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DETERMINATION OF D-DIMER, IRON, CALCIUM, PROTHROMBIN TIME, FERRITIN AND VITAMIN D3 IN PATIENTS WITH COVID-19 IN IRAQI PEOPLES

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By Murtadha Rahman Hasan HASAN

May 2022

We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science

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ABSTRACT

DETERMINATION OF D-DIMER, IRON, CALCIUM, PROTHROMBIN TIME, FERRITIN AND VITAMIN D3 IN PATIENTS WITH COVID-19 IN IRAQI PEOPLES

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Master of Science in Chemistry

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May 2022

The primary purpose of this study is to determine the prevalence and effectiveness of covid19 through biochemical testing of ferritin, D3, and iron levels in the presence of risk factors such as age and gender and clinical-pathological testing. Comorbidities showed a slightly significant difference between severe and non-severe cases compared to diabetes. Still, they were highly influential in the case of asthma and non-significant in the case of smoking and heart disease. In extreme cases, hypertension has a slightly significant effect compared to other groups. The most prevalent signs and symptoms of sars-covid19 were fever and dry cough (55 percent and 78 percent, respectively). The relationship between SARS-CoV-19 infection and white blood cell count was highly significant, with the highest percentage of severe cases showing a reduction in white blood cell count. This was equally true for patients who were not in critical condition. Our findings revealed a highly significant association between CRP and Ferritin in severe instances and vitamin D deficiency with calcium in severe cases when compared to healthy subjects. However, there was no correlation between Iron in both groups.

2022, 46 pages

Keywords: COVID-19, D-Dimer, Vitamin D3, Prothrombin time, Blood clotting.

ÖZET

IRAK HASTALARINDA KOVİD-19 HASTALARINDA D-DİMER, DEMİR, KALSİYUM, PROTROMBİN ZAMANI, FERRİTİN VE D3 VİTAMİNİ TAYİNİ

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Kimya, Yüksek Lisans

Tez Danışmanı: Doç. Dr. Şevki ADEM

Mayis 2022

Bu çalışmanın birincil amacı, yaş ve cinsiyet gibi risk faktörlerinin varlığında ferritin, D3 ve demir düzeylerinin biyokimyasal testi ve klinik-patolojik testler yoluyla covid19 prevalansını ve etkinliğini belirlemektir. Komorbiditeler, diyabete kıyasla şiddetli ve şiddetli olmayan vakalar arasında biraz anlamlı bir fark gösterdi. Yine de, astım durumunda oldukça etkiliydiler ve sigara ve kalp hastalığı durumunda önemsizdi. Aşırı durumlarda, hipertansiyon diğer gruplara göre biraz daha önemli bir etkiye sahiptir. Sars-covid19'un en yaygın belirti ve semptomları ateş ve kuru öksürüktü (sırasıyla yüzde 55 ve yüzde 78). SARS-CoV-19 enfeksiyonu ile beyaz kan hücresi sayısı arasındaki ilişki oldukça anlamlıydı ve en yüksek şiddetli vaka yüzdesi beyaz kan hücresi sayısında bir azalma gösteriyordu. Bu, durumu kritik olmayan hastalar için de aynı derecede doğruydu. Bulgularımız, sağlıklı deneklere kıyasla ciddi vakalarda CRP ve Ferritin ile ciddi vakalarda kalsiyum ile D vitamini eksikliği arasında oldukça anlamlı bir ilişki olduğunu ortaya koydu. Ancak her iki grupta da demir arasında korelasyon yoktu.

2022, 46 sayfa

Anahtar Kelimeler: COVID-19, D-Dimer, D3 Vitamini, Protrombin zamanı, Kan pıhtılaşması.

PREFACE AND ACKNOWLEDGEMENTS

I would like to thank my thesis advisor, Assoc. Prof. Dr. Şevki ADEM, for his patience, guidance and understanding.

Murtadha Rahman Hasan HASAN
Çankırı-2022

CONTENTS

LIST OF SYMBOLS

%	Percent
±	Plus-minus
°C	Degrees Celsius
μg	Micromole
g	Gram
L	Liter
mg	Milligram
mL	Milliliters

LIST OF ABBREVIATIONS

A	Absorbance
ADMA	Asymmetric dimethylarginine
ANOVA	Analysis of variance
COVID-19	Corona virus disease 2019
DD	D-dimer
DM	Diabetes melletius
EIZA	Enzyme immunoassay
FBS	Fasting blood suger
FER	Ferrtin
Hb	Hemoglobin
PE	Pulmonry embolsim
Vit D3	Vitamin D3

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1. INTRODUCTION

 As of the time of this writing, the SARS-CoV2 virus has caused outbreaks in a number of nations (coronavirus illness 2019; formerly 2019nCoV). The World Health Organization's Emergency Committee cited increased case notification rates as the primary reason for the global health emergency that was declared on January 30, 2020. These rates were particularly high in China. Monitoring of the case detection rate in close to real-time is possible at Johns Hopkins University and other forums. In spite of falling mortality and morbidity rates in other Asian countries, Europe, and North America, China's death toll will continue to rise until February 2020.

There are RNA viruses, such as coronaviruses, that are capable of infecting humans as well as animals, and these viruses are known to cause illness. In the bodies of people who had the common cold in 1966, Tyrell and Bynoe found coronaviruses. This discovery was made. As a result of the royal nature of their lineage, the Latin word "corona," which literally means "crown," was applied to them. It is possible to separate them into the Alpha, Beta, Gamma, and Delta subfamilies. It is commonly believed that pigs and birds were the original hosts of the alpha, beta, and gamma coronaviruses, despite the fact that these viruses may be detected in mammals (White *et al.* 2020).

The typical size of a genome falls somewhere in the range of 26 to 32 kilobases. Even though coronaviruses are known to cause severe illness and even death, the majority of cases of alphacoronavirus infection are never recorded. SARSCoV2 and SARSCoVs 3, 4, 5, and 6 are very closely related to one another due to the fact that they are all beta coronaviruses. HKU1 beta coronaviruses have an extra membrane glycoprotein than other coronaviruses do (Alanagreh *et al.* 2020).

There is a possibility that vitamin D levels will have an effect on the COVID-19 test results. The senior residents of nursing homes who had high COVID-19 levels were given bolus doses of vitamin D3 as part of an experiment to see whether or not this drug

extended the participants' life spans. In the year 2020, molecular and biochemical biology will be focused on steroids.

Therefore, thrombosis is the major pathogenic mechanism that is associated with COVID-19. As a direct consequence of this, we started looking into the clinical and chemical signs of heparin resistance among COVID-19 patients who were being treated in our critical care unit (White *et al.* 2020).

Almost no one believes or has reported that the COVID-19 pandemic has had a direct impact on the onset of cardiovascular disease, either through an increase in the severity of illness and death in patients with pre-existing heart disease or through the linkage of COVID-19 infection to cardiovascular complications like acute myocardial infarction, arrhythmias, and deep vein thrombosis (VTE) (Garcia-Olivé *et al.* 2020). This is because almost no one

According to the findings of this research, 3.75–68.0 percent of COVID-19 patients had D-dimer readings that were significantly higher than the average. Those diagnosed with chronic obstructive pulmonary disease (COPD) and community-associated pneumonia had greater death rates related with D-dimer levels than patients diagnosed with any other cause (CAP and COPD). Patients diagnosed with COVID-19 who have dimers with a D-significance level require additional testing. In this study, the biomarker known as D-dimer was utilized to categorize patients into groups according to clinical severity, imaging staging, and in-hospital mortality. (Yao *et al.* 2020).

1.1 Objective of Thesis

The aim of present study is to show the effect and estimate of D-Dimer, prothrombin time, ferritin and vitamin D3 for corona virus patients and their use in diagnosis and follow-up of COVID-19 patients.

2. LITERATURE REVIEW

2.1 Introduction of Covid 19

In December, sequencing from samples taken from the lower respiratory tract connected a pneumonia outbreak in Wuhan to the SARS-CoV-2 virus (Hubei, China). In January of 2020, an unique SARS-CoV-2 virus was discovered for the very first time following intensive sequencing of samples taken from lower respiratory tracts (McCullough *et al.* 2020).

Nearly 1800 persons lost their lives and over 77,000 were infected in the first fifty days of a new coronavirus pandemic in Wuhan, which is the burgeoning economic powerhouse of China. Researchers believe that the pathogenicity of this virus derives from the coronavirus family. The /-virus is a member of the Coronavirus (CoV) family, which encompasses four separate genera of viruses. Both the simian immunodeficiency virus, also known as SIV, and the coronavirus, often known as CoV, are capable of infecting mammals (Centers for Disease Control and Prevention 2020).

The Wuhan coronavirus, also known as the novel coronavirus of 2019, was discovered by Chinese researchers (2019-nCov). An organization known as the International Virus Taxonomy Committee (ICTV). The severity of a patient's condition is influenced by their unique set of clinical traits as well as the risk factors they are exposed to. The infection quickly spread across the environment as a result of coughing and sneezing. Because the disease can be passed on before an infected individual even exhibits symptoms, it has a greater chance of spreading when someone is already afflicted with it (Yang *et al.* 2020).

