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VALIDATION OF ANTIBODY RAPID TEST FOR SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 INFECTION IN BETHESDA HOSPITAL YOGYAKARTA

Fenty[1*)], Ivan Lim [1]., Frida E. W[2]., Kristiani D[2]., Rizaldi Pinzon[2]

[1]Faculty of Pharmacy, Sanata Dharma University, Paingan, Maguwoharjo, Depok, Sleman, Yogyakarta, 55282, Indonesia
[2]Bethesda Hospital Yogyakarta, 55224, Indonesia

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ABSTRACT

Since March 2020, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection has been around in Indonesia with a case fatality rate was 4.7% on August, 1th 2020. So far, the Real-Time Polymerase Chain Reaction (RT-PCR) method is the gold standard for the SARS-CoV-2 infection diagnosis. This method, however, has some limitations where it has a long turnaround time, complicated operations, and high prices. Hence, the rapid test kits are now readily available to identify the SARS-CoV-2 patients. The purpose of this study is to measure the diagnostic performance, including sensitivity, specificity, positive and negative predictive value, likelihood ratio or LR of antibody rapid test if compared with RT-PCR for the SARS-CoV-2 suspected patients in Bethesda Hospital Yogyakarta. This research was analytical observational research with a cross-sectional design approach, in which data were collected retrospectively. The instruments used in this study included e-medical record (ERM), *Laboratory Information System* (LIS) data from patients with suspected SARS-CoV-2 infection in Bethesda Hospital Yogyakarta. We collected demographic data of patients, RT-PCR results, antibody rapid test results using Standard Q COVID-19 IgM/IgG Combo. The data were obtained from 50 patients. The results showed that the Rapid test kit has a 100% sensitivity value, 74.4% specificity value, 38.9% positive and 100% negative predictive value, 3906 positive likelihood ratio compared with the RT-PCR results.

Keywords: Rapid antibody test; RT-PCR; SARS-CoV-2

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection is an ongoing respiratory disease outbreak caused by Coronavirus that firstly emerged in Wuhan City, China, in December 2019 (WHO, 2020). Since the first case of the disease was reported at the end of 2019 in Wuhan, it has spread widely to entire China and multiple countries (WHO, 2020).

According to the statistic information from the Indonesian Health Ministry on August, 1st 2020, there were 109,936 cases confirmed for SARS-CoV-2, which divided into 36,824 active cases, 67,919 cured cases, and 5193 death cases. There are 1,517,381 specimen tested coming from 875,894 Indonesian citizens. In Daerah Istimewa Yogyakarta, there were 10,126 suspected cases, 741 confirmed cases, 410 cured cases, and 21 death cases until August 1, 2020 (PEMDA DIY, 2020).

Indonesia has recorded an 8.4% fatality rate in April 2020 and decreased to 4.72% in August 2020. Meanwhile, in August, the positivity rate in Indonesia was still 12.6%, which was considered very high and exceeded the limit set by WHO (2020) that is less than 5%. The increasing SARS-CoV-2 infection cases in Indonesia have caused a few complex problems, including the availability of facilities to screen and

*Corresponding author: Fenty
Email: *fenty@usd.ac.id*

confirm a COVID-19 diagnosis. Currently, the Real-Time Polymerase Chain Reaction method (RT-PCR) is the gold standard of SARS-COV-2 testing (Kahfarhood *et al*., 2020).

However, there are some limitations to the RT-PCR method. It will need a certified laboratory with a specific classification for safety. It also takes a long time from sample preparation until the test result. Also, it is costly and complicated in operations (Li *et al*., 2020). Even though RT-PCR is the gold-standard method in diagnosing the SARS-CoV-2 infection, the sensitivity of this method is only 50% to 70% due to the small number of virus particles in some infected patients. The best specimen for virus detection is Broncho Alveolar Lavage (BAL). However, until now, the test majorly takes the samples from the nasopharyngeal or oropharyngeal swabs. The false-negative could happen if the sampling quality or the sample management is poor. It could also give false-negative results in the early infection periods, or there is an analytical problem at the laboratory (Joseph, 2020; Susilo *et al.*, 2020).

Because of these limitations, especially in this pandemic, we need simple and accurate testing to identify the SARS-CoV-2 infection quickly to prevent the virus from spreading and produce the proper handling for the suspected SARS-CoV-2 infection patient (Joseph, 2020; Li *et al*., 2020).

In this case, the government has widely distributed the rapid test kit to detect the antibody of SARS-CoV-2. Rapid test detection has many practical advantages, including quick test results, low cost, and patient convenience. This test can identify the carrier patients and patients without symptoms (Joseph, 2020; Li *et al*., 2020).

