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Systems biology models to identify the influence of SARS-CoV-2 infections to the progression of human autoimmune diseases

Md Al-Mustanjid a, S. M. Hasan Mahmud b,**, Farzana Akter a, Md Shazzadur Rahman c, Md Sajid Hossen a, Md Habibur Rahman d, Mohammad Ali Moni e,*

a Department of Software Engineering, Faculty of Science and Information Technology, Daffodil International University, Dhaka-1207, Bangladesh
b Department of Computer Science, American International University-Bangladesh, Dhaka, 1229, Bangladesh
c Department of Computer Science & Engineering, Faculty of Science and Information Technology, Daffodil International University, Dhaka-1207, Bangladesh
d Department of Computer Science and Engineering, Islamic University, Kushtia-7003, Bangladesh
e Department of Computer Science and Engineering, Palma Science & Technology University, Palma, 6600, Bangladesh

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been circulating since 2019, and its global dominance is rising. Evidences suggest the respiratory illness SARS-CoV-2 has a sensitive effect on causing organ damage and other complications to the patients with autoimmune diseases (AD), posing a significant risk factor. The genetic interrelationships and molecular appearances between SARS-CoV-2 and AD are yet unknown. We carried out the transcriptomic analytical framework to delve into the SARS-CoV-2 impacts on AD progression. We analyzed both gene expression microarray and RNA-Seq datasets from SARS-CoV-2 and AD affected tissues. With neighborhood-based benchmarks and multilevel network topology, we obtained dysfunctional signaling and ontological pathways, gene disease (diseasome) association network and protein-protein interaction network (PPIN), uncovered essential shared infection recurrence connectivities with biological insights underlying between SARS-CoV-2 and AD. We found a total of 77, 21, 9, 54 common DEGs for SARS-CoV-2 and inflammatory bowel disorder (IBD), SARS-CoV-2 and rheumatoid arthritis (RA), SARS-CoV-2 and systemic lupus erythematosus (SLE) and SARS-CoV-2 and type 1 diabetes (T1D). The enclosure of these common DEGs with bimolecular networks revealed 10 hub proteins (FYN, VEGFA, CTNNB1, KDR, STAT1, B2M, CD3G, ITGAV, TGFB3). Drugs such as amlodipine besylate, vorinostat, methylprednisolone, and disulfiram have been identified as a common ground between SARS-CoV-2 and AD from drug repurposing investigation which will stimulate the optimal selection of medications in the battle against this ongoing pandemic triggered by COVID-19.

1. Introduction

COVID-19, commonly known as SARS-CoV-2, is a highly contagious viral respiratory infection that swept over the world. It has gotten even worse, infiltrating people’s lungs most and rapidly weakening their immune systems. Several health issues associated with COVID-19 emerged over time and AD is the most common of them. AD is a form of disease where the body’s immune system mistakenly attacks healthy tissue [1]. COVID-19 patients with AD have experienced respiratory problems and organ damaging issues. Patients infected with COVID-19 who already have AD are more at risk as SARS-CoV-2 and AD have characteristics and parthenogenesis in common [2,3]. So, we explored the correlations between SARS-CoV-2 and AD including IBD, RA, SLE and T1D, in view of the fact that these are the most widespread and jeopardizing to humans.

IBD refers to two disorders (Crohn’s disease and ulcerative colitis) that are characterized by significant inflammation in the gastrointestinal system, according to the Crohn’s & Colitis Foundation of the United States [4]. The most recent SARS-COV-2 strain has spread quickly to areas where IBD is more widespread, revealing a growing risk of infection in IBD patients [5]. COVID-19 has also considered hazardous in IBD patients as the aqueous version of ACE2 is thought to perform as a strong cofactor for SARS-CoV-2, protecting viruses and inhibiting them from adhering to the cellular full-length ACE2 protein [6]. Respiratory


2. Methodology

2.1. Datasets employed in this study

Since multiple observational experiments have already shown that people with AD are at elevated risk of COVID-19 intervention. Both RNA-seq, the outcome of rapid advancements in nanotechnology and conventional microarray based gene expression analysis are extensively used and efficient tools for evaluating and assessing viral infections at the molecular scale [17,18]. To figure out the complex molecular effects and correlations alluded to SARS-CoV-2 and AD, both microarray and RNA-Seq datasets were retrieved from the Gene Expression Omnibus (GEO) database of the National Center for Biotechnology Knowledge (NCBI) [19]. The RNA-Seq dataset [20] of SARS-CoV-2 (GEO Accession: GSE147507) is a gene expression profiling of COVID-19 lung biopsy in reaction to respiratory illnesses with 30 control groups and 80 disease samples utilizing high throughput sequencing on the Illumina NextSeq 500 platform. The AD dataset (GSE Accession: GSE59071) is a microarray dataset consisting of 11 controls and 105 disease samples obtained from AD patients who received biopsies in the most affected regions but far from ulcerations [21]. Then microarray analysis was carried out on the U133A Array platform between 20 control and 59 disease groups using a rule-based classification in the RA dataset (GSE Accession: GSE55457) [22]. The SLE dataset (GSE Accession: GSE81622) was a gene expression profile of peripheral blood mononuclear cells from 25 healthy controls and 30 SLE patients with HumanHIT-12 Beadchips and Illumina Human Methy450 chips [23]. The T1D dataset (GSE Accession: GSE106148) was analyzed residual beta cells and alpha cells persisting in the islet endocrine compartment from 5 healthy controls and 3 T1D patients; this high throughput sequencing experiment was performed on Illumina HiSeq 2500 platform [24]. Fig. 1 illustrates a general overview of the work process obtained in this study.

