Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Bioinformatics approach to analyse COVID-19 biomarkers accountable for generation of intracranial aneurysm in COVID-19 patients

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ABSTRACT

COVID-19 became a health emergency on January 30, 2020. SARS-CoV-2 is the causative agent of the coronavirus disease known as COVID-19 and can develop cardiometabolic and neurological disorders. Intracranial aneurysm (IA) is considered the most significant reason for hemorrhagic stroke,and it accounts for approximately 85% of all subarachnoid hemorrhages (SAH). Retinoid signaling abnormalities may explain COVID-19's pathogenesis with inhibition of AEH2, from which COVID-19 infection may enhance aneurysm formation and rupture due to abrupt blood pressure changes, endothelial cell injury, and systemic inflammation. The objective of this study was to investigate the potential biomarkers, differentially expressed genes (DEGs), and metabolic pathways associated with both COVID-19 and intracranial aneurysm (IA) using simulation databases like DIsGeNET. The purpose was to confirm prior findings and gain a comprehensive understanding of the underlying mechanisms that contribute to the development of these conditions. We combined the regulated genes to describe intracranial aneurysm formation in COVID-19. To determine DEGs in COVID-19 and IA patient tissues, we compared gene expression transcriptomic datasets from healthy and diseased individuals. There were 41 differentially expressed genes (DEGs) shared by both the COVID-19 and IA datasets (27 up-regulated genes and 14 down-regulated genes). Using protein-protein interaction analysis, we were able to identify hub proteins (C3, NCR1, IL10RA, OXTR, RSAD2, CD38, IL10RB, MX1, IL10, GFAP, IFIT3, XAF1, USP18, OASL, IFI6, EPSTI1, CMPK2, and ISG15), which were not described as key proteins for both COVID-19 and IA before. We also used Gene Ontology analysis (6 significant ontologies were validated), Pathway analysis (the top 20 were validated), TF-Gene interaction analysis, Gene miRNA analysis, and Drug-Protein interaction analysis methods to comprehend the extensive connection between COVID-19 and IA. In Drug-Protein interaction analysis, we have gotten the following three drugs: LLL-3348, CRx139, and AV41 against IL10 which was both common for COVID-19 and IA disease. Our study with different cabalistic methods has showed the interaction between the proteins and pathways with drug analysis which may direct further treatment development for certain diseases.

1. Introduction

COVID-19 is caused by SARS-CoV-2, which mainly affects the respiratory system and causes symptoms such as fever, cough, and shortness of breath. It also leads to more severe respiratory illnesses, including interstitial pneumonia and acute respiratory distress syndrome (ARDS), particularly in older individuals or those with underlying health conditions. ARDS is a serious condition where fluid accumulates in the lungs, making it difficult to breathe and reducing oxygen levels in the bloodstream, and may require mechanical ventilation to support breathing [1]. On January 30, 2020, COVID-19 was designated as a public health emergency of international concern (PHEIC) [2]. COVID-19 can be transmitted through different mechanisms, such as airborne transmission through small droplets called aerosols, droplet transmission through larger droplets, contact with contaminated surfaces, oral transmission through saliva, and fecal transmission through contaminated sewage systems or fecal-oral contact. The relative importance of each mode of transmission may vary depending on the context and specific circumstances of each case [3]. Research indicates that individuals with significant comorbidities, such as diabetes, hypertension, and obesity, exhibit a heightened susceptibility to COVID-19 and are at an elevated risk of experiencing severe

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illness and mortality [4]. The pathophysiological mechanisms of COVID-19 remain unclear. Nevertheless, current literature and research findings suggest that a disruption in retinoic acid (RA) metabolism and retinoid signaling dysfunction may constitute a fundamental element underlying COVID-19's detrimental pathophysiology [5]. The cells are afflicted by the virus in the ACE2 (Angiotensin-converting enzyme 2) receptor [6]. COVID-19 has been shown to elicit cardiovascular disease and may elevate mortality rates in patients with comorbidities such as diabetes mellitus and obesity. Furthermore, COVID-19 may also prompt neurological complications, such as ischemic stroke [7–9].

An intracranial aneurysm is a neurological inflammation that can be developed in a COVID-19 patient [10]. COVID-19 infection may increase the risk of aneurysm expansion and rupture, most likely due to severe breathing or cough-related changes in systemic blood pressure or endothelial cell injury in combination with a systemic inflammation-mediated mechanism [11]. An intracranial aneurysm (IA) refers to an atypical bulging of an artery, which commonly manifests within the cerebral vasculature [12]. The development of an aneurysm may occur due to severe weakness in a muscular layer called the congenital muscular layer or pathological changes in the inner stretchy membrane, or for both reasons [13]. There are ruptured and unruptured aneurysms with different flow angles, sizes, and shapes. This acquaints one with the calculation of the probability that they will develop an aneurysm [14]. It is considered the most significant reason for hemorrhagic stroke, and it accounts for approximately 85% of all subarachnoid hemorrhages (SAH) [15]. A recent analysis has shown that the genes found in COVID-19, like OTG, interacted with PANO1 and express risk factors for neural disease [16]. A protein named ACE2 is responsible for the pathogenesis of both COVID-19 and IA [6,17]. Our study aims to investigate the differentially expressed genes (DEGs), biochemical pathways, and potential biomarkers associated with the comorbidity of COVID-19 and intracranial aneurysm (IA). The focus is to identify shared proteins and pathways that may contribute to the development of IA in COVID-19 patients in order to prevent the possible emergence of this condition in the patient population.

2. Materials and methods

2.1. Datasets employed in this study

The datasets used in this research were procured from the esteemed sources of NCBI and GEO, both known for their reliable gene expression data [18]. The selection of datasets was based on stringent criteria, including sample size, RNA-seq-based analysis, and the presence of control conditions. The chosen datasets were scrutinized for optimal formatting and relevance to the research focus. Ultimately, two datasets (GSE152418 and GSE158558) were identified as highly pertinent to the study objectives, with suitable samples of control and disease-affected conditions. The COVID-19 dataset (GSE152418) comprises immune system assessments of 1 convalescent and 16 COVID-19 patients, along with 17 healthy controls. The IA dataset (GSE158558) includes sequencing data for 4 intracranial aneurysm wall tissues and 4 superficial temporal artery tissue samples (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?). These datasets have acquired through the Illumina NovaSeq 6000 and HiSeq 4000 platforms, respectively, for Homo sapiens organisms.

