Genetic and inflammatory signatures associated with worse prognosis in hospitalized patients with severe SARS-CoV-2 infection with and without diabetes.

# Introduction

Coronavirus Disease of 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was announced as a pandemic by the WHO at the beginning of 2020 due to its rapid communicability and disease severity.1 By October 2022, COVID-19 had caused over 6.5 million deaths.2 Primarily a condition that affects the respiratory system, the disease presents in patients with a wide range of symptoms, ranging from asymptomatic and mild to severe. In the most critical cases, patients may require intensive critical care (ICU) and mechanical intubation, among other intensive interventions.1 A variety of risk factors are suggested to increase the risk for severe illness, including age greater than 65 years, hypertension, smoking, and diabetes.3

Multiple meta-analyses of the clinical correlation between diabetes and SARS-CoV-2 have demonstrated that individuals with diabetes are at higher risk for severe disease and mortality, reporting odds ratios as high as OR = 2.75 (95% CI: 2.09-3.62; p < 0.01) for severe disease.1,4,5 Diabetes has been previously implicated in other infectious conditions, including being associated with over a four-fold risk of ICU admission in patients with the Influenza A infection of 2009 (H1N1).6 Furthermore, diabetes has been observed to be associated with critical illness and identified as an independent risk factor for 90-day mortality in patients with Middle East respiratory syndrome coronavirus (MERS-CoV).7 Other studies further corroborate a bi-directional link between diabetes and COVID-19, including cases and systematic reviews that found a higher incidence rate of new-onset diabetes and hyperglycemia in patients previously infected by COVID-19.8,9 Despite the substantial data that supports diabetes as a risk factor for diabetes, the mechanism that mediates this risk is largely unknown.

Although poorly elucidated, the mechanism of disease severity in diabetes mellitus patients may be connected to angiotensin-converting enzyme 2 (ACE2) and cytokine/chemokine gene expression. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) uses the ACE2 receptor to enter host cells.10 Upon entry, there is a downregulation of surface ACE2 expression. Circulating angiotensin 2 (Ang-II) is elevated in COVID-19 patients compared to healthy controls, providing evidence of renin-angiotensin system (RAS) imbalance in the disease.11 Increases in Ang-II lead to increases in disintegrin and metalloproteinase 17 (ADAM17) activity and subsequent release of tumor necrosis factor α (TNF- α) and other inflammatory cytokines.10 Nuclear factor erythroid 2–related factor 2 (NRF2) and NRF2-related genes are regulators of cellular redox balance and are involved in releasing inflammatory cytokines and chemokines secondary to stress. NRF2 activation downregulated a variety of cytokines that were reported to be elevated in COVID-19, suggesting reduced NRF2 activity as a contributor to the “cytokine storm” seen in COVID-19.12

Chemokines are an important secretory protein responsible for immune signaling and have been implicated in various lung pathologies. For example, CCL2 [chemokine (C-C motif) ligand 2; monocyte chemoattractant protein-1, (MCP-1)] and its receptor CCR2 are involved in monocyte/macrophage migration, Th2 cell polarization, and the production of TGF-β and procollagen in fibroblast cells.13,14 This chemokine is associated with acute respiratory distress syndrome and pulmonary fibrosis15 – both observed in COVID-19. CCL2 elevation has also been found to be associated with severe SARS-CoV.16 Various chemokines have been reported to be elevated in COVID-19 infection, but there has not been an evaluation of differential patterns of expression in individuals with and without diabetes17.

This study evaluated gene and protein expression patterns in individuals hospitalized with diabetes mellitus infected with SARS-CoV-2 and examined the relationship between these patterns and disease severity.

# Methods

Data source and sample collection

We performed a single-center, IRB-approved cohort study using data from electronic health records and leftover clinical specimens at a large community medical center. All subjects 18 years of age or older with remnant clinical blood specimens within 48 hours of hospital admission were eligible for inclusion. Pregnant patients and those discharged directly from the Emergency Department were excluded. An aliquot of leftover whole blood specimens collected in EDTA tubes was immediately frozen for each patient. The remaining whole blood was centrifuged at 3000 x *G* for 10 minutes, and plasma was drawn off. All samples were stored at -80°C until analysis.

## Data extraction and collection

All data were extracted from the electronic health record (EPIC Systems; Wisconsin, USA). Patient age, sex, race/ethnicity, comorbidities, vaccination status, concomitant medications, COVID-related treatment interventions, and other relevant clinical laboratory data were extracted from the records. Patient comorbidities were identified using the International Classification of Diseases, tenth revision, clinical modification (ICD-10-CM) codes. The overall comorbidity status of patients was defined by the scoring of the Charlson-Deyo comorbidity Index (CCI).

## RNA-Sequencing

RNA sequencing was performed “fee-for-service” by Singulomics (Bronx, NY). Messenger RNA was purified from total RNA using poly-T oligo-attached magnetic beads. After fragmentation, the first strand cDNA was synthesized using random hexamer primers, followed by the second strand cDNA synthesis using either dUTP for directional library or dTTP for non-directional library. For the non-directional library, it was ready after end repair, A-tailing, adapter ligation, size selection, amplification, and purification.

## Cytokine and chemokine multiplex assay

Plasma cytokine and chemokine concentrations were measured using ProcartaPlexTM Human Cytokine Storm 21-Plex (Invitrogen; EPX210-15850-901) on the Luminex platform. The multiplex panel measured the plasma concentration of IFN- α, IFN- γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8 (CXCL8), IL10, IL-12p70, IL-17A (CTLA-8), IL-18, IP-10 (CXCL10), MCP-1 (CCL2), MIP-1α, MIP-1β, TNFα, and TNFβ. Briefly, 25 µL of plasma and internal controls were plated on a 96-well plate, incubated with magnetic beads, and washed before adding 25 μL of detection antibody. The plate was then incubated for 30 minutes, followed by adding 50 μL of Streptavidin-PE to each well. The concentration of analytes was reported as pg/mL.

## ACE2 and DPP-IV ELISA

Circulating ACE2 and DPP-IV were measured by sandwich ELISA (Invitrogen; EH489RB; InvitrogenTM; EHDPP4). Briefly, 100 μL of standards and 100 μL of diluted plasma samples using the assay-specific dilient were plated on a 96-well plate. After a series of washes, 100 μL of biotin was added to each well, followed by a 1-hour incubation period at room temperature with gentle shaking. The solution was discarded, the plate was washed, and 100 μL of streptavidin-HRP was added. The plate was incubated for 45 minutes with gentle shaking. After the solution was discarded and the plate washed, 100 μL of TMB substrate was added and incubated for 30 minutes. Once the stop solution was added, the plate was read at an absorbance of 450 nm, and an assay-specific standard curve was used to obtain the protein concentrations. The plasma ACE2 and DPP-IV concentrations were reported as ng/mL and pg/mL, respectively.

## Primary and Secondary Outcomes

Patients were stratified into those with COVID-19 and those without COVID-19, as well as those with diabetes and those without diabetes. The primary endpoint was the identification of differentially expressed genes between individuals with and without COVID-19 stratified by diabetes status. Secondary endpoints include differences in inflammatory mediator expression, circulating ACE2 circulating DPPIV, and clinical outcomes such as death, length of hospital stay, and WHO-OSCI score.

## Statistical Analysis

Statistical analysis and data visualization were performed using *R* 4.3.1 software.18 All data are presented with summary statistics. Categorical variables are represented as proportions, and continuous data are represented by means and standard errors. Differences in baseline characteristics were analyzed utilizing a t-test or analysis of variance (ANOVA) for continuous data and chi-squared or Fisher’s exact test for categorical data. All comparisons were adjusted for multiplicity.

RNA-seq data were analyzed with the DESeq2 R package based on the negative binomial distribution for differential gene expression analysis.19 Pathway analysis was conducted with the ReactomPA package.20

# Results

The study included 182 hospitalized adult patients with an admitting diagnosis of COVID-19 (n=110) and control subjects admitted for any other reason (n=72). All available remnant blood samples were obtained within 48 hours of hospital presentation. Table 1 summarizes patients’ baseline characteristics, including demographics, vaccination information, comorbidities, medications, baseline lab work, and clinical scores, stratified by diabetes mellitus (DM) diagnosis. Overall, individuals with DM regardless of COVID-19 status had higher comorbidity as described by the Charlson Deyo Index. Available clinical laboratory values are summarized in Table 2. A significant proportion of laboratory values were missing for the no COVID-19 group, likely due to the patient diagnosis and the necessity for a specific laboratory order. Inherently, individuals with COVID-19 were more likely to be on remdesivir, tocilizumab, and corticosteroids (Table 3). In terms of background diabetes therapeutics, all individuals with DM, regardless of COVID-19 status, received similar medications. Individuals with DM were more likely to receive anticoagulants, and those with COVID-19 were more likely to be on full-dose anticoagulation (81.8% versus 72.2%).

## Differential Gene Expression Analyses

In total, 58,708 protein-coding and long noncoding genes and gene variants were found in the 92 RNA-seq samples. Of these, 19,909 were protein-coding genes. Note that 15 genes had two variants each. For these genes, the variant counts were added up within each sample.

Genes with a small number of hits were filtered out. Based on examining the number of genes remaining after filtering using varying the minimum number of hits per sample and the minimum number of samples with at least that many hits (**Figure 1**), it was decided to set both numbers to 10. Hence, 14,223 genes with at least 10 hits in at least 10 out of 92 samples were used in the analysis.

Next, we identify coding genes differentially expressed in COVID patients compared to controls (at least 2-fold change and adjusted p-value ≤ 0.05). 2 genes were downregulated and 16 upregulated in COVID patients compared to non-COVID. The list of the 18 genes and the estimates of the differences (on log2 scale and representing the number of 2-fold changes in COVID vs. non-COVID patients’ samples) is presented in **Table X**. **Figure X** shows the total number of hits for each of the 18 genes in each sample.

