Original Article

Association of C-reactive protein and D- dimer in patients with covid 19

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Abstract

Coronaviruses are enveloped non-segmented positive sense RNA viruses belonging to the coronaviridae family and order Nidovirales and broadly distributed in humans and other mammals. The out break of Corona virus disease (COVID-19) has affected more than 174,5 millions people in most countries this number reported by WHO till 12 June 2021 at 7:19 a.m. with mortality rate of 4.02% and has become a major global health concern. This study includes (124) COVID-19 patients , 40 females and 84 males, their ages range from 25 - 65 years old . Thirty-two apparently healthy individual were taken as a control group.

As for measuring the concentration of C-reactive protein, the study showed that there was a high increase of C-reactive protein in patients with secondary and concomitant infection with the Corona virus, compared with the control group, and statistical analysis proved the existence of high significant differences and at the level of probability p (0.001).

D-dimer is the principal breakdown fragment of fibrin and is used as a biomarker of fibrin formation and degradation, the study have shown that Ddimer is a valuable marker of activation of coagulation and fibrinolysis. There is increasing evidence that SARS- CoV-2 induces, a cytokine storm that triggers the coagulation cascade, causing thrombotic complications especialy in sever cases . This is clinically relevant as the activation of the coagulation cascade is a common feature of disseminated intravascular coagulation (DIC) and adverse clinical outcomes in COVID-19 patients and appears to be more frequent than what observed in patients suffering from severe forms of SARS- CoV in 2003.

INTRODUCTION

Coronaviruses are enveloped non-segmented positive sense RNA viruses belonging to the family Coronaviridae and the order Nidovirales and broadly distributed in humans and other mammals. It causes illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARSCoV). A novel coronavirus (nCoV) is a new strain that has not been previously identified in humans. (1) They contain four major structural proteins on their surface: the membrane protein M, the envelope protein E, and the spike S. In fact, the projection of the spike on the virus surface causes the corona (Latin: crown) appearance. Inside the virion, a vacuum separating the inner core from the envelope was observed using cryo electron microscopy. These cores are formed by the genomic RNA associated with the nucleoprotein N. (2)

The immune response to the SARS-CoV-2 involves innate immune activation and antigen-specific responses of B and T cells. Protection from viral infection is mainly achieved by virus-neutralizing antibodies, a principle that applies to the vast majority of viral infections to which humans acquire robust immune protection due to infection or vaccination. It is urgent to develop vaccines aiming at the induction of protective immune responses, primarily through virus-neutralizing antibodies specific for SARS-CoV-2. (3)

C-reactive protein is a frequent diagnostic test that is primarily used to assess chronic inflammation, It has a 19-hour plasma half-life, It is produced without a memory response, and is a key protein in the acute phase response that appears in the blood between 6 and 10 hours after any tissue-damaging event. (4,5)

Although its presence in blood is linked to continuous inflammatory responses, even in patients with documented ongoing, substantial inflammation, it does not specifically deposit into any tissue or organ, Its fractional catabolic rate is also independent

of plasma concentration, indicating that the rapidly fluctuating blood concentration more closely represents the rate of its synthesis than that of its consumption. (5)

Baseline CRP levels in blood are said to be less than 10 ng/mL in normal, healthy people, with detected CRP levels below this cutoff being referred to as "high sensitivity CRP" results, Within 10-72 hours of the initiating cause, CRP blood levels (sometimes referred to as "conventional CRP" values) might increase 10-100 times, with higher levels corresponding to more severe disease, This can happen in cases of tissue trauma or disease, Although values between 10 and 50 ng/mL are indicative of a continuous, acute or chronic inflammatory response, but levels exceeding 100 ng/mL in any condition are indicative of fulminant inflammation and are linked to a bad prognosis for the disease, The U.S. Department of Health and Human Services' interpretation of the diagnostic importance of CRP guidelines explain the distinction between conventional and high sensitivity readings but only offer advice for conventional CRP levels. (5,6)