2.2. Differential expression analysis and raw counts pre-processing

To better understand how genes are regulated, a quantitative approach is needed, which can be achieved through RNA-seq [19]. This technique involved gathering gene expression data from the GREIN (Gene Expression Omnibus datasets) and comparing healthy and diseased tissue to identify Differentially Expressed Genes (DEGs) [20]. The focus of this analysis was to extract DEGs from two specific datasets, GSE152418 and GSE158558, by applying a set of criteria that defines their significance. We determined the number of significant genes with DEGs using the following criteria: the absolute log fold change value ≥ 1 and adjusted p-value ≥ 0.05. Using the virtual VENN analysis tool InteractiVenn, the bilateral DEGs for GSE152418 and GSE158558 were determined [21].

2.3. Molecular pathway and gene ontology mapping

EnrichR was utilized to identify the biological pathways and gene ontology (GO) linked to overlapping DEGs in IA and COVID-19 [22,23]. The pathway-based analysis is a powerful tool that helps to comprehend the shared biological mechanisms underlying complex diseases. Pathways are essential to organism functions [24]. GO is a theoretical model that explains the activity of genes and their regulation [25,26]. We took the following five pathway databases: KEGG [27], Reactome [28], WiKi [29], BioCarta [30],and Elsevier as well as the Gene Ontology (GO) domain.

2.4. Evaluation of protein-protein interactions

STRING is a global network that aims to establish physical and functional links between proteins [31]· We used sequence data to implement Protein-Protein Interaction (PPI) based on proteins represented by COVID-19 and Intracranial Aneurysm. Cytoscape, an open-source network visualization platform, was used to analyze and conduct further tests on the PPI network. Cytoscape was chosen because of its versatility in combining multiple datasets to generate optimal performance for various types of interactions, including PPIs, genetic interactions, protein-DNA interactions, and others. The version of Cytoscape used in the study was 3.9.1 [32].

2.5. Analysis of MicroRNA interactions with transcription factors

We assessed TF-gene interaction, Gene-mRNA interaction, and Protein-drug interaction using the NetworkAnalyst tool to determine the DEGs' post-transcriptional and transcriptional regulators [33]. Encode and Jasper databases for TFs-Gene network analysis, TarBase and miRTarBase databases for Gene-mRNA interaction network analysis, and the DrugBank database for protein-drug interaction analysis were integrated and used [34–38]. The entire assessment was conducted with Network Analyzer in Ccvytoscape and Network Analyst [32,33].

2.6. Evaluation of applicant drugs

Investigation of protein-drug interactions (PDI) is critical to understand the theoretical underpinnings of agonist selectivity [39,40]. A medicament should first establish the drug-receptor complexes before it can interact with receptor sites or be metabolized by bioindicators [41]. Computational approaches can be used to anticipate proteomics for a specific therapeutic agent or to react with medicines for specific target molecules or proteins [39,42]. NetworkAnalyst was used to predict protein-drug interactions in our study [43]. In order to generate PDI, the database at DrugBank was consulted [38].

2.7. An overview of the Analytical Approach

Fig. 1 provides an overview of the study's approach to understanding the development of intracranial aneurysms (IA) in COVID-19 patients. To identify differentially expressed genes in RNA-Seq data, we used GEOquery to obtain GEO datasets and then transformed the expression set class [18]. The R programming language was used for the project, with the source code available upon request. This study used R Studio and version 4.2.0 of R. By analyzing gene expression, disease gene association networks, signaling pathway mechanisms, gene ontology (GO) data, protein-protein interactions (PPIs) network, DEGs-TFs interaction analysis, and DEGs-miRNA interaction analysis; we identified potential biomarkers that could discriminate between COVID-19 and IA.

