frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 30 June 2023
DOI 10.3389/fmed.2023.1169562

OPEN ACCESS

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RECEIVED 19 February 2023
ACCEPTED 15 June 2023
PUBLISHED 30 June 2023

CITATION
Song Y, Huang T, Pan H, Du A, Wu T, Lan J, Zhou X, Lv Y, Xue S and Yuan K (2023) The influence of COVID-19 on colorectal cancer was investigated using bioinformatics and systems biology techniques.
Front. Med. 10:1169562.
doi: 10.3389/fmed.2023.1169562

The influence of COVID-19 on colorectal cancer was investigated using bioinformatics and systems biology techniques

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Introduction: Coronavirus disease 2019 (COVID-19) is a global pandemic and highly contagious, posing a serious threat to human health. Colorectal cancer (CRC) is a risk factor for COVID-19 infection. Therefore, it is vital to investigate the intrinsic link between these two diseases.

Methods: In this work, bioinformatics and systems biology techniques were used to detect the mutual pathways, molecular biomarkers, and potential drugs between COVID-19 and CRC.

Results: A total of 161 common differentially expressed genes (DEGs) were identified based on the RNA sequencing datasets of the two diseases. Functional analysis was performed using ontology keywords, and pathway analysis was also performed. The common DEGs were further utilized to create a protein-protein interaction (PPI) network and to identify hub genes and key modules. The datasets revealed transcription factors-gene interactions, co-regulatory networks with DEGs-miRNAs of common DEGs, and predicted possible drugs as well. The ten predicted drugs include troglitazone, estradiol, progesterone, calcitriol, genistein, dexamethasone, lucanthone, resveratrol, retinoic acid, phorbol 12-myristate 13-acetate, some of which have been investigated as potential CRC and COVID-19 therapies.

Discussion: By clarifying the relationship between COVID-19 and CRC, we hope to provide novel clues and promising therapeutic drugs to treat these two illnesses.

KEYWORDS

COVID-19, colorectal cancer, differentially expressed genes, gene ontology, protein–protein interaction, hub gene, drug molecule

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a betacoronavirus, belonging to the subgenus *Sarbecovirus*, which is transmitted primarily through the respiratory tract and is highly potent and infectious (1). SARS-CoV-2 has unique features compared with previously known coronavirus genomes, including an optimum affinity for the

angiotensin-converting enzyme 2 (ACE2) receptor and a polybasic cleavage site at the S1/S2 spike junction, which determines infectivity and host range (2). In addition, it was shown that SARS-CoV-2 also enters host cells with the primary or auxiliary help of host proteases transmembrane protease serine 2 (TMPRSS2) and FURIN (3), glucose-regulating protein 78 (GRP78) receptor (4), dipeptidyl peptidase 4 (DPP4), (5), cluster of differentiation 147 (CD147) transmembrane protein (6), tyrosine-protein kinase receptor UFO (AXL) (7), phosphatidylinositol 3-phosphate 5-kinase (PIKfyve), two pore channel subtype 2 (TPC2) and cathepsin L (8). The respiratory illness coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2 (9). Infection with SARS-CoV-2 can stimulate both innate and adaptive immune responses, whereas an uncontrolled inflammatory innate response and a defective adaptive immune response may lead to detrimentally local and systemic tissue damage (9, 10). Patients with COVID-19 frequently experience symptoms such as fever, coughing, vomiting, diarrhea, abdominal pain, shortness of breath, and severe cases that can develop to acute respiratory distress syndrome (ARDS), pneumonia, and multi-organ failure (10, 11). Since its emergence, COVID-19 has continued to affect many parts of the world and threaten millions of lives worldwide (12). Wang et al. have shown that the case fatality rate of COVID-19 patients ranges from 2 to 3% (13). Although the lung is the primary target of coronavirus infection, the digestive system has also been identified to have ACE2, the SARS-CoV-2 functional receptor, suggesting that in addition to the respiratory system, COVID-19 can also infect people through this system (1, 14).

Several studies have been published on the effects of COVID-19 on cancer patients (15–17). A previous study has shown that cancer patients are more vulnerable to infection than individuals without cancer due to the systemic immunosuppressive state created by cancer and anticancer treatment, such as chemotherapy or surgery (17). Yeo et al. further found that cancer was linked to a 2.84-fold greater risk of severe disease in COVID-19 patients and a 2.60-fold increased risk of mortality (18). Colorectal cancer (CRC) is the world's second-largest cause of cancer death and the third most common malignancy (19). A subgroup analysis based on place of origin showed that Chinese CRC patients had a significant risk of infection, with the global burden of COVID-19 infection in CRC patients being 45.1% (20). According to Burgueño et al., the ileum, colon, and intestinal epithelial cells express ACE2 and TMPRSS2, which permits COVID-19 access into colon cells (21). Immunosuppression, malignancy, and anticancer therapy may play a role in the increased COVID-19 susceptibility in CRC (22). Therefore, it is crucial to explore how COVID-19 influences CRC patients and to search for possible therapeutic agents for CRC patients with COVID-19.

This study attempts to search the shared biological pathways and possible drugs between CRC and COVID-19 by bioinformatics and systems biology techniques. The COVID-19 datasets (GSE196822) and CRC datasets (GSE142279) were from the Gene Expression Omnibus (GEO) database, respectively. Initially, COVID-19 and CRC differentially expressed genes (DEGs) were found, and then common DEGs of the two illnesses were discovered. The obtained common DEGs served as the foundation for subsequent research. Then, employing common DEGs, enrichment analysis and pathway analysis were used to better understand the biological process of gene expression. Protein–protein interaction (PPI) networks were also utilized to gather hub genes based on common DEGs. Transcriptional regulators and miRNAs were then identified using common DEGs. Finally, prospective drugs are offered, as well as gene-disease associations. Figure 1 depicts the overall workflow of this study.

2. Materials and methods

2.1. Data collection

To determine the common gene interrelationship between COVID-19 and CRC, we downloaded RNA-seq datasets of COVID-19 and CRC from the GEO database of the National Center for Biotechnology Information (NCBI)[1] (23). The GEO accession ID of COVID-19 was GSE196822, which included RNA-seq profiling from 9 uninfected samples and 34 infected samples using the high throughput sequencing Illumina HiSeq 4,000 (*Homo sapiens*) platform (24). Similarly, the sequencing of CRC (GSE142279) was gained by high throughput sequencing HiSeq X Ten (*Homo sapiens*) platform from 20 pairs of colorectal tumors with matched adjacent normal colorectal tissue.

2.2. Determination of differentially expressed genes and mutual DEGs among COVID-19 and CRC

A gene is believed to be expressed differently when there is a transcription level statistically significant difference between distinct test conditions (25). To extract DEGs for datasets GSE196822, we utilized the "DESeq2" package (26) of the R program (version 4.2.2) with False Discover Rate (FDR) < 0.05 and $|\log_2 \text{Fold Change}| > 1$. The dataset GSE142279 was retrieved by the "limma" package (27) and the criteria for considering the difference in expression as FDR < 0.05 and $|\log_2 \text{Fold Change}| > 1$. Common DEGs of the two datasets were obtained from the online Venn analysis program Jvenn[2] (28).

2.3. Gene ontology and pathway enrichment analysis

The Gene Ontology is a globally standardized gene functional classification system with three ontologies: molecular function, cellular component, and biological process. The primary biological functions of DEGs were identified using this analysis (29). By comparing DEGs to the whole genome background, pathway enrichment analysis showed significantly enriched metabolic or signal transduction pathways. Pathway databases included KEGG (Kyoto Encyclopedia of Genes and Genomes), WikiPathways, Reactome, and BioCarta. In this research, we utilized the online gene-set enrichment tool EnrichR[3] to investigate the biological processes and signaling pathways linked to common DEGs (30). To quantify the most important functional items and pathways, *p*-values of 0.05 was employed as standardized metrics.

1 https://www.ncbi.nlm.nih.gov/
2 http://jvenn.toulouse.inra.fr/app/index.html
3 https://maayanlab.cloud/enrichr/

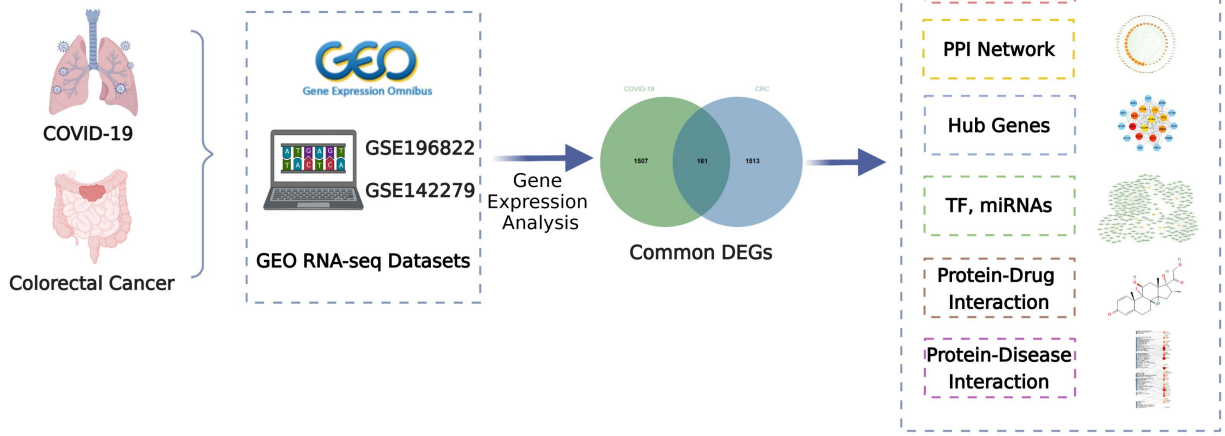


FIGURE 1
Overall flowchart of this research.

