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RESEARCH ARTICLE

Diagnostic Values of SARS-COV-2 Antibodies using Lifotronic ECL-8000

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ABSTRACT:

One of the most definitive diagnostic tests for COVID-19 infection is rRT-PCR. Another modality developed to diagnose COVID-19 infection is the antibody (serological) assay. This essay can be performed quickly and easily but requires high sensitivity and specificity. This study aims to analyze the diagnostic values of anti-SARS-CoV-2 IgM and IgG using Lifotronic ECL-8000 and the development of antibodies based on time after the onset of the symptoms of COVID-19 in patients with confirmed COVID-19 infection. The serum of the patients with confirmed COVID-19 infection by rRT-PCR was collected between day 1 and day 21 after the onset of the symptoms. Anti-SARS-CoV-2 IgM and IgG from each sample were measured using Lifotronic ECL-8000 to determine their sensitivity, specificity, PPV, and NPV. This assay detects IgM against SARS-CoV-2 N and SRBD proteins, as well as IgG against SARS-CoV-2 SRBD proteins. The anti-SARS-CoV-2 IgM serological assays using Lifotronic ECL-8000 indicated that IgM had 91.6% sensitivity, 87.03% specificity, 90.4% PPV, and 88.67% NPV. Meanwhile, the anti-SARS-CoV-2 IgG serological assays using Lifotronic ECL-8000 showed that IgG had 93.05% sensitivity, 88.88% specificity, 91.78% PPV, and 90.56% NPV. The development of antibodies was observed on days 0-7 after the onset of the symptoms, and the positivity rate of anti-SARS-CoV-2 IgM was higher than that of anti-SARS-CoV-2 IgG. Starting from day 8 after the onset of the symptoms, the positivity rate of anti-SARS-CoV-2 IgG increased and remained higher than that of anti-SARS-CoV-2 IgM. It was concluded that anti-SARS-CoV-2 IgM and IgG serological assays using Lifotronic ECL-8000 could be utilized to support the diagnosis of patients with suspected COVID-19 infection with high sensitivity and specificity.

KEYWORDS: IgM IgG anti-SARS-CoV-2, antibody serological assay.

INTRODUCTION:

SARS-CoV-2 (COVID-19) infection has been a global health problem since December 2019 and was declared a pandemic by WHO on March 11, 2020. As of November 14, 2020, 52, 852, 674 million people worldwide were declared infected with the virus, resulting in 1,295,328 deaths. As of the same date, 457, 735 people in Indonesia were infected with the virus, and 15,037 of them died.[1] The high number of daily cases and deaths indicated the high transmission rate and the fatal impact caused by COVID-19 infection.[2-6]

One of the most definitive diagnostic tests for COVID-19 infection is rRT-PCR.[7-13] This test uses samples from the upper respiratory tract. Another modality developed to assist in the diagnosis of COVID-19 infection is the antibody (serological) assay, in which antibodies in the form of IgM, IgG, or total antibodies are observed. This assay can be performed quickly and easily but requires many considerations, especially the problem of validating the instruments.[2,7,14-17]

Antibody (serological) assays can detect past exposure to SARS-CoV-2 that cannot be detected by rRT-PCR or for nasopharyngeal swab samples that result in false negatives. In order to have sufficient positive predictive value, an antibody (serological) assay requires high sensitivity and specificity, especially when the seroprevalence is low.[3] To date, most antibody (serological) assays for SARS-CoV-2 on the market

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have inadequate performance characteristics for clinical testing.[2,12,14] In this study, the researchers aim to evaluate anti-SARS-CoV-2 IgM and IgG serological assays using Lifotronic ECL-8000 and evaluate antibody development based on time after the onset of the symptoms of COVID-19 in patients with confirmed SARS-CoV-2 infection by PCR test. This test detects IgM against SARS-CoV-2 N and SRBD proteins and IgG against SARS-CoV-2 SRBD proteins.

MATERIALS AND METHODS:

This is an analytic observational study using a cross-sectional design with a diagnostic test approach. This study was conducted in the Clinical Pathology Department of Dr. Soetomo Regional Public Hospital (RSUD Dr. Soetomo). Anti-SARS-CoV-2 IgM and IgG tests using Lifotronic ECL-8000 were conducted from November 2020 to December 2020.

The samples were divided into COVID-19 positive and negative groups. The diagnosis was made based on 2020 WHO COVID-19 Diagnosis Guidelines with positive SARS-CoV-2 PCR test results. The PCR-positive group included patients and health workers with positive SARS-CoV-2 PCR test results, while the PCR-negative group included patients and health workers with negative SARS-CoV-2 PCR test results. This study involved 73 PCR-positive samples and 53 PCR-negative samples.