The COVID-19 virus is most commonly transmitted through personal contact with an infected individual. During a cough, there may be as many as three thousand separate mucus particles produced. However, there are microscopic particles in the air, and some of these particles can land on people or cover nearby objects. People should be sure to

fully wash their hands after using the restroom or bathroom in order to prevent the spread of the virus as well as other respiratory ailments such as the flu. Infection with Covid-19 can be passed from person to person by inhaling infectious secretions from the upper respiratory tract (Zhang *et al.* 2020).

Iraq was the scene of two separate occurrences on February 24 and March 9, 2020. At first, there was a relatively modest number of newly reported cases. We do not understand why the virus only affects a limited number of people at the beginning of its propagation, after which it affects a significantly greater number of people. Infections with COVID-19 may have been less common in Iraq since borders between Iraq and other countries, such as Iran, which is assumed to have been the principal source of the early COVID-19 infections, have been closed. (Zhang *et al.* 2020).

2.2 Epidemiology of SARS-CoV-19

Researchers observed that between 49 and 66 percent of patients had come into contact with a variety of exotic animals when conducting their grocery shopping at the Huanan seafood market in China, which featured poultry, bats, and pangolins among other unusual animals. There is a possibility that Wuhan's most recent outbreak of COVID-19 was caused by wild animals (Zhang *et al.* 2020)

Virus samples obtained from the Huanan seafood market were found to be positive for SARS-CoV-2, according to the data provided by the WHO. As of the 21st of December in the year 2020, the WHO had established that COVID-19 was present in 75,704,857 individuals, leading to 1,690,061 fatalities. As of the 21st of December in the year 2020, the Iraqi COVID-19 strain was associated with 585,345 cases and 12,710 fatalities. (Zhang *et al.* 2020).

2.3 Virology and Pathogenesis

When spread by zoonotic single-stranded RNA viruses, for instance, the coronavirus can cause more substantial difficulties with the respiratory system, the digestive system, and the nervous system than the typical cold (Yu *et al.* 2020).

Researchers from Huanan Seafood Market gathered 585 environmental samples between the 1st of January and the 12th of December in the year 2020. This was done with the intention of determining the origin of the COVID-19 infection that was detected at Huanan Seafood Market. For the first time, researchers have demonstrated a connection between SARS-CoV-2 and the intake of wild animals as a potential risk factor. In the study laboratories, the researchers looked into the lungs, blood, and throats of a total of fifteen individuals. The findings of the laboratory indicate that the unique nucleic acid sequences possessed by the virus are distinct from those possessed by other human coronavirus species. The coronaviruses that have been associated to sars share numerous similarities with CoV-2 and other beta coronaviruses that are transmitted by bats. (Du *et al.* 2020).

2.4 Clinical Features

The first forty patients all presented with a variety of symptoms, the most prevalent of which were fever, cough, and muscle pain. The generation of sputum was the most prevalent symptom, occurring in 28 percent of patients, followed by headaches (8 percent), hemoptysis (5 percent), and diarrhea (5 percent) (5 percent). Four percent of the overall population More than one-half of the patients, and more than one-third of the cases, were found to be suffering from dyspnea (Li 2020).

A blood test revealed that the WBC and lymphopenia levels were either low or normal. The nearly majority of the people who had chest CT scans showed evidence of bilateral involvement. A chest CT scan done after the patient was transported to the intensive care unit revealed several lobular and subsegmental consolidations on both sides of the

body. On CT scans of the chests of patients who are not currently being treated in the intensive care unit, ground-glass opacity and subsegmental consolidation can be observed. In a study involving 1324 laboratory-verified cases, the symptoms that were observed the most frequently were fever (87.9 percent), cough (67.7 percent), and diarrhea (70.7 percent) (0.3 percent). Patients diagnosed with lymphopenia were required to spend at least one night in an intensive care unit in 80,1 percent of the cases. (Colafrancesco *et al.* 2020).

2.5 Routes of Transmission

It is common knowledge at this point that the two most common ways for an infection to be spread are through respiratory droplets and through direct touch. It has been shown that SARS-CoV-2 infection can be found in the urine and feces of people who have been sick, which suggests that the virus could spread by fecal-oral routes. Nobody knows for certain whether or not getting sick from consuming food that is infected with a virus is actually possible. According to the findings of recent investigations, the SARS-CoV-2 virus cannot be transferred by aerosols or from a mother to her kid during pregnancy or childbirth. (Rosário *et al.* 2013).

2.6 Immune Dysfunction

In a particularly severe instance, the amount of CD4 and CD8 T cells present in the patient's peripheral circulation was reduced but at the same time they were hyperactivated. It was feasible to discover both proinflammatory CD4 and toxic granular CD8 T cells during the antiviral immune response and the overactivation of T cells. T cells. Immune cell counts were shown to be lower in severe cases than in mild cases, and these immune cell counts declined more abruptly in severe cases than in mild cases; nevertheless, immune cell counts increased in mild cases. This was one of the findings of a different study (Kondo *et al.* 2000). To put it another way, people who have COVID-19 have increased levels of inflammatory mediators in their body, such as interferon and tumor necrosis factors. There is not much of a difference in the severity

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between severe instances and moderate ones when comparing them. (Kondo *et al.* 2000).

2.7 Diagnosis

2.7.1 Nucleic Acid Test

Virus identification is the primary focus of COVID-19's defensive efforts. The scientific community has created new technologies of the next generation of sequencing in order to ascertain the sequence of the virus after the original epidemic. The China Food and Drug Administration (CFDA) has given their stamp of approval to devices that do quantitative fluorescence testing as well as nucleic acid sequencing (Delogu *et al.* 2006).

The testing of nucleic acids is plagued by the presence of false-negative results. Rapid diagnostic techniques have been developed as a means of overcoming the low detection effectiveness of diagnostics based on viral nucleic acid. On nucleic acid test papers, SARS-CoV-2 can be seen with the naked eye in about three minutes after being exposed to the test. (Delogu *et al.* 2006).

2.7.2 Serologic Diagnosis

Patients with SARS-CoV-2 have demonstrated to have immediate serological responses. Appropriate detection reagents have been speedily created using immunochromatography, colloidal gold, and other technologies (Lai and Kondo 2008).

2.7.3 Imaging Technology

Imaging techniques such as CT and MRI play an important role in clinical diagnosis. According to the results of many CT scans, the ground glass in several of the COVID-19 cases was opaque. In order to diagnose COVID-19, a deep learning system is

required because it is necessary to extract radiological graphic features. A CT scan may be analyzed by an AI system in about 20 seconds with an accuracy rate of 96 percent, which enables diagnostics to be performed more quickly and with more precision. In various medical contexts, this methodology is currently being utilized. (Lugus *et al.* 2009).

2.8 Genomic Variations in SARS-CoV-19

Both SARS-CoV-19 and the previous human coronavirus share a genomic sequence that is identical to a 99.9 percent degree (the SARS-like bat CoV). Two examples of genes that produce structural proteins are denoted by the letters N and S, respectively: nucleocapsid and spike (Figure 2.1). Pp1ab and 15 naps are both encoded by the orf1ab gene, which is the largest gene in the SARS-CoV-2 virus. The result of the orf1a gene is called pp1a, and it contains 10 different NSPs. Within the context of the evolutionary tree, the SARS-coronavirus family is closely connected to the SARS-CoV-2 virus.

Both SARS-CoV-1 and SARS-CoV-2 are distinct from one another because the 8a protein in SARS-CoV-1 has been removed, and the amounts of amino acids in the 8b and 3c proteins have been altered. The structure of the spike glycoprotein produced by the Coronavirus has been altered as a result of recombination. The glycoprotein that is produced by this virus is the result of a combination of an unidentified Beta-CoV and the SARS-CoV that is found in bats. According to the results of fluorescence experiments, SARS-CoV-2 used the same cell receptor and entrance method into the host cell as ACE2 (angiotensin-converting enzyme 2) (Liu *et al.* 2020).
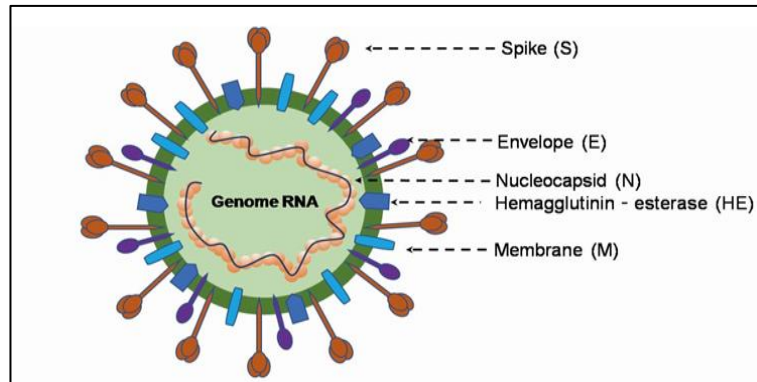
Figure 2.1 The β-coronavirus particle (Liu *et al.* 2020)

2.9 CBC and the Severity of SARS-CoV

A blood count can provide an accurate diagnosis for a wide variety of illnesses and conditions. [Citation needed] Leukocyte differential counts and blood film tests can be highly helpful in the early phases of the diagnostic process when looking for a possible cause of disease. [Case in point] [Case in point] In spite of the fact that qualitative and quantitative (morphologic) examination of blood cells may produce the same results, the term "quantitative" is increasingly being used to describe what was formerly known as "qualitative." During a whole blood count, the cells that are present in the blood are examined (CBC). Plasmodium fluid is made up of three different kinds of cells: platelets, white blood cells (also known as WBCs), and red blood cells (also known as RBCs) (PLTs). The majority of the time, stem cells are generated in the bone marrow, and then they are distributed throughout the rest of the body based on what is required. Research is being carried out by a group of scientists right now (Kernan and Carcillo 2017).

