Does the quality and type of the immune response in patients with COVID-19 affect their clinical outcome?

By: Keala Minna-Choe (9th grade, Canyon Crest Academy)

**Background:** COVID-19 disease has rapidly become our society's most pressing medical issue. With over 20 million reported cases and hundreds of thousands of deaths worldwide\(^1\), many scientists are racing to find solutions for this pandemic.

Two important factors of SARS-COV-2 virus are 1) the virus’s rapid spread between people\(^2\) and 2) the variation in severity of COVID-19 disease. Some people have no symptoms at all while others die despite our best efforts\(^3\). What protects us from infection and helps us overcome COVID-19 disease is our immune system. However, while the immune system overcomes infection, this same system can overreact to make certain people extremely ill\(^4\).

There are two major efforts related to COVID-19 disease treatments. The first is to develop an effective vaccine that prevents infection. The second is to develop ways to calm our bodies’ overreaction to the virus. Currently, there is a large amount of work being done on developing vaccines to generate antibodies that would block virus infection\(^5\). While we all anxiously await positive results of these vaccine trials, it is also important to study immune responses in individuals naturally infected with the virus.

Recently, a fascinating study was published that compared the antibody responses between deceased and convalescent individuals with COVID-19 disease\(^6\). Researchers found that the type of antibodies produced were different between the groups. The deceased group produced antibodies that fought against the nucleocapsid which is a protein that protects the genome and allows for the reliable and functional transmission of the virus\(^7\). On the other hand, patients that successfully recovered from the virus produced antibodies designed to fight off the spike protein. The spike protein is the protruding pieces commonly seen on the virus’s cell, giving it the distinctive ‘crown’ features. This protein allows the virus to attach and infiltrate the lung cells\(^8\). If this study is true, this information will have a large effect on how scientists fight the virus by allowing them to know which type of antibodies are most effective for fighting the SARS-COV-2 infection. Therefore, it is important to try to replicate and extend this study to see if the quality and type of antibody responses correlate with the clinical severity of disease.

**Why I chose this topic:** The COVID-19 pandemic has impacted our lives in ways that could never have been imagined. Large portions of the world have been shut down in order to protect others. Many people have had their lives uprooted. I chose this topic to help all the individuals that have been affected by the COVID-19 pandemic. I am also interested in immunology and biology, so COVID-19 disease and the research currently underway is very fascinating to me. Further, I am passionate about helping others through medicine and research. The implications of this research makes me excited because not only will it help the individuals with COVID-19, but it also can pave the way for dealing with future viral infections.

**Hypothesis:** The clinical outcome of patients infected with COVID-19 can be determined by the type and quality of their humoral immune response (the ability of antibodies to block infection). If a patient produces antibodies that block infection and target a certain protein, then there is a higher chance that their clinical outcome will be successful.

**Specific Aims:**

1. After obtaining informed consent, collect blood samples from patients documented to have COVID-19 disease (SARS-COV-2 infection) 18 days after the first viral-positive test. Clinical data that will also be collected include demographics (age, gender, race, comorbid conditions/current health status), virus-related data (hospitalization days, ICU days, ventilator status), and clinical outcome/survival. A simple key clinical aspect I will monitor is the patient’s oxygen
status by using a finger pulse oximeter\(^9\). I will divide the patients into those with oxygen percentages over 90% versus those 90% and under.

2. Determine the humoral immune response using quantitative antibody assays\(^{10}\) against defined SARS-COV-2 viral proteins. This includes the titer and class of the antibodies and which viral proteins they detect/fight against (the spike protein and the nucleocapsid protein).

3. Determine the function of antibodies from different patients to block infection of SARS-COV-2 virus on human’s lung epithelial cells\(^{11}\) using tissue culture assays\(^{12}\). Also, to compare the ability of antibodies to block infection in human lung cells from several individuals.

4. Statistical Analysis of antibody findings correlated with the clinical outcome and details.

**Methods:**

The first step is identifying the patients that the study will be conducted on. The patients should be hospitalized to ensure they receive the same care and are in a controlled environment. They will be closely monitored with a finger pulse oximeter. The patient should consent to participate and be fully informed.

Next, the clinical data and blood samples should be taken. To allow the virus to naturally develop, blood samples will be taken 18 days after the first viral-positive test.

Using the ELISA method (enzyme-linked immunosorbent assay)\(^{13}\), which uses the antibodies produced by the body in response to SARS-COV-2 viral proteins (spike protein and nucleocapsid) to determine the humoral immune response. Quantitative information about the humoral immune response includes the titer and class of the antibodies and importantly the antibodies’ function. I will be looking at the antibodies that fight against the spike protein and the nucleocapsid protein.

I will also be assaying the virus neutralization\(^{14}\), to determine how effective the antibodies are at neutralizing the virus. Ideally, the antibodies would be potent, which means that in the future less antibodies have to be used in order to “cure” the patient, preventing fewer side effects from occurring. This will be assayed by tissue cultures on the lungs’ epithelial cells.

Then, I will be using statistics to correlate all of this data to determine if the type of antibody produced and it’s neutralizing effect can determine the patient’s clinical outcome.

**Analysis:**

**Assay Reproducibility:** To check reproducibility, I will perform antibody titer determinations against the viral proteins at least 4 times and take the average of the 4 tests. If the test is an outlier using standard deviation, I will repeat that sample again.

**Power Calculation:** Using ClinCalc Sample Size Calculator\(^{15}\) that assuming differences between the two groups (non-hypoxic versus hypoxic) for antibodies against viral spike protein are 75% and 50% and the same for nucleocapsid antibodies in the other direction (50% and 75%), show I need at least 58 patients per group to find a statistical difference (0.05) with a power of 0.8.

**Conclusion:** This research stems from my interest and fascination with science, biology, and immunology in general, combined with a need and passion for helping all the people who have been negatively affected by COVID-19 disease. If this study is conducted and the results are similar to what has been predicted and analyzed in this paper, then antibodies combined with other solutions can help patients successfully recover from COVID-19 disease. This information will help us evaluate the vaccines to know if they are generating antibodies that would correlate with positive clinical outcomes. It can also help guide patient care, and help doctors determine which patients are developing the helpful antibodies as opposed to which are not. Looking into the future, the knowledge and methods used in this paper can help with other virus infections, and ensure that a coronavirus such as this one never becomes a pandemic again.
References:


17. Britannica Tissue [Website](https://www.britannica.com/science/tissue-culture)


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