2.4. PPI network analysis and hub gene prediction

PPI is an important part of the cellular biochemical response network and can be used to map the functional and structural knowledge of cellular protein networks (31). STRING[4] (version 11.5) was utilized to perform the key assessment of protein–protein interactions based on the common DEGs. With a combined score larger than 0.4, the PPI network was created and visualized using Cytoscape (v.3.9.1). The most entangled nodes in the PPI network are referred to as hub genes. To rank and analyze the major nodes in the PPI network module and identify the key genes, we used the Cytoscape plugin cytoHubba. The top ten hub genes in the PPI network were chosen using the Maximal Clique Centrality (MCC) method (32).

2.5. Identification of transcription factors and MiRNAs

TFs are proteins that bind to specific genes and regulate the transcription rate of genetic information. They built a sophisticated system that regulated genome expression and contributed significantly to molecular understanding (33). The DEGs-TFs interaction network was established using the JASPAR database from the online website NetworkAnalyst. NetworkAnalyst was developed in response to the crucial requirement for analyzing gene expression data within the framework of PPI networks to obtain information on biological mechanisms, functions, and interpretations (34). JASPAR is the most complete database of TF-DNA binding site motifs available to the public (35). MiRNAs that target gene interactions were incorporated to identify miRNAs with the potential to bind to gene transcripts and so negatively impact protein production. The miRTarBase, based on NetworkAnalyst and focused on topological analysis, was utilized to identify DEG-miRNA interaction networks. MiRTarBase is the most famous overall miRNA-target interaction database and an important database for evaluating the validity of miRNA-target gene interaction experiments (36). Cytoscape was used to display the TF-gene and miRNA-gene interaction networks.

2.6. Evaluation of potential drugs

Predicting protein-drug interactions (PDI) or identifying pharmacological molecules is an essential part of this research. The Drug Signatures database (DSigDB) database was employed to identify the common DEGs by accessing the enrichment of Enrichr under the Diseases/Drugs function on the online website. DSigDB is a gene set resource for identifying targeted drugs associated with DEGs (37). Further screening of significant drug molecules was performed based on the *p*-value.

2.7. Gene-disease association analysis

DisGeNET,[5] one of the biggest and most thorough databases of human gene-disease connections, integrates and standardizes data on disease-associated genes and variants from various sources while also providing a variety of biomedical aspects of the disease (38). The NetworkAnalyst platform was used to construct a gene-disease interaction network to discover diseases and chronic complications linked to common DEGs (39).

4 www.string-db.org

5 http://www.disgenet.org/

3. Results

3.1. Identification of DEGs and common DEGs between COVID-19 and CRC

To investigate the interrelationship and impact between COVID-19 and CRC, we collected corresponding human RNA-seq datasets, respectively. We identified a total of 1,668 differentially expressed genes between COVID-19 patients and healthy controls, 839 of which showed up-regulated and 829 down-regulated. At the same time, 1,674 in total DEGs were found between colorectal tumors and normal colorectal tissues in CRC patients, including 751 up-regulated DEGs and 923 down-regulated DEGs (Table 1). We discovered 161 common DEGs from COVID-19 and CRC datasets through cross-comparison analysis using the Jvenn (28), a reputable Venn analysis platform, suggesting that they may be related to the biological link between these two conditions (Figure 2). The results of the differential expression study showed that COVID-19 and CRC interacted and shared certain molecular similarities.

3.2. Gene ontology and pathway enrichment analysis

Enrichr was employed for gene ontology and pathway enrichment analysis to discover the biological significance and enriched pathways of the shared DEGs. The gene ontology enrichment method is widely employed to represent interactions between genes and gene ontology terms. The top ten terms in the categories of biological process, molecular function, and cellular component were gathered in Table 2. Figure 3 presents the total ontological analysis as a linear bar graph for each category. In the biological process, the GO terms are important in relation to neutrophils and interferon-gamma. Pathway analysis demonstrates that the organism responds to its inherent modifications. To assemble the most enriched pathways of the common DEGs, four global databases (KEGG, WikiPathways, Reactome, and BioCarta) were used. Table 3 summarizes the top ten pathways identified by pathway analysis, and the results are presented more intuitively in the bar graph of Figure 4. Acute myeloid leukemia, the immune system, and cyclins and cell cycle regulation pathways are critical in the analysis.

3.3. PPI network analysis and recognition of hub genes

PPI network can visually show the correlation between different proteins, indicating the potential mechanism of protein action. Key proteins that affect how cells and systems function biologically have been discovered due to the assessment and analysis of the PPI network (39). The PPI network was created with STRING based on common DEGs and visualized in Cytoscape. The results are shown in Figure 5, which includes 151 nodes and 286 edges. In the PPI network, the majority of interconnected nodes are referred to as hub genes. A submodule network was further constructed with the latest MCC procedure of the Cytohubba plugin in Cytoscape to analyze potential hub genes. The top 10 genes were listed as the most influential genes, including CDK1, KIFC1, CDCA5, MKI67, UBE2C, PLK1, TPX2, KIF20A, HJURP, CENPA (Figure 6).

3.4. Determination of transcriptional factors and miRNAs engaged

We used NetworkAnalyst to identify regulatory TFs and miRNAs to characterize the significant alterations at the transcriptional level and better comprehend the regulatory key proteins. Figures 7, 8 depict the interactions of TF regulators and miRNA regulators with hub genes. Forty-two TFs and 248 miRNA regulatory signals were projected to affect numerous common differential genes, implying that they interact.

3.5. Prediction of potential therapeutic agents and exploration of gene-disease associations

Interactions between drugs and proteins play an important role in understanding and recommending structural features for receptor sensitivity. Based on DSigDB, which has the most gene sets connected to drugs/compounds to date, Enrichr was used to screen out the top ten drug molecules with *p*-values from the common DEGs (Table 4). The ten potential drugs include troglitazone, estradiol, progesterone, calcitriol, genistein, dexamethasone, lucanthone, resveratrol, retinoic acid, phorbol 12-myristate 13-acetate. These drugs have the potential to be employed in the treatment of COVID-19 and CRC. Deciphers the connection between genes and disease begins with the development of technologies for illness therapy. DisGeNET is a platform for managing knowledge that unifies and standardizes information on genes and variants linked to disease from many sources. Based on DisGeNET, gene-disease association analysis was performed by NetworkAnalyst. The results showed that lung neoplasms, autoimmune diseases, liver cirrhosis, unipolar depression, and colonic neoplasms were most concordant with the common DEGs (Figure 9).

4. Discussion

The COVID-19 epidemic, caused by SARS-CoV-2, has been designated a worldwide emergency due to the damage for its quick

TABLE 1 Overview of the datasets used in this study along with their geo-features and quantitative measurements.