Even if the patient does not exhibit any symptoms, it is possible to easily identify COVID-19 as long as the patient has eosinopenia. Following lymphoma and thrombocytopenia, neutropenia and neutropenia after lymphoma were shown to have the second and third highest occurrence, respectively. Certain of these abnormalities tend to be more prevalent in more severe cases (96.1 percent vs. 80.4 percent lymphopenia, 57.7 percent thrombocytopenia, and 61.1 percent leukopenia). In the vast

majority of cases, lymphocyte dysfunction is brought on by the coronavirus. This might occur either directly or indirectly. When it comes to medical monitoring and making adjustments to a patient's medication, an analysis of the patient's lymphocyte count is a reliable indicator of the severity of the illness (Lu *et al.* 2020).

Patients infected with COVID-19 can still have a blood count performed, which is a common method in biological diagnostics. The lymphocyte and platelet counts are examples of prognostic markers that can be used by medical professionals to make educated guesses regarding the prognosis of a disease while also altering the treatment plan for a patient. A recent study found that (Lu *et al.* 2020).

2.9.1 Neutrophil-lymphocyte-ratio (NLR) may reflect the severity of inflammation

Patients diagnosed with COVID-19 tend to have a greater ratio of neutrophils to lymphocytes (NLR). Researchers have found that NLR is an effective predictor of the outcome of events. The NLR was also found to be relevant in individuals who were severely ill, however these findings came from relatively small investigations. According to the findings of Zhichao *et al.*, COVID-19 patients who had a higher NLR at the time of admission experienced more severe pneumonia than those who had a lower NLR (Luo *et al.* 2020).

Only 9.1 percent of individuals under the age of 50 with NLRs greater than 3.13 were found to have acute illnesses, in contrast to the 50 percent of patients who had NLRs less than 3.13. Conclusions According to the findings of Zhang et alstudy, .'s 94 percent of COVID-19 patients who passed away had an NLR of higher than 5. A screening test that is reliable and well-established, such as an increased NLR, can be utilized in order to identify patients who are at a high risk. 2020 Research carried out by Luo *et al.*2020

2.10 Ferritine

Ferritin is an essential intracellular iron storage protein, and many inflammatory illnesses, especially acute infections, can cause levels of ferritin, which can rise. Diseases such as macrophage activation syndrome, catastrophic antiphospholipid syndrome, and adult-onset Still's disease are associated with hyperferritinemia. To put it another way (Cheng *et al.* 2020).

The direct immunosuppressive and pro-inflammatory consequences of hyperferritinemia, which can lead to a cytokine storm, are one of the many factors that contribute to immunological dysregulation. The devastating results of COVID-19 demonstrate that the severity of illness is influenced by cytokine storm syndrome (Para *et al.* 2022).

Beyond COVID-19, we need to investigate what's producing the elevated plasma ferritin levels and whether or not the protein is contributing to inflammation after it has been released. This is because COVID-19 is only one of the potential causes. It's possible that an inflammatory condition could cause an increase in the production of ferritin. It is possible that macrophages, which are responsible for the production of cytokines and account for the great majority of immune cells in the lungs, are to blame for the release of serum ferritin. Patients diagnosed with COVID-19 who had high levels of IL-6 in their blood were associated with a deterioration of their illness. In addition to functioning as a protein that stores iron, ferritin may also be capable of performing a variety of other functions at the site of an infection. Ferritin has been shown to have interactions with signaling molecules as well as immunological mediators, according to a growing body of research. Regarding the question of whether or not ferritin is harmful during inflammation and whether or not ferritin and cytokines have complicated feedback loops, there is much debate among researchers. Ferritin has the ability to trigger both pro-inflammatory and anti-inflammatory cytokines, and it also has the ability to enhance the production of cytokines. The year 2022 is one example among several others (Para *et al.* 2022).

In the future, investigations might find it useful to look at the structure of plasma ferritin in COVID-19 patients. H and L are the two subunits that make up ferritin in the body. According to the findings of the study, H-ferritin may have effects that are both pro-inflammatory and immunosuppressive. To the best of my knowledge, (Lin *et al.* 2020).

2.11 D-dimer and COVID-19

 D dimers are widely utilized in the diagnosis (exclusion) of venous thrombosis. This is due to the fact that D dimers are products of the breakdown of fibrin. The capability of D-dimers to forecast outcomes is useful for treating a wide variety of diseases and conditions, including cancer and cardiovascular disease. Coagulation issues in COVID-19 patients have been the subject of substantial research, both in clinical settings and in laboratory settings (Leonard-Lorant *et al.* 2020).

Since December 2019, the severity of the COVID-19 pandemic has continued to rise. According to the findings of this research, patients with severe illnesses who test positive for COVID-19 have a greater risk of developing coagulopathy. A recent autopsy revealed that systemic microvascular thrombosis is the leading cause of mortality in the United States. [Citation needed] [Citation needed] Despite the fact that this is the case, very little information is available concerning the coagulation parameter D-dimer during COVID-19 (Favaloro and Thachil 2020).

In the event that a patient is critically ill, there is a possibility that they will not survive their condition. Roughly half of the patients had levels of D-dimer that were greater than normal, which has been linked to less favorable outcomes. An embolism or an infarction could have been the underlying cause of unexpected fatalities that occurred in otherwise healthy people. In patients diagnosed with SARS, the incidence of DVT was recorded at a rate of 20.5 percent, and the incidence of PE was documented at 11.4 percent; in contrast, no DVT nor PE was identified in any COVID-19 patients. When the D-dimer levels of 21 Spanish patients were analyzed, it was discovered that the odds ratios of pulmonary embolism increased to 1.7, 2.4, and 2.4 in the days following the initial measurement of the D-dimer levels. Patients in France who were being evaluated

for possible PE had D-dimer values that were as high as 2,660 mg/L, which is well outside of the normal range. (Pf6) An even higher threshold was established when looking at the 156 COVID-19 patients who did not have a diagnosis of deep vein thrombosis (DVT). (Dai *et al.* 2020).

2.12 Realation Ship Between D3 and COVID-19

A reduction in 25(OH)D levels in the blood might be brought on by illness. Insufficiency in vitamin D has been associated to a deficiency in immunologic mediators in numerous autoimmune, cardiovascular, and viral illnesses. Vitamin D supplementation reduces levels of the inflammatory cytokines TNF-alpha and IL-6, as well as NFkB activation (Dror *et al.* 2022).

A lack of vitamin D is a widespread issue that affects people all over the world, including in the Middle East. People who have darker skin and spend less time in the sun are at a greater risk of suffering from vitamin D deficiency than the general population. Vitamin D deficiency is especially prevalent in some racial and ethnic groupings of women, particularly those who like to cover their arms with long sleeves. There is a correlation between having low levels of 25-hydroxyvitamin D (25(OH)D) and having an increased risk of getting the flu and other respiratory illnesses. Vitamin D was found to significantly reduce the chance of acquiring acute respiratory infection when compared to a placebo (Dror *et al.* 2022).

A deficiency in vitamin D has also been connected to several types of respiratory diseases. Higher 25(OH)D blood levels have been linked to worse illness severity and clinical outcomes in the COVID-19 hospital patients who participated in the study. They exhibit lower levels of 25(OH)D compared to both the general population and the outpatients who participated in COVID-19. After a patient's stay at a COVID-19 hospital, their serum levels of 25(OH)D are typically checked and evaluated. It can be challenging to establish a connection between chronic COVID-19 disease and 25(OH)D levels in the blood. As a consequence of this, there is no direct connection that can be

made between a patient's pre-infection vitamin D level and the patient's clinical presentation during an active COVID-19 infection (Leaf and Ginde 2021).

In order to study the relationship between low pre-infection 25(OH)D blood levels and the severity of acute COVID-19 sickness, pre-infection 25(OH)D blood levels were employed. Estimating 25(OH)D levels based on preinfection 25(OH)D values was accomplished with the use of an innovative cosinor modeling approach. It was found that having lower levels of 25(OH)D was associated with a larger risk of COVID-19 disease severity. (Leaf and Ginde 2021).