2.2. Data preprocessing and identification of differentially expressed genes

This study obtained both RNA-Seq and microarray datasets from the NCBI’s GEO. When there is a statistically relevant discrepancy between multiple experimental conditions at the transcription phase, a gene is classified as expressed differently. We normalized the gene expression data incorporating control state and disease state by applying Z-score transformation (Zq) for each dataset to prevent experimental complications; this conversion enables direct comparison of the values of gene expression of different diseases on different platforms.

\[ Z_q = \frac{g_{ij} - \bar{X}}{\sigma_i} \]

where \( \sigma_i \), initiates the standard deviation and \( g_{ij} \), indicates the gene expression magnitude in sample j. This modification enables clear and simple measurements of gene expression traits and morbidity. For evaluation of selectively expressed genes in patients compared to normal samples, unpaired T-test static was included. In order to perform the dataset analysis, R programming language environment and Bioconductor packages were selected. We normalized datasets by log2 transformation and utilized the statistical strategy using the R package Linear Models for Microarray Data (Limma) [25] with Benjamini-Hochberg correction to control the level of false discovery rate. Subsequently, high throughput sequencing datasets were analyzed centered on the negative binomial distribution to classify gene expression data using DESeq2. Based on the standard statistical criteria, a threshold of at least 1 log2 fold change (logFC) and an Adj. p-value of 0.05 \( (\text{Adj. } p \text{-value} < 0.01 \text{ and } \logFC > 1.0) \) was followed to extract significant DEGs. Cutoff conditions \( (\text{Adj. } p \text{-value} < 0.01 \text{ and } \logFC > = 1.0) \) for up-regulated genes and other criteria \( (\text{Adj. } p \text{-value} < 0.01 \text{ and } \logFC <= -1.0) \) for down-regulated genes were selected. From each dataset, gene symbols as well as names were extracted to continue further analysis; empty or incomplete gene symbol records were eliminated from each disease dataset. To locate common DEGs that each AD shares with SARS-CoV-2, a Venn analysis was performed using the web tool Jvenn [26].

2.3. Identification of ontological terms and enriched pathways

Gene ontology (GO) and pathway enrichment test was undertaken using Enrichr (https://maayanlab.cloud/Enrichr/) – a robust gene set enrichment web tool [25] to get more insights into functional biological terms and signal pathways interleaved between SARS-CoV-2 and AD. Gene set enrichment analysis is a key empirical task to reveal hidden biological insights, such as biological processes or chromosome
locations affiliated with different closely linked diseases [27]. GO as well as functional process was explored into three categories: biological process, cellular component, and molecular functions and 4 pathway databases: KEGG [28], Wiki [29], Reactome [30], Bio Carta [31] were considered for pathway analysis.

2.4. Gene disease association network

Diseases are correlated to each other when at least one significantly dysregulated gene is shared by diseases among themselves [32]. In order to determine correlations among SARS-CoV-2 and AD, we employed neighborhood benchmarking and topological strategies to place a gene-disease association network (GDAN). As a result of the process, we generated a GDAN utilizing Cytoscape (version 3.7.1) to presume and determine correlations among SARS-CoV-2 and AD, we employed neighborhood benchmarking and topological strategies to place a gene-disease association network (GDAN). As a result of the process, we generated a GDAN utilizing Cytoscape (version 3.7.1) to presume and determine correlations among SARS-CoV-2 and AD. For this analysis, we regarded a collection of human diseases labeled by D and a set of human genes also labeled by G to seek out whether there is an attachment or presence of a gene g ∈ G with the disease d ∈ D.

Besides, we consider that if Ga and Gb have the association of disease Da or Db with the substantial up and down-regulated genes respectively, then the amount of shared dysregulated genes (na,b) associated with both diseases Da and Db is quantified; the following estimation is defined as follows [17]:

\[ n_{ab} = N(G_a \cap G_b) \]  

(2)

Jaccard coefficient methods [24] were employed to recognize shared neighbors and co-occurrence is the number of common genes between two diseases in the GDAN

\[ E(a, b) = \frac{N(G_a \cap G_b)}{N(G_a \cup G_b)} \]  

(3)

2.5. Protein-protein interaction network analysis

PPIN is central to all cell functions as they resemble the physical interactions between two or more protein entities. We utilized STRING (https://string-db.org/) (version 11.0)-a web platform and database to build PPIN network of proteins encoded from our shared DEGs as STRING provides insights into PPIN leveraging active channels of interaction which includes text mining, experimental databases, co-expressions, culture, gene fusions, and co-occurrences [33]. In the STRING, PPIN network can be built with different confidence scores and means of topological analysis is a convenient technique for recognizing its biological importance. Concerning topological analysis, we concentrated on the centrality analysis of our PPIN derived from shared DEGs. Topological analysis was conducted by Network Analyzer-a built in Cytoscape plugin and NetworkAnalyzer is a useful platform that quantifies and demonstrates a wide range of topological parameters such as node count, centralization, and so on [26]. Closeness centrality metric was applied to determine how rapidly data will flow from one node to another and also measured shortest paths [36] between nodes following equation (2).

\[ CC(a) = \frac{N - 1}{\sum_{b=1}^{N} d(a, b)} \]  

(4)

where a and b imply node, da,b is the length of the shortest paths between nodes a and b in the network and N is the number of nodes. Betweenness centrality base depends largely on the communication flow of nodes in the network; the node with the maximum betweenness centrality is essentially in the transmission path and therefore can simultaneously regulate the flow of information. Besides that, the node with the most betweenness centrality represents proteins that are involved in signaling pathways that ultimately influence drug target prediction as well as a therapeutic design [22] following equation (3).

\[ C_b(n_i) = \sum_{j,k} g_{jk} (n_i) / g_{jk} \]  

(5)

where gjk is the number of shortest paths connecting jk and gjk(ni) is the number that node i is on.

The most interconnected proteins known as hub proteins in PPIN have determined based on topological parameters (degree ≥ 15). Subsequently, topological analysis of hub proteins was performed to delve more into their biological significance.

