Analysis of Major Laboratory Test Result Abnormalities in Mild and Severe COVID-19 Infections

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Abstract: - Declared a pandemic in March of 2020, the coronavirus disease 2019 (COVID-19) infection took thousands of lives in the Philippines and over a million worldwide in less than a year. To alleviate the problem, diagnostic procedures must be performed in order to provide the patients' appropriate treatment regimens. Aside from these diagnostic tools, other specific laboratory values can be used to monitor the patients' condition and aid in their treatment. This research's general objective, derived from these laboratory values, is to associate these laboratory values with the chosen levels of severity of the infection which are mild and severe, through the use of statistical analysis. To fulfill this objective, the formulated research problem seeks to answer the question: Which laboratory test value(s) will predict the severity of COVID-19 infection through statistical analysis called logistic regression. Specific attributes were chosen to determine the study participants, mild and severely infected COVID-19 infected inpatients of the chosen tertiary hospital in Manila given no comorbidities contracted prior to the infection. The study applied a census technique to acquire the best data set to evaluate the patient history and laboratory value received from the hospital. The data was interpreted with logistic regression to determine each laboratory value's individual efficacy to the severity of infection. With respect to the generated outcome of results, the researchers arrived at the conclusion that seven out of the eight laboratory values namely neutrophils, lymphocytes, ALT, CRP, LDH, ferritin and d-dimer were significant predictors of the severity of COVID-19 infection. Procalcitonin was not considered significant. Recommendations for the clinical setting involve focusing on the increased biomarkers (neutrophils, ALT, CRP, LDH, ferritin, and d-dimer) and control the production of these biomarkers to prevent the adversary effects that may happen if the elevation is prolonged. Meanwhile, lymphocyte count was decreased, which means that treatments that can further suppress its production should not be administered.

Key Words— *COVID-19, Severity of Infection, Mild, Severe, Laboratory Values, Laboratory Parameters, Predictors, Logistic Regression.*

I. INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is a newly discovered viral strain, is an infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Cennimo, 2020). The infection originated in Wuhan, China and was reported back in December 2019. Few months after, the World Health Organization announced COVID-19 as a global pandemic which affects 123 countries worldwide (WHO, 2020).

Although the COVID-19 infection source has not been firmly established or determined, most evidence from reports suggests that it is a zoonotic disease with bats, pangolins, or seafood as possible hosts (WHO, 2020). Furthermore, the disease in humans is transmitted via direct contact and droplet infection when coughing or sneezing. According to several reports, symptomatic patients are the predominant transmission source (Ouassou et al. 2020).

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The standard diagnostic procedure for the infection is Real-Time Polymerase Chain Reaction (RT-PCR), which detects the genome of the virus in infected patients (FDA, 2020). Aside from the RT-PCR other specific laboratory tests are also done to monitor the patient's condition and aid the treatment of the patients. These pertain to routine tests such as Complete Blood Count (CBC) for lymphocyte and neutrophil; tests for inflammation such as levels of C-reactive protein, ferritin, and procalcitonin; coagulation assay; and fibrinolysis process test like D-dimer; as well as serum alanine aminotransferase, and lactate dehydrogenase.

The different classifications of severity for the COVID-19 infection include mild, moderate, severe, and critical (WHO, 2020). Mild diseases are found in patients who experience specific signs and symptoms such as fever, cough, fatigue, and nonspecific symptoms like headache, sore throat, and nasal congestion without findings of pneumonia or hypoxia. On the other hand, moderate diseases and severe diseases are associated with pneumonia and severe pneumonia. Lastly, critical diseases entail acute respiratory distress syndrome (ARDS) with a distinct clinical insult such as pneumonia or more aggravated respiratory symptoms.

Given that the COVID-19 infection is still an ongoing pandemic, this study takes advantage of its timely, relevant, and indeterminate nature. Thus, to address the limited information known about the said disease, this study seeks to determine the relationship between the aforementioned laboratory test values and the disease severity classification.

A. Statement of the Problem

SARS-CoV-2, due to being a novel respiratory virus, has a distinct gap of studies in specific fields. There is explicitly a lack of literature that looks into the predictive capability of specific laboratory values to the severity of COVID-19 infection. The few available either note the abnormal laboratory values of infected patients or only look into one or two particular values. This study is done to identify whether these laboratory values can predict COVID-19 infection severity between mild and severe infection: lymphocyte, neutrophil, serum alanine aminotransferase, lactate dehydrogenase, C-reactive protein, ferritin, D-dimer, and procalcitonin. The following are the research problems:

- How many COVID-19 cases are classified as mild or severe?
- What are the results of the mentioned laboratory values in mild and severe COVID-19 infected patients?
- What can significantly predict COVID-19 severity using the said laboratory values?

B. Objectives of the Study

Serving as the general objective of this study is the identification of the laboratory test values that will predict COVID-19 infection severity through the use of statistical analysis. Moreover, this study seeks to determine whether there is a significant difference–either increased or decreased–in the laboratory values of neutrophil, lymphocyte, ferritin, d-dimer, procalcitonin, lactate dehydrogenase, serum alanine aminotransferase, and c-reactive protein in the blood between COVID-19 positive patients classified as mild and severe. The study further aims to achieve the objectives that are aligned to address the following problems:

- To determine the prevalence of COVID-19 cases classified as mild and severe;
- To collate the results of the said laboratory values in mild and severe COVID-19 infected patients utilizing descriptive statistics; and
- To determine which laboratory parameter can significantly predict the severity of COVID-19 infection.

C. Hypothesis of the Study

These are the following hypotheses that will be tested to conclude the significance of laboratory test findings with the severity of COVID-19 infection:

H_a: At least one of the following laboratory values such as lymphocyte, neutrophil, serum alanine aminotransferase, lactate dehydrogenase, C-reactive protein level, ferritin levels, D-dimer, or procalcitonin can significantly predict the severity of COVID-19 infection.

H_0: The laboratory values such as lymphocyte, neutrophil, serum alanine aminotransferase, lactate dehydrogenase, C-reactive protein level, ferritin levels, D-dimer, and procalcitonin cannot significantly predict the severity of COVID-19 infection.

D. Research Impediments

This study assessed the correlation of the specific laboratory values to the severity of infection. The chosen laboratory parameters were only limited to the prominent laboratory parameters reported by the article published in 2020 by the Center for Disease Control and Prevention (CDC) that was entitled, "Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)." These laboratory parameters are neutrophils, lymphocytes, alanine aminotransferase, aspartate aminotransferase, c-reactive protein, lactate dehydrogenase, ferritin, d-dimer, and procalcitonin. However, since the chosen hospital does not monitor the aspartate aminotransferase levels, the said parameter was excluded from the study. The study was also limited to mild and severe infections only, thus, patients under moderate and critical were excluded. Correlation of the laboratory values to the severity of infection was done to evaluate the clinical significance of the laboratory values to the severity of infection, and also with the intention of finding out which laboratory value has the most significant effect on the severity of infection.

A number of 113 mildly and severely COVID-19 infected inpatients were chosen through a census technique due to limited data. The age range was from 18 - 59 years old and the majority of the patients had complete laboratory values. The patients were also tested and confirmed by RT-PCR and have no comorbidities prior to infection. Patients that presented insufficient or unnecessary information such as lacking half or more than half of the laboratory data, aging below 18 or above 59, and not included in the mild or severe category, were taken out from the study.

E. Significance of the Study

The Philippines is one of the countries with the greatest numbers of recorded cases and deaths in the Western Pacific Region. Before the research for COVID-19 infection, its detection in mild and severe patients had already been considered in several studies. Despite this, there is still an absence of supporting studies that correlate with the aggravation of infection in COVID-19 patients. The result of this study will be of great benefit to the following:

Researchers: Having satisfied the primary objective, which is to identify the significant laboratory test values that indicate the aggravating factors of the COVID-19 infection, this study benefits researchers to improve their comprehension of the COVID-19 infection. Moreover, researchers will be able to establish a link between this study and other similar studies done.

Society: In analyzing the contributing laboratory results from mild and severe COVID-19 infected patients, the study will provide the public a better understanding by laying out further information and analysis regarding the aggravation of COVID-19 infection.

COVID-19 infected patients: This study is of great importance to all COVID-19 infected patients (from asymptomatic to critical cases) as this assists them in the overview of how the COVID-19 infection aggravates in their body. In addition, this can further help patients understand the effects of COVID-19 infection in their laboratory findings.

Medical personnel: Medical practitioners, particularly physicians and nurses, may utilize this study to further recognize the conditions of mild and severe COVID-19 infected patients by analyzing the statistical values made based on their significant laboratory findings. Moreover, this study leads more medical practitioners to perform effective treatment, management, and prevention of the COVID-19 infection.

Future researchers: This study serves as a guide for the future researchers who aim to conduct further studies on the contributing laboratory values seen in COVID-19 infection cases.

F. Definition of Terms

The definition of terms provides the different significant terminologies that will be used throughout this study.

Asymptomatic. Asymptomatic patients infected with a disease but do not show any clinical signs or symptoms.

Biomarkers. Biomarkers refer to any value used as an indicator for the presence or absence of disease. These are associated with the laboratory values.

Dependent variable. Dependent variables are the ones being tested in this research. They can vary according to the independent variables.

Independent variable. Independent variables are constant and are the ones that can change the results of the dependent variables.

Laboratory abnormalities. Laboratory abnormalities refers to laboratory results that fall outside of the laboratory reference ranges.

Laboratory values. Laboratory markers can be referred to as the laboratory parameters. They serve as the independent variables in this study. The values of the biomarkers to be measured are as follows: lymphocytes, neutrophils, serum alanine aminotransferase (ALT), lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, D-dimer, and procalcitonin (PCT).

Logistic regression. Logistic regression is a statistical model that uses a set of independent variables to predict a categorical dependent variable.

Mild. Mild infection refers to the symptomatic patients that have been established to have the COVID-19 infection but do not have viral pneumonia or hypoxia.

Severe. Severe infection refers to the symptomatic patients that have been established to have the COVID-19 infection but has viral pneumonia or other pulmonary complications.

Severity of infection. Severity of infection describes how ill the patient is. In this study, severity is in the form of mild and severe. It serves as the independent variables in this study that will entirely depend on the laboratory values or the independent variables.

Statistical analysis. Statistical analysis is a term used to determine trends, patterns, and relationships between variables using quantitative data

Symptomatic. Symptomatic patients infected with a disease that do show clinical signs or symptoms.

II. Review Of Related Literature

Today, the world is facing perhaps one of the most serious health issues to date: the coronavirus pandemic. The coronavirus disease, commonly known as COVID-19, is a highly transmissible infection brought about by the SARS-CoV-2 virus. (Harapan et al., 2020) This new strain of coronavirus causes respiratory and extra-respiratory presentations that could be lethal depending on the severity of symptoms (Cascella et al., 2020). Coronavirus outbreaks have been recorded in the past years, including the Middle East respiratory syndrome (MERS) outbreak of 2014 and the severe acute respiratory syndrome (SARS) outbreak of 2003. However, this year's pandemic involves a novel coronavirus later named the SARS-CoV-2, which will be discussed further in the succeeding paragraphs.

A. SARS-CoV-2

SARS-CoV-2 was first identified from a throat swab sample (Harapan et al. 2020). It was then identified in the respiratory tract of patients with pneumonia back in December 2019 in the same area. It was first indicated as a new β-coronavirus (nCoV) (Astuti & Ysrafil, 2020). It is the seventh of its kind that infects humans and the third in this classification capable of causing severe diseases together with SARS-CoV and MERS-CoV. It is a novel infectious respiratory virus that originated from Wuhan province, China (Han et al. 2020). Derived from bats, the virus was proven to be zoonotic in origin through transmission from pangolins to humans. Comparative genetic analysis indicates that SARS-CoV-2 exhibits closer similarities to others of the coronaviridae family, like SARS-CoVthan those of coronaviruses originating from pangolins (Li et al. 2020).

