Bioinformatics and system biology approach to identify the influences of SARS-CoV-2 infections to idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease patients

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), better known as COVID-19, has become a current threat to humanity. The second wave of the SARS-CoV-2 virus has hit many countries, and the confirmed COVID-19 cases are quickly spreading. Therefore, the epidemic is still passing the terrible stage. Having idiopathic pulmonary fibrosis (IPF) and...
chronic obstructive pulmonary disease (COPD) are the risk factors of the COVID-19, but the molecular mechanisms that underlie IPF, COPD, and COVID-19 are not well understood. Therefore, we implemented transcriptomic analysis to detect common pathways and molecular biomarkers in IPF, COPD, and COVID-19 that help understand the linkage of SARS-CoV-2 to the IPF and COPD patients. Here, three RNA-seq datasets (GSE147507, GSE52463, and GSE57148) from Gene Expression Omnibus (GEO) is employed to detect mutual differentially expressed genes (DEGs) for IPF, and COPD patients with the COVID-19 infection for finding shared pathways and candidate drugs. A total of 65 common DEGs among these three datasets were identified. Various combinatorial statistical methods and bioinformatics tools were used to build the protein–protein interaction (PPI) and then identified Hub genes and essential modules from this PPI network. Moreover, we performed functional analysis under ontologies terms and pathway analysis and found that IPF and COPD have some shared links to the progression of COVID-19 infection. Transcription factors–genes interaction, protein–drug interactions, and DEGs-miRNAs coregulatory network with common DEGs also identified on the datasets. We think that the candidate drugs obtained by this study might be helpful for effective therapeutic in COVID-19.

Key words: SARS-CoV-2; idiopathic pulmonary fibrosis; chronic obstructive pulmonary disease; differentially expressed genes; gene ontology; protein–protein interaction (PPI); hub gene; drug molecule

Introduction
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that belongs to the families of Coronaviridae and the class of Pisoniviricetes [1–3]. SARS-CoV-2 is a respiratory disease since it is reported that certain forms of infection that may cause breathing problems are respiratory diseases. Respiratory diseases may go through in a severe condition by a continuous lung infection or injury. Moreover, it is the leading cause of idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and COVID-19. Some common symptoms go through all kinds of respiratory diseases such as shortness of breath, dry hacking cough, fast and shallow breathing, tiredness, aching joints and muscles, and clubbing (widenning and rounding) of the tips of the fingers or toes [2, 4–9]. Researchers in [4, 6] assume that there could be subtle associations between these contagious diseases [10–13]. IPF is a respiratory disease that causes scarring (in medical terms, it is called fibrosis) of the lungs. It causes severity in the lungs that originate and makes it difficult to breathe [12]. Furthermore, lung function abruptly collapses, and it is the execution of respiratory failure. This is a severe form of the disease that can inflict injury to the tissue around the alveoli or airbags in the lungs [14]. COPD is also a respiratory disease, and diagnosed patients with this disease have a long-term breathing problem and inadequate ventilation. While smoking is the root cause of this concern, almost 25% of patients are nonsmokers and have a long-term lung torment issue [8]. Nevertheless, according to the WHO records, COPD is ranked 5th for death and 7th for disease burden in the world.

IPF and COPD infection produce a hostile amount of angiotensin-converting enzyme 2 or ACE2 that blocks the airways and is the primary source of intense coughing and develops into pneumonia. Actually, IPF and COPD are most common human lung infections that cause shortness of breath. But COPD and IPF cause different forms of chronic damage to human lungs. In IPF, lungs become stiff, scarred, and thick, and the progressive damage isn’t convertible. In COPD, the air sacs and airways in lungs become congested, but it is possible to control the symptoms even in complex cases of the disease. Most common forms of COPD are chronic bronchitis and emphysema. Authors of this paper [2] demonstrated implicitly that in SARS-CoV-2 cases, pneumonia occurs for the same explanation as ACE2 rises in the cell membrane in connection with viral infections as it is proven that the density level of ACE2 is extremely progressive in the lungs in both IPF patients and COPD patients [15, 16]. SARS-CoV-2 is covered with spherical lipid bilayer along with an eminent fringe and heavily glycosylated type I glycoprotein spikes, which look like petals and mainly spike protein. However, the virus enters the lung through the nose, eye, or mouth mostly. Continuing the infection process, the virus spike binds to ACE2 (attached to the cell membranes of cells located in the lungs) and replicates by invading epithelial cells, introducing new visions to release and infecting the next target cell [10]. As previously said, the density of the high ranges of ACE2 causes shortness of breath, and as the consequences, the patient can die [2, 13].

In this study, three datasets were used to discover the biological relationship between IPF, COPD, and COVID-19. Those datasets were collected from the Gene Expression Omnibus (GEO) database where GSE147507, GSE52463, and GSE57148 for COVID-19, IPF, and COPD, respectively. Initially, differentially expressed gene (DEGs) were identified for datasets and then found common DEGs genes for three diseases. Here, the common DEGs are the primary experimental genes for the whole study. Using these common DEGs, further experiment and analysis were performed, including pathway analysis and enrichment analysis, to understand the biological processes of genome-based expression studies. Extracting hub genes from common DEGs is an essential part of predicting potential drugs mainly relying on hub genes. The network of protein–protein interactions (PPIs) is also designed from common DEGs to gather hub genes. Herein, transcriptional regulators are also traced based on the similar DEGs of GSE147507, GSE52463, and GSE57148. Finally, potential drugs are suggested. The sequential workflow of our research is presented in Figure 1.

Materials and methods
Datasets employed in this study
To determine shared genetic interrelations among SARS-CoV-2, IPF, and COPD, we assumed both microarray and RNA-seq datasets from the GEO database of the National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/geo/) [17]. The GEO accession ID of the SARS-CoV-2 dataset is GSE147507, which is transcriptional profiling of COVID-19 lung biopsy in response to respiratory infections through high throughput sequencing Illumina NextSeq 500 platform for
Bioinformatics approach to identify the influences of SARS-CoV-2

Figure 1. Schematic illustration of the overall general workflow of this study.

