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Coronavirus Pandemic

The performance of point-of-care antibody test for COVID-19 diagnosis in a tertiary hospital in Bandung, Indonesia

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Abstract

Introduction: We aim to describe the performance of combined IgM and IgG point-of-care antibody test (POC-Ab) (Wondfo®) compared to real-time reverse transcriptase (rRT-PCR) (Allplex™ 2019-nCoV Assay) in detecting coronavirus disease 2019 (COVID-19).

Methodology: We compared POC-Ab with rRT-PCR results among patients in a tertiary hospital from January to March 2020 in Bandung, Indonesia. We selected presumptive COVID-19 patients with positive rRT-PCR consecutively and 20 patients with negative rRT-PCR results were selected randomly from the same group of patients as controls. We described the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) with corresponding 95% confidence interval using serum and capillary blood samples. We also tested POC-Ab using non-COVID-19 (confirmed dengue and typhoid) patients' sera.

Results: Twenty-seven patients with positive rRT-PCR result and 20 negative controls were included (68.1% males, mean age 46 (SD: 15.4)). Using the serum, the sensitivity of the POC-Ab was 63.0% (42.4-80.6), specificity was 95.0% (75.1-99.9), PPV was 94.4% (72.7-99.8), NPV was 65.5% (45.7-82.1). A subset of 20 patients was tested using a capillary blood sample. The accuracy of the capillary blood sample is lower compared to serum (50.0% vs. 78.7%). None of the non-COVID-19 sera tested were reactive.

Conclusions: POC-Ab for COVID-19 has a high specificity with no false-positive result in non-COVID-19 sera. Therefore, it can be used to guide diagnostic among symptomatic patients in resource limited settings. Given its low sensitivity, patients with high suspicion of COVID-19 but non-reactive result should be prioritized for rRT-PCR testing.

Key words: SARS-CoV-2; IgM/IgG test; point-of-care testing.

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Introduction

Real-time reverse transcriptase-polymerase chain reaction (rRT-PCR), the gold standard for diagnosing coronavirus disease 2019 (COVID-19) requires trained operators, standardized laboratories, and expensive. Indonesia has only one laboratory equipped and certified to conduct this test at the beginning of the pandemic, and even though the number of laboratories has expanded to 164 laboratories per July 2020 [1], rRT-PCR testing remained unreachable to many people in remote areas. Of 34 province in Indonesia, only 1 province, DKI Jakarta, the capital city of Indonesia reached WHO standard of testing 1/1000 people per week [2]. Today, molecular testing for COVID-19 in Indonesia remains one of the lowest among South East Asian countries (https://ourworldindata.org/coronavirus-testing).

Wondfo SARS-CoV-2 antibody test (Guangzhou

Wondfo Biotech Co., Ltd) detects combined IgM and IgG in blood samples within 15 minutes without a high skill required [4]. We aim to describe the performance of the point-of-care antibody test (POC-Ab) compared to rRT-PCR (Allplex™ 2019-nCoV Assay) in detecting COVID-19 cases to determine whether the test has a place in settings where rRT-PCR is not available.

Table 1. Characteristics of presumptive COVID-19 patients included in this study.

