PNEUMONIA: Natural History Laboratory Abnormality In COVID-19

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***Abstract:Introduction:** COVID19 is a new disease caused by the SARS CoV-2 virus which became pandemic in 2019. In October 2020, COVID 19 cases in Indonesia continued to increase, reaching 304,007 cases. The mortality rate of this disease is 3.6%. This disease shows many symptoms such as asymptomatic, fever, cough, diarrhoea, severe shortness of breath.*

***Case:** 53 years-old man with fever for five days with cough, sore throat, and tightness. Physical examination revealed a temperature of 38 °C and bilateral lung crackles with ground-glass opacity of the right lung in pulmonary CT scan. PCR results obtained positive SARS-CoV 2.*

***Discussion:** In the early phase of COVID19 infection, complete peripheral blood tests tended to be normal with a mild increase in CRP. When ARDS occurs, there is a significant decrease in absolute lymphocyte, and increased CRP levels. The decreased Hb levels accompanied by increased LDH is suspected hemolysis of erythrocyte. Other laboratory examination shows an increase of acute phase reactants such as D-dimers, fibrinogen, and ferritin that indicate a severe inflammatory state. By the progression of the disease, laboratory abnormality such as decreased absolute lymphocytes and increased inflammatory markers happened on the 12th day after symptoms.*

***Key-words:** pneumonia, COVID-19, ARDS*

***Key Messages: Abbreviations:** ARDS = acute respiratory distress syndrome, CoV = coronavirus, COVID-19 = novel coronavirus 2019, FiO2 = fraction of inspired oxygen, ICU = intensive care unit, PCR= polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2*

1. INTRODUCTION:

Coronavirus disease 2019 (COVID-19) is a disease caused by infection of the new type of beta coronavirus that became pandemic in 2019. On February 11th, 2020, the World Health Organization named the novel virus as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1,2] The first epidemiology shows that 66% of patients expose to the seafood market or live market in Wuhan, Hubei Province of China. Based on epidemiological data up to February 12th 2020, the worldwide mortality rate is 2.1%, while specifically in the Wuhan is 4.9%.[3,4] Protein S or spike protein is one of the viral antigen proteins that play a role in the entry of viruses into the cell host. SARS-CoV-2 survives approximately 72 hours on plastic

and stainless steel surfaces. Transmission occurs primarily via droplets, direct and indirect contact, and possibly airborne. SARS-CoV-2 could infect the gastrointestinal tract based on the report that there were positive biopsy results from epithelial cells of the stomach, duodenum, and rectum. The incubation period of this virus between 2-14 days. [4,5]

Case History:

Patient with fever since five days before treated in hospital accompanied by cough, sore throat, and tightness. The CT scan result from the previous hospital showed ground-glass opacity of the right lung. The patient has contact with a patient who has tested positive for COVID-19. On the physical examination, the blood pressure 141/68 mmHg, temperature 38 ° C, breath rate 17x / minute, with 99% oxygen saturation, and bilateral crackles on lung auscultation. There is no previous history of chronic disease. The chest X-ray showed inhomogeneous consolidation in the midfield of the right lung with bilateral paracardial infiltrates according to pneumonia. The patient was diagnosed with a confirmed case of COVID-19 with positive PCR results. This patient laboratory examination shows a slight increase in CRP with no other laboratory abnormalities. After nine days of symptoms, the patient's condition worsened with severe cough, shortness of breath increased and high frequency of breath (35-40x/minute). The oxygen saturation decreased to 93% with an increased consolidated lung in pulmonary CT scan. According to the criteria, the patient was diagnosed as mild ARDS with a PaO2 / FiO2 ratio of 215mmHg (200-300 mmHg). The patient was transferred to the intensive care unit and treated with 3L oxygen nasal cannula per minute. In laboratory tests, there was a decrease in haemoglobin levels and a significant decrease in absolute lymphocyte count. Other laboratory abnormalities occur such as a significant increased of CRP, increased ferritin, and increased liver transaminase enzyme twice of upper limit normal. Also, there is a decrease in sodium levels accompanied by coagulation disorders characterized by increased levels of fibrinogen and D-dimer. The blood gas analysis indicated respiratory alkalosis with an increase in pH level and low pCO2. Patients have treated with Zithromax 500 mg once a day, 1000 mg ascorbic acid twice a day, zinc 20 mg once a day, hydroxychloroquine 200mg twice a day, actemra 600mg once a day, with tamiflu 150mg twice day. The 14th day of disease after treatment showed that the PCR COVID-19 results were positive with a reactive of IgM and IgG antibodies. The patient condition became better on the 17th day and allowed to go home on the 21st day.