2.6. Identification of transcription factors and miRNAs

To hold on to insights into regulatory molecules such as transcription factors (TFs) and miRNAs at the transcriptional and post-transcriptional level which regulate with shared DEGs, we have analyzed both DEGs-TFs and DEGs-miRNAs interaction networks via NetworkAnalyst-a comprehensive web portal for meta-analysis of gene expression data and insights into metabolic processes, activities, and understandings [37]. The NetworkAnalyst has a filtering function feature that allows users to construct interaction networks related to a specific tissue’s intent, so we chose the lung tissue as the root of our two disease origins. DEGs-TFs interaction network originated from the Jasper database, while DEGs-miRNAs interaction network was derived from the mirTarbase and Tarbase databases. JASPAR is a widely open directory of TFs profiles from various species across six taxonomic groups [38] and the foremost exploratory validity resources for miRNAs-target gene

Fig. 1. The overall workflow of the proposed methodologies.
interactions are Tarbase and mirTarbase [39]. To give a boost to visibility and appearance, both DEGs-TFs and DEGs-miRNAs interaction networks were incorporated into Cytoscape (v.3.7.1).

2.7. Drug repurposing analysis

Specific drugs for the proper treatment of SARS-CoV-2 have not yet been found, and researchers from all around the globe are working tirelessly to discover a cure for COVID-19 so that the world can be rid of this dreadful pandemic. Drug repurposing, also known as repositioning, is a scientific approach to testing current accessible drugs against diseases other than those for which they were developed, in order to cut costs and time in the formation of new drugs. To repurpose the drugs of AD and SARS-CoV-2 interconnected with individual and shared genes, we utilized a transcriptomic-based computational drug repurposing process that will eventually take the ongoing SARS-CoV-2 drug placement one step further. L1000CDS2 (https://maayanlab.cloud/l1000cchs2/#/index) is a drug repurposing web tool developed by Ma’ayan Lab using the L1000 dataset [40,41]. For acquiring the shared drugs, we submitted our list of common up and down regulated DEGs shared by AD and SARS-CoV-2 to L1000CDS2; we have also uploaded list of up and down regulated DEGs of each AD and SARS-CoV-2 in order to obtain drugs for individual disease. After submitting the list of up and down regulated DEGs to L1000CDS2, the tool has returned the top 50 drug findings, which are ranked in descending order based on the overlap of genes between the input and tested signatures weighted by the actual input (intersection of input genes and L1000 genes). From the returned top 50 drug list, we chose drugs that were unique with an overlap or inhibition score close to 1 (100%) and also had accessibility in Drugbank-a web-based repository for keeping detailed molecular information on drugs, their mechanisms, interactions, and targets [42]. Before moving on to additional studies with this drug list, it is necessary and vital to examine other elements of drugs such as structural score, as well as harmful side effects [41]. We retrieved the SMILE (Simplified molecular-input line-entry system) format of our listed drugs from drugbank and used the SMILE format to evaluate each drug’s structural score employing SwissADME (http://www.swissadme.ch/index.php) - Systems and processes such as BOILED-Egg, iLOGP, and bioavailability locator are part of the SwissADME online service, which gives free exposure to a collection of swift but powerful prediction models for physicochemical characteristics, pharmacokinetics, drug similarities, and medicinal chemistry compatibility [43]. Lipinski’s rules’ violations are followed and applied to measure the structure and the more rules a drug violates the less structural score it receives. We used SIDER (http://sideeffects.embl.de/) - an online platform that captures and keeps information about adverse reactions to drugs including side effect frequency, drug and side effect classifications, and connections to additional information on the marketplace gleaned from public documents and package instructions to determine each drug’s side effect score [41]. We listed the side effects and label percentage score of each drug retrieved from SIDER. Further analyses were discarded for drugs with a higher structural score (1 ≤ structural score) and no side effect score or both. 

3. Result

3.1. Gene expression analysis and mutual DEGs identification

When a gene behaves differently from its normal form, it is recognized as DEGs. The gene expression analysis was conducted to distinguish significant and common DEGs that are shared by SARS-CoV-2 and AD, paving the way for a molecular investigation of the relationship between SARS-CoV-2 and AD. We used the R language environment and the limma package to assess both microarray and RNA-Seq datasets from NCBI GEO counting on quantitative parameters. According to the analysis, based on significant terms (Adj. P-value < 0.01 & \(|\logFC|\geq1\)) 620 genes were differentially expressed, with 112 genes up-regulated and 508 genes down-regulated for SARS-CoV-2 response. In the same way, 705 DEGs (519 up-regulated and 186 down-regulated) for IBD, 472 DEGs (250 up-regulated and 222 down-regulated) for RA, 68 DEGs (19 up-regulated and 49 down-regulated) for SLE, 1399 DEGs (580 up-regulated and 819 down-regulated) for TID. The overall gene expression analysis is depicted in Table 1. Besides that, using the Jvenn tool, cross-comparison analysis revealed common DEGs between each AD and SARS-CoV-2; the Venn diagram depicted in Fig. 2 shows the overall common DEGs assessment. We found that SARS-CoV-2 shares 77, 21, 9, 54 DEGs with IBD, RA, SLE, and TID, respectively. Moreover, we also found that AD shares 15, 1, and 6 significantly up-regulated DEGs for the IBD, RA, and TID whereas 10, 3, 2, and 25 significantly down-regulated genes for the IBD, RA, SLE, and TID respectively. SARS-CoV-2 and SLE have not shared any up-regulated DEGs among them.

3.2. Identification of ontological terms and enriched pathways

Enrichr was utilized to obtain understanding across ontological terminologies and enriched pathways that are commonly expressed by each AD and SARS-CoV-2. An ontology is a collection of procedures that characterize a body of knowledge in a particular sense. GO takes in gene mechanisms and their attributes to include a broad variety of computational knowledge tools. In addition, ontology also encompasses a model of a biological structure, which is useful in biological applications [44]. The GO study was divided into three functional sections (biological process, cellular component, molecular function) with annotations originating from the GO database. The top 10 biological terms of each functional section are summarized in supplementary Table I Pathways are essential to stimulus-response in cells, and pathway-based assessment is a newly formed framework for understanding how diverse disorders can be coupled by their corresponding molecular pathways to each other [45]. Pathways were extracted using the Enrichr once more to obtain insight into SARS-CoV-2 and AD complications using four different pathway databases as origins. Both overly represented pathways and ontological terms were discarded; pathways and terms that fulfilled the preceding metric (P-value ≤ 0.05) were listed to get hold of significant pathways. The significant pathways shared between each AD and SARS-CoV-2 are listed in supplementary Table II.