Moreover, many companies have developed Rapid test kits to detect human antibodies in SARS-CoV-2 patients (Guo *et al*., 2020). A rapid test needs reconsidering of the exposure onset and symptoms duration before deciding the results. In this case, the test can detect the IgM and IgA sooner. It is detected three up to six days after the onset of the symptoms. Meanwhile, it detects the IgG within 10 to 18 days after the initial symptoms (Guo *et al*., 2020).

In April 2020, the COVID-19 team for West Java province, Indonesia, performed a validation test for rapid test using 'Wondfo' compared with the RT-PCR. The sensitivity, specificity, and accuracy rates in serum specimens in that test were 62.9%, 95.2%, and 77.1%, respectively. Meanwhile, in the capillary, the rates were 44.4%, 100%, and 54.4% taken from 22 samples (Tim Tanggap COVID-19, 2020). Li *et al.* (2020) stated that the antibody-rapid test showed 88.66% sensitivity and 90.63% specificity, measured from 397 confirmed patients with RT-PCR and 128 negative patients in eight health facilities.

Since the rapid-test kits may have varied sensitivity and specificity values, a validation test for the rapid-test compared with the RT-PCR is crucial, especially concerning the situation of the outbreak in Indonesia. This research took place at Bethesda Hospital because it is one of the referral hospitals in Yogyakarta.

The purpose of this study is to measure the diagnostic performances, including sensitivity, specificity, accuracy, positive predictive value, negative predictive value, and likelihood ratio of the antibody-rapid test compared with the RT-PCR as the best method for the SARS-CoV-2 suspected patient in Bethesda Hospital, Yogyakarta.

METHODS

This study was analytical observational research with a cross-sectional design approach, and data sampling was collected retrospectively. The research variables were SARS-CoV-2 antibody rapid test as independent variable and SARS-CoV-2 RT-PCR as dependent variable.

Instruments in this study were electronic medical record (ERM) and *Laboratory Information System* (LIS) data from SARS-CoV-2 suspected patients in Bethesda Hospital, Yogyakarta. We collected demographic data of patients with RT-PCR of SARS-CoV-2 results from the Center for

Environmental Engineering and Disease Control (BBTKLPP) of Yogyakarta. Meanwhile, we obtained the antibody-rapid tests data using the Standard Q COVID-19 IgM/IgG Combo made in Korea. This study has the approval number No.99/KEPK/-RSB-VII/20 issued by the Medical and Health Research Ethics Committee of Bethesda Hospital Yogyakarta, Indonesia.

This study began from May to June 2020. The inclusion criteria were SARS-CoV-2 suspected patient who was clinically determined by attending physician, taking nasopharyngeal/oropharyngeal swab RT-PCR or antibody-rapid test, with no immunocompromised problems**.**

The validation test for the SARS-CoV-2 antibody rapid test of Standard Q COVID-19 with immunochromatography compared with SARS-CoV-2 RT-PCR was calculated using a 2x2 table with a 95% level of confidence, done with a diagnostic test calculator.

RESULTS AND DISCUSSION

Fifty subjects took the antibody-rapid test and had data on the results of the RT-PCR examination, consisting of 24 males and 26 females. From May until June 2020, seven patients had confirmed SARS-CoV-2 infection based on the RT-PCR (Table 1).

Table 1. Characteristics of study subjects

Characteristics	**n=50 (100%)**
Sex	
Male	24 (48%)
Female	26 (52%)
Age	
< 18 years	1 (2%)
≥ 18 years	49 (98%)
RT-PCR	
Positive	7 (14%)
Negative	43 (86%)

Table 2. Comparison Ig M and Ig G to RT-PCR results

	RT-PCR positive	**RT-PCR negative**	**Total**
Ig M reactive	4	23	27
Ig M non reactive	3	20	23
Total	7	43	50
Ig G reactive	6	11	17
Ig G non reactive	1	32	33
Total	7	43	50

Table 3. Comparison Ig M/Ig G to RT-PCR results

	RT-PCR positive	**RT-PCR negative**	**Total**
Ig M/Ig G reactive	7	11	18
Ig M/Ig G non reactive	0	32	32
Total	7	43	50

According to Table 2 and 3, there were four reactive IgM and six reactive IgG from seven positive confirmed RT-PCR. Three patients had reactive IgM and IgG, and only three patients had a reactive IgG, while only one patient had a reactive IgM. Based on the Standard Q COVID-19 IgM/IgG Combo leaflet, individuals with reactive results for IgM or IgG will show a reactive antibody SARS-CoV-2 result.

From the seven positive confirmed patients by RT-PCR, the antibody SARS-CoV-2 could show reactive results between 7 to 14 days after the onset (two patients) and more than 14 days after the initial symptom (three patients). Also, two asymptomatic

patients were confirmed positive by RT-PCR. Meanwhile, Table 4, 5, and 6 show the validation tests for the antibody rapid test Standard Q COVID-19 IgM/IgG Combo compared with RT-PCR. Based on the tables, the validation test result for Standard Q COVID-19 IgM/IgG Combo, the antibody IgG was better than IgM.

