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Impact of Post COVID-19 on patients and the role of D-Dimer & CRP in early diagnosis of the disease

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ABSTRACT

A novel coronavirus (CoV) named ‘2019-nCoV’ or ‘2019 novel coronavirus’ or ‘COVID-19’ by the World Health Organization (WHO) is in charge of the current outbreak of pneumonia that began at the beginning of December 2019 near in Wuhan City, Hubei Province, China.COVID-19 is a pathogenic virus. From the phylogenetic analysis carried out with obtainable full genome sequences, bats occur to be the COVID- 19 virus reservoir, but the intermediate host(s) has not been detected till now. Though three major areas of work already are ongoing in China to advise our awareness of the pathogenic origin of the outbreak. These include early inquiries of cases with symptoms occurring near Wuhan during December 2019, ecological sampling from the Huanan Wholesale Seafood Market as well as other area markets, and the collection of detailed reports of the point of origin and type of wildlife species marketed on the Huanan market and the destination of those animals after the market has been closed

The first symptoms are commonly recognized as fever, dry cough, tachypnea, and shortness of breath Although diarrhea was present in about 20–25% of patients with MERS-CoV or SARS-CoV infection, intestinal symptoms are rarely seen in patients with COVID-19. In another study, confusion, chest pain, vomiting, and nausea were also reported as COVID-19 symptoms.

ARS-CoV-2 can spread through both direct means (droplet and human-to-human transmission) and by indirect contact (contaminated objects and airborne contagion). Meanwhile, personal protective equipment (PPE) could also be the source of airborne infections .

The D-dimer is a by-product of the blood clotting and break-down process that can be measured via analysis of a blood sample. The most notable abnormalities among thrombotic markers were the rapid increase in D-dimer levels from day 9 after illness onset along with a rapid decrease in platelet counts beginning on day 12 among non-survivors.

A significant increase of CRP was found with levels on average 20 to 50 mg/L in patients with COVID-19. Elevated levels of CRP were observed up to 86% in severe COVID-19 patients. Patients with severe disease courses had a far elevated level of CRP than mild or non-severe patients

Chapter one

INTRODUCTION

A Brief History of the Coronavirus Outbreak

A novel coronavirus (CoV) named '2019-nCoV' or '2019 novel coronavirus' or 'COVID-19' by the World Health Organization (WHO) is in charge of the current outbreak of pneumonia that began at the beginning of December 2019 near in Wuhan City, Hubei Province, China.COVID-19 is a pathogenic virus. From the phylogenetic analysis carried out with obtainable full genome sequences, bats occur to be the COVID- 19 virus reservoir, but the intermediate host(s) has not been detected till now. Though three major areas of work already are ongoing in China to advise our awareness of the pathogenic origin of the outbreak. These include early inquiries of cases with symptoms occurring near Wuhan during December 2019, ecological sampling from the Huanan Wholesale Seafood Market as well as other area markets, and the collection of detailed reports of the point of origin and type of wildlife species marketed on the Huanan market and the destination of those animals after the market has been closed.[1]

Coronaviruses mostly cause gastrointestinal and respiratory tract infections and are inherently categorized into four major types: Gamma coronavirus, Delta coronavirus, Beta coronavirus, and Alphacoronavirus re-arrange from alpha to gamma. The first two types mainly infect birds, while the last two mostly infect mammals. Six types of human CoVs have been formally recognized. These comprise HCoVHKU1, HCoV-OC43, Middle East Respiratory Syndrome coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) which is the type of the Beta coronavirus, HCoV229E, and HCoV-NL63, which are the member of the Alphacoronavirus. Coronaviruses did not draw global concern until the 2003 SARS pandemic .preceded by the 2012 MERS .and most recently by the COVID-19 outbreaks. SARS-CoV and MERS-CoV are known to be extremely pathogenic and spread from bats to palm civets or dromedary camels and eventually to humans.[1]

COVID-19 is spread by dust particles and fomites while close unsafe touch between the infector and the infected individual. Airborne distribution has not been recorded for COVID-19 and is not known to be a significant transmission engine based on empirical evidence; although it can be imagined if such aerosol-generating practices are carried out in medical facilities. Fecal spreading has been seen in certain patients, and the active virus has been reported in a small number of clinical studies. Furthermore, the fecal-oral route does not seem to be a COVID-19 transmission engine; its function and relevance for COVID-19 need to be identified…[1]