Type of examination	Result		
Imunoserology	**04/14/2020**	**04/21/2020**	**04/25/2020**
SARS CoV-2 Real time PCR			
Sample	Nasopharyngeal and oropharyngeal swab		
Result	**Positive**	**Positive**	**Positive**
		04/27/20	
POCT Antibodi SARS CoV-2			
Antibodi SARS CoV-2 IgG		**Reactive**	
Antibodi SARS CoV-2 IgM		**Reactive**	

Type of examination	Result				Unit	Reference value
Darah Perifer Lengkap	**4/13/20**	**4/19/20**		**4/22/20**		

Haemoglobin	14.1	**12.7**		**12.8**	g/dL	13.0 – 17.0
Hematocrit	**38.8**	**35.3**		**35.6**	%	40.0 – 50.0
Erythrocyte	**4.43**	**4.02**		**4.00**	$10^6/\mu L$	4.50 – 5.50
MCV	87.6	87.8		89.0	fL	83.0 – 101.0
MCH	31.8	31.6		32.0	pg	27.0 – 32.0
MCHC	**36.3**	**36.0**		**36.0**	g/dL	31.5 – 34.5
Thrombocyte	155	259		302	$10^3/\mu L$	150 – 410
Leucocyte	5.92	8.41		9.12	$10^3/\mu L$	4.00 – 10.00
Diff count						
Basophil	0.2	0.1		0.2	%	0 – 2
Eosinophil	0.0	0.0		0.5	%	1 – 6
Neutrophil	62.6	**80.8**		74.3	%	40.0 – 80.0
Lymphocyte	27.7	**12.7**		**15**	%	20 – 40
Monocyte	9.5	6.4		10	%	2 – 10
RDW-CV	12.4	12.1		12.2		11.6 -14.0
RDW-SD	39.8	39.4		39.8		
Neutrophil to lymphocyte ratio						
Absolute neutrophil	3.71	6.79		6.77	$10^3/\mu L$	1.70-7.50
Absolute lymphocyte	1.64	1.07		1.37	$10^3/\mu L$	1.00-3.20
NLR	2.26	**6.35**		**4.94**		
Hemostasis			**4/21/20**			
PT patient			13.4		Detik	11.6-14.5
control			14.4		Detik	
Fibrinogen level			**700**		mg/dL	176-430
d-Dimer			**1080**		µg/L	<500
Blood chemistry	**4/13/20**	**4/15/20**	**4/21/20**	**4/22/20**		
AST	**41**			**69**	U/L	5.00-34.00
ALT	28			**93**	U/L	0.00-55.00
Ferritin		**688.20**	**2277.08**		ng/mL	20.00-500.00
LDH				**319**	mg/dL	125-220
Electrolytes	**4/13/20**	**4/17/20**				
Natrium	**133**	**128**			mEq/L	136-145
Kalium	3.6	3.8			mEq/L	3.5-5.1
Chloride	103.2	99.9			mEq/L	98-107