Disease name	GEO accession	GEO platform	Total DEGs count	Up regulated DEGs count	Down regulated DEGs count
COVID-19	GSE196822	GPL20301	1,668	839	829
CRC	GSE142279	GPL20795	1,674	751	923

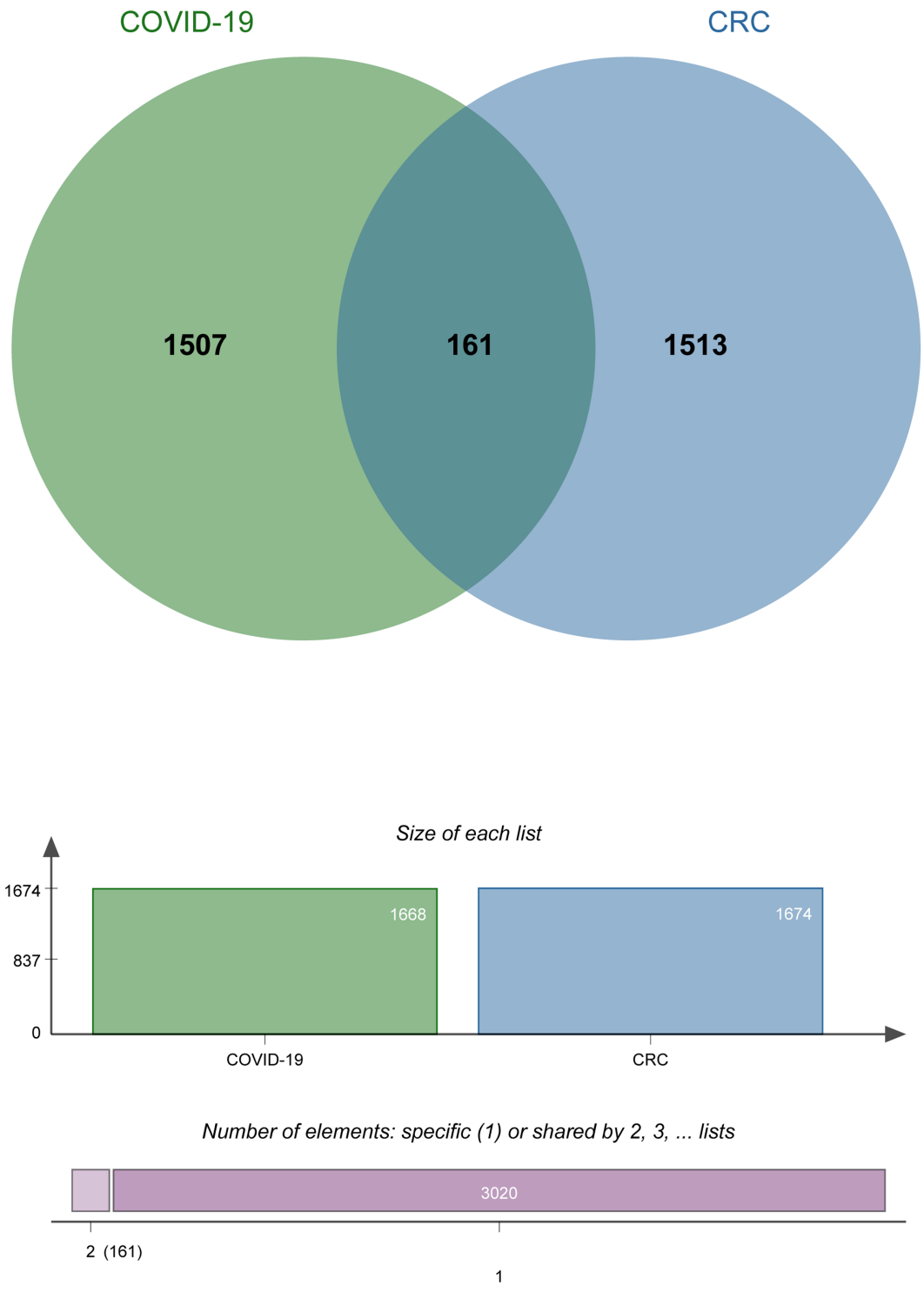


FIGURE 2
The Venn diagram of the DEGs shared by COVID-19 and CRC.

spread and high mortality (10). CRC is the largest cause of cancer mortality worldwide, and it is one of the cancers whose incidence is increasing, accounting for 11% of all cancer diagnoses (40). Previous research has shown that cancer patients are more sensitive to infection than individuals without cancer, and Chinese patients with colorectal cancer have a significant risk of infection (18, 20, 41). In this study, we investigated the potential interactions between CRC and COVID-19 using bioinformatics and systems biology techniques. We screened 1,668 and 1,674 DEGs from GSE196822 and GSE142279 datasets, respectively, and identified 161 common DEGs. Then, based on common DEGs, we analyzed GO, pathways, PPI network, hub genes, TF-gene interaction network, miRNA-gene coordination node network, candidate drugs, and gene-disease.

TABLE 2 Ontological analysis of the mutual DEGs between CRC and COVID-19.

Category	Term	*p*-value	Genes
GO Biological Process	Neutrophil degranulation (GO:0043312)	1.82E-09	GSN/TNFAIP6/ANXA3/SLC11A1/HSPA6/MMP9/CEACAM1/PLAU/TCN1/CEACAM6/ANPEP/P2RX1/S100A12/CTSG/S100P/CD14/S100A9/S100A8/ELANE/CD177
	Neutrophil activation involved in immune response (GO:0002283)	2.10E-09	
	Neutrophil mediated immunity (GO:0002446)	2.33E-09	
	Regulation of inflammatory response (GO:0050727)	1.17E-08	MACIR/TNFAIP6/SERPINE1/OSM/MMP9/SBNO2/GPER1/PDCD4/S100A12/ENPP3/S100A9/S100A8/ELANE
	Cytokine-mediated signaling pathway (GO:0019221)	2.55E-06	IFITM3/IL1RN/IFITM1/CCL23/TNFRSF12A/MAOA/IL1R2/IFI6/OSM/MMP9/SOCS3/MT2A/CA1/CEACAM1/COL1A2/OAS3/PDCD4/CTSG
	Regulation of interferon-gamma production (GO:0032649)	5.82E-06	CD2/SLC11A1/SLAMF6/CD14/INHBA/VSIR/LGALS9C
	Negative regulation of viral entry into host cell (GO:0046597)	8.66E-06	IFITM3/IFITM1/GSN/LY6E
	Defense response to bacterium (GO:0042742)	1.24E-05	ANXA3/SLC11A1/OAS3/SERPINE1/S100A12/CTSG/S100A9/S100A8/ELANE
	Negative regulation of viral life cycle (GO:1903901)	1.73E-05	IFITM3/IFITM1/GSN/LY6E
	Regulation of cell migration (GO:0030334)	2.56E-05	ACVRL1/IFITM1/SERPINE1/SEMA3B/MMP9/VSIR/CXCL16/COL1A1/CEACAM1/PLAU/CEACAM6/GPER1/SGK1
GO Cellular Component	Collagen-containing extracellular matrix (GO:0062023)	1.11E-08	COL17A1/C1QB/C1QA/GDF15/SERPINE1/SEMA3B/CLU/MMP9/LOXL1/COL1A1/COL1A2/MMRN1/COL7A1/CTSG/S100A9/S100A8/ELANE
	Secretory granule lumen (GO:0034774)	9.41E-06	GSN/MMRN1/TCN1/SERPINE1/HSPA6/S100A12/CTSG/S100P/CLU/S100A9/S100A8/ELANE
	Specific granule (GO:0042581)	3.08E-04	CEACAM1/PLAU/TCN1/ANXA3/P2RX1/ELANE/CD177
	Cytoplasmic vesicle lumen (GO:0060205)	3.27E-04	GSN/HSPA6/S100A12/S100P/S100A9/S100A8
	Tertiary granule (GO:0070820)	3.58E-04	CEACAM1/TNFAIP6/PLAU/TCN1/SLC11A1/MMP9/CD177
	Secretory granule membrane (GO:0030667)	3.71E-04	CEACAM1/PLAU/CEACAM6/ANPEP/SLC11A1/P2RX1/CA4/CD14/CD177
	Tertiary granule membrane (GO:0070821)	0.0027972	CEACAM1/PLAU/SLC11A1/CD177
	Microtubule (GO:0005874)	0.0034919	TPX2/KIF18B/KIFC1/PLK1/CDK1/KIF20A
	Phagocytic vesicle membrane (GO:0030670)	0.0055745	ANXA3/SLC11A1/TAP1
	Anchored component of plasma membrane (GO:0046658)	0.0059288	CA4/CD14/CD177
GO Molecular Function	RAGE receptor binding (GO:0050786)	4.07E-05	S100A12/S100A9/S100A8
	Serine-type peptidase activity (GO:0008236)	6.65E-05	PLAU/HTRA3/GZMA/PCSK9/CTSG/MMP9/ELANE
	Carbonate dehydratase activity (GO:0004089)	7.91E-05	CA12/CA1/CA4
	Serine-type endopeptidase activity (GO:0004252)	2.00E-04	PLAU/GZMA/PCSK9/CTSG/MMP9/ELANE
	Icosatetraenoic acid binding (GO:0050543)	9.34E-04	S100A9/S100A8
	Arachidonic acid binding (GO:0050544)	9.34E-04	S100A9/S100A8
	Cobalamin binding (GO:0031419)	9.34E-04	TCN2/TCN1
	Endopeptidase activity (GO:0004175)	0.0010049	ADAMTS2/ADAM28/PLAU/HTRA3/GZMA/PCSK9/CTSG/MMP9/ELANE
	Icosanoid binding (GO:0050542)	0.0013009	S100A9/S100A8
	ATP binding (GO:0005524)	0.0018243	ACVRL1/ABCB1/KIFC1/OAS3/PLK1/HSPA6/TAP1/TRIP13

GO terms were selected with mutual DEGs and based on *p*-values. For the biological process, neutrophil degranulation, neutrophil activation involved in immune response, neutrophil mediated immunity, and regulation of interferon-gamma production were important GO terms. Neutrophils perform an essential part in the course of COVID-19 infection. The immune response of COVID-19