2.13 Covid 19 and Prothrombin Time

 When evaluating the state of the blood, standard coagulation laboratory markers are among the most helpful diagnostic tools. When the Doppler Doppler (DD) decreases, which indicates that there is a higher degree of activity in the body, there is an increase in fibrinolytic solubilization. Early signs of DIC can be identified by making use of both the exogenous and endogenous components of the coagulation system. Fg, which is one of the most important coagulation proteins produced by the liver, plays a role in the production of fibrin in the circulation as well as its breakdown. The presence of several thrombotic diseases can be indicated by a high Fg level. The sensitive indicators DD, PT, Fg, and APTT can be used to assess whether or not coagulation is functioning normally. As a consequence of this, it was determined to look into whether or not the severity of COVID-19 was connected to these symptoms. (Wang *et al.* 2020).

3. MATERIALS AND METHODS

3.1 Subjects

The prospective study was conducted in the laboratories of hematology and Biochemistry Departmentin Ramadi Teaching Hospital from the period between December 2021 to march2022,fifty (50) Iraqi citizen subject were participated in this study, their age between (18- 80) years were dividing into following groups.

3.1.1 Patients groups (SARS-CoV-2)

Al-Ramadi Teaching Hospital gathered (40) blood samples from patients who have recovered from coivd-19 between September and December 2020.

A survey data sheet was used to collect data from patients Age, weight, and smoking habits were used to divide the patients into three distinct groups. In Table 3.1 you can see the group's classifications.

Table 3.1 Classification of study groups according to their age range

AGE	12 - 25	25 - 45	MORE THAN 45
male	3	12	10
female	2	10	3

3.1.2 Healthy control group

There are ten (20) healthy males from Anbar, Iraq, who served as the control group in this study. Their ages range from (25 to more than 45). In this study, ten (20) healthy subjects (4 male and 6 female) were separated into three groups based on their age (between 18 and 65). (Table 3.2).

Table 3.2 Classification of healthy study groups according to their age range

AGE	12 - 25	25 - 45	MORE THAN 45
male	0	8	2
female	0	8	2

3.1.3 Blood Samples Collection

All patients and controls had their venipuncture samples drawn with a 5 mL plastic syringe, which were then placed in 15-minute gel tubes before being tested. The serum was obtained by centrifugation at 3500 rpm for 10 minutes and stored in the freezer at -20°C until needed.

3.2 Materials

3.2.1 Instruments and equipment

The general instruments and equipment used in this study are listed in Table 3.3.

Table 3.3 Instruments used in this study

NO	EQUIPMENT	ORIGIN	COMPANY
1	Eliza	Korea	Boditech
2	Test Cartidage	Korea	Boditech
3	Shaker instrument	Germany	Heidoliph
4	Incubator	Brasilia	Fanem
5	CBC	Sweden	Sewlab
6	Centrifuge	Taiwan	Gemmy
7	Gel Tube	Italian	F L Medical
8	EDTA Tube	Italian	F L Medical

3.3 Methods

3.3.1 Determination of ABO blood groups

Agglutination of antigens on red blood cells is achieved using the tube method (Biotec, Germany) (Biotec, Germany). Centrifuged for one minute at 1000 rpm with PBS as a phosphate buffer, the RBC pellet was separated from its cellular components. The RBC pellet was spun again at the same speed and time to eliminate any leftover red blood cells. To achieve a 3-5 percent RBC cell suspension, the RBCs were cleaned three times in PBS. Cells in the red blood cell tube had been coated with anti-A or anti-B chemicals (10 x 75 mm). After one minute of incubation at room temperature, the tubes were spun in a centrifuge for ten seconds at 1000 rpm. The agglutination of red blood cells was examined. A clumping of red blood cells by the ABO antigen indicates the presence of the correct antigen in the cells being examined. If agglutination is lacking, there is no conclusive proof.

3.3.2 Ferritin

The ST AIA-PACK FER can only be used to assess FER in human serum or heparinized plasma. The formation of hemoglobin, myoglobin, and other iron-rich proteins is impossible without this iron-storing protein. The liver, spleen, and bone marrow's precursors to red blood cells all have large concentrations of FER-positive cells. The amount of FER found in various tissue extracts varies substantially. Acidic iso-FER is seen in the tissues of many cancers. It's more common to find iso-FER in blood, spleen and liver. Iso-f FER from human liver or kidney is commonly used to measure FER concentrations in immunoassays. According to studies on patients with iron deficiency and excess disorders, ferritin concentrations can be used to measure the body's iron storage capacity.

The essential principle of the Assay:

A two-site immunoenzymemetric technique is used to conduct the tests. Cups like this one from St AIA-PACK FER are useful. In the test cups, enzyme-labeled monoclonal antibodies bind to the ferredoxin (FER) in the test sample. Enzyme-labeled monoclonal antibodies remove any antibodies that have not been attached to magnetic beads. Thanks to a 4-methylumbelliferyl phosphate treatment, the blossoms are able to open their petals (4MUP). When the FER in the test sample is larger, enzyme-labeled monoclonal antibodies in contact with bead surfaces are less prevalent. Analyzing standard curves can help researchers determine the quantities of unknown samples, as antibodies that come into contact with beads are influenced by sample concentration.

3.3.3 D-dimer

D-dimer is present in thromboembolic disease in outpatients with DVT or PE. Pulmonary embolism can be caused by serious illnesses such as peripheral artery embolism (PAE) and deep vein thrombosis (DVT) (PE). Detection of subclinical DVT is based on the plasma D-Dimer levels. A normal D-dimer level can exclude people at low or moderate risk of developing deep vein thrombosis (DVT). Due to factors such as age, hemiplegia, and abnormalities in the coagulation process, deep vein thrombosis might raise the risk of stroke (DVT). As a result, D-Dimer levels and the occurrence and characteristics of DVT in patients with acute stroke must be continuously examined. Patients in chronic stroke rehabilitation can have their plasma D-dimer levels checked for DVT. In the development of new diagnoses, several biomarkers have been recommended for use by national and international scientific authorities. D-Dimer is a crucial tool for monitoring patients' post-treatment clinical condition and analyzing their response to treatment because it is a well-known predictor of cardiovascular illness.

When an antigen-antibody complex is found on the test strip, it is caught by the other antigen-antibody complex on the strip and deposited in a buffer.

The Instrument for ichromaTM investigations processes fluorescence signals from D-Dimer detector antibodies to determine D-Dimer concentration.

3.3.4 Vitamin D3

The Human Vitamin D3 ELISA quantitates D3 in human serum, plasma, or cell culture medium. The assay will exclusively recognize both natural and recombinant D3by ElabscienceE-EL-0012 USA.

3.3.5 Prothrombin time

A blood clotting test, the prothrombin time (PT) is also known as the PT or pro time test. Prothrombin is a protein produced by the liver. Clotting is made easier by a variety of blood components, and this one is just one of them.

3.3.6 CRP

In reaction to interleukin-6, the liver is responsible for the production of C-Reactive Protein (CRP), which is both a well-known acute-phase reactant and an inflammatory marker. CRP is a protein that may be measured in the blood to check for tissue damage and inflammation (acute-phase protein). A variety of diseases, including inflammation, infection, or cancer, can set off the acute-phase response (APR), which in turn causes nonspecific physiological and biochemical processes to take place in the body. As a result of viral infections and other types of acute inflammatory reactions, it is possible for CRP levels to skyrocket to 500 mg/L from their typical range of 5 mg/L. The progression of rheumatoid arthritis (RA) can be tracked in patients through the measurement of their CRP levels, which is employed in clinical practice.

After being taken from the test strip, the antigen-antibody complex can next be evaluated. This is accomplished by first depositing the antigen-antibody combination into a buffer and then removing the buffer from the test strip. The ichromaTM test, which detects CRP levels by utilizing fluorescence signals from the detectable antibody, becomes brighter as a result of the presence of antigen

3.4 Statistical Analysis

 SPSS-22 was used to perform statistical analysis on the data (Statistical Packages for Social Sciences- version 22).

Useful metrics like percentage, mean and standard deviation were used in the presentation of the data (minimum-maximum values).

To establish the significance of a disparity between two independent means, it was utilized to compare more than two independent means (quantitative data). The Fisher Exact test or the Pearson Chi-square test (two-test) with Yate's correction were employed to determine the significance of percentage differences (qualitative data). The Pearson correlation between two quantitative variables was tested for significance using the t-test. This means that there is no association between the score of 0.3 or less and the score of between 0.5 and 0.75, but there is a strong correlation between the score of 0.75 or more and the score of more than 0.75. Some additional metrics were also utilized in addition to correlation, such as the r2 (coefficient of determination), which means knowing these numbers can explain 34% of variation in how important something is (y or x). If the P-value was less than 0.05, statistical significance was established.