Blood gas analysis		4/19/20				
pH		7.524				7.350-7.450
pCO2		29.4			mmHg	35.00-45.00
pO2		186.7			mmHg	75.00-100.00
HCO3		24.4			mmol/L	21.00-25.00
Total CO2		25.3			mmol/L	21.00-27.00
Base Excess		3.00			mmol/L	-2.5 - +2.5
O2 saturation		98.8			%	95-98
Standard HCO3		27.1			mmol/L	22.0-24.0
Standard Base Excess		1.4			mmol/L	
Immunoserology	4/13/20	4/15/20	4/19/20	4/21/20		
CRP	7.1	10.3	75.4	95.5	ng/L	<5

2. DISCUSSION

When the patient was admitted, there were so many symptom like fever, cough and sore throat, with the ground glass opacity of the right lung. His profession is internal medicine doctors who has high risk contact with COVID19 patients. Based on the early warning score criteria that is mentioned by Song et al, this patient score was 12 which proper with highly suspected COVID19 infection. This patient was diagnosed as PDP according to the operational definition stated in the Guidelines for the prevention and control of coronavirus disease (COVID19).[6-8] In accordance with the disease progression of COVID19, the patient was in the early phase of the disease (7-14 days) where the symptoms of the disease are mild without significant laboratory abnormalities.

The results of the patient's swab showed that SARS-CoV-2 was detected on the 7th day after symptoms and still detected until the 18th day. In addition, IgG and IgM antibodies were reactive on day 21st and still reactive until the fifth week. The laboratory result of PCR and immunoserology was appropriate with the course of COVID19 infection. It has been reported that SARS-CoV-2 could be detected in nasopharyngeal swab from the first week to the sixth week after symptoms appear. The IgM and IgG antibodies increased simultaneously and could be detected in the second week until the sixth week.[9] This patient was confirmed as a case of COVID19. Positive nasopharyngeal swab with reactive IgM and IgG antibodies indicating active infection phase.[10]

On the 9th day of treatment, the patient's condition worsened. According to the clinical criteria stated by the Indonesian Lung Doctors Association, the patient was appropriate with severe pneumonia accompanied by mild ARDS with a ratio of PaO2 / FiO2 215mmHg (<300 mmHg).[1] According to the blood gas analysis result, this patient has respiratory alkalosis. This condition may be caused by hyperventilation as compensation for mild ARDS in the inflammatory phase of COVID-19 patients.

In this patient, there was a significant reduction in absolute erythrocyte count followed by a decrease in haemoglobin levels compared to baseline, see Figure 1. The decreased of absolute erythrocyte and haemoglobin levels in COVID19 infection has been reported in an epidemiological study by Chen et al that cited by Wenzhong et al, in 99 patients with pneumonia confirmed COVID19. This decreased could be due to the inflammatory process that occurred in this patient. This process cause release of proinflammatory cytokines such as IL-1, IL-6, INF-γ, and TNF-α. Based on several studies, these cytokines can interfere in synthesis erythrocyte or cause erythrocyte destruction. The mechanism was neocytolysis caused by IL-1, inhibit erythropoietin (EPO) production which caused by TNF-α and IL-1. Also, IL-6 could inhibit haemoglobin production and erythroid cell maturation. Wenzhong et al also reported that the viral protein could be attached to haemoglobin through the hemolysis process with a direct viral infection of erythrocytes.[11,12]
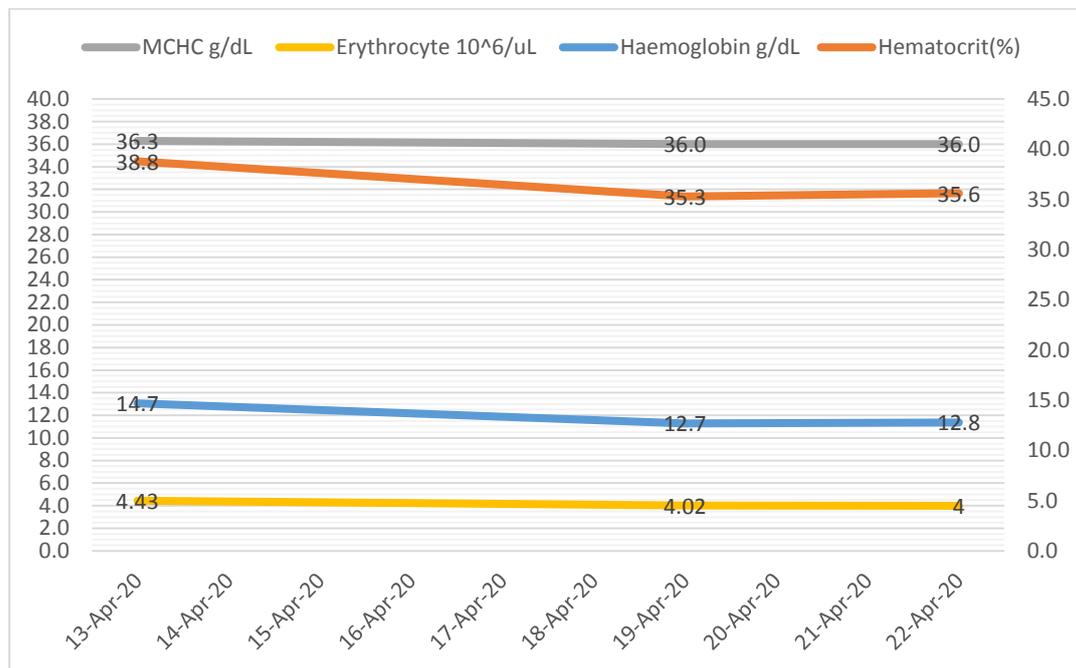