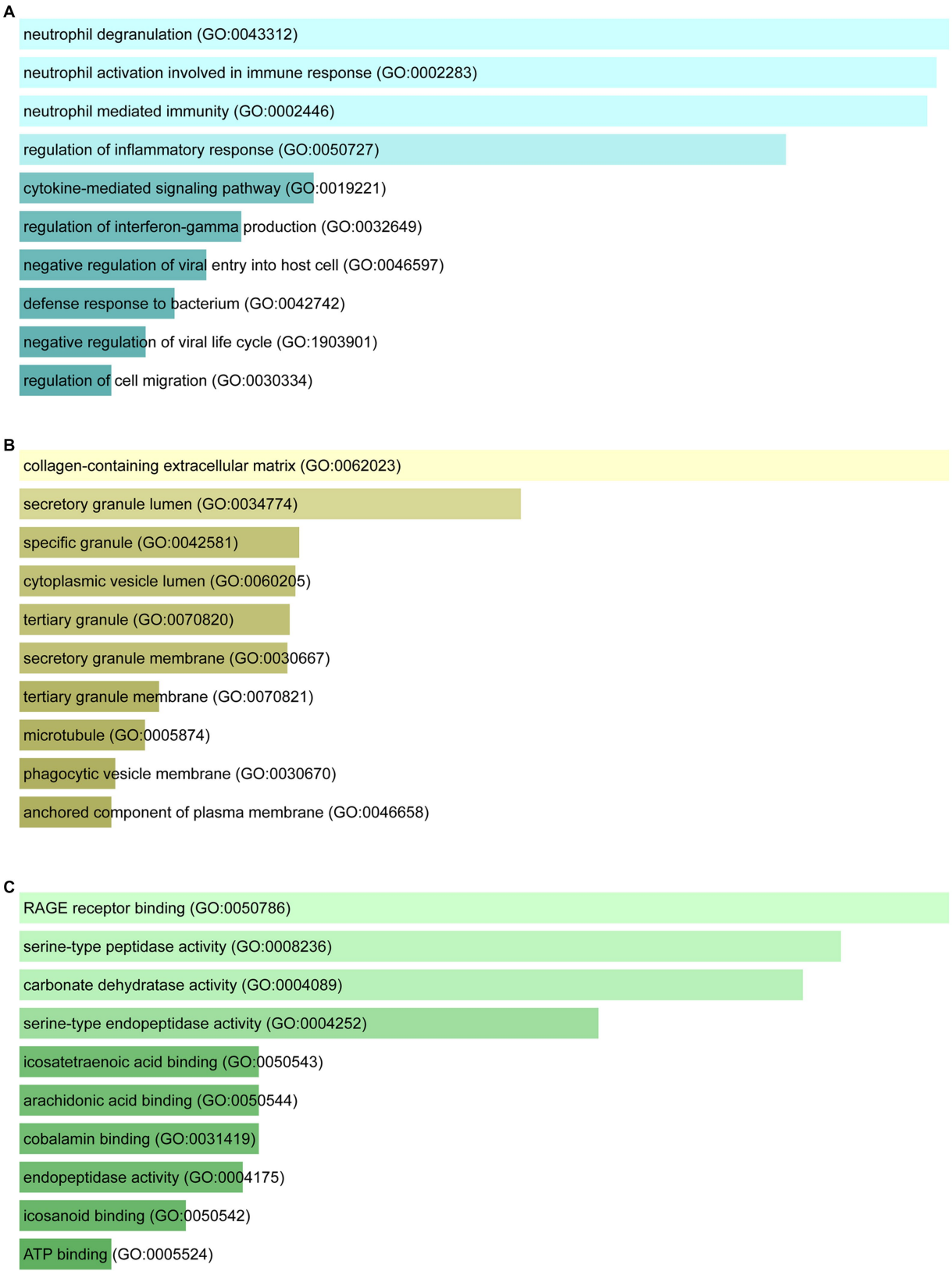


FIGURE 3
Ontological analysis of shared DEGs: **(A)** Biological processes, **(B)** cellular components, and **(C)** molecular functions.

patients with different severity levels includes increased neutrophil degranulation (42). By releasing neutrophil extracellular traps (NETs), neutrophils recruited to infection sites protect against viral challenges (43). NETs are condensed extracellular chromatin filaments composed of nuclear and cytoplasmic proteins, which are associated with many gastrointestinal diseases, including CRC. It was found that NET

TABLE 3 Pathway enrichment analysis of mutual DEGs.

Category	Term	*p*-value	Genes
KEGG 2021 Human	Complement and coagulation cascades	5.38E-06	C1QB/C1QA/CR2/CFH/PLAU/SERPINE1/CLU
	Hematopoietic cell lineage	1.45E-04	CD2/CR2/ANPEP/IL1R2/CD14/MS4A1
	Nitrogen metabolism	3.15E-04	CA12/CA1/CA4
	Cytokine-cytokine receptor interaction	6.32E-04	ACVRL1/IL1RN/CCL23/TNFRSF12A/GDF15/IL1R2/OSM/INHBA/CXCL16
	Transcriptional misregulation in cancer	9.13E-04	PLAU/IL1R2/ZBTB16/CD14/MMP9/ETV4/ELANE
	Prostate cancer	0.0010972	PLAU/IL1R2/TCF7/E2F1/MMP9
	Amoebiasis	0.0013735	COL1A1/COL1A2/IL1R2/CTSG/CD14
	Protein digestion and absorption	0.0094521	COL17A1/COL1A1/COL1A2/COL7A1
	Renin-angiotensin system	0.0144123	ANPEP/CTSG
	Acute myeloid leukemia	0.0165684	ZBTB16/TCF7/CD14
WikiPathways Human	Complement and coagulation cascades	3.92E-07	C1QB/C1QA/CR2/CFH/PLAU/SERPINE1/CLU
	Mammary gland development pathway - involution (stage 4 of 4)	5.79E-05	SOCS3/E2F1/MMP9
	Senescence and autophagy in cancer	2.00E-04	COL1A1/GSN/PLAU/SERPINE1/E2F1/INHBA
	Vitamin D receptor pathway	6.67E-04	CEACAM1/ABCB1/SEMA3B/G0S2/CD14/S100A9/S100A8
	Male infertility	0.001152	ABCB1/TCN2/EPSTI1/TRIP13/CLU/MMP9
	Gastric cancer network 1	0.0015759	TPX2/UBE2C/S100P
	IL-18 signaling pathway	0.0015911	COL1A1/SOCS3/COL1A2/RGS16/ACACB/MMP9/S1PR4/CXCL16
	Type I collagen synthesis in the context of osteogenesis imperfecta	0.0022987	COL1A1/ADAMTS2/COL1A2
	Vitamin B12 metabolism	0.0074793	TCN2/TCN1/SERPINE1
	Melatonin metabolism and effects	0.0352811	PER1/MAOA
Reactome	Immune system	1.14E-10	IFITM3/C1QB/C1QA/IL1RN/IFITM1/CFH/KLRB1/TNFAIP6/MAOA/IFI6/CLU/SOCS3/MT2A/CA1/PLAU/ANPEP/S100A12/SLAMF6/CTSG/ELANE/CD177/CR2/GSN
	Neutrophil degranulation	7.04E-09	GSN/TNFAIP6/SLC11A1/HSPA6/RNASE1/MMP9/CEACAM1/PLAU/TCN1/CEACAM6/ANPEP/P2RX1/S100A12/CTSG/S100P/S100A9/S100A8/ELANE/CD177
	Extracellular matrix organization	9.60E-08	COL17A1/PCOLCE2/SERPINE1/MMP9/LOXL1/COL1A1/CAPN13/ADAMTS2/CEACAM1/COL1A2/CEACAM6/COL7A1/CTSG/ELANE
	Collagen formation	6.26E-07	COL17A1/COL1A1/ADAMTS2/COL1A2/PCOLCE2/COL7A1/MMP9/LOXL1
	Regulation of complement cascade 977,606	1.50E-06	C1QB/C1QA/CR2/CFH/CLU/ELANE
	Innate immune system	2.56E-06	C1QB/C1QA/CR2/GSN/CFH/TNFAIP6/SLC11A1/HSPA6/CLU/RNASE1/MMP9/CEACAM1/PLAU/TCN1/CEACAM6/ANPEP/P2RX1/S100A12/CTSG/S100P/S100A9/S100A8
	Complement cascade	5.00E-06	C1QB/C1QA/CR2/CFH/CLU/ELANE
	Collagen biosynthesis and modifying enzymes	1.59E-05	COL17A1/COL1A1/ADAMTS2/COL1A2/PCOLCE2/COL7A1
	Cytokine signaling in immune system	4.92E-05	IFITM3/IL1RN/IFITM1/TNFRSF12A/MAOA/IL1R2/IFI6/MMP9/SOCS3/MT2A/CA1/COL1A2/OAS3/PDCD4/S100A12/CTSG/S100A9
	Metabolism of angiotensinogen to angiotensins	0.0089463	ANPEP/CTSG