One of the most striking differences found in this part of the analysis was the overexpression of the Interferon-Alpha Inducible Protein 27 (IFI27) coding gene, with a 2-fold difference of 2.37 (SEM = 0.49). In this study, most of the patients who had gene sequencing data and died in hospital had their IFI27 expression levels elevated compared to those who were discharged alive (**Figure 3, left panel**). No obvious patterns were observed for critical care as an outcome (**Figure 3, right panel**).

Next, DM's association with gene expression was tested. In total, 431 genes were differentially expressed in DM patients vs. the controls (non-DM), with 45 genes upregulated by DM and 386 genes downregulated (Table X).

Out of all genes found to be differentially expressed in COVID/non-COVID and DM/non-DM patients, there were 5 genes in common: GRASP, KRT8, MYZAP, PRKG1 and SMIM24. The number of hits in the samples, grouped by COVID and DM diagnoses, are presented in **Figure 4**.

## Inflammatory signature analysis

Cytokines and chemokines were measured using a multiplex ELISA assay. In total, 21 plasma protein concentrations were measured in 54 COVID and 68 non-COVID patients (**Table X, Figure 5**). IFN alpha and IL-10 were increased in individuals with COVID-19 without DM versus those without either disease. IL-4, IL-5, and IP-10 in all individuals with COVID versus those without infection, regardless of DM status. There was a numerical increase in TNF alpha and IL-6 in individuals with COVID and DM versus those without either disease; however, the difference failed to reach significance.

## DPP-IV and ACE2 signature analysis

Plasma ACE2 and DPP-IV were measured using ELISA. Plasma ACE2 was significantly higher in individuals with COVID-19 versus those without (2.03 ± 18.1 pg/mL versus 8.43 ± 18.47 pg/mL; p=0.008). In patients with COVID-19, those with DM did not have significantly higher plasma ACE2 concentrations versus those without DM (11.88 pg/mL ± 26.98 versus 6.61 ± 11.91 pg/mL; p=0.414). DPP-IV was significantly lower in individuals with COVID-19 versus those without the infection (322.62 ± 175.97 pg/mL versus 1217.3 ± 463.80 pg/mL; p<0.001).

## Clinical outcomes

Out of 110 patients admitted with COVID-19, 12 (10.9%) died during hospitalization compared to 3 out of 72 non-COVID-19 patients (4.2%). Three (3) out of the 12 COVID-19 patients who died in the hospital were admitted for shortness of breath (ICD10 R06.02), unspecified fever (ICD-10 R50.9), or fatigue (ICD-10 R53.83). The 3 non-COVID in-hospital deaths occurred in patients admitted for pneumonia (ICD-10 J18.9) or acute respiratory distress (ICD-10 R06.03).

There was no significant association between DM and COVID-19 patients’ in-hospital death rate (**Table 4**), with 6 DM (17.6%) and 6 non-DM (7.9%) COVID-19 patients dying in hospital (Chi-square test p-value = 0.236). Similarly, obesity and BMI were not significant factors associated with in-hospital death (p-values of 0.760 and >0.999, respectively). However, the odds of in-hospital death were 21.5 times higher (95% CI = 5.2 to 88.3, p-value< 0.001) for the COVID patients admitted to the critical care unit (ICU) compared to those who were not admitted to the ICU. Specifically, 7 out of 13 ICU-admitted patients died in hospital compared to 5 deaths occurring in 97 non-ICU patients.

The odds ratio of in-hospital death for patients admitted with COVID-19 versus non-COVID-19 patients was not statistically significantly different from 1 (OR=2.82, 95%CI = 0.86 to 12.70, p-value = 0.119). After adjusting for ICU, the association of COVID-19 diagnoses with death became significant (OR = 6.79, 95%CI = 1.73 to 36.07, p-value = 0.012).

COVID-19 severity was measured on the World Health Organization Original Scale for Clinical Improvement (WHO OSCI) scale (**Table 5**). COVID-19 patients were grouped by the WHO OSCI into Moderate (score < 5) and severe (>=5 and <8) cohorts. WHO OSCI score of 8 signified deaths. At the admission, 77 out of 110 COVID patients had a WHO OSCI score of 5 or higher. Notable, 5 out of the 13 COVID-19 patients admitted to the ICU had a score of 5, and another 8 score of 6.s At the same time, 64 out of 97 non-ICU patients (66.0%) scored 5 or above at the admission. Additionally, all 12 COVID-19 patients that died in the hospital had WHO OSCI scores of 5 or 6 at admission, and their scores did not decrease until their death except for a single patient whose score declined from 5 to 4 on Day 3, just before death (Table 2).

On average, COVID-19 patients were admitted for a slightly shorter period compared to non-COVID patients (mean+/-SEM = 7.3+/-0.9 and 8.8+/-1.1 days, respectively). The patients who died in the hospital were hospitalized for longer times compared to those discharged alive (12.5+/-2.4 vs 7.5+/-0.7, respectively). The difference between COVID and non-COVID patients’ length of stay was even larger for those who were not discharged on the day of admission (i.e., stayed for more than one day), with LOS of 10.1+/-1.2 days for non-COVID patients discharged alive vs. 7.4+/-0.9 days for the COVID patients discharged alive. For the patients who died in the hospital, the LOS were 11.0+/-3.8 and 12.8+/-2.9 for non-COVID vs. COVID patients, respectively.

# Discussion

Our study compares gene expression, protein expression, and clinical outcomes in patients hospitalized with COVID-19 stratified by diabetes. First, we evaluated the differential expression of several genes between COVID and non-COVID groups. The relevance of these gene pathways in the pathophysiology of COVID-19 has been documented in the literature or is biologically plausible (**Supplemental Table 1**). Several of these gene pathways contribute to disease progression, such as AXL, BAMBI, CLEC6A, IFI27, Krt8, Nectin-2, PRKG1, and PDE2A.21-24 The summary of select differentially expressed genes and their potential roles in COVID-19 is provided below. The remaining genes’ connection to COVID-19 remain poorly elucidated and further studies are required to definitely understand their role in the pathogenesis of this disease.

AXL functions as a tyrosine receptor kinase within the TAM subfamily of receptor tyrosine kinases and functions to control mechanisms of inflammation and coagulation. Like other TAM receptors (Tyro3 and Mer), Axl has important effects on hemostasis and inflammation.25 TAM subfamily of receptor tyrosine kinases, when activated, have also been demonstrated to reduce the production of cytokines, including type I IFNs, IL-6, and TNF, following activation of various TLRs, including TLR-3, 4, and 9.26 TLR-9 is associated with cellular defense against viral infections and is hypothesized to function similarly against COVID-19 thus, TAM activation may downregulate important cytokine function in the immune and inflammasome response.27 Our study demonstrated a differential increase in AXL expression, which may stunt immune responses to COVID-19 and increase the risk of disease complications. In addition to AXLs role in cytokine production, previous research suggests that AXL may play a role in the entry of SARS-CoV-2 virus into human cells along with ACE2, especially given the elevated expression of AXL in comparison to ACE2 in human pulmonary and bronchial tissue.28 Increased expression of AXL thus may predispose specific patients to be more susceptible to COVID-19 infection.

Another potential mechanism of AXL in the pathogenesis of SARS-CoV-2 is described by its role in platelet activation. Mouse models have demonstrated that binding of growth arrest-specific gene 6 (Gas6) to AXL receptors contributes towards platelet thrombus formation and similarly, inhibition of such an interaction inhibits platelet aggregation and degranulation.29 Thrombosis is commonly seen in SARS-CoV-2, and several mechanisms, including inflammation and spike protein-ACE2 binding, have been cited as pathways of platelet activation.30 Although thrombosis outcomes were not assessed in the patients of this study, the increased AXL expression and activation may similarly contribute towards the formation of platelet-derived thrombosis. Importantly, understanding the role of AXL may improve the selection of anticoagulant strategies in this patient population. For example, warfarin blocks Gas6-mediated AXL activation, while direct oral antithrombotics and heparins do not.31,32 Nonetheless, full-dose anticoagulation in hospitalized patients with COVID-19 who are not critically ill is recommended by several treatment guidelines without specific recommendations for a specifc agent.33 In critically ill patients, standard prophylaxis is recommended unless the patient’s presentation is consistent with thrombosis.

BAMBI, also known as BMP and activin membrane-bound inhibitor, has been demonstrated to modulate the expression of ACE2 at the mRNA level.24 When upregulated in cells, BAMBI increases the proportion of COVID-19-infected cells.24 SARS-CoV-2 viral entry into human cells has been observed through the binding of the spike protein to the ACE2, promoting attachment and fusion. SARS-CoV-2 has a significantly higher affinity for ACE2 than SARS-CoV, contributing towards the greater degree of pathogenicity of the newer disease.34 Increased expression of BAMBI in COVID-19 patients may be indicative of underlying susceptibility to viral invasion and infection. BAMBI is also highly expressed in platelets and endothelial cells and has a role in thrombus formation.35

CLEC6A, also known as dectin-2, is a member of the C-type lectins that are typically expressed on macrophages and dendritic cells as part of C-type lectin receptors (CLRs). Activation of these receptors are responsible for a myriad of cellular functions such as cell adhesion, stimulation of endocytosis, tissue repair, activation of platelets, and the natural immune system.36 The activation of CLRs via CLEC6A (and other pathways) stimulated the recruitment of tyrosine kinases and beta cell lymphoid tissue 10 to form complexes triggering the NF‐kB and MAPKs pathways.37 Although the role of CLEC6A is not well elucidated in COVID-19, there are data that suggest its relevance in the pathogenesis of MERS-CoV, a very closely related virus. In MERS-CoV, the increased activation of CLRs has been shown to contribute towards a stronger immune response and promote viral recognition, triggering a proinflammatory response.38 It is possible that CLEC6A plays a similar role in COVID-19 and may contribute to the “cytokine storm” that is often cited as the catalyst for COVID-19 mortality.