D-dimer is a biological marker of hemostatic problems as well as an indicator of intravascular thrombosis; it is an indirect sign of fibrinolysis and fibrin turnover, As a result of the fibrinolytic mechanism's systematic breakdown of vascular thrombi, D-dimer is a soluble byproduct of fibrin degradation, The D-dimer is therefore useful as a marker of activation of coagulation and fibrinolysis in a variety of clinical situations. (7)

D-dimer is the primary fibrin breakdown product and is utilized as a biomarker of fibrin synthesis and degradation, Research has revealed that D-dimer is an important indicator of activation of coagulation and fibrinolysis. (8)

D-dimer is frequently used for this indication since it has been thoroughly studied for ruling out the diagnosis of venous thromboembolism (VTE), Additionally, D-dimer has been tested for diagnosing and monitoring disseminated intravascular coagulation as well as other conditions where a patient is at a high risk of bleeding or thrombosis, These conditions include VTE patients, who should take anticoagulants for the shortest amount of time possible, The assay's limitations include a lack of clinical consistency and D-dimer rise in a number of clinical circumstances (age, pregnancy, and malignancy). (9)

Through the breakdown of cross-linked fibrin during fibrinolysis, D-dimer molecules are produced, Three enzymes are necessary for the production of D-dimers: thrombin, activated factor XIII (factor XIIIa), and plasmin, The process begins when the coagulation system's produced thrombin changes soluble fibrinogen into fibrin monomers, When thrombin cleaves fibrinopeptides from the N-terminal domain of the protein, these monomers transform into fibrin polymers through noncovalent interactions based on allosteric alterations in the protein, Fibrin is strengthened through interactions with factor XIII, which is activated by thrombin and subsequently cross-links the D domains of nearby fibrin monomers, The breakdown of the fibrin clot by plasma results in the production of the D-dimer molecule. (9,10)

The Control Group

The Healthy controls (HCs) group (Group A), which consists of 32 Iraqi individuals of the same sex and age as the patients, is not infected with COVID 19, Additionally, they had no history of smoking or drinking alcohol, and at the time of the sample, they were free of acute illnesses or infections. HCs were not specific for any prescribed medications, dietary restrictions, or other conditions that were not included.

Patients Group (COVID 19)

Group B The study was included 124 patients of covid 19 The age scope of the subjects (controls and patients) was 25 to 65. Between December 2021 and March 2022, the study was conducted at the Heet general hospital, a Ramadi teaching hospital in Al-Anbar Province. The history of treatment and way of life were taken into consideration when we collected the samples following clinical examination by the consulting physicians and approval from the patients.

Collection of Blood Samples

two ml of blood was placed in a tube containing sodium streat to estimate the D-dimer. These blood samples were taken from each patient and control using a venipuncture and a disposable 5 ml syringe. The remaining blood was placed in a gel tube and allowed to coagulate at place temperature (18–25 °C) for about 20 minutes. To collect serum, it was then centrifuged at 4000 x g for 10 minutes. The 2.5 ml of serum was divided into two separate aliquots. The estimation of the serum CRP level

Level of CRP.

The study showed that the patient group's CRP level was higher than that of the control group, This difference was statistically extremely significant (P. value 0.001) as shown in Figure