Table 1. Overview of datasets with their geo-features and their quantitative measurements in this analysis

| Disease name | GEO accession | GEO platform | Total DEGs count | Up regulated DEGs count | Down regulated DEGs count |
|--------------|---------------|--------------|------------------|-------------------------|--------------------------|
| SARS-CoV-2   | GSE147507     | GPL18573     | 1184             | 293                     | 891                      |
| IPF          | GSE52463      | GPL11154     | 1444             | 783                     | 661                      |
| COPD         | GSE57148      | GPL11154     | 1461             | 1022                    | 439                      |

extracting RNA sequence [18]. The IPF dataset was (GEO accession ID: GSE52463) of human lung tissue (differential splicing events) containing eight IPF lung samples and seven healthy controls, which was sequenced by a high-throughput sequencing system called Illumina HiSeq [Homo sapiens] contributed by Nance et al. [19]. The COPD dataset with GEO accession ID: GSE57148 were collected from 91 subjects with normal spirometry and 98 COPD subjects [20]. Gene expression was measured through Cufflinks software, and the RNA isolated from the COPD samples was performed using HiSeq 2000 with RNA-seq. The summarized information of the datasets is listed in Table 1.

Identification of DEGs and mutual DEGs among IPF, COPD, and COVID-19

A gene is characterized as being expressed differently when there is a statistically significant difference between diverse test conditions at the transcription level [21]. This analysis’s key role is to obtain DEGs for the datasets GSE147507, GSE52463, and GSE57148. The DEGs were identified from the long-expression values using the LIMMA package with Benjamini-Hochberg correction to control the rate of false discovery and DESeq2 of R programming language (v 4.0.2) in multiple testing options. Cutoff criteria (P-value < 0.05 and |logFC| ≥ 1.0) was applied to detect significant DEGs from all the datasets. The mutual DEGs of GSE147507, GSE52463, and GSE57148 was acquired using an online VENN analysis tool called Jvenn [22].

Gene ontology and pathway enrichment analysis

Gene set enrichment analysis is a significant analytical effort to classify common biological insights such as biological processes or chromosomes’ positions associated with different interlinked diseases [23]. Gene ontology as well as functional enrichment (biological processes, cellular component, and molecular functions) and pathway enrichment studies were conducted utilizing Enrichr (https://maayanlab.cloud/Enrichr/)—a comprehensive gene set enrichment web tool [24] to characterize biological mechanisms and signaling pathways of shared DEGs. At this time, we regarded four databases, including KEGG (Kyoto Encyclopedia of Genes and Genomes), WikiPathways, Reactome, and BioCarta as origins of pathway classification to specify the shared pathways among IPF, COPD, and COVID-19. Typically, the KEGG pathway is known to grasp the metabolic processes and makes the considerable utility of genomic analysis. The P value < 0.05 was considered as a standard metric for quantifying the top listed pathways.

Protein–protein interaction network analysis

Proteins conclude their journey into a cell with a similar protein affiliation formed by a protein–protein network, which indicates the protein mechanisms. In cellular as well as systems biology, the assessment and analysis of the PPI network and its functionalities is the foundation and key objective for interpreting and acquiring insights into cellular machinery operations [25-27]. We utilized the STRING (https://string-db.org/) (version 11.0) [25] repository to construct the PPI network of proteins derived from shared DEGs to portray functional and physical interactions among IPF, COPD, and COVID-19. STRING envisages expanded insights into PPI using active channels of interaction, including text mining, experimental databases, coexpression, culture, gene fusion, and cooccurrence under the setting of different
Hub gene extraction and submodule analysis

The PPI network consists of nodes, edges, and their connections, and here the most entangled nodes are considered as hub genes. Cytohubba (http://apps.cytoscape.org/apps/cytohubba)—a novel Cytoscape—plugin for ranking and extracting central or potential or targeted elements of a biological network based on various network features. Cytohubba has 11 methods for investigating networks from various viewpoints, and Maximal Clique Centrality (MCC) is the best of them [29]. We recognized the top 15 hub genes from the PPI network applying the MCC method of Cytohubba. We also classified the shortest available paths across hub genes based on Cytohubba’s close neighborhood ranking features.

Recognition of transcription factors and miRNAs engage with common DEGs

Transcription factors (TFs) are the protein that attaches to a particular gene and governs the rate of transcription of genetic information; hence, it is essential for molecular insights [30]. We have utilized the NetworkAnalyst platform to locate topologically credible TFs from the JASPAR database that tend to bind to our mutual DEGs. JASPAR is a publicly available resource for TFs profiles of multiple species within six taxonomic groups [31]. NetworkAnalyst is a wide-ranging online platform for meta-analyzing gene expression data and gaining insights into biological mechanisms, roles, and interpretations [32]. Further, miRNAs targeting gene interactions were incorporated to trace miRNAs that strive to attach with gene transcripts to affect protein expression [33] adversely. Tarbase and mirTarbase are the major experimental validity databases for miRNAs-target gene interactions [33, 34]. From the interaction of miRNAs—gene interaction via networkAnalyst, we have extracted miRNAs from both Tarbase and mirTarbase that interact with common DEGs focused on topological analysis. Both TFs—gene and miRNAs—gene interaction networks were illustrated in Cytoscape. This tool helps researchers filter top miRNAs with high degrees and detect biological functions and features to lead to the effective biological hypothesis.

Evaluation of applicant drugs

In this research, prediction protein–drug interaction (PDI) or drug molecules identification is one of the significant parts. Drug molecule was identified using the Drug Signatures database (DSigDB) via Enrichr based on the DEGs of COVID-19, IPF, and COPD. Enrichr is a popular web portal with a vast array of diverse gene-set libraries to explore gene-set enrichment across a genome-wide scale [24]. DSigDB is the global archive for recognizing targeted drug substances linked to DEGs [35]. This database has 22,527 gene sets, and an accessible way of DSigDB database is through Enrichr under the Diseases/Drugs function.

