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Laboratory Diagnostic and Monitoring at Early Stages of SARS-CoV-2 Infection: Case Report and Literature Review

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ABSTRACT

COVID-19 is a new respiratory disease caused by severe acute respiratory syndrome Coronavirus type 2 (SARS-CoV-2) and became a pandemic in early 2020. Since the clinical presentation of this viral infection can mimic other types of viral infection (e.g., dengue, influenza, and another respiratory disease), the laboratory approach becomes essential, particularly at the early stages of infection. This case-literature review approach described an outpatient case of a 39-year-old male patient with mild-to-moderate COVID-19 who recovered after 49 days of self-quarantine. Lymphopenia and mild thrombocytopenia can be used as early screening for COVID-19 at the early stages of infection and mainly occur in outpatient settings. Meanwhile, Neutrophil-to-Lymphocyte Count Ratio (NLCR), C-Reactive Protein (CRP), and Liver Function Test (LFT) can be used for severity prediction and/or follow-up the outcome of the infected patient. Therefore, the integrated clinical-laboratory finding at the early stages of infection is vital to provide better and effective patient management.

Keywords: COVID-19, early stages of SARS-CoV-2, laboratory diagnosis

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2), or novel coronavirus 2019 (COVID-19), is a new Coronaviridae family infection and was declared a global pandemic.[1,2] The new type of Coronavirus has caused high mortality, particularly in critically ill patients. The previous report has shown various information about the SARS-CoV-2 infection between regions and countries.[1,3-7] Since the clinical presentation of this viral infection can mimic other types of viral infection (e.g., dengue, influenza, and another respiratory disease), laboratory approach and interpretation become essential. Although specific laboratory parameters, i.e., Neutrophil-to-Lymphocyte Count Ratio (NLCR), C-Reactive Protein (CRP), IL-6, and D-dimer, have been proven useful as diagnostic and monitoring instruments in SARS-CoV-2 infection, there is limited information at the early stages of SARS-CoV-2 diseases.[1] Therefore, the authors aimed to describe the outpatient case report with a relevant literature review to show the utility of laboratory parameters in COVID-19 infection from the initial until the follow-up progression.

CLINICAL CASE AND LABORATORY INVESTIGATION

A 39-year-old Indonesian male came to the primary medical doctor complaining of fever, weakness, shortness of breath, and cough for three days. About two days before the symptom onset, he had direct contact with an individual who tested positive for COVID-19. His vital sign revealed a temperature of 39^{o}C, heart rate of 90 beats per minute, respiratory rate of 18 per minute, and blood pressure of 130/90 mmHg. It fluctuated oxygen saturation ranging between 93 and 95% on room air. The physical exam was unremarkable, except significant dry cough. He was diagnosed with a probable COVID-19 infection and sent for COVID-19 testing. The first laboratory test was carried out on the fourth day of symptom onset, including complete blood count, CRP, and SARS-CoV-2 molecular testing. Unfortunately, he did not perform chest X-ray testing as an initial screening. He took self-quarantine and was treated symptomatically. He was asked to report his condition daily to the primary medical doctor. The laboratory results of Complete Blood Count (CBC) on different dates were summarized in Table 1.

A complete blood count was carried out as the initial step to distinguish etiology according to the symptom onset. Mild thrombocytopenia was observed on day 6 (100.000 to 150.000 per uL), which is typical for viral infection.[2,8] This study followed the absolute lymphocyte count due to its reported role in viral infection. Lymphopenia was observed as the critical finding of this infection, as shown on day 6, day 12, and day 16. In addition, an increase in Erythrocyte Sedimentation Rate (ESR) was a sign of the inflammation process, although it was not a specific parameter (Table 1).