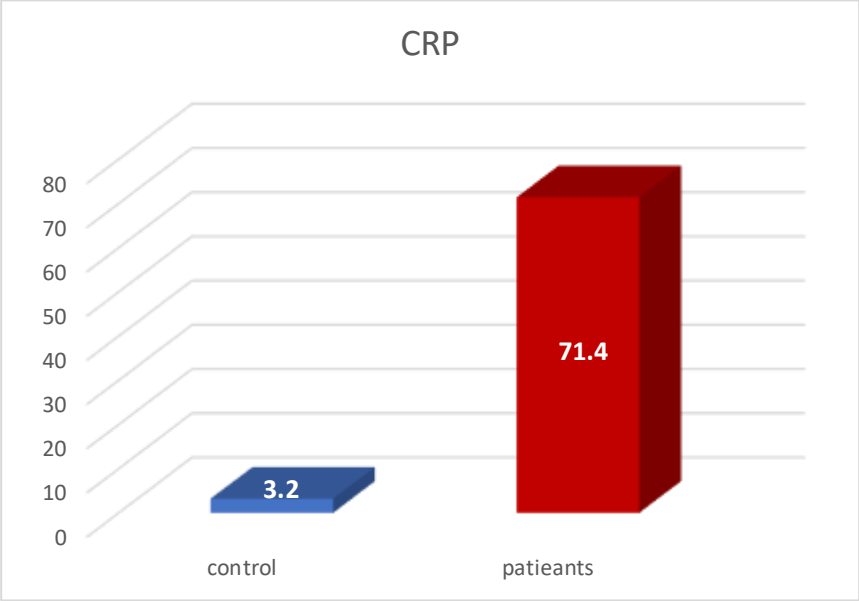

Figure 1: The mean of CRP level in serum of patients and control group.

The mean CRP level was greater in the sick group (71.4 mg/L and 3.2 mg/L, respectively) than the control group, this could be brought on by the pathological characteristics of COVID-19, The results of the current study showed a clear and significant increase in the level of CRP protein concentrations, Reactivity in patients infected with COVID19 and associated with secondary bacterial infections, As its concentration increases with increasing severity of injury. (11) The level of CRP was significantly different between the patients and the control group, which was caused by a positive association between the CRP level and the lung lesion in COVID-19 patients, When viral infections were cleared, the immune system reacted more forcefully by creating a variety of immunological molecules, including the generation of CRP, which has been directly connected to the induction of acute kidney damage and the severity of cardiac injury. (12).

The results of this study were consistent with other studies where CRP results were higher in corona patients and related to disease severity. (13)

Level of D-dimer.

This study demonstrates that there was a significant difference in D-dimer levels between patients and controls, as shown by the p.value (0.001) as shown in Figure

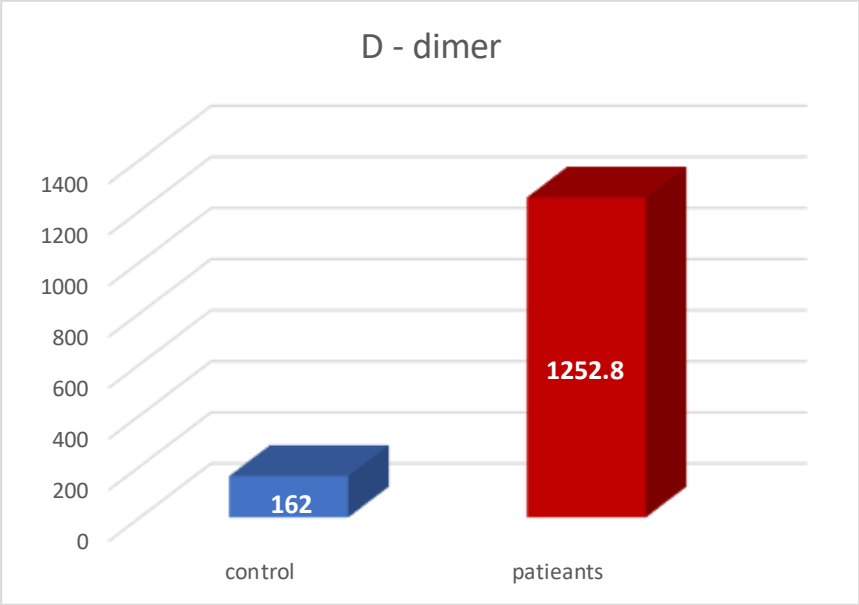

Figure 2: Level of D-dimer.