4. RESULTS AND DISCUSSION

4.1 Clinicaland Pathological Study

The design of study was in three parts:

1. The first part was the related risk factors that participate in coronavirus by comparing:

  - Study sampleat newly diagnosed withbeginning of infection(N= 25)
  - Study sample with receiving sever case (n= 15).

2. The second part is study of the biochemical marker in the blood of these groups.
3. The third part is the hematological-marker essay in the blood of these groups.

4.1.1 Risk factors that related to participate in coronavirus

50 confirmed COVID-19 patients were admitted to single rooms, with 17 (33.5 percent) requiring ICU treatment, as shown in Table 4.1.

Women and men made up the vast majority of those who sought treatment (35 [70 percent]). Most of the patients are white, although (15 [30 percent]).

Asthma and heart disease comorbidities indicated a marginally significant difference between severe and non-severe patients, but diabetes comorbidities were significantly substantial.

When compared to another group, hypertension has a marginally significant influence in extreme situations. Severe acute respiratory syndrome, or SARS, is characterized by high fever and dry cough (55 percent and 78 percent, respectively).

Table 4.1 Demographic and clinical characteristics of patient

CHARACTERISTICS	MEAN ± SD			P-VALUE
	Total (50 patients)	Sever N0=17	Non-sever NO=33	
Age (years)	39 (18-80)	64±2.1	36± 1.9	P<0.001
Sex				
Male	35 (70%)	20±1.1 (58%)	14.7±0.84 (42%)	P<0.001
Female	15 (30%)	3±0.32 (20%)	12±0.87 (80%)	
Comorbidities				
smoking	3 (5%)	1 (33%)	2(66%)	NS
Hypertension	-	-	-	-
Diabetes	13 (26%)	9 (68%)	4 (32%)	0.003
Cardiac disease	3 (7%)	0	3 (100%)	NS
Asthma	5 (10%)	1 (20%)	4 (80%)	P<0.001
Signs and symptoms 2				
Fever	28 (55.5%)	17 (60%)	11(40%)	-
Headache	9 (18%)	2 (22%)	7(78%)	-
Dry cough	39 (78%)	15(37%)	24 (63%)	-
Chest pain	11 (22%)	9 (81%)	2(19%)	-
Abdominal pain	5 (10%)	4(80%)	1(20%)	-
Vomiting	9 (18 %)	1 (11%)	8 (89%)	-
Diarrhea	11 (21%)	2 (18%)	9 (82%)	-

Following the discovery of SARS-CoV-1 in 2003 and MERS-CoV in 2012, this is the third coronavirus to be found in the last two decades. Between the years 2002 and 2003, the SARS-CoV-1 infection was responsible for the deaths of 8,096 people. In 2012, there was an outbreak of MERS-COV for only a brief period of time; nevertheless, the disease was promptly contained after it had spread thus far. Because of this calamity, the lives of roughly one in three people were taken (Park 2020).

The clinical and biochemical characteristics of fifty individuals with COVID-19 who were residing in the government zone of AL-anbar were investigated. The elderly have a larger risk of contracting COVID-19, which in turn increases the likelihood that they may pass away from the disease or from another ailment that threatens their lives. In research of the SARA-covid19 virus, it was discovered that the mortality rates of SARS and MERS were greatly impacted by older age. As a result, persons who were 65 years old or older were at the greatest risk of dying as a result of the virus. Because elderly people tend to have lower levels of cellular immunological activity and inflammation (particularly in response to viral infections), they may be at a greater risk of dying from an illness (Severin and Jacobson 2020).

The severity of COVID-19 can be predicted using gender in some cases. According to the findings of Iranian experts, sexual desire was not the primary motivator behind acts of violence (Gebhard *et al.* 2020).

Patients infected with COVID-19 require at least one-fifth of the available beds in medical intensive care units (ICUs) in the majority of the world's least developed nations, particularly in Africa. The death rate for persons over the age of 60 is six times higher than the death rate for people under the age of 50, and the death rate for patients is still above 1.4 percent (Chen *et al.* 2020).

As a diabetic, you have a reduced risk of contracting COVID-19. If you have diabetes, heart disease, or any condition that makes it difficult for your body to fight off an infection, then other viruses, including this one, pose a significant risk to your life (Chen *et al.* 2020).

Patients who have diabetes usually deal with both weight gain and hypertension. Diabetes is a potential contributor to the increased mortality and morbidity rates that have been related to COVID-19. According to the findings of several research, diabetic patients whose glycemic control was inadequate had a more dire outlook. The five routes identified by Muniyappa and Gubbi, which include higher cellular binding affinity and successful virus entry, reduced viral clearance, poor T-cell function, and the presence of cardiovascular disease, have the potential to influence the blood sugar levels of diabetics (Wasim *et al.* 2021).

Previous research has not established a link between the severity of the Corona virus and anything else we've found. The risk of developing Covid-19 was found to be four times lower in smokers compared to the risk that was seen in non-smokers in the reports. Is there any evidence that smoking is good for your health? You have it completely backwards.. (Shastri *et al.* 2021).

4.2 ABO Blood Groups

According to the ABO classification, there were no significant differences in the prevalence of blood categories A, B, AB, and O among the two primary groupings (Table 4.2).

Table 4.2 Distribution of ABO group with COVID-19 infection

ABO BLOOD GROUPS	SAMPLES			
	Sever case		Non-sever	
	NO	%	NO	%
A	12	71	19	58
B	2	12	6	18
O	3	17	7	21
AB	0	0	1	3
Total	17	100	33	100
$X2 = 7.719$, P=0.05219053, P> 0.05 non-significant				

It was discovered that having blood type A was a risk factor for both men and women, as can be seen in the numbers that follow (4-2). According to the findings of a study conducted in Iran, those with blood type AB are more prone to contracting infections than individuals with blood type A. The disparities seen between these populations are almost certainly attributable to underlying biological distinctions. According to the findings of several studies, people with blood type O had a decreased risk of contracting a strain of SARS-CoV-2 known as CoV2 than people with other blood types. There is evidence to back up the hypothesis that those who have the blood types A, B, or AB are more likely to contract the condition. According to the results of their research, patients who had blood type A had a greater probability of passing away than those who had blood type B. (Goel *et al.* 2021).

4.3 Relation of Hematological Parameter with SARS –CoV-19

As shown in Table 4.3, the most severe instances of SARS-CoV-19 infection had much lower white blood cell counts than non-severe patients, and this was true for both groups.

Table 4.3 Relation of hematological parameter with severity of SARS –CoV-19

HEMATOLOGICAL PARAMETER	PATIENTS WITH SARS-COV-2		
	Sever case	Non-sever	p-value
	Mean± SD		
WBC COUNT	6.11±1.17	5.08 ±1.49	0.051 NS
Neutrophils (10^9 /L)	4.32±1.09	2.17±0.80	P<0.001
Lymphocytes (10^9 /L)	0.60±0.07	1.55 0.13	P<0.001
Hemoglobin (g/L)	13.6±1.5	12.7 ± 0.89	0.316 NS
Platelets (10^9 /L)	220±18.5	233.5 ±47.5	0.476

The lymphomas of several of our patients have worsened while they were here receiving treatment. Several explanations have been proposed regarding the pathogenesis of lymphopenia in SARS-CoV-2 infection; all of these hypotheses have some level of support for them. Researchers in China studied patients suffering from mild and severe versions of the illness, analyzing their hemograms as well as the subpopulations of their lymphocytes. Patients who were in the most critical condition had a ratio of neutrophils to lymphocytes that was higher, and they also had lower levels of other inflammatory markers (CRP, ferritin, interleukin-6, interleukin-8, and interleukin-10). Despite having lower numbers of CD4 memory and regulatory T cells, patients with severe lymphopenia were more likely to have CD4 lymphopenia than those with less severe lymphopenia. This was the case even when patients with severe lymphopenia had lower CD4 lymphopenia levels. COVID-19 has the potential to reduce lymphocyte counts, in particular CD4 and CD8 cells (Pozdnyakova *et al.* 2021). Before spreading to other cells, infectious influenza virus particles initially target respiratory mucosal ciliated epithelial cells. These cells have an ACE2 receptor. White blood cells (WBCs) and other immune cells are impacted as a direct result of this cytokine storm (lymphocytes). This fact was demonstrated by a meta-analysis that was carried out by

Henry and his colleagues. The ability of the virus to repair lymphocytes that have been killed by COVID-19, in particular CD4 cells, has been identified as a biomarker. This biomarker can also predict the severity of the illness and the fatality rate. (Zheng *et al.* 2020).

4.4 Relation of Biochemical Parameter with SARS –CoV-19:

Table 4.4 the present study shown a highly significant correlation between CRP, D-dimer and ferritin with severity of infected by corona virus especially ferritin in sever case as compared with another group, as shown in Figure 4.1, 4.2, 4.3..