Gene–disease association analysis

DisGeNET is a comprehensive database of gene–disease associations that synchronize relationships from several origins featuring various biomedical aspects of illnesses. It emphasizes the emerging insight into human genetic disorders [36]. We also examined the gene-disease relationship via NetworkAnalyst to uncover associated diseases and their chronic complications with common DEGs.

Result

Identification of DEGs and common DEGs among IPF, COPD, and COVID-19

To examine the interrelationships and implications of IPF and COPD with COVID-19, we analyzed the human RNA-seq dataset and microarray datasets from the NCBI to classify the disordered genes that stimulate COVID-19, IPF, and COPD sequentially. The RNA-seq and microarray dataset experiments were conducted in the R language environment featuring DESeq2 and limma packages with Benjamin-Hochberg false discovery rate. Firstly, 1184 genes were differentially expressed for COVID-19, including 293 up-regulated and 891 down-regulated genes exposure. In the same way, this analysis selected the most significant DEGs for IPF and COPD after completing the different process of statistical analysis. We identified 1444 DEGs (783 up-regulated and 661 down-regulated) in the IPF dataset and 1461 DEGs (1022 up-regulated and 439 down-regulated) in the COPD dataset. All significant DEGs are extracted on the basis of P-value < 0.05 and |logFC| ≥ 1. After performing the cross-comparative analysis on the Jvenn—a reliable web portal for Venn analysis, we identified 65 common DEGs from IPF, COPD, and SARS-CoV-2 datasets. This common gene set is employed to accomplish further experiments. These three disorders are related together as they share one or more common genes with one another [37]. Figure 2 represented the cumulative comparative evaluation of the three datasets and retrieval of the mutual DEGs.

Gene ontology and pathway enrichment analysis

Gene ontology and pathway enrichment analysis were performed using Enrichr to identify the biological significance and enriched pathways underlined in this study shared DEGs. Gene ontology takes consideration of gene functions and their components to offer extensive computable knowledge resources. An ontology defines a body of information—thereoretically within a given context. Both ontology and annotation are meant to perform a detailed biological structure model that is essentially assisted in biological applications [38]. The gene ontology analysis was acquired within three categories (biological process, cellular component, and molecular function), and the GO database was selected as an annotation source. The top 10 terms in the biological process, molecular functions, and cellular components category are summarized in Table 2. Figure 3 has also characterized the overall ontological analysis linearly in the bar graph for each category.

Pathways analysis reveals the organism reacts to its inherent modifications. It is a model technique for demonstrating the interaction between various diseases through basic molecular or biological processes [39]. The most impacted pathways of the common DEGs among IPF, COPD, and COVID-19 were gathered from four global databases, including KEGG, WikiPathways, Reactome, and BioCarta. Table 3 enlists the top pathways obtained from the selected datasets. To illustrate more precisely,
Table 2. Ontological analysis of common DEGs among SARS-CoV-2, IPF, and COPD

| Category                  | GO ID     | Term                                                                 | P-values     | Genes                                                                 |
|---------------------------|-----------|----------------------------------------------------------------------|--------------|----------------------------------------------------------------------|
| GO Biological Process     | GO:0060333| interferon-gamma-mediated signaling pathway                         | 2.80E−09     | IRF4;HLA-B;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1                        |
|                           | GO:0019221| cytokine-mediated signaling pathway                                  | 1.21E−08     | IL24;HLA-B;HLA-C;HLA-A;HLA-F;PSMB8;EREG;BATF;IL6;CXCL12;IRF4;IL2RA;HLA-DQA1;HLA-DQB1 |
|                           | GO:0002480| antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-independent | 1.26E−08     | HLA-B;HLA-C;HLA-A;HLA-F                                              |
| GO Cellular Component     | GO:0071357| cellular response to type I interferon                              | 6.61E−08     | IRF4;HLA-B;HLA-C;HLA-A;HLA-F;PSMB8                                  |
|                           | GO:0060337| type I interferon signaling pathway                                 | 6.61E−08     | IRF4;HLA-B;HLA-C;HLA-A;HLA-F;PSMB8                                  |
|                           | GO:0071346| cellular response to interferon-gamma                                | 9.70E−08     | IRF4;HLA-B;HLA-C;HLA-A;HLA-F;HLA-F;HLA-DQA1;HLA-DQB1                |
|                           | GO:0072540| Thelper 17 cell lineage commitment                                  | 6.51E−07     | IL6;IRF4;BATF                                                        |
|                           | GO:0002295| T-helper cell lineage commitment                                    | 1.81E−06     | IL6;IRF4;BATF                                                        |
|                           | GO:0072539| T-helper 17 cell differentiation                                     | 1.81E−06     | IL6;IRF4;BATF                                                        |
|                           | GO:0002474| antigen processing and presentation of peptide antigen via MHC class I | 1.96E−06     | HLA-B;HLA-C;HLA-A;HLA-F                                              |
| GO Molecular Function     | GO:0008237| metallopeptidase activity                                           | 2.03E−05     | ADAMTS4;MME;ADAMTS9;MMP10;PAPPA2                                   |
|                           | GO:0004222| metalloendopeptidase activity                                       | 5.93E−05     | ADAMTS4;MME;MMP10;PAPPA2                                             |
|                           | GO:0070011| peptidase activity, acting on L-amino acid peptides                 | 3.38E−04     | ADAMTS4;MME;ADAMTS9;PSMB8;PAPPA2                                    |
|                           | GO:0032395| MHC class II receptor activity                                      | 4.60E−04     | HLA-DQA1;HLA-DQB1                                                    |
|                           | GO:0004175| endopeptidase activity                                              | 0.01011001   | ADAMTS4;MME;MMP10;CFB;PSMB8;PAPPA2                                  |
|                           | GO:0019956| chemokine binding                                                   | 0.001370599  | CX3CR1;CXCR4                                                        |
|                           | GO:0004950| chemokine receptor activity                                         | 0.002098714  | CX3CR1;CXCR4                                                        |
|                           | GO:0005126| cytokine receptor activity                                          | 0.010079705  | IL6;CXCL12;GDF5                                                     |
|                           | GO:0005125| cytokine activity                                                   | 0.014044934  | IL6;CXCL12;GDF5                                                     |
|                           | GO:0005113| patched binding                                                     | 0.01934497    | IHH                                                                 |
| GO Cellular Component     | GO:0071556| integral component of lumenal side of endoplasmic reticulum membrane | 4.17E−10     | HLA-B;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1                          |
|                           | GO:0042611| MHC protein complex                                                 | 2.57E−09     | HLA-B;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1                          |
|                           | GO:0012507| ER to Golgi transport vesicle membrane                               | 2.13E−08     | HLA-B;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1                          |
|                           | GO:0030134| COPII-coated ER to Golgi transport vesicle                          | 1.57E−07     | HLA-B;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1                          |
|                           | GO:0030176| integral component of endoplasmic reticulum membrane                | 3.70E−06     | HLA-B;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1                          |
|                           | GO:0030670| phagocytic vesicle membrane                                         | 6.90E−06     | HLA-B;HLA-C;HLA-A;HLA-F                                             |
|                           | GO:0050538| recycling endosome membrane                                         | 1.63E−05     | HLA-B;HLA-C;HLA-A;HLA-F                                             |
|                           | GO:0031901| early endosome membrane                                             | 9.34E−05     | HLA-B;HLA-C;HLA-A;HLA-F                                             |
|                           | GO:0045535| phagocytic vesicle                                                  | 1.54E−04     | HLA-B;HLA-C;HLA-A;HLA-F                                             |
|                           | GO:0000139| Golgi membrane                                                      | 5.66E−04     | NOTCH4;HLA-B;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1                    |