Clinical Presentation

The incubation period of COVID-19 infection has been estimated to have a median of 5.1 days (95% CI; 4.5-5.8 days) with 97.5% of those who will develop symptoms doing so within 11 days of exposure (95% CI: 8.2 – 15.6 days). This has informed the time interval of 14 days for quarantining of potentially exposed individuals [(1)]. The ratio of asymptomatic to symptomatic infection is currently unknown, and there may be differences in the rates in children compared to adults. The largest studies from adults in China estimated that less than 1% of PCR confirmed cases had no symptoms. One large pediatric study however reported up to 13% of PCR confirmed infected children being asymptomatic. In contrast higher rates of PCR positive asymptomatic (or pre-symptomatic) people were described amongst passengers on board the Diamond Princess Cruise Ship. This is an area of great ongoing interest. Symptomatic COVID-19 infection usually presents as a respiratory syndrome, most commonly with fever and cough . Fever has been reported in up to 99% of people at some time during their illness, but importantly has been reported to be present at the time of hospital presentation in only 44% of patients, and at some time during the hospital admission in 89% (4). Other common symptoms are cough, dyspnoea, fatigue, anorexia, anosmia, myalgia, and confusion. Symptoms reported much less frequently Of those who require hospitalization, the median time from first symptoms to the onset of dyspnoea is 5 days (IQR 1-10),the median time to hospital admission is 7 days (IQR 4-8) and the median time to acute respiratory distress syndrome (ARDS) is 8 days (IQR 6-12) (2). Approximately one-quarter of patients who are hospitalized generally need transfer to the intensive care unit for the management of complications such as hypoxaemic respiratory failure or hypotension requiring vasopressor support. In a presentation, to the hospital, the most common laboratory feature of COVID-19 infection is lymphopenia (reported in 70.3% of cases). Radiologic imaging can reveal a clear chest or unilateral or bilateral consolidation or ground-glass opacity. Clinical features that have been identified more often in COVID-infected patients who have had a fatal outcome compared to those who survive are reports of dyspnoea at presentation (median 70.6% versus 24.7%, $p<0.001$).[2]

Diagnosis

Nasopharyngeal specimens or lower respiratory samples (sputum, bronchoscopy samples) sent for molecular detection of SARS-CoV-2 by PCR are currently the best means of specific diagnosis of COVID-19 in Australia. Faecal samples may also be PCR positive for COVID-19 but the role of the oral-faecal route for transmission remains unclear (8). Patients with more severe disease tend to have higher viral loads in respiratory samples. Mild cases have been shown to clear virus earlier with over 90% testing PCR negative by day 10 compared to severe cases who more often remain PCR positive beyond day 10 (9). Prolonged viral shedding up to 24 days after the onset of symptoms has been described in a Singaporean cohort (10). The virus has also been detected by PCR in asymptomatic patients with comparable viral loads to those still symptomatic..[2]

Clinical consequences

The first symptoms are commonly recognized as fever, dry cough, tachypnea, and shortness of breath Although diarrhea was present in about 20–25% of patients with MERS-CoV or SARS-CoV infection, intestinal symptoms are rarely seen in patients with COVID-19. In another study, confusion, chest pain, vomiting, and nausea were also reported as COVID-19 symptoms.

Other symptoms include sore throat, sneezing, nasal congestion, sputum production, anosmia and dyspepsia, rash on the skin, or discoloration of fingers or toes, and viral conjunctivitis. Some laboratory studies have shown the occurrence of cytokine storm, sepsis, and RNAaemia in COVID-19. Clinical chemistry studies have shown increases in lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine transaminase (ALT), C-reactive protein (CRP), creatine kinase (CK), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, D-dimer level, procalcitonin, urea, and creatinine. Decreases in hemoglobin, lymphocyte count, eosinophil count, and serum albumin have been detected in COVID-19 patients . The most common radiological findings in patients with COVID-19 were a ground-glass opacity in the lungs . Moreover, SARS-CoV-2 can affect the cardiovascular system [16], gastrointestinal tract , and can cause acute kidney failure. Moreover, evaluation of liver manifestations in 148 patients with COVID-19 indicated that more than one-third of the COVID-19 patients admitted to the hospital had an abnormal liver function, and these patients were hospitalized for a more extended period [21]. It must be mentioned that it is likely that a substantial number of asymptomatic patients can be carriers of the virus. The variable clinical manifestations and outcomes underline the importance of adhering to hygienic and preventive principles, in addition to finding and developing new sensitive diagnostic approaches and therapeutic options..[3]

