High D-dimer and CRP Levels in an Asymptomatic COVID-19 Patient: A Case Report and Brief Literature Review

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ABSTRACT
SARS-CoV-2 is a highly transmittable virus and now declared as pandemic. Many of individuals infected by this novel coronavirus remain asymptomatic. The asymptomatic patients are challenging to manage because they could easily act as source of transmission and could also be at risk of worse outcome. Thrombosis is one of the factors associated with severe COVID-19 infection. In this report, we present a case of 60-year-old asymptomatic woman who was confirmed positive for COVID-19. Although asymptomatic, she had increased D-dimer and CRP level, which is associated with the risk of thrombosis. The patient was treated with standard regimen of oseltamivir, azithromycin, and vitamin B complex. Patient was given rivaroxaban 15 mg once a day for seven days in conjunction with elevated D-dimer level. On the last day of treatment, D-dimer level was decreased. The presence of high D-dimer in asymptomatic patients suggest that even with no symptoms, COVID-19 patients are at risk of worse outcome, for example, pulmonary embolism or venous thromboembolism due to prothrombic state induced by the infection. Thus, D-dimer and CRP monitoring are important in order to minimize the risk of thrombotic formation. Prophylactic anticoagulant might be given to patients with high risk of thrombotic events.

Keywords: SARS-CoV-2, Thrombotic, Coagulopathy, Inflammation, Anticoagulant

1. INTRODUCTION

COVID-19 still becomes major health problem. The infection was firstly found in December 2019 in China, then spread worldwide and declared as pandemic by WHO in March 2020. In Indonesia, COVID-19 is an ongoing battle. This novel coronavirus has infected more than 500.000 people and led to the death of more than 16.000 people. COVID-19 cases are dominated by asymptomatic patients. Individuals who are asymptomatic could be a source of transmission of SARS-CoV-2, and some of which are growing rapidly, and even lead to acute respiratory distress syndrome (ARDS) with a high case fatality.[1,2] Thrombosis plays an important role in the development of severe COVID-19 and could be identified by several biomarkers, including D-dimer as coagulation biomarker. Thrombosis is initiated by inflammation that could be identified using biomarker such as C-Reactive Protein (CRP). This report discusses an asymptomatic COVID-19 patient with high D-dimer and CRP.

2. CASE ILLUSTRATION

A 60-year-old woman was admitted to the COVID-19 Emergency Hospital, Wisma Atlet Kemayoran, with no symptoms of COVID-19. She was tested positive for 3 days prior to her hospital visit. Upon admission, she was compos mentis with normal vital signs (blood pressure: 120/80 mmHg; heart rate: 82 bpm; temperature: 36.7^{O}C; SpO_2: 98% room air). She was then admitted to the ward for ten days and given standard therapy, including 75 mg of Oseltamivir twice a day for seven days, 500 mg of azithromycin once a day for five days, and one tab of vitamin B complex twice a day. Patient was given 15 mg of oral anticoagulant rivaroxaban once a day for seven days due to her elevated level of D-dimer.

The patient's condition was monitored as stable and showed no additional symptoms during her stay as shown in Table 1. Laboratory examination and chest x-ray were done on the first and last day of hospital stay as shown in Table 2, Table 3, and Figure 1. D-dimer and C-Reactive Protein (CRP) test results showed an increase on the initial day of treatment, namely 807.7 ng/mL and 48.48 mg/L, and then they decreased on the last day of treatment to 390 ng/mL and 0.62 mg/L. Chest X-Ray was done at the first day and showed an increase in bronchovascular features that tend to be normal on the last day of hospital stay. The patient was discharged from hospital after ten days of treatment, after PCR swab test showed negative result.