The protein coded by IFI27 was previously shown to be associated with other viral infections, including Hepatitis C, respiratory syncytial virus (RSV) infection, and Enterovirus 71 (EV71) hand, foot, and mouth disease. IFI27 has also been proposed as a biomarker to differentiate between influenza versus bacterial respiratory infection, although its ability to differentiate between different viruses is limited.39 More recently, IFI27 has been proposed as a biomarker for an early prediction of COVID-19 outcomes.23 IFI27 counteracts innate immune responses and has a positive effect on SARS-CoV-2 replication.40 Therefore, there is mechanistic evidence suggesting that elevated IFI27 leads to elevated SARS-CoV-2 viral load. While there is conflicting evidence on viral load and COVID-19 outcomes, older individuals with higher viral loads had worse outcomes, and overall transmissibility increases as viral load increases.41

Krt8 is a gene that is expressed by transitional alveolar epithelial cells during lung injury. Type 1 and type 2 alveolar epithelial cells consititute the functioning lung parenchyma. Following an injury event, the lung will undergo a recovery process that involves the proliferation of type 2 alveolar epithelial cells, which will then undergo a transitional state and then fully differentiate into the type 1 alveolar epithelial cells. This transitional state is characterized by the expression of specific gene signatures, one of which being Krt8.42 Several studies have shown that there is an abundance of Krt8+ transitional cells in patients with COVID-19. In lethal cases, however, it has been shown that the increase in Krt8+ is not matched by an increase of type 1 alveolar epithelial cells, indicating a disrupting differentiation process and suggesting that regenerative processes are impaired in the COVID-19 disease state.42,43 Chronically, Krt8 may also be implicated in the development of fibrotic patterns following COVID-19 infection. In bleomycin-induced models of pulmonary fibrosis, Krt8+ cells showed increased expression of pro-fibrotic proteins such as Areg and Hbegf and presence of myofibroblasts.44 Examination of gene profiles in non-resolvable COVID-19 revealed increases in both fibrotic gene and Krt8 expression similar to those in idiopathic pulmonary fibrosis.45 Severe COVID-19 has been characterized by the development of fibrosis with increased collagen deposition, supporting the proposed fibrotic pathological process.46,47

Nectin-2 is a member of the nectin family involved in cellular adhesion molecules (CAMs), which regulate important cell-cell interactions. One of these interactions is with the DNAX accessory molecule 1 (DNAM-1), which is mediates the activation of natural killer cells and cytotoxic T cells.48 A study investigating the expression of natural killer cell ligands and receptors in COVID-19 found an increased proportion of activated natural killer cells in moderate to severe COVID. Paradoxically, however, there was a decrease in the amount of the activating DNAM-1 receptor despite an increase in nectin-2 expression.49 This response is hypothesized to be a stress-induced response down-regulation in which high stress environments will promote the receptor endocytosis and subsequent lysosome degradation. The loss of DNAM-1 receptors eventually impairs the function of natural killer cells.50 Thus, the high activity of nectin-2 in patients with COVID-19 is primarily a response to the initial infection, but overactivity may ultimately stunt long term natural killer cell effectiveness.

PRKG1, also known as cGMP-dependent protein kinase 1, phorphoryles many targets, regulating functions such as platelet activation and adhesion and cardiomyocyte cGMP.51,52 Within PRKG1, however, is a ELDKY gene motif that demonstrates strong molecular mimicry to the COVID-19 spike protein.53 ELDKY has been scene to elicit antibody responses following COVID-19 immunization with the spike protein mRNA vaccine and increased antibody response to ELDKY has been observed in patients with severe COVID-19.54,55 It is hypothesized that the cross-reactivity of the ELDKY motif and the spike protein may be responsible for antibody-mediated effects on both platelet and cardiac function seen in COVID-19.30,53 Another study examining genomic data of COVID-19 patients found that PRKG1 alleles have also been found to be linked with increased mortality in the middle-aged European-American population (ages 45-54), although the definitive mechanism of this risk factor is remains unknown.56

Phosphodiesterases (PDEs) play important roles in hydrolyzing and inactivating cAMP and cGMP in cellular processes. PDE2A, however, is specifically stimulated by cGMP to preferentially hydrolyze cAMP.57 These intracellular cyclic nucleotides have been known to play a role in the maintenance of the endothelial cell barrier.58 Although little data specifically connecting PDE2A to COVID-19 exists, this gene has been previously implicated in the development of lung injury. In mouse studies, PDE2A has been found to downregulate lung nitric oxide synthase (NOS) in early stage injury thus promoting alveolar inflammation and lung injury.59 In late stage injury, however, PDE2A functions to inhibit macrophage NOS expression, which have been suggested to promote lung-injury resolution following initial insult.57 The mechanism of this pathological process is hypothesized to involve pulmonary endothelial barrier dysfunction caused by decreases in cAMP catalyzed by increased PDE2A expression.60 A separate study evaluating the effects of tumor necrosis factor-α (TNF-α) found an up-regulation in PDE2A downstream and increased membrane permeability. PDE2 inhibition in mice lungs found reduced wet-to-dry ratio and albumin movement, demonstrating minimized fluid translocation.61 PDE2A’s role in the development of lung injury through disrupted endothelial membrane barriers likely reflects the upregulation of this gene in COVID-19 patients and the increased risk for pulmonary complications such as acute respiratory distress syndrome (ARDS).

In addition to gene expression, we measured a panel of cytokines and chemokines and circulating ACE2, and circulating DPP-IV. While we did not find significant differences in TNF and IL-6 between groups, individuals with COVID-19 and DM did have numerically higher values than those without either disease. Previous literature has highlighted elevated cytokines and chemokines leading to “cytokine storm” in individuals with severe COVID-19.62 Importantly, nearly 80% of patients included in the current study received dexamethasone, and others received alternative corticosteroids. These drugs are frequently administered at the earliest sign of severe illness to prevent cytokine storm.63 As such, the relatively small changes in cytokines and chemokines may have been influenced by drug therapy. In addition, individuals with DM were more likely to receive tocilizumab, an IL-6-directed monoclonal antibody.

Serum ACE2 has been shown to be associated with more severe COVID-19 infection.64,65 Similarly, circulating DPP-IV has been reported as lower in individuals with severe COVID-19.66,67 Our findings affirm these previous observations.

Finally, clinical outcomes were assessed and we found an increased mortality in patients with COVID-19 and concomitant diabetes versus COVID-19 alone (X% vs X%); however, the difference did not reach statistical significance. Of note, the study was not designed to evaluate clinical outcomes and likely had insufficient power to detect significant differences.

The strengths of this study include the sample size and the quality of sample collection. As far as we are aware, the sample size of 182 patients is larger than most analyses of differential gene expression in patients with and without COVID-19. Furthermore, the study utilized whole blood, which likely reflects a more accurate representation of gene expression relative to samples from other sources, such as nasal swabs.

Conclusions

Gene expression is altered in individuals with COVID-19 with and without DM. Many of the differentially expressed genes are involved in the COVID-19 disease process, representing potential drug targets.