3.3. Identification of gene-disease association

We have already perceived from our cross-comparison investigation that SARS-CoV-2 shares significantly up and down-regulated DEGs with AD. The following are the most important up-regulated genes: (a) STAT1, HLA-DQA1, RNF213, PARP9, IFITM2, MX2, ZBP1, SAMD9L, IFI6, OAS2, LOXL2, KNYU, SELL, LAMP3, MLKL originating from the GO database. The top 10 biological terms of each functional section are summarized in supplementary Table I Pathways are essential to stimulus-response in cells, and pathway-based assessment is a newly formed framework for understanding how diverse disorders can be coupled by their corresponding molecular pathways to each other [45]. Pathways were extracted using the Enrichr once more to obtain insight into SARS-CoV-2 and AD complications using four different pathway databases as origins. Both overly represented pathways and ontological terms were discarded; pathways and terms that fulfilled the preceding metric (P-value ≤ 0.05) were listed to get hold of significant pathways. The significant pathways shared between each AD and SARS-CoV-2 are listed in supplementary Table II.
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3.4. Protein-protein interaction network (PPIN) analysis

Proteins are the foundation blocks of our bodies that enable us to function at maximum capacity. We have used STRING—a web resource to explore the PPIN triggered by our collective common DEGs of AD and SARS-CoV-2, then the network brought into Cytoscape for additional sub-module analysis. When two or more diseases share commonly associated protein subnetworks, they are considered to be interconnected [46]. As shown in Fig. 5, the PPIN is constituted of 103 nodes and 388 edges. Then topological analysis was determined by the NetworkAnalyzer feature in Cytoscape and the most significant as well as highly interacting proteins are extracted which is also known as hub gene. Fig. 6 elucidates the generalized and more summarized sub-network of PPIN. This sub-network highlights the inclusion of existing and relevant functional pathways in our enriched gene sets, which would be helpful for therapeutic goals in the long run. The overview of hub proteins is put on view in Table 2.

3.5. DEGs-TFs and DEGs-miRNAs interaction network analysis

TFs are the proteins of gene expression in all living organisms that regulate at the transcription level which plays a vital role in the cellular process. Again, miRNAs are the short RNA species involved in the post transcriptional level [65]. To get comprehensions into regulatory elements shared mutually by each AD and SARS-CoV-2 at the transcriptional and post-transcriptional level, we analyzed both DEGs-TFs interaction networks as shown in Fig. 8 and DEGs-miRNAs interaction network via NetworkAnalyst as shown in Fig. 7.

3.6. Identification of repurposed drugs

Drug repurposing is the process of using drugs that have been approved for use in other diseases, and it is particularly useful for speeding up and lowering the cost of silico drug repurposing since it lists the numerically ranked ranking of re-established drugs for the diseases. To get additional insight into drug discovery, drug repurposing studies have already been conducted on other illnesses such as Alzheimer’s, small cell lung cancer, breast cancer, and so on [66]. The utilization of drug repurposing for AD and SARS-CoV-2 is essential since it might lead to major interconnections between the diseases and existing drugs, as both ad and covid have shared underlying mechanisms. We have come across 4 drugs namely amlodipine besylate, vorinostat, methylprednisolone and disulfiram shared between SARS-CoV-2 and IBD, 2 drugs namely glimepiride and finasteride between SARS-CoV-2 and TID; vorinostat was commonly found for IBD and RA. The founded drugs are listed on Table 3. Further analysis was conducted on those initiated drugs.

4. Discussion

SARS-CoV-2 has a considerable susceptibility of inducing respiratory difficulties and organ dysfunction in AD patients. Similarly, people with severe lung conditions are more likely to be infected with COVID-19, and patients with AD often experience shortness of breath. In this study, a methodology is formulated to investigate the quality verbalization plans from two types of datasets (one is RNA-Seq and another one is microarray) of COVID-19 patients and AD; distinguished sub-atomic focuses that may help as possible biomarkers shared between SARS-CoV-2 and AD. It could likewise give significant data about their impacts on arising explicit illnesses or conditions. Articulation profiling by high throughput sequencing datasets is utilized in biomedical and system biology research has become a crucial asset for recognizing biomarker applicants of various illnesses. We uncovered common DEGs associated with SARS-CoV-2 and AD through investigating microarray and RNA-Seq datasets. Essentially, these significant common DEGs were required to assess further experiments in this study.

GO refers to the ‘Gene Ontology’ is an enormous bioinformatics project that looks to normalize the depiction of gene and gene items ascribed to all living beings. One of the key functions of the GO is to do improvement research on consistency sets. It evaluates progressively by knowing biological terms about gene activities and their synchronizations of several metaphorical elements [44,67,68]. Enrichr was used to evaluate three types (biological process, cellular component, molecular function) of functional enrichment with our common DEGs. IBD and SARS-CoV-2’s pathological features have driven out that ECM was responding highly in both diseases [60,61]. As per the authors in Ref. [69], SARS-CoV-2 infection could exacerbate angiocentric inflammation in COVID-19 induced respiratory failure. Again, it was observed that angiogenesis in COVID-19 patients is rapid and huge; further investigation is necessary to clarify how intussusceptive angiogenesis hinders COVID-19 therapeutic efficacy [70].