Infection in children

Unlike adults, children with COVID-19 have milder symptoms and better clinical outcomes ; among the COVID-19 patients under 18 years of age, children under one year old seem to be at the highest risk of the severe form of the disease . Although early studies showed that children with COVID-19 were less likely to develop severe symptoms than other age groups, one new study has shown that children are as likely to develop COVID-19 as adults . So, prevention and finding appropriate treatment for children is as important as for adults. In one study, 1391 children with a median age of 6.7 years were surveyed, and 171 were diagnosed with COVID-19. Intensive Care Unit (ICU) and mechanical ventilation were needed for only three children, who had underlying conditions. By March 8th, 2020, one child with intussusception had died, 21 children remained in a stable condition in the ward, and 149 cases were discharged . It should be mentioned that recently scientists and clinicians have reported that young infants who were diagnosed with COVID-19, also had classic Kawasaki disease (KD) or a KD-like disease, which indicates that more investigation into the clinical manifestations of pediatric COVID-19 and its potential association with KD is needed..[3]

Transmission of COVID-19

ARS-CoV-2 can spread through both direct means (droplet and human-to-human transmission) and by indirect contact (contaminated objects and airborne contagion). Meanwhile, personal protective equipment (PPE) could also be the source of airborne infections . As mentioned before, the person-to-person spread of SARS-CoV-2 is supposed to occur mainly via respiratory droplets, when a patient coughs, sneezes, or even talks or sings. Droplets typically cannot traverse more than six feet (almost two meters) and remain in the air for a limited time. However, SARS-CoV-2 remains intact and contagious in droplets (less than five microns in diameter) and can be suspended in the air for up to three hours . Therefore, airborne isolation, room ventilation, and appropriate application of disinfectant (especially in toilets) might restrict the aerosol spread of the virus . COVID-19 can occur if a person touches a surface contaminated with SARS-CoV-2, and then the hands come into direct contact with mucous membranes such as the eyes, nose, or mouth . Thus, sufficient washing of hands with soap and water or hand sanitizers is recommended. The reported contagion rates from a patient with symptomatic infection vary by location and efficiency of infection control measures. Based on a joint WHO-China report, the rate of secondary COVID-19 infection ranged from one to five percent among tens of thousands of confirmed patients in China . The spread of SARS- CoV-2 from asymptomatic individuals (or individuals within the incubation period), without any radiological findings, has also been reported . Therefore, there is a need for improvements in rapid and sensitive diagnostic methods for detecting infected individuals…[3]

Covid-19 management

Management of mild COVID-19: symptomatic treatment

Patients with mild disease may present to an emergency unit, primary care/outpatient department, or be encountered during community outreach activities, such as home visits or by telemedicine, WHO recommends patients with mild COVID-19 be given symptomatic treatment such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration.[4]

Management of moderate COVID-19: pneumonia treatment

Patients with moderate disease may present to an emergency unit or primary care/outpatient department, or be encountered during community outreach activities, such as home visits or by telemedicine, WHO recommend that patients with suspected or confirmed moderate COVID-19 (pneumonia) be isolated to contain virus transmission. Patients with moderate illness may not require emergency interventions or hospitalization; however, isolation is necessary for all suspect or confirmed cases.[4]

Management of severe COVID-19: severe pneumonia treatment

recommend immediate administration of supplemental oxygen therapy to any patient with emergency signs during resuscitation to target SpO2 ≥ 94% and to any patient without emergency signs and hypoxaemia (i.e. stable hypoxaemic patient) to target SpO2 > 90% or ≥ 92–95% in pregnant women..[4]

Special therapies

- Paracetamol.
- Lopinavir-ritonavir.
- Remdesivir.
- Corticosteroids…[5]

Chapter two : materials and methods

1- D-dimer

is a fibrin degradation product, a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two D fragments of the fibrin protein joined by a cross-link.

