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A meta-analysis of comorbidities in COVID-19: Which diseases increase the susceptibility of SARS-CoV-2 infection?

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ABSTRACT

Comorbidities in COVID-19 patients often lead to more severe outcomes. The disease-specific molecular events, which may induce susceptibility to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, are being investigated. To assess this, we retrieved array-based gene expression datasets from patients of 30 frequently occurring acute, chronic, or infectious diseases. Comparative analyses of the datasets were performed after quantile normalization and log2 transformation. Among the 78 host genes prominently implicated in COVID-19 infection, ACE2 (receptor for SARS-CoV-2) was positively regulated in several cases, namely, leukemia, psoriasis, lung cancer, non-alcoholic fatty liver disease (NAFLD), breast cancer, and pulmonary arterial hypertension (PAH). FURIN was positively regulated in some cases, such as leukemia, psoriasis, NAFLD, lung cancer, and type II diabetes (T2D), while TMPRSS2 was positively regulated in only 3 cases, namely, leukemia, lung cancer, and T2D. Genes encoding various interferons, cytokines, chemokines, and mediators of JAK-STAT pathway were positively regulated in leukemia, NAFLD, and T2D cases. Among the 161 genes that are positively regulated in the lungs of COVID-19 patients, 99–111 genes in leukemia (including various studied subtypes), 77 genes in NAFLD, and 48 genes in psoriasis were also positively regulated. Because of the high similarity in gene expression patterns, the patients of leukemia, NAFLD, T2D, psoriasis, and PAH may need additional preventive care against acquiring SARS-CoV-2 infections. Further, two genes CARBONIC ANHYDRASE 11 (CA11) and CLUSTERIN (CLU) were positively regulated in the lungs of patients infected with either SARS-CoV-2, or SARS-CoV or Middle East Respiratory Syndrome Coronavirus (MERS-CoV).

1. Introduction

Coronavirus disease (COVID-19) caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the most dreaded pandemic of recent times. As per the global data released on December 25, 2020, by COVID-19 dashboard of the World health organization, SARS-CoV-2 has infected 77,920,564 people of which 1,731,901 people have died. A significant proportion of the COVID-19 patients have been reported to suffer from other pathophysiological conditions as well. For instance, in a cohort of 1590 COVID-19 patients from China, Guan et al. (2020) reported that 399 patients (25.1%) were having at least one comorbidity, while 130 patients (8.2%) had two or more comorbidities [1]. They reported that hypertension, diabetes, cardiovascular diseases, and chronic kidney diseases were among the most frequent comorbidities, which occurred in 16.9%, 8.2%, 3.7%, and 1.3% of all COVID-19 patients, respectively. Also, COPD and malignancy were identified as critical risk factors associated with severe COVID-19 conditions. Another study by Chen et al. (2020) reported that in a cohort of 99 COVID-19 patients in China, 50 patients (51%) suffered from chronic medical illnesses [2]. The reported comorbid diseases were cardiovascular or cerebrovascular diseases (40.4%), diabetes (12%), digestive system disease (11%), and malignant tumor (0.01%) that were identified in 40, 12, 11, and 1 patient, respectively. Similarly, others have also reported cancer of lungs [3] and of blood [4], NAFLD [5], and HIV infections (Human Immunodeficiency Virus) [6], as frequently occurring comorbidities that often worsen the outcome and increase the risk of...
Patients infected with either SARS-CoV (GSE1739), SARS-CoV-2 (GSE65194), Cervical Cancer (GSE63514), Multiple Myeloma (MM, GSE51082, GSE9476), Breast Cancer (GSE124226), Polycystic Ovary Syndrome (PCOS, GSE25462, GSE38642, GSE27949), Multiple Sclerosis (MS, GSE21942), Psoriasis (GSE78097), Blood Cancer or Leukemia (GSE51082, GSE9476), Breast Cancer (GSE65194), Cervical Cancer (GSE63514), Multiple Myeloma (MM, GSE85837), Lung Cancer (GSE136043), Lung adenocarcinoma or Non-small cell lung cancer (NSCLC, GSE118370), Liver Cancer (GSE88839), Pancreatic Ductal Adenocarcinoma (PDAC, GSE101448), AIDS (GSE73968), Tuberculosis (TB, GSE139825), Malaria (GSE119150), Acute Kidney Injury (AKI, GSE30718), and COVID-19 (GSE150316). In order to identify the common differentially expressed genes, we performed a meta-analysis with gene expression datasets in 30 widely prevalent acute, chronic, and infectious diseases to identify the gene expression signatures that could promote the pathogenesis of SARS-CoV-2. Therefore, we used a data-integration strategy as described in the previous sections. The overall methodology of this study is shown in Fig. 1 (Created with BioRender.com).