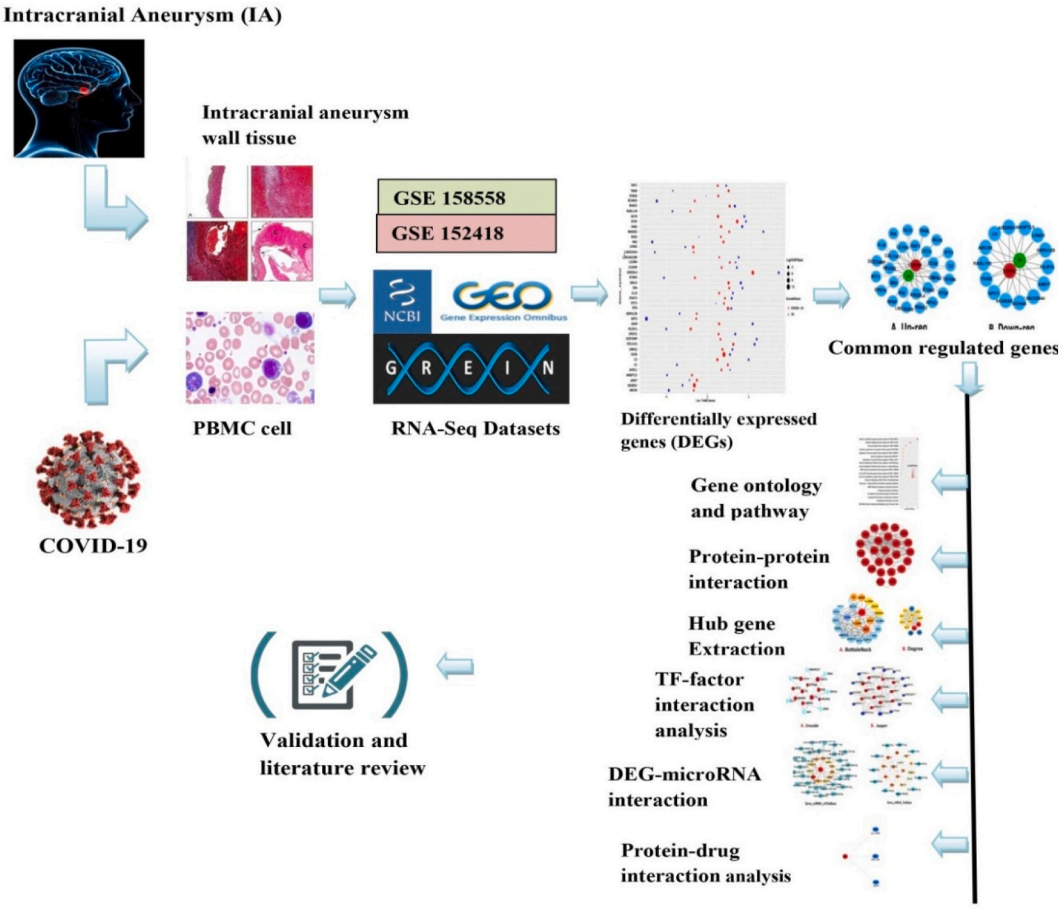

Fig. 1. Overview of the analytical approach.

3. Results

3.1. Comparative analysis of gene expression and transcriptomic data

In this study, we analyzed RNA-Seq data from the NCBI to identify differentially expressed genes (DEGs) between COVID-19 and Intracranial Aneurysm (IA). We used adjusted p-values, FDR, and absolute logFC values to identify significant DEGs in COVID-19. Our analysis revealed a list of commonly up-regulated and down-regulated genes between the two conditions. The up-regulated genes included IFI6, KIR2DL4, OTOF, CD38, LINC02289, NCR1, LILRB4, DCSTAMP, LILRA6, IFIT1, APOC1, XAF1, INA, IFIT3, C2, IL10, STRA6, NKAIN2, EPSTI1, CMPK2, MX1, GFAP, OASL, ISG15, RSAD2, OXTR, and COL11A1. The down-regulated genes included ADGRD1, ANGPTL5, LPAR1, HSPA12B, FILIP1L, AMOT, KCNA5, LINC02544, SCARA5, GPC3, TNXB, RASL11B, ABCA6 and C3 (see Fig. 2). Our findings have provided valuable insights into the potential gene expression impacts of COVID-19 on IA. However, further validation and functional studies may require confirming the role of these DEGs in the pathogenesis of both conditions.

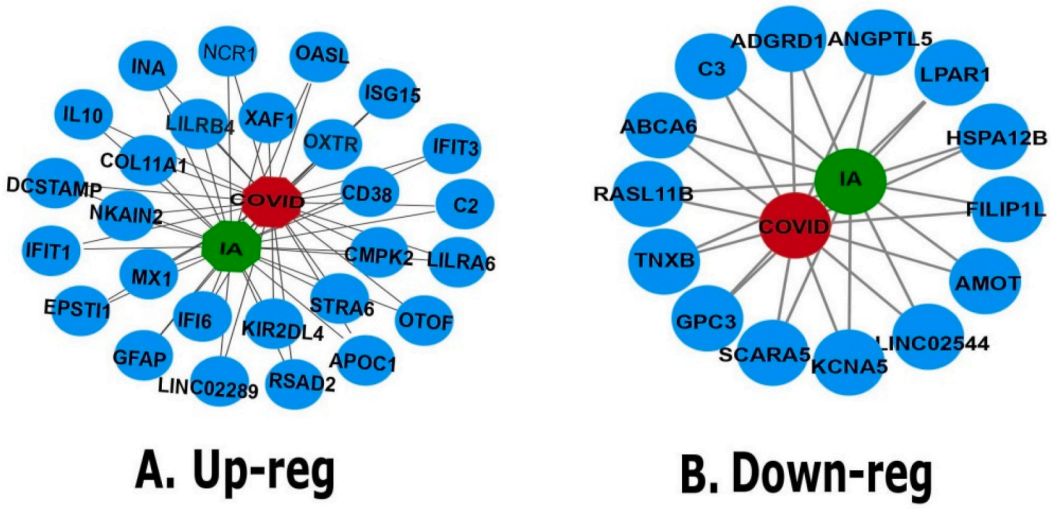

Fig. 2. A. Up_regulated and B. Down_regulated genes between IA and COVID-19.

3.2. Identification of DEGs and common DEGs among COVID-19 and intracranial aneurysm

Table 1 presents a summary of the statistical data obtained from our methodology, which conforms to our study's standards. The table encompasses relevant information for COVID-19 and Intracranial Aneurysm (IA), including the disease names, GEO platforms, GEO accession numbers, tissue/cell descriptions, the number of raw and significant genes, the number of case and control samples, and up-regulated and down-regulated genes for each disease. The Illumina HiSeq 4000 (Homo sapiens) and Illumina NovaSeq 6000 (Homo sapiens) platforms were used to collect the RNA-seq data for IA and COVID-19, respectively. The IA study collected RNA-seq data from intracranial aneurysm wall tissue, while PBMC was used for the COVID-19 study. We selected GEO accession ID-GSE 158558 for IA and GEO accession ID-GSE 152418 for COVID-19. Our IA study comprised 8 samples, with 4 cases and 4 controls. After differential expression analysis, we identified 20,995 differentially expressed genes (DEG) also called signature data for IA. We have evaluated the signature data under two criteria, including "Adjusted P-Value" and "Log2 Fold-Change," and discovered 1059 relevant genes with adjusted p-values less than or equal to 0.05 and abs (LogFC) greater than or equal to 1.0. Of the significant genes, 323 showed up-regulated expression, while 719 demonstrated down-regulated expression. For COVID-19, we identified the most significant DEGs (2375) from 21134 Raw Genes through statistical analysis. We found 1940 up-regulated and 325 down-regulated DEGs, with an adjusted p-value less than or equal to 0.05 and absolute (LogFC) greater than or equal to 1.0 indicating significant DEGs (see Fig. 3).