![Fig. 2. Venn graph reflects the distribution of common DEGs among SARS-CoV-2 and AD.](image-url)
with immune cells modifies mitochondrial functions in host cells and generates a responsive intracellular environment for viral replication in infected cells, which may lead to disease progression in COVID-19 cases [71]. The pathogenesis of COVID-19 has been tied to elastic fiber pathologies as well as vitamin K deficiencies, which may contribute to the discovery of the missing piece between lung damage and thrombogenicity [72]. During the COVID-19 disease outbreak, it was realized that interferon-alpha response was closely linked with COVID-19 infection in terms of determining clinical, pathologic, and laboratory characteristics in patients with chilblain-like lesions [73]. Histidine has a significant impact on SARS-CoV-2 infection on serum amino acid levels, according to metabolomics studies, and tends to decrease, particularly in the moderate-high IL6 group [74]. Responsive and intrinsic immune responses were shown to be involved and modulated endothelial cell proliferation in SLE and RA diseases [75]. In the cellular component (gene regulates function), SARS-CoV-2 and its spike protein are specifically accountable for accelerating platelet activity, particularly alpha granule [76,77]. The authors in Ref. [78] recommended further investigations into MHCII alleles as it has recognized as emerging COVID-19 risk factors. COVID-19 T cell receptor assemblies sequenced by Next-Generation sequencing gained crucial insight into SARS-CoV-2 adaptive immunity, and the authors in Ref. [79] delivered a much-needed resource for the scientific world to bring up to date clinical principles and vaccine production. From the molecular function observations, it has been found that the irregularity of the tyrosine kinase receptor (TKR) family and its signaling mechanisms are closely aligned to a significant percentage of diagnosed cancers. According to the study [80] of interference between SARS-CoV-2 and tyrosine kinase receptor signaling in cancer, propositioning of clinically formulated anti-TKR cancer drugs in COVID-19 as therapeutic agents could be useful for treating various types of cancer. Phosphoinositide 3-kinase was inhibited in the first phase of canonical and non-canonical autophagy of SARS-CoV-2 at a nano-molar level that could be a forthcoming focus for the treatment of COVID-19 [81]. The defensive action towards COVID-19 at various levels is required to include zinc chelating agents such as citrate and ethylenediaminetetraacetic acid (EDTA) alone or in conjunction [82]. Any use of chemical compounds including MG132, epoxomycin, and bortezomib to constrain the proteasome helps to trim down virus entry into eukaryotic cells and hence the necessity for SARS-CoV-2 protein expression [83]. Proportionally, proteasome inhibitors could open up new prospects for the treatment of SARS-CoV-2.

In bioinformatics, pathway inspection approaches may be castoff to identify key proteins within a previously defined pathway based on a complex obsessive disorder or to rebuild a pathway from proteins that have been identified as key affected components. Pathway analysis is the systematic opportunity to review an organism’s reactions to internal modifications [32]. SARS-CoV-2 responded about T cell (cTFH) activation and it worked against SARS-CoV-2 spikes to recover patients [84, 85]. Relatedly, T cell activation is capable of controlling the AD and T-cell co-stimulatory pathways are actively evolving in IBD [86-88]. Then again, IL6 signaling pathway can be accelerating the treatment of SARS-CoV-2 and it has provisory intention towards another disease in...
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RA [89, 90]. LCK and Hub protein FYN tyrosine kinases in the initiation of the T cell receptor activation pathway are very much responsive to SARS-CoV as well as considerably affected in SLE [91, 92]. The impact of pertussis toxin-insensitive CCR5 signaling pathway in SARS-CoV-2 is astonishing and can play an effective character in SARS-CoV-2 treatment [93]. Nevertheless, CCL5 levels were lower in remitters and positively correlated with HbA1c, indicating a Th1-related development of the T1D [94,95].

From the PPIN, we attained the most interacted genes also known as hub proteins. Kinase inhibitors are the major substance of human body that control functioning, cell signaling and many other processes. Recent studies have discovered FYN to be a prominent kinase inhibitor and a therapeutic target for COVID-19 in order to manage the infectious life cycle and mitigate lung-damaging signs of illness [47,48]. Clinically pro-inflammatory cytokine IL-6 was shown functioning at an elevated concentration in the pathophysiology of COVID-19 [47,51]. FYN, one of the hub proteins, initiates a phosphorylation immunoreceptor motive of tyrosine-based motivation, eventually leading to the release of IL-6 proinflammatory cytokines. The use of IL-6 antagonists like Tocilizumab during the COVID-19 drug trial has been evidenced in this IL-6 overproduction [49]. FYN activity was found to be quite high in CD4+ T cells from SLE patients, according to Anna Kozlowska and his team [50]. In addition, the tyrosine-protein kinase ITK, which promotes cytokine production, was shown to be substantially elevated in CD4+ T cells from SARS-CoV-2 patients with gastric cancer. SARS-CoV-2 infection pathogenesis evaluation has uncovered how cytokine storm plays a critical part in COVID-19 treatment, and ITK suppression has been proposed as a viable therapeutic option against COVID-19 [47].

Authors in Ref. [51] found high levels of ACE2 expression in endothelial cells as a major participant and regulator of SARS-CoV-2 as well as inflammatory responses. While VEGFA has already been implicated in endothelial stimulation and dysfunction, it has also been attained up-regulated VEGFA in infected lungs in patients who have died of COVID-19. Authors also speculated that therapies aiming signaling pathways generated by VEGFA might be more prosperous for COVID-19. The level of enrichment of VEGFA in AD has been highly observed and targeting this biomarker might make available more insights on the challenges and activities of AD patients [52]. Likewise, VEGFA interfering pathway with SARS-CoV-2 spike protein has already been detected to interact with pain signals and destabilization of the VEGFA signaling pathway boosts neuropathic pain [47]. Shrinking consistency of the KDR known as vascular endothelial growth factor receptor 2 (VEGF2) might well be connected to the development of COVID-19 and also leading to pathogenesis [55]. In RA interpretation, a higher KDR serum was noticed that has several actions progressing to RA [56]. In monocyte-derived dendritic cells, the SARS-CoV-2 has opened a diminished interferon response, and therefore this lessened immune response to SARS-CoV-2 is aligned with viral antagonism of STAT1 phosphorylation [57]. It was assumed that a catastrophic cascade of failures was led by COVID-19 pathophysiology which is initiated by NSP1 and ORF6 proteins -the gene products of SARS-CoV-2. Afterward, these molecules provoke STAT1 malfunction as well as accomodative STAT3 hyperactivation; the study [58] has also alluded that maximization of STAT1 activity and restriction of STAT3 functions might well be undermined the worsening STAT3 cycle that is indispensable to COVID-19. In SARS-CoV-2 infected cells, STAT1 was also involved in regulation [56]. CTNNB1 was a cytotoxin and gene control target of miRNAs encoded from SARS-CoV-2 [53]. The propensity of MALAT1’s to suppress fibroblast-like synoviocyte proliferation and inflammation by fostering CTNNB1 promoter methylation and retardation the Wnt signaling pathway could be used as a diagnostic biomarker for RA [54]. Further, the gene B2M was shared by all AD [57]. The authors emphasized that the level of B2M should be closely monitored in COVID-19 patients because the tier of IL-6 somehow doesn’t significantly decrease during treatment with Tocilizumab—an immunosuppressive medication employed to combat RA and systemic juvenile idiopathic arthritis and that it’s been recommended as a promising biomarker in the advancement of a treatment strategy for Tocilizumab. Ivermectin, an anti-parasite medicine that received FDA approval, can significantly avert the reproduction of SARS-CoV-2 in vitro, and B2M

