ORIGINAL ARTICLE

The Correlation of Rapid Antibody Results with SARS-CoV-2 PCR in COVID-19 Patients in Ulin General Hospital Banjarmasin

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ABSTRACT

Introduction: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the cause of clinical disease, better known as COVID-19. The most common method to detect COVID-19 is serological testing of IgM and IgG in response to viral infections using rapid diagnostic test (RDT). Several other guidelines consider polymerase chain reaction (PCR) as the gold standard for diagnosis because PCR has high sensitivity and specificity values in detecting SARS-CoV-2.
Methods: This was a descriptive analytical study. The samples were taken from medical records of COVID-19 patients in Ulin General Hospital Banjarmasin from March to October 2020. Statistical Package for the Social Sciences (SPSS) 16.0 software and Chi-Square test were used for data analysis.
Results: From 751 COVID-19 patients, 408 patients (54.32%) had rapid antibody with positive PCR, 132 patients (17.57%) had reactive rapid antibody with negative PCR, 152 patients (20.23%) had non-reactive rapid antibody with positive PCR, and 59 patients (7.85%) had non-reactive rapid antibody with negative PCR. The rapid antibody had sensitivity of 72.85% and specificity of 30.89%. From Chi-Square test, reactive rapid antibody was not correlated with PCR positive results; values of p = 0.320, odds ratio (OR) 1.20.
Conclusion: The rapid test antibody could not be recommended as a diagnostic tool. In this study, it was also found that there was no relationship between reactive rapid test results and positive SARS-CoV PCR.

INTRODUCTION

After the first case report of acute respiratory syndrome of unknown etiology in Wuhan, Hubei on 31 December 2019, Chinese authorities identified a new coronavirus, namely Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which causes clinical disease called coronavirus disease or better known as COVID-19.[1,2] On 11 March 2020, World Health Organization (WHO) declared SARS-CoV-2 as a pandemic, considering the high number of cases outside China.[3] The virus outbreak spreads rapidly, significantly affecting all continents and has spread to nearly 213 countries and territories with more than 746,800 deaths among >20.2 million infected people (as of 10 August 2020).[1,2,4] Lack of effective treatment preventive strategies has contributed to an increase in the number of cases, as well as increased health care costs with hospitalization. In addition, there are diagnostic limitations due to the available test tools.[1]

Center for Disease Control and Prevention (CDC) guidelines recommend a molecular polymerase chain reaction (PCR) test for detecting SARS-CoV-2 from upper and lower airway specimens. Some other guidelines also consider PCR as the gold standard for diagnosis because PCR has high sensitivity and specificity values in detecting SARS-CoV-2.[1,5] The aim is to detect viral RNA in respiratory samples,

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such as nasopharyngeal swab or bronchial aspiration, where the sensitivity depends on the type of sample, sampling technique, anatomical location, time of infection, and viral load.[1,2]

Compared to PCR, serological testing is currently advantageous because the required completion time is faster and simpler.[6] The most common method used is serological testing of IgM and production of IgG in viral infection response using rapid diagnostic test (RDT). RDT can be used to improve antibody detection or performed for screening purposes to assess the antibody profile in a large population. Given that SARS-CoV-2 is a new virus, the antibody response in COVID-19 patients is still unknown, because antibodies are usually detected only 1-3 weeks after the onset of symptoms. This test is used to assess overall infection in the society, including infection rates in patients who are asymptomatic or in remote areas where molecular PCR is not available.[1]

Until now, there is still no data regarding the rapid relationship between antibody tests and PCR SARS-CoV-2 in COVID-19 patients in Ulin General Hospital Banjarmasin. Rapid antibody tests are still considered to determine whether a patient should be admitted to the isolation room. Therefore, it is necessary to conduct this study hoping that it can become a reference for diagnosis. The purpose of this study was to determine whether rapid antibodies can be used as a reference tool for the diagnosis of COVID-19.

METHODS

This was a descriptive analytical study. It was conducted in Ulin General Hospital Banjarmasin from March to October 2020. Data were collected from medical records in Ulin General Hospital Banjarmasin. This study had been declared as ethically valid by the Ethics Committee of Ulin General Hospital Banjarmasin with the certificate number 67/IX-Reg Riset/RSUD/ 2021.