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| Table 1. Subject demographic and clinical characteristics stratified by the presence and absence of diabetes and COVID-19. | | | | | | |
|  | **No Covid** | | **COVID** | | **Overall** | |
| No DM  **(N=39)** | Any DM  **(N=33)** | No DM  **(N=76)** | Any DM  **(N=34)** | No DM  **(N=115)** | Any DM  **(N=67)** |
| Hospital disposition |  |  |  |  |  |  |
| Inpatient | 34 (87.2%) | 30 (90.9%) | 69 (90.8%) | 31 (91.2%) | 103 (89.6%) | 61 (91.0%) |
| ER | 4 (10.3%) | 2 (6.1%) | 5 (6.6%) | 2 (5.9%) | 9 (7.8%) | 4 (6.0%) |
| OP | 1 (2.6%) | 1 (3.0%) | 2 (2.6%) | 1 (2.9%) | 3 (2.6%) | 2 (3.0%) |
| Age |  |  |  |  |  |  |
| Mean (SD) | 67.5 (18.1) | 64.2 (16.8) | 61.4 (16.4) | 67.0 (13.7) | 63.5 (17.2) | 65.6 (15.2) |
| Median [Min, Max] | 74.0 [22.0, 92.0] | 66.0 [28.0, 94.0] | 61.5 [21.0, 93.0] | 68.5 [36.0, 89.0] | 64.0 [21.0, 93.0] | 68.0 [28.0, 94.0] |
| Sex |  |  |  |  |  |  |
| Male | 18 (46.2%) | 17 (51.5%) | 45 (59.2%) | 20 (58.8%) | 63 (54.8%) | 37 (55.2%) |
| Female | 21 (53.8%) | 16 (48.5%) | 31 (40.8%) | 14 (41.2%) | 52 (45.2%) | 30 (44.8%) |
| Race |  |  |  |  |  |  |
| White Non-Hispanic | 27 (69.2%) | 18 (54.5%) | 48 (63.2%) | 24 (70.6%) | 75 (65.2%) | 42 (62.7%) |
| Black | 3 (7.7%) | 3 (9.1%) | 7 (9.2%) | 1 (2.9%) | 10 (8.7%) | 4 (6.0%) |
| Asian | 4 (10.3%) | 2 (6.1%) | 14 (18.4%) | 6 (17.6%) | 18 (15.7%) | 8 (11.9%) |
| Hispanic | 3 (7.7%) | 3 (9.1%) | 7 (9.2%) | 3 (8.8%) | 10 (8.7%) | 6 (9.0%) |
| Other | 2 (5.1%) | 7 (21.2%) | 0 (0%) | 0 (0%) | 2 (1.7%) | 7 (10.4%) |
| Weight (kg) |  |  |  |  |  |  |
| Mean (SD) | 80.5 (24.5) | 85.7 (22.6) | 90.6 (30.8) | 88.8 (22.0) | 87.2 (29.1) | 87.3 (22.2) |
| Median [Min, Max] | 73.1 [48.0, 134] | 89.4 [45.4, 141] | 86.0 [42.0, 217] | 84.8 [45.2, 154] | 82.3 [42.0, 217] | 84.9 [45.2, 154] |
| BMI |  |  |  |  |  |  |
| Mean (SD) | 27.8 (6.97) | 29.5 (6.49) | 31.5 (9.87) | 31.9 (7.35) | 30.3 (9.13) | 30.7 (6.99) |
| Median [Min, Max] | 25.8 [18.9, 47.7] | 29.1 [16.7, 43.9] | 29.0 [20.0, 71.6] | 31.6 [19.5, 50.7] | 28.0 [18.9, 71.6] | 29.8 [16.7, 50.7] |
| Obesity Class |  |  |  |  |  |  |
| I | 11 (28.2%) | 8 (24.2%) | 13 (17.1%) | 11 (32.4%) | 24 (20.9%) | 19 (28.4%) |
| II | 3 (7.7%) | 4 (12.1%) | 10 (13.2%) | 5 (14.7%) | 13 (11.3%) | 9 (13.4%) |
| III | 2 (5.1%) | 2 (6.1%) | 9 (11.8%) | 3 (8.8%) | 11 (9.6%) | 5 (7.5%) |
| CCI |  |  |  |  |  |  |
| Mean (SD) | 5.26 (3.82) | 6.39 (3.79) | 2.22 (1.87) | 4.24 (2.43) | 3.25 (3.04) | 5.30 (3.33) |
| Median [Min, Max] | 5.00 [0, 14.0] | 6.00 [1.00, 18.0] | 2.00 [0, 7.00] | 3.50 [1.00, 9.00] | 3.00 [0, 14.0] | 5.00 [1.00, 18.0] |
| Heart Failure | 12 (30.8%) | 6 (18.2%) | 1 (1.3%) | 5 (14.7%) | 13 (11.3%) | 11 (16.4%) |
| Cerebrovascular Disease | 9 (23.1%) | 10 (30.3%) | 2 (2.6%) | 1 (2.9%) | 11 (9.6%) | 11 (16.4%) |
| Dementia | 2 (5.1%) | 2 (6.1%) | 6 (7.9%) | 5 (14.7%) | 8 (7.0%) | 7 (10.4%) |
| COPD | 5 (12.8%) | 6 (18.2%) | 9 (11.8%) | 5 (14.7%) | 14 (12.2%) | 11 (16.4%) |
| Renal Disease | 5 (12.8%) | 11 (33.3%) | 4 (5.3%) | 5 (14.7%) | 9 (7.8%) | 16 (23.9%) |
| Hypertension | 26 (66.7%) | 26 (78.8%) | 39 (51.3%) | 30 (88.2%) | 65 (56.5%) | 56 (83.6%) |
| Hyperlipidemia | 24 (61.5%) | 23 (69.7%) | 23 (30.3%) | 26 (76.5%) | 47 (40.9%) | 49 (73.1%) |
| Metabolic Syndrome Criteria |  |  |  |  |  |  |
| 0 | 11 (28.2%) | 0 (0%) | 22 (28.9%) | 0 (0%) | 33 (28.7%) | 0 (0%) |
| 1 | 6 (15.4%) | 3 (9.1%) | 19 (25.0%) | 2 (5.9%) | 25 (21.7%) | 5 (7.5%) |
| 2 | 22 (56.4%) | 10 (30.3%) | 23 (30.3%) | 3 (8.8%) | 45 (39.1%) | 13 (19.4%) |
| 3 | 0 (0%) | 19 (57.6%) | 9 (11.8%) | 15 (44.1%) | 9 (7.8%) | 34 (50.7%) |
| 4 | 0 (0%) | 1 (3.0%) | 3 (3.9%) | 14 (41.2%) | 3 (2.6%) | 15 (22.4%) |
|  | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- |
| Table 2. Available patient clinical laboratory values upon hospital presentation | | | | | | |
|  | **No Covid** | | **COVID** | | **Overall** | |
| No DM  **(N=39)** | Any DM  **(N=33)** | No DM  **(N=76)** | Any DM  **(N=34)** | No DM  **(N=115)** | Any DM  **(N=67)** |
| HbA1c |  |  |  |  |  |  |
| Mean (SD) | 5.98 (0.911) | 8.85 (2.57) | 6.21 (0.586) | 8.48 (2.48) | 6.08 (0.779) | 8.66 (2.50) |
| Median [Min, Max] | 5.60 [4.80, 8.80] | 8.50 [5.40, 13.1] | 6.30 [5.50, 7.50] | 7.80 [6.00, 14.3] | 5.90 [4.80, 8.80] | 7.95 [5.40, 14.3] |
| Missing | 22 (56.4%) | 14 (42.4%) | 62 (81.6%) | 15 (44.1%) | 84 (73.0%) | 29 (43.3%) |
| Serum vitamin D |  |  |  |  |  |  |
| Mean (SD) | NA (NA) | 21.6 (6.94) | 83.1 (13.5) | 66.2 (73.5) | 83.1 (13.5) | 48.3 (57.5) |
| Median [Min, Max] | NA [NA, NA] | 21.6 [16.7, 26.5] | 88.0 [63.5, 93.0] | 36.0 [12.6, 150] | 88.0 [63.5, 93.0] | 26.5 [12.6, 150] |
| Missing | 39 (100%) | 31 (93.9%) | 72 (94.7%) | 31 (91.2%) | 111 (96.5%) | 62 (92.5%) |
| ALT |  |  |  |  |  |  |
| Mean (SD) | 22.6 (10.6) | 23.3 (31.7) | 46.7 (49.6) | 73.7 (165) | 38.8 (42.5) | 48.9 (121) |
| Median [Min, Max] | 20.0 [8.00, 49.0] | 15.0 [7.00, 186] | 31.0 [8.00, 286] | 29.0 [8.00, 915] | 27.0 [8.00, 286] | 22.0 [7.00, 915] |
| Missing | 3 (7.7%) | 1 (3.0%) | 3 (3.9%) | 1 (2.9%) | 6 (5.2%) | 2 (3.0%) |
| AST |  |  |  |  |  |  |
| Mean (SD) | 26.3 (20.8) | 22.5 (22.0) | 55.0 (53.7) | 96.6 (241) | 45.3 (47.2) | 60.1 (175) |
| Median [Min, Max] | 19.5 [11.0, 118] | 16.5 [9.00, 134] | 39.0 [11.0, 325] | 36.0 [14.0, 1350] | 32.5 [11.0, 325] | 26.0 [9.00, 1350] |
| Missing | 1 (2.6%) | 1 (3.0%) | 2 (2.6%) | 1 (2.9%) | 3 (2.6%) | 2 (3.0%) |
| hs-CRP |  |  |  |  |  |  |
| Mean (SD) | 0.0400 (NA) | NA (NA) | 9.00 (7.31) | 9.14 (7.68) | 8.44 (7.41) | 9.14 (7.68) |
| Median [Min, Max] | 0.0400 [0.0400, 0.0400] | NA [NA, NA] | 10.1 [0.118, 23.3] | 7.75 [1.55, 25.0] | 8.23 [0.0400, 23.3] | 7.75 [1.55, 25.0] |
| Missing | 38 (97.4%) | 33 (100%) | 61 (80.3%) | 26 (76.5%) | 99 (86.1%) | 59 (88.1%) |
| CRP |  |  |  |  |  |  |
| Mean (SD) | 2.45 (2.82) | 14.5 (9.31) | 9.49 (10.2) | 5.15 (3.27) | 7.73 (9.35) | 9.30 (7.88) |
| Median [Min, Max] | 1.63 [0.0300, 6.52] | 14.8 [2.79, 25.5] | 5.73 [0.300, 33.1] | 5.53 [0.590, 8.74] | 3.87 [0.0300, 33.1] | 7.54 [0.590, 25.5] |
| Missing | 35 (89.7%) | 29 (87.9%) | 64 (84.2%) | 29 (85.3%) | 99 (86.1%) | 58 (86.6%) |
| Fibrinogen |  |  |  |  |  |  |
| Mean (SD) | 357 (267) | 986 (NA) | 539 (156) | 539 (113) | 532 (161) | 561 (147) |
| Median [Min, Max] | 357 [168, 546] | 986 [986, 986] | 509 [269, 887] | 567 [218, 697] | 509 [168, 887] | 574 [218, 986] |
| Missing | 37 (94.9%) | 32 (97.0%) | 29 (38.2%) | 14 (41.2%) | 66 (57.4%) | 46 (68.7%) |
| D-Dimer |  |  |  |  |  |  |
| Mean (SD) | 1260 (1380) | 1270 (1160) | 436 (962) | 722 (959) | 529 (1040) | 777 (973) |
| Median [Min, Max] | 662 [322, 4350] | 1010 [267, 2540] | 17.6 [0.320, 7290] | 559 [0.210, 4330] | 322 [0.320, 7290] | 577 [0.210, 4330] |
| Missing | 31 (79.5%) | 30 (90.9%) | 13 (17.1%) | 7 (20.6%) | 44 (38.3%) | 37 (55.2%) |
| ESR |  |  |  |  |  |  |
| Mean (SD) | 25.5 (27.4) | 50.3 (29.4) | 27.7 (21.3) | 43.6 (34.8) | 27.3 (21.8) | 45.8 (32.4) |
| Median [Min, Max] | 19.5 [3.00, 60.0] | 44.5 [22.0, 101] | 24.0 [1.00, 80.0] | 31.5 [1.00, 115] | 24.0 [1.00, 80.0] | 37.0 [1.00, 115] |
| Missing | 35 (89.7%) | 27 (81.8%) | 57 (75.0%) | 22 (64.7%) | 92 (80.0%) | 49 (73.1%) |
| Ferritin |  |  |  |  |  |  |
| Mean (SD) | 214 (234) | 691 (928) | 1020 (1190) | 1490 (2890) | 967 (1170) | 1310 (2600) |
| Median [Min, Max] | 169 [27.0, 607] | 283 [16.1, 2880] | 541 [18.7, 5750] | 305 [116, 12700] | 516 [18.7, 5750] | 297 [16.1, 12700] |
| Missing | 34 (87.2%) | 24 (72.7%) | 6 (7.9%) | 2 (5.9%) | 40 (34.8%) | 26 (38.8%) |
| LDH |  |  |  |  |  |  |
| Mean (SD) | 485 (404) | 298 (100) | 340 (170) | 326 (160) | 348 (187) | 323 (153) |
| Median [Min, Max] | 325 [209, 1080] | 268 [219, 438] | 293 [148, 890] | 286 [142, 824] | 293 [148, 1080] | 286 [142, 824] |
| Missing | 35 (89.7%) | 29 (87.9%) | 6 (7.9%) | 3 (8.8%) | 41 (35.7%) | 32 (47.8%) |
| Lactic Acid |  |  |  |  |  |  |
| Mean (SD) | 1.99 (1.76) | 2.26 (1.77) | 5.86 (21.4) | 9.33 (30.8) | 4.79 (18.2) | 6.30 (23.4) |
| Median [Min, Max] | 1.70 [0.700, 8.50] | 1.65 [1.00, 7.50] | 1.30 [0.700, 118] | 1.60 [0.800, 150] | 1.40 [0.700, 118] | 1.60 [0.800, 150] |
| Missing | 21 (53.8%) | 15 (45.5%) | 29 (38.2%) | 10 (29.4%) | 50 (43.5%) | 25 (37.3%) |
| Procalcitonin |  |  |  |  |  |  |
| Mean (SD) | 0.944 (2.00) | 3.04 (5.76) | 0.932 (4.02) | 0.430 (0.953) | 0.933 (3.84) | 1.25 (3.46) |
| Median [Min, Max] | 0.157 [0.0340, 5.02] | 0.474 [0.0510, 18.9] | 0.130 [0.0400, 27.7] | 0.160 [0.0300, 4.65] | 0.130 [0.0340, 27.7] | 0.190 [0.0300, 18.9] |
| Missing | 33 (84.6%) | 21 (63.6%) | 27 (35.5%) | 8 (23.5%) | 60 (52.2%) | 29 (43.3%) |
| Plasma glucose |  |  |  |  |  |  |
| Mean (SD) | 122 (34.9) | 226 (107) | 118 (26.1) | 204 (96.2) | 120 (29.3) | 215 (101) |
| Median [Min, Max] | 110 [82.0, 215] | 198 [97.0, 515] | 112 [84.0, 257] | 173 [111, 498] | 112 [82.0, 257] | 189 [97.0, 515] |
| Missing | 0 (0%) | 1 (3.0%) | 1 (1.3%) | 1 (2.9%) | 1 (0.9%) | 2 (3.0%) |
| Serum creatinine |  |  |  |  |  |  |
| Mean (SD) | 1.15 (0.892) | 1.41 (0.945) | 2.39 (9.78) | 1.96 (3.22) | 1.96 (7.95) | 1.69 (2.39) |
| Median [Min, Max] | 0.843 [0.429, 5.06] | 1.07 [0.484, 3.84] | 0.850 [0.290, 82.0] | 0.860 [0.500, 18.0] | 0.850 [0.290, 82.0] | 0.960 [0.484, 18.0] |
| Missing | 0 (0%) | 1 (3.0%) | 1 (1.3%) | 1 (2.9%) | 1 (0.9%) | 2 (3.0%) |