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**Fig. 4.** Down-regulated gene-disease association network (GDAN) between SARS-CoV-2 and AD; the common down-regulated gene nodes are distinguished by light green color in the shape of circle node which is interlinked to different types of disease nodes symbolized by red color in the shape of hexagon node.

**Fig. 5.** Protein interaction network (PPIN) of common DEGs between SARS-CoV-2 and AD. The hexagon nodes stand for top most interacted genes, whereas circle nodes symbolize DEGs and edges constitute interactions between nodes. The PPI network includes 103 nodes and 388 edges. String was utilized to obtain this PPIN network and then conceptualized in Cytoscape.
was claimed to be regulated by Ivermectin [98]. Again, from the analysis of peripheral blood immune cells in COVID-19 patients [61], it was unearthed that the CD3G hub gene had a downregulated expression level in the cluster of blood immune cells known as CD4+ and CD8+. Both cells are also associated with COVID-19 patients with gastric cancer [47] and AD disease activities [50]. Following low-density lipoprotein particle receptor pathway activity in transcriptome study, ITGAV gene expression was found downregulated in COVID-19 patients [62]. ITGAV is integrins and integrin signals related gene; ITGAV was unpredictably expressed at a very high level in the lungs, signifying that it was more vulnerable to assaulting lung cells than other cells of the respiratory tracts and nasopharynx, according to an analysis of the transcriptome of COVID-19 patients with nasopharyngeal samples and other SARS-CoV-2 infections [97]. Most lung diseases are caused by oxidative stress, and TGFB3 was attained to be a target for lung damage and recovery [63].

### Table 2
An overview of hub proteins derived from PPIN.

| Hub Gene | Degree | Closeness Centrality | Betweenness Centrality | Remarks                                                                 | Ref     |
|----------|--------|----------------------|------------------------|-------------------------------------------------------------------------|---------|
| FYN      | 25     | 0.52406417           | 0.29810382             | Considered as key kinase inhibitor and medicinal targets for COVID-19 remedy; engaged in the release of the proinflammatory cytokines, therefore leads to the initiation of COVID-19; found highly occupied in CD4+ T cells from SLE patients and connectivity with COVID-19 therapeutics. | [47–50] |
| VEGFA    | 22     | 0.46666667           | 0.11766869             | Stayed upregulated in lung infected patients who have died from COVID-19 and recognized as conceivable therapeutic target for COVID-19 treatment; acquired highly enriched in AD activities and severity. | [51,52] |
| CTNNB1   | 22     | 0.44545455           | 0.13809635             | Identified as gene control target of miRNAs encoded from SARS-CoV-2; Identified as a diagnostic biomarker for RA. | [53,54] |
| KDR      | 18     | 0.44144144           | 0.08063474             | Involved in the development of COVID-19 and its leading pathogenesis; noticed several actions in the progression of RA. | [55,56] |
| STAT1    | 18     | 0.4516129            | 0.2131105              | Aligned with immune response activities of SARS-CoV-2; involved in regulation of SARS-CoV-2 infected cells; | [57,58] |
| B2M      | 16     | 0.41590211           | 0.06292203             | Engaged in AD; claimed to be regulated by ivermectin drug of SARS-CoV-2. | [59,60] |
| CD3G     | 16     | 0.406639             | 0.05465393             | Detected in the cluster of blood immune cells (CD4+ and CD8+) from COVID-19 patients. | [61]    |
| ITGAV    | 16     | 0.42241379           | 0.0534754              | Expressed in downregulated level in surviving patients with COVID-19; Identified more vulnerable to invading lung cells than other cells of the respiratory tracts and nasopharynx. | [62,63] |
| TGFB3    | 15     | 0.37984496           | 0.04488816             | Redirected to adopt Bacille CalmetteGuérin vaccination in a tuberculosis pathway enrichment test. | [64]    |
TFs play a critical role in determining the transcription of their various target genes, allowing them to identify potential biomarkers. In this study, we have classified top TFs which are essential as regulators of DEGs-TFs interaction network in the pathogenesis of SARS-CoV-2 and AD. The acknowledged TFs regulate between SARS-CoV-2 and IBD are FOXC1, FOXL1, GATA2, YY1, PPARG, by the same token NFIC and SRF between SARS-CoV-2 and RA. Correspondingly, RELA, JUN are between SARS-CoV-2 and SLE; E2F1 is between SARS-CoV-2 and T1D. FOXC1, FOXL1, NFIC, and SRF were found regulated by potential key genes of SARS-CoV-2 and again has been also marked as repurposable drug as pirants for COVID-19 [89, 90]. RELA was the novel cause behind the autoimmune lymphoproliferative syndrome-a primary immune disorder distinguished most frequently by deficient lymphocytic apoptosis (in immune cells and homeostasis, apoptosis plays a key role. Increased apoptosis of the lymphocytes may trigger cell loss of immunodeficiency. In contrast, apoptosis inhibition can contribute to autoimmunity or lymphoma developments) [99]. In consequence, we revealed that E2F1, FOXC1, GATA2, NFIC, and YY1 are broadly line up with lung cancer [100–102]. Simultaneously, GATA2 is connected to disseminating of parenchymal lung disease and the scarcity of GATA-2 in both children and adults was instigating serious pulmonary alveolar proteinosis which is a rare lung disorder distinguished by an abnormal accumulation of surfactant-derived lipoprotein compounds within the alveoli of the lung [103]. Yet again, according to the findings in Ref. [104], PPARG could drive as an encouraging treatment approach for lung squamous cell carcinoma. Besides this, it was also disclosed that E2F1 was regulated in different ways in both bronchoalveolar lavage fluid (a lower respiratory tract screening technique in which a bronchoscope is placed through the mouth or nose into a compatible trachea of the lungs, a detectable volume of fluid is introduced, and then obtained for analysis) and COVID-19 cases [105]. Moreover, as JUN expression could be modulated by treatment with Pirfenidone which will be a conceivable
Pirfenidone is a drug that inhibits the creation of fibroblasts, fibrosis-associated proteins, and cytokines thus mounting biosynthesis and extracellular matrix aggregation through cytokine growth factors such as transforming growth factor-beta (TGF-β) and platelet-derived development factor. It is also used to cure idiopathic pulmonary fibrosis [103].