The sampling technique used a total sampling method. All samples were obtained from patients who had undergone rapid antibody tests, ignoring certain rapid brands and PCR results. Samples were taken regardless of age, gender, duration of symptoms, severity of the disease, and CT-values. Reactive rapid results were used based on one or both of the reactivity markers (IgG and IgM).

All data of rapid test results for antibody by PCR SARS-CoV-2 were taken from medical records of the patients. Chi-Square test was used for data analysis. If the p value < 0.05, then reactive rapid test was associated with positive PCR result. On the other hand, if the p value > 0.05, rapid antibody was not associated with positive PCR result.

RESULTS

Table 1 shows 751 samples were obtained. The data were grouped into reactive rapid antibodies with positive SARS- CoV-2 PCR results with total of 408 patients (54.32%), reactive rapid antibodies with negative SARS-CoV-2 PCR results with total of 132 patients (17.57%), non-reactive rapid antibodies with positive SARS-CoV-2 PCR results with total of 152 patients (20.23%), and non-reactive rapid antibodies with negative SARS-CoV-2 PCR results with total of 59 patients (7.85%). The data were taken from March to October 2020.

The sensitivity and specificity values of rapid antibody test were 72.85% and 30.89%, respectively (Table 1). It means that rapid antibody had high sensitivity but low specificity. Therefore, rapid antibodies could not be used as a diagnostic tool for COVID-19. This test could not differentiate between a non-diseased patient and a completely non-ill patient.

Tabel 1. The ratio of patients according to the results of SARS-CoV-2 rapid and PCR tests

	PCR Test				Total	p-value	OR
	Positive		Negative				
	Patients	Ratio (%)	Patients	Ratio (%)			
Reactive Rapid	408	72.86 *	132	69.11	540	.320	1.20
Non-Reactive Rapid	152	27.14	59	30.89 **	211		
Total	560	100.00	191	100.00	751		

Note: * sensitivity ** specificity

Characteristics of subject regardless of age, gender, duration of symptoms, severity of the disease, and CT-values

Table 2. Chi-Square test of SARS-CoV-2 rapid and PCR tests

Chi-Square Tests					
	Value	Df	Asymp.Sig. (2-sided)	Exact.Sig.(2-sided)	Exact.Sig. (1-sided)
Pearson Chi-Square	.990[a]	1	.320	-	-
Continuity correction[b]	.813	1	.367	-	-
Likelihood ratio	.978	1	.323	-	-
Fisher's exact test	-	-	-	.351	.183
Linear-by-linear Association	.989	1	.320	-	-
N of valid cases[b]	751	-	-	-	-

Table 3. Odds ratio of SARS-CoV-2 rapid and PCR test

Risk Estimate			
	Value	95% Confidence Interval	
		Lower	Upper
Odds ratio for rapid test (reactive/non-reactive rapid test)			
For diagnostic swab cohort = positive swab	1.200	883	1.718
For diagnostic swab cohort = negative swab	1.049	.952	1.155
N of valid cases	.874	.672	1.137
	751	-	-

DISCUSSION

RDT is a commonly used test to detect the presence of antibodies in the blood of people who are believed to have been infected with COVID-19. Antibodies will be produced several days or weeks after the onset of viral infection. The strength of the body's response to produce antibodies depends on several factors, such as age, nutritional status, disease severity, and certain medications or infections, such as HIV, which weakens the immune system.[7] Current RDTs have been widely developed and are often used in early detection of COVID-19. Their nature becomes important, along with the development of COVID-19 pandemic, and coupled with a lack of testing tools. In general, this detection method is more concise and requires relatively fast time.