2. Dataset, methods, and techniques

2.1. Data retrieval

Publicly available datasets of human acute, chronic, infectious diseases, and various types of cancer were retrieved from NCBI’s GEO database [8]. We favored the expression profile GSEids with highest number of samples while focusing on the tissue of origin, and devoid of any treatments or other afflictions. We retrieved datasets of patients and controls for the following conditions: Asthma (GSE64913), Chronic Obstructive Pulmonary Disorder (COPD, GSE112811), Cardiovascular diseases (GSE109048), Hypertension (GSE113439), NAFLD (GSE49541, GSE107037), Atherosclerosis (Athero, GSE28829), T2D (GSE15653, GSE25462, GSE38642, GSE72949), Polycystic Ovary Syndrome (PCOS, GSE124226), Multiple Sclerosis (MS, GSE21942), Psoriasis (GSE78097), Blood Cancer or Leukemia (GSE1082, GSE9476), Breast Cancer (GSE65194), Cervical Cancer (GSE63514), Multiple Myeloma (MM, GSE85837), Lung Cancer (GSE136043), Lung adenocarcinoma or Non-small cell lung cancer (NSCLC, GSE118370), Liver Cancer (GSE88839), Pancreatic Ductal Adenocarcinoma (PDAC, GSE101448), AIDS (GSE73968), Tuberculosis (TB, GSE139825), Malaria (GSE119150), Acute Kidney Injury (AKI, GSE30718), and COVID-19 (GSE150316). In order to identify the common differentially expressed genes in different viral infections, we analyzed the datasets from the patients infected with either SARS-CoV (GSE1739), SARS-CoV-2 (GSE150316), MERS-CoV (GSE100496), H1N1 (GSE21802), or other influenza viruses (GSE22319, H7N1, H5N1, H3N2, H5N2). Furthermore, we studied six subtypes of leukemia that were retrieved from the GSE1082 and GSE9476 datasets, namely Acute myeloid leukemia (AML), B-cell chronic lymphocytic leukemia (BCLL), Chronic myelogenous leukemia (CML), Myelodysplastic syndrome (MDS), B-acute lymphoblastic leukemia (BALL), and T-cell acute lymphoblastic leukemia (TALL). The dataset on cardiovascular diseases included an equal number of patients suffering from coronary artery disease (CAD) and acute myocardial infarction (AMI), and the dataset of breast cancer included both breast cancer and triple-negative breast cancer tissues (TNBC) samples. Of the 29 samples in the GSE28829 dataset of atherosclerosis (Athero), 16 samples were from advanced atherosclerotic plaque (ATHERO-Adv), and 13 samples were from early atherosclerotic plaque (ATHERO-Early) regions. In the cases of leukemia and NAFLD, we obtained expression profiles of diseased and control samples from separate GSEids. Therefore, we used a data-integration strategy as previously explained by Hamid et al. (2009) for data analysis in leukemia and NAFLD cases [9,10]. The platform of microarray experiment, type of tissue sample, sample size, experimental design, and data processing strategy, are summarized in Table 1.

2.2. Data normalization

The datasets used in this study were all quantile normalized, and log2-transformed in R [11]. Briefly, raw expression values were quantile normalized using the normalize Quantiles function of LIMMA package in R, irrespective of their normalization status to maintain uniformity [12]. Subsequently, the average expression value of all probes for each gene in all the disease and control samples was obtained using collapse R rows function of WGCNA R package [13]. The normalized values were subsequently log2-transformed, provided the dataset was not already log2-transformed.

2.3. Data analysis

Principal Component Analysis (PCA) is a dimensionality reduction technique that identifies patterns in data, and highlights their similarities and differences. Elucidation of the principal components is based on identifying the variables most strongly correlated with each component. We used ‘premp’ function in R base package for PCA to analyze the segregation of datasets based on linear correlation and variance in gene expression values of 10,296 genes for all subjects in each disease [14]. The ‘ggtreeplot’ function of ggplot2 package in R was used for graphical representation of PCA results [15].

Literature mining was carried out to identify 78 genes, which includes those encoding receptors, proteases, and others that are implicated in the replication and pathogenesis of one or other human infecting coronaviruses including SARS-CoV-2. The fold change values in the expression of these genes were computed and used to generate a clustered heatmap using pheatmap R package [16]. In addition, another heatmap was prepared using the gene expression values of 182 differentially expressed genes (at fold change > 2 or < 0.5 and p < 0.05) in COVID-19 patients compared to healthy controls. We used student’s t-test (p < 0.05 as the level of significance) to analyze the gene expression data from SARS-CoV-2 infected human lung tissue. Additionally, the p-adjusted values (FDR<0.05) were used for identifying the highly significant dysregulated pathways in different disease cases. The data has been plotted as mean ± standard error from mean, and each dot represents individual reading. The graphical representation of gene expression values was obtained using GraphPad Prism (version 8.0.0) software. The overall methodology of this study is shown in Fig. 1 (Created with BioRender.com).