Note: Top 10 terms of each category are listed.
we have also constructed a submodule network (Figure 6) to
Since hub genes are potential, with the Cytohubba plugin’s aid,
also lead to new therapeutic strategies for investigated diseases.
CD28. These hub genes can be potential biomarkers, which may
PSMB8, DAXX, RASD2, EPN3, DIRAS1, BATF, GDF5, RGS4, and
(21.54%) DEGs as the most influential genes. The hub genes are
dating the Cytohubba plugin in Cytoscape, we listed the top 14
genes in a PPI network. From the PPI network analysis incorpo-
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Identification of candidate drugs
Assessment of protein–drug interactions is important to under-
stand the structural features recommended for receptor sensi-
tivity [37, 40]. In the aspects of common DEGs as potential drug
targets in IPF, COPD, and COVID-19, we identified 10 possible
drug molecules using Enrichr based on transcriptome signatures
from the DSigDB database. The top 10 chemical compounds are
extracted based on their P-value. These potential drugs are sug-
gested for the common DEGs; these drugs can be common chem-
ical compounds for three diseases. Table 4 shows the effective
drugs from the DSigDB database for common DEGs.

Identification of disease association
The circumstances in which different diseases can be correlated
or associated are that they must usually have one or more similar
genes [37]. Therapeutic design strategies for disorders initiate
unveiling the relationship between genes and disorders [41].
From the analysis of the gene-disease association by Network-
Analyst, we noticed that rheumatoid arthritis, schizophrenia,
exanthema, atopic dermatitis, and autosomal recessive predis-
position diseases are most coordinated to our reported hub
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nia is a complicated illness including dysregulation of various
paths in its pathophysiology. Glutamatergic, dopaminergic, and
GABAergic neurotransmitter systems are affecting schizophrenia
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to the disease’s pathophysiology. The pathophysiology of atopic
dermatitis is multifactorial and difficult, involving IgE-mediated
hypersensitivity, elements of barrier dysfunction, alterations in
cell, and environmental factors. The association between gene-
disease is displayed in Figure 9.

Classification of hub proteins and submodule
We scrutinized the PPI network from STRING and visualized in
Cytoscape to anticipate common DEGs’ interactions and adhe-
sion pathways. The PPI network of common DEGs consists of
781 nodes and 968 edges and is depicted in Figure 5. At the
same time, most interconnected nodes are acknowledged as hub
genes in a PPI network. From the PPI network analysis incorpor-
rating the Cytohubba plugin in Cytoscape, we listed the top 14
(21.54%) DEGs as the most influential genes. The hub genes are
namely NOTCH4, FLNC, Indian hedgehog (IHH), FOSL1, CXCR4,
PSMB8, DAXX, RASD2, EPN3, DIRAS1, BATF, GDF5, RGS4, and
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Since hub genes are potential, with the Cytohubba plugin’s aid,
we have also constructed a submodule network (Figure 6) to
deeper understand their near connectivity and proximity. The
expanded network of hub–gene interactions derived from the PPI
network is shown in Figure 6.

Determination of regulatory signatures
To identify substantial changes happening at the transcriptional
level and get insights into the hub protein’s regulatory molecules
or common DEGs, we employed a network-based approach to
decode the regulatory TFs and miRNAs. TFs regulators inter-
action with the common DEGs is pictured in Figure 7. Again,
Figure 8 represents the interactions of miRNAs regulators with
common DEGs. From TFs–genes and miRNAs–gene interaction
network analysis, it has been ascertained that 112 transcriptional
factors (TFs) and 68 post-transcriptional (miRNAs) regulatory
signatures regulate with more than one common DEGs, which
essentially indicates a strong interference between them.