Table 1. Vital signs and symptoms monitoring

Result	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**
Oxygen saturation	98-99%	98-99%	98-99%	98-99%	98-99%	a98-99%	98-99%	98-99%	98-99%	98-99%
Blood pressure	130/80 mmhg	120/70 mmhg	120/80 mmhg	130/70 mmhg	120/80 mmhg	130/80 mmhg	120/70 mmhg	120/70 mmhg	120/80 mmhg	130/80 mmhg
Heart rate	88 bpm	86 bpm	83 bpm	84 bpm	85 bpm	84 bpm	84 bpm	86 bpm	82 bpm	84 bpm
Respiratory rate	18-20 bpm	18-20 bpm	16-18 bpm	16-18 bpm	16-18 bpm	16-18 bpm	16-18 bpm	16-18 bpm	16-18 bpm	16-18 bpm
Temperature	36.7^{0}C	36.5^{0}C	36.8^{0}C	36.4^{0}C	36.5^{0}C	36.6^{0}C	36.6^{0}C	36.7^{0}C	36.8^{0}C	36.6^{0}C
Symptoms	None	None	None	None	None	None	None	None	None	None

Table 2. Complete blood count examination

Variable	Day 1	Day 3	Day 10	Normal value
Hemoglobin	13.7	12.4	11.9	12-14 g/dL
Red Blood Cell Count	4.69	4.32	3.99	4 – 5 x 10^6/uL
Hematocrit	42	36	36.2	37 - 43 %
White Blood Cell Count	6.28	8.2	5.5	5 – 10 x 10^6/uL
Neutrophil	54	56	60	50 – 70 %
Eosinophil	1	0	1	1 – 3 %
Basophil	0	0	0	0 – 1 %
Lymphocyte	35	36	32	20 – 40 %
Monocyte	10	8	4	2 – 8 %
Platelets	241	271	189	150-5000 x 10^3/uL
ESR	20	28	32	0 -15 mm/hour
MCV	89	85.2	90.7	82 – 92 %
MCH	29	29.2	28.8	27 – 31 %
MCHC	33	34.3	31.8	32 – 36 %

Table 3. Serologic, coagulation, and other laboratory examinations

Variable	Day 1	Day 10	Normal value
AST	37	28	5-34 U/L
ALT	47	47	0-50 U/L
CRP	48.48	0.62	0 – 5 mg/L
D-dimer	807.7	390	<500 ng/mL
PCR Test	Positive	Negative	

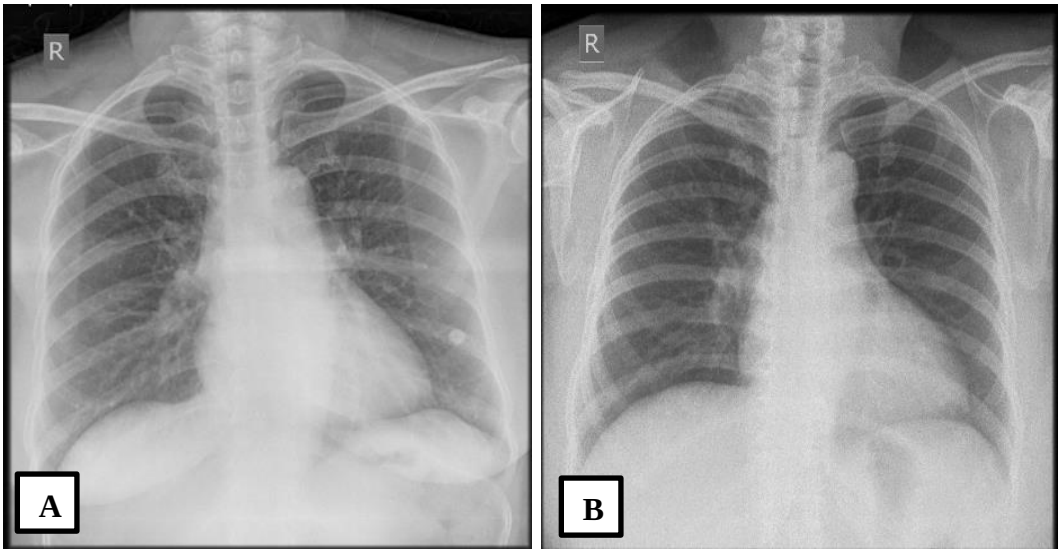

Figure 1. Radiological imaging: (**A)** Radiological imaging on the first day of treatment; and **(B)** Radiological imaging on the last day of treatment.