(Continued)

TABLE 3 (Continued)

Category	Term	*p*-value	Genes
BioCarta	Granzyme A mediated apoptosis pathway	0.0039824	SET/GZMA
	RB Tumor suppressor/checkpoint signaling in response to DNA damage	0.0046818	E2F1/CDK1
	Platelet amyloid precursor protein pathway	0.0054336	PLAU/SERPINE1
	Fibrinolysis pathway	0.0062368	PLAU/SERPINE1
	Classical complement pathway	0.0062368	C1QB/C1QA
	Cyclins and cell cycle regulation	0.0144123	E2F1/CDK1
	Stathmin and breast cancer resistance to antimicrotubule agents	0.0156408	CD2/CDK1
	Cell cycle: G1/S check point	0.0182269	E2F1/CDK1
	Erk and PI-3 kinase are necessary for collagen binding in corneal epithelia	0.02541	GSN/ZYX
	Multi-drug resistance factors	0.0470557	ABCB1

formation not only increases the proliferation of CRC cells but also stimulates the transfer process (44). Interferon-gamma, an antiviral agent, is an immunomodulator and plays a key role in humoral and cellular immunity. It has also been shown to be possible to try broad-spectrum antiviral therapy including COVID-19 (45). Under cellular component, collagen-containing extracellular matrix and secretory granule lumen were the top two GO terms. In molecular function, RAGE receptor binding and serine-type peptidase activity were the top two GO terms.

A total of 161 common DEGs were used to search for similar pathways in COVID-19 and CRC. In KEGG pathways, acute myeloid leukemia is significant. Acute myeloid leukemia (AML) is a deadly hematologic cancer. Patients with AML have substantial immunosuppression, and infections are frequently carried on by harsh chemotherapy treatment and disease-related reduced immunity (46). According to the literature, COVID-19 is usually present in a severe clinical form in AML patients, who also frequently have respiratory distress and a very high mortality rate (47). WikiPathways results show that vitamin B12 metabolism and melatonin metabolism and effects are the two pathways of significant importance. In addition to acting as an immunomodulator to regulate cellular immune responses and support hematopoiesis, vitamin B12 can inhibit viral replication in host cells (48, 49). According to Shakeri et al., clinical outcomes in COVID-19 patients are impacted by the host immunological response to viral infections, inflammatory activity, and serum levels of micronutrient deficiencies such as zinc and vitamin B12 deficiency (50). Melatonin is the primary neurohormone secreted by the pineal gland that regulates the sleep–wake cycle. It is also a multifunctional hormone with immunomodulatory, anti-inflammatory, and antiapoptotic properties, as well as having an impact on the metabolism of most organs (51, 52). A randomized clinical trial including 96 COVID-19 patients showed that although melatonin was not associated with a reduction in clinical symptoms and death, melatonin plus standard therapy significantly improved sleep quality and saturation of peripheral oxygen (SpO2) in COVID-19 patients treated for 7 days compared to standard therapy alone. And the effect of melatonin on oxygen delivery and its utilization in tissues may be responsible for the significant improvement in blood oxygen saturation (53). Under Reactome pathways, the immune system and metabolism of angiotensinogen to angiotensins show their importance. When the body is infected with COVID-19, the innate and adaptive immune systems make an effort to eradicate the virus. However, occasionally, the virus interacts with the body in a way that stimulates immune and non-immune cells, resulting in an overactive immunological response (54). Some patients with severe COVID-19 may also experience an overactive cytokine storm or "cytokine release syndrome" caused by an imbalance in the immune system regulation (55). Angiotensinogen, the starting substrate, is cleaved by renin to angiotensin I (Ang I). Ang I is then cleaved by angiotensin-converting enzyme (ACE) to angiotensin II (Ang II), which is metabolized by ACE2 to the beneficial peptide angiotensin 1–7 (Ang 1–7), (56). Importantly, SARS-CoV-2 attacks alveolar cells *via* ACE2 receptors, causing lung infection and leading to COVID-19 (57). In BioCarta pathways, cyclins and cell cycle regulation pathway is critical. COVID-19 patients showed some specific differential features in the expression patterns of some cell cycle-related genes compared to other respiratory diseases. It is important to note that cell cycle characteristics predominated in blood leukocytes (B, T, and natural killer cells) of COVID-19 patients and correlated with their severity and disease trajectory (58).

The PPI network was constructed by using DEGs genes to realize the shared biological functional characteristics of proteins and predict potential drugs. Based on the PPIs network and the MCC method, the top ten hub genes are CDK1, KIFC1, CDCA5, MKI67, UBE2C, PLK1, TPX2, KIF20A, HJURP, and CENPA. Cyclin-dependent kinase 1 (CDK1) is the sole essential required cyclin-dependent kinase that enables the G2-M transition and regulates G1 progression and G1-S transition (59). It has been demonstrated that not only does CDK1 regulate the cell cycle, but it also plays a part in tumor cell proliferation (60–62). Zhang et al. claimed that CDK1 is overexpressed in CRC cells and is apoptosis-sensitive (61). Furthermore, Tong et al. showed that dipeptidyl peptidase 3 (DPP3)/CDK1 contributes to the advancement of CRC by modulating cell proliferation, apoptosis, and migration (62). Kinesin family member C1 (KIFC1) is involved in multiple biological functions and plays a key role in cancer cell centrosome clustering (63). In CRC patients, KIFC1 can regulate ZW10 interacting kinetochore protein (ZWINT) to promote CRC progression and may induce poor prognosis (64).

FIGURE 4
Pathway enrichment analysis: **(A)** KEGG, **(B)** WikiPathways, **(C)** Reactome, and the **(D)** BioCarta.

Cell division cycle associated 5 (CDCA5), originally recognized as a substrate that promotes late complexes, has been reported to be associated with the development and progression of multiple human cancers (65). Shen et al. showed that CDCA5 expression was increased in CRC patients and that overexpression of CDCA5 was associated with poor patient survival. Activation of the extracellular

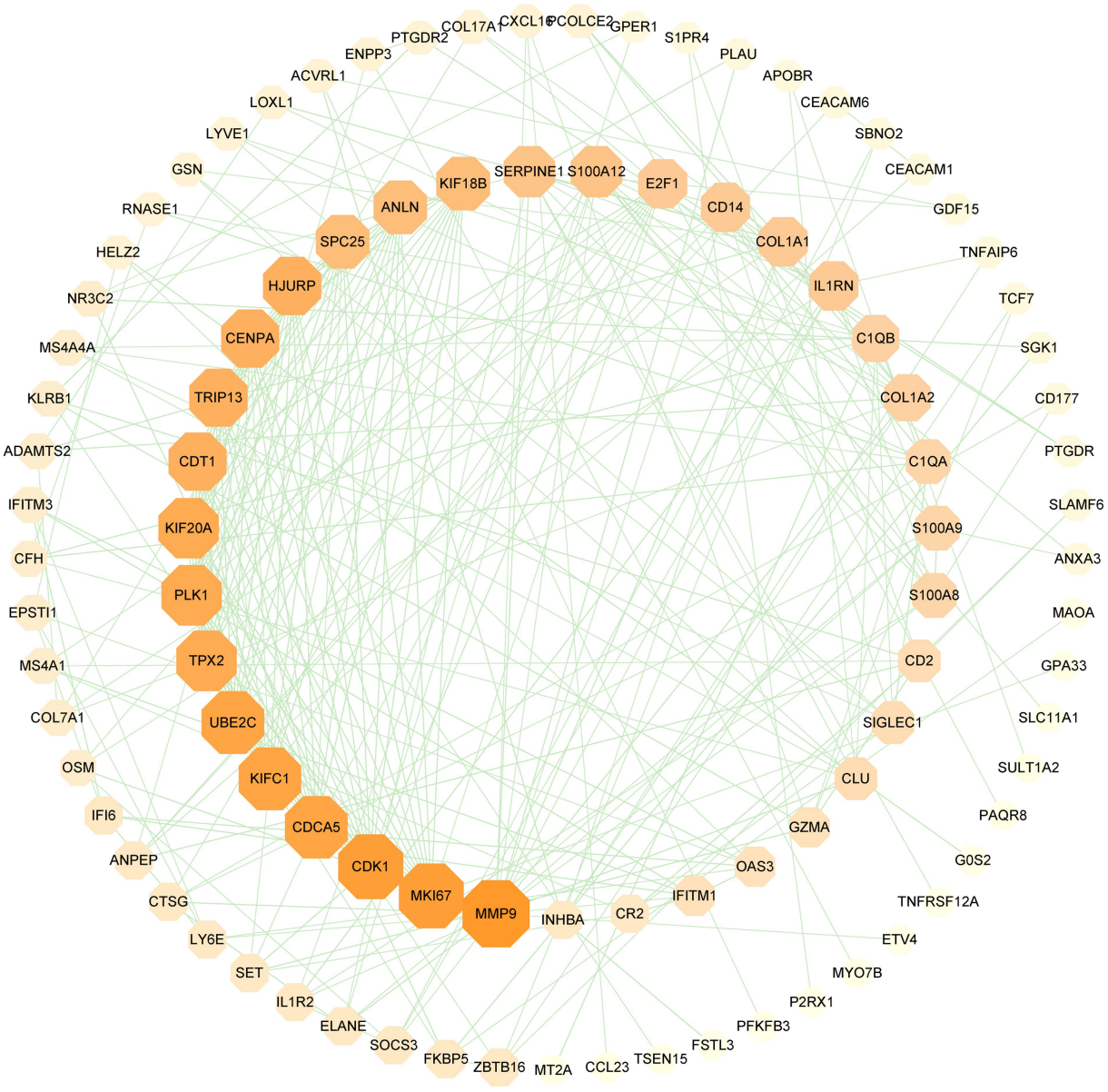


FIGURE 5
PPI network of SARS-CoV-2 and CRC shared DEGs. The octagons in the figure represent DEGs, while the edges represent node interactions. The PPI network comprises 151 nodes and 286 edges and the size and color depth of the octagon indicate the extent to which proteins are connected.

