COVID-19, caused by SARS-CoV-2, is presented with a variety of symptoms and has impacted the entire world. SARS-CoV-2 can disproportionally affect individuals leading to broad-spectrum clinical manifestations ranging from mild illness to acute respiratory distress syndrome (ARDS) with severe pneumonia and some cases, long-COVID. COVID-19 disease severity and mortality have been linked to various pre-existing chronic conditions as well as genetic factors, but it is not a fully understood area. Patients with severe COVID-19-associated ARDS usually exhibit biochemical abnormalities like those triggered by human herpesviruses (HHVs), such as Cytomegalovirus (CMV) and Epstein Barr Virus (EBV). Therefore, it is likely that SARS-CoV-2 triggers “latent” viruses to reactivate and augment the disease severity among certain individuals. Using nasopharyngeal swabs and peripheral blood mononuclear cells (PBMCs) in a cohort of 147 SARS-CoV-2 infected adult patients, we investigated the plausible link between HHVs and COVID-19 disease severity.

In this retrospective cohort study, consisting of 147 patients recruited from Renown Regional Medical Center between 2021-June 2022, we determined whether reactivation of persisting HHVs contributed to the COVID-19 disease severity among those infected individuals. We detected a higher rate of EBV reactivation among individuals with severe COVID-19 symptoms. Additionally, we found that SARS-CoV-2 can cause the reactivation of EBV and another homolog of EBV, HHV8 in the cell culture model. Interestingly, our transcriptomic data of cellular genes revealed that the levels of inflammatory genes, MNDA, IFITM2, CXCR1, CXCR2, FCGR3B, and FCGR2A were upregulated among severe COVID-19 patients, compared to the mild and asymptomatic patients. In addition, we found that the critical COVID-19 subgroup had a significant reduction in RGCC and EPHB1 gene expression than mild and asymptomatic subgroups.

In summary, we found EBV, HCMV, and HHV1 reactivation in severe COVID-19 patients compared to mild/asymptomatic patients. Our findings identified several key and novel cellular genes, MNDA, IFITM2, CXCR1, CXCR2, FCGR3B, and FCGR2A, to be markedly elevated in patients with severe COVID-19 symptoms. Elevated levels of MNDA and IFITM2 genes may contribute to effective SARS-CoV-2 replication and COVID-19 infection in severely ill patients. We also observed Streptococcus pneumoniae, Streptococcus oralis, and Cryobacterium sp. LW097 in a small proportion of critically ill COVID-19 individuals.