3. DISCUSSION

SARS-CoV-2 infection is similar to other kinds of coronavirus including SARS-CoV and MERS-CoV. Although COVID-19 has lower mortality (2.08%) compared to SARS-CoV (10.87%) and MERS-CoV (34.77%), it is more contagious.[1] Clinical manifestation of COVID-19 varies but typically characterized by fever or cough, although in some cases, it might be asymptomatic.[2] Many viral infections are asymptomatic or with mild symptoms, including influenza, SARS-CoV-1, -2, or MERS-CoV.[3] This could be caused by many factors such as type of virus, genetic background, or individual adaptive immunity to the virus.[4] Patients might also present as asymptomatic because they were treated and detected during their incubation or pre-symptomatic period. In this case, patients showed no symptoms and signs from her first day of admission up to her discharge. During hospitalization or after being discharged, the signs and symptoms might show, and it could cause death with pulmonary embolism as the most common symptom.[5]

Prevalence of COVID-19 patients in China showed that 13% to 30% of total population was asymptomatic.[6,7] Asymptomatic patients have lower viral load than symptomatic patients.[8] In this report, the patient was a 60-year-old woman, similar to a report from Ferrari et al. that found that the average women infected with SARS-CoV-2 were 61 years old. Older adults are at higher risk of infection, including COVID-19, due to decreased immune system.[9] Fernandez et al. showed that gender was not a significant parameter to COVID-19, but the ACE-2 receptor activity, which played role in viral entry to the cell, was found higher in older women compare to younger women.[10] Older patients are at higher risk of severe infection. Thus, the treatment should be done cautiously.[11]

ESR levels were elevated, from 20 mm/hour on the first day to 32 mm/hour on the last day. Ge et al. also reported elevated ESR in 84.8%.[12] Although ESR is less specific in COVID-19 infection, ESR level should be considered in determining patient's severity.[13]

Patients' D-dimer level were elevated to 807.7 ng/ml. High D-dimer is a serious problem in COVID-19 and should be concerned due to high mortality. Increased D-dimers at the time of patients' initial admission were found to have an 18-fold risk of death compared to patients with normal D-dimer levels.[14]

D-dimer is associated with high fatality rate. Zhou et al. reported that D-dimer level of >1000 ng/ml was found related to poor prognosis in COVID-19 patients. Multivariate analysis showed that

increased hospital death was related to high D-dimer level of >1000 ng/ml (OR 18.42(2.64-128.55 CI 95%, p=0.03).[14]

The presence of thrombosis in patients with COVID-19 remain uncertain. Deep vein thrombosis (DVT) and pulmonary embolism (PE) was found to be 20.5%, and 11.4% respectively in SARS cases.[15] Thromboembolic formation was seen in pathological studies from autopsy or biopsy in SARS and MERS infection.[16,17] D-dimers are currently being developed as one of the parameters of routine examinations and should be done serially to detect thromboembolic formation.

The cause of death due to COVID-19 was determined based on post mortem data analysis, and showed that thrombus (macrothrombus or microthrombus) was the cause of death.[18] Thrombus was found in pulmonary small vessels, which were consistent with an increase in macrothrombus as DVT and pulmonary embolism. SARS-CoV-2 causes endothelial dysfunction which will damage organs. The presence of pulmonary embolism, DVT, and microthrombus events are the main causes of death caused by COVID-19.[19,20] Some histological literature suggests the cause of death is thrombotic heterogeneity which indicates clinical manifestations of the disease, including VTE and PE, despite the anticoagulant therapy.

Thrombosis is resulted in the imbalance of Virchow's triad which consists of blood vessels, blood flow, and hypercoagulability.[21] Viral infection could impair coagulation cascade by inducing procoagulant state.[22] Inflammation of lung parenchymal cells and endothelial cells of pulmonary blood vessel will induce the release of procoagulant factors. It will increase coagulation cascade and lead to thrombosis and fibrin disposition on pulmonal vessels. Hyper inflammation will also impair the endothelial cells.[23]

Clot formation in COVID-19 patients is suggested to be fast and difficult to degrade. Deposition of complement system component, such as C5b-9 in affected blood vessels of COVID-19 patients, is likely related to pro-thrombotic mechanism. Neutrophil extracellular traps (NETs) were also found on autopsy of COVID-19 patients. NETs are associated with high circulating levels of free DNA from histones, which activate the prothrombotic pathways, resulting in increased thrombin production. Spike protein of SARS-CoV-2 was observed to have higher affinity to CD147, glycoprotein membrane, and extracellular metalloproteinase matrix that could induce expression of various hematopoietic cells, which were associated with thrombosis mechanism and inflammation in arteries and veins.[24]