B. Classification & Viral Structure

SARS-CoV-2 is identified as a single-stranded ribonucleic acid (RNA) virus consisting of 29,891 nucleotides that encodes around 9,860 amino acids. It often sports a pleomorphic form, can also be round or elliptic, and has a 60-140 nm diameter. The virus is classified under the Coronaviridae family, named after its crown-shaped morphology observed under an electron microscope and the genome, Betacoronavirus (Cascella et al., 2020). The virus is composed of four major structural proteins: the spike (S) glycoprotein, nucleocapsid (N) protein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and the. Firstly, the spike (S) protein is an outer transmembrane protein that creates homotrimers on the viral surface. With its attraction to the angiotensin-converting enzyme 2 (ACE2), this protein aids in the adhesion of the virus to the host cells. Second is the nucleocapsid (N) protein which is confined between the endoplasmic reticulum and the Golgi body regions. It is attached to the nucleic acid component of the virus and its binding process is a component of both the viral replication cycle and the cellular response of the host cell. Third is the small envelope (E) glycoprotein, the smallest protein among the four, which is involved in both the production and maturation of the virus. Lastly, the membrane (M) glycoprotein aids in determining the morphology of the virus. In addition, it

stabilizes the nucleocapsid protein which further helps complete the viral assembly.

C. Mode of Transmission

Based on current evidence and studies, SARS-CoV-2 is transmitted by either humans and possibly bats as it is proven to be the reservoir of the virus. This transmission of the virus can be in the form of indirect contact with contaminated items or surfaces as well as with close contact with infected people through mouth and nose secretions. These secretions carrying the virus could be in the form of saliva or respiratory secretions and droplets, which can be expelled through sneezing or coughing. (WHO, 2020).

Upon the virus' entry into the body via infected droplets, it then enters various organs such as the heart, lungs, kidney, and gastrointestinal tract. The virus then adheres itself to the ACE2 receptor of the host cells, which initiates the fusion of the virus and the human cell. Organs having the highest amount of ACE2 receptors include the nasal epithelial cells of the respiratory tract. Once adhered, the virus will then deliver its genomic material, which would be further translated into proteins. A number of 14 open reading frames further encodes these proteins, which increases the virus' virulence capability. The other proteins are further translated into accessory and structural proteins, which will then be isolated between the endoplasmic reticulum and the Golgi body of the host cell. Finally, these structural proteins will be combined with the nucleocapsids, forming small vesicles that would then be delivered outside the cell via exocytosis. As a result, this causes an irregular response to the antiviral T cell due to T cell apoptosis (Mohammadi et al., 2020). This eventually leads to decreased immune functioning and the development of the COVID-19 infection (Astuti & Ysrafil, 2020).

D. Clinical Manifestations

The most common clinical signs and symptoms associated upon admission with positive COVID-19 patients were fever, cough, and expectoration, according to a retrospective cohort study conducted by Yang et al. in Zheijang, China. In a total of 149 patients examined from different hospitals, 114 (76.51%) patients had a fever, 87 (58.39%) had a cough, and 48 (32.21%) were expectorating. Dyspnea and vomiting were rare, only attributing to 2 (1.3%) patients each. As for further complications concerning the respiratory and excretory systems, none were detected, with the sole exception of mild pneumonia.

Clinical characteristics observed in mild COVID-19 infected patients experience the following conditions: fever, respiratory related symptoms, CT features of viral pneumonia, and positive RT-PCR result (Liu et al. 2020). While severe COVID-19 infected patients experience the following conditions: shortness of breath, a respiratory rate ≥30 breaths/minute, and a resting oxygen saturation ≤93%. Moreover, patients in a critical condition experience respiratory failure that requires the use of mechanical ventilation. Some critically ill patients are admitted to the intensive care unit (ICU) because of multiple organ dysfunction (Chen et al, 2020).

Early clinical manifestations present in 87% of patients were pneumonia, 60% had a dry cough. In the CT scans of the patients, the lesions observed are referred to as ground-glass opacities (GGO's). More than half of the cases that involved lesions present in two or more lobes of the lungs had the lesions located peripherally. Vascular thickening is also found in 80% of the cases (Han et al. 2020).

E. Pathophysiology

To address the underlying lack of information regarding the pathophysiology of COVID-19 infection, a study authored by Polak et al. (2020) established a timeline and correlation between histopathological findings and COVID-19 infection clinical stages by conducting a systematic review of published case reports and series. From the 198 individual cases and 42 articles encompassing the study, the main pulmonary pathological findings were as follows: pneumonitis related to COVID-19 infection exhibited the same epithelial, vascular, and fibrotic patterns in lung injury. To further expound, changes in the epithelium were evident across all disease stages, vascular damages were detected, and characteristics of acute fibrinous and organizing pneumonia were identified in the early stages. Moreover, nonspecific pathological findings were also established in other tissue organs such as the heart, liver, kidneys, spleen, skin, placenta, lymph nodes, and gastrointestinal tract. It has been discovered that during the late stages of COVID-19 infection, the kidney, liver, and gastrointestinal tract harbors inflammatory infiltrates and epithelium damage. Likewise, microvascular injuries were also evident.

F. Epidemiology

Currently, the main source of infection for COVID-19 is the patients themselves (Jin, 2020). Patients with severe cases of infection are far more contagious compared to those with mild cases. In addition, asymptomatic persons deemed as carriers of the disease and those in the incubation period are also considered potential sources of infection. The epidemiologic characteristic of COVID-19 infection can be attributed to a spatiotemporal kind of distribution. The disease source is Wuhan, China, and the start of the outbreak was in December 2019. In terms of population distribution, the data from the CDC in China reported that the bracket for COVID-19 infected patients is mainly from 30-70 years of age. Four months into the outbreak, the World Health Organization (WHO) divulged data accounting for 190 countries that were already affected. As for the routes of transmission, respiratory droplets and direct contact are the main ways to pass on the disease.

Due to SARS-CoV-2's nature as a respiratory virus, droplet transmission allowed for the faster spread of infection. The disease was first presumed to be a nosocomial infection then determined to be a novel respiratory virus that caused acute respiratory distress syndrome along with other complications (Rothan & Byrareddy, 2020). The transmission was later traced back to a fish market in Wuhan province where the initial patients had visited. The disease shows a predilection for more severe infection for the older age groups and the immunocompromised.

In the Philippine setting, the first suspected case of COVID-19 infection was recorded in late January 2020 and was first detected from two Chinese nationals (hereby indicated as first and second patients). Among them, Patient 2, a 44-year-old male, was the first who exhibited symptoms such as fever back in Wuhan, China. Between the dates of January 20 and 25, they traveled from Wuhan to Hongkong and eventually reached several areas in the Philippines. Eventually, the first patient exhibited a manifestation of sore throat and dry cough. They were then sent to San Lazaro Hospital, and upon examination, the second patient was categorized under COVID-19 PUI (Person Under Investigation) and was isolated. The first patient was discharged in early February; however, the second patient further developed pneumonia. Despite treatments given to him, he succumbed to the disease and first confirmed death due to COVID-19 infection outside China. A third confirmed case was revealed early in February, also from a female Chinese national from Wuhan. Contact tracing was performed of the three confirmed patients. In addition to these, three hospital staff assigned to the given patients developed symptoms and were classified under PUI.

G. Diagnosis

In the Philippines, the most efficient way of detecting SARS-CoV-2 infection is done using real-time polymerase chain reaction (RT-PCR). By far, the test is known to have the least amount of time and high specificity and sensitivity to detect the new coronavirus. The procedure identifies the presence of the virus by converting its RNA into DNA through reverse transcription and DNA amplification. Specimens used to detect COVID-19 infection are nasopharyngeal swabs from possible patients (WHO, 2020).

H. Laboratory Findings

SARS-CoV-2 viral load (RNAemia) and Interleukin 6 (IL-6) levels in patients with COVID-19 were examined to determine the COVID-19 severity. In the study done by Chen et al., serum and throat swabs samples were obtained to determine IL-6 and viral RNA level of COVID-19 infected patients. It has been indicated in the study that COVID-19 is correlated to an elevated IL-6 in the plasma. Chen et al. suggested that Il-6 can serve as a biomarker for the severity of COVID-19 infection. The study showed that the IL-6 levels of critically ill COVID-19 infected patients are higher in severe infections. High levels of IL-6 are said to be a useful driving force of cytokine storms that causes dysfunction in multiple organs of patients who are in critical condition. In addition, patients with RNAemia show higher IL-6 levels than other COVID-19 patients without RNAemia, which indicates that all patients with RNAemia have a higher risk of having multiple organ dysfunction (CHEN et al., 2020).

To assess the immune status as well as the predictors that are associated with COVID-19 infection severity, He et al. (2020) conducted a study that was composed of 204 COVID-19 positive patients with pneumonia. In the said study, the patients were divided into two groups which are as follows: patients that have severe COVID-19 infection with pneumonia and patients that are non-severe but have COVID-19 infection with pneumonia. Furthermore, a chest CT was performed on all of the patients in order to determine if there are any diagnosis for pneumonia in COVID-19 infection. In most of the patients with COVID-19 infection, the results of the chest CT have shown any indication of bilateral and multiple lobe lesions. The

laboratory results observed in the COVID-19 infection patients with pneumonia include median white blood cell count, platelet count, Lymphocyte, Urea, C-reactive protein, Neutrophil, Lactate dehydrogenase, D-dimer, and Aspartate aminotransferase. In addition, lymphocyte subsets were also counted such as B cell and NK cell (CD16+ 56+), CD8+ T cell, CD4+ T cell, as well as CD3+ T cell. Based on the study, the lymphocyte subsets count observed in severe patients is significantly lower compared to the lymphocyte subsets count of non-severe patients. In the humoral immune function, high IgG, Complement C3, and low IgM were observed in severe patients.

Furthermore, the observations in Interleukin 4 (IL-4) and TNF-α are higher in severe patients than non-severe patients. In contrast, the results conducted by He et al. (2020) indicate that the levels of IL-4, TNF-α, IgG, and C3 are negatively correlated with the T cell counts in severe patients with COVID-19 infection pneumonia. In contrast, IgM has shown a positive correlation with the T cell count in severe patients with COVID-19 infection pneumonia.

Significant laboratory findings in the patients include leucopenia with decreased leukocyte counts that are more prominent in severe cases (Gao et al. 2020) (Rothan & Byrareddy, 2020). Other Blood Cells also experience a significant decrease in severe infections like the eosinophils and platelets (Liao et al. 2020). Liao et al. mention how D-dimer and fibrin degradation products (FDP) were substantially higher in more severely infected cases (2020). In concurrence with the former, fibrinogen concentrations were significantly decreased in more afflicted patients. An increase in CRP levels above the normal range was noted by Rothan & Byrareddy (2020).

I. Other Similar Studies

The Usage of Logistic Regression on the Severity of Infection:

Liu et al. (2020) decided to address the risk assessment for clinical management in Renmin Hospital of Wuhan University due to the report of the WHO that the number of COVID-19 infected patients challenged the frontline clinical staff. A total of 99 patients with moderate and severe COVID-19 infections were used as the sample population: 61 non-severe patients and 38 severe patients. The instruments used were: demographic data, clinical data, laboratory findings, and treatment data. The severity of infection and the length of hospital stay were investigated using specific statistical methods to derive the risk factors that affect these variables. For the severity of infection, statistical analysis such as multivariate and univariate logistic regression were both used. Laboratory findings such as lymphopenia, elevated neutrophil count, LDH, increased CRP, and specific symptoms including dyspnea, fatigue, and anorexia or lethargy were associated with severe COVID-19 infection cases.

Moreover, to evaluate the tendency of long or short hospital stays, Spearman's correlation technique was used to associate the findings and the number of stays in the hospital. With this, it was discovered that the length of hospital stay is prolonged in COVID-19 infected patients with lymphopenia. Using statistical analysis, logistic regression, this study showed accuracy in associating the laboratory findings and the severity of infection. This study perfectly utilized these variables to show the role of the laboratory values in the causation of the severity of infection. Spearman's correlation technique was also used for the length of hospital stay, but that is out of the scope of this research already, so it will not be explored further.

All in all, the study by Liu et al. and this research are both quite similar. The difference is that this research aims to have an equal amount of the mild and severe population as much as possible. If not equal, the gap should not be as big as 61 and 38 since there will be much more accuracy if the two populations were equal or near equal. Having a much smaller amount for either of the population might not be enough to say that that amount of population applies to everyone.

The Usage of Central Tendency on the Severity of Infection:

The study conducted by Fan et al. (2020) examined the atypical hematological parameters found in COVID-19 infected patients. Common findings in COVID-19 infected patients were Leukopenia and Lymphopenia. ICU bound subjects also had LDH levels higher than the peak LDH levels of non-ICU subjects. During their stay in the hospital, patients developed neutrophilia. Certain limitations in the study were that certain laboratory tests had not been performed on all the subjects of the study. The LDH values were taken only in a subset of the total patients making the data slightly biased. The subjects of the study also make it so that the values derived from it are somewhat unreliable in terms of the comparison of values between mild and severely infected patients due to the larger population of 58 non-ICU patients compared to the 9 ICU patients. The data gathered in the study does reflect similar

values to other analogous studies. However, the statistical analysis applied to the study shows a very shallow understanding of the data gathered due to Fan et al. (2020) usage of central tendency to show a correlation in some of the values. The usage of other more statistically significant methods such as linear regression or logistic regression for more reliable data analysis and quantitation.