2.4. Co-expression analysis

Co-expression analysis describes the correlation pattern in gene expression across different samples and it is frequently used for identifying the clusters (or modules) of highly correlated genes. We have used the weighted gene correlation network analysis (WGCNA) technique using WGCNA R package for identifying the highly correlated modules [13]. For co-expression analyses of individual disease cases, we have used the quartile normalized log2 values of gene expression in disease samples. For co-expression analysis of multiple diseases, we have used log2(FC) values. To ensure a scale-free topology of the network, soft-threshold power (ranged between 6 and 10) was chosen as per the Power Estimate value provided by pickSoft Threshold function in WGCNA R package. The pathway analysis for the genes in the identified modules were performed using DAVID [17]. The networks were drawn using Cytoscape 3.8 [18].

STAR METHODS:

LEAD CONTACT: The relevant information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Srinivasan Ramachandran (ramu@igib.res.in).

MATERIALS AVAILABILITY: This study did not generate any new material.

DATA AND CODE AVAILABILITY: This study did not generate any unique dataset or code.
| Disease Type | Disease/Condition | GSE ID | Platform | Tissue | Experimental Design | Data Processing |
|-------------|-------------------|--------|----------|--------|---------------------|----------------|
| Chronic     | Asthma            | GSE64913 | GPL570 [HG-U133_Plus_2] Affymetrix | Epithelial brushings from central and peripheral airways | 42 healthy volunteer, 28 asthmatic patients | Preprocessed: Normalization and log2 transformation by GCRMA method |
|             | Obstructive Pulmonary Disorder | GSE11281 | GPL570 [HG-U133_Plus_2] Affymetrix | Blood | 20 COPD patients, 22 healthy volunteers before administration of LPS or saline | Preprocessed: Normalization and log2 transformation by RMA |
| Cardiovascular |                | GSE109048 | GPL17586 [HTA-2_0] Affymetrix | Blood platelets | 19 Healthy donors, 19 CAD patients, 19 AMI patients | Preprocessed: SST-RMA normalization and log2 transformation |
| Hypertension |                  | GSE113439 | GPL6244 [HuGene-1_0-st] Affymetrix | Lung | 15 patients with Pulmonary Arterial Hypertension and 11 normal controls | Preprocessed: Normalization and log2 transformation by RMA |
| Non-Alcoholic Fatty Liver Disease |            | GSE49541 | GPL570 [HG-U133_Plus_2] Affymetrix | Liver | 72 patients with NAFLD | Preprocessed: Normalization and log2 transformation by GCRMA method |
|             | Atherosclerosis   | GSE28829 | GPL570 [HG-U133_Plus_2] Affymetrix | Carotid artery | Samples from atherosclerotic carotid artery segments of 29 patients | Preprocessed: Normalization and log2 transformation by RMA |
| Type 2 Diabetes |               | GSE15653 | GPL196 [HG-U133A] Affymetrix | Liver | 4 type 2 diabetes and 5 control subjects | Preprocessed: Mass5.0 signal intensity. |
|             | Type 2 Diabetes   | GSE25462 | GPL570 [HG-U133_Plus_2] Affymetrix | Muscle | 10 subjects with type 2 diabetes and 15 healthy subjects | Preprocessed: Mass5.0 signal intensity. |
| Polycystic Ovary Syndrome |           | GSE38642 | GPL6244 [HuGene-1_0-st] Affymetrix | Pancreas | 54 non-diabetic and 9 diabetic cadavers | Preprocessed: Normalization and log2 transformation by RMA |
| Multiple Sclerosis |            | GSE27949 | GPL570 [HG-U133_Plus_2] Affymetrix | Adipose | 12 Normal and 11 T2D subjects | Preprocessed: Normalization and log2 transformation by RMA |
| Psoriasis    |                  | GSE78097 | GPL570 [HG-U133_Plus_2] Affymetrix | Skin | 6 normal skin tissues and 27 psoriatic skin lesions | Preprocessed: Normalization GCRMA method |
| Cancer       | Blood Cancer (Leukemia) | GSE51082 | GPL196 [HG-U133A] Affymetrix | Bone Marrow | 37 AML, 41, B-ALL, 22 CML, 10 MDS, 17 B-ALL, 12 T-ALL | Preprocessed: Normalization and log2 transformation by RMA |
| Cancer       | Breast Cancer     | GSE65194 | GPL570 [HG-U133_Plus_2] Affymetrix | Bone Marrow | 38 healthy donors | Preprocessed: Normalization and log2 transformation by RMA |
| Cancer       | Cervical Cancer   | GSE63514 | GPL570 [HG-U133_Plus_2] Affymetrix | Breast sample | 11 control breast sample, 98 breast cancer samples, 55 TNBC samples | Preprocessed: Normalization and log2 transformation by GCRMA method |
| Cancer       | Multiple Myeloma  | GSE85837 | GPL10558 Illumina HumanHT-12 V4.0 | Bone Marrow | 24 normal and 28 cancer specimens | Preprocessed: Normalization and log2 transformation by GCRMA method |
| Lung Cancer  |                  | GSE136043 | GPL13497 Agilent-026652 | Lung | 9 control and 9 multiple myeloma patients with bone lesion | Preprocessed: Robust spline normalization and log2 transformation by lum R package |
| Lung adenocarcinoma (Non-small cell lung cancer) |     | GSE18370 | GPL570 [HG-U133_Plus_2] Affymetrix | Lung | 5 lung cancer tissue and 5 lung non-tumor tissues | Preprocessed: Normalization by Agilent Feature Extraction Software |
| Lung adenocarcinoma (Non-small cell lung cancer) |     | GSE88839 | GPL570 [HG-U133_Plus_2] Affymetrix | Lung | 6 invasive lung adenocarcinoma tissues and 6 normal lung tissues | Preprocessed: Normalization and log2 transformation by Mass5.0 algorithm |
| Liver Cancer |                  | GSE101448 | GPL10558 Illumina HumanHT-12 V4.0 | Pancreas | 35 ICA liver tumours and 3 normal liver samples | Preprocessed: Normalization by RMA |
| Pancreatic Ductal Adenocarcinoma |     | GSE101448 | GPL10558 Illumina HumanHT-12 V4.0 | Pancreas | 18 with pancreatic tumor and 13 non-tumor pancreatic tissue samples | Preprocessed: Normalization and log2 transformation by Illumina’s BeadStudio Data Analysis Software |
| Infectious | AIDS              | GSE73968 | GPL6244 [HuGene-1_0-st] Affymetrix | T Cells | 9 healthy control and 6 HIV positive patients | Preprocessed: Normalization and log2 transformation by RMA |
| Tuberculosis |                  | GSE109825 | GPL10558 Illumina HumanHT-12 V4.0 | Alveolar Macrophages | Alveolar Macrophages from 5 TB patients and 5 control subjects |
| Malaria      |                  | GSE119150 | GPL15207 [Prime View] Affymetrix | Blood | 6 falciparum malaria and 6 normal subjects | Preprocessed: Normalization and log2 transformation by RMA |
| Acute        | Acute Kidney Injury | GSE30718 | GPL570 [HG-U133_Plus_2] Affymetrix | Kidney | | |