The D-dimer is a by-product of the blood clotting and break-down process that can be measured via analysis of a blood sample. D-dimer is released when a blood clot begins to break down More specifically, platelets in the blood are connected to a D subunit. When blood clots form, the D group between two platelets form a bond..[11]

D-DIMER DIAGNOSTIC TEST

DEVICE NAME : **STA R Max®**

The STA R Max® is a fully automated multiparameter coagulometer using clotting (viscosity-based detection system), chromogenic and immunologic assays. STA R Max® is equipped with an **.**innovative software (STA Coag Expert®) designed to assist laboratory in accreditation[12]

Fig1: **STA R Max®** device

INTENDED USE

The STA®- Liatest® D-Dikit is an immuno-turbidimetric assay for the quantitative determination of D-dimer in venous plasma (in 3.2 % sodium citrate) for use on STA-R®, STA Compact ® and STA Satellite ® analyzers by professional laboratory personnel. The STA®-Liatest®D-Di is intended for use in conjunction with a clinical pretest probability (PTP) assessment model to exclude pulmonary embolism (PE) and deep venous thrombosis(DVT) in outpatients suspected of PE or DVT.[13]

•Fibrinolysis

The specific degradation of fibrin (i.e., fibrinolysis) is the reactive mechanism responding to the formation of fibrin (14).Plasmin is the fibrinolytic enzyme derived from the inactive plasminogen. Plasminogen is converted into plasmin by plasminogen activators. The main plasminogen activators are the tissue plasminogen activator (tPA) and the pro-urokinase which is activate dinto urokinase (UK) by, among others, the contact system of coagulation [13]

2- CRP

C-reactive protein (CRP) is a pentameric protein synthesized by the liver, whose level rises in response to inflammation. CRP is an acute-phase reactant protein that is primarily induced by the IL-6 action on the gene responsible for transcription of CRP during the acute phase of an inflammatory/infectious process.[14]

DEVICE NAME: The COBAS INTEGRA 400

The COBAS INTEGRA 400 (Roche Diagnostics GmbH) is a random access analyzer with a consolidated test menue for routine clinical chemistry, specific proteins, drugs of abuse screening and therapeutic drug monitoring (TDM) and different measuring technologies.[15]

Fig2: COBAS INTEGRA 400

Chapter three: Results

Table 1: D-dimer

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
D-dimer	Equal variances assumed	9.584	.004	2.151	38	.038	103.58000	48.14792	6.10963	201.05037
	Equal variances not assumed			2.151	19.058	.044	103.58000	48.14792	2.82595	204.33405

Table 2: CRP

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
CRP	Equal variances assumed	9.690	.004	2.303	38	.027	5.44750	2.36539	.65901	10.23599
	Equal variances not assumed			2.303	19.003	.033	5.44750	2.36539	.49672	10.39828

The most notable abnormalities among thrombotic markers were the rapid increase in D-dimer levels from day 9 after illness onset along with a rapid decrease in platelet counts beginning on day 12 among non-survivors aPTT, prothrombin time, and INR increased over time in the early mortality cohort , whereas no differences in fibrinogen levels were observed over the time course between non-survivors and survivors

43.9% of patients with raised D-dimer at admission compared with 18.5% of those with a normal D-dimer at admission developed a critical illness. Similarly, patients with elevated D-dimer at admission were more likely to require mechanical ventilation (29.9% v 13.9%)

The magnitude of D-dimer elevation at admission was found to be independently associated with risk of all these serious clinical outcomes. After controlling for age, sex, a defined list of co-morbidities and the use of a defined list of prescribed drugs, critical illness was found to be 1.8 times more likely if D-dimer was in the range 0.23-0.50 µg/ml (230-500 ng/ml) than if it were normal (< 0.23 µg/ml (230 ng/ml)), 3.1 times more likely if D-dimer was in the range 0.5-2.0 µg/ml (500-2000 ng/ml) and 5.6 times more likely if D-dimer at admission was > 2.0 µg/ml (2000 ng/ml)..