Table 4. Validity of IgM to RT-PCR results

Variable	Results	95% CI
Sensitivity	0.571	0,25–0,842
Specificity	0,465	0,325-0,611
PPV	0,148	0,059-0,325
NPV	0,870	0,679-0,955
LR+	1,067	0,531-2,15
LR-	0,923	0,37-2,297

Table 5. Validity of IgG to RT-PCR results

Variable	Results	95% CI
Sensitivity	0,857	0,487-0,974
Specificity	0,744	0,598-0,851
PPV	0,353	0,173-0,587
NPV	0,970	0,847-0,995
LR+	3,348	1,852-6,061
LR-	0,192	0,031-1,188

Table 6. Validity of IgM/IgG to RT-PCR results

Variable	Results	95% CI
Sensitivity	1	0,646-1
Specificity	0,744	0,598-0,851
PPV	0,389	0,203-0,614
NPV	1	0,893-1
LR+	3,906	2,348-6,508

According to the manufacturer, the specificity evaluation was done on 235 PCR-negative samples and turned out to be 95.74% for both IgM and IgG. The sensitivity of this test compared to the RT-PCR from 66 specimens between 7 to 14 days after onset was 89.39% for IgM/IgG, while from other 98 samples within 14 days after onset was 96.94% for IgM/IgG (SD biosensor, 2020). On the other hand, our results showed that the specificity value from 43 patients with negative RT-PCR was 74.7%, while the sensitivity value from seven patients with positive RT-PCR was 100%. *Positive Predictive Value* (PPV) was 38.9%, meaning that 61.6% reactive result from this test showed a false-positive compared with the RT-PCR result. *Negative Predictive Value* (NPV) was 100%, meaning that the non-reactive result from this test showed that the patient did not get infected by SARS-CoV-2 based on the RT-PCR. Meanwhile, the likelihood ratio (LLR) value was equal to 3,906, denoting that in every one false positive, there were four correct positive results. The greater the positive likelihood ratio value is, the better it is to detect disease (Putra et al., 2016).

In July 2020, the Indonesian Association of Clinical Pathologists and Laboratory Medicine (PDS PATKLIN) studied 63 different kinds of SARS-CoV-2 antibody rapid tests from the communities and hospitals in all the branches of PDS PATKLIN in Indonesia. The result of the study showed that the accuracy of SARS-CoV-2 antibody rapid tests varied greatly. The sensitivity and specificity of IgG ranged around 33% to 96% and 19% to 100%. Meanwhile, the sensitivity and specificity of IgM ranged between 16% to 100% and 7% to 97%, respectively.

However, the result of our study showed that the combination between the antibody SARS-CoV-2 Standard Q COVID-19 Combo IgG and IgM had better accuracy if compared to either IgG or IgM only, and the performance of IgG was better than IgM. Detection of IgM antibodies is often interpreted as an indicator of acute infection, while the detection of IgG antibodies represents previous infection/immunity (Castro *et al*., 2020). Yet, in this study, we found three samples with positive RT-PCR results that were only reactive IgG. It showed that IgG could appear in the acute phase. Our result was consistent with the PDS PATKLIN survey. Long *et al*. (2020) found that IgM seroconverted later than IgG. Thus, they recommended that either IgM or IgG seroconversion become a confirmation criterion of recent SARS-CoV-2 infection.

So far, the RT-PCR method has some limitations that involve the quality of specimens, long turnaround times, complicated operations, fluctuations of viral load in different phases of SARS-CoV-2 infection, virus mutation probability, and high prices. Therefore, the antibody-rapid test is advisable, especially in screening the specific population, individual traveling, and contact tracing (Li *et al*., 2020; Long *et al*., 2020; Kemenkes RI, 2020).

Based on Prevention Guidelines for COVID-19, Fifth Revision Edition, the rapid test was no longer recommended for diagnosis. However, the study of Guo *et al*. (2020) stated that the positive detection rate increased by using combinations of antibody rapid test and RT-PCR, especially if there was a false negative from RT-PCR result from the patient with highly suspected SARS-CoV-2.

Meanwhile, our study has its limitations. Firstly, the proportion of confirmed positive cases for SARS-COV-2 was relatively small (seven patients only) and from only one health facility center (Bethesda Hospital).

CONCLUSION

The Standard Q COVID-19 IgM/IgG Combo rapid test had a 100% sensitivity value, 74.4% specificity value, 38.9% positive predictive value, 100% negative predictive value, and 3,906 positive likelihood ratio.

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