Table 1. Laboratory test results of complete blood count

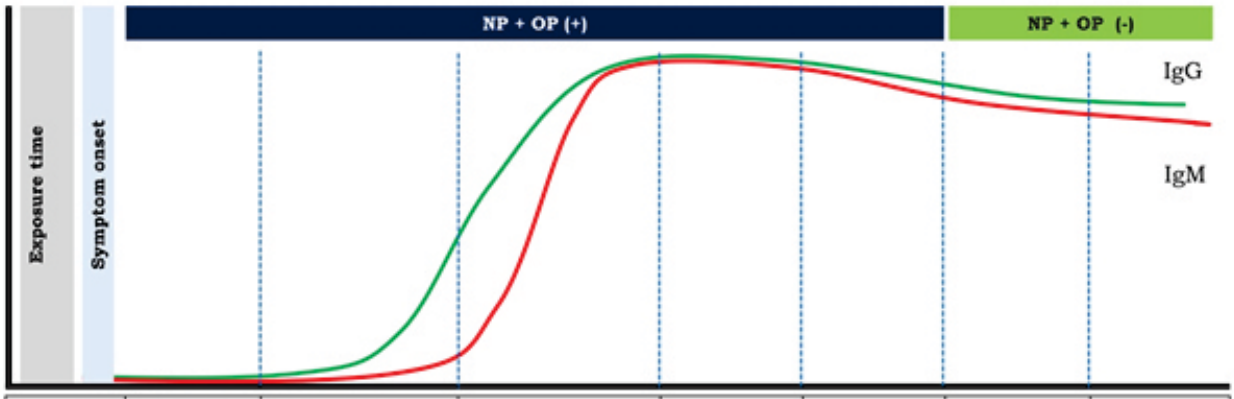
Test	Result/Date							Unit	Reference Range
	Week 1		Week 2		Week 3	Week 4	Week 5		
	D-4	D-6	D-12	D-16	D-18	D- 25	D-34		
	7/9	9/9	15/9	19/9	21/9	28/9	7/10		
HGB	17.5	17	13.7	15.5	15.4	15.8	16.1	g/dL	13.2–17.3
HCT	49.9	49.8	41.7	46.0	46.9	47.3	49.3	%	40.0–52.0
RBC	5.72	5.66	4.61	5.14	5.23	5.28	5.43	10^6/uL	4.4–5.9
MCV	87.2	88.0	90.5	89.5	89.7	89.6	90.8	fL	80–100
MCH	30.4	30.0	29.7	30.2	29.4	29.9	29.7	pg/mL	26–34
MCHC	34.9	34.1	32.9	33.7	32.8	33.4	32.7	%	32–36
RDW	12.2	12	12.3	12	12.1	12.8	12.9	%	11.5–14.5
WBC	5.5	4.5	6.8	**13.6**	**15.6**	6.3	5.5	10^3/uL	3.8–10.6
PLT	163	**143**	295	275	399	251	170	10^3/uL	150–450
DIFF count									
BAS%	-	0.2	0.1	0.0	0.3	0.6	0.7	%	0–1
EOS%	-	1.2	0.7	0.0	0.3	3.3	7.5	%	2–6
NEU%	-	58.6	**81.7**	**84.0**	**80.2**	55.7	52.4	%	50–70
LYM%	-	29.5	**10.0**	**10.0**	**12.8**	27.1	29.7	%	25–40
MON%	-	10.6	7.5	5.0	6.4	**13.3**	**9.7**	%	2–8
ALC	-	**1350**	**680**	**1360**	1990	1710	1630	/uL	>1500
NLCR	-	1.9	8.2	8.4	6.3	2.1	1.8		
ESR	-	**27**	**82**	**48**	**47**	**21**	**17**	mm/h	0–15

Abbrev: HGB, hemoglobin; HCT, hematocrit; RBC, Red Blood Cell; MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Hemoglobin; MCHC, Mean Corpuscular Hemoglobin Concentration; RDW, Red Cell Distribution Width; WBC, White Blood Cell; PLT, platelet; BAS, basophil; EOS, eosinophil; NEU, neutrophil; LYM, lymphocyte; MON, monocyte; ALC, Absolute Lymphocyte Count; NLCR, Neutrophil-to-Lymphocyte Ratio; ESR, Erythrocyte Sedimentation Rate; D, refer to the day of observation based on symptom onset; Bold letter, refers to abnormal value compared to a reference range; dash (-), not tested

Table 2. Laboratory test results of inflammation biomarker (serology and clinical chemistry)

Test	Result/Date							Unit	Reference Range
	Week 1		Week 2		Week 3	Week 4	Week 5		
	D-4	D-6	D-12	D-16	D-18	D- 25	D-34		
	7/9	9/9	15/9	19/9	21/9	28/9	7/10		
Serologic									
PCT			0.14					ng/mL	<0.5
CRP	**27.5**		**172.25**	**9.53**	3.25			mg/L	< 5
Dengue antibody									
IgM dengue		NR							NR
IgG dengue		NR							NR
Clinical chemistry									
AST		**70**	**85**	**45**		29	**37**	U/L	< 33
ALT		**91**	**103**	**145**		**86**	**72**	U/L	< 50

Abbrev: PCT, procalcitonin; CRP, C-reactive protein; IgM, immunoglobulin M; IgG, immunoglobulin G; AST, aspartate transaminase; ALT, alanine transaminase; NR, non-reactive; R, reactive; D, refer to the day of observation based on symptom onset; Bold letter, refers to abnormal value compared to a reference range