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| --- | --- | --- | --- | --- | --- | --- |
| Table 3. Comparison of medication usage between patient with and without COVID-19 and diabetes | | | | | | |
|  | **No Covid** | | **COVID** | | **Overall** | |
| No DM  **(N=39)** | Any DM  **(N=33)** | No DM  **(N=76)** | Any DM  **(N=34)** | No DM  **(N=115)** | Any DM  **(N=67)** |
| Tocilizumab | 0 (0%) | 0 (0%) | 6 (7.9%) | 6 (17.6%) | 6 (5.2%) | 6 (9.0%) |
| Remdesivir | 0 (0%) | 0 (0%) | 55 (72.4%) | 26 (76.5%) | 55 (47.8%) | 26 (38.8%) |
| Dexamethasone | 6 (15.4%) | 4 (12.1%) | 58 (76.3%) | 27 (79.4%) | 64 (55.7%) | 31 (46.3%) |
| Methylprednisolone | 5 (12.8%) | 3 (9.1%) | 3 (3.9%) | 2 (5.9%) | 8 (7.0%) | 5 (7.5%) |
| Prednisone | 8 (20.5%) | 1 (3.0%) | 1 (1.3%) | 0 (0%) | 9 (7.8%) | 1 (1.5%) |
| Hydrocortisone | 0 (0%) | 0 (0%) | 1 (1.3%) | 3 (8.8%) | 1 (0.9%) | 3 (4.5%) |
| Azithromycin | 3 (7.7%) | 1 (3.0%) | 5 (6.6%) | 0 (0%) | 8 (7.0%) | 1 (1.5%) |
| Hydroxychloroquine | 1 (2.6%) | 1 (3.0%) | 7 (9.2%) | 1 (2.9%) | 8 (7.0%) | 2 (3.0%) |
| ACEi | 2 (5.1%) | 8 (24.2%) | 6 (7.9%) | 7 (20.6%) | 8 (7.0%) | 15 (22.4%) |
| ARBs | 7 (17.9%) | 6 (18.2%) | 9 (11.8%) | 5 (14.7%) | 16 (13.9%) | 11 (16.4%) |
| ARNI | 2 (5.1%) | 0 (0%) | 0 (0%) | 2 (5.9%) | 2 (1.7%) | 2 (3.0%) |
| Insulin | 11 (28.2%) | 30 (90.9%) | 12 (15.8%) | 28 (82.4%) | 23 (20.0%) | 58 (86.6%) |
| Metformin | 0 (0%) | 5 (15.2%) | 1 (1.3%) | 6 (17.6%) | 1 (0.9%) | 11 (16.4%) |
| Glimepiride | 1 (2.6%) | 3 (9.1%) | 0 (0%) | 3 (8.8%) | 1 (0.9%) | 6 (9.0%) |
| Glipizide | 0 (0%) | 2 (6.1%) | 0 (0%) | 3 (8.8%) | 0 (0%) | 5 (7.5%) |
| Sitagliptin | 0 (0%) | 3 (9.1%) | 0 (0%) | 4 (11.8%) | 0 (0%) | 7 (10.4%) |
| Full Dose Anticoagulation | 25 (64.1%) | 27 (81.8%) | 61 (80.3%) | 29 (85.3%) | 86 (74.8%) | 56 (83.6%) |
| Prophylactic Anticoagulation | 21 (53.8%) | 16 (48.5%) | 66 (86.8%) | 28 (82.4%) | 87 (75.7%) | 44 (65.7%) |
|  | | | | | | |