signal-regulated kinase (ERK) pathway may show a beneficial role in the oncogenic activity of CDCA5 (66). MKI67, or proliferation marker protein Ki-67, is a nuclear protein that is expressed in all proliferative vertebrate cells and is commonly used as a biomarker to quantify the fraction of proliferating cells to grade tumors (67). MKI67 expression is a late marker of cell cycle entry and has a key role in many CRC-associated genes (68). Downregulation of MKI67 will inhibit cell growth in CRCs (69). The ubiquitin conjugating enzyme E2 C (UBE2C) modifies cellular short-lived or abnormal proteins. Rectal cancer with overexpressed UBE2C regulates miR-381 expression, encouraging rectal carcinoma cell proliferation and invasion (70). Polo-like kinase 1 (PLK1) is a conserved Ser/Thr kinase that has evolved over time and is well known for its function in controlling the cell cycle. It is mostly expressed during the G2/S and M stages of the cell cycle (71). PLK1, which has been found to be overexpressed in numerous cancers, regulates several important transcription factors and promotes cell proliferation, transformation, and epithelial-to-mesenchymal transition (71, 72). In CRC, upregulated PLK1 signaling is frequently accompanied by dysregulation of cell cycle-related pathways. And abnormal PLK1 signaling has been linked to recurrence and a poor prognosis in CRC patients (73). Targeting protein for Xenopus kinesin-like protein 2 (TPX2) is an indirect target of miR-485-3p prediction and has an important part in mitotic spindle assembly and cancer progression. It has been demonstrated that TPX2 is overexpressed in several cancers and highly expressed in CRC tissues (74). The kinesin family member 20A (KIF20A), which is found on chromosome 5q31.2, is crucial for the occurrence and growth of malignancies. KIF20A is

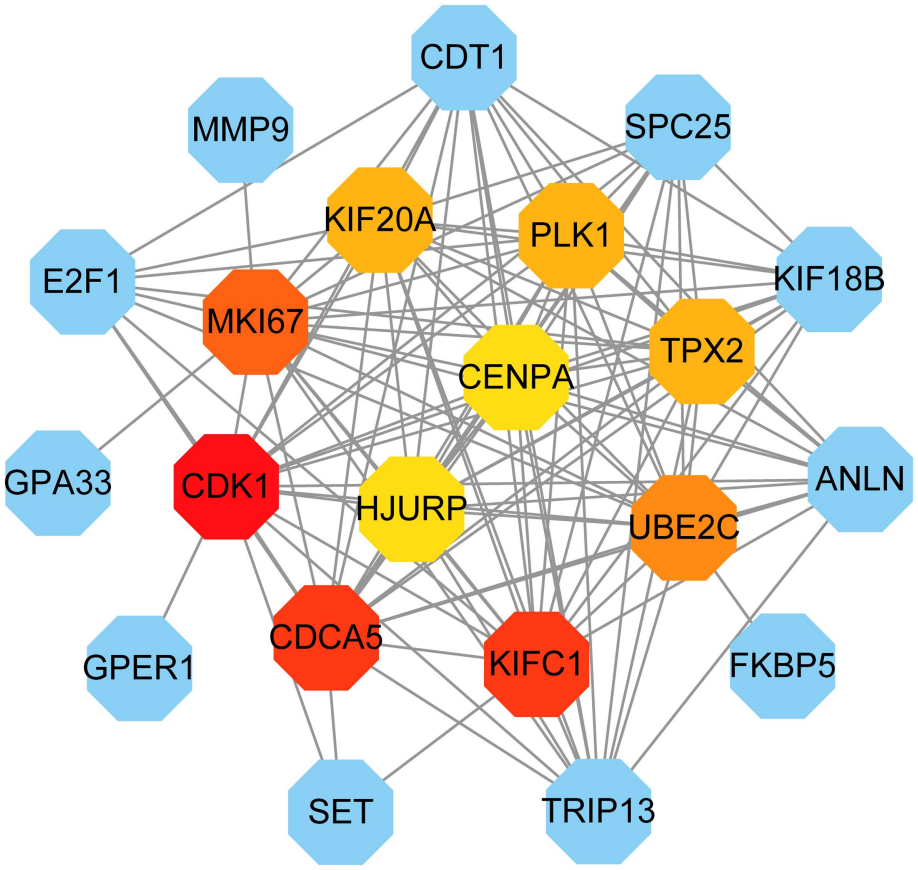


FIGURE 6
Identification of the hub genes from the PPI network. Here, the highlighted top 10 hub genes and their interactions with other molecules are shown by the red, orange, and yellow nodes (their rank was indicated by a gradient from red to yellow). The network consists of 21 nodes and 117 edges.

overexpressed in CRC tissues and is significantly linked to patients' poor prognoses. While silencing KIF20A expression can prevent CRC cell lines from migrating and proliferating by activating the janus kinases (JAKs)/signal transducer and activator of transcription 3 (STAT3) signaling pathway (75). The centromeric protein holliday junction recognition protein (HJURP, or hFLEG1) is essential for the incorporation and maintenance of the histone H3-like variant centromere protein A (CENPA) in centromeres. HJURP knockdown reduces CRC cell migration, proliferation, invasion, and tumorigenicity; therefore, it may be used as a prognostic biomarker and a new target for therapeutic development (76). And CENPA can recruit histone acetyltransferase (HAT) general control of amino acid synthesis (GCN)-5 to the karyopherin α_2 subunit gene (*KPNA2*) promoter region to epigenetically activate its transcriptional activity, resulting in glycolysis and malignant growth in colon cancer (CC) cells (77). Therefore, these hub genes are likely to be potential biomarkers.

To identify the transcriptional and post-transcriptional regulators of the hub genes, we also explore the interactions between the TFs–gene and miRNAs. Among TFs, NFIC, GATA2, YY1, NFYA, E2F1, PRDM1, MEF2A and SREBF1 are associated with cancer (78–85). Nuclear factor I C (NFIC) belongs to the nuclear factor I family. One study reported that NFIC was a low expression in human Lung Squamous Cell Carcinoma (LUSC) tissues and cell lines, and it inhibited the proliferation of LUSC cells and promoted apoptosis *in vitro* and *in vivo*. Additionally, NFIC prevented LUSC cells from migrating and invading other tissues (78). E2F1 is a transcription factor that controls cell cycle progression and was the first member of the E2F transcription factors (E2Fs) to be discovered. It is highly expressed in the majority of cancer cells and prompts the transcription of kinases relevant to the cell cycle. E2F1 regulates the cell cycle in CRC by encouraging spindle construction, where E2F1-induced stathmin1 and transforming acidic coiled-coil-containing protein 3 (TACC3) improve the stability of spindle fiber (82). For DEG-miRNAs, hsa-mir-193b-3p, hsa-mir-192-5p, hsa-mir-215-5p, and hsa-mir-16-5p are associated with cancer. Overexpression of hsa-mir-193b-3p inhibited lung cancer cell invasion and migration and reduced their clonogenic ability. In contrast, hsa-mir-193b-3p inhibition boosted lung cancer's capacity for metastatic spread and colony formation (86). In cases of colorectal cancer and other malignancies, hsa-mir-192/215-5p can function as a tumor suppressor (87). For hsa-mir-16-5p, in addition to its association with cancer, it was also shown to affect SARS-CoV-2 infection possibly by regulating the ACE2 receptor related network (88, 89). Using data based on single-cell RNA-seq, Li et al. identified hsa-mir-16-5p as one of the probable virus-targeting miRNAs in various cell types in bronchoalveolar lavage fluid samples (89). The previous study also has shown that miRNA hsa-mir-155-5p leads to B cells and T cells