Meta-Analytic Study on the Laboratory Findings of COVID-19 Infected Patients:

A total of 19 articles were laid out from the study of Pourbagheri-Sigaroodi, et al. (2020) that suggest a comprehensive analysis of the laboratory findings of COVID-19 infected patients. The documented laboratory findings were correlated with the diagnosis and prognosis of COVID-19 infected patients. Pourbagheri-Sigaroodi et al. (2020) analyzed the complete blood count, PT, aPTT, D-dimers, erythrocyte sedimentation rate (ESR), CRP, PCT and biochemical factors of COVID-19 infected patients to evaluate how the aforementioned laboratory findings were affected in the aggravation of COVID-19 infection. In relation, the diagnostic values reported showed that the leukocytes and neutrophils are significantly higher in the complete blood count of severe COVID-19 infected patients as compared to non-severe COVID-19 infected patients. The gathered diagnostic results from the published articles were summarized and examined through meta-analysis. To conclude, the study of Pourbagheri-Sigaroodi et al. (2020) correlated the frequency of lymphocytes, leukocytes and, neutrophils in the severe patients and non-severe patients, concluding that the elevated neutrophil-to-lymphocyte ratio (NLR) could predict prognosis for COVID-19 infected patients. Although in this study of Pourbagheri-Sigaroodi et al. (2020) it must be noted that using frequency alone provides insufficient data to generate a well-supported and comprehensive analysis on the correlation of the laboratory findings from patients with COVID-19 infection. Moreover, the values Pourbagheri-Sigaroodi et al. used in the study were only gathered from the published articles that have been selected by the researchers, which have failed to establish accuracy on uncontrollable data.

J. Theoretical Study

Laboratory Findings:

The primary basis of this study is the article published in 2020 by the Center for Disease Control and Prevention (CDC) that was entitled, "Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)." According to their findings, the anomalous laboratory values prevalent in patients infected with COVID-19 include: lymphopenia, neutrophilia, elevated serum alanine aminotransferase (ALT) and AST levels, elevated LDH, high CRP, high ferritin levels, elevated D-dimer, and increased PCT. These biomarkers serve as the independent variables used in this study. Aside from the paper of CDC, other related studies by various researchers were used to corroborate and reinforce the contents of the paper.

a. Increased Ferritin, ESR, ALT, and D-Dimer Levels:

Chowdhurry et al. (2020) also conducted a study that was able to garner the results of increased values of CRP and Prothrombin time in all patients. The other laboratory values such as ferritin, ESR, ALT, and D-Dimer levels were also shown to be elevated in most of the patients. Some presented with lymphocytopenia, while several presented with mild erythrocytopenia. Their study deduced that the possible usage of CRP, Prothrombin time, serum ferritin, ESR, ALT, D-Dimer, erythrocytopenia and lymphocytopenia as a diagnosis for initial hematological findings also has the capability for COVID-19 infection prognosis.

A different study conducted by Pizzi et al. (2020), also elicited that patients infected with COVID-19 showed a significant increase in CRP, LDH and ferritin levels in comparison to non-COVID-19 infected patients.

b. High C-reactive Protein:

Zhu et al. (2020) evaluated patients with COVID-19 infection that had increased amounts of IL-6, CRP and hypertension. These abnormal values were found to be independent predictors for COVID-19 infection severity. These three laboratory values were elaborated to exhibit the highest correlation to the severity of infection.

Furthermore, the findings regarding the results of other laboratory values such as notable increase of NLR, fibrinogen, sialic acid, IL-10, and IFN-γ in patients with severe COVID-19 infection in comparison to patients with non-severe COVID-19 infection were also shown. On the other hand, the value of lymphocyte levels and platelets were remarkably lower in patients with severe COVID-19 infection than in patients with non-severe COVID-19 infection.

c. Neutrophilia:

Li et al. (2020) analyzed that neutrophilia and elevated ultrasensitive cardiac troponin I were both independently associated with COVID-19 infected patient death. These findings were also more oriented toward elderly patients than younger patients.

d. Elevated D-Dimer:

The main focus of a study by Zhang et al is the elevation of D-dimer levels of patients diagnosed with COVID-19 infection. In the study, it was discovered that the D-dimer level of the patients is greater than 2.0 μg/mL upon their admission and is an effective independent predictor for mortality of in-patients with COVID-19. Out of 343 patients examined, 67 patients had a ≥ 2.0 μg/mL upon admission, meanwhile, 267 patients had a < 2.0 μg/mL of D-dimer level upon admission. During their stay in the hospital, a total of 13 patients died from the disease. The patients with D-mer levels that are lower than 2.0 μg/mL upon admission attributed to an increased mortality rate than of the patients with a greater than or equal to 2.0 μg/mL D-dimer level upon admission. The probable reasons theorized were that viral infections induce inflammatory response that cause the endothelial cells to over function thus increasing thrombin synthesis; severe COVID-19 infection causes hypoxia which stimulates thrombosis; COVID-19 infected patients of the older age are predisposed to certain conditions that are considered risk factors for thrombosis; some cases may cause sepsis-induced coagulopathy or disseminated intravascular coagulation which are unfavorable situations that may elevate D-dimer levels.

Increased Ferritin, and PCT Levels:

Ferritin is a protein that is composed of 24 H- and L-subunits which are present in the body fluids of a person, specifically in blood plasma and serum (Wang et al. 2010). Prior to assessment of disease severity, Kappert, Jahic & Tauber. (2020) analyzed the immunological and laboratory characteristics of 21 COVID-19 infected patients. All patients were classified as severe and moderate cases. Among the 21 patients, 12 patients presented a remarkably increased serum ferritin value. In addition, other inflammatory biomarkers were observed in patients which include high-sensitive CRP, IL-6, and PCT. These markers are significantly higher in severe cases than moderate cases. In this case, Kappert et al. suggests that the high level of systemic inflammation and high level of inflammatory biomarkers demonstrated in patients, correlates with the severity of the disease. The documented laboratory serum ferritin in several COVID-19 infection studies indicates that ferritin can be used as a biomarker in assessing the severity of COVID-19 infection in hospitalized patients.

Classification of the Severity of Infection:

a. Classification of Mild and Severe Infections by CDC:

The CDC (2020) has established its own classification of the severity of infection for the COVID-19 infected patients. The COVID-19 infected patients have been classified into three: Mild to moderate, severe, and critical. However, only the classifications mild to moderate and severe will be tackled.

Mild to moderate clinical presentations exclude the presence of viral pneumonia and hypoxia. This level of severity does not initially require hospitalization and can be managed at home. The decision for hospitalization depends on the clinical presentation, supportive care requirement, potential risk factors for severe disease, and how the person can self-isolate at home.

Severe clinical presentations include the presence of pneumonia, hypoxemic respiratory failure or acute respiratory distress syndrome (ARDS), sepsis, cardiomyopathy, and acute kidney injury. This level of severity requires hospitalization for proper care and treatment. There are some scenarios wherein long periods of hospitalization account for the severity of infection due to the acquired complications. These complications are as follows: secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness neuropathy or myopathy.

b. Classification of Mild and Severe Infections by WHO:

The severity of COVID-19 infection has several classifications as per the official published Interim Guidelines for its clinical management issued by WHO in 2020. COVID-19 infection severity can be categorized as mild, moderate, severe, and critical.

Mild diseases are associated with symptomatic patients who present classic signs and symptoms such as fever, cough, fatigue, and shortness of breath, along with other nonspecific symptoms like headache, nasal congestion, and sore throat; however, there is no clinical manifestation of viral pneumonia or hypoxia.

On the other hand, diseases that are classified as moderate are common in adults and adolescents with clinical manifestations of pneumonia (excluding the presentations in severe cases of pneumonia) such as cough, fever, and hyperpnea. Similarly, children with moderate diseases express difficulty in breathing, rapid breaths, and cough which are signs of pneumonia that is categorized as non-severe.

Severe diseases are accompanied by severe pneumonia. In adolescents and adults, clinical signs of pneumonia are manifested with the addition of severe respiratory distress. Meanwhile, children with severe disease exhibit signs of pneumonia along with at least one of the other manifestations such as severe respiratory distress, central cyanosis, and general danger signs— convulsions, lethargy, inability to breastfeed or drink.

Critical diseases are associated with several conditions like ARDS, septic shock, and sepsis. The aforementioned disease manifestations pose a serious threat to life.

c. Classification of Mild and Severe Infections in association with Laboratory Diagnosis:

A study of Bhargava et al. (2020) evaluated the severity of COVID-19 infection by analyzing the laboratory findings and clinical parameters including vital signs, presenting symptoms, presence of comorbid condition, and status on intubation and intensive care unit admission of 197 hospitalized COVID-19 infected patients.

In this study, patients with mild COVID-19 infection frequently demonstrated a presence of sore throat and cough. Moreover, severe infection is shown to be caused by an increase in inflammatory response, white blood cell counts, CRP levels, and PCT level. However, it demonstrated a low lymphocyte and platelet counts compared with patients with mild COVID-19 infection. The gathered results indicate that patients aged 60 years and older are more expected to have a severe COVID-19 infection, which would require intubation and admission to the intensive care unit compared with patients with mild infection. Patients with severe COVID-19 infection are also more susceptible to have at least one comorbid condition, significantly like diabetes, renal disease, and chronic pulmonary diseases. Additionally, severely infected patients are expected to be tachypneic, which would lead to low oxygen saturation during the time of hospital admittance.

Clinical Statistical Tool:

a. An Overview of Logistic Regression:

Logistic regression is commonly utilized in the clinical setting by estimating whether there will be a presence or an absence of a symptom or an increase or decrease of a variable in the connection to an independent variable. It usually studies the past clinical manifestations of patients in estimating the odds of a result by mathematically simulating those manifestations and describing it through a regression equation. In this way, a relationship between a dependent variable like age, symptoms, or routine laboratory test values and an independent variable like a presence or absence, or the severeness (either acute or chronic) of a disease (Anderson, et. al., 2003).

b. Logistic Regression Analysis of Clinical Laboratory Data to Determine Patients with Severe COVID-19 Infection:

In a study conducted by Gao et al., the researchers aim to identify for warning indices present in severe COVID-19 infected patients using laboratory data such as alanine aminotransferase (ALT), glucose (GLU), interleukin-6 (IL-6), procalcitonin (PCT), and D-dimer (D-D) levels. Initially, the given data were not normally distributed but eventually were further compared between two groups using the Mann-Whitney U tests. The subsequent results were then shown using the interquartile range. The logistic regression, the confidence interval of the receiver operator curve, and the area under the curve (AUC) were then computed using the predicted probability of severe COVID-19 infection and were further analyzed using the SPSS software. The prediction of the disease severity was determined with the use of Youden's index. From the analysis, the researchers were able to deduce that IL-6 and D-D levels are possible parameters which can be used to estimate COVID-19 infection severity. This proves that the following parameters can be measured in order to diagnose the severity.

c. The Usage of Logistic Regression on Mortality Rate of the Severity of Infection:

In the study conducted by Liao et. al. (2020), logistic regression was applied as the statistical analysis. This functions to evaluate the chosen independent variables and the effects on the mortality of severely and critically infected COVID-19 patients. The variables determined were select hematologic parameters such as D-dimer, Prothrombin Time, activated

partial thromboplastin time (aPTT) etc. that were determined to have some effect on patient mortality. The binomial dependent variable in this case is the severe and critical classification which is related statistically to the independent hematologic variables through use of logistic regression. The logistic regression establishes a relationship and degree of effect similar to multiple linear regression, by use of the odds ratio of each independent variable in relation to the target event, which is the binomial dependent variable (Sperandei, 2014).

K. Conceptual Framework

The paradigm of the study will be as follows:

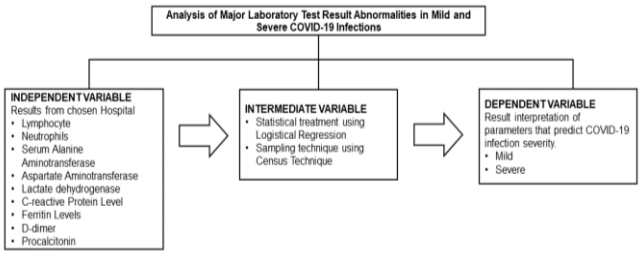

Fig.1. Conceptual Framework

The paradigm of the study was based on the research done by Shanget al. (2020), wherein they collated laboratory data of COVID-19 infected patients from Wuhan Forth Hospital. Medical records and laboratory results of the said patients were gathered. The values for leukocyte, neutrophils, lymphocytes, NLR, hemoglobin, platelets, D-dimer, ESR, CRP, PCT, LDH, uric acid, creatinine, and albumin results were analyzed statistically to find out the connection of the values to the severity of COVID-19 infection.