3.3. Pathway enrichment and gene ontology analysis

We utilized Enrichr to conduct gene ontology and pathway enrichment analysis in this study to gain insights into the biological relevance and enriched pathways associated with the DEGs we investigated. Gene ontology is a concept that involves examining the functions and components of genes to generate extensive computerized information that enables us to construct a model of the organization of biological systems, incorporating both ontologies and annotations [44]. We utilized five databases, BioCarta, Elsevier Pathway, KEEG, Reactome, and Wiki Pathway, to identify pathways that are associated with illness and condition of both diseases. We used the common DEGs between IA and COVID-19 to identify highly expressed pathways and categorize them into functional categories. Initially, we identified a total of 390 signaling pathways associated with sickness and condition of both diseases. We used manual curation to reduce the overall number of paths, keeping pathways with adjusted p-values less than 0.05. As a result, we obtained

Table 1
The summary of the transcriptomic data and analysis, which provides the dataset accession number with sample source and number, including total raw and significant genes.

Name of Disease	GEO Platform	Tissues/Cells	GEO Accession	RAW Genes	Case Samples	Control Samples	Significant Genes	Up Reg. Genes	Down Reg. Genes
Intracranial aneurysm	Illumina HiSeq 4000 (Homo sapiens)	Intracranial aneurysm wall tissue	GSE158558	20995	4	4	1059	323	719
COVID19	Illumina NovaSeq 6000 (Homo sapiens)	PBMC	GSE152418	21134	16	17	2375	1940	325

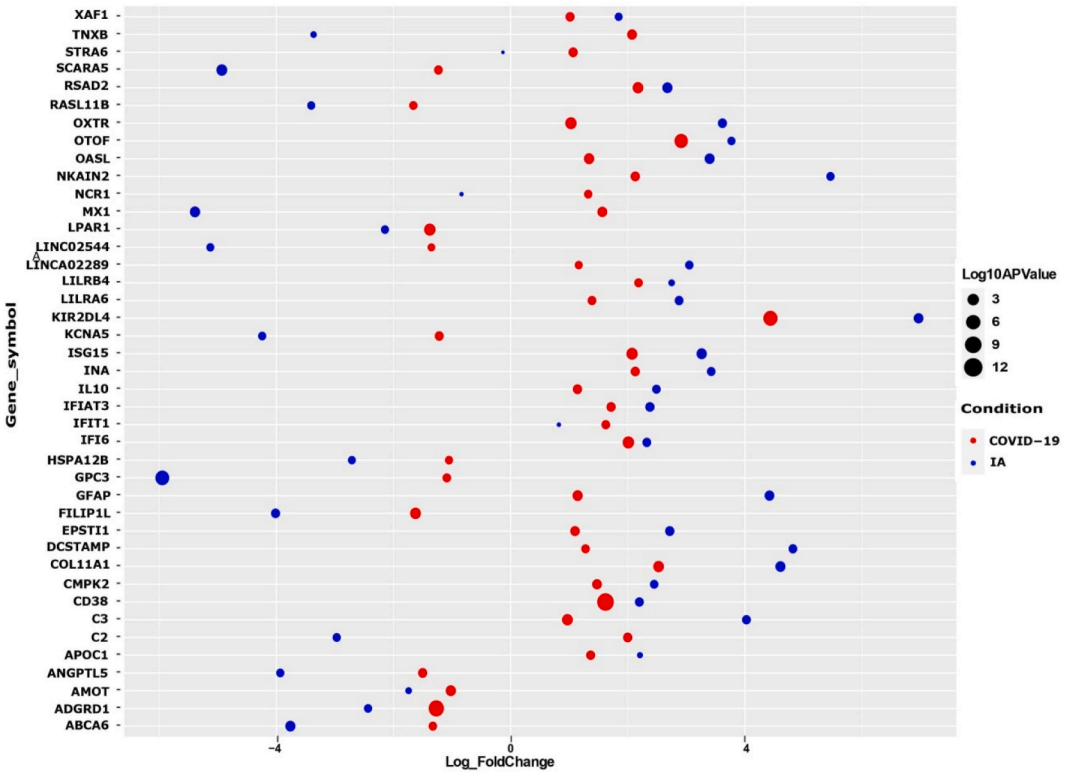

Fig. 3. A bubble plot of common biomarker genes with their adjusted p-value and Log2 fold change. Transcriptomic analysis was depicted graphically in this image. Together in the Venn diagram, IA and COVID-19 had common biomarkers.

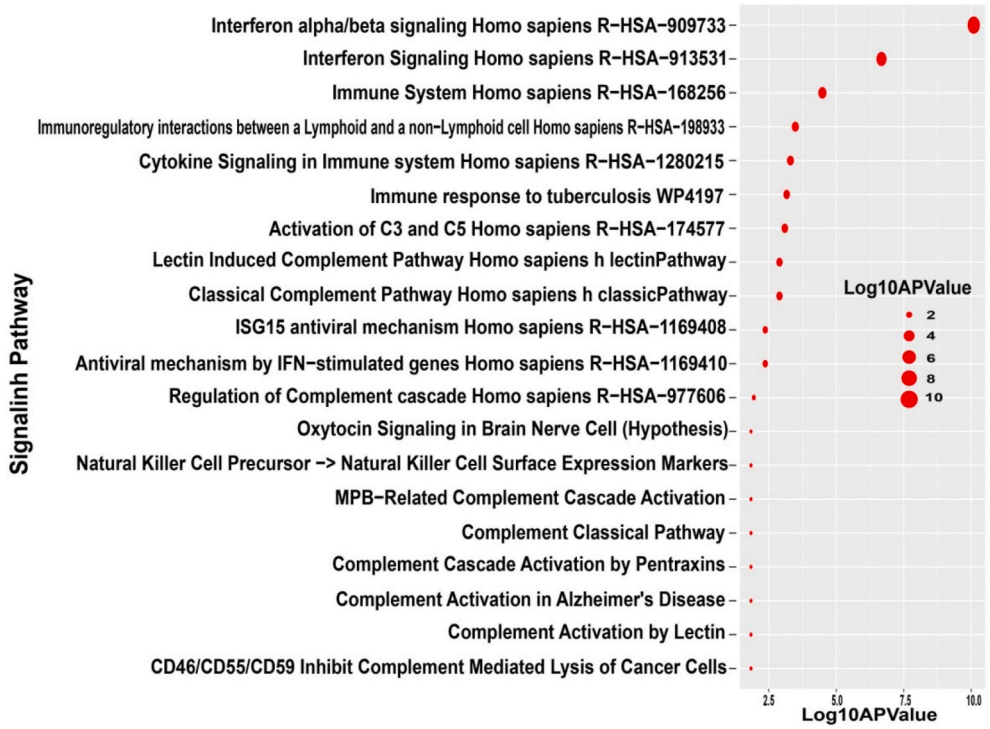

Fig. 4. Using a bubble plot, we can see the top 20 pathways associated with both conditions in the transcriptome study.