Table 4.4 Relation of some parameterwithseverity of SARS –CoV-19

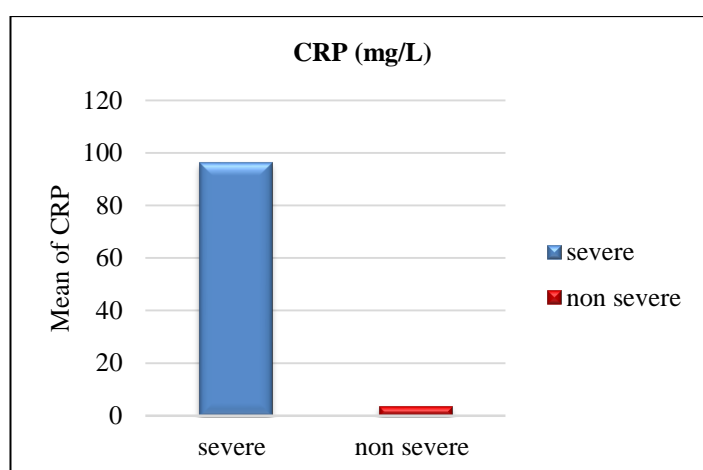| BIOCHEMICAL PARAMETER	PATIENTS WITH SARS-COV-19		
	Sever case	Non-sever	
	Mean± SD		p-value
CRP (mg/L)	96.2±19.6	3.6 ± 0.99	P<0.001
D-dimer (µg/L)	1.228± 0.47	0.501 ±0.22	P<0.001
Ferritin (µg/L)	633.9 ±192.5	130 ±67.39	P<0.001

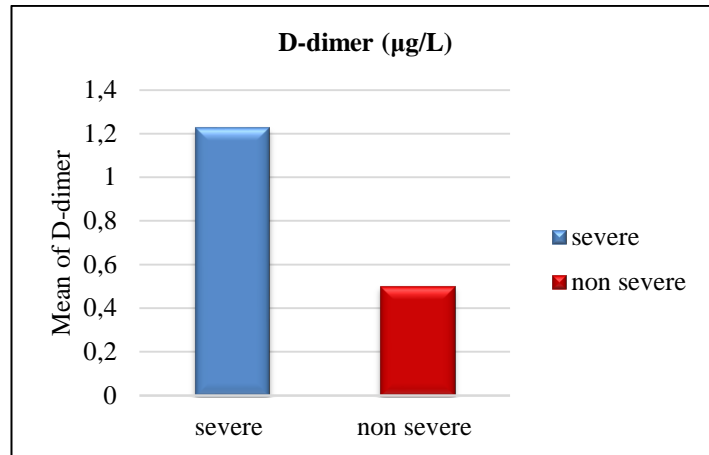**Figure 4.1** Mean ans SD of CRP in covid 19

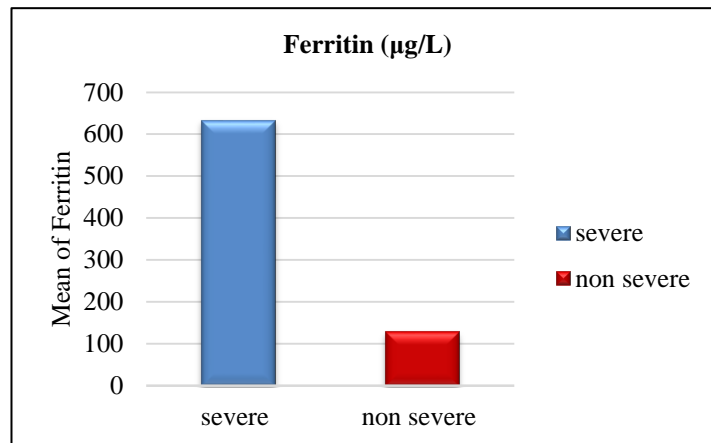**Figure 4.2** Mean and SD of D-dimer in covid 19

Figure 4.3 Mean and SD of ferrtinin covid 19

Tables 4.4 and Table 4.5 illustrate that persons with HIV have serum ferritin levels that are significantly higher than normal. Patients diagnosed with COVID-19 have been shown to have abnormally high levels of serum ferritin in Iraq, Kurdistan, Indonesia, and Wuhan, China. When ferritin levels are high, the immune system may function at its most efficient.

Inflammation and the production of cytokines are the consequences that follow from the inhibition of the immune system caused by ferritin. Those who were infected with SARS-CoV-2 and respiratory distress syndrome had higher ferritin levels in their blood than the general population. It was discovered that SARS-CoV-2 had a secondary

hemophagocytic lymphohistocytosis, also known as sHLH (sHLH). Cytokine storming is a word used to describe inflammation that has spread throughout the body and can be lethal if it occurs. This type of inflammation can occur when an immune system becomes overwhelmed (Verity *et al.* 2020).

According to our findings, infection with SARS-CoV-19 was closely connected to D-Dimer levels in those who were suffering the most from their illness. Researchers in Indonesia, Japan, Greece, and Wuhan, China found a correlation between D-dimer levels and the severity of SARS-CoV-19 infections in those countries (China). Individuals infected with SARS-CoV-19 who had thrombocytopenia and died as a result of an increased or decreased coagulation time as a direct result of the thrombocytopenia.

Patients affected with COVID-19 have an increased risk of developing disseminated intravascular coagulation (DIC), in comparison to patients who do not have this condition. In patients with severe pneumonia, activated platelets, leukocytes, and endothelial cells can have both local and systemic effects. It has been demonstrated that the presence of thrombin is necessary for the activation of platelets and the production of fibrinolysis in the absence of naturally occurring anticoagulants. (Yuan *et al.* 2020).

4.5   Relation of D3 Panale with Prothrombin Time Parameter with SARS –CoV-19

In present study shown a significant decrease of vitamin d3 as compared with severity of covid infection, also levels of calcium may be affected by increasing of covid infection espicially in critical casee as shown in Table 4.5,wherase no significant were shown in iron studeied, as shown in Figure 4.4.

Table 4.5 Relation of some parameterwithseverity of SARS –CoV-19

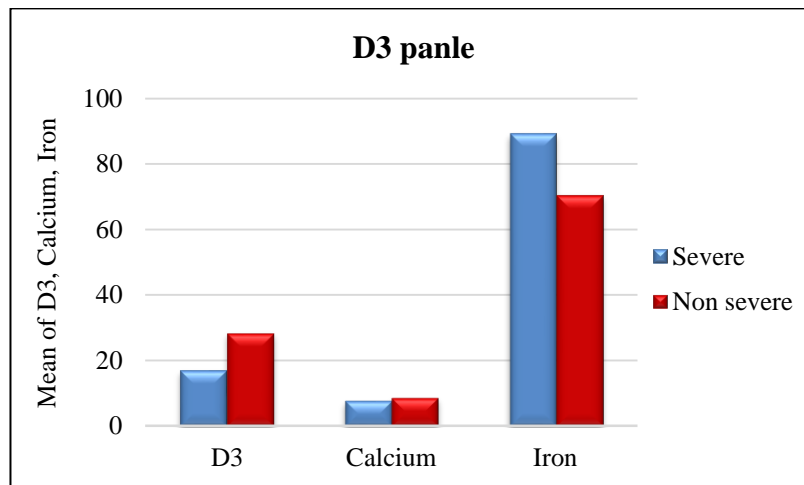| BIOCHEMICALPARAMETER	PATIENTS WITH SARS-COV-2		
	Sever case	Non-sever	p-value
	Mean	Mean	
D3 (mg/L)	17.2 ±5.87	28.61±7.30	0.018
Calcium	7.9±1.2	8.82±1.03	P<0.001
IRON (μg/L)	89.34±18.9	70.65±20.53	0.074

Figure 4.4 Mean and SD of D3 panle in COVID 19 groups

The COVID-19 virus is being studied to determine whether or not taking vitamin D supplements can prevent infection or lessen the likelihood of dying from the disease. According to the findings of several studies, vitamin D may have an impact on the COVID-19 status. Vitamin D was found to reduce the risk of COVID-19 infection, severity, and mortality in all 11 of the studies that were included in this systematic review because they fulfilled the inclusion criteria. The conclusions of an investigation that was carried out by Hastie and his colleagues had significant repercussions. As a consequence of this, those who are deficient in vitamin D have a lower risk of developing COVID-19, which in turn implies they have a lower risk of being unwell from the infection or disease and ultimately passing away as a consequence of it (Looi 2020).