The study will apply a similar approach to that done by Shang et al. (2020) and in which the concepts of the research are shown in the framework above. The given framework shows the flow of the concepts and the relationships between the study variables, which aims to interpret laboratory findings to the severity of COVID-19 infection. The independent variables given include the results, which are requested from the hospital from infected COVID-19 inpatients using eight laboratory values. These values will then be analyzed through the intermediate variables, which are the logistical regression statistical treatment and the purposive sampling. Lastly, the dependent variable is the final interpretation of the values and parameters that could predict the COVID-19 infection severity as either mild or severe.

III. RESEARCH METHODS

This chapter outlines the methods utilized in the study. Firstly, the research design illustrates the methods and framework required to address the research question. Following are the target participants, which were identified by the sampling technique, the inclusion and exclusion criteria, and any relevant rationale for the decisions made. Next, the data gathering and handling methods applied to ensure proponent safety and patient confidentiality–and finally, the statistical treatments and analysis applied on the data.

A. Research Design

A quantitative research design was employed by the researchers in conducting the study. Quantitative research, according to Steber (2017), emphasizes the numerical analysis of data collected in response to relational inquiry of variables within the research. In addition, the study also utilized an analytic retrospective research design. This is due to the fact that the study aims to determine the relationship of several variables with specific target variables. The relationship established is then used to predict a corresponding outcome. By definition, analytical studies assess the hypothesis by using the variables in order to create causal relationships (Ranganathan & Aggarwal, 2018). Meanwhile, included under the types of analytical studies is the retrospective approach which pertains to the specific time of conducting the research with respect to the observation of results. In a retrospective study, the outcome has already happened and the data is acquired from records (Parab & Bhalerao, 2010).

In particular, this study made use of correlation analysis that utilizes logistic regression. Correlation analysis determines whether the significant routine laboratory values are associated with the severity of the COVID-19 infection. Logistic regression model has a fixed number of parameters that are dependent on the number of input variables, which output as a categorical predictor (Hoffman, 2019).

In this study, clinically significant routine laboratory values from the secondary data of COVID-19 infected patients were obtained from the chosen tertiary hospital in Manila. This set of data is the laboratory values such as lymphocyte count, neutrophil count, serum alanine aminotransferase level, lactate dehydrogenase level, C-reactive protein level, ferritin level, D-dimer level, and procalcitonin level will be used as variables in

determining the major contributory laboratory abnormalities in patients with mild and severe COVID-19 infection.

B. Participants

Sampling Technique:

The sample population in this study is considered as heterogenous in which the census technique was used. As opposed to a sampling technique where only a fraction of the population that matched the criteria is studied, census technique involves studying each and every unit of the population that is suitable for the study (Mertinez-Mesa et al., 2016). Thus, by analyzing the entirety of the population, it makes the analysis more accurate and reliable compared to sampling technique. In addition, the population does not contain a margin of error since the entire population was selected that matched the given criteria.

Due to the limited available data for this study, the researchers chose to include all eligible records totalling to 113 patients records. There are specifically 58 patients from the mild cases and 55 patients from the severe cases who were confined in the chosen tertiary hospital in Manila from March 2020 to January 2021. Since the entirety of the population of interest is being studied, sampling techniques are no more applicable in this case. Thus, a computation for the sample size would not be provided.

There was no manner of recruitment since the information was based on the secondary data obtained from the clinical laboratory in the chosen tertiary hospital in Manila.

Inclusion Criteria:

The general focus and purpose of this study is to use statistical analysis on various laboratory parameters as predictors of COVID-19 infection. Eight parameters will be analyzed including lymphocytes, neutrophils, ALT, LDH, CRP, ferritin, D-dimer, and PCT.

This study made use of secondary data, which were derived from the laboratory records of inpatients with confirmed COVID-19 infection, validated through RT-PCR test, and are either classified as mild or severe infection by the chosen hospital. The data summed up a total of 113 patients.

As for the patient profile, patients of both genders with ages ranging from 18-59 years old, with the aforementioned laboratory parameters on record, are included. The data were segregated according to the infection severity which was assigned by the hospital. The medical record stating the patient's severity of infection was only asked if the hospital failed to categorize the patients' condition whether mild or severe infection in the patients' laboratory results.

Exclusion Criteria:

Patients that lack half or more than half of the laboratory data were excluded from the study. In addition, all patients with existing disease or comorbidity prior to COVID-19 infection were also not included. The patient admission status must only be 'inpatient', thus, outpatients are excluded in the study.

To ensure that all data collected meets the desired parameters set by the researchers in the inclusion criteria, a thorough manual data review was done to ascertain that the right data were excluded for the study. All excluded data were removed from the samples to be statistically analysed and were deleted permanently from all devices.

Withdrawal Criteria:

Due to the nature of the study, there are no direct individual participants involved but rather only collated data previously collected by the hospital that were used for patient diagnosis and care. Therefore, there are no withdrawal criteria for safety concerns regarding human participants in an experimental study. The only withdrawal criteria applicable would be if the hospital rescinds approval to conduct study with the hospital's data and prohibits the publishing of the data acquired.

Suitability of Study Site:

The suitability of the site must be determined in order to ensure that the information acquired from the said source is factual and relevant to the topic of interest (LibreTexts, 2019). It is important to consider a site or source that can directly address or sufficiently contribute in answering the research problems and objectives.

The hospital chosen is classified as a tertiary hospital and with a fully operating laboratory information system (LIS) to ensure that the data could be procured digitally.

The researchers went to the hospital to personally gain access to the medical records and results. Data collected from the

tertiary hospital were manually checked and it was ensured that it fulfills the required criteria set forth by the researchers. All medical laboratory data of the patients included in the study were organized on a spreadsheet for proper organization and were statistically treated as mentioned on the data analysis section of the paper.

C. Data Measure/Instrumentation

The data used in this research are secondary data requested from a tertiary hospital. This research studied the laboratory values of patients with mild and severe COVID-19 infection. Therefore, the chosen hospital wherein the values were acquired was a COVID-19 infection referral hospital, which admits patients with the aforementioned disease. Furthermore, since the laboratory values included in this study are lymphocyte count, neutrophil count, serum alanine aminotransferase, ferritin, C-reactive protein, D-dimer, lactate dehydrogenase, and procalcitonin, the chosen hospital was made sure to be able to accommodate the required parameters. The chosen tertiary hospital was located in the Philippines. Moreover, the chosen tertiary hospital already identified the classification of severity–mild or severe–and distinguished the patients of COVID-19 infection with co-morbidities.

All secondary data came from the values derived from the patients' laboratory records confined in the hospital. Laboratory test values came from the subjects' complete blood count tests (lymphocytes and neutrophils), assays for coagulation and fibrinolysis cascades (D-dimers), biochemical tests (lactate dehydrogenase), ALT tests (serum alanine aminotransferase), and inflammation-related parameters (CRP, ferritin, and PCT).

Table.1. Reference Ranges of the Laboratory Values (Dependent Variables)

Laboratory Parameters	**Reference Range**	**Unit of Measurement**
Neutrophils	0.55 - 0.70	U/L[1]
Lymphocytes	0.25 - 0.40	U/L
Serum Alanine Aminotransferase	14 - 54	U/L
Lactate dehydrogenase	135 - 225	U/L
C-reactive protein	0 - 5	mg/L[2]
Ferritin	12 - 336	mg/L
D-Dimer	< 0.5	ug/mL[3]
Procalcitonin	0.5 - 2	ng/mL[4]

Note: Reference values were taken from the laboratory where the data was acquired.
1 U/L means units per liter
2 mg/L means milligram per liter
3 ug/mL means microgram per milliliter
4ng/mL means nanogram per milliliter

The table shows the eight laboratory values that act as the dependent variables in this study. Each laboratory parameter has its own reference range, which is considered normal; and it should be noted that any value not within the respective reference range is considered either increased or decreased. The laboratory parameters are as follows:

Complete Blood Count:
Neutrophils are a type of white blood cell that arises in certain conditions such as infections, injuries or other types of stress because it heals damaged tissues and resolves infections (Huizen, 2020). The neutrophil count should be within the reference range of 0.55 to 0.70 U/L.

Lymphocytes are also a type of white blood cell considered to be one of the body's main types of immune cells. There are two types of lymphocytes: (1) B-cells function mainly for immunity wherein recurring infections are quickly eliminated, and (2) T-cells kill pathogens that neutrophils are not capable of eliminating (Silva, 2020). The lymphocyte count should be within the reference range of 0.25 to 0.40 U/L.

ALT Test:
ALT is an enzyme that is found in many tissues and predominantly has high concentrations in the liver. Thus, it used to diagnose liver diseases (Bishop, 2017). Normal ALT levels range from 14 - 54 U/L.

Biochemical Test:
LDH is an enzyme that turns sugar into energy. Its activity is increased when the enzyme is released from ruptured red blood cells (Keohane, et. al, 2020). The normal level of LDH is 135 - 225 units per liter.

Assay for Coagulation and Fibrinolysis Cascades:
D-Dimer in the bloodstream indicates current or recent coagulation and subsequent fibrinolysis. As a result, D-Dimer serves as an indirect coagulation and fibrinolysis marker

(Bishop, 2020). The normal value of D-Dimer is < 0.5 micrograms per milliliter.

Inflammation-Related Parameters:
Ferritin is a protein that stores iron and functions within the cells. Ferritin levels indicate the amount of iron that is stored in the body and has a normal range of 12 - 336 mg/L (Keohane, et. al, 2020).

CRP is an inflammatory marker found in the bloodstream, produced by the liver. The C-reactive protein test measures the concentration of CRP present in the blood which helps diagnose chronic and acute inflammatory conditions (Huizen, 2018).

PCT is commonly produced in reaction to bacterial infections but it can also be produced in response to tissue injury. Identification of septic patients with this laboratory parameter has a higher specificity compared to other proinflammatory markers (Jin & Khan, 2010). The normal value of PCT is 0.5 - 2 nanograms per milliliter.

The instruments utilized in this study includes the patients' information that were admitted from March 1, 2020 up to January 6, 2020. The idea behind this date is that around March was the time when the COVID-19 cases in the Philippines started to surge up again (Roser, et al. 2020). Moreover, the Philippine government announced a state of calamity in the country and declared "community quarantine" for Metro Manila in March 2020 (Duddu, 2020). Any data after January 6, 2021 is excluded from the study. This is to prevent the utilization of the new strain of the COVID-19 infection that emerged in December 2020 (WHO, 2020) that was only reported in the Philippines on January 7, 2021 (DOH, 2021).

D. Data Gathering Procedure

The laboratory test results from the mild and severe COVID-19 infected patients were acquired from the chosen hospital. The secondary data was requested specifically from the hospital administrators. With this, a letter of request was sent to the hospital outlining a summary of the study and its future applications, as well as a list of all the laboratory values needed for the study. The said data were gathered along with a letter of consent, in which the administrators will grant their approval. Since the researchers do not have any contact with the patients, the consent and approval came from the hospital administrators themselves.

This documentation warrants that the data to be presented in this research are valid. The researchers directly went to the hospital itself to provide the hospital administrator with the letter that requests for the pertinent data together with the consent of approval. After acquiring the hospital's approval, researchers went to the hospital to collect the data personally due to the administrator's preference regarding data security. The data was handled with extreme caution regarding patient privacy and prevented any leakage of patient information. All the records were uploaded to the master data file in software like Microsoft Excel and was further analyzed.

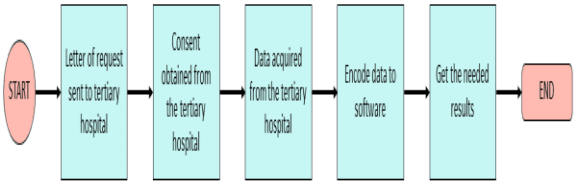

Fig.2. Procedural Flowchart

E. Ethical Considerations

To address and minimize the possible risks associated with this study, the researchers will also abide by the established guidelines of the World Medical Association's Declaration of Helsinki, which consists of statements of ethical principles for medical research that involves human subjects and also researches on identifiable human material and data; and it mainly serves physicians but is applicable to all medical researches involving any human subjects or data (World Medical Association, 2013). Since the study involves the analysis of laboratory values, as well as possibly medical records, it is mandatory to submit to the governing principles of the said declaration.