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Discussion
IPF and COPD are a type of chronic lung disease regarded as a
high-risk factor for COVID-19 infections. If humans’ lung tissue is
affected, then the functionality of the lung decline to its task. The
most common symptoms between these two diseases include
shortness of breath, cough, and chest pain or tightness with
sputum production [42]. People with chronic lung diseases are
at a high possibility of getting infected by the SARS-CoV-2. In
this study, a network-based approach is developed to investi-
gate the gene expression patterns from three RNA-seq datasets
of IPF, COPD, and COVID-19 patients and identified molecular
targets that may help as potential biomarkers of COVID-19. It
could also provide crucial information about their effects on
emerging specific diseases or conditions. Expression profiling by
high throughput sequencing datasets is used in biomedical and
system biology research and has become a significant resource
for identifying biomarker candidates of different diseases [43].
Recently, RNA-Seq, a next-generation sequencing concept, facil-
itates the ability to look at gene fusion, mutations/SNPs post-
transcriptional modifications, and gene expression differences
in different sets or treatments [44]. Here, the analysis of the IPF,
COPD, and SARS-CoV-2 transcriptomics revealed that common
65 DEGs show similar expression patterns in three diseases.
Identified 65 common DEGs were evaluated by Gene Ontology

![Figure 2](Image 67x464 to 295x729)

Figure 2. This study incorporates two microarrays and one RNA-seq dataset
comprising IPF (GSE52463), COPD (GSE57148), and SARS-CoV-2 (GSE147507). This
integrated analysis revealed 65 common DEGs are shared among SARS-CoV-2,
IPF, and COPD.

Figure 4 also represented the pathway enrichment analysis in
the bar graphs.

![Figure 4](Image 67x464 to 295x729)

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Table 3. Pathway enrichment analysis of common DEGs among SARS-CoV-2, IPF, and COPD

| Category     | Pathways                                                                 | P-values     | Genes                                                                 |
|--------------|--------------------------------------------------------------------------|--------------|----------------------------------------------------------------------|
| WikiPathways | Allograft Rejection WP3228                                               | 3.18E−11     | CXCL12;L2RA;HLA-B;CD28;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1           |
| Human        | Ebola Virus Pathway on Host WP4217                                       | 2.01E−07     | HLA-B;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1                           |
|              | Proteasome Degradation WP183                                              | 1.74E−06     | HLA-B;HLA-C;HLA-A;HLA-F;PSMB8                                      |
|              | Hematopoietic Stem Cell Differentiation WP2849                           | 7.62E−04     | IL6;TNXB;CXCR4                                                      |
|              | GPCRs, Class B Secretin-like WP394                                        | 0.00274051   | VIPR1;CALCRL                                                      |
|              | T-cell antigen Receptor (TCR) Signaling Pathway WP69                     | 7.53E−04     | CD28;FLNC;HLA-B;HLA-C;HLA-A;HLA-F;IL6;CD28;PSMB8                  |
|              | Selective expression of chemokine receptors during T-cell polarization WP4494 | 0.00301075   | CD28;CXCR4                                                      |
|              | Inflammatory Response Pathway WP453                                      | 0.00462289   | IL2RA;CD28;HLA-B                                               |
|              | Prion disease pathway WP3995                                              | 0.005146053  | IRF4;BATF                                                         |
|              | Type II interferon signaling (IFNG) WP619                                | 0.00023709   | IRF4;HLA-B                                                        |
| BioCarta      | Pertussis toxin-insensitive CCR5 Signaling in Macrophage Homo sapiens h  | 3.69E−04     | CXCL12;CXCR4                                                      |
|              | Ccr5Pathway                                                              |             |                                                                      |
|              | CXCR4 Signaling Pathway Homo sapiens h ccxcr4Pathway                     | 5.61E−04     | CXCL12;CXCR4                                                      |
|              | Antigen Processing and Presentation Homo sapiens h mhcPathway            | 6.72E−04     | HLA-A;PSMB8                                                      |
|              | Ras-independent pathway in NK cell-mediated cytotoxicity Homo sapiens h  | 0.002303759  | CD28;HLA-A                                                        |
|              | nkCellsPathway                                                           |             |                                                                      |
|              | Beta-arrestins in GPCR Desensitization Homo sapiens h bArrestinPathway    | 0.0031232278 | CXCL12;CXCR4                                                      |
|              | Activation of cAMP-dependent protein kinase, PKA Homo sapiens h gsPathway | 0.00099019    | CXCL12;CXCR4                                                      |
|              | Role of Beta-arrestins in the activation and targeting of MAP kinases Homo sapiens h barr-mapkPathway | 0.0004166289 | CXCL12;CXCR4                                                      |
|              | Roles of Beta-arrestin-dependent Recruitment of Src Kinases in GPCR Signaling Homo sapiens h bArrestin-srcPathway | 0.00545628 | CXCL12;CXCR4                                                      |
|              | ChREBP regulation by carbohydrates and cAMP Homo sapiens h chrebpPathway  | 0.007949132  | CXCL12;CXCR4                                                      |
|              | Activation of Csk by cAMP-dependent Protein Kinase Inhibits Signaling through the T Cell Receptor Homo sapiens h CskPathway | 0.008619309 | CXCL12;CXCR4                                                      |
| Reactome      | Interferon gamma signaling Homo sapiens R-HSA-877300                     | 6.53E−10     | GBP7;IRF4;HLA-B;HLA-C;HLA-A;HLA-F;PSMB8;HLA-DQA1;HLA-DQB1          |
|              | Interferon Signaling Homo sapiens R-HSA-913531                           | 1.38E−08     | HLA-F;HLA-DQA1;HLA-DQB1                                           |
|              | Endosomal/Vacuolar pathway Homo sapiens R-HSA-1236977                    | 4.93E−08     | HLA-B;HLA-C;HLA-A;HLA-F;PSMB8;EREG;IL6;IRF4;IL2RA;HLA-DQA1;HLA-DQB1 |
|              | Cytokine Signaling in Immune system Homo sapiens R-HSA-1280215           | 8.05E−08     | HLA-B;HLA-C;HLA-A;HLA-F;PSMB8;EREG;IL6;IRF4;IL2RA;HLA-DQA1;HLA-DQB1 |
|              | Interferon alpha/beta signaling Homo sapiens R-HSA-909733                | 8.70E−08     | IRF4;HLA-B;HLA-C;HLA-A;HLA-F;PSMB8                                |
|              | Antigen Presentation: Folding, assembly and peptide loading of class I MHC Homo sapiens R-HSA-983170 | 1.22E−06 | HLA-B;HLA-C;HLA-A;HLA-F                                           |
|              | ER-Phagosome pathway Homo sapiens R-HSA-1236974                          | 2.20E−06     | HLA-B;HLA-C;HLA-A;HLA-F;PSMB8                                     |
### Table 3. Continued