(continued on next page)
3. Results

3.1. Human genes implicated in the pathogenesis of COVID-19 are upregulated in leukemia, psoriasis, NAFLD, and type II diabetes cases

In leukemia and NAFLD condition, there were more than one dataset, namely one GSEid for samples and another GSEid for controls. In addition, in leukemia and breast cancer, the sample size of individual datasets was large. Therefore, we performed a principal component analysis (PCA) on the expression values of 10296 genes to explore the variability between datasets. We observed that the gene expression profile of datasets in a given disease correlated with each other, and each disease produced isolated galaxies of points closely spaced to each other (Fig. 2A). We then investigated the differential gene expression in a set of chronic, acute, and infectious disease conditions to identify the gene expression patterns that may induce susceptibility to SARS-CoV-2 infection. The molecular details of SARS-CoV-2 infection and spread are still under active research, and some steps in the pathogenesis of SARS-CoV-2 have been reported as either identical or similar to that of other pathogenic human coronaviruses (HCoVs), namely, SARS-CoV and MERS-CoV. Since gene expression pattern is characteristically correlated with the pathogenesis of diseases [19,20], we examined the expression patterns of human genes, which are implicated in the replication and pathogenesis of SARS-CoV-2 or other HCoVs, in different disease conditions. To this end, we performed a literature mining exercise and identified 78 genes that were reported to have important implications in the entry and pathogenesis of HCoVs. These genes are enlisted in Supplementary Table 1. Some of these genes have been identified with key roles in promoting the pathogenesis of SARS-CoV-2, namely ACE2, FURIN, and TMPRSS2. The heatmap of log₂(FC) fold changes in expression values of these 78 genes, in all 30 disease cases including COVID-19, is shown in Fig. 2B. It is evident that several of these genes are upregulated in patients with SARS-CoV-2 infection and patients of all the studied subtypes of leukemia (hereafter, collectively referred to as leukemia; 45–50 genes), NAFLD (32 genes), psoriasis (22 genes), breast cancer (17 genes), cervical cancer (12 genes), NSCLC1 (7 genes), and type II diabetes liver (7 genes). It is noteworthy that the differential gene expression pattern was particularly pronounced in leukemia (log₂(FC) in the range 2–6) and NAFLD (log₂(FC) in the range 2–5).