The principles used to further elaborate the ethical considerations are from the World Medical Association's Declaration of Helsinki in 2013:

- In compliance with the 22nd principle under "Scientific Requirements and Research Protocols", the ethical considerations have been included and clearly explained in the chapter. Dedicated sections are also provided in the succeeding parts of this paper to further expound on the conflict of interests, and incentives or compensation.

- As for the 23rd principle under "Research Ethics Committees" and 32nd principle under "Informed Consent," necessary forms were filled out and submitted to the UST Faculty of Pharmacy Research Ethics Committee (FOPREC) for evaluation and approval. The researchers were also required to allow FOPREC to monitor the study, as well as to submit a final report including the summary of findings and conclusions of the study.
- In response to the 7th, 8th, and 9th principles under "General Principles"; and 24th principle under "Privacy and Confidentiality," the ethical considerations addressed are confidentiality and anonymity. The method in which the researchers gathered information was in accordance with Republic Act No. 10173 also known as the "Data Privacy Act of 2012" and the Health Privacy Code Administrative Order No. 2016-00022 "Privacy Guidelines for the Implementation of the Philippine Health Information Exchange". The Data Privacy Act of 2012 the law that protects individual personal information stored in information systems in both government and private organizations. Furthermore, Section 2 of the Data Privacy Act of 2012 states that, "*the State recognizes the vital role of information and communications technology in nation-building and its inherent obligation to ensure that personal information in information and communications systems in the government and in the private sector are secured and protected.*". As for the Health Privacy Code Administrative Order No. 2016-00022, this specifically implements the aforementioned republic act in exchanging health information. The Health Privacy Code Administrative Order No. 2016-00022 was integrated in the study and served as the main guideline to protect the confidentiality of the patients afflicted with COVID-19 infection. The researchers selected a tertiary hospital laboratory in which the data were collected, however, the name of the hospital was stated in the entire study. Afterward, consent was obtained from a duly authorized staff. As such, the consent was received from a social worker or an attending physician (Rule 1, Section 1.3). Furthermore, as per Rule 10, Section 4, subsection D, the medical records to be acquired must be subjected to technical anonymization procedures and must be declared clear for public access by a duly constituted ethics committee. To ensure a systematic classification, the anonymization procedure employed is the assignment of a numerical code to the patient (e.g. Patient 1, Patient 2). The data were stored in a flash drive to secure data privacy. Access to the data was restricted only to the researchers and the statistician who shall use the data only within the time period of the research proper, which is from August 2020 to May 2021. Afterwards, all the necessary data were deleted permanently from all devices (e.g. researcher's laptop, flash drive, and all possible devices). The implementation of these actions will lessen the risk of data leakage and will protect the reputation of the hospital.
- In response to the 12th principle under "General Principles," the research was conducted by medical technology students from University of Santo Tomas Faculty of Pharmacy and is supervised by their thesis adviser.

Risks:

Risk is characterized as the likelihood of harm as a result of involvement in a research study, whether it is physical, psychological, social, legal, or in economics (Human Subjects Protection Program Policy Manual, 2021). In conducting research, some risks can be encountered. The possible risk that may be encountered as well as their corresponding mitigation measures are shown in the table below.

Table 2. Risks and Mitigation

Risk Category	Identified Risks	Strategies to Mitigate Risks
Social, Economic, and Legal Risks	Leakage of data to other institutions or individuals	If the data will be given digitally, only one email address will be given to the hospital where they will send the data. The researchers should ensure that the given email address is active and correctly inputted to avoid falsely sending the data to other emails. Prior to access, the statistician must first sign an agreement form in regards to the confidentiality of the given data.
	Hospital does not classify COVID-19 patients as mild and severe.	If no classification was done by the hospital, the researchers will request for the medical records of the patients to classify them in terms of COVID-19 severity.

	Incomplete or lacking of data for mild patients in the chosen hospital	The researchers will settle with the procured data. The parameters are not usually affected and are expected to be in normal range so they are not being tested on mild patients.

Benefits:

There are no direct benefits to participants. According to Luna-Lucero (2018) benefit does not require to be directed to participants of the study, as it may provide benefit to the public or in the research field.
Moreover, the results of this study may further improve the understanding about COVID-19 infection. Lastly, the hospital that gave the data will have access to the results of the study once the study is finished.

Incentives or Compensation:

No incentives or compensation will be provided as the study only makes use of secondary data and thus, has no study participants nor contact with the patients where the data originated from.

Conflict of Interest:

The researchers declare no conflict of interest in preparing this study. As stated by the University of Queensland (2020), conflict of interest arises when individuals differ from his or her own interest, and obligations over the given duties and responsibilities needed to adhere as a researcher.
This study is to be conducted independently in a form of educational requirement in the academe undertaken by BS Medical Technology students. Therefore, the study will not receive specific grants from any organization in the public, commercial, or profit sectors.

Data Analysis:

Firstly, to accomplish the first objective, the data, which includes the laboratory values and the severity of infection, was outlined through descriptive statistics. Descriptive statistics was used for the simple description and comprehension of the details of a specific data set by giving a summary of the data. This is usually applied to rearrange large quantitative data into short and understandable descriptions (Kenton, 2019).

The fulfillment of the second objective was done by calculating the measure of central tendency such as the mean; and measure of variability such as the standard deviation will be used. In order to summarize the obtained data from the chosen hospital, the use of central tendency will determine the center of the distribution and provide a probability distribution value to describe the set of data. Mean is used as the average value of the set of data (La Trobe University, 2020). Furthermore, this study made use of measures of variability to provide descriptive information about the distribution of variables within the data. Standard deviation was utilized to measure the average distance between the values of the data in the set and the mean (La Trobe University, 2020). The laboratory parameters that have indefinite results were sorted categorically and be interpreted using the frequency count and percentage. The frequency count determines the number of times a variable occurs (Stephanie, 2019). Moreover, the independent variables such as the laboratory results were subsequently interpreted through the use of the mean and standard deviation. Percentage, on the other hand, shows the prevalence of a certain category. Eventually, the overall data were presented visually using graphs and charts.

After establishing the overview of the data, to carry out the last objective, the data were analyzed with the use of a higher statistical analysis tool, which is logistic regression. This particular statistical treatment associates the binary dependent variable and a set of independent variables (Swaminathan, 2018). In this study, the categorical dependent variable, also called as the response variable, is the severity of infection (i.e., mild and severe); and the set of independent variables are the selected laboratory values. The dependent variables are dichotomous wherein the mild case is classified as “0” and the severe case is classified as “1”. Through this analysis, each laboratory value will form a tool used to establish the likelihood of severe COVID-19 infection. Logistic Regression measures how the dependent variable is correlated with the independent variable (Sarstedt and Mooi, 2014). Logistic regression has a fixed number of parameters that are dependent on the number of input variables or the categorical predictor (Hoffman, 2019). Furthermore, binary logistic regression can determine the impact of the variables - in this case, the laboratory values - to predict which category they are more likely to belong (Hua, et. al, 2021). This describes how significant laboratory values are numerically related to the severity of COVID-19 infection. In doing so, the concept of odds ratio is used. Odds ratio shows the constant effect of a predictor (independent variable) on the

likelihood that one outcome will occur (Martin, 2012). Ultimately, a set of laboratory values are established as a tool in predicting which has the most significant effect in the severity of the COVID-19 infection.

IV. Results And Discussion

This chapter includes the presentation, analysis and interpretation of the data. It tackles the prevalence of the COVID-19 cases by severity through the usage of percentage. Moreover, the characteristics of the patients in terms of their laboratory test results are also shown. Mean and standard deviation, as well as median and IQR, were computed. Lastly, the estimated logistic regression models are also discussed which presents the individual laboratory parameters in predicting the severity of COVID-19 infection. The results were generated from R software ver. 4.1.0 running on RStudio ver. 1.4.1717.

A. Presentation and Analysis of Data

Prevalence of COVID-19 Cases Classified as Mild and Severe:

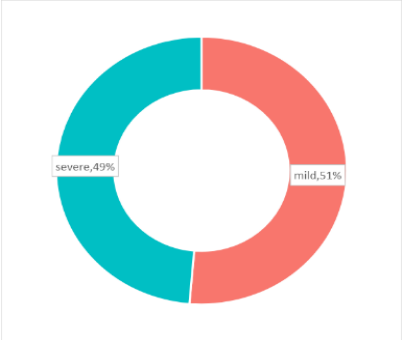

Fig.3. Distribution of COVID-19 Cases by Severity

This figure presents the distribution of COVID-19 severity among the selected patients. Fifty-eight patients or about 51.3% of them had mild symptoms of COVID-19 while the remaining 48.7% had experienced severe symptoms of COVID-19. According to this figure, there is a relatively high prevalence of severe COVID-19 patients when observed together with mild COVID-19 patients.

Laboratory Values of Mild and Severe COVID-19 Cases:

Table.3. Summary Statistics of Laboratory Results of the Selected Patients with Mild and Severe Case of COVID-19

	Mild		Severe	
Laboratory Result	Mean (SD)*	Median (IQR)**	Mean (SD)*	Median (IQR)**
Neutrophils (U/L)	0.60 (0.13)	0.59 (0.18)	0.77 (0.14)	0.81 (0.16)
Lymphocytes (U/L)	0.30 (0.11)	0.31 (0.16)	0.17 (0.14)	0.13 (0.13)
Alanine aminotransferase (U/L)	43.94 (41.80)	25 (29)	89.45 (84.74)	71.5 (64)
C-reactive protein (mg/L^2)	6.27 (16.21)	1.08 (2.52)	78.58 (91.69)	44.285 (103.48)
Lactate Dehydrogenase (U/L)	186.63 (42.93)	182 (39)	437.81 (232.26)	409 (211)

*Numbers inside the parentheses are computed standard deviations. ** Numbers inside the parentheses are interquartile ranges.

The table above presents the summary statistics of the laboratory results of the selected patients with mild and severe symptoms of COVID-19. Based on the table above, the mean neutrophil count in mild cases is 0.60 with a standard deviation of 0.13. Its corresponding median is 0.59 which is not far from the computed mean value which suggests that the distribution of neutrophils is more or less symmetric across all patients with mild COVID-19 symptoms. On the other hand, the mean neutrophil count is 0.77 (SD = 0.14) and the median is about 0.81 for patients with severe COVID-19 symptoms. It also suggests that the mean and median neutrophil count of patients with severe symptoms of COVID-19 is higher than those with mild symptoms of COVID-19.

In patients with mild cases, the mean and median values for lymphocytes are 0.30 and 0.31, respectively, with the standard deviation of 0.11. In patients with severe cases, however, the mean and median values for Lymphocytes are 0.17 (SD = 0.14) and 0.13, respectively. This suggests that the mean and median lymphocyte count of patients with severe cases of COVID-19 is lower than normal compared to those with mild cases of COVID-19.

Meanwhile, the mean ALT for patients with mild cases is 43.94 with the standard deviation of 41.80. Its mean is about 19 units higher than the median indicating that its distribution is skewed to the right. On the other hand, for patients with severe cases,

the mean and median values for ALT are 89.45 (SD = 84.74) and 71.5, respectively.

Next, the mean CRP for patients with mild cases is 6.27 (SD = 16.21) which is about 5 times greater than the median value. This suggests that its distribution is highly skewed to the right. For patients with severe cases, however, the mean and median values for CRP are 78.58 (SD = 91.69) and 44.285, respectively.

Lasty, for patients with mild cases, the mean LDH is 186.63 (SD = 42.93) which is 80 times greater than its median value. Although for patients with severe cases, the mean LDH is 437.81 (SD = 232.26) and the median is about 409. This means that the distribution of LDH is skewed to the right. This suggests that the mean and median ALT, CRP, and LDH of patients with severe symptoms of COVID-19 are higher than those of patients with mild cases.

With the aid of the logistic curve generated through the logistical regression model, the data dispersion between the mild and severe cases was shown. The predicted probabilities of having severe COVID-19 infection were plotted using a logistic curve, as shown by the red line that lies across the independent variable's ranges of values. Moreover, the relationship between the independent and outcome variable was determined by the slope of the curve. Therefore, in a positive slope, the probability of having severe COVID-19 increases when the value of the independent variable also increases. Conversely, in a negative slope (inverted S), the probability of having severe COVID-19 decreases when the value of the independent variable increases.