Because of this, the influence that vitamin D has on the state of COVID-19 is viewed with a healthy amount of suspicion. It is dependent on a number of different factors as to whether or not a COVID-19 patient will benefit from receiving vitamin D therapy. A person's overall health is determined by a number of factors, some of which are their age, gender, diet, level of physical activity, and present state of health. Despite the inclusion of these potentially confusing factors, there is a strong possibility that vitamin D status and COVID-19 status are related to one another. According to one piece of research, the influence of vitamin D on the status of COVID-19 is confounded by the presence of confounding variables. When other factors were taken into account, there was no evidence that vitamin D levels were significantly correlated with COVID-19 status. According to Martineau and Forouhi, research of this nature are prone to residual and unmeasured confounding, which is what has caused inconsistencies in the impact that vitamin D has on COVID-19 status. The authors of many of the research that were looked at for this investigation all agreed that there is a widespread problem with vitamin D insufficiency. It's possible that the conclusions would be affected negatively if the amount of vitamin D considered insufficient wasn't consistent from study to study. Because our search for previous research only included papers that were published between December 2019 and November 2020, the results of our most recent investigation could have been skewed as a result. This type of bias is quite typical in research that have been published and that rely on secondary data sources. (Ebadi and Montano-Loza 2020).

As of the 7th of June in 2021, there were roughly 173 million confirmed cases of COVID-19 coronavirus disease worldwide. It has been determined that a coronavirus known as SARS-COV-2 is to blame for the illness. This pandemic is significantly more deadly than the Spanish flu epidemic that occurred in 1918, which is known for being the deadliest infectious disease outbreak ever recorded. People who follow the Daoist religion are known as Daoists. The World Health Organization (WHO) has designated it as a pandemic ever since the first case of COVID-19 was found in Wuhan, China, in December of 2019.

The most prevalent mechanism of transmission for COVID-19, a virus that can cause respiratory illness, is direct contact with an infected person's droplet or direct contact between droplets. Direct contact between droplets can also spread the virus. In most cases, the incubation period for 2020 SARS-COV-2 lasts anywhere from two to fourteen days (Organization 2020, Pereira *et al.* 2020). It has been discovered that virus particles can be found in a variety of physiological fluids. Blood serum, ocular fluid, nasopharyngeal secretions, and spittle are some examples of these, but the list is not exhaustive. pee breast milk placental membranes feces (Organization 2020, Heller *et al.* 2020, Hindson 2020). You still have a problem that has to be treated, even though there are no signs of infection appearing on your body at this time. In children, fevers of a low grade can produce a broad variety of symptoms, such as respiratory distress, sore throats, coughs, lethargy, diarrhea, headaches, and anosmia. Thromboembolic disorders can also be caused by fevers of a low grade (Rothan and Byrareddy 2020; Garca 1441). Ischemia and pulmonary embolisms are both conditions that have the potential to be life-threatening. Pulmonary embolisms also have this capability. Ischemia can manifest in a number of ways, including heart attacks and strokes. The term "cardiovascular disease" is used to refer to a number of conditions that can lead to death. These conditions include diabetes and hypertension.

Recent studies have uncovered a connection between a deficiency in vitamin D in the COVID-19 environment and an increased prevalence of disease (Biesalski 2020, Bilezikian *et al.* 2020). In northern European countries other than those in Scandinavia, there was a correlation between low levels of vitamin D and an increased risk of dying from COVID-19. This was not the case in Scandinavia (Biesalski 2020). A very high number of cases have been reported in countries that are located beyond the latitude range (Latitude and respiratory infection susceptibility). According to yet another piece of research, a deficiency in vitamin D was associated with an increase in the chance of dying from COVID-19 that was almost four times as high. Individuals diagnosed with COVID-19 Acute Respiratory Failure have been shown to have low vitamin D levels, which lends support to the hypothesis that this may be an indication of a bad prognosis (Becky 2020). More than 40 clinical trials of vitamin D are now being conducted in various locations throughout the World.

Taking vitamin D supplements can lessen the severity of COVID-19 and SARS-COV-2 infections and even delay their onset. Taking vitamin D pills is one way to protect oneself against SARS-COV-2 illness (McCartney *et al.* 1971). According to the findings of clinical investigations and meta-analyses including patients with COVID-19, hypovitaminosis D is more common in those with severe disease than in those with moderate disease. This was determined by comparing those with severe disease to those with mild disease. This was found out by the efforts of Pereira and others. In spite of the fact that COVID-19 patients were more likely than healthy individuals to have low serum 1,25(OH)D levels (regardless of severity), there was found to be no effect on the likelihood of contracting SARS-COV-2 infection. This was discovered through research. There is no evidence that SARS-COV-2 infection is associated to hypovitaminosis D; nonetheless, the researchers observed that it was related with an elevated mortality risk, particularly in cases of severe sickness. [Cases of severe illness] (Alguwaihes *et al.* 2021). According to the findings of an experiment that was carried out by Murai and colleagues, there is no evidence to suggest that taking 200,000 international units of vitamin D on a daily basis will minimize the amount of time spent in the hospital or critical care unit (Murai *et al.* 2021). It is clear that these data contain a number of contradictions, which means that additional research is required.

In 82.2 percent of the COVID-19 cases, Hernandez and colleagues found that patients had hypovitaminosis D. When compared to the 47.2% found in the control group, this represents a significant departure. In the presence of an active COVID-19 infection, there is a connection between high levels of ferritin in the blood and low vitamin D levels in the body. This is one way in which the correlation between serum ferritin and 1,25(OH)D levels can be demonstrated (P 0.013). (Gold *et al.* 2020)

According to the findings of Hernandez et al2020research, COVID-19 patients with vitamin D insufficiency had significantly higher risks of cardiovascular illness, hypertension, and hospitalizations in critical care units. Patients who had inadequate levels of vitamin D in their serum had a 1.77-fold higher risk of having COVID-19 infection than those who had enough levels of vitamin D in their blood. This was one of the findings made by Meltzer and his colleagues. This was confirmed by a study that

had 489 patients (Meltzer *et al.* 2020). Supplementation with 1,25(OH)D has been shown to improve the results of a variety of COVID-19 and hypovitaminosis D test profiles. As can be seen in the diagram below, patients with COVID-19 and hypovitaminosis D both display inflammatory immunological abnormalities. Regardless of how serious the illness is, these anomalies will always be present in the patient.

According to the findings of a study that involved 383 different institutions, those who are obese have a threefold increased risk of developing severe COVID-19 symptoms in comparison to those who maintain a healthy body weight. They frequently suffered from flu-like symptoms, such as a high fever and a cough. According to the comprehensive study conducted by Popkin *et al.*, patients who were overweight or obese had a mortality rate that was 48 percent (P 0.001) higher, a 74 percent higher likelihood of being admitted to an intensive care unit, and a substantially higher rate of COVID-19 positivity than patients who were at a healthy weight. The results of yet another comprehensive investigation, which was this time headed by Zhao *et al.* (2020)

Because of the increased amounts of angiotensin converting enzyme 2 in their bloodstreams, obese people have a greater risk of contracting COVID-19 than people of a healthy weight (Kassir 2020). It is the ACE2 receptor that is responsible for the invasion of SARS-cell COV-2 (virulence factor). Adipose tissue, often known as the fat storage organ of the body, is where the ACE2 receptor is found to be expressed at the highest levels (Kassir 2020). During the course of the same experiment, scientists looked for signs of the COVID-19 virus and the influenza virus in the adipose tissue that was being studied (Kassir 2020). According to the findings of the study, those who are fat have a greater risk of contracting COVID-19 and suffering from the symptoms of the virus.

During the development phase of adipocytes, the accumulation of lipids and adipose-stimulating transcription factors is inhibited by vitamin D. This has an effect on the overall body fat composition of individuals, regardless of whether they are healthy or obese. Through the action of vitamin D, lipogenesis is controlled by two proteins: PPARgamma (PPAR) in adipose tissue and SREBP1 (sterol regulatory element binding

protein 1) in the liver. Both of these proteins are responsible for the production of fatty acids. In addition to its role in thermogenesis, calcitriol plays a regulatory role in the enzymes fatty acid synthase, hormone-sensitive lipase, and lipase (lipoprotein lipase). Calcitriol may induce the adipose tissue that is located in the abdominal cavity to migrate toward the anterior region of the belly (Slusher *et al.* 2015)

It is common knowledge that vitamin D and the receptor for vitamin D control the process of de novo adipogenesis, also known as the formation of new fat cells (Slusher *et al.* 2015, Wong *et al.* 2009). The results of this study indicate that preadipocytes are capable of expressing VDR. Studies on lipid synthesis have demonstrated a connection between C/EBP and an enzyme similar to fatty acid synthesise, which is a necessary step in the production of fats and is a key precursor to the process (CCAAT-enhancement binding proteins, transcription factors). When included in a meal, 1,25(OH)D has a direct impact on the amount of C/EBP mRNA as well as C/EBP protein. This occurs because 1,25(OH)D is converted to 1,25(OH)D. (CCAAT-enhancement binding proteins, a family of transcription factors)

It has been proven that vitamin D can inhibit the growth of premature adipocytes, which suggests that vitamin D plays an essential role in the differentiation of adipocytes in vivo. Calbindin-D28K, which is frequently referred to simply as Calbindin-D28K, has been identified as a transporter for vitamin D. Calbindin-D28K has the same effect on the metabolic process of vitamin D as well as on the binding of globular actin and immunomodulation by fatty acids (Tsalamandris *et al.* 2019). According to these findings, vitamin D might play a part in the rising prevalence of obesity.