ID	Age	Gender	Patient criteria	Fever	Sniffle	Sore throat	Cough	Dyspnoea	Pneumonia in X-ray	Disease severity	rRT-PCR result	POC-Ab serum result	Time from OS to POC Ab test (day)	Time from rRT-PCR test to POC Ab test (day)	Validation category
1	70	M	Symptomatic	Yes	No	Yes	Yes	Yes	Yes	Severe	Positive	Reactive	6	0	TP
2	42	M	Symptomatic	Yes	Yes	Yes	Yes	Yes	No	Moderate	Positive	Reactive	6	0	TP
3	47	M	Symptomatic	Yes	Yes	No	Yes	Yes	Yes	Moderate	Positive	Reactive	9	-4	TP
4	40	M	Symptomatic	Yes	No	No	Yes	Yes	Yes	Severe	Positive	Reactive	11	2	TP
5	41	M	Symptomatic	Yes	No	No	Yes	Yes	Yes	Moderate	Positive	Reactive	11	0	TP
6	54	M	Symptomatic	Yes	No	No	Yes	Yes	Yes	Severe	Positive	Reactive	11	4	TP
7	58	M	Symptomatic	Yes	No	No	Yes	Yes	Yes	Severe	Positive	Reactive	11	3	TP
8	70	M	Symptomatic	Yes	No	No	Yes	No	No	Mild	Positive	Reactive	12	-1	TP
9	43	M	Symptomatic	No	No	No	No	Yes	Yes	Mild	Positive	Reactive	12	3	TP
10	40	M	Symptomatic	Yes	No	Yes	Yes	No	Yes	Moderate	Positive	Reactive	13	4	TP
11	59	F	Symptomatic	Yes	Yes	No	Yes	No	Yes	Moderate	Positive	Reactive	14	3	TP
12	50	M	Symptomatic	Yes	No	No	No	Yes	Yes	Moderate	Positive	Reactive	17	0	TP
13	61	F	Symptomatic	Yes	No	No	Yes	Yes	Yes	Moderate	Positive	Reactive	17	5	TP
14	32	M	Symptomatic	Yes	Yes	No	Yes	No	No	Mild	Positive	Reactive	19	1	TP
15	53	M	Symptomatic	No	No	No	Yes	Yes	Yes	Severe	Positive	Reactive	ND	2	TP
16	18	F	Case contact	No	No	No	No	No	ND	Mild	Positive	Reactive	NA	-2	TP
17	44	F	Case contact	No	No	No	No	No	No	Mild	Positive	Reactive	NA	8	TP
18	58	F	Symptomatic	Yes	Yes	No	Yes	No	Yes	Mild	Negative	Reactive	10	-1	FP
19	57	F	Symptomatic	Yes	Yes	Yes	Yes	Yes	Yes	Severe	Positive	Non-reactive	4	1	FN
20	40	F	Symptomatic	Yes	Yes	Yes	Yes	No	No	Mild	Positive	Non-reactive	4	-1	FN
21	52	M	Symptomatic	Yes	No	Yes	Yes	Yes	Yes	Mild	Positive	Non-reactive	4	0	FN
22	46	M	Symptomatic	Yes	Yes	No	Yes	Yes	Yes	Severe	Positive	Non-reactive	6	-1	FN
23	32	M	Symptomatic	Yes	No	No	Yes	No	Yes	Mild	Positive	Non-reactive	6	2	FN
24	24	M	Symptomatic	Yes	Yes	No	Yes	Yes	Yes	Mild	Positive	Non-reactive	7	-1	FN
25	62	M	Symptomatic	Yes	No	No	No	Yes	Yes	Moderate	Positive	Non-reactive	8	0	FN
26	53	M	Symptomatic	Yes	No	No	Yes	Yes	Yes	Mild	Positive	Non-reactive	11	-1	FN
27	45	F	Symptomatic	Yes	No	No	Yes	No	Yes	Moderate	Positive	Non-reactive	12	0	FN
28	31	F	Case contact	No	No	No	No	No	No	Mild	Positive	Non-reactive	NA	3	FN
29	45	M	Symptomatic	Yes	Yes	No	Yes	No	Yes	Mild	Negative	Non-reactive	1	0	TN
30	36	M	Symptomatic	Yes	Yes	No	Yes	Yes	Yes	Moderate	Negative	Non-reactive	2	0	TN
31	41	M	Symptomatic	Yes	No	Yes	Yes	Yes	ND	Moderate	Negative	Non-reactive	2	1	TN
32	60	M	Symptomatic	Yes	No	No	Yes	Yes	Yes	Severe	Negative	Non-reactive	3	1	TN
33	56	M	Symptomatic	Yes	Yes	No	Yes	No	No	Mild	Negative	Non-reactive	3	0	TN
34	25	M	Symptomatic	Yes	No	No	Yes	Yes	Yes	Severe	Negative	Non-reactive	3	0	TN
35	61	F	Symptomatic	Yes	Yes	No	Yes	No	No	Mild	Negative	Non-reactive	4	0	TN
36	19	M	Symptomatic	Yes	Yes	Yes	Yes	Yes	No	Mild	Negative	Non-reactive	4	3	TN
37	58	M	Symptomatic	Yes	No	No	Yes	Yes	Yes	Mild	Negative	Non-reactive	4	0	TN
38	26	F	Symptomatic	Yes	No	Yes	Yes	Yes	No	Mild	Negative	Non-reactive	4	0	TN
39	32	M	Symptomatic	No	No	No	No	Yes	Yes	Mild	Negative	Non-reactive	6	0	TN
40	54	M	Symptomatic	Yes	No	No	No	No	Yes	Mild	Negative	Non-reactive	7	0	TN
41	20	F	Symptomatic	Yes	No	No	Yes	Yes	Yes	Moderate	Negative	Non-reactive	9	0	TN
42	28	M	Symptomatic	Yes	No	No	No	No	Yes	Moderate	Negative	Non-reactive	10	0	TN
43	78	F	Symptomatic	Yes	ND	ND	Yes	Yes	Yes	Moderate	Negative	Non-reactive	10	0	TN
44	30	M	Symptomatic	Yes	Yes	Yes	Yes	Yes	Yes	Mild	Negative	Non-reactive	11	1	TN
45	77	F	Symptomatic	Yes	No	Yes	Yes	Yes	Yes	Moderate	Negative	Non-reactive	12	-1	TN
46	51	M	Symptomatic	Yes	No	No	Yes	Yes	Yes	Mild	Negative	Non-reactive	12	2	TN
47	23	F	Symptomatic	Yes	ND	Yes	Yes	Yes	Yes	Mild	Negative	Non-reactive	15	-1	TN