Inpatients and health workers scheduled to perform the PCR test had their nasopharyngeal swab samples collected. The specimens for the PCR test were stored in 1 VTM and then tested for SARS-CoV-2 PCR with SD Biosensor Standard M nCoV Real-Time Detection Kit. The inpatients and health workers also had their venous blood samples collected for anti-SARS-CoV-2 IgM and IgG tests using Lifotronic ECL-8000 according to the insert kit.

The statistical analysis aspects included sensitivity, specificity, positive predictive value, and negative predictive value, which were calculated using a 2x2 table. The gold standard used was a PCR test from the SD Biosensor Standard M nCoV Real-Time Detection Kit.

Data on anti-SARS-CoV-2 IgM and IgG levels were analyzed using IBM SPSS Statistics 25. The normality of the data distribution was tested using the Shapiro-Wilk test. If the data were normally distributed, the different anti-SARS-CoV-2 IgM and IgG levels on days 1-7, 8-14, and 15-21 would be analyzed using the One-Way Anova test. Meanwhile, if the data was not normally distributed, the Kruskal-Wallis test would be applied. The results would be deemed to be statistically significant if $p < 0.05$.

RESULTS AND DISCUSSION:

Table 1: Distribution of demographics, characteristics, and clinical symptoms in the study samples with confirmed SARS-CoV-2 infection by rRT-PCR

	COVID-19	Non-COVID-19
Age, years		
Mean ± SD	48.6 ± 14.3	40.5 ± 14.62
Range	17-75	19-68
≤ 25	6 (8%)	7 (13%)
26-50	33 (45%)	32 (60%)
51-75	34 (47%)	14 (27%)
Sex		
Male	44 (60%)	21 (40%)
Female	29 (40%)	32 (60%)
Disease Severity		
Mild	30 (41%)	-
Moderate	40 (59%)	-
Severe	-	-
Sampling time after the onset of the symptoms of COVID-19		
≤7	58 (80%)	-
8-15	9 (12%)	-
15-21	6 (8%)	-
Symptom		
Fever	65 (89%)	-
Cough	51 (69%)	-
Dyspnea	34 (46%)	-
Muscle pain	40 (54%)	-
Diarrhea	23 (31%)	-
More than two symptoms	68 (93%)	-
Fever and Cough	49 (67%)	-
Fever and Dyspnea	32 (43%)	-
Fever and Muscle Pain	26 (35%)	-

Diagnostic values of IgM and IgG anti-SARS-CoV-2 with Lifotronic ECL-8000

Table 2 Serological assay results of anti-SARS-CoV-2 IgM using Lifotronic ECL-8000

	rRT PCR (+)	rRT PCR (-)	Total
Anti-SARS-CoV-2 IgM (+)	66	6	72
Anti-SARS-CoV-2 IgM (-)	7	47	54
Total	73	53	126

Table 3 Serological assay results of anti-SARS-CoV-2 IgG using Lifotronic ECL-8000

	rRT PCR (+)	rRT PCR (-)	Total
Anti-SARS-CoV-2 IgG (+)	67	5	72
Anti-SARS-CoV-2 IgG (-)	6	48	54
Total	73	53	126

Table 4: Diagnostic values of serological assay results of anti-SARS-CoV-2 IgM and IgG using Lifotronic ECL-8000

SARS-CoV-2 with Lifotronic ECL-8000	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Anti-SARS-CoV-2 IgM	91.6	87.03	90.4	88.67	89.68
Anti-SARS-CoV-2 IgG	93.05	88.88	91.78	90.56	91.26

IgM and IgG Serological Assay Results Based on Time After the Onset of the Symptoms of COVID-19 in Patients with Confirmed SARS-CoV-2 Infection by PCR:

Of the 73 samples of patients with confirmed SARS-CoV-2 infection by rRT-PCR tests at the Laboratory of the Department of Clinical Pathology of Dr. Soetomo Regional Public Hospital (RSUD Dr. Soetomo), 58 patients had their serum samples collected on days 0-7 after the onset of the symptoms of COVID-19, 9 patients had their serum samples collected on days 8-14 after the onset of the symptoms of COVID-19, and 6 patients had their serum samples collected on days 15-21 after the onset of the symptoms of COVID-19.