37 of the most important signaling pathways, which were ranked based on their adjusted p-value. Fig. 4 shows the top 20 pathways that were associated with IA and COVID-19. Furthermore we evaluated the BP database of the GO method, which categorized biological process (BP), cellular component (CC), and molecular function (MF). We found 598 common GO terms between IA and COVID-19, and the most significant GO terms were those with an adjusted p-value less than 0.05. We discovered 18 enriched GO terms between the criteria, with Table 2 summarizing the top 7 most important GO terms for BP, CC, and MF between IA and COVID-19.

Table 2
Ontological analysis of common DEGs among COVID-19 and Intracranial Aneurysm (IA).

Category	GO ID	Term	P-Value	Genes
BP	GO:0071357	cellular response to type I interferon	6.99E-13	RSAD2; MX1; IFI6; ISG15; IFIT1; XAF1; IFIT3; OASL
	GO:0060337	type I interferon signaling pathway	6.99E-13	RSAD2; MX1; IFI6; ISG15; IFIT1; XAF1; IFIT3; OASL
	GO:0140546	defense response to symbiont	5.60E-09	RSAD2; MX1; IFI6; ISG15; IFIT1; IFIT3; OASL
	GO:0051607	defense response to virus	9.13E-09	RSAD2; MX1; IFI6; ISG15; IFIT1; IFIT3; OASL
	GO:0045071	negative regulation of viral genome replication	8.26E-08	RSAD2; MX1; ISG15; IFIT1; OASL
	GO:0045069	regulation of viral genome replication	2.47E-07	RSAD2; MX1; ISG15; IFIT1; OASL
	GO:0048525	negative regulation of the viral process	3.09E-07	RSAD2; MX1; ISG15; IFIT1; OASL
Celluler Response	GO:0005887	integral component of plasma membrane	0.002314845	NCR1; ADGRD1; OXTR; SCARA5; LPAR1; KCNA5; LILRB4; KIR2DL4; STRA6
	GO:0031235	a fundamental constituent of the face of the plasma membrane that faces the cytoplasm	0.016285505	LILRB4
	GO:0042627	chylomicron	0.020316294	APOC1
	GO:0005788	endoplasmic reticulum lumen	0.020486512	C3; COL11A1; GPC3
	GO:0005740	mitochondrial envelope	0.027917842	MX1; IFI6
	GO:0034385	a triglyceride-rich plasma lipoprotein particle	0.030322908	APOC1
	GO:0034361	very-low-density lipoprotein particle	0.030322908	APOC1
Molecular Function	GO:0005887	an integral component of the plasma membrane	0.002314845	NCR1; ADGRD1; OXTR; SCARA5; LPAR1; KCNA5; LILRB; KIR2DL4; STRA6
	GO:0031235	a fundamental constituent of the face of the plasma membrane that faces the cytoplasm	0.016285505	LILRB4
	GO:0042627	chylomicron	0.020316294	APOC1
	GO:0005788	endoplasmic reticulum lumen	0.020486512	C3; COL11A1; GPC3
	GO:0005740	mitochondrial envelope	0.027917842	MX1; IFI6
	GO:0034385	a triglyceride-rich plasma lipoprotein particle	0.030322908	APOC1
	GO:0034361	very-low-density lipoprotein particle	0.030322908	APOC1

3.4. Protein-protein interactions (PPIs) analysis

We employed the software tools STRING and NetworkAnalyst to generate predicted protein-protein interaction (PPI) networks using our optimized gene sets for shared diseases. These virtual graphical tools were used to construct and analyze the PPI networks [31,43]. Interactomics is a term that refers to the impact of abnormal PPIs on the development of various diseases in the body. When two diseases share one or more protein sub-networks, they may be connected. The results of our analysis and preparation using Cytoscape are displayed in Fig. 5. To construct the simplified PPI networks, we used CytoHubba and applied the BottleNeck and Degree algorithms in Cytoscape, as shown in Fig. 6 (A and B) [45]. The PPI network between COVID-19 and IA consists of 25 nodes and 150 edges, representing their relationship. We used topological features, such as degree greater than 15, to identify proteins with strong interactions. By applying the Bottoleneck and Degree algorithms, we identified 23 and 13 hub proteins, respectively, with 10 highly significant genes common to both algorithms. The 18 most significant hub proteins identified by both algorithms were C3, NCR1, IL10RA, OXTR, RSAD2, CD38, IL10RB, MX1, IL10, GFAP, IFIT3, XAF1, USP18, OASL, IFI6, EPSTI1, CMPK2, and ISG15. Among these proteins, MX1 and RSAD2 were found in both algorithms (see Table 3).

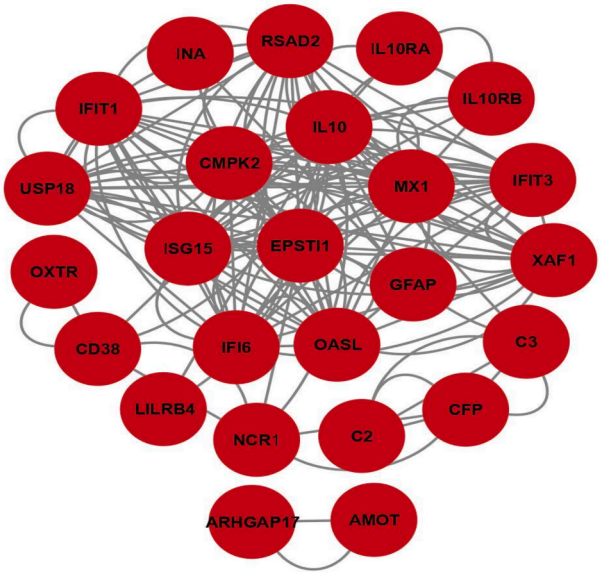

Fig. 5. Highly dysregulated genes shared by COVID-19 and intracranial aneurysms are used to construct a protein-protein interactions (PPIs) network.