Two cases studied by Traugott Marianna, *et al*. showed that RDT has no potential to aid in the diagnosis of COVID-19 and should be thoroughly tested to evaluate the specifics of its use, as well as finding that certain RDTs may not have sufficient sensitivity and specificity for widespread use in a population. For large seroprevalence studies (especially when used as a single test), other tests may be useful in differentiating between groups of patients under different circumstances.[8]

As shown in Table 1, it is found that RDT examination in COVID-19 patients in Ulin General Hospital Banjarmasin only showed a sensitivity level of 72.85% and a specificity of 30.89%. Similar to the study conducted by Ong, *et al*., where it was found that RDT showed low sensitivity in patients with suspected COVID-19 who were admitted to the hospital. Several other RDTs were also reported to have a sensitivity of <20% in patients with acute symptoms who were referred to the emergency department.[9] Eslande, *et al*. also stated in their study that the sensitivity of RDTs was only 30.2% and 31.7%, where the results of their study were also confirmed by a recent report from Cassaniti, *et al*. by not recommending the use of the SARS-CoV-2 IgM/IgG RDT for detecting COVID-19 in patients who came to the emergency department, revealing a sensitivity of <20% in the patient population.[10] Although RDT examination does not require equipment, special training can be done with the use of basic personal protective equipment and the results can be obtained in a relatively short time. However, these results clearly indicate that RDT is not recommended as a diagnostic tool for COVID-19.[11]

Asymp Value. Sig (2-Sided) in Table 2 shows the p value or the significance of the OR value. If $p<0.05$, then at 95% confidence level, the OR is declared significant, which means it can represent the entire population. In Table 2, the results of the p value were 0.32, the OR value (Table 3) was 1.20. It means that the results of a reactive rapid test have a risk of positive PCR result as well as 1.2 times of a non-reactive rapid result. From this results, it can be concluded that reactive rapid results were not related to positive PCR results or the OR was not significant.

From an inspection point of view, the use of RDT and its incorrect application can lead to errors, thus the results may not show. In addition, it is also possible that there was contamination from outside which resulted in an unsuccessful reading of RDT.[12] The existence of a positive result on RDT can also still be caused by a previous infection by another COVID-19.[13]

False negative results can also appear on the rapid test, this could be due to the long window period, and it is not certain when the patient was infected or how long the patient was infected. When antibodies have not been formed or the formed concentrations are still low or have been reduced in the body, the levels cannot be detected by the equipment.[14,15] In addition, false negative results of rapid tests can occur in immunocompromised patients (antibody formation disorders) infected with COVID-19.[16] The occurrence of cross-reactivity of antibodies with various other viruses (COVID-19, dengue virus) also allows false positive results. The cross-reactivity study investigated by Guo, *et al*. showed a strong cross-reactivity between SARS-CoV-positive human plasma and SARS-CoV-2. This could be because both viruses use the same receptor, angiotensin-converting enzyme-2 (ACE2).[17]

Cross-reactivity can also occur between COVID-19 and dengue fever. It has been reported in Singapore, Thailand, and Indonesia, where dengue antibodies were detected in confirmed COVID-19 patients (e.g. false positive dengue serology among COVID-19 patients).[18,19] The data in Masyeni, *et al*.'s study also mentioned the possibility of cross-reactivity between DENV and SARS-CoV-2 which causes false positive COVID-19 serology among dengue fever patients. It was also previously reported in Italy where 1 in 44 DENV positive serologies mentioned a false positive result for COVID-19 antibody.[20] A recent study found that a false positive result could occur both in COVID-19 patients and dengue fever patients. Cross-reactivity between SARS-CoV-2 and DENVs when using rapid serology tests will be a significant barrier to laboratory diagnosis of COVID-19 (including dengue fever, especially in the early phase of infection). A systematic review of 15,976 SARS-CoV-2 antibody samples revealed inadequate combined results for IgG, IgM, IgA, total antibody, and IgG/IgM (using a combination ELISA, chemiluminescence immunoassay, and lateral flow immunoassay/LFIA). While the sensitivity of all approaches was less than 30.1% during the first week of symptom onset, the numbers increased by the second week and reached the highest value at the third week: 72.2% (day 8-14), 91.4% (day 15-20), and 96.0% (day 21–35) for IgM/IgG combination. It indicates that the use of an antibody test, in particular rapid test, has limitations as point-of-care testing.[21]