M: male; F: female; ND: no data; NA: not applicable; rRT-PCR: real-time reverse transcriptase polymerase chain reaction; POC Ab: point-of-care testing for antibody; OS: onset of symptoms; TP: true positive; FP: false positive; FN: false negative, TN: true negative.

Methodology

We used serum and capillary blood samples from presumptive COVID-19 patients who have positive rRT-PCR results from nasopharyngeal and oropharyngeal swab specimens between 27 January and 31 March 2020 in Hasan Sadikin Hospital Bandung, Indonesia. Negative controls, defined as patients with negative rRT-PCR results, were randomly selected from the same group of patients. We also used sera from confirmed non-COVID-19 patients (dengue and typhoid) collected prior to the pandemic (2014-2018). The POC-Ab testing was performed according to the manufacturer's instruction [5]. The Clinical and Laboratory Standards Institute recommends that clinical sensitivity be assessed by analysing at least 50 positive specimens from confirmed cases [6]. Due to logistic constraint at that time, we only managed to include samples from 27 patients for data analysis. We described the clinical characteristics and the POC-Ab results of patients who had a positive rRT-PCR with those who had a negative result. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of POC-Ab using serum and capillary blood samples were determined. The Kappa agreement between serum and capillary blood samples were calculated. All statistical analysis was done using Stata v 13.0 (StataCorp, College Station, TX, USA).

Results

There were 145 patients in the isolation ward during the study period, and 47 patients were included in this study, leaving 98 patients not included. There was no difference in age and gender between patients who were included and not included. Of 98 patients not included, 64 (65.3%) patients did not have rRT-PCR done. Among those with rRT-PCR done (n=34), 19 (55.9%) had a positive rRT-PCR result, and 15 (44.1%) were tested negative. Among patients included (N = 47), 68.1% males, mean age 46 years old, 27 (57.4%) patients with positive rRT-PCR result and 20 (42.5%) were negative controls. A subset of 20 (17 positive rRT-PCR and 3 negative rRT-PCR) patients had a capillary blood samples taken. There were three patients who were asymptomatic being admitted to isolation ward included in this study as they were close contact to a confirmed COVID-19 case. Of all patients with positive rRT-PCR result (N = 27), 17 had reactive POC-Ab results (true positive) and 10 had non-reactive POC-Ab results (false negative) (Table 1). Among those with negative rRT-PCR results (N = 20), one patient had POC-Ab reactive result (false positive) and 19 had non-reactive POC-Ab results (true negative). Patients in true positive group were tested using serum after 5 days from the onset of symptom (ranged from 6 to 19 days). One patient in the false positive group had her POC-Ab tested 10 days after the onset of symptom. Three of the patients in false negative group had POC-Ab tested four days from the onset of symptom, six others were tested after 5 days (ranged from 6 to 12 days) and one patient was asymptomatic (Table 1). The time difference between blood withdrawal and naso/oropharingeal swab sampling varied from -4 to 8 days, with 40% patients had their blood taken at the same day as swab sampling (Table 1). The sensitivity of POC-Ab using serum and capillary blood samples were 63.0% (95% CI: 42.4-80.6) and 41.2% (18.4-67.1) respectively (Table 2). The specificity was 95.0% (95% CI: 75.1-99.9) using sera compared to 100.0% (95% CI: 29.2-100.0) using capillary blood samples. The PPV were 94.4% (95% CI: 72.7-99.8) and 100.0% (95% CI: 59.0-100.0) using serum and capillary blood samples, respectively. The NPV using sera was 65.5 (95% CI: 45.7-82.1) compared to 23.1% (95% CI: 5.0-53.0) using capillary blood samples. The accuracy is higher using sera (78.7%; 95% CI: 64.3-89.3) compared to capillary blood samples (50.0%; 95% CI: 27.2-72.8). The Kappa value between serum and capillary blood samples was 0.50 (moderate agreement). None of the POC-Ab results were reactive when tested on 10 acute phase dengue patient's sera, 1 convalescent phase dengue patient's serum, 7 convalescent phase typhoid patients' sera, and 3 interim phase typhoid patients' sera.