Further, to investigate any prospective covet genetic feature, we performed the co-expression analysis of 78 genes, which are implicated in the pathogenesis of coronaviruses, in these diseases. First, we examined the disease samples separately for each disease and identified 38 genes that co-expressed (turquoise) per disease condition (Supplementary Figs. 1–5). 38 genes were observed to co-express...
in each of these disease types (Supplementary Fig. 6). We obtained different hub genes in each of these diseases, namely, MAPK1 in SARS-CoV-2, PCSK6 in leukemia, NFKB1 in PAH, TYK2 in psoriasis, and CTSD in T2D liver (Supplementary Figs. 7–11). However, in the case of NAFLD, we did not obtain any module of co-expressed genes.

Thereafter, we performed another co-expression analysis using integrated log\(_2\) (FC) values for SARS-CoV-2, leukemia (6 subtypes were considered separately), NAFLD, psoriasis, PAH, and T2D liver (Supplementary Fig. 12). We obtained two modules with 62 and 16 genes, however, only one module was significant wherein PCSK6 was identified as the hub gene (Supplementary Fig. 13). Pathway analysis with these genes showed the prominent enrichment of Toll-like receptor signaling, JAK/STAT signaling, TNF signaling and NF-\(\kappa\)B signaling pathways (Supplementary Table 2).

3.2. The expression of ACE2, FURIN, and TMPRSS2 is increased in leukemia, NAFLD, and psoriasis patients

The earliest steps in establishing COVID-19 include cellular entry of SARS-CoV-2, which is critically dependent on the host’s ACE2 receptor and serine proteases FURIN and TMPRSS2. ACE2 functions as the receptor for the entry of SARS-CoV-2 by binding to the viral spike protein, whereas, the FURIN and TMPRSS2 proteases are essential for processing the spike protein that facilitates viral entry into the cells [21,22]. Therefore, we investigated the expression patterns of ACE2, FURIN, and TMPRSS2 in the distinct disease cases (as identified in Fig. 2B), namely breast cancer, cervical cancer, leukemia, NAFLD, NSCLC1, psoriasis, and T2D. The expression of ACE2 was upregulated in leukemia, psoriasis, NAFLD, lung cancer, breast cancer, and cervical cancer patients (Fig. 3A). The expression of FURIN was upregulated in leukemia, psoriasis, NAFLD, lung cancer, and in T2D liver whereas it was downregulated in breast cancer (Fig. 3B). We observed that TMPRSS2 was upregulated in leukemia, lung cancer, and T2D, but it was downregulated in psoriasis, NAFLD, lung cancer, breast cancer, and cervical cancer (Fig. 3C). It is worthwhile to mention that after the interaction of the viral spike protein with ACE2 receptor, the host’s FURIN protease cleaves the spike protein at the interface of two subunits of the trimeric spike. Thus, the protease activity of FURIN is critical in promoting spike mediated entry of SARS-CoV-2 and it is also known to be crucial for protein processing in other infectious diseases and in cancer [23].

3.3. Disease-associated dysregulation of innate and adaptive immune response in patients with other diseases

Following entry, the presence of viral RNA in cellular milieu evokes an immune response in the host. Apart from the receptors and proteases, the heatmap in Fig. 2B also shows the differential expression of genes, which are involved in the innate and acquired immune responses to SARS-CoV-2 invasion. The genes Interferon-alpha and Interferon-beta (IFNA2, IFNA8, IFNA10, IFNA14, IFNA16, IFNA21, and IFNB1) are the initial response elements of the innate immune signaling pathway. These responses activate several interferon-stimulated genes (ISGs) via JAK1/STAT1 pathway, which leads to early clearance of the viral load [24].

We prepared a heatmap of the log\(_2\) (FC) of the expression of the interferons that were differentially expressed in any of the 30 diseases (\(p < 0.05\), Fig. 4A). We also examined the expression of genes encoding cytokines that underlie the anti-viral immune responses, namely IL6, CXCL10, JAK1, and STAT1 (Fig. 4B–E). The genes IFNA2, IFNA8, IFNA10, IFNA14, IFNA16, IFNA21, and IFNB1 were upregulated in leukemia (log\(_2\) (FC) ranged from 1.003 to 4.63) and in NAFLD (log\(_2\) (FC) ranged from 1.09 to 1.93), whereas they were downregulated in T2D liver (log\(_2\) (FC) ranged from -1.09 to -1.61). The expression of JAK1 was slightly decreased (log\(_2\) (FC) from -0.63 to -0.94) in leukemia except in BCLL cases, whereas STAT1 was slightly decreased in TALL (log\(_2\) (FC) -0.41) and was unchanged in other types of leukemia. Both JAK1 and STAT1 were increased in NAFLD (log\(_2\) (FC) ranged from 1.52 to 1.96) and in T2D muscles (log\(_2\) (FC) ranged from 1.52 to 3.88). The initial interferon-mediated response is followed by a specific cell-mediated adaptive immune response to clear viral invasion. To this end, the cytokines IL6 and CXCL10 are produced by helper T cells and macrophages that promote the migration of immune cells to the site of infection. They are also associated with the cytokine storm observed in COVID-19 associated mortalities [25]. We observed that the expression of IL6 and CXCL10 was upregulated in leukemia (log\(_2\) (FC) ranged from 1.92 to 3.55). But the expression of IL6 was slightly decreased in NAFLD (log\(_2\) (FC) -0.4). The expression of CXCL10 was increased in NAFLD (log\(_2\) (FC) 5.23) and PDAC (log\(_2\) (FC) 2.095).