| Category | Pathways | P-values | Genes |
|----------|----------|----------|-------|
| **Antigen processing-Cross presentation Homo sapiens** | R-HSA-1236975 | 6.97E−06 | HLA-B;HLA-C;HLA-A;HLA-F;PSMB8 |
| **Immune System Homo sapiens** | R-HSA-168256 | 1.02E−04 | GBP7;IL24;HLA-B;HLA-C;HLA-A;HLA-F;PSMB8;IREG1;IL6;IRF4;IL2RA;CD28;CFB;HLA-DQA1;HLA-DQB1 |
| **Extracellular matrix organization Homo sapiens** | R-HSA-1474244 | 3.12E−04 | ADAMTS4;CAPN13;TNXB;ADAMT5;GDF5;MMP10 |

**KEGG 2019 Human**

| Pathways | P-values | Genes |
|----------|----------|-------|
| Graft-versus-host disease | 6.99E−13 | IL6;HLA-B;CD28;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1 |
| Allograft rejection | 3.20E−11 | HLA-B;CD28;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1 |
| Type I diabetes mellitus | 8.07E−11 | HLA-B;CD28;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1 |
| Autoimmune thyroid disease | 3.76E−10 | HLA-B;CD28;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1 |
| Vinal myocarditis | 8.20E−10 | HLA-B;CD28;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1 |
| Intestinal immune network for IgA production | 1.03E−08 | IL6;CXCL12;CD28;CXCR4;HLA-DQA1;HLA-DQB1 |
| Cell adhesion molecules | 2.24E−08 | CLDN5;HLA-B;CD28;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1 |
| Human T-cell leukemia virus 1 infection | 3.61E−08 | FOSL1;IL6;IL2RA;HLA-B;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1 |
| Antigen processing and presentation | 1.84E−07 | HLA-B;HLA-C;HLA-A;HLA-F;HLA-DQA1;HLA-DQB1 |

**Note**: The top pathways of each database are listed.
(GO) pathway analysis functions based on the P-values to acquire insight into the biological importance in the pathogenesis of IPF, COPD, and COVID-19.

GO is a gene regulation context based on the generic theoretical model that facilitates genes and their internal relationship. The evolutions gradually did by attaining biological knowledge regarding gene functions and their regulations on different ontological categories [45]. From the Enrichr, three types of GO analysis, such as biological process (molecular activities), cellular component (gene regulates function), and molecular function (activities of molecular level) were conducted with the GO database as an annotation source in the ontological processes [46]. For the biological process, interferon-gamma-mediated (7 genes) and cytokine-mediated signaling pathway (15 genes) are among the top GO terms. Interferon-gamma (IFN-γ) is a cytokine that plays significant roles in immune responses
Figure 4. The bar graphs of pathway enrichment analysis of shared DEGs among SARS-CoV-2, IPF, and COPD performed by the Enricher online tool: here, (A) wikipathway, (B) biocarta pathway, (C) reactome pathway, and (D) KEGG 2019 human pathway.
IFN-$\gamma$ signaling is mainly related to inflammation and cell-mediated immune responses [48]. It also indicates antitumor cytokine, which is responsible for immunosurveillance in human tumor cells [48]. Several studies disclose a strong connection between interferon-gamma and SARS-CoV virus, where interferon-gamma inhibits the replication of SARS-associated coronavirus [45, 46]. In the molecular function experiment, metallopeptidase (five genes) and metalloendopeptidase activity (four genes) are two top GO pathways. Metallopeptidase activity (MMP group genes) affects respiratory disorders, including ARDS, acute lung injury, lung cancer, and pulmonary fibrosis. The significance of metalloproteinase as a biomarker for infected lung patients with COVID-19 was investigated in [49, 50]. According to the cellular component, top GO terms are integral components of the luminal side of the endoplasmic reticulum membrane (six genes) and MHC protein complex (five genes). For the SARS-CoV, the membrane protein, spike glycoprotein, and envelope protein are produced by the ribosome and implanted into the endoplasmic reticulum membrane during replication SARS-CoV-2.
Figure 6. Determination of hub genes from the PPI network by using the Cytohubba plugin in Cytoscape. The latest MCC procedure of Cytohubba plugin was pursued to obtain hub genes. Here, the red nodes indicate the highlighted top 14 hub genes and their interactions with other molecules. The network consists of 140 nodes and 275 edges.

The pathway analysis is the best way of reflecting an organism’s reactions through internal changes. The KEGG pathway of 65 common DEGs is identified to find a similar path for IPF, COPD, and COVID-19. Top 10 KEGG Human pathway includes graft-versus-host disease (GVHD), allograft rejection, type I diabetes mellitus, autoimmune thyroid disease, viral myocarditis, intestinal immune network for IgA production, cell adhesion molecules, human T-cell leukemia virus 1 infection, and antigen processing and presentation. Here, GVHD is a common complication mediated by dysregulated inflammatory cytokines and cytotoxic T-cell effectors [51]. Recently diagnosed lung injury patients by COVID-19 produce a massive amount of pro-inflammatory cytokines [52].