The y-axis depicts the severity of infection where a value that falls in line “0” is considered a “mild case” and a value that falls in line with “1” is considered a “severe case”. Meanwhile, the x-axis represents the level of the laboratory values.

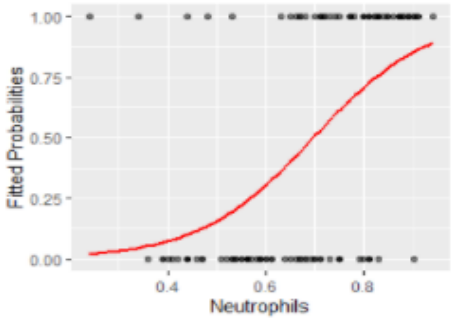

Fig.4. Logistic Curve of Neutrophils

Neutrophil count has a reference range that is from 0.55 to 0.70 U/L. As seen in Figure 4, the logistic curve proves the existence of mild and severe cases in all low, normal, and high levels. From this, it is evident that the data are widely distributed.

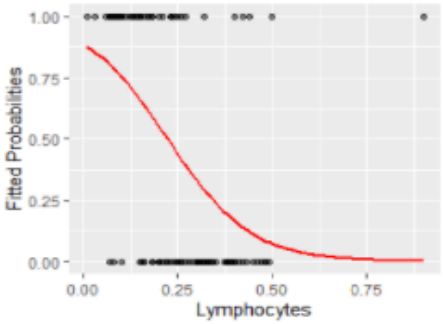

Fig.5. Logistic Curve of Lymphocytes

The logistic curve of lymphocytes is exhibited by Figure 5. The lymphocyte count has a reference range of 0.25 to 0.40 U/L. The figure indicates that in low and normal levels, both mild and severe cases occur. Hence, the data are distributed widely.

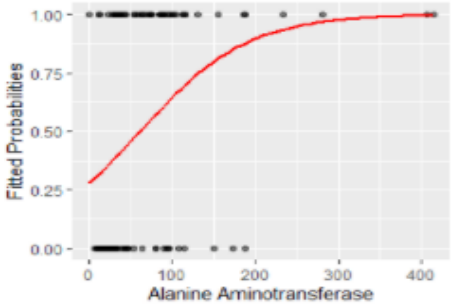

Fig.6. Logistic Curve of ALT

Displayed in Figure 6 is the logistic curve of ALT. ALT has a reference range of 14 to 54 U/L. This exhibits data that are widely distributed since the occurrence of both mild and severe cases appears in all low, normal, and high levels. In addition, the curve also presents the premise that any value greater than 200 U/L will only result in a severe COVID-19 case.

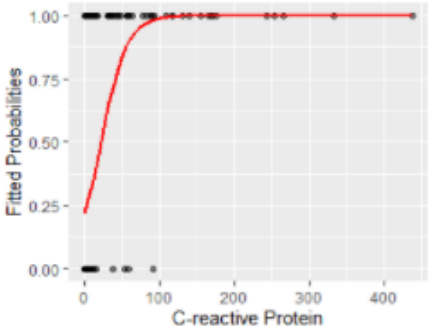

Fig.7. Logistic Curve of CRP

As for the logistic curve of CRP, it is shown in Figure 7 above. Moreover, the data for CRP are described to be widely distributed. This is because of its reference range which is from 0 to 5 mg/L, expressing the existence of both mild and severe cases in both normal and high levels. Furthermore, this curve also reveals that any value greater than 100 mg/L will only result in a severe COVID-19 case.

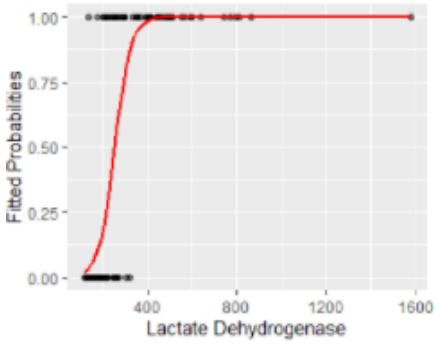

Fig.8. Logistic Curve of LDH

In Figure 8 shown above, the logistic curve of LDH is depicted. The reference range is found to be from 135 to 225 U/L, which expresses that in all low, normal, and high levels, both mild and severe cases occur. From this, it is conclusive to say that the data are widely distributed. Additionally, the curve also suggests that any value greater than or equal to 400 U/L will only result in a severe COVID-19 case.

Some variables, however, have values that are indefinite (eg. > 1200) hence, computation of summary statistics does not apply to them. The researchers transformed these variables into categorical ones to analyze them using frequency and percentages. Note that the ranges were arbitrarily made only based on the empirical distribution of the variables. The ranges are selected such that each category or level has a sufficient element that can be used in further analyses. Furthermore, missing values are recorded into the No data category. The following table presents the result of the variable transformations.

Table.4. Frequency Distribution of Laboratory Results of the Selected Patients with Mild and Severe Case of COVID-19

Laboratory Result	**Mild**		**Severe**	
	Frequency	**Percentage**	**Frequency**	**Percentage**
Ferritin (ng/mL)				
Low	2	3.6%	1	1.8%
Normal	42	75%	5	9.1%
High	12	21.4%	49	89.1%
D-Dimer (ug/mL)				
Normal	54	93.1%	23	41.8%
High	3	5.2%	28	50.9%
No data	1	1.7%	4	7.3%
Procalcitonin (ng/mL)				
Low	37	63.8%	41	74.5%
Normal	0	0%	8	14.5%
No data	21	36.2%	6	10.9%

Table 4 presents the frequency distribution of the variables Ferritin, D-Dimer, and Procalcitonin levels. Based on the table, about 75% of patients with mild symptoms of COVID-19 have normal Ferritin levels; and about 89.1% of the patients with severe COVID-19 have high levels of Ferritin. Moreover, 54, or about 93.1% of the patients with mild COVID-19 have normal levels of D-dimer. In contrast, more than half of patients, about 50.9% of severed COVID-19 have elevated D-dimer levels. Finally, no patient with mild symptoms of COVID-19 has a normal level of procalcitonin while a greater proportion of patients, about 74.5% with severe COVID-19 have low levels of procalcitonin.

Once again, with the aid of the logistic curve, the data dispersion between mild and severe cases were observed.

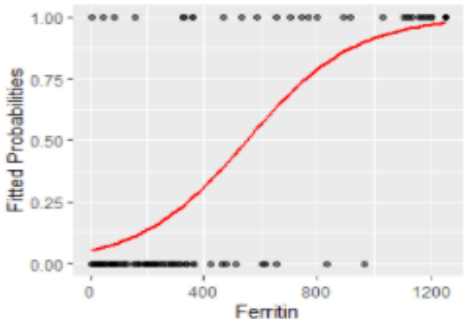

Fig.9. Logistic Curve of Ferritin

Demonstrated in Figure 9 is the logistic curve of ferritin. The reference range of ferritin is from 20 to 350 ng/mL. Based on this, both mild and severe cases exist in all low, normal, and high levels. Therefore, the data are described to be widely distributed. Aside from that, this curve also shows that any

value greater than approximately 1000 ng/mL will only result in a severe COVID-19 case.

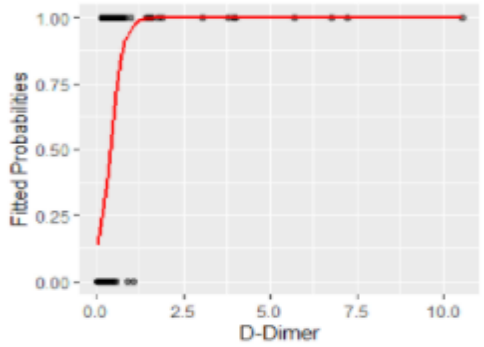

Fig.10. Logistic Curve of D-Dimer

Figure 10 shows the logistic curve of D-dimer. The reference range for D-dimer is less than 0.5 ug/mL, which shows that in all low, normal, and high levels, severe cases exist. Additionally, majority of the mild cases had normal levels. Lastly, it can be seen that a value greater than 0.9 ng/mL will only result in a severe COVID-19 case.

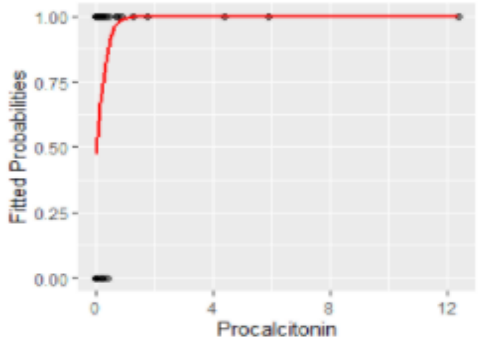

Fig.11. Logistic Curve of Procalcitonin

Fig.11. shows the logistic curve of procalcitonin. The reference range for Procalcitonin is 0.5 to 2 ng/mL, which shows that in all low, normal, and high levels, severe cases exist. Moreover, it was also shown that mild cases will tend to have much lower value than severe cases since a value greater than 0.39 ng/mL will only result in a severe COVID-19 case. Additionally, all mild cases had low procalcitonin levels.

Determining the Significant Predictors of COVID-19 Severity:

This section will discuss the estimated logistic regression models to determine which laboratory results can be used to predict the severity of symptoms experienced by a COVID-19 patient. The model with all the independent variables entered in the model is shown in the following table.

Table.5. Summary of Odds Ratio Estimates from Logistic Regression of COVID-19 Severity

Laboratory Result	**Odds Ratio**	**95% Confidence Interval**		**p-value**
		Lower	**Upper**	
Intercept	0.00	NA		0.999
Neutrophils	0.92	0.00	9.72E+13	0.9943
Lymphocytes	156.16	0.00	7.40E+19	0.7557
Alanine aminotransferase	1.03	1.00	1.06	0.099
C-reactive protein	1.01	0.99	1.05	0.5034
Lactate Dehydrogenase	1.03	1.01	1.08	0.0902
Ferritin (baseline: 0 to 100)				
101 to 500	0.05	0.00	1.02	0.1055
501 to 1200	2.49E+16			0.997
> 1200	1.36E+23	0.00		0.9966
D-Dimer (baseline: < 0.10)				
0.10 to 0.40	3.94E+07	0.00		0.9993
0.41 to 0.70	1.53E+07	0.00		0.9993
0.70 to 1.0	8.06E+06	0.00		0.9994
> 1.0	3.52E+16	0.00		0.9986
Procalcitonin (baseline: < 0.05)				
0.05 to 0.50	5.98E-18	0.00	0.00	0.9969
> 0.50	2.87E-12	0.00		0.9986

The table above presents the calculated odds ratio with their corresponding confidence intervals for the logistic regression model with all lab results as the independent variables in the model. As seen on the table, we can observe that there are absurd estimates such as very low values of odds ratio (e.g. 5.98×10-18 or almost 0 for Procalcitonin: 0.05 to 50) and also some very high odds ratio (e.g. the estimates for Ferritin). Some

of the computed confidence intervals range from 0 to infinity which are too absurd and very uninformative. Upon investigation, these ridiculous values are primarily due to: 1) the independent variables are highly correlated in which the model has a problem of multicollinearity, and 2) there exists a quasi-complete separation in the data. Multicollinearity occurs when the independent variables of a linear model are highly correlated which inflates the standard error of the estimates and thus, gives us insignificant results and confidence intervals that are too wide. Meanwhile, quasi-complete separation exists when one cell of a given table has no element (existence of zero cells). This happens when one or more levels of the independent variable can determine the outcome variable with 100% certainty. Due to these problems, the researchers will scrap the first model and try to create multiple simple logistic regression models using every independent variable. The results are shown in the following tables.

Table.6. Summary of Odds Ratio Estimates from Logistic Regression of COVID-19 Severity with Neutrophil Count as Predictor

Laboratory Result	Odds Ratio	95% Confidence Interval		p-value
		Lower	Upper	
Intercept	0.00255	0.00018	0.02434	< 0.0001**
Neutrophils	5317.62	220.43	2.16E+05	< 0.0001**

***denotes significance at 1% alpha*

Table 6 gives us the summary of the logistic regression model with neutrophils as the predictor variable. Since the p-value of the estimated regression coefficient for neutrophil is less than 0.0001 then the coefficient is deemed significant at a 1% significance level. Therefore, a 0.01-unit increase in the neutrophil count of the patient will increase their odds of having severe COVID-19 by a factor of 53.18. Hence, the risk of having severe COVID-19 increases as the level of neutrophils increases.