Figure 1. Alteration in hematological value of erythrocyte during the progression of COVID-19 infection

In the first admission, the level of haemoglobin is still in normal range with a slight decreased absolute erythrocyte count. When the clinical condition worsened, the level of haemoglobin decreased. It caused by erythrocyte destruction and hemolysis which causes free haemoglobin in the plasma. So, the decrease in the number of erythrocytes is not in line with decreased haemoglobin. The study by Cavezzi et al, declared that SARS-CoV-2 attacks haemoglobin molecules through the receptors on the surface of erythrocytes. Those receptors were ACE2, CD147, CD26 that will induce hemolysis and release heme.[13]

There was also a significant decrease in the absolute lymphocyte followed by an increase in the neutrophil-lymphocyte ratio, see Figure 2. Those marked a worsened condition. In accordance to the study stated by Wang et al, Young et al, Arents et al that there is a decreased the absolute number of lymphocytes indicates a deteriorating state of the patient in an inflammatory phase. The lymphocyte reduction mechanism was because of the expression of the ACE2 receptor on the lymphocyte surface. So, the virus can directly infect lymphocytes and cause cell lysis. The presence of cytokine storms also aggravates the destruction of lymphocytes. It characterized by an increased of pro-inflammatory cytokines such as IL-6, IL-2, IL-7, granulocyte colony-stimulating factor, interferon-γ, MCP-1, MIP1-