Chapter four

Discussion

In the present study, there is a significant correlation between D-dimer levels and disease severity stratified by the area of affected lungs on chest CT, oxygenation index, as well as clinical staging according to the interim guideline. In addition, a higher percentage of D-dimer elevation was seen in the present study than previously reported [2, 5]. This may be due to the higher percentage of severe/critically ill cases referred to our hospital, which is another demonstration of the correlation between D-dimer level and disease severity. This suggests that the assay may be used early as a marker of severity before chest .CT scans or as a complement to CT and clinical staging

In-hospital mortality was also associated with increased D-dimer levels, suggesting that the assay may be used as a single useful biomarker for clinical outcome in patients with COVID-19. Zhou et al. reported that D-dimer > 1 μg/ml is a risk for mortality [6]. The study objective, design, population, and statistical analysis of Zhou's study and those of ours are different. Zhou's study was a retrospective cohort study to describe risk factors for mortality and clinical course, which included patients who had been discharged or had died by January 31, 2020. The mortality rate was higher compared to that in our study (28.3% vs. 6.9%)..[6]

Significant differences between group1 (covid group) and group 2(control group) for D_dimer in table 1.

Evaluation of thrombotic biomarkers The most notable abnormalities among thrombotic markers were the rapid increase in D-dimer levels from day 9 after illness onset along with a rapid decrease in platelet counts beginning on day 12 among non-survivors .aPTT, prothrombin time, and INR increased over time in the early mortality cohort , whereas no differences in fibrinogen levels were observed over the time course between non-survivors and survivors ,so D-dimer levels are commonly elevated in patients infected with SARS-CoV-2. Significantly higher levels are found in those with critical illness and may be used as a prognostic marker for in- hospital mortality[7]

Thrombosis correlating to the severity of the infection

Severe acute respiratory syndrome coronavirus 2/coronavirus disease 2019 frequently induces hypercoagulability with both microangiopathy and local thrombus formation, and a systemic coagulation defect that leads to large vessel thrombosis and major thromboembolic complications, including pulmonary embolism in critically ill hospitalized patients. d-dimers and fibrinogen levels should be monitored, and all hospitalized patients should undergo thromboembolism prophylaxis with an increase in therapeutic anticoagulation in certain clinical situations.[7]

D-dimer level is associated with the severity of COVID-19

Abnormal coagulation function has been demonstrated to be involved in the disease progression of COVID-19. However, the association between D-dimer levels and the severity of COVID-19 is not clear. The study was aimed to investigate the association between D-dimer levels and the severity of COVID-19 based on a cohort study and meta-analysis.

In our cohort study, patients with severe disease were more likely to exhibit dysregulated coagulation function, and a significantly higher D-dimer level (median 1.8 μg/ml [interquartile range 0.9–4.6] vs 0.5 [0.3–1.1], $p < 0.001$) was found in severe cases than the mild ones, on admission. In the meta-analysis of 13 cohort studies (including the current study), patients with severe disease had an increase in mean D-dimer value by 0.91 (95% confidence interval, 0.51–1.31, $p < 0.001$) μg/ml compared to those with non-severe disease, and odds of severe infection was associated with D-dimer greater than 0.5 μg/ml (odds ratio = 5.78, 95% confidence interval, 2.16–15.44, $p < 0.001$) on admission. Conclusions: Patients with severe COVID-19 have a higher level of D-dimer than those with non-severe disease, and D-dimer greater than 0.5 μg/ml is associated with severe infection in patients with COVID-19.[8]

SARS-CoV-2/COVID-19 frequently induces hypercoagulability with inflammation driving increased levels of procoagulant clotting factors and disruption of the normal homeostasis of vascular endothelial cells resulting in microangiopathy, local thrombus formation, and a systemic coagulation defect leading to large vessel thrombosis and major thromboembolic complications including PE in critically ill hospitalized patients. In patients with infection-induced coagulopathies, a critical component of management is treating the underlying disease. In COVID-19, because we currently do not have a standard antiviral therapy, we believe some of the unique microvascular and macrovascular hypercoagulability clinician are observing represent thromboinflammatory responses to the continuing infection. As a result, sequential monitoring of coagulation tests every 2–3 days is recommended. Surveillance for development of VTE is important with heightened suspicion in patients with sudden decompensation not attributable to other factors. All hospitalized patients should receive VTE prophylaxis; higher than conventional doses of LMW heparin are currently being investigated in clinical trials, although many centers have adopted escalated or intermediate doses for VTE prophylaxis. Whether anticoagulation alone is sufficient to prevent these thrombotic events, especially those driven by endothelial dysfunction, is unknown. Additional strategies and studies to address all factors that result in microvascular and macrovascular thrombosis are needed.[7]

Significant differences between group1 (covid group) and group 2(control group) for CRP