Table.7. Summary of Odds Ratio Estimates from Logistic Regression of COVID-19 Severity with Lymphocytes Count as Predictor

Laboratory Result	Odds Ratio	95% Confidence Interval		p-value
		Lower	Upper	
Intercept	7.70	3.13	21.0093	< 0.0001**
Lymphocytes	0.00011	0.000002	0.0039	< 0.0001**

***denotes significance at 1% alpha*

Table 7 gives us the summary of the logistic regression model with lymphocytes as the predictor variable. Since the p-value of the estimated regression coefficient for lymphocytes is less than 0.0001 then the coefficient is deemed significant at a 1% significance level. Therefore, a 0.1-unit increase in the lymphocyte count of the patient will decrease their odds of having severe COVID-19 by a factor of 0.000011. Hence, the risk of having severe COVID-19 decreases as the level of lymphocytes increases.

Table.8. Summary of Odds Ratio Estimates from Logistic Regression of COVID-19 Severity with Alanine Aminotransferase as Predictor

Laboratory Result	Odds Ratio	95% Confidence Interval		p-value
		Lower	Upper	
Intercept	0.39	0.19	0.743	0.0061**
Alanine aminotransferase	1.02	1.01	1.027	0.0024**

Table 8 gives us the summary of the logistic regression model with alanine aminotransferase as the predictor variable. Since the p-value of the estimated regression coefficient for alanine aminotransferase is less than 0.0024 which is less than 0.01, then the coefficient is deemed significant at a 1% significance level. Therefore, a 10-unit increase in the alanine aminotransferase of the patient will increase their odds of having severe COVID-19 by a factor of 10.2. Hence, the risk of having severe COVID-19 increases as the level of alanine aminotransferase increases.

Table.9. Summary of Odds Ratio Estimates from Logistic Regression of COVID-19 Severity with C-reactive Protein as Predictor

Laboratory Result	Odds Ratio	95% Confidence Interval		p-value
		Lower	Upper	
Intercept	0.28	0.15	0.489	< 0.0001**
C-reactive protein	1.06	1.03	1.094	< 0.0001**

***denotes significance at 1% alpha*

Table 9 gives us the summary of the logistic regression model with C-reactive protein as the predictor variable. Since the p-

value of the estimated regression coefficient for C-reactive protein is less than 0.0001 then the coefficient is deemed significant at a 1% significance level. Therefore, a 10-unit increase in the C-reactive protein of the patient will increase their odds of having severe COVID-19 by a factor of 10.6. Hence, the risk of having severe COVID-19 increases as the level of C-reactive protein increases.

Table.10. Summary of Odds Ratio Estimates from Logistic Regression of COVID-19 Severity with Lactate Dehydrogenase as Predictor

Laboratory Result	Odds Ratio	95% Confidence Interval		p-value
		Lower	Upper	
Intercept	0.001	0.00003	0.008	< 0.0001**
Lactate Dehydrogenase	1.029	1.019	1.042	< 0.0001**

***denotes significance at 1% alpha*

Table 10 gives us the summary of the logistic regression model with lactate dehydrogenase as the predictor variable. Since the p-value of the estimated regression coefficient for lactate dehydrogenase is less than 0.0001 then the coefficient is deemed significant at a 1% significance level. Therefore, a 10-unit increase in the lactate dehydrogenase of the patient will increase their odds of having severe COVID-19 by a factor of 10.29. Hence, the risk of having severe COVID-19 increases as the level of lactate dehydrogenase increases.

Table.11. Summary of Odds Ratio Estimates from Logistic Regression of COVID-19 Severity with Ferritin as Predictor

Laboratory Result	Odds Ratio	95% Confidence Interval		p-value
		Lower	Upper	
Intercept	0.1190	0.0411	0.2736	0.0030**
Ferritin (normal)				
Low	4.2	0.1769	52.6078	0.274
High	34.3	12.0707	117.1811	< 0.0001**

***denotes significance at 1% alpha*

Table 11 gives us the summary of the logistic regression model with Ferritin as the predictor variable. Based on the table, there is no significant difference in the odds of having severe COVID-19 patients with low levels of ferritin compared to those with normal levels of ferritin (p-value = 0.274). On the other hand, there is a significant difference in the odds of having severe COVID-19 on patients with a high level of ferritin compared to those with normal levels of ferritin (p-value < 0.0001). In particular, the odds of having severe COVID-19 of patients with high levels of Ferritin (> 350 mg/L) is 34.3 times higher compared to those with normal levels of ferritin.

Table.12. Summary of Odds Ratio Estimates from Logistic Regression of COVID-19 Severity with D-Dimer as Predictor

Laboratory Result	Odds Ratio	95% Confidence Interval		p-value
		Lower	Upper	
Intercept	0.4259	0.2566	0.6845	0.0006**
D-Dimer (baseline: normal)				
High	21.9130	6.9069	98.2317	< 0.0001**
No data	9.3913	1.3030	189.1538	0.0505

***denotes significance at 1% alpha*

Table 12 gives us the summary of the logistic regression model with D-dimer as the predictor variable. Based on the table, there is no significant difference in the odds of having severe COVID-19 of patients with no information on D-dimer compared to those with normal levels of D-dimer (p-value = 0.0505). On the other hand, there is a significant difference in the odds of having severe COVID-19 on patients with elevated D-dimer compared to those with normal D-dimer (p-value < 0.0001). In particular, the odds of having severe COVID-19 of patients with elevated D-dimer (> 0.5 ng/mL3) is 21.9 times higher compared to those with normal D-dimer.

Table.13. Summary of Odds Ratio Estimates from Logistic Regression of COVID-19 Severity with Procalcitonin as Predictor

Laboratory Result	Odds Ratio	95% Confidence Interval		p-value
		Lower	Upper	
Intercept	1.1081	0.7104	1.7343	0.6508
Procalcitonin (baseline: low)				
Normal	38394100	0	NA	0.990
No data	0.2578	0.0868	0.6742	0.0085**

Table 10 shows the summary of the logistic regression model with the predictor variable Procalcitonin. The estimate for the odds ratio for the group with a normal level of procalcitonin level is too large due to the quasi-complete separation where all of the patients with normal procalcitonin levels have severe symptoms of COVID-19. Meanwhile, those patients with no information on procalcitonin levels have a significantly lower odds of having severe COVID-19. Particularly, the odds of having severe COVID-19 is 0.2578 times lower than patients with low levels of procalcitonin. Additionally, no data were found to be higher than the reference range.

B. Interpretation of Data

Prevalence of COVID-19 Cases Classified as Mild and Severe:

Differences between mild and severe may be attributed to race, gender, and age (Weill Cornell Medicine, 2020). Underlying medical conditions are not included since the researchers excluded patients with comorbidities.

A study from the University of East Anglia asserted that patients with preexisting disease are at a higher risk to be infected by COVID-19. This study was supported by an article written by Mayo Clinic (2021) which states that older patients with health problems like heart or lung conditions, diabetes, obesity, and weak immune system are at a greater risk to be infected by COVID-19 in contrast to younger and healthier patients. However, a study by Harvard Health Publishing (2021), stated that healthy patients can also get infected by COVID-19. Additionally, everyone in any age group was recommended to get vaccinated. This explains why out of the hundreds that are admitted in the chosen hospital, only 113 patients (55 severe; 55 mild) matched the criteria for the study. This limited data are mostly due to the criteria 'without comorbidities'.

Laboratory Values of Mild and Severe COVID-19 Cases:

Neutrophils:
A study by Cavalcante-Silva et al. (2021) stated that neutrophils are the first responders in inflammatory reaction and additionally, the process of neutrophil activation and degranulation are highly activated in COVID-19 infection. Additionally, a study conducted by Reusch et al. (2021) demonstrated increased neutrophils in the nasopharyngeal epithelium and distal parts of the lung upon COVID-19 infection. Since the body continues to respond to the COVID-19 infection, Wang et al. (2020) posits that the neutrophils contribute to the frequent occurrence of cytokine storms in severe cases coinciding with lung injury attributed to COVID-19, which explains why neutrophils are still elevated in severe cases. Lastly, Cavalcante-Silva et al. (2021) also said that although the neutrophils provide protection, prolonged activation can produce a harmful effect in the lungs and progress to pneumonia and/or acute respiratory distress syndrome (ARDS). Supported by the study of Reusch et al. (2021), the neutrophil defense mechanisms, when done excessively, can activate the endothelial cells and worsen the inflammatory circuit or actively damage endothelial tissue.

The results of the study also showed that mild patients had normal neutrophil levels. This finding is supported by Mardani, et al. (2020) since their study also resulted in the same finding. Their team then concluded that SARS-CoV-2 does not affect the neutrophils in the initial phase of the disease albeit being the first responders in an inflammatory reaction.

Lymphocytes:
Zhao et al. (2020) attribute it to possibly being caused by necrosis or apoptosis of the lymphocyte due to viral infection and damage similar to the mechanism of action of SARS-CoV (2020). Others postulate the cause of the significant decrease in lymphocyte count in accordance with infection severity as a consequence of the immune suppressive environment that hypercytokinemia brings, causing the destruction of lymphocytes. Furthermore, their results show that lymphopenia can serve as a rapid tool to be able to quickly identify a severe COVID-19 case. This supports the idea that patients with mild COVID-19 cases have normal lymphocyte results since lymphopenia, or severe low lymphocyte count, is persistently seen in most cases of severe infection (Yang et al., 2020).

ALT:
The elevation of aminotransferases, which includes alanine aminotransferase (ALT), was noted to be the most common abnormality in liver enzymes of COVID-19 patients, exhibiting an increase of 1-2 times the upper limit of normal, according to a study conducted by Moon & Barritt (2021). Among the potential causes of the said elevation include direct liver injury, drug-induced liver injury, hepatic ischemia, muscle breakdown, congestive hepatopathy, and inflammatory responses. Hence, a value of 200 U/L or greater is often seen in severe cases. Meanwhile, another study by Cai et al. (2020) supported this by

stating that the SARS-CoV-2 virus binds to angiotensin-converting enzyme 2 (ACE2) on cholangiocytes. This eventually results in cholangiocyte dysfunction, as well as systemic inflammation, which ultimately causes liver injury. Thus, an increase in ALT, which is the enzyme released into the blood during liver injury, is seen in severe cases with damage to the said organ. In another study by Wang et al. (2020), most COVID-19 patients with mild cases had normal ALT levels because they maintained normal liver function throughout the course of the disease. The mild cases were also identified to rarely have a case of fatty liver and any liver biochemistry abnormality, thus, ALT levels were within the normal range.

CRP:

As a response to the occurrence of infection, inflammation, and tissues, the liver produces C-reactive protein (Sadeghi-Haddad-Zavareh, e al., 2021). Furthermore, C-reactive protein is considered to be an acute phase reactant that is non-specific and is declared to be an indicator of COVID-19 infection severity by Stringer et al. (2021). In infections such as COVID-19, the production of C-reactive protein is associated with the rise in inflammatory cytokines (Ali, 2020). Moreover, an increase in C-reactive protein is also observed in pneumonia and lung infections which are commonly noted as clinical manifestations of COVID-19 infection. The said increase is mostly seen in severe cases since there is more damage in the lungs as caused by the infection (Wang, 2020). Another study by Bozkurt et al. (2021) posited that elevated C-reactive protein levels were found in COVID-19 cases that are severe rather than mild. Myocardial injury, higher troponin-T levels, and the development of ARDS attribute to the said finding since they are more correlated with severe cases. Thus, normal C-reactive protein levels were observed in mild cases.

LDH:

Lactate dehydrogenase (LDH) is an intracellular enzyme which catalyzes the interconversion of both pyruvate and lactate with NADH and NAD+. In a study conducted by Henry et.al. (2020), this enzyme is a biomarker of interest for COVID-19 prognosis as its increased levels have been linked with patients with severe respiratory viral infections such as the Severe Acute Respiratory Syndrome (SARS). Due to the presence of LDH in lung tissues, patients with severe COVID-19 infections exhibit interstitial pneumonia which releases high amounts of LDH into the circulation and could remain there up to 7 days. This is further supported by the study of Shi et.al. (2020) wherein their findings of increased LDH in early phases of severe COVID-19 cases indicate possible subclinical tissue damage. Contrarily, mild cases are shown to have no sign of pneumonia on thoracic imaging (Xia, et.al., 2020). It was then concluded that elevated LDH values were associated with a sixfold-odds increase of severity in COVID-19 disease (Henry et.al., 2020).

