**Diabetes mellitus and the risk of severe SARS-CoV-2 infection**

Marshall Yuan, Davit Sargsyan, Ronald G, Nahass, Ah-Ng Kong, Luigi Brunetti

Robert Wood Johnson Medical School, Piscataway, NJ, USA

IDCare, Hillsborough, NJ, USA

Ernest Mario School of Pharmacy, Department of Pharmaceutics, Piscataway, NJ, USA

Ernest Mario School of Pharmacy, Department of Pharmacy Practice, Piscataway, NJ, USA

Robert Wood Johnson University Hospital, Somerville, NJ, USA

Keywords

Word Count

**Abstract**

**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. By October 2022, COVID-19 had caused over 6.5 million deaths. Primarily a condition that affects the respiratory system, it presents in patients with a wide range of symptoms, ranging from asymptomatic and mild to severe. In the most critical cases, patients may require ICU care and mechanical intubation, among other intensive interventions. A variety of risk factors are suggested to increase the risk for severe illness, including 65 years of age and older, hypertension, smoking, and diabetes.

Multiple meta-analyses of the clinical correlation between diabetes and SARS-CoV-2 have demonstrated that patients with diabetes are at higher risk for severe disease and mortality, reporting odds ratio as high as OR = 2.75 (95% CI: 2.09-3.62; p < 0.01) for severe disease. 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). 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). 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. 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. Upon entry, there is a downregulation of surface ACE2 expression. Circulating angiotensin 2 (Ang-II) are elevated in COVID-19 patients compared to healthy controls providing evidence of renin-angiotensin system (RAS) imbalance in the disease. Increases in Ang-II leads to increases in a disintegrin and metalloproteinase 17 (ADAM17) activity and subsequent release of tumor necrosis factor α (TNF- α) and other inflammatory cytokines. Nuclear factor erythroid 2–related factor 2 (Nrf2) and Nrf2 related genes are regulators of cellular redox balance and are involved in the release of inflammatory cytokines and chemokines secondary to stress. Nrf2 activation downregulated a variety of cytokines reported to be elevated in COVID-19 suggesting reduced Nrf2 activity as a contributor to the “cytokine storm” seen in COVID-19.

Chemokines are an important secretory protein responsible for immune signaling and have been implicated in a variety of 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. This chemokine is associated with acute respiratory distress syndrome and pulmonary fibrosis7 – both observed in COVID-19. CCL2 elevation has also been found to be associated with severe SARS-CoV. A variety of 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 diabetes or other stratifications such as race.

Diabetes is also associated with renin-angiotensin system (RAS) dysregulation, ACE2 downregulation, low-grade inflammation, cytokine/chemokine upregulation, and altered Nrf2 activity. The combination of COVID-19 and diabetes may contribute to exaggerated ACE2 depletion and elevations in circulating Ang-II following by release of cytokines/chemokines mediated by Nrf2 as well as altered immune function. In terms of immune signaling, regulation of T cell function has been linked to Ang-II. ACE2 is expressed in leukocytes and the lungs, kidneys, heart, and gastrointestinal tract (all organs affected by COVID-19) subjecting these organs to damage from inflammation. Furthermore, individuals with diabetes are already at an increased risk for cardiovascular events; and myocardial inflammation associated with downregulation of ACE2 in COVID-19 has been previously reported representing additive risk. Collectively, there are many similarities between the COVID-19 and diabetes pathophysiology that suggest increased risk for worse outcomes. Moreover, the association between cytokine/chemokine gene expression patterns and disease severity may be used as a predictive biomarker.

The purpose of this study was to evaluate biomarker and gene expression patterns in individuals hospitalized with diabetes mellitus infected with SARS-CoV-2. In addition, the relationship between these patterns and disease severity was examined.

**Methods**

**Data source and patient collection**: We performed a single-center, IRB-approved, cohort study using data from electronic health records at a large community medical center. Inclusion/exclusion criteria.

**Data extraction and collection**: All data were extracted from the electronic health record (Epic Systems). Patient age, sex, race/ethnicity, comorbidities, vaccination status, concomitant anti-hyperglycemic medications, COVID treatment interventions, and other basic relevant 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. Overall comorbidity status of patients was defined by the scoring of the Charlson-Deyo comorbidity Index (CCI). Patients’ baseline characteristics including demographics, vaccination information, comorbidities, medications, lab work, clinical scores and ELISA protein concentration were summarized in Table 1.

**RNA-Sequencing**

**Cytokine and chemokine multiplex assay**

**ACE2 and DPPIV ELISA**

**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 differences in inflammatory mediator expression profile between COVID-19 patients with and without diabetes. Secondary endpoints include differences in inflammatory mediator expression profile between diabetes patients with and without COVID-19 and occurrence of severe illness (defined by mechanical ventilation, ICU admission, or mortality).

**Statistical Analysis**: Patient demographics were assessed using descriptive statistics. Continuous data are represented with means and standard deviation, while nominal data is represented with percentages and standard deviations. Differences in baseline characteristics were analyzed utilizing t-tests for continuous data and chi-squared or Fischer’s exact test for categorical data.

**Results**

Between January 1st 2022 and May 30th 2022, 183 adult patients were enrolled within the specified timeframe, of which 91 patients had blood samples extracted. Patients’ blood samples were obtained within 2 days of hospital admission.

Out of 110 patients admitted with COVID-19, 12 (10.9%) died in hospital compared to 3 out of 72 non-COVID-19 patients (4.2%).

There was no significant association between DM and COVID-19 patients’ death rate, with 6 DM and 6 non-DM COVID-19 patients dying in hospital (Chi-square test p-value = 0.236). Similarly, obesity and BMI were not found to be 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 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). However, 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 World Health Organization Original Scale for Clinical Improvement (WHO OSCI) scale. 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 WHO OSCI score of 5 or higher. Notable, 5 out of the 13 COVID patient admitted to the CC unit had the score of 5, and another 8 score of 6. At the same time, 64 out of 97 non-CCU patients (66.0%) were scored 5 or above at the admission.

Patients’ comparison (medications, treatments administered, length of stay, vaccination status)

Outcomes (inflammatory mediator expression profile, statistical analysis)

**Discussion**

Inflammatory mediators measured:

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

**References**