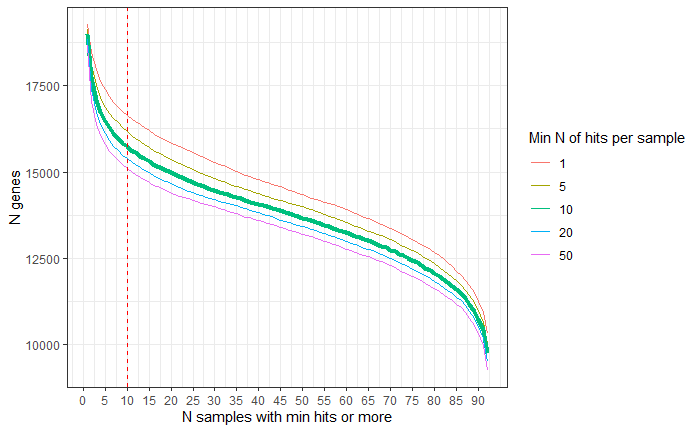
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| --- | --- | --- | --- | --- | --- | --- |
| Table 4. Patient hospital disposition after admission | | | | | | |
|  | **No Covid** | | **COVID** | | **Overall** | |
| No DM  **(N=39)** | Any DM  **(N=33)** | No DM  **(N=76)** | Any DM  **(N=34)** | No DM  **(N=115)** | Any DM  **(N=67)** |
| Critical Care | 14 (35.9%) | 6 (18.2%) | 6 (7.9%) | 7 (20.6%) | 20 (17.4%) | 13 (19.4%) |
| ICU LOS |  |  |  |  |  |  |
| Mean (SD) | 2.90 (7.36) | 1.55 (4.40) | 0.553 (2.50) | 2.91 (8.60) | 1.35 (4.84) | 2.24 (6.84) |
| Median [Min, Max] | 0 [0, 43.0] | 0 [0, 20.0] | 0 [0, 19.0] | 0 [0, 47.0] | 0 [0, 43.0] | 0 [0, 47.0] |
| LOS |  |  |  |  |  |  |
| Mean (SD) | 8.21 (9.80) | 9.48 (8.61) | 6.70 (7.91) | 8.71 (11.1) | 7.21 (8.58) | 9.09 (9.89) |
| Median [Min, Max] | 4.00 [0, 46.0] | 6.00 [0, 34.0] | 4.00 [0, 41.0] | 4.00 [0, 53.0] | 4.00 [0, 46.0] | 6.00 [0, 53.0] |
| Expired | 2 (5.1%) | 1 (3.0%) | 6 (7.9%) | 6 (17.6%) | 8 (7.0%) | 7 (10.4%) |
|  | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- |
| Table 5. Comparison of disease progression with the WHO Ordinal Scale for Clinical Severity | | | | | | |
|  | **No Covid** | | **COVID** | | **Overall** | |
| No DM  **(N=39)** | Any DM  **(N=33)** | No DM  **(N=76)** | Any DM  **(N=34)** | No DM  **(N=115)** | Any DM  **(N=67)** |
| WHO-OSCI D1 |  |  |  |  |  |  |
| 0 | 0 (0%) | 0 (0%) | 2 (2.6%) | 1 (2.9%) | 2 (1.7%) | 1 (1.5%) |
| 3 | 0 (0%) | 0 (0%) | 5 (6.6%) | 3 (8.8%) | 5 (4.3%) | 3 (4.5%) |
| 4 | 0 (0%) | 0 (0%) | 16 (21.1%) | 6 (17.6%) | 16 (13.9%) | 6 (9.0%) |
| 5 | 0 (0%) | 0 (0%) | 45 (59.2%) | 19 (55.9%) | 45 (39.1%) | 19 (28.4%) |
| 6 | 0 (0%) | 0 (0%) | 8 (10.5%) | 5 (14.7%) | 8 (7.0%) | 5 (7.5%) |
| 7 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Missing | 39 (100%) | 33 (100%) | 0 (0%) | 0 (0%) | 39 (33.9%) | 33 (49.3%) |
| WHO-OSCI D3 |  |  |  |  |  |  |
| 0 | 0 (0%) | 0 (0%) | 1 (1.3%) | 1 (2.9%) | 1 (0.9%) | 1 (1.5%) |
| 4 | 0 (0%) | 0 (0%) | 18 (23.7%) | 7 (20.6%) | 18 (15.7%) | 7 (10.4%) |
| 5 | 0 (0%) | 0 (0%) | 31 (40.8%) | 12 (35.3%) | 31 (27.0%) | 12 (17.9%) |
| 6 | 0 (0%) | 0 (0%) | 8 (10.5%) | 7 (20.6%) | 8 (7.0%) | 7 (10.4%) |
| 7 | 0 (0%) | 0 (0%) | 2 (2.6%) | 1 (2.9%) | 2 (1.7%) | 1 (1.5%) |
| Missing | 39 (100%) | 33 (100%) | 16 (21.1%) | 6 (17.6%) | 55 (47.8%) | 39 (58.2%) |
| WHO-OSCI D7 |  |  |  |  |  |  |
| 0 | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2.9%) | 0 (0%) | 1 (1.5%) |
| 4 | 0 (0%) | 0 (0%) | 4 (5.3%) | 0 (0%) | 4 (3.5%) | 0 (0%) |
| 5 | 0 (0%) | 0 (0%) | 5 (6.6%) | 2 (5.9%) | 5 (4.3%) | 2 (3.0%) |
| 6 | 0 (0%) | 0 (0%) | 9 (11.8%) | 7 (20.6%) | 9 (7.8%) | 7 (10.4%) |
| 7 | 0 (0%) | 0 (0%) | 1 (1.3%) | 1 (2.9%) | 1 (0.9%) | 1 (1.5%) |
| Missing | 39 (100%) | 33 (100%) | 57 (75.0%) | 23 (67.6%) | 96 (83.5%) | 56 (83.6%) |
| WHO-OSCI D14 |  |  |  |  |  |  |
| 5 | 0 (0%) | 0 (0%) | 3 (3.9%) | 0 (0%) | 3 (2.6%) | 0 (0%) |
| 6 | 0 (0%) | 0 (0%) | 1 (1.3%) | 4 (11.8%) | 1 (0.9%) | 4 (6.0%) |
| 7 | 0 (0%) | 0 (0%) | 2 (2.6%) | 1 (2.9%) | 2 (1.7%) | 1 (1.5%) |
| Missing | 39 (100%) | 33 (100%) | 67 (88.2%) | 29 (85.3%) | 106 (92.2%) | 62 (92.5%) |
| WHO-OSCI D21 |  |  |  |  |  |  |
| 4 | 0 (0%) | 0 (0%) | 1 (1.3%) | 0 (0%) | 1 (0.9%) | 0 (0%) |
| 5 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 6 | 0 (0%) | 0 (0%) | 2 (2.6%) | 3 (8.8%) | 2 (1.7%) | 3 (4.5%) |
| 7 | 0 (0%) | 0 (0%) | 2 (2.6%) | 1 (2.9%) | 2 (1.7%) | 1 (1.5%) |
| Missing | 39 (100%) | 33 (100%) | 71 (93.4%) | 30 (88.2%) | 110 (95.7%) | 63 (94.0%) |
| WHO-OSCI D28 |  |  |  |  |  |  |
| 4 | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2.9%) | 0 (0%) | 1 (1.5%) |
| 5 | 0 (0%) | 0 (0%) | 1 (1.3%) | 0 (0%) | 1 (0.9%) | 0 (0%) |
| 6 | 0 (0%) | 0 (0%) | 1 (1.3%) | 1 (2.9%) | 1 (0.9%) | 1 (1.5%) |
| 7 | 0 (0%) | 0 (0%) | 1 (1.3%) | 2 (5.9%) | 1 (0.9%) | 2 (3.0%) |
| Missing | 39 (100%) | 33 (100%) | 73 (96.1%) | 30 (88.2%) | 112 (97.4%) | 63 (94.0%) |
| WHO-OSCI DISCHARGE |  |  |  |  |  |  |
| 1 | 0 (0%) | 0 (0%) | 50 (65.8%) | 18 (52.9%) | 50 (43.5%) | 18 (26.9%) |
| 2 | 0 (0%) | 0 (0%) | 19 (25.0%) | 8 (23.5%) | 19 (16.5%) | 8 (11.9%) |
| 4 | 0 (0%) | 0 (0%) | 1 (1.3%) | 2 (5.9%) | 1 (0.9%) | 2 (3.0%) |
| 8 | 0 (0%) | 0 (0%) | 6 (7.9%) | 6 (17.6%) | 6 (5.2%) | 6 (9.0%) |
| Missing | 39 (100%) | 33 (100%) | 0 (0%) | 0 (0%) | 39 (33.9%) | 33 (49.3%) |
|  | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- |
| Table 6. Plasma inflammatory cytokine and chemokine comparison between subjects with and without COVID-19 and diabetes mellitus | | | | | | |
|  | **No Covid** | | **COVID** | | **Overall** | |
| No DM  **(N=39)** | Any DM  **(N=33)** | No DM  **(N=76)** | Any DM  **(N=34)** | No DM  **(N=115)** | Any DM  **(N=67)** |
| G-CSF (CSF-3) |  |  |  |  |  |  |
| Mean (SD) | 1.83 (2.65) | 1.10 (1.28) | 2.17 (2.85) | 1.97 (1.77) | 1.99 (2.73) | 1.44 (1.53) |
| Median [Min, Max] | 1.04 [0, 11.6] | 0.880 [0, 5.04] | 1.19 [0, 10.5] | 1.83 [0, 6.11] | 1.19 [0, 11.6] | 1.04 [0, 6.11] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| GM-CSF |  |  |  |  |  |  |
| Mean (SD) | 4.38 (15.6) | 1.30 (4.26) | 2.54 (6.67) | 1.12 (2.25) | 3.50 (12.1) | 1.23 (3.59) |
| Median [Min, Max] | 0 [0, 77.1] | 0 [0, 19.1] | 0 [0, 25.7] | 0 [0, 6.59] | 0 [0, 77.1] | 0 [0, 19.1] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IFN alpha |  |  |  |  |  |  |
| Mean (SD) | 0.0754 (0.236) | 0.0648 (0.156) | 1.28 (2.57) | 0.242 (0.565) | 0.652 (1.88) | 0.133 (0.377) |
| Median [Min, Max] | 0 [0, 1.30] | 0 [0, 0.743] | 0.390 [0, 11.7] | 0.0650 [0, 2.42] | 0 [0, 11.7] | 0 [0, 2.42] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IFN gamma |  |  |  |  |  |  |
| Mean (SD) | 3.12 (3.63) | 1.98 (1.92) | 1.92 (1.09) | 2.41 (2.55) | 2.54 (2.77) | 2.15 (2.17) |
| Median [Min, Max] | 1.34 [0.290, 14.4] | 1.26 [0.145, 8.51] | 1.89 [0, 4.50] | 1.49 [0.415, 11.6] | 1.71 [0, 14.4] | 1.37 [0.145, 11.6] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IL-1 beta |  |  |  |  |  |  |
| Mean (SD) | 0.859 (1.58) | 0.544 (0.935) | 1.18 (1.78) | 0.988 (1.05) | 1.01 (1.67) | 0.716 (0.996) |
| Median [Min, Max] | 0.418 [0, 6.67] | 0 [0, 3.74] | 0.435 [0, 7.66] | 0.720 [0, 3.73] | 0.435 [0, 7.66] | 0.290 [0, 3.74] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IL-2 |  |  |  |  |  |  |
| Mean (SD) | 1.13 (4.41) | 1.52 (4.12) | 3.18 (8.47) | 1.90 (2.81) | 2.11 (6.70) | 1.67 (3.64) |
| Median [Min, Max] | 0 [0, 26.0] | 0 [0, 19.5] | 0 [0, 35.1] | 0.725 [0, 9.05] | 0 [0, 35.1] | 0 [0, 19.5] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IL-4 |  |  |  |  |  |  |
| Mean (SD) | 7.61 (9.95) | 7.10 (9.53) | 13.1 (9.06) | 13.5 (10.1) | 10.3 (9.87) | 9.58 (10.1) |
| Median [Min, Max] | 4.40 [0, 54.2] | 4.24 [0.415, 48.5] | 9.64 [0, 41.0] | 9.82 [0.365, 34.1] | 7.54 [0, 54.2] | 6.24 [0.365, 48.5] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IL-5 |  |  |  |  |  |  |
| Mean (SD) | 0.599 (0.850) | 0.962 (1.69) | 2.54 (4.85) | 1.99 (1.79) | 1.53 (3.52) | 1.36 (1.78) |
| Median [Min, Max] | 0.113 [0, 2.81] | 0 [0, 6.64] | 0.680 [0, 18.1] | 1.50 [0, 6.88] | 0.460 [0, 18.1] | 0.490 [0, 6.88] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IL-6 |  |  |  |  |  |  |
| Mean (SD) | 9.27 (14.8) | 11.9 (19.4) | 9.02 (9.85) | 72.4 (245) | 9.15 (12.6) | 35.4 (154) |
| Median [Min, Max] | 1.75 [0, 59.9] | 3.61 [0, 86.2] | 5.28 [0, 27.5] | 3.32 [0, 1070] | 2.88 [0, 59.9] | 3.52 [0, 1070] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IL-8 (CXCL8) |  |  |  |  |  |  |
| Mean (SD) | 3.16 (6.64) | 2.26 (2.24) | 1.33 (1.17) | 4.08 (10.3) | 2.28 (4.92) | 2.96 (6.61) |
| Median [Min, Max] | 0.600 [0, 30.9] | 1.47 [0, 9.57] | 1.04 [0, 4.23] | 0.940 [0, 45.8] | 0.930 [0, 30.9] | 1.31 [0, 45.8] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IL-10 |  |  |  |  |  |  |
| Mean (SD) | 0.204 (0.495) | 0.985 (4.02) | 0.751 (1.32) | 0.768 (2.07) | 0.466 (1.01) | 0.901 (3.37) |
| Median [Min, Max] | 0 [0, 2.38] | 0 [0, 22.0] | 0.420 [0, 7.04] | 0.0750 [0, 9.13] | 0 [0, 7.04] | 0 [0, 22.0] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IL-12p70 |  |  |  |  |  |  |
| Mean (SD) | 1.97 (4.09) | 0.952 (1.41) | 1.32 (1.98) | 1.15 (1.28) | 1.66 (3.25) | 1.03 (1.35) |
| Median [Min, Max] | 0.738 [0, 17.5] | 0.233 [0, 5.84] | 0.485 [0, 8.14] | 0.695 [0, 4.69] | 0.730 [0, 17.5] | 0.540 [0, 5.84] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IL-13 |  |  |  |  |  |  |
| Mean (SD) | 4.33 (10.5) | 1.44 (3.89) | 1.45 (3.06) | 0.538 (0.951) | 2.95 (7.96) | 1.09 (3.11) |
| Median [Min, Max] | 0 [0, 48.9] | 0 [0, 19.7] | 0 [0, 12.0] | 0.150 [0, 3.58] | 0 [0, 48.9] | 0 [0, 19.7] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IL-17A (CTLA-8) |  |  |  |  |  |  |
| Mean (SD) | 0.913 (2.84) | 0.597 (0.916) | 1.23 (2.42) | 0.871 (1.01) | 1.06 (2.63) | 0.703 (0.951) |
| Median [Min, Max] | 0.135 [0, 17.3] | 0.190 [0, 3.90] | 0.350 [0, 13.2] | 0.520 [0, 3.51] | 0.345 [0, 17.3] | 0.390 [0, 3.90] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IL-18 |  |  |  |  |  |  |
| Mean (SD) | 103 (118) | 83.3 (110) | 58.8 (30.8) | 83.1 (122) | 81.7 (89.9) | 83.2 (114) |
| Median [Min, Max] | 51.4 [11.9, 533] | 54.8 [14.1, 619] | 55.8 [0, 128] | 42.5 [18.8, 551] | 54.0 [0, 533] | 49.6 [14.1, 619] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| IP-10 (CXCL10) |  |  |  |  |  |  |
| Mean (SD) | 16.4 (20.6) | 18.9 (21.7) | 27.9 (16.5) | 25.6 (19.6) | 21.9 (19.5) | 21.5 (21.0) |
| Median [Min, Max] | 8.80 [1.58, 114] | 13.5 [2.80, 93.0] | 26.1 [0, 66.9] | 19.8 [6.72, 85.6] | 15.4 [0, 114] | 14.4 [2.80, 93.0] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| MCP-1 (CCL2) |  |  |  |  |  |  |
| Mean (SD) | 35.6 (30.1) | 29.5 (21.8) | 36.3 (27.0) | 43.8 (46.8) | 36.0 (28.5) | 35.1 (34.0) |
| Median [Min, Max] | 25.2 [1.72, 110] | 20.2 [5.00, 106] | 22.0 [0, 90.8] | 33.4 [4.71, 200] | 25.1 [0, 110] | 22.0 [4.71, 200] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| MIP-1 alpha (CCL3) |  |  |  |  |  |  |
| Mean (SD) | 0.912 (1.45) | 0.792 (1.35) | 0.881 (1.79) | 1.19 (3.12) | 0.897 (1.61) | 0.948 (2.19) |
| Median [Min, Max] | 0.0225 [0, 4.96] | 0.205 [0, 5.67] | 0.0150 [0, 6.68] | 0.0200 [0, 11.2] | 0.0150 [0, 6.68] | 0.0800 [0, 11.2] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| MIP-1 beta (CCL4) |  |  |  |  |  |  |
| Mean (SD) | 10.8 (16.4) | 8.05 (13.7) | 18.3 (21.5) | 10.6 (16.8) | 14.4 (19.2) | 9.05 (14.9) |
| Median [Min, Max] | 3.83 [0, 70.1] | 2.59 [0, 67.1] | 6.56 [0, 69.0] | 2.51 [0, 51.6] | 4.56 [0, 70.1] | 2.51 [0, 67.1] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| TNF alpha |  |  |  |  |  |  |
| Mean (SD) | 1.34 (1.51) | 1.03 (0.945) | 1.40 (1.30) | 2.00 (2.04) | 1.37 (1.40) | 1.40 (1.52) |
| Median [Min, Max] | 0.865 [0, 8.60] | 0.680 [0, 3.61] | 0.945 [0, 4.99] | 1.18 [0.470, 9.01] | 0.890 [0, 8.60] | 1.06 [0, 9.01] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
| TNF beta |  |  |  |  |  |  |
| Mean (SD) | 0.617 (1.81) | 0.242 (0.729) | 0.900 (2.16) | 0.200 (0.404) | 0.753 (1.98) | 0.225 (0.618) |
| Median [Min, Max] | 0 [0, 9.98] | 0 [0, 3.34] | 0 [0, 10.0] | 0 [0, 1.40] | 0 [0, 10.0] | 0 [0, 3.34] |
| Missing | 1 (2.6%) | 3 (9.1%) | 41 (53.9%) | 15 (44.1%) | 42 (36.5%) | 18 (26.9%) |
|  | | | | | | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table 7. Differentially expressed genes in hospitalized patients with COVID-19 versus hospitalized patient admitted for other acute illnesses | | | | |
| Gene | Median hits  in non-COVID | Median hits  in COVID | Log2 Fold Change (SE) | Adjusted  p-Value |
| AC233755.2 | 0 | 2 | 3.43 (0.79) | 0.016 |
| ALKAL2 | 1 | 9.5 | 1.91 (0.46) | 0.028 |
| AXL | 1 | 8.5 | 2.36 (0.52) | 0.015 |
| BAMBI | 10 | 51 | 1.42 (0.33) | 0.016 |
| BFSP2 | 1 | 9 | 1.81 (0.41) | 0.016 |
| BMP6 | 124 | 421 | 1.10 (0.25) | 0.016 |
| CLEC6A | 73.5 | 17 | -1.46 (0.35) | 0.028 |
| CRYM | 5 | 39 | 1.82 (0.43) | 0.024 |
| GRASP | 112 | 312 | 1.57 (0.33) | 0.010 |
| IFI27 | 310 | 22806 | 2.37 (0.49) | 0.007 |
| KRT8 | 5 | 17 | 1.24 (0.31) | 0.040 |
| LIPN | 294 | 95.5 | -1.36 (0.32) | 0.019 |
| MYZAP | 7.5 | 62.5 | 1.42 (0.35) | 0.040 |
| NECTIN2 | 191 | 499 | 1.18 (0.28) | 0.024 |
| PDE2A | 42.5 | 149.5 | 1.41 (0.29) | 0.007 |
| PRKG1 | 4.5 | 18 | 1.53 (0.38) | 0.041 |
| SMIM24 | 122 | 315 | 1.58 (0.39) | 0.040 |
| TXNDC5 | 25.5 | 207.5 | 1.63 (0.37) | 0.016 |
|  | | | | |