Ferritin:

Ferritin is a significant intracellular iron storage protein. The study Carubbi et al. (2021) emphasizes that iron metabolism may boost the immune system's response to invading microbes, including viral infections, by increasing ferritin levels. For viral replication to occur, host cells must have an improved cellular metabolism and optimum iron levels. Thus, decreasing iron bioavailability is necessary for interfering with virus replication. In relation to this, according to Gómez-Pastora et al. (2020) in a systematic review on the use of ferritin in COVID-19. Ferritin values in COVID-19 patients were generally within the normal range in patients with the non-severe condition. However, patients with severe COVID-19 infection had hyperferritinemia. With this, a study by Liu et. al. (2019) reported that, when the health of the patients started to improve, their ferritin and IL-6 levels decreased. In addition, in severe COVID-19, ferritin has been identified as an acute phase reactant as well as a modulator of immunological dysregulation. Therefore, this could support the idea that hyperferritinemia is linked to inflammatory states in SARS-CoV-2 infection, and that ferritin could be more than just a marker of the inflammatory environment; it could also be a key actor in the cytokine storm that characterizes severe COVID-19 infection.

D-dimer:

D-dimer is produced when fibrin from clots is broken down (Yao et al., 2020). Any process or disorder involving fibrin production or breakdown causes increase in D-dimer levels. Inflammation, specifically proinflammatory cytokines, cause an increase in D-dimer levels (Yu et al., 2020). Conversion of fibrinogen to fibrin, fibrin reticulation and fibrin degradation by plasmin all elevate D-dimer levels (Moreno et al., 2021). Disseminated Intravascular Coagulopathy (DIC) is a complication prominent in severe COVID-19 infections, along with hypercoagulability (Moreno et al., 2021), that can be caused by sepsis with intense inflammatory reaction among others (Levi, 2018). The mechanism is the activation of monocytes and endothelial cells which causes an uncontrolled release of cytokines (Moreno et al., 2021). The uncontrolled

release of proinflammatory cytokines as well as the endothelial damage and fibrinolysis induced by the infection cause the elevated D-dimer levels (Levi & Iba, 2020). Levi & Iba (2020) also found that while D-dimer levels displayed gradual elevation during the progression of the disease, a significant portion of the severe and a lesser still significant portion of the non severe cases showed D-dimer elevation. While the severe infection displayed extremely elevated values, cases of normal D-dimer values were also present with the severe infection. The elevated levels found in severe infections are attributed to the multiple possible coagulation related complications brought upon by the extended uncontrolled release of proinflammatory markers that cause accumulation of inflammatory cells as postulated by (Levi & Iba, 2020).

Procalcitonin:

Procalcitonin is usually produced during bacterial infection but some studies also suggest its relevance in COVID-19 infection, as mentioned by Hu et al. (2020). A high level of procalcitonin is usually seen in bacterial infections such in the case of bacterial pneumonia. On the other hand, viral infections, such as in the case of COVID-19 infections, procalcitonin level is low; this is the main reason why procalcitonin is seen low in both mild and severe COVID-19 infection (Schuetz, 2021). In severe COVID-19 infection, a slightly higher or within a normal reference range is seen due to the probable co-existence of a bacterial infection during the duration of COVID-19 infection (Vanhomwegen et al., 2021).

Lastly, a study conducted by Nasir et al. (2021) states that some hospitalized COVID-19 patients were infected with gram-negative bacteria; however, the chances of coinfection with bacteria for hospitalized patients are still unknown. Furthermore, the said study also states that there is a very little to no difference between the levels of procalcitonin of patients with different COVID-19 severity infection; with the severe having a slightly higher result because they are more vulnerable to bacterial infection. This explains why there is a low level of procalcitonin in mild cases and a normal result in severe cases.

Determining the Significant Predictors of COVID-19 Severity:

Neutrophils:

As the COVID-19 infection progresses into a severe case, the neutrophil count in the bloodstream also increases. With this, elevated neutrophil levels can be used to predict the severity of infection. Neutrophil Extracellular Traps (NETs), which are produced by the neutrophils, control the infection. These NETs, in turn, exacerbate inflammation. Increased production of NETs also contributes to the venous and arterial thrombosis in COVID-19 patients. This finding shows that NETs can trigger cytokine release and multi-organ damage that leads to respiratory failure and coagulopathy. Moreover, high levels of chemokine ligands in COVID-19 patients can lead to the recruitment of more neutrophils to the site of infection, which further aggravates the pulmonary inflammatory response. (Wang et al, 2020)

Lymphocytes:

Lymphocytes are affected by both the viral mechanism and hypercytokinemia as suggested by both Wagner et al. (2020), and Zhao et al. (2020). The decline in lymphocyte count is associated with lymphocyte exhaustion due to extended or prolonged stimulation and stress from hypercytokinemia (Fathi & Rezaei, 2020); moreover, lymphocytes produced during lymphocyte exhaustion also have impaired functionality (Fathi & Rezaei, 2020).

ALT:

Alanine aminotransferase (ALT) is a liver enzyme that is released in the bloodstream when the liver is afflicted by damage. In a research conducted by Ampuero et al. (2020), COVID-19 patients who have liver injury were recorded to have notably higher risk of further developing severe cases as opposed to patients whose liver function tests presented normal results.

As supported by the studies mentioned earlier, ALT exhibits a directly proportional relationship with COVID-19 severity due to the fact that the virus, SARS-CoV-2, binds to angiotensin-converting enzyme 2 (ACE2) on cholangiocytes, causing its dysfunction which leads to liver injury. Aside from that, increased ALT levels and intensified severity may also be caused by other factors such as hepatic ischemia, muscle breakdown, and congestive hepatopathy among others.

CRP:

C-reactive protein level greater than 100 mg/L is usually manifested in severe cases of COVID-19 due to tissue destruction caused by the hyperactivity of the immune system (Wang, 2020).

The elevation of CRP is related to the production of cytokines which are usually observed in patients with COVID-19. The destruction of tissues caused by the viral infection is the main reason for the increase in CRP (Ali, 2020).

LDH:

From the study of Aggarwal et. al. (2020), elevated LDH levels in COVID-19 patients indicate high severity of the infection. As mentioned previously, this is due to the interstitial pneumonia caused by the disease in which the present LDH-3 in the pneumocytes is inherently released into the bloodstream. From the pooled analysis in the said study, elevated LDH values are commonly associated with a sixfold increased odds of getting a severe COVID-19 disease. This indicates that the severity of the disease is directly proportional to the increase and decrease of the LDH values obtained from patient serum samples.

Ferritin:

The study of Habib et al. (2021) indicated that Hyperferritinemia (condition in which ferritin levels are abnormally high) is commonly used as a marker for the "hyperferritinemic syndromes" linked to severe COVID-19 infection. COVID-19 systemic inflammatory reaction and "hyperferritinemic syndromes" cause symptoms such as elevated serum ferritin and sustained cytokine storm-generated hyper-inflammation which brings about multiorgan failure. Furthermore, since Ferritin is an iron-storing protein, the free iron released into the bloodstream may cause iron overload, resulting in damage to the lungs and other organs. It's also been suggested that the COVID-19 virus has hepcidin-mimicking properties, which could lead to an increase in ferritin levels independent of the inflammatory response, increasing the risk of coagulopathy.

D-dimer:

As stated earlier D-dimer is a byproduct of fibrin breakdown. The increase in D-dimer levels may be attributed to the uncontrolled inflammatory response of the body causing elevated prothrombotic activity, endothelial injury, and coagulation (Yu et al., 2020). According to Zhou et al. (2020), elevated D-Dimer levels (> 1 μg/ml) are related to the deadly COVID-19 infection outcome. While others refute it, a study by Ye et al. (2020) indicated that patients with COVID-19 infection with an increased D-dimer levels (>2.14 mg/L) on hospital admission may be at higher risk of in-hospital mortality (Ye et al., 2020), which supports the findings of D-dimer levels reaching up to 8 times the ULN in severe cases.

Procalcitonin:

According to the study conducted by Hu et al. in 2020, procalcitonin is seen elevated in COVID-19 infections. In severe cases it can be as high as 4 times from the normal range; additionally, it is lower in patients with mild COVID-19 cases. Furthermore, Schuetz (2020) also claimed that severe COVID-19 patients have an elevated level of procalcitonin due to development of inflammatory syndrome like pneumonitis during the course of COVID-19 infection.

V. CONCLUSION

The following chapter discusses a brief summary and interpretation of the data gathered from the previous chapter, along with the conclusions of significance derived with logistic regression model from the laboratory parameters on severity. Following are the recommendations for further study that the proponents came up with to compensate for any inadequacies or deficiencies in the current study.

A. Summary of Findings

The prevalence of COVID-19 cases was determined with the use of descriptive statistics, frequency and percentage on the mild and severe cases. The data set collected displayed a relatively similar distribution of 48.7% or 55 severe COVID-19 patients in comparison to the 51.3% or 58 mild COVID-19 patients.

The results gathered from the laboratory test results of selected patients with mild and severe cases of COVID-19 infection were measured and analyzed using descriptive statistics. Evidently, patients with severe COVID-19 symptoms have greater mean and median neutrophil counts, ALT, CRP, and LDH levels than patients with mild COVID-19 symptoms. Patients with mild COVID-19 symptoms, on the other hand, had a greater mean and median lymphocyte count than those with severe COVID-19 symptoms. For Ferritin, D-Dimer, and PCT, since some variables have indefinite values, the variables for each respective laboratory parameter were analyzed categorically. The results showed that 75% of COVID-19 patients with mild symptoms have normal Ferritin levels, and 89.1% of COVID-19 patients with severe symptoms have high Ferritin levels. Furthermore, 93.1% of patients with mild COVID-19 have normal D-dimer values. Those with severed COVID-19, on the other hand, have increased D-dimer levels in more than half of the cases with the percentage of 50.9%. Finally, no patient with mild COVID-19 symptoms has a normal PCT level, whereas 74.5% of patients with severe COVID-19 symptoms have low PCT levels.

By utilizing the logistic regression as the statistical model, it was shown that multiple simple logistic regression produces a better result where each independent variable was individually analyzed. Among the eight available independent variables, seven were found to be significant predictors. Including the insignificant predictors, the predictors will be categorized into: (1) significant, (2) significant at a high level, and (3) insignificant.

Significant:

Neutrophil, ALT, CRP, and LDH were found to be significant predictors, which are directly proportional. This means that as their level increases, the odds of having a severe case also increases.

Lymphocyte was also found to be a significant predictor but it has an inversely proportional relationship with the severity of infection. This means that as the level of lymphocytes decreases, the odds of having a severe case increase.

Significant at a High Level:

Ferritin and D-dimer were also found to be significant, however, only at high levels since high levels of these predictors tend to result in a severe case. On the other hand, the low and normal levels of these predictors will result in both mild and severe cases.

Insignificant:

Procalcitonin was found to be insignificant. This is due to the fact that all patients with normal procalcitonin are severe cases; and all mild patients have low procalcitonin. Additionally, the majority of the severe cases also had low procalcitonin. This finding makes it difficult for procalcitonin to be deemed as a significant predictor.

B. Conclusion

With respect to the generated outcome of results, the researchers arrived at the conclusion of accepting the alternative hypothesis and rejecting the null hypothesis; seven of the laboratory values namely neutrophils, lymphocytes, ALT, CRP, LDH, ferritin, and D-dimer, were significant predictors of the severity of COVID-19 infection.

C. Recommendation

From this thesis, the researchers would also like to propose that medical professionals should focus on monitoring neutrophils, ALT, CRP, LDH, ferritin, and D-dimer since the increase of these parameters can be indicative of severe COVID-19 infection. Low levels of lymphocytes, on the other hand, are associated with severe cases.

- These laboratory values can be used as an early measure before symptoms set in to determine treatment and application of medication to mitigate adverse symptoms and complications associated with severe COVID-19 infection.
- Since there is a possibility that these markers are increased due to the body's protective responses, a recommended alternative or supportive treatment could be to strengthen or control the production of these increased biomarkers.
- Treatments such as increasing the lymphocyte level back to normal can also be given to patients. Contrarily, administering treatments that further suppress lymphocyte production may threaten the patient's life.

There are also some recommendations to future researchers who will be writing similar studies:

- Use a wider set of laboratory parameters in analyzing the severity of COVID-19 infection.
- Include the moderate and critical classifications to be able to analyze the complete scope of the severity of COVID-19 infection and work with a larger set of population
- Focus on the analysis of similar studies on a particular age group.
- Include the patients with comorbidities to know how these affect the overall condition and classification of COVID-19 infection.

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