Using the DEGs genes, a PPI network was built on understanding the biological characteristics of proteins in-depth and predicting drug targets. Here, we identified hub proteins based on the topological metric (i.e., degree), which can be key drug-target or biomarkers in COVID-19 and associate with various pathological and biological mechanisms. The top hub proteins indicate different diseases, most risk factors for the IPF, COPD, and COVID-19. A total of 10 hub-proteins (NOTCH4, FLNC, IHH, FOSL1, CXCR4, PSMB8, DAXX, RASD2, EP30, DIRAS1,
BATF, GDF5, RGS4, CD28) identified involved in these diseases. Here, the cutoff (parameter) of the topological metric for hub proteins was 15 (degree). The protein NOTCH signaling shows a vital role in the growth and homeostasis of various organs, including the lung [53]. Dysregulation of NOTCH4 signaling causes complex airway epithelial changes that eventually contribute to airway diseases like IPF and COPD [54]. COPD, generally caused by smoking, is significantly associated with the NOTCH4 pathway responsible for the functional mutations [55]. This gene could be associated with COVID-19 infections as well. NOTCH4 is one of the possible therapeutic targets for different cancer. In cancer cells, NOTCH4 inhibition reduced invasiveness and proliferation, and NOTCH4 overexpression amplified invasiveness and proliferation. NOTCH4 can minimize the tumor volume of tumorigenicity animal xenografts. Cancer cells show a higher frequency of nuclear translocation of NOTCH4 than other cells. Another hub-protein CXCR4 is a significant hub gene involved in the COPD high-risk group of COVID-19, indicating the importance of cytokine signaling as one of the pathogenesis in COPD patients with COVID-19, Diabetes and COPD patients with increased pro-inflammatory immune stage develop the Cytokine-storm of COVID-19 [56]. Furthermore, the COPD expressed genes PSMB8 in ATII cells linked with antigen processing [57]. Recent studies indicate a co-relation among three diseases IPF, COPD, and COVID-19, through the PSMB8 gene [58]. In Tam et al. [59], the research shows that airway epithelial PTCH1 protein with secreted IHH ligands up-regulated in COPD epithelium.

Moreover, IHH is a primary receptor, and expressed in the developmental signaling pathway is up-regulated in IPF [60]. The molecular pathway analysis shows that both IL6 and FOSL1 are deregulated genes in COPD patients, and the findings disclose...
that COVID-19 is similar to an acute mode of COPD produced by the SARS-CoV-2 infection [61]. A study revealed that DAXX is directly associated with HDAC2 and found a link with COPD in lung tissue of patients with increasing clinical stages [62, 63]. Moreover, Fas expression was up-regulated in alveolar epithelial cells of IPF patients where Fas activates the JNK pathway through the adaptor protein DAXX. DAXX is correlated to IPF and COPD, so this gene could be linked to COVID-19 and may disclose essential information for drug targets. E Fuerst et al. [64] identified the role of the RASD2 in both IPF and COPD disease. So RASD2 gene could be one of the target genes for COVID-19 infections. The FLNC gene corresponds to lung pathologies and vital biomarkers of disease severity in IPF [69, 70]. Therefore, identified hub–genes can be considered potential biomarkers or, if the biological insight in COVID-19 is confirmed, as novel drug target.

We also analyze the TFs–gene and miRNAs interaction to find the transcriptional and post-transcriptional regulators of the common DEGs. TFs handle the ratio of transcription, and miRNAs plays a key role in gene regulation and RNA silencing on the post-transcription level. TFs and miRNAs are significant activation in IPF, cystic fibrosis, and PAH model [67, 68]. Christa Gaskill et al. [68] identified the role of the RASD2 in both IPF and COPD disease. So RASD2 gene could be one of the target genes for COVID-19 infections. The FLNC gene corresponds to lung pathologies and vital biomarkers of disease severity in IPF [69, 70]. Therefore, identified hub–genes can be considered potential biomarkers or, if the biological insight in COVID-19 is confirmed, as novel drug target.
Bioinformatics approach to identify the influences of SARS-CoV-2

Table 4. List of the suggested drugs for COVID-19

| Name                  | P-value      | Chemical Formula | Structure |
|-----------------------|--------------|------------------|-----------|
| curcumin CTD 00000663 | 0.0003894    | C_{21}H_{20}O_{6} |           |
| hyoscymine CTD 00005451 | 0.0006377    | C_{17}H_{23}N_{3}O_{3} |           |
| Chromium(III) oxide CTD 00001091 | 0.0008400 | Cr_{2}O_{3} |           |
| triclosan CTD 00006933 | 0.001039     | C_{12}H_{7}Cl_{3}O_{2} |           |
| ellipticine PC3 UP    | 0.001428     | C_{17}H_{14}N_{2} |           |
| tamoxifen CTD 00006827 | 0.001861     | C_{26}H_{29}NO |           |
| Deguelin CTD 00003487 | 0.001877     | C_{23}H_{22}O_{6} |           |

to understand disease development. In this way, our analysis revealed relationships among the common DEGs, TFs, and miRNAs. The identified TFs, such as FOSL1, DAXX, HSPB6, CFB, FLNC, VARS2, TMEM238, PSMB8, EPN3, and DNAAF1, are associated with different types of respiratory diseases. Further, some miRNAs involve in lung cancer (e.g., miR-146a-5p, hsa-mir-34a-5p, hsa-mir-873-5p, hsa-mir-195-5p, hsa-mir-335-5p) [71–75], immunity disorder (e.g., hsa-mir-124-3p, hsa-mir-155-5p) [76, 77], and different chronic cancer (e.g., hsa-mir-1-3p, hsa-mir-29a-5p, hsa-mir-142-3p) [78–81]. Gene-TFs and gene-miRNAs basically target main proteins to change the appearance in the progress of particular diseases. Hsa-mir-195-5p, hsa-mir-128-3p, and hsa-mir-129-2-3p target IL6 in these studies [74, 82]. Furthermore, hsa-mir-941, hsa-mir-374a-5p, hsa-mir-17-3p, and hsa-mir-129-2-3p are targeted by the FLNC [82, 83]. Remarkably, we also predicted four miRNAs (hsa-mir-16-5p, hsa-let-7e-5p, hsa-mir-26a-5p, and hsa-mir-146a-5p) that are associated with different genes of IFN and COPD [71]. Most of the miRNAs are related to cancer tissue and lead to the different types of cancer in the human body, especially lung cancer.