# Figures



**Figure 1.** Number of genes evaluated versus number of hits per gene in the total sample.



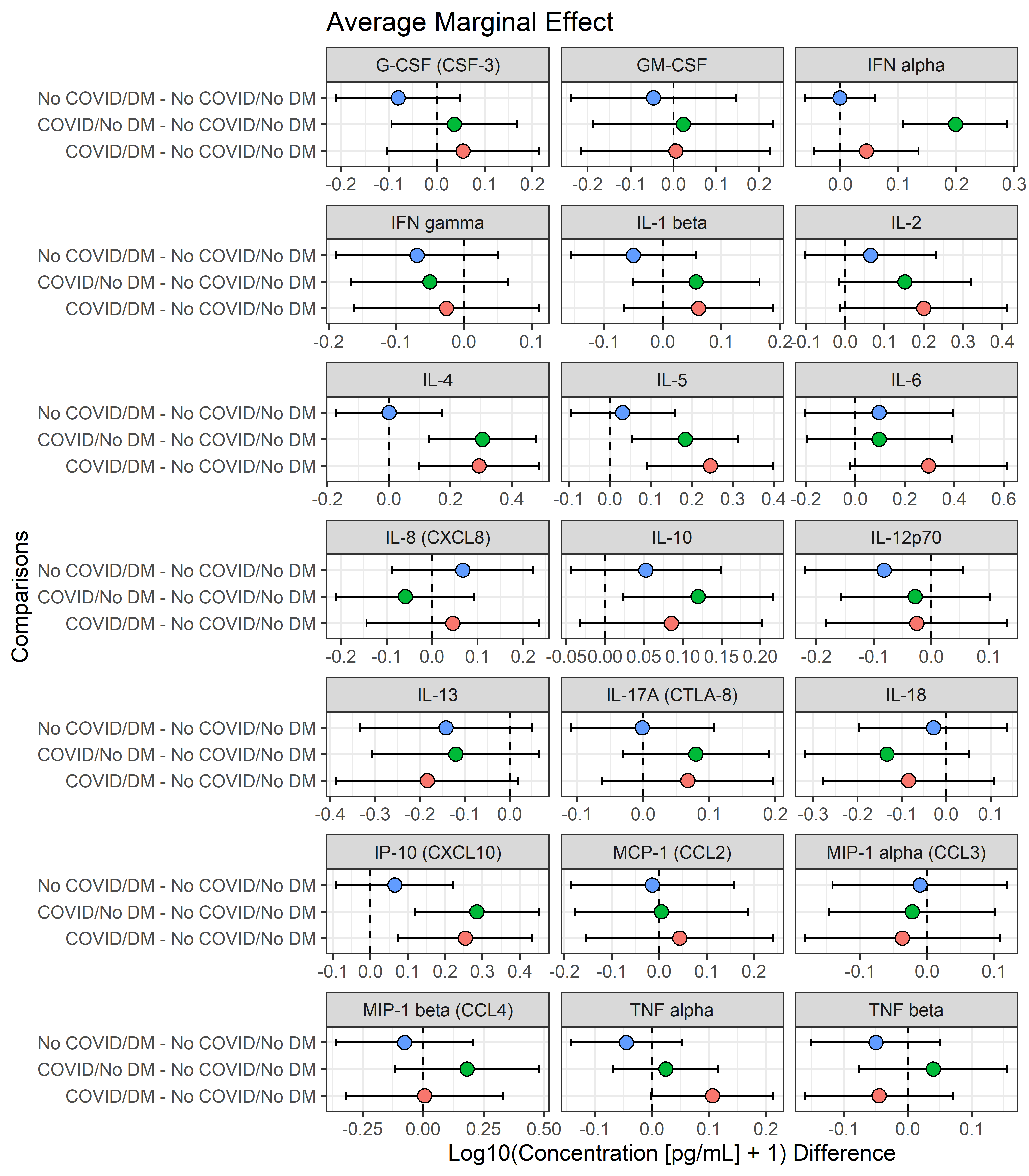
**Figure 2.** Differentially expressed genes in individuals hospitalized with and without COVID-19. Patients with diabetes are delineated with light blue coloring.