Of the 58 SARS-CoV-2 positive patients whose serum samples were collected on days 0-7 after the onset of the symptoms of COVID-19, 91% were detected to have anti-SARS-CoV-2 IgM, and 89% were detected to have anti-SARS-CoV-2 IgG. Of the 9 SARS-CoV-2 positive patients whose serum samples were collected on days 8-14 after the onset of the symptoms of COVID-19, 88% were detected to have anti-SARS-CoV-2 IgM, and 100% were detected to haveanti-SARS-CoV-2 IgG. Of the 6 SARS-CoV-2 positive patients whose serum samples were collected on days 15-21 after the onset of the symptoms of COVID-19, 83% were detected to have anti-SARS-CoV-2 IgM, and 100% were detected to haveanti-SARS-CoV-2 IgG.

Table 5 Serological assay results of anti-SARS-CoV-2 IgM using Lifotronic ECL-8000 on the study samples with confirmed COVID-19 infection based on time after the onset of the symptoms of COVID-19

	IgM+	IgM-	Total
Days 0-7 of Sickness	53	5	58
Days 8-14 of Sickness	8	1	9
Days 15-21 of Sickness	5	1	6
Total			73

Table 6: Serological assay results of anti-SARS-CoV-2 IgG using Lifotronic ECL-8000 on the study samples with confirmed COVID-19 infection based on time after the onset of the symptoms of COVID-19

	IgG+	IgG-	Total
Days 0-7 of Sickness	52	6	58
Days 8-14 of Sickness	9	0	9
Days 15-21 of Sickness	6	0	6
Total			73

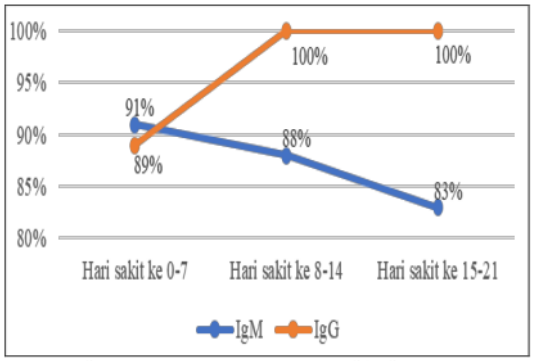
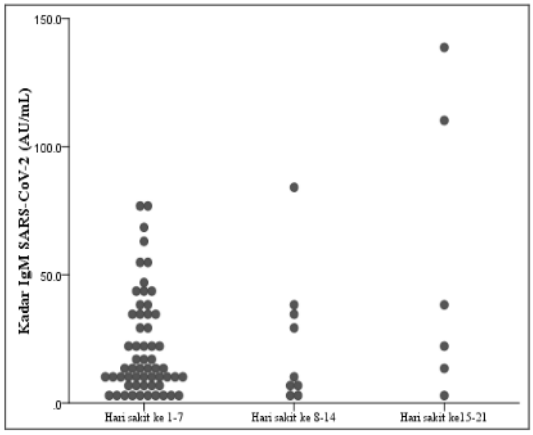


Figure 5 Serological assay results of anti-SARS-CoV-2 IgM and IgG using Lifotronic ECL-8000 on the study samples with confirmed COVID-19 infection by rRT-PCR

Table 7: Anti-SARS-CoV-2 IgM and IgG levels using Lifotronic ECL-8000 in the study samples with confirmed COVID-19 infection by rRT-PCR

	IgM Levels (AU/mL)			
	Days 1-7 of Sickness	**Days 8-14 of Sickness**	**Days 15-21 of Sickness**	**p-sig**
Mean	21.83	24.07	53.73	0.0001
Minimum	1.3	2.7	2.1	
Maximum	77.4	84.1	138.7	
	IgG Levels (AU/mL)			
	Days 1-7 of Sickness	**Days 8-14 of Sickness**	**Days 15-21 of Sickness**	**p-sig**
Mean	210.06	248.72	491.41	0.00001
Minimum	1.6	86	217.3	
Maximum	598.3	609.2	763.1	



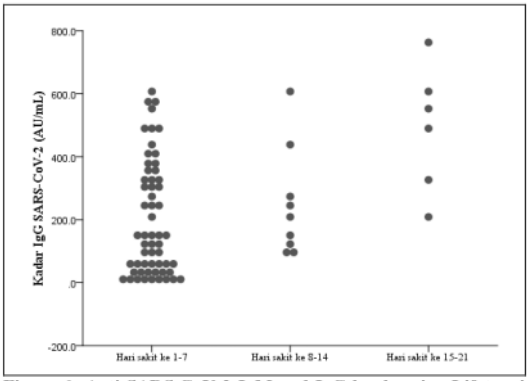


Figure 6: Anti-SARS-CoV-2 IgM and IgG levels using Lifotronic ECL-8000 on the study samples with confirmed COVID-19 infection by rRT-PCR