PCR-based detection of SARS-CoV-2 RNA in respiratory samples was the only specific diagnostic test in the early phase of the pandemic in Wuhan. PCR plays a very important role in early detection of patients infected with SARS-CoV-2[7,22] as conducted by Dohla, where 38 of the 49 samples studied showed negative rapid results and 11 positive samples. Compared to PCR, it found 22 positive samples and 27 negative samples. This study showed that RDT has a low sensitivity, namely 36.4%, therefore it is not recommended to be used as a single detection potential for infection. RDT is substantially lower than PCR test, therefore it should not be used for individual risk assessment or for making decisions about public health action. However, if there is an urgent need, then examination with an antigen-based system would probably be more appropriate.[23]

A study conducted by Garcia Felipe, *et al*. showed different things, namely a sensitivity of 88% and a specificity of 100%. Samples were taken with SARS-CoV PCR results which were known to be positive and the onset of uniform sampling was on the 14th day using the same rapid test. Antibodies for SARS-CoV-2 are known to appear 5 to 14 days after symptoms appear. IgM antibodies are detectable within 5 days of infection, with higher IgM levels during week 2 or 3 of disease, while IgG response is first seen about 14 days after symptom onset. Maximum antibody levels are thought to be in the third or fourth week after the onset of symptoms.[24] Until now, the reliability of RDT is still being debated and requires further research. To date, WHO does not recommend the use of antibody detection-based RDT for patient care, but these tests can assist in disease surveillance and epidemiological research.[7,25] The importance of surveillance is to determine the dynamic spread of the virus in the society and to find how many people in a population have become immune.[26]

Acer O and Ozudogru O have conducted research on the comparison of Reverse Transcriptase/RT-PCR with IgG and IgM antibodies for the diagnosis of SARS-CoV-2 infection. Slightly different from the previously mentioned study, this study took samples based on the degree of disease severity and obtained positive ratio results which was obtained respectively in mild patients, namely 80.3% PCR and 39.3% in total IgG and IgM in moderate grade samples. The positive ratio was 85.7% for PCR and 54.5% for total IgG and IgM, while the degree of gravity of the positive ratio obtained was 75.9% both on PCR results and total IgG and IgM antibodies. In this study, it was concluded that the use of the IgM/IgG antibody test could significantly contribute to improve the accuracy of clinical diagnosis in hospitalized patients with negative molecular test results and in patients who have recently undergone RT-PCR but have clinical support for SARS-CoV-2 infection.[27]

In contrast to other studies, a study conducted by Liu R, *et al*. compared the superiority of IgM-IgG antibodies to RT-PCR for the diagnosis of SARS-CoV-2 infection. The samples examined were 133 patients with SARS-CoV-2 infection (44 cases of moderate degree, 52 cases of severe degree, and 37 cases of critical degree). It was concluded that the positive ratio of IgM antibody was higher than PCR detection (positive ratio of 65.91% for moderate degree, 71.15% for severe degree, and 67.57% for critical degree) and the detection of IgM/IgG antibodies was 79.55%/93.18% for moderate degree, 82.69%/100% for severe degree and 72.97%/97.30% for critical degree. It was stated that the IgG-IgM antibody-based test showed a higher sensitivity which was possibly related to its concentration. It is recommended that IgG and IgM antibody test can be an effective complementary test in patients with negative results from the nucleic acid test for the diagnosis of SARS-CoV-2 infection.[28]

CONCLUSION

Based on the study of the rapid test results of COVID-19 patients in Ulin General Hospital Banjarmasin from March to October 2020 with a total of 751 samples, it was found that the rapid test had a sensitivity of 72.85% with a specificity of 30.89%. Therefore, the rapid test could not be recommended as a diagnostic tool. In this study, it was also found that there was no relationship between reactive rapid test results and positive SARS-CoV PCR.

LIMITATION

The use of different types of RDT and different onset of the disease at the time of sampling in Ulin General Hospital Banjarmasin might have influenced the results of the assessment in this study.

SUGGESTION

RDT is less useful as a screening tool in health facilities which have PCR devices, thus further research is needed regarding the accuracy of the results and the factors that influence these results. RDT should be used in hospitalized patients with pneumonia of unknown etiology with 14 days or more of onset of symptoms with a negative but clinically positive PCR result. In the event of a COVID-19 epidemic, this rapid test can be used as an alternative in surveillance as an epidemiological objective that can be checked quickly.

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