Numerous studies have found that people who are obese have lower levels of vitamin D in their blood than people who are not obese. This is the case when compared to people who are not obese. The findings of this study are comparable to those of Buffington and colleagues in that 62 percent of obese women had low levels of vitamin D in their blood (range from 16 to 74 ng/ml) (Wortsman *et al.* 2000). Vitamin D levels were discovered to have an inverse relationship with body mass index (BMI) in a study that was carried out by Parikh et al (P 0.0001). (The study that Parikh and his colleagues did in 2004). It

is feasible that the use of vitamin D as a treatment for COVID-19 will have some contemporary consequences if obesity is an effect modifier. If this is the case, then the possibility exists. Even if obese persons spend enough time in the sun, their reduced bioavailability of vitamin D can still cause hypovitaminosis d (low vitamin D levels in the blood). This is the case regardless of whether or not the patient takes vitamin D supplements (Parikh *et al.* 2004). According to Zhu and colleagues' research, having higher blood levels of vitamin D has been associated to having improved metabolic health (Zhu *et al.* 2013).

Goncalves and his colleagues found that the levels of hypovitaminosis D in 94.2 percent of COVID-19 patients were less than 30 ng/ml. This was determined through research that included 176 patients. According to the findings of the researchers, serum 25(OH)D and BMI had a significant inverse connection with one another as a bivariate variable. Because of the complications connected with COVID-19, the vast majority of these patients were required to be hospitalized to an intensive care unit in order to receive therapy. Due to the fact that the results of this test can assist in providing an estimate of the risk of infection outcome in patients who have been diagnosed with COVID-19 and who are obese (Goncalves *et al.* 2020).

D-dimer is an extremely helpful diagnostic tool since it acts as a serological biomarker for coagulation and fibrinolysis. When fibrin is broken down, thrombin is produced as a byproduct of the process. The levels of D-dimer in patients diagnosed with COVID-19 have been shown to accurately predict the severity of the disease, according to the findings of more than 170 separate studies. According to the findings of one study, individuals with COVID-19 and high D-dimer levels had an increased risk of passing away while undergoing therapy in the hospital. On the other hand, incorrect numbers have a detrimental effect on the D-utility. the dimer's D dimer Neither the products nor the manufacturers of D-dimer were mentioned in the vast majority of the investigation. For instance, the vast majority of articles neglected to specify whether the D-dimer levels were provided in fibrinogen equivalent units (FEUs) or D-dimer units, which are approximately four times distinct from one another. They didn't only use a few

predetermined threshold levels; rather, they used a wide array of diverse comparison units. This allowed them to get more accurate results. (Wang, et al 2020)

There has never been a previous investigation of the metalloids and COVID-19 virulence markers found in whole blood. The levels of essential minerals like calcium and chromium, as well as dangerous metal(loid)s like mercury and arsenic, were measured in the complete blood of 36 people with COVID-19 as part of a retrospective investigation into the correlation between the severity of their condition and the levels of these substances (severe or non-severe). The magnesium, cadmium, chromium, and manganese concentrations in whole blood of the deceased and recovered groups were significantly different (P.05) from those of the deceased and recovered groups. This was determined by comparing the concentrations of these elements in the whole blood of the deceased and recovered groups (P .05). There is a possibility of a connection between the involvement of COVID-19 in a fatal outcome and the appearance of hazardous metals and vital minerals in whole blood. There are a number of additional potential links to take into consideration, in addition to the risk factors that have been well-documented for COVID-19-induced severe illness and mortality (Zhao *et al.* 2020)

In the meantime that the world waits for an effective vaccination, the mortality and morbidity rates of patients who suffer from important mineral deficiencies could be lowered. During the COVID-19 outbreak, it is absolutely necessary to eat healthily in order to keep one's immune system functioning properly. At least eight or nine different types of vitamins and minerals should be included in a diet that is considered healthy. This intracellular cation, which follows potassium in over 600 separate enzymatic pathways, may be responsible for some of the heightened immunological and inflammatory responses that are seen in COVID-19 patients. 19 In individuals who are low in magnesium, an increase in the amount of cytokines causes a rise in the levels of phagocyte activation, endothelial cell activation, and endothelial cell activation. Chronic inflammation and endothelial dysfunction seen in COVID-19 are analogous to metabolic mechanisms that have been identified in people suffering from latent subclinical magnesium deficits. The Iotti et alhypothesis is corroborated by our findings, which demonstrate that the magnesium levels of COVID-19 severe patients

are much lower than those of non-serious patients. In order to halt the progression of the disease, medical professionals recommended to their patients that they have their magnesium levels examined on a regular basis.

In the laboratory, it was established that calcium is necessary for the fusion of several enveloped viruses, such as SARS, MERS, and Ebola viruses. [Citation needed] This was discovered once all of the experiments had been carried out to completion. Those who were infected with COVID-19 showed significantly decreased serum calcium levels, both in terms of total and ionized calcium.Page, B. (2018).

Sufferers who were afflicted with illnesses caused by the SARS and Ebola viruses have previously demonstrated symptoms of hypocalcemia, and it is quite likely that COVID-19 patients will do the same. 22 The researchers showed that the calcium levels in the blood of critically ill patients were significantly higher than the calcium levels in the blood of healthy controls (68.20 mg/L as opposed to 63.55 mg/L). Patients who had severe COVID-19 were more likely to have an RBC count that was lower than normal (3.15 vs. 4.13, 1012/L), compared to patients who had normal COVID-19. It will be necessary to conduct additional research in order to verify the conclusions of this study.

Chromium, a heavy metal, has been found in a range of habitats, according to samples taken from the environment. In order to maintain a steady level of sugar, fat, and protein in the body, the metabolism of these macronutrients is dependent on the micronutrient insulin. According to the findings of a previous investigation, the amount of chromium found in the urine of diabetics is noticeably higher than that of people who do not have diabetes. Chromium has an effect not only on T and B cells, but also on macrophages, cytokines, and the immune system as a whole. This means that ingestion of chromium may result in hypersensitivity reactions. 26 There is a need for additional research into how the immunological dysfunction can be linked to the reported levels of chromium in COVID-19 patients who are very unwell or who have passed away. Patients diagnosed with severe COVID-19 typically have abnormalities in their lymphocytes as well as their cytokines. Cappellini *et al.*(2020) will publish their findings in the this year.

Transition metals are essential for all kinds of life, whether they are manganese, iron, copper, or zinc. Metal cofactors are essential for the proper functioning of around thirty percent of all enzymes. Manganese, iron, and zinc levels in the blood of individuals with COVID-19 were much lower than normal. This condition was relatively moderate Manganese levels were significantly lower than normal. According to the findings of this study, being deficient in vital nutrients is associated with an increased risk of illness as well as an increased risk of passing away28–30. Multiple investigations have led researchers to the conclusion that manganese plays an important part in both the innate immune system and antiviral defense. The introduction of viruses into cells triggers the activation of these signaling pathways, and manganese amplifies the activation of signaling pathways such as cGAS and STING. 28 Recent research has shown that COVID-19 hyperinflammation and an iron deficit in the body are linked to each other. The severity of COVID-19 as well as the likelihood of death has been linked by the researchers to a correlation between serum iron levels and the variable. According to the findings of our research, in 2012 COVID-19 went from a moderate state to a severe and critical state when serum iron levels were reduced32, 33. This development was reported by Hood *et al.* (2012). There is some evidence that the antiviral effects of zinc, which is a micronutrient, can help reduce the severity of respiratory infections caused by SARS-CoV-2. Increased susceptibility to pneumonia is associated with zinc deficiency, which lowers the immune system's ability to fight off infections at the cellular level. Because chloroquine is a zinc ionophore, it is one of the reasons that it is being repurposed so that it can be used in COVID-19. Because of the activity of the zinc metalloenzyme produced by the host, at least 36 distinct strains of SARS-CoV and SARS-CoV-2 are able to penetrate cells (ACE2). According to our findings, COVID-19 patients had lower blood levels of zinc, manganese, and iron, all of which were related with a more severe version of the disease. The correlation coefficients between these metals suggest that they could be utilized in conjunction with one another to combat disease (Zhou *et al.* 2020).

5 CONCLUSIONS AND RECOMMENDATION

According to the findings of this research, it is possible to draw the following conclusions:

5.1 Conclusions

1. Patients with -CoV-19 may lead to reduce the levels of WBCs and esppically in lymphocytes,
2. A rise in serum ferritin, D-dimer, and C-reactive protein levels. In Falluja, the vast majority of patients had blood types A and B.
3. Levels of d3 also decrese with increasing the severity of COVID 19
4. Calcium level have asignificant decrease also within critical case of covid 19
5. No significant was shown when we compared levels of iron in sever case and control groups.

5.2 Recommendations

1. Using another test concerning in clotting that formed accompanied with SARS-CoV-19 especially plasmin and clotting factor.
2. estimation of ACE especially in asthma case.

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