Table 3
Outline of DEG-encoded hub proteins shared by COVID-19 and IA discovered through protein-protein interaction studies.

Protein Symbol	Description	Feature
C3	Complement C3	Complement system activation
NCR1	Natural Cytotoxicity Triggering Receptor 1	Cell defense-related
IL10RA	Interleukin 10 Receptor Subunit Alpha	IL10 cell surface receptor involved in anti-inflammatory effects
OXTR	Oxytocin Receptor	G-protein-coupled oxytocin receptor
RSAD2	Radical S-Adenosyl Methionine Domain Containing 2	Intrinsic immune signaling and antiviral response in cell
CD38	CD38 Molecule	Synthesis and hydrolysis of intracellular calcium ion mobilizing messenger cyclic adenosine 5′-diphosphate-ribose
IL10RB	Interleukin 10 Receptor Subunit Beta	Interleukin 10 receptor accessory chain
MX1	MX Dynamin Like GTPase 1	Antiviral cellular reaction
IL10	Interleukin 10	Immunoregulatory and anti-inflammatory actions
GFAP	Glial Fibrillary Acidic Protein	A maturation marker for astrocytes and other glial cells
IFIT3	Interferon-Induced Protein with Tetratricopeptide Repeats 3	Protein binding activity
XAF1	XIAP Associated Factor 1	Counteracts IAP(inhibitor of apoptosis)protein inhibition
USP18	Ubiquitin Specific Peptidase 18	Degrade ubiquitin from ubiquitinated protein substrates
OASL	2′-5′-Oligoadenylate Synthetase Like	Promotes DNA- and double-stranded RNA-binding
IFI6	Interferon Alpha Inducible Protein 6	Regulation of apoptosis
EPSTI1	Epithelial Stromal Interaction 1	Invasion and metastasis of some malignant cancer cells
CMPK2	Cytidine/Uridine Monophosphate Kinase 2	Monocytic segmentation
ISG15	ISG15 Ubiquitin Like Modifier 13	Intracellular targets binding

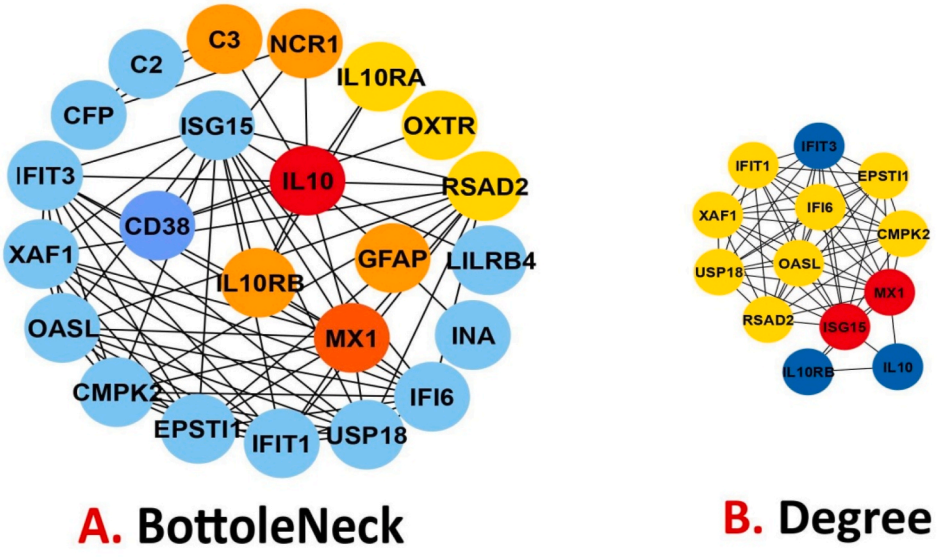

Fig. 6. COVID-19 and intracranial aneurysm hub proteins identified by two independent cyto-hubba algorithms (IA).

3.5. Identification of transcriptional and post-transcriptional gene regulators

Transcription factors (TFs) facilitate the transcription process by binding to specific DNA sequences and regulating the rate of transcription. They are essential in transcribing DNA sequences into mRNA, which eventually leads to the synthesis of proteins [46]. The analysis of TF-gene interactions was conducted to facilitate the process in this study. It has been established that microRNAs have significant involvement in neurological disorders at the post transcriptional level [47]. Gene-mRNA interaction analysis is important in drug discovery, but automated high-throughput screening methods are crucial for plasma protein-drug binding studies in the early stages of drug development [48]. The transcription factor-gene interactions were analyzed and the regulatory genes identified were CREB1, FOXC1, FOXL1, GATA2, GPC3, IFIT1, IFIT3, JUNKIR2DL4, MEF2A, MX1, NFIC, NFKB1, PPARG, SREBF1, TFAP2A, TNXB, TP53, USF2, YY1, OASL, STRA6, RSAD2, NKAIN2, APOC1, C2, CMPK2, ZNF24, STRA6, ISG15, TFDP1, C3, ELF1, IFI6IFIT3, IRF1, MAZ, SMARCE1, and ZEB1 (see Fig. 7). In gene-miRNA interactions, the regulatory genes identified were hsa-mir-4728-5p, hsa-mir-26b-5p, hsa-mir-1-3p, hsa-mira-6806-3p, hsa-mir-1273g-3p, hsa-mir-3613-3p, hsa-mir-124-3p, hsa-mir-98-5p, hsa-mir-6785-5p, hsa-mir-7106-5p, hsa-mir-375, hsa-mir-4252, hsa-mir-589-3p, hsa-mir-21-5p, hsa-mir-149-3p, hsa-mir-7151-3p, hsa-mir-6504-3p, hsa-mir-122-5p, hsa-mir-127-5p, hsa-mir-6883-5p, hsa-mir-3135b, hsa-mir-5095, hsa-mir-504-3p, hsa-mir-335-5p, hsa-mir-146a-5p, hsa-mir-3928-5p, and hsa-mir-4438. The regulatory genes identified in gene-miRNA interactions using the TarBase database were hsa-mir-212-3p, hsa-mir-210-3p, hsa-mir-146a-5p, hsa-mir-27a-5p, hsa-mir-21-3p, hsa-mir-129-2-3p, hsa-mir-34a-5p, hsa-mir-155-5p, hsa-mir-124-3p, hsa-mir-27a-3p, hsa-mir-16-5, C3, LPAR1, IFI6, GFAP, IFIT1, IFIT3, MX1, OASL, ISG15, XAF1, RSAD2, EPSTI1, CMPK2, and AMOT (see Fig. 8).