We focused on the early phases of the disease and observed that CRP levels markedly improved over hospitalization in survivors but remained elevated in those with early mortality (Figure 2A). Elevated WBC and decreased lymphocyte counts correlated with early mortality (Figure 2B-C). While TNF- levels were elevated only at admission, IL-6 levels remained high in those with early mortality (Figure 2D-E). In comparison with the late mortality group, the patients from the early mortality group had higher levels of IL-6 .These data suggest that early death in patients with COVID-19 was associated with the activation of the inflammatory immune cascade, a Evaluation of thrombotic biomarkers The most notable abnormalities .phenomenon already evident at admission among thrombotic marker[10]

White blood cell (WBC), lymphocyte, and platelet counts , tumor necrosis factor- (TNF-), interleukin-6 , C-reactive protein (CRP), D-dimer, and fibrinogen levels, and international normalized ratio (INR), activated partial thromboplastin time (aPTT), and prothrombin time [10]

A significant increase of CRP was found with levels on average 20 to 50 mg/L in patients with COVID-19. Elevated levels of CRP were observed up to 86% in severe COVID-19 patients. Patients with severe disease courses had a far elevated level of CRP than mild or non-severe patients. For example, a study reported that patients with more severe symptoms had on average CRP concentration of 39.4 mg/L and patients with mild symptoms CRP concentration of 18.8 mg/L. 12 CRP was found at increased levels in the severe group at the initial stage than those in the mild group. 1 In another study, the mean concentration of CRP was significantly higher in severe patients (46 mg/L) than non-severe patients (23 mg/L). 21 The patients who died from COVID-19 had about 10 fold higher levels of CRP than the recovered patients (median 100 vs 9.6 mg/L). 16 A recent study showed that about 7.7% of non-severe COVID-19 patients were progressed to severe disease courses after hospitalization, 3 and compared to non-severe cases, the aggravated patients had significantly higher concentrations of CRP (median 43.8 vs 12.1 mg/L). A significant association was observed between CRP concentrations and the aggravation of non-severe patients with COVID-19..[9]

The elevated levels of CRP might be linked to the overproduction of inflammatory cytokines in severe patients with COVID-19. Cytokines fight against the microbes but when the immune system becomes hyperactive, it can damage lung tissue. Thus, CRP production is induced by inflammatory cytokines and by tissue destruction in patients with COVID-19. In conclusion, elevated level of CRP may be a valuable early marker in predicting the possibility of disease progression in non-severe patients with COVID-19, which can help health workers to identify those patients an early stage for early treatment.[9]

it was observed that patients with low oxygen saturation ($SpO2 \leq 90\%$) had significantly higher levels of CRP (median 76.5 mg/L) compared with patients with high oxygen saturation ($SpO2 > 90\%$) (median 12.7 mg/L), 22 indicating that more severe patients with lung damage have elevated levels of CRP. So, higher levels of CRP indicate more severe disease course-linked to lung injury and worse prognosis. CRP levels are correlated well with the severity of symptoms of patients with COVID-19; therefore, it may be The elevated .a suitable marker in assessing a patient's conditions together with other clinical findings levels of CRP might be linked to the overproduction of inflammatory cytokines in severe patients with COVID-19. Cytokines fight against the microbes but when the immune system becomes hyperactive, it

can damage lung tissue. Thus, CRP production is induced by inflammatory cytokines and by tissue destruction in patients with COVID-19. In conclusion, elevated level of CRP may be a valuable early marker in predicting the possibility of disease progression in non-severe patients with COVID-19, which can help health workers to identify those patients an early stage for early treatment. Besides, COVID-19 patients with elevated levels of CRP need close monitoring and treatment even though they did not develop symptoms to meet the criteria for the severe disease course. However, CRP levels in patients with COVID-19 who may progress from non-severe to severe cases need to be further studied in large-scale multicenter studies [9]

Conclusion

In conclusion, D-dimer levels are commonly elevated in patients infected with SARS-CoV-2. Significantly higher levels are found in those with critical illness and may be used as a prognostic marker for in-hospital mortality.

And it was observed that patients with low oxygen saturation ($SpO2 \leq 90\%$) had significantly higher levels of CRP (median 76.5 mg/L) compared with patients with high oxygen saturation ($SpO2 > 90\%$) (median 12.7 mg/L), 22 indicating that more severe patients with lung damage have elevated levels of CRP. So, higher levels of CRP indicate more severe disease course-linked to lung injury and worse prognosis.

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