WEEK	Week-1		Week-2			Week-3			Week-4		Week-5		Week-6		Week-7	
DATE	D-6 9/9	D-9 12/9	D-12 15/9	D-14 17/9	D-16 19/9	D-20 23/9	D-21 24/9	D-23 26/9	D-25 28/9	D-30 3/10	D-37 6/10	D-35 8/10	D-46 19/10	D-49 22/10	D-61 3/11	D-64 6/11
RDT Ab		NR	NR	R	R		R	R		R			R			R
rt-PCR	+				+	+		+	+		+	+		-	-	-
CT value																
Gen E					28.10	34.94		35.85								
Gen N	13.52								38.67		37.81	ND		ND	ND	ND
Gen RdRp	13.94				27.47	33.9		34.71	ND		39.32	39.18		ND	ND	ND

Figure 1. The cumulative result of real-time Polymerase Chain Reaction (rt-PCR) and antibody testing of SARS-CoV-2

Abbrev: RDT ab, rapid diagnostic test antibody; rt-PCR, real-time polymerase chain reaction; NR, non-reactive; R, reactive; D, refer to the day of observation based on symptom onset; Bold letter, refers to abnormal value compared to a reference range; CT-value, cycle threshold value; NP, nasopharyngeal; OP, oropharyngeal; Gen E, envelope protein; Gen N, RNA and Nucleocapsid protein; Gen RdRp, RNA-dependent RNA polymerase; [+], positive; [-], negative

On day 12, the CRP was remarkably increased (Table 2). C-reactive protein is a plasma protein synthesized by the hepatocytes, and its level rises in response to inflammation or cell injury due to various pathogens. A high level of CRP indicated the progression of the inflammation process of COVID-19, which could be used as a severity marker of the disease.[9,10] The inflammation's severity or progression could also be observed with the NLCR. There was an increased NLCR result on day 12 and day 16. It was reported that the cut-off of NLCR was more significant than 3.3, indicating a greater possibility of transforming into a severe case of COVID-19. This finding agreed with the daily report of the patient's condition, which showed desaturation to 90% on pulse oximetry during week 2. Therefore, it highlighted the role of CRP and NLCR as the severity inflammatory marker of COVID-19 infection.[11-13] Liver function test (AST, ALT) was remarkably increased because hepatic Kupffer cells were triggered to clear the virus and initiate the inflammatory reaction.[14] On day 18, his symptoms showed significant improvement, characterized by an oxygen saturation >95%. On day 35, he underwent for chest X-ray, but the result showed no abnormalities.

Figure 2. Rapid diagnostic test for the antibody of SARS-CoV-2: three-month post-COVID-19 infection. The arrow showed the red line appearing in the IgG region, indicating a reactive result to the SARS-CoV-2 antibody

Confirmatory testing of SARS-CoV-2 (PCR) was detected on day six and undetected on day 49. The cycle threshold value (CT-value) of the PCR was increased along with clinical improvement. IgM and IgG Antibody of SARS-CoV-2 was detected on day 14, compared with his baseline result of antibody for SARS-CoV-2 on day 9 (Figure 1). The negative result of confirmatory testing of SARS-CoV-2 was obtained on day 61. Three months after the recovery from COVID-19 infection, the patient took immunochromatography SARS-CoV-2 antibody testing, and the result remained reactive to IgG-SARS-CoV-2 (Figure 2). This result was then confirmed by quantitative antibody measurement (S-RBD protein) of SARS-CoV-2 with the electrochemiluminescence immunoassay (ECLIA) method and resulted in a concentration above 250 U/mL.

