secretion of macrophages, alleviating the inflammatory response of established fat streaking lesions. CCR1 is critical mediators of monocyte/macrophage polarization and tissue infiltration, which are pathogenic hallmarks of severe COVID-19. The use of monocyte CCR1 in arterial recruitment is due in part to activated chemokines of platelet deposition, which is important in the early stages of atherosclerosis. MS4A4A is a novel M2 macrophage cell surface marker, which is essential for dectin-1-dependent activation of NK cell-mediated anti-metastatic properties. Silva-Gomes et al. found that MS4A4A was expressed by MΦs or alveolar MΦs in COVID-19 bronchoalveolar lavage fluid.

Through DO analysis, we also found several neurological disorders associated with COVID-19, such as focal epilepsy, temporal lobe epilepsy, migraine, epilepsy syndrome, neuroblastoma, and lateral sclerosis. There have been a large number of reported cases of these conditions, with a seizure prevalence ranging from 0 to 26% in COVID-19 patients. Moreover, seizures may be related to cerebrovascular disease and central nervous system infection. Vascular endothelial injury leads to hypercoagulability and microembolism, resulting in reduced cortical blood flow accompanied by hypoxia. Vascular endothelial dysfunction can lead to changes in the nervous system, resulting in neurological sequelae. The Atherosclerosis Risk in Communities (ARIC) study also revealed that migraine patients were more susceptible to retinopathy (retinal hemorrhage, macular oedema, retinal microvascular abnormalities, venous bleeding, etc.) than non-migraine patients, and retinopathy was more strongly associated with migraine in people without a history of diabetes or hypertension. Interestingly, we also discovered DEGs enrichment in retinopathy. Besides, previous animal-based experimental studies of the coronavirus infection reported retinal diseases such as retinal vasculitis and retinal degeneration. Moreover, blood-retinal barrier breakdown revealed the possibility of immune-privileged site infectivity by SARS-CoV-2. We believe that SARS-CoV-2 causes vascular injury and may lead to retinal degeneration. Results also revealed different types of cancer, such as pancreatic cancer, kidney cancer, breast carcinoma, stomach cancer, esophageal cancer, and ovarian cancer. In patients with COVID19, severe illness and mortality are closely related to cancer. SARS CoV 2 may promote tumor progression and stimulate metabolic switching in tumor cells to initiate tumor metabolic modes with higher production efficiency, such as glycolysis, for facilitating the replication of SARS CoV 2. Meanwhile, we also established that muscular disease, such as myositis, is

| Gene symbol | Gene description | Degree |
|-------------|------------------|--------|
| C1QA        | Complement C1q A chain | 24     |
| C1QB        | Complement C1q B chain | 23     |
| C1QC        | Complement C1q C chain | 22     |
| CD163       | CD163 molecule     | 22     |
| SIGLEC1     | Sialic acid binding Ig like lectin 1 | 21     |
| APOE        | Apolipoprotein E   | 19     |
| MS4A4A      | Membrane spanning 4-domains A4A | 19     |
| VSIG4       | V-set and immunoglobulin domain containing 4 | 18     |
| CCR1        | C-C motif chemokine receptor 1 | 18     |
| STAB1       | Stabilin 1        | 18     |

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associated with COVID-19. Previous studies have demonstrated that patients with dermatomyositis have three immunogenic linear epitopes with a high degree of sequence identity to the SARS-CoV-2 protein, so potential exposure to the coronavirus family may lead to the development of dermatomyositis (45). Effective Janus kinase (JAK) inhibitors for dermatomyositis, including tofacitinib, ruxolitinib, and baricitinib, may provide new directions for COVID-19 treatment.

In conclusion, the study provides new insights for the common pathogenesis of COVID-19 and atherosclerosis by looking for common transcriptional features. The DEGs identified by bioinformatics data analysis, including C1QA, C1QB, C1QC, CD163, SIGLEC1, APOE, MS4A4A, VSIG4, CCR1, and STAB1, may be therapeutic targets for the atherosclerosis caused by COVID-19. However, more wet lab-based studies are required to validate the impact of COVID-19 severity on atherosclerosis. Studies on the long-term effects of SARS-CoV-2 infection, the effect of persistent endothelial dysfunction on atherosclerosis, and the role of preventive therapy are also needed.

**Data availability statement**

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article-supplementary material.

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**Author contributions**

JZ performed the data analyses and wrote the manuscript. LZ helped perform the analysis with constructive discussions. Both authors approved the final version of the manuscript.

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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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