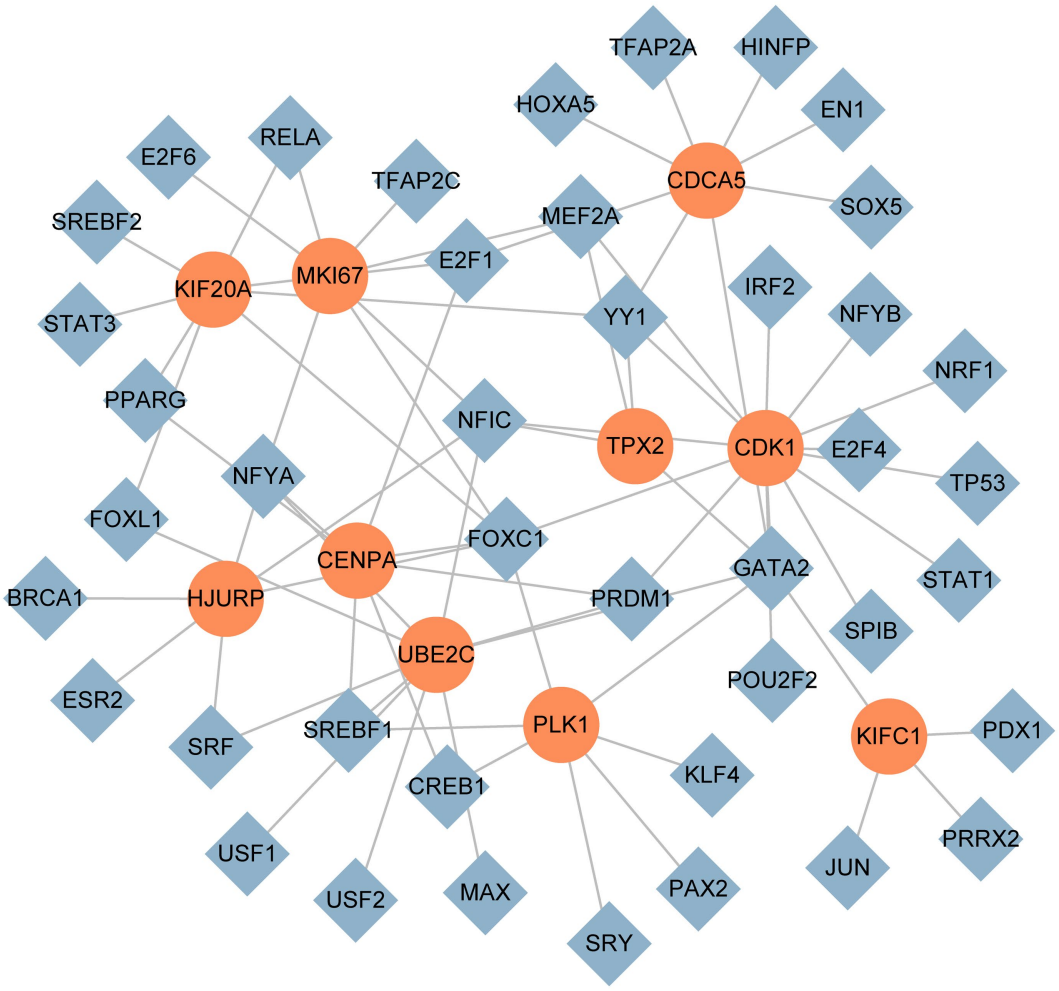


FIGURE 7
The DEG-TF cohesive regulatory interaction network. The diamond shape nodes in this diagram represent TFs, while the circle nodes represent gene symbols interacting with TFs.

activation and exerts immune functions (90). Hsa-mir-34a-5p is one of the promising therapeutics for SARS-CoV-2 (91).

To determine the relationship between significant DEGs and various diseases, we completed a gene-disease analysis. The results showed various types of disease associated with COVID-19, including the brain, blood, skin, heart, liver, joints, and different types of tumors. Brain-related diseases include schizophrenia, unipolar depression, bipolar disorder, epilepsy, and autistic disorder. Individuals with a diagnosis of schizophrenia spectrum disorder were shown to have a higher risk of mortality in a study of adults with SARS-CoV-2 positive test results in a large New York medical system (92). In particular, anxiety disorders are becoming more common than ever before due to the psychosocial impacts of SARS-CoV-2, which in turn may precipitate the onset of a number of co-morbid psychiatric conditions like depression and bipolar disorder (93). In this sense, viral infections are linked to a higher incidence of anxiety and/or depression (94). We also discovered skin problems including contact dermatitis. According to solid data, the COVID-19 pandemic has led to an increase in the prevalence of allergic and irritating contact dermatitis. The most typically reported symptoms are skin dryness, itchiness, and redness (95). Furthermore, Grivas et al. used detailed information from nearly 5,000 patients with COVID-19 and cancer to confirm that COVID-19 severity and mortality are high in cancer patients. This was particularly the case for older age, male sex, non-Hispanic non-white racial/ethnic group, worse eastern cooperative oncology group performance status, hematologic malignancies, and selected laboratory measures (96).

Through the common DEGs, we predicted ten drugs, including troglitazone, estradiol, progesterone, calcitriol, genistein, dexamethasone, lucanthone, resveratrol, retinoic acid, phorbol 12-myristate 13-acetate. Several substances have been evaluated as CRC and COVID-19 therapies. Endogenous reproductive hormones estradiol and progesterone are produced in large amounts in the periphery by the adrenal glands and ovaries, and *de novo* by the brain. They have a significant physiological impact by controlling inflammatory behaviors and processes (97). In the azoxymethane/dextran sulfate sodium (AOM/DSS) mouse model, estradiol inhibits the development of CRC and downregulated inflammation (98). And progesterone, which could inhibit CRC proliferation by blocking the cell cycle and inducing apoptosis in turn limits malignant tumor progression (99). In COVID-19, women with high

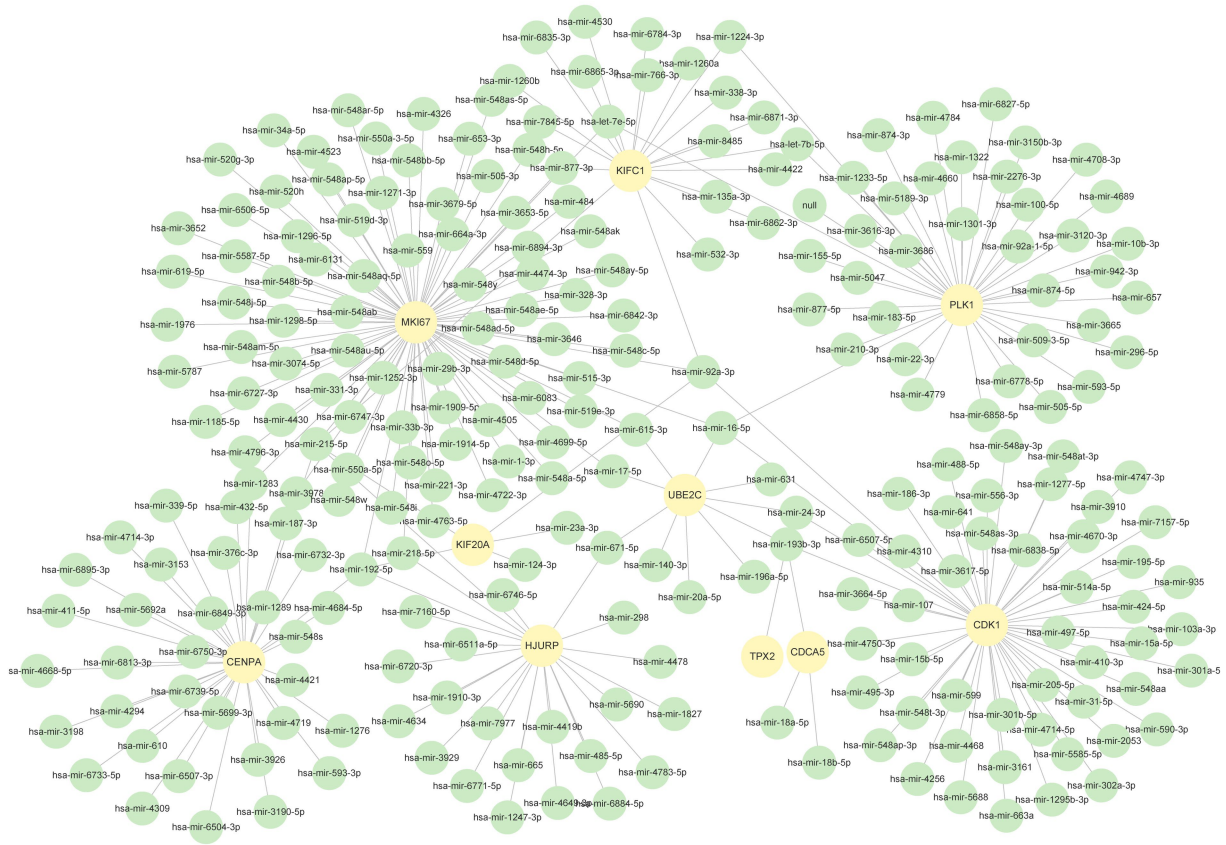
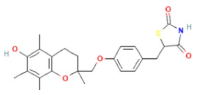
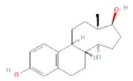
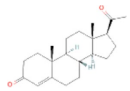
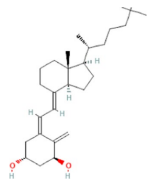
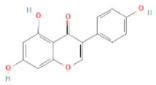
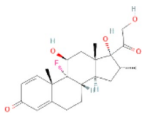
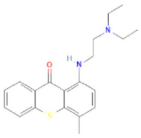
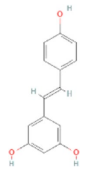
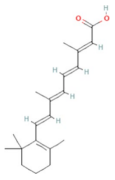
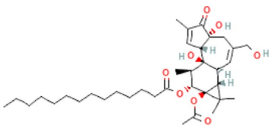


