“Determining the biological differences in the impact of COVID-19 on smoking and non-smoking lung cancer patients”

**Background:** Despite remarkable progress in clinical management and development of vaccines, the COVID-19 pandemic caused by SARS-Cov-2 remains a major public health problem. The pandemic has caused and continues to cause unprecedented suffering and loss of human life globally. One of the major challenges in the COVID-19 pandemic era pivots around clinical management of cancer patients. Among the cancer patients impacted with COVID-19, individuals diagnosed with lung cancer are the most impacted and have the highest mortality rate. Patients with lung cancer have consistently been reported to suffer from an increased risk of death compared with other cancers. Unfortunately, the molecular mechanisms driving the severity of COVID-19 remains poorly understood. The objective of this investigation was to comprehensively characterize the association between lung cancer smokers and nonsmokers with COVID-19 and to determine whether the network states and signaling pathways driving the severity of COVID-19 in the two patient groups differ. Our working hypothesis was that molecular perturbations in human lungs affected with COVID-19 and lung cancer smokers and nonsmokers could lead to measurable changes explaining the differences in the impact of COVID-19 in smokers and non-smokers diagnosed with lung cancer. We further hypothesized that the association between COVID-19 and lung cancer in smokers and nonsmokers are driven by different signaling pathways.

**Methods:** We address these hypotheses using a bioinformatics approach integrating genomics data from lung cancer individuals on smokers and nonsmokers with genomics data from COVID-19 affected lungs and controls. Specifically, we compared gene expression levels between lung cancer smokers and controls, lung cancer nonsmokers and controls and between COVID-19 and controls to discover signatures of genes associated with each patient group. Using integrative bioinformatics strategies we integrated data on COVID-19 with data on lung cancer smokers and nonsmokers to signatures of genes associating lung cancer in smokers with COVID-19 and signatures of genes associating lung cancer in nonsmokers with COVID-19. We performed network and pathway analysis to discover the network states and signaling pathways driving the associations between lung cancer in smokers with COVID-19 and lung cancer in nonsmokers with COVID-19.

**Results:** The investigation revealed a signature of 557 genes uniquely associating lung cancer in smokers with COVID-19. In addition, the investigation revealed a signature of 490 genes uniquely associating lung cancer in nonsmokers with COVID-19. Pattern recognition analysis revealed on each set of genes revealed that many genes were functionally related. Network and pathway analyses revealed different network states and signaling pathways driving the association between COVID-19 in lung cancer smokers and nonsmokers.

**Conclusion:** We discovered the differences in the molecular mechanisms associating COVID-19 with lung cancer in smokers and nonsmokers. Additionally, we discovered the differences in gene regulatory networks and signaling pathways driving the association between COVID-19 and lung cancer in smokers and nonsmokers. Further research is recommended using data derived from patients affected with both lung cancer and COVID-19 to validate the results.