Hypoxemia will also occur in COVID-19 patients. This condition will cause vasoconstriction and inflammation. Hypoxemic conditions will activate hypoxia inducible factors which will activate cytokines, tissue factor, and Plasminogen activator inhibitor-1 (PAI-1) which can cause thrombosis.[25] COVID-19 infection would increase production of proinflammation cytokines, such as tumor necrosis factor (TNF)-α, IL-1β, monocyte chemoattractant protein (MCP)-1, and Damage-Associated Molecular Patterns (DAMPs), which might result in coagulation impairment in severe infection. Increased TNF-related apoptosis induces ligand (TRAIL) and stimulates lymphocytes apoptosis, resulting in lymphoid cells depletion in lymph nodes which manifest as lymphopenia that is commonly seen in SARS-CoV-1 and -2 infections.[26] Etiology of pulmonary thrombosis in COVID-19 patients were inflammation of endothelial cells, impairment of blood flow due to parenchymal response, imbalance of Virchow's triad in lung, and pulmonary emboli due to complication of DVT.[27]

The relationship between D-dimer levels and COVID-19 may fluctuate along with the development of the disease. High D-dimer levels in COVID-19 patients are associated with the presence of inflammation, which can limit its role in predicting the presence of a thrombotic state. Although D-dimer levels correlate with inflammatory markers and tend to normalize at the healing stage in the majority of patients, this anomalous rise may be an indicator of active anticoagulant therapy. The increase in D-dimer is followed by an increase in CRP level, which is a diagnostic marker of ongoing inflammatory processes. CRP will begin to appear in the blood 6-10 hours after tissue damage, with plasma half-life of 19 hours. CRP is produced without memory response.[2,28,29]

Detection of CRP levels can be associated with a sustained inflammatory response and does not selectively accumulate into tissues or organs. CRP levels in COVID-19 were varied among reports.

In the case, CRP level was elevated to 48.48 mg/L. Zhang et al. reported that 140 hospitalized COVID-19 patients with SARS-CoV-2 infection had various CRP levels, from 28.7 μg/mL in the non-severe group (n = 82; range, 9.5-52.1 μg/mL) to 47.6 μg/mL in the severe group (n = 56; range, 20.6–87.1 μg/mL).[30] Higher CRP levels were found in viral infections that coexist with the presence of bacterial infection, and this result has been used to help determine antibiotic therapy. [2,28,29]

On the last day of treatment, the 60-year-old patient's D-dimer level decreased to 390 ng/ml, and the CRP level decreased to 0.62 mg/l. The decrease in D-dimer and CRP levels indicates a gradually improving inflammatory process. Postero-Anterior (PA) chest X-ray examination was performed before and after treatment of the patient. Although it has a lower sensitivity than CT scan (69%), the chest X-ray is the initial examination which plays an important role, especially in health facilities that does not have a CT scan. CT scan is recommended for asymptomatic patients with COVID-19 pneumonia. CT scan plays an important role in early detection, observation, and evaluation of disease in COVID-19.[31] In this case, chest X-ray on the first day of treatment showed that there was an increase in bronchovascular features that tended to improve after treatment. In asymptomatic patients, it was found that 43.9% had normal chest radiographs, and 56.1% had abnormal results with the highest percentage of ground glass opacities (39%).[32]

Siddiqi et al. classified the course of COVID-19 infection into 3 degrees. Grade I or mild is the initial infection stage where viral response phase occurs. In this phase, SARS-CoV-2 will replicate in host cells, mainly the respiratory system. Lymphopenia may presence in this phase. Grade II or moderate, commonly called the pulmonary phase, is divided into two, namely stage IIa that is without hypoxia and IIb with hypoxia. At this stage, the host inflammatory response phase occurs. The replicating virus will cause inflammation, causing symptoms depending on the location of the inflammation, such as fever or coughing and tightness. At this stage, laboratory profile will show an increased inflammatory profile and one of them is the coagulation profile. In grade III or severe, systemic hyperinflammation will result in damage to all organs and the patient will fall into a critical condition, so that an increase in the profile of infection, inflammation, and coagulation could be found and a picture of lung damage could also be found on a CT scan. This classification could help determine the appropriate treatment based on a patient's infection stage. In our case, there was an increase in D-dimer and CRP level in the absence of clinical symptoms, so it was possible that the patient was in asymptomatic moderate grade (grade IIA).[33]