Investigational evidence recommends that miRNAs can patch up an intracellular resistance mechanism against some RNA viruses [106]. Along with that, we studied the DEGs-miRNAs interaction network to spot relevant miRNAs as probable targets for SARS-COV-2 and AD. The distinguished miRNAs act together between SARS-CoV-2 and IBD are hsa-miR-1273g-3p, hsa-miR-1273e, hsa-miR-6511a-5p, hsa-miR-196a-5p, hsa-miR-125a-5, hsa-miR-149-3p, hsa-miR-1307-3p, hsa-miR-149-3p, hsa-miR-34a-5p, hsa-miR-4701-3p are culpable for lung injuries and growing cancer cells such as lung cancer, squamous cell carcinoma, melanoma cancer [108–114]. Conversely, hsa-miR-196a-5p was acclaimed as vitally influential in the pathogenesis of non-small cell lung cancer by elevating in adherens junctions, relaxing signaling pathways, axon guidance, and transcriptional misregulation; hsa-miR-2052 was taken [102] to be a downregulated reaction to SOX2 in small cell lung cancer, which catalyzes cisplatin resistance, and it was also alleged to be a prospective candidate for chemoresistant therapy in the same way. Once more, hsa-miR-449a inhibits cancer cell proliferation and promotes apoptosis which upturns the sensitivity to the chemotherapeutic drug resistance, so it has been considered as a therapeutic goal to alleviate chemotherapeutic drug resistance in cancer that will upsurge the effectiveness of chemotherapy [115]. hsa-miR-1184 has deregulated flow in the blood of children

Fig. 8. DEGs-TFs interaction network between SARS-COV-2 and AD. Hexagon nodes resemble TFs, even as circular nodes portray the molecules that interact as target of TFs. Viewings for (a) SARS-CoV-2 and IBD as well as the network consists of 71 nodes and 152 edges (b) SARS-CoV-2 and RA as well as the network the network consists of 83 nodes and 183 edges (c) SARS-CoV-2 and SLE as well as the network consists of 90 nodes and 356 edges (d) SARS-CoV-2 and T1D and the network consists of 583 nodes and 1441 edges.
affected with Sepsis (Sepsis is a presumably harmful disease that happens when the body’s immune system attacks its own tissues in response to an infection), along with that it can be an valuable recipient for the treatment of children with sepsis since it smears prohibited effects on inflammatory responses and apoptosis through assaulting TRADD (Tumor necrosis factor receptor type 1-associated DEATH domain protein) [116]. As well as hsa-mir-1976 has been termed as a non-invasive diagnostic object and therapeutic focus for sick sinus syndrome that is accompanying shortness of breath with opportunities to come across standpoints for mutually noticeable pathogenesis [117].

Both hsa-mir-2052 and hsa-mir-410–5p interact with RA, hsa-mir-676–3p and hsa-mir-4693–3p interact with SLE and T1D have been symbolized as common miRNAs that target multiple viral proteins, notably the Spike protein in SARS-CoV-2. Even so, by assimilating with ACE2, they help out with viral attachment and host cell entry [118]. The presumed SARS-CoV-2 affecting miRNAs (hsa-mir-1273g-3p, hsa-mir-1273e, hsa-mir-6511a-5p, hsa-mir-196a-5p engaged with IBD, hsa-mir-1184 engaged with RA, hsa-mir-1976 engaged with SLE and hsa-mir-4701–3p, hsa-mir-1299 engaged with T1D) in human lung epithelial cells or respiratory epithelial cells including macrophages, that are elemental in COVID-19 pathogenesis. Drug repurposing is a powerful approach for getting new intuitions from an existing drug, which contributes to the emergence of a new drug at a lesser rate and with a shorter development period. COVID-19 patients with hypertension are treated with therapeutically validated calcium channel blockers, that are contained in the Vero-6 cell line, and have a heightened chance of increasing SARS-CoV-2 infection. The addition of chlorine to the calcium channel blocker has been shown to be significantly effective in relieving SARS-CoV-2, including amlodipine besylate therapy, which was associated with reduced case mortality without having any strong cytotoxic effects; Researchers have suggested that amlodipine besylate could be an effective drug for COVID-19 patients with hypertension [122]. On the other hand, substantial inflammatory consequences have been tied to severe COVID-19, and researchers believe that antiviral effectiveness along with CCB to attenuate the inflammatory response might perform in an integrated manner [123].