3.4. The patterns of differential gene expression are similar in SARS-CoV-2, leukemia, and NAFLD

We analyzed the expression pattern of 193 differentially expressed genes from 16 SARS-CoV-2 infected patients. Out of these 193 differentially expressed genes, we found that the expression values for only 182 genes were available in the datasets of all disease types included in our study. Therefore, we generated a clustered heatmap (Fig. 5A) and a
scatter plot (Supplementary Fig. 14) depicting the expression of these 182 differentially expressed genes in 30 diseases and COVID-19 conditions. It is evident from the heatmap that the pattern of gene expression is similar in COVID-19 and PDAC, which are segregated together in the heatmap. Similarly, lung cancer and NSCLC also clustered together. Among the 161 genes upregulated in the lungs of COVID-19 patients (log2(FC) ranged from 1 to 3.45), 99–111 genes in leukemia (log2(FC) ranged from 1 to 5.86), 77 genes in NAFLD (log2(FC) ranged from 1 to 5.58), and 48 genes in psoriasis (log2(FC) ranged from 1 to 6.27) were upregulated. Pathways enrichment analysis of these 182 genes using DAVID [26, 27] showed significant enrichment of the host’s immune response to viral infection or infection-related immune pathways (Fig. 5B). Furthermore, we inferred the expression of 10 topmost significantly altered up- and down-regulated genes in COVID-19 patients and compared them to the disease cases showing similar pattern of gene expression, namely, T2D liver, NAFLD, psoriasis, leukemia, PDAC, lung cancer, NSCLC, TNBC, breast cancer, and cervical cancer (Supplementary Fig. 15). We observed that three genes, namely RAMP3 (Receptor Activity Modifying Protein 3), S100A2 (S100 Calcium Binding Protein A2), and CLCA2 (Chloride Channel Accessory 2) with a functional role in calcium signaling, were prominently upregulated in at least 7 studied disease types (including all subtypes of leukemia).

3.5. Pathogenic HCoVs differentially regulate the expression of CARBONIC ANHYDRASE 11 and CLUSTERIN gene

We extended our investigation to identify the genes, whose expression may be commonly altered by the dreaded viruses of recent times. We analyzed the differential gene expression in patients with different viral infections, namely, SARS-CoV, SARS-CoV-2, MERS-CoV, H1N1, and other influenza viruses (H7N1, H5N1, H3N2, and H5N2). We observed that no gene was commonly altered in these viral infections (at a fold change > ±2, p < 0.05; Fig. 6A). However, two genes, namely CARBONIC ANHYDRASE 11 (CA11) and CLUSTERIN (CLU) were commonly altered in the patients infected by pathogenic HCoVs, namely SARS-CoV, SARS-CoV-2, and MERS-CoV (at a fold change > ±2, p < 0.05; Fig. 6B). Based on the similarities in the patterns of differential gene expression in COVID-19 and other 30 diseases, we examined the expression of CA11 and CLU in breast cancer, cervical cancer, leukemia, NAFLD, NSCLC, psoriasis, and T2D patients. The expression of CA11 was significantly upregulated in COVID-19 and leukemia (Fig. 6C), whereas CLU was upregulated in COVID-19 only (Fig. 6D).

4. Discussion

COVID-19 associated comorbidities have been reported with several acute and chronic diseases, which lead to poor outcomes. For instance, diabetes, cardiovascular disease, renal and pulmonary diseases, are frequently observed comorbidities that increase the case fatality rate in
acute respiratory diseases caused by SARS-CoV [28], MERS-CoV [29, 30], and SARS-CoV-2. Our study revealed that the characteristic gene expression patterns in the disease cases, namely, leukemia, NAFLD, psoriasis, T2D, and PAH are highly similar to that of COVID-19. It is likely that the similarities in gene expression pattern offer a favorable environment to SARS-CoV-2 infection.

ACE2 is the functional receptor of three human infecting coronaviruses, namely NL-63, SARS-CoV, and SARS-CoV-2 [21,31]. Previous reports suggest that the expression of ACE2 is moderate in lung alveolar epithelium cells, high in enterocytes of the small intestine, and to a lesser extent in the vascular endothelial and smooth muscle in several organs including kidney, liver, bone marrow, skin, and brain [32]. Through ACE2, these organs may provide an easy port of entry for SARS-CoV-2, and the gene expression data suggests that more severe symptoms could develop upon SARS-CoV-2 infection particularly in the respiratory tract and the gut. The degree of ACE2 expression, in association with a 10–20 fold higher binding affinity of SARS-CoV-2 spike compared to SARS-CoV spike, could underlie the efficient cellular entry and higher infectivity of SARS-CoV-2 compared to SARS-CoV [33,34]. We observed that the basal expression of ACE2 was significantly high in many pathological conditions, namely leukemia, cancer of lungs, breasts, and cervix, NAFLD, psoriasis, and PAH. Hence, the increased number of available cellular receptors that facilitate viral entry can account for the increased susceptibility of these disease cases to SARS-CoV-2 infection.