Based on the relatively high levels of D-dimer at the start of the infection, the patient was given anticoagulant. In COVID-19 patients, prevention and treatment of thrombus must be considered. The risk of bleeding is assessed using the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) scoring.[34] The scoring can also determine the safety of anticoagulant therapy administration for the patient. The patient's IMPROVE score was 1.5, so anticoagulant therapy was safe to administer. It is not recommended to give anticoagulants if IMPROVE score is >7, because of the risk of bleeding. In Indonesia, prophylactic anticoagulant is given to moderate patients and some mild patients based on the D-dimer levels. The recommended prophylactic anticoagulant is Low Molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) at a dose of 40 mg of LMWH subcutaneously once a day, or 5000 units of UFH subcutaneously twice a day. Prophylactic anticoagulant administration is given while the patient is being hospitalized, with monitoring of anticoagulant side effects such as bleeding or other complications. In patients in critical condition, 40 mg of enoxaparin subcutaneously twice a day or 7500 subcutaneous units of UFH thrice a day are given as prophylactic anticoagulant.[35]

The administration of UFH and LMWH is more recommended compared to direct oral anticoagulant (DOAC) in symptomatic COVID-19 patients due to anti-inflammatory effects by protecting endothelial cells and inhibiting the binding of the spike glycoprotein structure of SARS-CoV-2 with ACE2 receptors in the lungs and alveoli. The patient in this report was treated with anticoagulant therapy rivaroxaban supported with inhibition of factor Xa.[23] DOAC administration also has anti-inflammatory effects by different mechanisms. Factor Xa is involved in cellular activity, including inflammation, endothelial revascularization, and tissue fibrosis. Much of this Factor Xa activity is

mediated via the PAR-1 and PAR-2 genes.[36] Furthermore, in the vascular endothelium, thrombin is able to mobilize adhesive molecules to the endothelial surface and stimulate cytokine production.[37] PAR-1 has been shown to mediate most of the pro-inflammatory effects of thrombin.[36] In our case, administration of rivaroxaban also reduced the level of inflammation, as seen from the decreased levels of CRP as a parameter of inflammation. Specific inflammatory role in COVID-19 is not yet clear. There are several things that need to be considered and need further study.

Rivaroxaban was given before the recommendation of the Indonesian Doctors Association regarding guidelines for administering anticoagulant therapy in symptomatic COVID-19 patients. In the asymptomatic group, there are no recommendations regarding prophylactic anticoagulant administration in inpatient care or outpatient care as prophylactic drugs that need further research.

4. CONCLUSION

Clinical and laboratory monitoring in asymptomatic patients are important. D-dimer and CRP should be monitored as indicators of coagulopathy and inflammation disorders. D-dimer examination should be done serially to monitor the presence of a thrombosis which could turn severe anytime. Other tests such as PT, APTT, and Fibrinogen are needed to further evaluate coagulopathy disorder. In asymptomatic patients, coagulopathy examinations are recommended to be done due to the presence of thrombotic events that may occurred in various conditions of COVID-19. The coagulopathy in COVID-19 patients is not completely understood, so it needs further study on the relationship between COVID-19 and the coagulation factors, which will result in thrombosis events. The administration of rivaroxaban as a prophylactic anticoagulant in mild COVID-19 patients with an increase in D-dimer or moderate degree with no respiratory function insufficiency needs further research, considering the results of our case report showed an improvement in the D-dimer value and CRP. Anticoagulant can be administered as early as possible to reduce the mortality caused by thrombosis process. However, the interaction between oseltamivir and anticoagulants such as rivaroxaban requires further research or reporting of related data.

5. Disclosure

The author reports no conflicts of interest in this work.

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