3.6. Exploration of candidate drugs

In the context of IA and COVID-19, we have identified three potential therapeutic compounds through the use of Enrichr, which relies on DSigDB transcriptomic markers [22]. Based on the adjusted p-value, the three chemical compounds that show promise as potential therapeutic

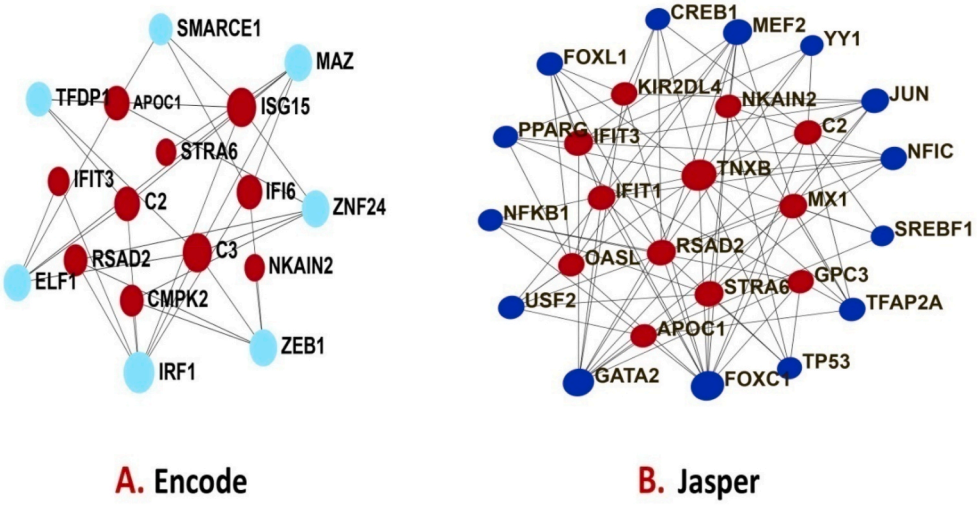

Fig. 7. Visualization of the DEGs and TFs interaction between COVID-19 and IA using 2 different databases, Encode and Jasper.

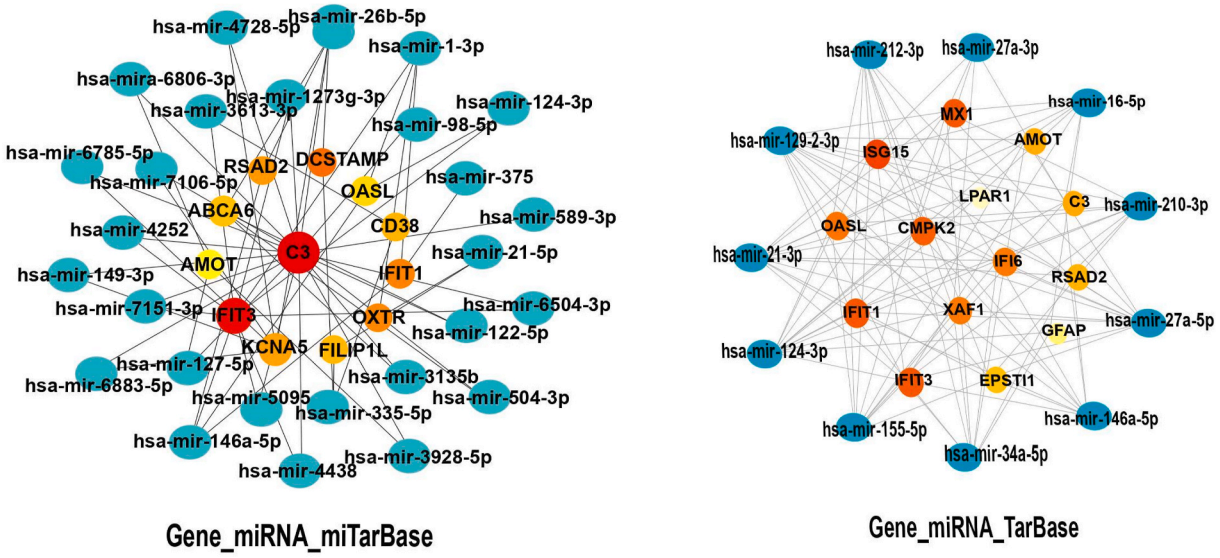

Fig. 8. There are two algorithms, mirTarBase and TarBase, that are used to distinguish between IA and COVID-19 in terms of miRNA gene identification.

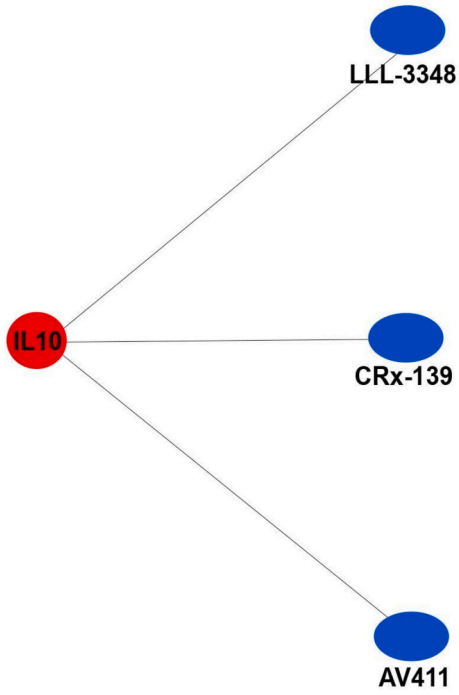

Fig. 9. Protein-drug interaction.

agents for both IA and COVID-19 have been identified. These drug compounds, named LLL-3348, CRx-139, and AV411, are listed in Fig. 9 as possible DEG medicines for the two diseases.