a, and TNF-α. That cytokine causes the occurrence of lymphocyte apoptosis. Activation of these cytokines also causes atrophy of lymphoid organs includes the spleen, which disrupts lymphocyte turnover.[14-16] The increase leukocytes in this patient is thought to be bacterial coinfection. It recommends examining a sputum culture to confirm the diagnosis.
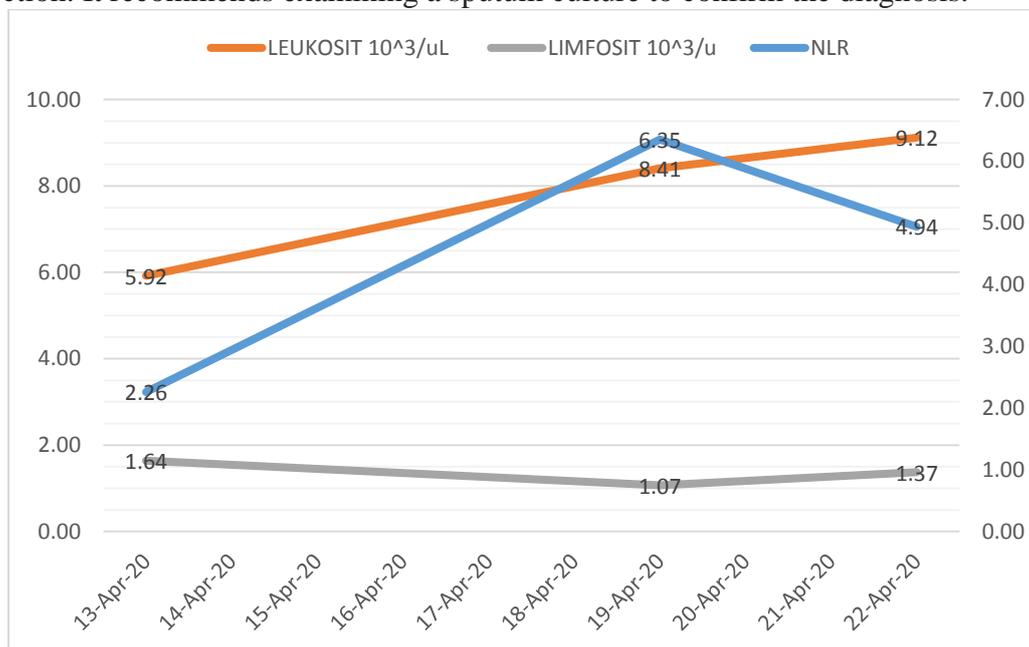

Figure 2. Alteration in hematological value of leucocyte during the progression of COVID-19 infection

This patient entered an inflammatory phase characterized by a significant increase in CRP, ferritin, LDH in 12 days after symptoms. CRP is a protein that plays a role in the inflammatory process where the transcription of CRP genes is induced, especially in the liver. Elevated LDH and ferritin have associated with a poor prognosis in COVID19 infection. The increase in ferritin associate with iron release from the reticuloendothelial system and reduces iron transport from the spleen. Also, there were increased intracellular ferritin synthesis and release with increased ferritin production by the liver. The increased LDH will mark organ damage such as the heart, liver, lymph nodes, and skeletal muscles as well as a marker for hemolysis.[13,17] There was also an increase in AST and ALT levels, as well as a decrease in haemoglobin levels, possibly mild erythrocyte destruction or liver disorders.

Increased level of d-Dimer and fibrinogen happen in a worsened condition of COVID19 infection. Increased D-dimers from lysis of cross-linked fibrin indicates excessive activation of coagulation and fibrinolysis. Furthermore, SARS-COV-2 can directly infect the vascular endothelium that will induce abnormal coagulation and sepsis. Abnormal coagulation characterized by increased D-dimers and fibrin degradation products (FDP).[18, 19-22]

Hyponatremia happened in this patient with the serum sodium level was 128 mEq/L. The study by Berni et al stated that the hyponatremic mechanism in COVID-19 patients involving IL-6 that released by monocytes and macrophages in the inflammatory phase.[23-27] This cytokine plays a role in inducing the release of antidiuretic hormone causing electrolyte disturbances.[28-29] Syndrome of inappropriate antidiuretic hormone secretion could not be confirmed, because of incomplete laboratory data.

3. CONCLUSION

In the laboratory examination of the early COVID-19 infection, there were no significant

laboratory abnormalities. The results of the patient's nasopharyngeal and oropharyngeal swab showed that confirmed with COVID19. By the course of the COVID-19 disease, there was a significant decrease in absolute lymphocytes and increased inflammatory markers on day 12th after symptoms. This condition showed the patient entered an inflammation phase of COVID19 pneumonia with mild ARDS. There were also abnormal liver function and electrolyte imbalance. In this phase, increased d-Dimer and fibrinogen are indicating a poor prognosis.

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