Following the initial interaction of viral spike with ACE2 receptors, the pre-activation of viral spike by cleavage at polybasic S1/S2 site in the spike is mediated by proprotein convertase FURIN that enables a second cleavage by the cellular serine protease TMPRSS2. Both these proteolytic cleavages are important in facilitating viral entry. Inactivation of either FURIN [22] or TMPRSS2 [21] has been reported to inhibit cell-cell fusion and entry of SARS-CoV-2 in lung cells. Other cellular proteases such as TMPRSS4 [35] Cathepsin B and L [34] may have a cumulative effect on the FURIN-mediated promotion of SARS-CoV-2 entry into enterocytes or liver or lungs cells. Except in CLL, BALL, and

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**Fig. 4.** (A) Clustered heatmap of log2(FC) fold change values in the expression of genes encoding interferons that are differentially expressed in COVID-19 and 30 other studied disease patients. Quantification of (B) IL6, (C) CXCL10, (D) JAK1, and (E) STAT1 expression in patients and in their respective controls from 12 selected diseases including COVID-19 wherein these genes were found to be differentially regulated. Each point represents fold changes from individual patient or control. Bars depict standard error of mean.
TALL, wherein \textit{CATHEPSIN A, B, and D} were downregulated, we observed that majority of the host proteases were highly upregulated in other subtypes of leukemia. Although cathepsins have an additive effect, they may not be indispensable for viral entry. Yet their increased expression along with that of \textit{FURIN} and \textit{TMPRSS2} can promote the processing of viral spike and enhance cellular entry of SARS-CoV-2 \cite{21}. Taken together these data suggest that the patients of leukemia are highly prone to SARS-CoV-2 infection. Similarly, the expression of \textit{FURIN} was observed to be higher in NAFLD and psoriasis patients. Recently the abundance of either \textit{FURIN} or \textit{TMPRSS2} was shown to be sufficient in promoting the cellular entry of SARS-CoV-2 \cite{21}. Although the relevant information on psoriasis is missing in the literature, Dong et al. (2020) have recently observed NAFLD comorbidity in COVID-19 patients \cite{5}. Therefore, we propose that the increased expression of
ACE2 and FURIN could result in COVID-19 associated comorbidities. However, studies aimed at testing the redundancy of proteases are required to arrive at a definite conclusion.

Following the proteolytic cleavage of viral spike, the viral envelope fuses with host membrane and subsequently evokes the primary defense response of the host. This response is composed of the interferon-mediated innate immune response [36]. The production and binding of type I and type III interferons to their respective cellular receptors culminate into activating JAK1/STAT1 mediated transcription of several anti-viral interferon-stimulated genes [37]. It has been reported that the JAK1 deficient mice exhibit poor lymphoid development, and defective response to cytokines and interferons and die perinatally [38]. Similarly, mice with disrupted expression of STAT1 have compromised innate immunity [39] and are prone to viral infections [40]. Somatic mutations and dysregulation of JAK1 mediated signaling have been frequently observed in acute lymphoblastic leukemia [41,42]. Also, the deficiency of TYK2 (tyrosine kinase 2) in humans, which constitutes a key component of type I and type III interferon response, was shown to induce cytokine signaling defects and susceptibility to infection [43]. We observed that the expression of IFNA2, IFNA8, IFNA10, IFNA14, IFNA16, IFNA21 and IFNB1 were increased, whereas that of JAK1, STAT1, and TYK2 did not change significantly in leukemia patients. Thus, the increased interferon response in leukemia patients may involve components other than JAK1, STAT1, and TYK2. In contrast, in NAFLD patients the increased expression of JAK1 and STAT1 corresponds well with the increased expression of the interferons encoding genes, namely, IFNA2, IFNA8, IFNA10, IFNA14, IFNA16, IFNA21 and IFNB1. On the other hand, the expression of JAK1 and STAT1 decreased in T2D muscle and the expression of interferons decreased in T2D liver. However, p-STAT1 levels must be quantified to conclusively reveal the correlation between STAT1 expression in COVID-19 associated comorbidities. The higher levels of interferons may be one of the reasons for the previously observed reports describing relatively milder symptomatic COVID-19 in CLL patients [44]. However, SARS-CoV-2 may use several escape or immune-suppression strategies including the formation of a replication organelle and 2′-O-methylated capping of viral RNA to proliferate despite of increased basal interferon levels in leukemia and NAFLD patients [45]. Thereafter, the specific adaptive immune response comes into effect for curbing the viral invasion. An optimal secretion of cytokines and chemokines (such as IL6 and CXCL10) from immune cells is essential to adjust the host’s immune response against foreign invaders. However, the excess release of cytokines, also known as cytokine storm, is associated with an increased severity of disease and poorer outcomes in SARS-CoV [46,47] and SARS-CoV-2 [48] infected patients. Earlier, the inhibition of NF-κB mediated production of IL6 was found to increase the survival in SARS-CoV infected mice [49] and IL6 blockade has been thought of as a mechanism to manage cytokine storm and save COVID-19 patients [50]. We observed a higher basal expression of CXCL10 in leukemia, NAFLD, and PDAC patients that may subsequently lead to cytokine storm upon SARS-CoV-2 infection. Recently Malard et al. (2020) have also reported that patients with hematologic malignancies are at higher risk of developing a severe form of COVID-19 [51]. Thus, we propose that the inhibitors of IL6 and CXCL10 could be examined for clinical interventions in leukemia and NAFLD patients who have been tested positive for SARS-CoV-2.