The catecholamines contained in the neurotransmitter norepinephrine are also associated with COVID-19 because they played a major role in creating the conceivably disastrous cytokine storm. The neurotransmitter norepinephrine sedative vorinostat may also be used in the treatment of COVID-19 as recommended in Ref. [124]. Again, vorinostat has been reported to be useful in treating cancer since it is a broad-spectrum histone deacetylase inhibitor [125]. Patients with severe COVID-19 pneumonia who obtained low-dose methylprednisolone before having medication for acute respiratory distress syndrome reported improved treatment benefits [126]. Surprisingly, the authors in Ref. [127] revealed that high doses of methylprednisolone for COVID-19 patients with pneumonia showed a rapid and significant improvement after tocilizumab had failed to work. The authors in Ref. [128] studied a

| Repurposed Drug | Inhibition Score | Structural Score / Druglikeness | Side Effect Score (%) | Side Effect Score (Label) % | Score |
|-----------------|-----------------|---------------------------------|-----------------------|-----------------------------|-------|
| Amlodipine Besylate | 0.1607 | 0 | 2.24 | 0.04 |
| Vorostron | 0.1607 | 0 | 1.02 | 0.03 |
| Methylprednisolone | 0.1607 | 0 | 3.27 | 0.24 |
| Ditosirum | 0.1667 | 0 | 0.54 | 0.03 |

| Drugs found for SARS-CoV-2 and IBD |
|-----------------------------------|
| Glimepiride | 0.1429 | 0 | 1.79 | 0.22 |
| Hexitol hydrochloride | 0.1429 | 0 | NF | NF |
| Plesterider | 0.1429 | 0 | 0.078 | 0.21 |
| Metaxalone | 0.1429 | 0 | 0 | 0 |
| Merhoxsalen | 0.1429 | 0 | Postmarketing | Postmarketing |
| Pimoxide | 0.1429 | 1*Yes; 1 violation: MLOGP>4.15 |

| Drugs found for SARS-CoV-2 and T1D |
|-----------------------------------|
| BRD-KS2075040/Cerulain | 0.0675 | 0 | NF | NF |
| Vorosinost | 0.1607 | 0 | 1.02 | 0.01 |

| Drug found for RA |
|-------------------|
| Vorosinost | 0.1697 | 0 | 1.02 | 0.01 |

| Drugs found for SLE |
|---------------------|
| Menadione | 0.2034 | 0 | NF | NF |
| HY-T0139/Nilotinab | 0.1864 | 1*Liptitski Yes; 1 violation: MW>500 |

Table 3
Repurposed drug list for SARS-CoV-2 and AD; The drugs marked by yellow color was met the repurposing criteria and chosen for further investigation.

Table 8
Repurposed drug list for SARS-CoV-2 and AD; The drugs marked by yellow color was met the repurposing criteria and chosen for further investigation.

| Repurposed Drug | Inhibition Score | Structural Score / Druglikeness | Side Effect Score (%) | Side Effect Score (Label) % | Score |
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| Merhoxsalen | 0.1429 | 0 | Postmarketing | Postmarketing |
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| Drugs found for SARS-CoV-2 and T1D |
|-----------------------------------|
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| Vorosinost | 0.1607 | 0 | 1.02 | 0.01 |

| Drug found for RA |
|-------------------|
| Vorosinost | 0.1697 | 0 | 1.02 | 0.01 |

| Drugs found for SLE |
|---------------------|
| Menadione | 0.2034 | 0 | NF | NF |
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|-------------------|
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| Drugs found for SLE |
|---------------------|
| Menadione | 0.2034 | 0 | NF | NF |
| HY-T0139/Nilotinab | 0.1864 | 1*Liptitski Yes; 1 violation: MW>500 |
clinical trial with methylprednisolone for critically ill hospitalized patients with confirmed COVID-19 in the early pulmonary stage of the disease in Iran; based on their findings, they concluded that methylprednisolone pulse could be an efficacious remedy for patients with COVID-19 at the pulmonary stage. Experimental treatment with methylprednisolone enhanced the number of ventilator-free days and the likelihood of airway management in severe COVID-19 patients who required mechanical ventilation; however, the substantial difference in mortality was overlook [129]. Early intake of methylprednisolone at low or medium doses has resulted in favorable benefits in COVID-19 individuals under the age of 65, as well as an overactive immunologic response [130]. Disulfiram has been found to significantly suppress COVID-19-related behaviors in those who receive it for alcoholism [131]. Gilimpire, a medication to decrease glucose was observed to be beneficial in boosting cytokine profiles and immune response in COVID-19 individuals with type 2 diabetes mellitus [132]. Previous research has indicated that males are more than twice as likely as women to be contaminated with Covid-1 and to be transferred to the ICU. The majority of males infected with SARS-CoV-2 have androgenic alopecia, which is typically treated with androgens, and the authors suggest that finasteride may be more beneficial in this instance [133]. Regarding that, a short term of finasteride medication enhanced O2 sufficiency but had no effect on other outcomes in male patients over the age of 50, demanding a large-scale study with extended follow-up to elucidate the finasteride strategy [134]. Considering the common pathogenesis shared between AD and SARS-CoV-2, it was speculated that remedies for AD could be used as a possible treatment to prevent SARS-CoV-2, which in turn would alleviate COVID-19 outbreaks [3].

5. Conclusion

The current study deployed a bioinformatics and systems biology approach to ascertain the genetic effects of SARS-CoV-2 and AD from their transcriptomics datasets. We have identified ontological and pathway enrichment terminologies, built gene-disease association networks, identified regulatory transcription factors and protein-protein interaction sub-networks of SARS-CoV-2 and AD. The following findings showed biological associations between SARS-CoV-2 and AD at the molecular and cellular level and may possibly play a fundamental role in the progression of AD. Our substantiated insights would be highly valuable for more precisely predicting and diagnosing SARS-CoV-2 illness development in AD following gene-based evidence and traces. Furthermore, repurposed drugs uncovered from drug repurposing assessment, as well as their acclaimed affiliations, may conceivably give support to current vaccination and therapeutic development efforts for SARS-CoV-2 as a result of new perceptiveness into the underlying pathophysiology mechanisms connecting SARS-CoV-2 and AD. Adequate and necessary analysis with large-scale datasets in the future is needed to find out the further effectiveness of this study.

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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Abbreviations

Severe acute respiratory syndrome 2  SARS-CoV-2
Autoimmune diseases  AD

Inflammatory bowel disorder  IBD
Rheumatoid Arthritis  RA
Systemic lupus erythematous  SLE
Type 1 Diabetes  T1D
Gene expression omnibus  GEO
National Center for Biotechnology Information  NCBI
Protein-protein interaction network  PPIN
Transcription factors  TFs
GDAN  Gene disease association network

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.imu.2022.101003.

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