Table 8: Kruskal-Wallis test results on anti-SARS-CoV-2 IgM and IgG levels

		Mean Rank	*Kruskal-Wallis H*	*Asymp. Sig.*
Anti-SARS-CoV-2 IgM	Negative Control	30.03	77.4	0.000
	Days 1-7 of Sickness	87.03		
	Days 8-14 of Sickness	85.89		
	Days 15-21 of Sickness	98.17		
Anti-SARS-CoV-2 IgG	Negative Control	33.68	65.7	0.000
	Days 1-7 of Sickness	81.0		
	Days 8-14 of Sickness	93.3		
	Days 15-21 of Sickness	113.0		

In this study, it was found that on days 0-7 after the onset of the symptoms, the anti-SARS-CoV-2 IgM positivity rate reached 91%, and that of anti-SARS-CoV-2 IgG reached 89%. On days 8-14 after the onset of the symptoms, the positivity rate of anti-SARS-CoV-2 IgG increased to 100% and remained 100% on days 15-21 after the onset of the symptoms, while that of the anti-SARS-CoV-2 IgM decreased to 88%, and decreased again to 83% on days 15-21 after the onset of the symptoms.

These findings also add to the evidence of the persistence and absence of antibody responses after SARS-CoV-2 infection. The IgM response was shorter, and most individuals undergo seroreversion within two and a half months after the onset of the disease. However, IgG could persist for up to 90 days after the onset of the symptoms, and seroreversion was only observed in a few individuals.[5,10,15] The study by Jin et al. also indicated that antibody positivity rates at the early onset of the disease were quite low, possibly because antibodies were not yet formed. IgG had a higher positivity rate than IgM, with a percentage of 88.9% and 48.1%, respectively. During the seroconversion, when the virus was undetectable, IgM also began to be undetectable, while IgG remained detectable.[6,18-20]

Antibody (serological) assays cannot replace the virological test in determining the presence or absence of acute SARS-CoV-2 infection. People with suspected SARS-CoV-2 infection with a positive result on direct viral detection for SARS-CoV-2 (e.g., PCR or antigen detection tests) usually begin to develop measurable antibodies 7-14 days after the onset of the symptoms of COVID-19 and in the second week.[16] Most patients infected with SARS-CoV-2 have positive results on antibody assays. During this interval, the sensitivity of nucleic acids detection assays or antigen detection assays decreases while the sensitivity of antibody (serological) assays increases.[8] Detection of antibodies may be useful to support the diagnosis of COVID-19 infection or complications of COVID-19 infection in the following situations:

- Positive antibody assay results at least seven days after acute symptoms develop in patients with previously negative antibody assay results (seroconversion) and in patients with negative virological test results may indicate SARS-CoV-2 infection between the date of the negative and positive antibody assays.
- Positive antibody assay results can help support the diagnosis of patients with complications of SARS-CoV-2 diseases, such as multisystem inflammatory syndrome and other acute post-SARS-CoV-2 infection sequelae.[4]

Antibody (serological) assays with very high sensitivity and specificity are recommended since they are more likely to have high predictive values when performed at least three weeks after the onset of the symptoms of COVID-19.[4,18-23] The results of the anti-SARS-CoV-2 IgM and IgG diagnostic tests using Lifotronic ECL-8000 indicated good sensitivity and specificity values of the essay. According to the anti-SARS-CoV-2 IgM serological assay using Lifotronic ECL-8000, the sensitivity and specificity rates of IgM reached 91.6% and 87.03%, respectively. Meanwhile, according to the anti-SARS-CoV-2 IgG serological assay using Lifotronic ECL-8000, the sensitivity and specificity rates of IgG reached 93.05% and 88.88%, respectively.

This study has several limitations. First, only 73 patients with confirmed SARS-CoV-2 infection and 53 control patients were included. Due to the small sample size, the study results must be understood with caution. Second, the control group included only patients with negative SARS-CoV-2 rRT-PCR results, regardless of the presence or absence of symptoms of SARS-CoV-2 infection. Third, this study analyzed the development of antibodies based on time only up to day 21 after the onset of the symptoms in patients with confirmed SARS-CoV-2 PCR infection, so it could not analyze the

seroconversion process of antibodies against SARS-CoV-2.

CONCLUSION:

Anti-SARS-CoV-2 IgM and IgG serological assays using Lifotronic ECL-8000 can be utilized to support diagnosis in patients with suspected SARS-CoV-2 infection due to its relatively high sensitivity (91.6% for IgM and 93.05% for IgG) and specificity (87.03% for IgM and 88.88% for IgG). The development of antibodies based on time after the onset of the symptoms of COVID-19 indicated that the IgM positivity rate tended to decrease on days 8-14 and 15-21, while the IgG positivity rate tended to increase and was stable on 8-14 and 15-21 days.

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