4. Discussion

COVID-19 has far-reaching effects on worldwide economic and social life, and its effects on daily living are substantial [44,49,50]. Based on our research findings, COVID-19 has been observed to cause diverse health issues, including cardiovascular diseases, higher fatality rates in patients with diabetes mellitus (DM) or obesity, and the onset of neurological disorders [7–9]. Our study utilized bioinformatics to explore the molecular pathways that underlie the progression of COVID-19 and other diseases. In particular, we conducted detailed transcriptomic profiling of patients with intracranial aneurysm (IA) and COVID-19, utilizing Differential Expression Analysis to identify transcriptomic characteristics associated with cognitive dysfunction. Our analysis involved comparing transcriptomic data obtained from individuals with and without IA and COVID-19, as presented in Table 1. Our investigation identified a set of DEG-encoded hub proteins that are shared by both diseases, as outlined in Table 2. We further compared our findings with previous research, as documented in Table 4, to identify common genes, pathways, and protein-drug interactions. Our study suggested that C3-targeted therapy could potentially reduce complement-mediated inflammation in COVID-19 patients and immunologic markers, particularly complement C3, played a critical role in the relationship between COVID-19 and intracranial aneurysm [51,52]. Our investigation identified the involvement of the protein OXTR in the psychobiology and behavioral genetics of maternal COVID-19 patients. Additionally, we observed signs of differential expression of OXTR in the membrane of the intracranial aneurysm [53,54]. Recent studies have also suggested the potential involvement of the CD38 ectoenzyme and the CD38/NAD1 axis products in the pathogenesis of COVID-19 [55]. In the presence of an intracranial aneurysm, the helper T cell appears to play a significant role, similar to the situation with CD38 [56]. Our findings suggested that IL10 serves as a critical factor in the pathogenesis of both COVID-19 and intracranial aneurysm [57,58]. Our investigation also revealed that increased levels of GFAP in COVID-19 patients

Table 4
Previous research has been verified by the identified targetable genes that are associated with COVID-19 and Intracranial Aneurysms.

Gene	COVID-19	Intracranial aneurysm
C3	65	66
NCR1	67	–
IL10RA	68	–
OXTR	69	70
RSAD2	71	–
CD38	72	73
IL10RB	74	–
MX1	75	–
IL10	76	77
GFAP	78	79
IFIT3	80	–
XAF1	81	–
USP18	82	–
OASL	83	–
IFI6	84	–
EPSTI1	82	–
CMPK2	85	86
ISG15	87	88

may be associated with a decreased chance of survival. Additionally, we identified GFAP as a possible marker for intracranial aneurysm [59,60]. Our study demonstrated that COVID-19 patients who were co-infected with other viruses showed significant upregulation of CMPK2. Furthermore, we found that CMPK1 is present in cases of Subarachnoid Hemorrhage caused by intracranial aneurysm [61,62]. We also found COVID-19 patients carries elevated levels of the protein ISG15 in their serum one week after the onset of the disease and ISG15 is expressed in intracranial aneurysm disease [63,64]. This led us to investigate genetic links between COVID-19 and intracranial aneurysm (IA) using these proteins as markers. The presence of these proteins may indicate the development of IA in COVID-19 patients, allowing clinicians to advise on precautions that may inhibit their formation and reduce the likelihood of IA or other related complications.

We focused our research efforts on four pathways identified as having close similarities between IA and COVID-19 patients: interferon-alpha/beta signaling, interferon signaling, cytokine signaling in the immune system, and activation of C3 and C5. Previous studies showed that aneurysm growth can be inhibited by selectively eradicating the IFN receptor [65]. In addition, the angiotensin-II Type-1a Transmitter was reported to increase interferon transmission, which is able to culminate in aneurysmal pathophysiology [66]. The blood inside the aneurysm peritoneal cavity is possible to have more chemokines as well as cytokines (IL-1, IL-17, and TNF-) when an aneurysm bulges outward [67]. The inflammatory response caused by aneurysms is exacerbated by cytokines such as TNF-alpha, IFN-gamma, and IL-6, which communicate with one another via cytokine signaling. Blocking monocyte chemoattractants was found to reduce the likelihood of aneurysm formation [68–70]. Our study is the first to use bioinformatics methods to identify these pathways concerning COVID-19 and IA. Pathways from our results have also been documented. We have also identified a gene named IL10 that is connected to three drugs (LLL-3348, CRx-139 and AV411) associated with the development of intracranial aneurysm in COVID-19 patients. However, our findings suggest that the main treatment target should be preventing the development of IA in COVID-19 patients. Our study proposes new hypotheses about major disease pathogenesis pathways and highlights new potential biomarkers. Nevertheless, further in vivo and in vitro research is necessary to fully understand the genetic links between COVID-19 and IA.

5. Conclusions

Our research involved investigating the transcriptomes of COVID-19 and IA to identify potential links between the two diseases. We performed differential expression analysis on both datasets to identify

similarities and differences between them as well as identify genes present in both. Through this analysis, we identified 18 hub proteins that are involved in protein-protein, TF, and DEGs-miRNA interactions. These hub genes, pathways, transcription factors, and microRNAs have not been previously reported and are unique to these diseases. Our bioinformatics study showed that there was a significant association between COVID-19 and IA, suggesting patients with COVID-19 are at a higher risk of developing IA. Our research highlights the need to target the identified pathways and inhibit the functions of hub proteins to prevent the development of intracranial aneurysms in COVID-19 patients.

Credit author statement

All authors participated in the hypothesis, design, interpretation of the studies and analysis of the data, and review of the manuscript. MS (Mahajabin Snigdha) and AA(Azifa Akter) collected the data, conducted the analysis, and wrote the manuscript. MAA (Md. Al Amin) helped with the analysis tools and MZI (Md Zahidul Islam) has given final approval for the version.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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