Discussion

The POC-Ab test using serum sample has a high specificity and PPV, with no false-positive result in non-COVID-19 sera, suggesting there is no cross-reactivity to typhoid nor dengue antibodies, diseases

Table 2. Sensitivity, specificity, PPV, NPV, accuracy, and proportion of cases missed of POC-Ab compared to rRT-PCR using serum and using capillary blood samples.

Specimen	Sensitivity (%) (95 % CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Accuracy (%) (95% CI)	Cases missed (%) (95% CI)
Serum	63.0 (42.4-80.6)	95.0 (75.1-99.9)	94.4 (72.7-99.8)	65.5 (45.7-82.1)	78.7 (64.3-89.3)	37.0 (19.4-57.6)
Capillary	41.2 (18.4-67.1)	100.0 (29.2-100.0)	100.0 (59.0-100.0)	23.1 (5.0-53.8)	50.0 (27.2-72.8)	58.8 (32.9-81.6)

PPV: positive predictive value; NPV: negative predictive value; POC-Ab: point-of-care antibody test; rRT-PCR: real-time reverse transcriptase polymerase chain reaction; CI: confidence interval.

which are common in Indonesia. However, the sensitivity is relatively low, showing that a non-reactive result cannot be used to rule out infection. Our study shows a lower sensitivity (63.0% vs. 88.7%) but a higher specificity (95.0% vs. 90.6%) compared to the one conducted in China [7]. However, the test time in their study was from day 8 to 33 after symptoms appeared, longer than the test time in our research, which is likely to increase the sensitivity since the presence of antibodies in the patient's blood take days to weeks after infection [8]. The late presence of antibodies is also the reason why POC-Ab is not recommended by the WHO for patient care as a diagnostic tool since it showed a reactive result when the opportunity for clinical intervention already passed [8]. Italian study of 50 patients in a tertiary hospital found an even lower sensitivity (18.4%) and NPV (26.2%), although the specificity (91.7%) and PPV (87.5%) were similar to our study [9]. However, older age (mean age 61-year-old) may cause lower antibodies detected in their study. Another study regarding POC-Ab conducted in a community setting in Germany also found a low sensitivity (36.4%) and high specificity (88.9%) [10]. Lower sensitivity and specificity of POC-Ab in the community setting compared to patients with symptoms are expected. The WHO also did not recommend its use for screening since the antibodies are likely to be present in the recovery phase when the chance to interrupt disease transmission has gone [8]. We described one of the first validation study of POC-Ab for COVID-19 in Indonesia. Our study has several limitations; the confidence intervals are broad due to the small size. Also, we were only able to obtain fewer capillary blood samples from those with rRT-PCR negative, since they were quickly discharged from the hospital, resulting a possible selection bias. Our study has no data regarding patient's comorbidities which may alter immune system and affect the POC-Ab result. Although 2 out of 3 asymptomatic patients (case contacts) were categorized as true positive, the performance of POC-Ab in this study was evaluated among hospitalized patients who were mostly symptomatic and hence stronger antibody response. The sensitivity in this study may not be correlated to outpatients with milder or asymptomatic COVID-19 population. Finally, the high PPV in this study may not be generalized to other population since predictive values are influenced by the prevalence of the disease. Until today, COVID-19 prevalence in Indonesia remains uncertain due to low testing and underreporting. The simplicity of POC-Ab is attractive in areas with no laboratories equipped to conduct molecular test and there are many challenges to develop one [11]. In these settings, swab samples need to be transported to another city, causing possible pre-analytic problems. If the POC test has a high PPV but low NPV, patients with reactive results should be considered to have COVID-19, and non-reactive patients should be retested using molecular method [12]. This algorithm provides diagnostic guidance for clinicians when treating symptomatic patients with COVID-19 suspicion in settings where rRT-PCR is not readily available. Furthermore, the sensitivity of rRT-PCR decreases while the sensitivity of POC-Ab increases with days post symptom onset [13]. Considering that during pandemic patients may wait for their symptoms to get worse or prolonged before seeking medical advice, there is a possibility that some cases would be picked up by serologic test instead of the standard molecular test.

Conclusions

POC-Ab for COVID-19 has a high specificity when used among symptomatic patients, and it has no false-positive result in non-COVID-19 sera. However, due to its low sensitivity, non-reactive result cannot be used to rule out infection. Therefore, symptomatic patients with high suspicion of COVID-19 but non-reactive result should be prioritized for rRT-PCR testing. More extensive study, preferably with cohort design, is required to provide information on the antibody's kinetics and its relation to viral clearance timeline.

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