We performed a gene–disease (GD) analysis to predict the association of significant DEGs and different diseases. The experiment’s outcome shows the various types of diseases involved in COVID-19, including the brain, cardiac, blood, liver, skin, and different kinds of lung cancer. For example, we found some genes associated with brain diseases, such as schizophrenia, seizures, and glioma. Schizophrenia is the most risk factor for dying from COVID-19. Recent research had proved that persons with a psychiatric disorder, particularly depression and schizophrenia—a condition that reasons distortions in thinking and perception—had a high risk of becoming infected by SARS-CoV-2, the virus that causes COVID-19. We found multiple myeloma (MM) from our GD network; it is a cancer of white blood cells and responsible for weakening the immune system. Recently, the author analyzed the outcome of COVID-19 infection in MM patients [84]. We also found some skin diseases such as dermatitis, exanthema, erythema, psoriasis, and eczema from our network analysis. Recently, skin disease was reported in Italy with COVID-19 or SARS-CoV-2 infection in patients [85]. Side effect made by SARS-CoV-2 infection is a reason for increasing the itch in skin disease [86]. Moreover, a study reports that 2–11% of COVID-19 patients had primary chronic liver disease [87]. During the SARS epidemic in 2002–2004, almost 60% of patients were reported to grow different stages of liver injury [88]. The involvement of hepatic in COVID-19 is directly associated with the cytopathic effect of the virus, an abandoned immune response, drug-induced liver damage. Based on the clinical bulletin of ACC (American College of Cardiology), the death ratio of COVID-19 patients is higher.
Figure 9. The gene-disease association network represents diseases associated with mutual DEGs. The disorder depicted by the square node and also its subsequent gene symbols is defined by the circle node.

with previous disorders such as hypertension (6.0%), cancer (5.6%), diabetes (7.3%), and cardiovascular diseases (10.5%) \[89–91\]. Besides, 16.7% of patients face arrhythmia, and 7.2% developed acute cardiac problems with COVID-19-associated complications \[89\]. Cardiovascular injuries may reason for various mechanisms, including systemic inflammation and ischemia \[92\]. Here, we extracted several potential genes engaged in various cardiovascular disorders and some potential genes involved in diabetes mellitus-1. The current report shows that patients who died with COVID-19 infection were affected by different diseases such as chronic lung disease, diabetes, cardiovascular disease, and hypertension \[93, 94\].

Before, several chemical agents and drugs have been used as potential therapeutic against COVID-19. As an example, chloroquine and remdesivir have been testified to prevent SARS virus and COVID-19 \[95\]. Furthermore, favipiravir performed well to protect against Japanese flu and indicated a significant protective effect against COVID-19 \[96\]. Moreover, a clinical trial indicated a significant effect of hydroxychloroquine and azithromycin against COVID-19 by stopping the genomic replication \[97, 98\]. We identified Curcumin, which is used for disease relating to inflammation. The inflammation indicates the body mechanisms of protection against infections, toxins, and injuries \[99\]. The human body releases some chemicals from the immune system to protect the damaged cells.

Another extracted drug was Chromium, which is applied for controlling blood sugar with prediabetes in people, diabetes-1, and 2 \[100\]. The drug toxin that can be reason lung cancer and skin diseases. Another identified drug is Triclosan, which is an antifungal and antibacterial agent \[101\]. Moreover, Ellipticine, Tamoxifen, and Deguelin are also found as potential drugs in this study. Ellipticine is isolated from plants and shows promising performances for handling the different types of cancer, such as breast cancer, brain tumors, blood cancer (acute myeloblastic leukemia), and kidney cancer \[102, 103\]. Tamoxifen \[104, 105\] and Deguelin \[106, 107\] also used to decrease the chances of cancer in risk patients. The medication of those drugs can block the development of cancer. Besides respiratory disease, a wide
range of diseases is involved in COVID-19 infection, including renal, blood-related problems, cardiac [108, 109], brain, and different types of cancer [110]. Therefore, those can be treated for COVID-19 infection.

Conclusions

Our study has summarized the relations among these three disease genes in the context of transcriptomic analysis on IPF, COPD, and COVID-19. We have done DEGs among three datasets and identify the common genes and find out the disease responses between IPF, COPD, and SARS-CoV-2 affected lung cells. The bioinformatics analysis discloses that the IPF and COPD patients have a high risk to infect by SARS-CoV-2. So we have faced 65 common interrelated genes of these datasets. Then the common 65 genes were utilized obtained the PPI network, and we identified the 10 most significant hub genes from the PPI network. Multiple drug molecules and drug-target interactions are suggested from hub genes retrieve through the DSigDB database. Analyses among IPF, COPD, and COVID-19 indicate a way of identifying infections for various diseases. Therefore, it is possible to mitigate IPF and COPD patients’ risk of being affected by SARS-CoV-2. COVID-19 is a recently discovered disease; there have not much research on the risk factors and disease. Adequate analysis of COVID-19 is more important with the availability of the above datasets. Currently, there is some vaccine available for the prevention of COVID-19. But these vaccines are not showing effective in some cases, especially for different variants of SARS-CoV-2. Still, the scientific community is focusing on developing a more effective vaccine for the treatment of COVID-19. Therefore, we implemented transcriptomic analysis to detect common pathways and molecular biomarkers in IPF, COPD, and COVID-19 that help understand the linkage of SARS-CoV-2 to the IPF and COPD. Ten hub proteins were identified as involved in these diseases. All these hub genes play vital roles in different functional mutations. The identified TFs and miRNAs are associated with different types of respiratory diseases. So, our identified genes can be a novel therapeutic target for COVID-19 vaccine development.

Key Points

- The IPF and COPD had some significant common genes compared with the COVID-19 to assess the distinct genetic mechanism involved.
- Gene set enrichment-based analysis predicts Gene ontology terms for among IPF, COPD, and COVID-19–affected lung cells, and hub gene identification makes the prediction of drug compounds even more useful.
- Protein–protein interactions network-based analysis helps determine the definite genes related to IPF, COPD, and COVID 19. It can lead us to their coexpression partners about normal and disease states and assess risk factors.
- TFs–genes interaction and DEGs–miRNAs coregulatory network with common DEGs also identified on the datasets to find the transcriptional and posttranscriptional regulators of the common DEGs.
- The protein–drug interactions suggested 10 potential chemical compounds against COVID-19.

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