DISCUSSION

COVID-19 infection has become a global concern and an emerging disease worldwide. The SARS-CoV-2 virus has been spread widely and caused atypical symptoms in the infected person. This study reported the clinical-laboratory case of outpatient COVID-19 with a systematic approach-literature review as supporting information (search strategy can be assessed from https://bit.ly/3SHswF5). During the first phase of the COVID-19 pandemic, only limited information was available about the laboratory profile of COVID-19 infection, particularly in outpatient settings where the early stages of SARS-CoV-2 infection occurred. Based on this case, several important points were highlighted as the early initiating instruments to determine COVID-19, besides molecular testing as the confirmatory test. The complete blood count is the earliest and most simple parameter to identify the COVID-19 infection and differentiate it from other infectious diseases, e.g., dengue. The authors' literature review finds lymphopenia as the remarkable parameter in both severe and non-severe COVID-19 (Figure 3); however, other parameters vary in value.[1,3-5,12,13,15-23] In the early stages of SARS-CoV-2 infection, nasal-bronchial epithelial cells and pneumocytes as the target cells of infection bind to the Angiotensin Converting Enzyme 2 (ACE2) receptor. In the target cells, the type 2 transmembrane serine protease (TMPRSS2) activates and promotes viral uptake by cleaving ACE2, which mediates coronavirus entry into host cells. The viral load in the upper respiratory tract reaches the peak at the time of symptom onset. It continues with viral shedding, which begins approximately 2 to 3 days before symptoms start. At this stage, similar to other respiratory viral diseases, lymphopenia may occur in individuals with COVID-19 when SARS-CoV-2 infects and kills T lymphocyte cells. In addition to the viral inflammatory, which consists of both the innate and the adaptive immune response, the virus impairs lymphopoiesis and increases lymphocyte apoptosis.[2,9,20] lymphopenia accompanied by mild thrombocytopenia is among the most common abnormal findings focused on hematology results of patients with both severe and non-severe COVID-19 infection. Thrombocytopenia is common in viral infections due to immunological platelet destruction, Improper platelet activation and consumption, and impaired megakaryopoiesis.[8]

In the later stages of infection, when viral replication accelerates, SARS-CoV-2 infects pulmonary capillary endothelial cells, resulting in an inflammatory response and triggering an influx of monocytes and neutrophils. This process results in releases the cytokines and inflammatory markers, e.g., interleukins (IL-1, IL-6, IL-8, IL-120, and IL-12), Tumor Necrosis Factor-α (TNF-α), IFN-λ, and IFN-β, CXCL-10, Monocyte Chemoattractant Protein-1 (MCP-1) and Macrophage Inflammatory Protein-1α (MIP-1α), which later known as the cytokine storm. The cytokine storm is responsible for the subsequent inflammation and lung injury. Therefore, the inflammation-related parameters are highly elevated in acute phases, i.e., the ESR and CRP.[1,9-11,24] The systemic inflammation also affected the Liver Function Test (LFT). A previous study reported that elevated ALT and AST levels in COVID-19 patients were observed in 20% of cases, which may indicate virus-mediated liver impairment.[1,14]

The simple and valuable important finding of COVID-19 infection was the NLCR. A study by Liu *et al*. has demonstrated the use of NLCR as a good predictive factor for the severity of illness in COVID-19 by using an NLCR of 3.13 and an age stratification of 50 years.[12] Reflecting on this case, it can be seen that the initial NLCR (week 1) was below 3.13; however, NLCR was then elevated in the second week. This result was also accompanied by increased inflammatory markers (e.g., CRP, LFT) and decreased oxygen saturation, indicating the illness's severity. Thus, NLCR as a prognostic severity illness for COVID-19 should be monitored sequentially instead of a single measurement. Moreover, NLCR is also useful for the patient's management stratification, e.g., admission to the hospital or self-quarantine/ home isolation.[11,12]

SARS-CoV-2 antibody testing was the first designated instrument in the early COVID-19