Furthermore, calcium signaling was found to be perturbed in COVID-19 and at least 6 other studied disease types including leukemia, NAFLD, and psoriasis that manifested in the form of altered expression of...
RAMP3, S100A2, and CLCA2 genes. RAMP3 is a co-activator that targets the calcium-sensing receptor to cell surface [52,53]. CLCA2 regulates the calcium-activated chloride channel currents and enhances the store-operated cellular entry of calcium [54]. S100A2 encodes a cytoplasmic calcium-binding protein and is known to be dysregulated in human cancers [55]. Together, these three genes modulate the cellular calcium levels in response to various stimuli and were distinctly upregulated in leukemia, NAFLD, and psoriasis (Supplementary Fig. 1).

Recently, Sun et al. (2020) showed that calcium channel blockers inhibit the replication of SARS-CoV-2 in the cellular milieu and reduce the COVID-19 associated case-fatality rate [56]. Thus, cellular calcium levels may play a significant role in inducing susceptibility to SARS-CoV-2 infection. Furthermore, we found that the expression of CA11 and CLU genes were commonly altered in SARS-CoV, SARS-CoV-2, and MERS-CoV infected cases. These data indicate the uniqueness of the host gene expression patterns, thereby supporting the distinctive nature of these infections. Although CA11 was upregulated in leukemia, no trend was observed in the expression of CLU in the studied disease types.

As of now, no direct correlation has been identified between the expression of either CA11 or CLU with the pathogenesis of SARS-CoV-2. However, several authors have recently identified that COVID-19 may lead to ketosis, ketoacidosis [57], and altered glucose metabolism [58]. Because CA11 plays an important role in hepatic gluconeogenesis [59], it could be interesting to investigate the potential relationship between SARS-CoV-2 infection, differential CA11 expression, and the onset of diabetes in COVID-19 patients.

Our study has few associated caveats. At first, we have selected the gene expression datasets from 30 diseases with strict criteria, namely, human samples with disease-specific tissues. The datasets were generated through expression profiling by array and the cases were devoid of any other treatments or afflictions. Given the reasonable number of samples used in these studies, we believe that our observations could be generally applicable. However, the limited sample size could impose limitations on confirming these observations in other samples including patients from other populations. This study concludes that the patients of leukemia are relatively more susceptible to SARS-CoV-2 infection followed by NAFLD, psoriasis, T2D, and PAH. It has been reported that STAT1 signaling promotes the proliferation of leukemia [60] and non-alcoholic steatohepatitis [61], and the inhibition of JAK/STAT signaling has shown protective activity in leukemia [60] and type II diabetes [62]. Complementarily, recent reports have observed down-regulation of STAT1 [63] and upregulation of CXCL10 [64] post SARS-CoV-2 infection. These reports suggest a potential target avenue for the treatment of COVID-19.

Therefore, the strategy of inhibition of inflammatory cascade appears important for curbing SARS-CoV-2 infection with a concomitant increase in survival rates and for the added benefit of management of associated comorbidities. Therefore, our study indicates that disease-specific inhibition of IL6, CXCL10, JAK1, and STAT1 either alone or in various combinations could benefit in curbing COVID-19 associated comorbidities. Our report could support the healthcare systems across the globe in devising better management practices for preventing the complications of COVID-19 associated comorbidities.

Author contribution

MKS, AM, and AC: Conceptualization, Data curation, Formal analysis, Investigation, methodology, validation, visualization, writing – original draft, review & editing. SJ: Investigation, methodology, validation, visualization, writing – original draft, review & editing. SR: Data curation, Funding acquisition, Project administration, supervision, writing – review & editing.

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No disclosures to make.

Declaration of competing interest

Authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2021.104219.

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