FIGURE 8
The DEGs-miRNAs regulation interaction network. The green circle nodes in the figure denote miRNAs, whereas the yellow circles represent the genes that interact with miRNAs.

estrogen levels have a lower risk of severe symptoms and even lower mortality (100). Calcitriol, the biologically active form of vitamin D, is effective as a treatment for patients with hypocalcemia or secondary hyperparathyroidism caused by renal insufficiency (101). For other roles, calcitriol can inhibit glycolysis and cell growth in human CRC cells, suggesting an inhibitory role in CRC progression (102). And Elamir et al. have demonstrated improved oxygenation in hospitalized COVID-19 patients treated with calcitriol (103). Genistein is one of the main bioactive substances of soybean isoflavones that exert pharmacological functions (104). It can block cancer cell proliferation by various mechanisms, such as up-regulation of p21 levels and inhibition of tyrosine-specific kinase activity (105, 106). In human CRC cells, genistein exerts anti-invasive and anti-proliferative effects by inhibiting cell proliferation and inducing apoptosis (107). Additionally, RNA transcripts and protein synthesis from viruses like rotavirus can be inhibited by genistein (108). Therefore, genistein has the potential to be used as a lead chemical in the evaluation of new anti-CRC and antiviral drug candidates. Dexamethasone is a drug used to treat a variety of inflammatory diseases by effectively inhibiting the release of substances that cause inflammation, and it has been already in clinical use for cancer prevention (109). In addition, for patients who are receiving mechanical ventilation, the corticosteroid dexamethasone can lower the rate of COVID-19-related mortality in the critical care unit by 35%. Despite the varying efficiency of other combination medications in treating COVID-19 associated with ARDS, dexamethasone is widely employed in several COVID-19 therapy regimens (110). Resveratrol as a traditional Chinese medicine chemical monomer can effectively inhibit colon cancer cell growth by the ROS-dependent ferroptosis pathway (111). Retinoic acid is further processed from vitamin A (retinol) by several enzymes and exists in several stereoisomeric forms. In addition to its role in biological processes such as reproduction, differentiation, embryogenesis, and eye development, retinoic acid signaling has been shown to be a possible therapeutic target for CRC (112). Furthermore, McCreary and Sarohan et al. have also shown that resveratrol and retinoic acid may also be new perspectives for the treatment of COVID-19 (113, 114).

This study explored the correlation between CRC and COVID-19 using bioinformatics and systems biology techniques. Through high-throughput sequencing, this study identified COVID-19 and CRC-related biomarkers and potential drugs, which provide new clues for the treatment of both diseases. It is worth noting that there are still some limitations in this study. First, it is impossible to fully recapitulate the underlying genetic linkages using a computational biology technique because of information and method bias. Second, we currently do not have experiments *in vivo* or *in vitro* to validate the findings, and specific experiments will be conducted in the next

TABLE 4 The recommended drugs for COVID-19 and CRC.

Name	*p*-value	Chemical formula	Structure
Troglitazone CTD 00002415	1.11E-16	$C_{24}H_{27}NO_5S$	
Estradiol CTD 00005920	3.00E-14	$C_{18}H_{24}O_2$	
Progesterone CTD 00006624	4.86E-12	$C_{21}H_{30}O_2$	
Calcitriol CTD 00005558	1.05E-11	$C_{27}H_{44}O_3$	
Genistein CTD 00007324	3.57E-11	$C_{15}H_{10}O_5$	
Dexamethasone CTD 00005779	1.24E-09	$C_{22}H_{29}FO_5$	
Lucanthone CTD 00006227	1.85E-09	$C_{20}H_{24}N_2OS$	
Resveratrol CTD 00002483	2.98E-09	$C_{14}H_{12}O_3$	
Retinoic acid CTD 00006918	8.41E-09	$C_{20}H_{28}O_2$	
Phorbol 12-myristate 13-acetate CTD 00006852	1.17E-08	$C_{36}H_{56}O_8$	

step. Last, there is still a long way to go to translate experimental results into clinical applications.

5. Conclusion

In this study, the transcriptome datasets of CRC and COVID-19 were used to identify DEGs and elucidated the intrinsic link between the two diseases. A total of 161 common DEGs were found, based on which a PPI network was constructed to recognize the top ten hub genes. These target genes may be biomarkers of CRC or SARS-CoV-2 infection and thus translate into potential drug targets. We also investigated the relationship of these target genes with TFs and miRNAs to better understand their role in disease occurrence and progression. Meanwhile, multiple drug molecules and drug-target interactions of common DEGs were retrieved using the DSigDB database. However, further experiments are needed to verify whether these potential gene targets and drugs can be further used in clinical practice.

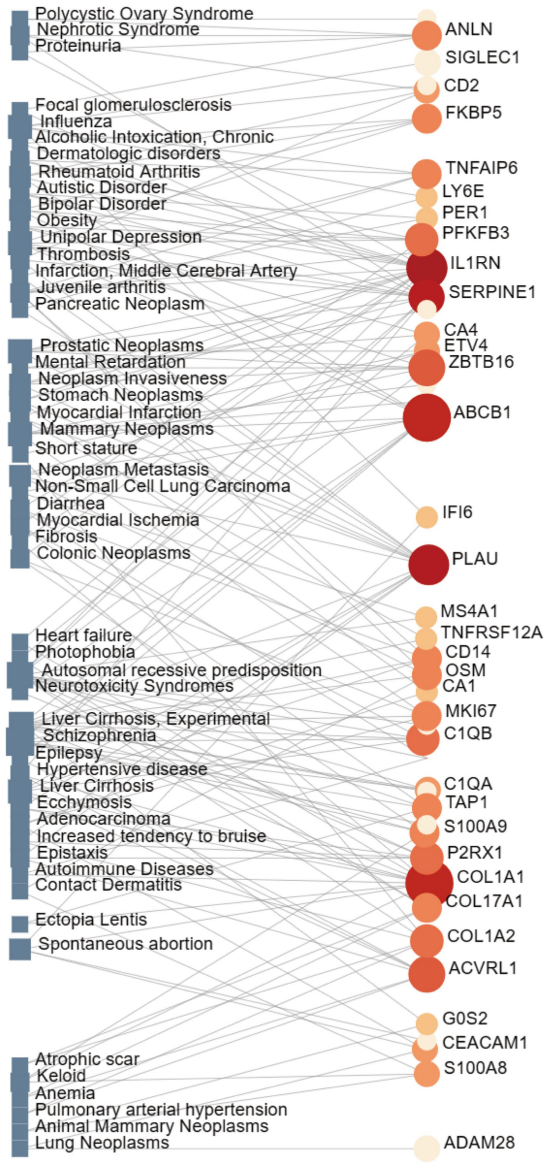


FIGURE 9
The network of gene-disease associations represents diseases linked by common DEGs. The square node indicates the disease, and the circular node defines the subsequent gene symbols.

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.

Author contributions

YS, TH, and HP contributed to the conception and design of the study. YS organized the database. TH performed the formal analysis. HP was responsible for the article methodology. AD, TW, JL, XZ, YL, and SX wrote sections of the manuscript. KY conducted the overall supervision and validation. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by grants from the National multidisciplinary collaborative diagnosis and treatment capacity building project for major diseases (TJZ202104), the Natural Science Foundation of China (82173248, 82272685, 82002967 and 82202260), the Postdoctoral Science the fellowship of China National Postdoctoral Program for Innative Talents (BX20200225), the Project funded by China Postdoctoral Science Foundation (2022TQ0221), the Science and Technology Major Program of Sichuan Province (2022ZDZX0019), the Sichuan Science and Technology Program (2023YFS0128, 2023NSFSC1874, 2021YJ0420), 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYJC18008, ZYGD22006), the Sichuan University postdoctoral interdisciplinary Innovation Fund (10822041A2103).

Acknowledgments

We thank all of the patients who participated in the study and donated samples, as well as the GEO database for providing the platform.

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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