The mean D-dimer level was greater in the sick group (1252.8ng/mL and 162.0 ng/mL, respectively) than the control group, this could be brought on by the pathological characteristics of COVID-19, which include pulmonary edema, desquamation of pneumocytes, and cellular fibromyxoid exudates as well as diffuse alveolar destruction, and lymphocyte-dominated interstitial mononucle inflammatory infiltrates, which are strikingly similar to those observed in coronavirus infections caused by SARS and MERS, The elevated D-dimer levels were likely caused by the SARS-COV2 infection, which is thought to have enhanced inflammatory load and a hyperfibrinolysis condition. (14, 15)

The findings of this study were consistent with those of other studies. (16) .

Comparison of CRP level in patients.

The level of CRP was higher in patients with severe and critical infection than those with moderate and mild infection. The difference was statistically highly significant (p.value < 0.001) .

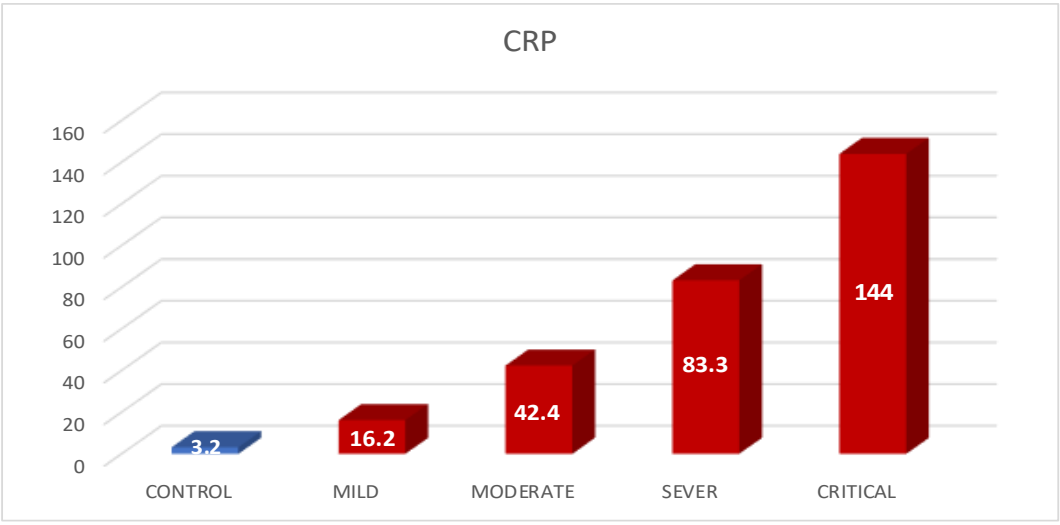

Figure 3: Comparison of CRP level in patients

A significant increase in CRP levels at the outset of an infection is one of the most significant inflammatory indicators, and a favorable correlation between growing CRP levels and early COVID-19 prediction has been shown to have high analytical precision, The overproduction of inflammatory cytokines in COVID-19 severe patients may be responsible for the high levels of CRP, Cytokines work to combat microorganisms, but when the immune system overreacts, lung tissue can be damaged, In COVID-19 patients, tissue damage and inflammatory cytokines both cause the production of CRP (3,5). In individuals with COVID-19, blood levels of CRP are a reliable way to gauge disease severity and forecast prognosis, The severity of COVID-19 pneumonia was positively linked with the amount of plasma CRP. The present study was similar to prior studies that found patients with severe illness courses had significantly higher levels of CRP than those with moderate disease courses, The proinflammatory cytokines (IL-6) were produced at significantly higher levels in participants with low vitamin D levels and high CRP compared to subjects with high vitamin D levels. (3,6) This study is identical to a previous study. (6)

Comparison of D-dimer level in patients.

The level of D-dimer was higher in patients with severe and critical infection than those with moderate and mild infection. The difference was statistically highly significant (p.value < 0.001) .