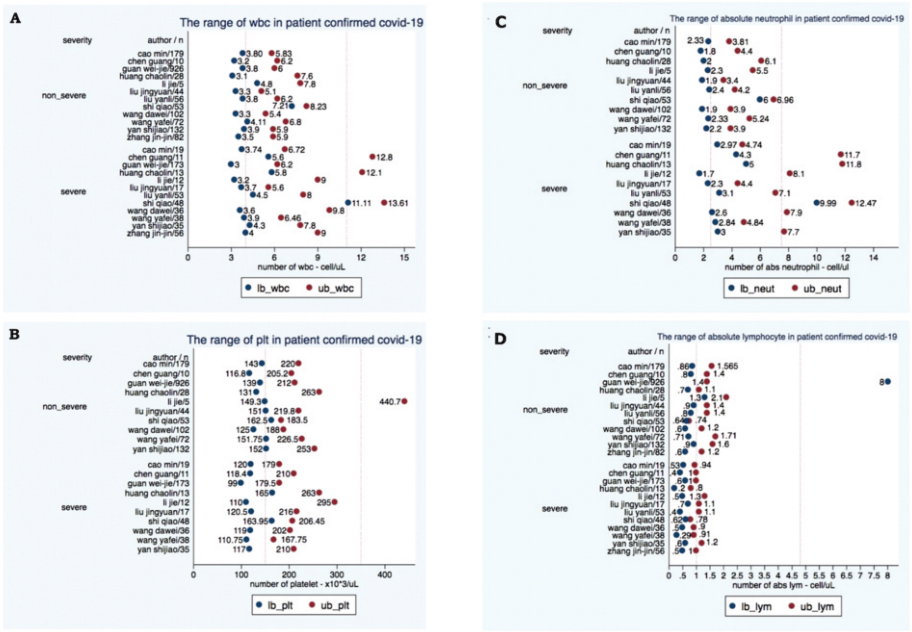


Figure 3. Literature review of white blood cell (WBC) count (A), platelet (PLT) count (B), absolute neutrophil count (C), and total lymphocyte count (D) in confirmed COVID-19 patients stratified by disease severity (severe and non-severe). The range of each parameter observed in the study was indicated by a blue dot (the lowest value, lower boundaries) and a red dot (the highest value, higher limitations). The vertical dash-line in each graph indicated the range of normal values as the standard reference in each parameter

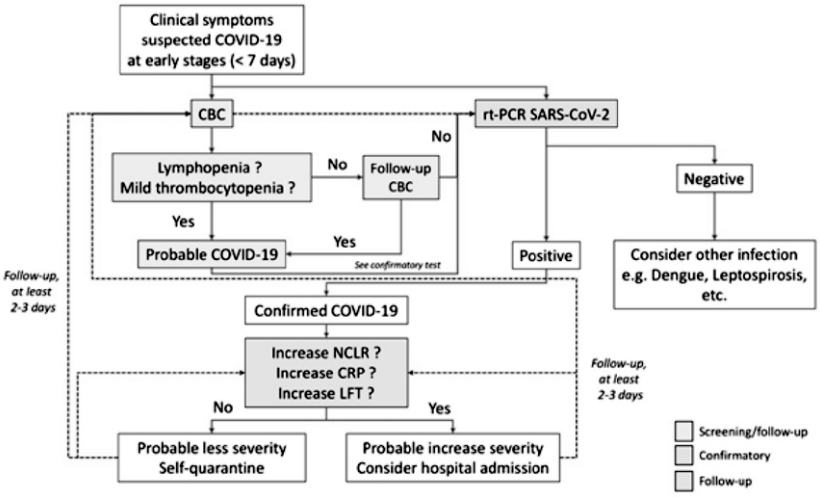


Figure 4. Proposed laboratory-diagnostic flowchart for screening and monitoring at early stages of SARS-CoV-2 infection for outpatient settings. The red-dash line indicates the follow-up and tracking of SARS-CoV-2 infection

Abbrev: CBC, complete blood count; rt-PCR, real-time, real-time polymerase chain reaction; NLCR, NLCR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; LFT, liver function test

pandemic. In the limited information available for COVID-19, this antibody test becomes the primary laboratory test to diagnose COVID-19 infection. Later, the present study observed that SARS-CoV-2 IgM and IgG antibodies were detectable within 4-5 days of the disease, with higher levels reported during weeks 2 to 3 of illness.[25,26] This observation seems true in this case, in which SARS-CoV-2 IgM and IgG antibodies started to be detected in week two and persisted until recovery. The SARS-CoV-2 testing has varied over time, with information starting to be revealed. However, although

SARS-CoV-2 antibody tests have improved and demonstrated high sensitivity, specificity, and accuracy for detecting antibodies, predicting protection against the virus based on antibodies has yet to be proven. Because the effect of neutralizing antibodies is not yet well understood in the SARS-CoV-2 virus, the exact titer of SARS-CoV-2 antibodies to indicate adequate protection against COVID-19 remains unclear.[26]

In this case, highlight the outpatient settings for COVID-19 since most COVID-19 cases attended to the hospital was at severe stages, and the information about the early characteristic of COVID-19 infection remains limited. In addition, difficulties in differentiating COVID-19 early stages have been addressed as an issue during the COVID-19 pandemic.[1,27-29] Therefore, this case clearly shows the importance of selecting the proper laboratory test in the early stages of COVID-19 (Figure 4).

CONCLUSION

This case report and literature review demonstrated the utility of specific laboratory parameters as part of SARS-CoV-2 virus detection and monitoring in a particular period. For example, Lymphopenia and mild thrombocytopenia can be used as early screening for COVID-19 at the early stages of infection. In addition, NLCR, CRP, and LFT can be used for severity prediction and/or follow-up of the outcome in the infected patient (Figure 4). Therefore, the integrated clinical-laboratory finding at the early stages of infection is vital to provide better and effective patient management. However, further investigation is still needed better to understand the rapid-dynamic changes of the SARS-CoV-2 virus.

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