**Figure 3:** IFI27 expression in COVID vs. non-COVID color-coded for in-hospital deaths (left) and critical care (right).



**Figure 4.** Number of hits for specific differentially expressed genes in samples, grouped by COVID and DM diagnoses.



Supplementary Tables.

|  |  |  |
| --- | --- | --- |
| Supplementary Table 1. Function and relevance of differentially expressed genes to COVID-19 (source: GeneCards database) | | |
| Gene | **Function** | **Relevance in COVID-19** |
| AC233755.2 | Synonymous with IGHV3-43D Gene, V region of the variable domain of immunoglobulin heavy chains that participates in the antigen recognition (PMID:24600447); Secreted immunoglobulins mediate the effector phase of humoral immunity, which results in the elimination of bound antigens (PMID: 22158414, 20176268) | None identified. |
| ALKAL2 | Enables receptor signaling protein tyrosine kinase activator activity and receptor tyrosine kinase binding activity. Involved in positive regulation of ERK1 and ERK2 cascade; positive regulation of ERK5 cascade; and positive regulation of neuron projection development. Predicted to be located in extracellular region. | Yes. |
| AXL | The protein encoded by this gene is a member of the Tyro3-Axl-Mer (TAM) receptor tyrosine kinase subfamily. The encoded protein possesses an extracellular domain which is composed of two immunoglobulin-like motifs at the N-terminal, followed by two fibronectin type-III motifs. It transduces signals from the extracellular matrix into the cytoplasm by binding to the vitamin K-dependent protein growth arrest-specific 6 (Gas6). This gene may be involved in several cellular functions including growth, migration, aggregation and anti-inflammation in multiple cell types. The encoded protein acts as a host cell receptor for multiple viruses, including Marburg, Ebola and Lassa viruses and is a candidate receptor for the SARS-CoV2 virus | Yes, strong data. |
| BAMBI | This gene encodes a transmembrane glycoprotein related to the type I receptors of the transforming growth factor-beta (TGF-beta) family, whose members play important roles in signal transduction in many developmental and pathological processes. The encoded protein however is a pseudoreceptor, lacking an intracellular serine/threonine kinase domain required for signaling. Similar proteins in frog, mouse and zebrafish function as negative regulators of TGF-beta, which has led to the suggestion that the encoded protein may function to limit the signaling range of the TGF-beta family during early embryogenesis | Yes, regulates ACE2 mRNA concentrations. |
| BFSP2 | More than 99% of the vertebrate ocular lens is comprised of terminally differentiated lens fiber cells. Two lens-specific intermediate filament-like proteins, the protein product of this gene (phakinin), and filensin, are expressed only after fiber cell differentiation has begun. Both proteins are found in a structurally unique cytoskeletal element that is referred to as the beaded filament (BF). Mutations in this gene have been associated with juvenile-onset, progressive cataracts and Dowling-Meara epidermolysis bullosa simplex. | None identified. |
| BMP6 | This gene encodes a secreted ligand of the TGF-beta (transforming growth factor-beta) superfamily of proteins. Ligands of this family bind various TGF-beta receptors leading to recruitment and activation of SMAD family transcription factors that regulate gene expression. The encoded preproprotein is proteolytically processed to generate each subunit of the disulfide-linked homodimer. This protein regulates a wide range of biological processes including iron homeostasis, fat and bone development, and ovulation. Differential expression of this gene may be associated with progression of breast and prostate cancer. Mutations in this gene may be associated with iron overload in human patients. | None identified. |
| CLEC6A | The protein encoded by this gene is a type II membrane receptor with an extracellular C-type lectin-like domain fold. The extracellular portion binds structures with a high mannose content and has been shown to recognize several pathogens, including C. elegans, S. cerevisiae, M. tuberculosis, C. neoformans, and house dust mite. When stimulated, the encoded protein initiates signalling through the CARD9-Bcl10-Malt1 pathway, leading to the induction of cytokines. Two transcript variants encoding different isoforms have been found for this gene | Yes. |
| CRYM | Crystallins are separated into two classes: taxon-specific and ubiquitous. The former class is also called phylogenetically-restricted crystallins. The latter class constitutes the major proteins of vertebrate eye lens and maintains the transparency and refractive index of the lens. This gene encodes a taxon-specific crystallin protein that binds NADPH and has sequence similarity to bacterial ornithine cyclodeaminases. The encoded protein does not perform a structural role in lens tissue, and instead it binds thyroid hormone for possible regulatory or developmental roles. Mutations in this gene have been associated with autosomal dominant non-syndromic deafness. | None identified. |
| GRASP | TAMALIN Gene? This gene encodes a protein that functions as a molecular scaffold, linking receptors, including group 1 metabotropic glutamate receptors, to neuronal proteins. The encoded protein contains conserved domains, including a leucine zipper sequence, PDZ domain and a C-terminal PDZ-binding motif. Alternately spliced transcript variants have been observed for this gene | None identified. |
| IFI27 | Enables RNA polymerase II-specific DNA-binding transcription factor binding activity; identical protein binding activity; and lamin binding activity. Involved in several processes, including cellular protein metabolic process; defense response to other organism; and extrinsic apoptotic signaling pathway. Acts upstream of or within negative regulation of transcription by RNA polymerase II and regulation of protein export from nucleus. Located in mitochondrial membrane and nuclear inner membrane | Yes, early predictor for COVID-19 outcomes (PMID 3665600) |
| KRT8 | This gene is a member of the type II keratin family clustered on the long arm of chromosome 12. Type I and type II keratins heteropolymerize to form intermediate-sized filaments in the cytoplasm of epithelial cells. The product of this gene typically dimerizes with keratin 18 to form an intermediate filament in simple single-layered epithelial cells. This protein plays a role in maintaining cellular structural integrity and also functions in signal transduction and cellular differentiation. Mutations in this gene cause cryptogenic cirrhosis. Alternatively spliced transcript variants have been found for this gene | Yes. |
| LIPN | The gene encodes a lipase that is highly expressed in granular keratinocytes in the epidermis, and plays a role in the differentiation of keratinocytes. Mutations in this gene are associated with lamellar ichthyosis type 4 | None identified. |
| MYZAP | This gene encodes a protein that is abundantly expressed in cardiac tissue. The encoded protein localizes to intercalated discs in cardiomyocytes and functions as an activator of Rho-dependent serum-response factor signaling. Alternative splicing results in multiple transcript variants. Readthrough transcription also exists between this gene and the neighboring downstream gene POLR2M | None identified. |
| NECTIN2 | This gene encodes a single-pass type I membrane glycoprotein with two Ig-like C2-type domains and an Ig-like V-type domain. This protein is one of the plasma membrane components of adherens junctions. It also serves as an entry for certain mutant strains of herpes simplex virus and pseudorabies virus, and it is involved in cell to cell spreading of these viruses. Variations in this gene have been associated with differences in the severity of multiple sclerosis. Alternate transcriptional splice variants, encoding different isoforms, have been characterized | Yes. |
| PDE2A | Enables several functions, including 3',5'-cyclic-nucleotide phosphodiesterase activity; anion binding activity; and metal ion binding activity. Involved in several processes, including cellular response to organic cyclic compound; cyclic-nucleotide-mediated signaling; and regulation of vascular permeability. Located in several cellular components, including cytosol; mitochondrial membrane; and perinuclear region of cytoplasm. Colocalizes with plasma membrane | Yes. |
| PRKG1 | Mammals have three different isoforms of cyclic GMP-dependent protein kinase (Ialpha, Ibeta, and II). These PRKG isoforms act as key mediators of the nitric oxide/cGMP signaling pathway and are important components of many signal transduction processes in diverse cell types. This PRKG1 gene on human chromosome 10 encodes the soluble Ialpha and Ibeta isoforms of PRKG by alternative transcript splicing. A separate gene on human chromosome 4, PRKG2, encodes the membrane-bound PRKG isoform II. The PRKG1 proteins play a central role in regulating cardiovascular and neuronal functions in addition to relaxing smooth muscle tone, preventing platelet aggregation, and modulating cell growth. This gene is most strongly expressed in all types of smooth muscle, platelets, cerebellar Purkinje cells, hippocampal neurons, and the lateral amygdala. Isoforms Ialpha and Ibeta have identical cGMP-binding and catalytic domains but differ in their leucine/isoleucine zipper and autoinhibitory sequences and therefore differ in their dimerization substrates and kinase enzyme activity | Yes. |
| SMIM24 | Predicted to be located in membrane. Predicted to be integral component of membrane. | None identified. |
| TXNDC5 | This gene encodes a member of the disulfide isomerase (PDI) family of endoplasmic reticulum (ER) proteins that catalyze protein folding and thiol-disulfide interchange reactions. The encoded protein has an N-terminal endoplasmic reticulum (ER)-signal sequence, three catalytically active thioredoxin domains and a C-terminal ER-retention sequence. Its expression is induced by hypoxia and its role may be to protect hypoxic cells from apoptosis. Alternative splicing results in multiple transcript variants. Read-through transcription also exists between this gene and the neighboring upstream BLOC1S5 gene | Yes. |

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