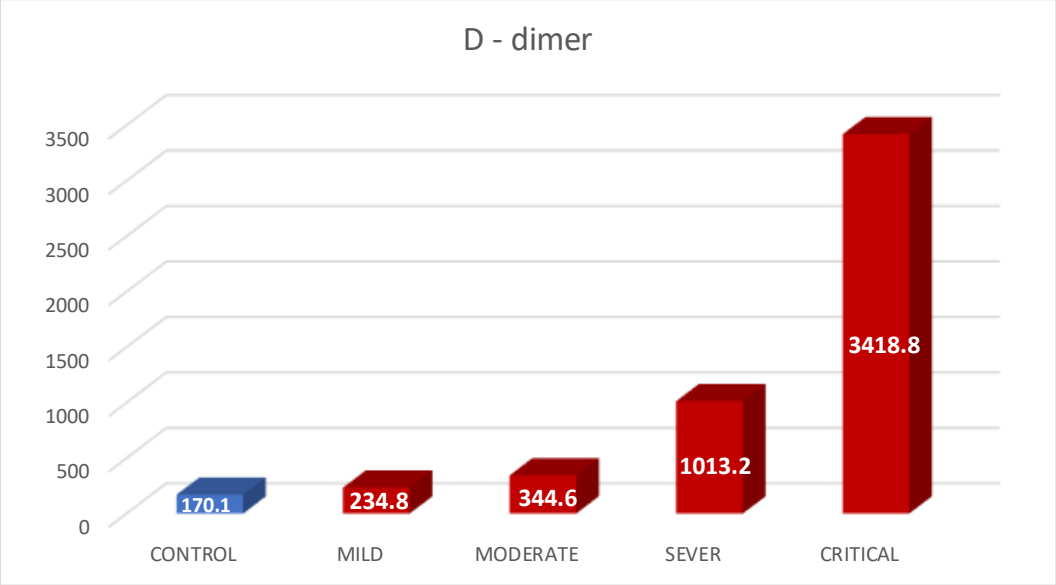

Figure 4: Comparison of D-dimer level in patients

The results of vitamin D were below the normal level in this investigation, however high D-dimer was seen in both severe and critical cases, Both the vitamin D and D-dimer values for the mild and moderate cases were within the usual range, Both the vitamin D and D- dimer readings for the control group were within the usual range, Due to the severity of the disease and vitamin D deficiency, this suggests an increased D-dimer. (7) An examination of patients with COVID-19 requires the laboratory test known as D-dimer measurement, There is mounting evidence that SARS CoV-2 can cause thrombotic problems by producing a cytokine storm that sets off the coagulation cascade in severe cases, The stimulation of the coagulation cascade, a frequent hallmark of disseminated intravascular coagulation (DIC), and the negative clinical outcomes in COVID-19 patients make this clinically significant. (14). The findings of the current investigation were comparable to those of prior studies that showed that patients with severe and critical COVID-19 infection had greater D-dimer levels than those with moderate and mild infection, The virus binds to a type of receptor found on several types of respiratory system and blood vessel cells as a result of acute inflammation that develops at the level of several systems in the body, This biological process causes an increase in the blood's ability to clot and the formation of blood clots, leading to an increase in the proportion of dimers in the blood. (14,17) This study is in agreement with a previous study. (18)

Conclusion

High D-dimer blood levels might be features of both COVID-19 infection. Previous reports focused on different thresholds of D-dimer blood levels upon admission to predict PE in COVID-19 patients . Both D-dimer and CRP blood levels are increased during the early stages of COVID-19 infection due to systemic inflammation. However, over time one would expect D-dimer and CRP blood levels to gradually decrease together as the COVID-19 infection resolves. Hence, one should measure the blood levels of both biomarkers over time, and if there is a discrepancy with an increase in D-dimer blood levels and a decrease in CRP blood levels, then VTE and PE should be suspected since this phenomenon may represent resolution of the COVID-19 infection, but also ongoing and possibly worsening VTE in the absence of full-dose anticoagulation therapy. This theory should be studied in large cohorts, but it is already easy to implement clinically.

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