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Diagnostic Performance of a Rapid Antigen Test for the Detection of SARS-CoV-2

● Sema Alacam*, ● Nuran Karabulut*, ● Alper Gunduz**, ● Busra Ozcan**,
● Ozlem Altuntas Aydin**

*University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinic of Medical Virology, Istanbul, Turkey **University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey

Abstract

Aim: The fight against the coronavirus disease-2019 (COVID-19) pandemic has proven crucial, necessitating the need for faster, cheaper, and more reliable detection methods. This study evaluated the performance of a rapid antigen test for the diagnosis of COVID-19 compared with reverse transcription-polymerase chain reaction (RT-PCR) results.

Methods: This prospective study included 169 participants. Two simultaneous nasopharyngeal swabs were collected from the participants. Samples were tested for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) using the Panbio[™] COVID-19 Ag rapid test (Abbott Rapid Diagnostics, Jena, Germany) and the Bio-Speedy® SARS-CoV-2 RT-PCR kit (Bioeksen, Istanbul, Turkey).

Results: Reverse transcription-polymerase chain reaction results were positive in 90 (53.2%) of 169 patients. The antigen rapid diagnostic test (Ag-RDT) was able to find 66 (73.3%) of the 90 RT-PCR positive samples as positive (p<0.001). In all positive samples by Ag-RDT, RT-PCR was positive. The sensitivity, specificity, negative predictive value, and positive predictive value of the Ag-RDT were 73.3%, 100%, 76.7%, and 100%, respectively. The virus detection performance of the Ag-RDT was significantly more successful in the cycle threshold \leq 20 (p<0.001). There was no correlation between PCR positivity and the time since vaccination.

Conclusion: The Ag-RDT test can be a good option for early detection of cases and early prevention, as it is quick and easy to implement in every laboratory and even at the point of care.

Keywords: SARS-CoV-2, COVID-19, rapid diagnostic tests, reverse transcriptase polymerase chain reaction

Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which has swept the world, is the greatest global health disaster of the century (1,2). As of January 2024, 774,469,939 cases were diagnosed worldwide (3). The clinical presentation of SARS-CoV-2 infection can be variable, ranging from asymptomatic infection to severe disease that can result in death. The most common symptoms of COVID-19 are fever and cough, fatigue, shortness of breath, and loss or change of smell and taste. Some patients also experience gastrointestinal symptoms (e.g., nausea and diarrhea), headaches, chest pain, and conjunctivitis (4,5). Coronavirus disease-2019 has symptoms similar to those of many diseases, so the need for differential diagnosis continues (6).

Diagnostic testing has played a central role in limiting the spread of infection throughout the COVID-19 pandemic (7,8). Nucleic acid amplification tests (NAAT) and antigen rapid diagnostic tests (Ag-RDT) have been commonly used to diagnose SARS-CoV-2 infection. Although reverse transcription-polymerase chain reaction (RT-PCR) tests are considered the gold standard in the diagnosis of COVID-19 in terms of sensitivity and specificity, these tests have some drawbacks, such as requiring trained personnel and specialized instruments,

Address for Correspondence: Sema Alacam, University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinic of Medical Virology, Istanbul, Turkey

Phone: +90 532 682 20 17 E-mail: semalacam@gmail.com ORCID: orcid.org/0000-0001-7957-2906 Received: 23.01.2024 Accepted: 05.03.2024



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being time-consuming, and having high costs (7,9). Compared with NAAT tests, some key advantages of Ag-RDTs are simpler handling, fast turnaround time, the absence of instruments, and low cost (10). In addition, although these tests are less likely to detect the virus than PCR tests, especially in infectious cases with a high viral load, positive results are very accurate and reliable (10,11). Because these tests are portable, they can be used wherever the patient is in non-healthcare environments, such as school or home (7). Antigen rapid diagnostic tests have been widely used around the world, especially in countries where prevalence is high (12). The prevalence of disease is known to affect the positive predictive value (PPV) of tests. As the prevalence increases, the PPV also increases, but the negative predictive value (NPV) decreases (13). The hypothesis of this study, conducted at a time when SARS-CoV-2 prevalence was relatively high, was that Ag-RDT could be used instead of SARS-CoV-2 PCR.

Sensitivity and specificity are the main parameters related to the performance of diagnostic tests. However, the sensitivity of antigen tests to detect SARS-CoV-2 remains controversial. Therefore, in this study, we aimed to evaluate the performance of the Panbio[™] COVID-19 Ag-RDT compared to RT-PCR, the gold standard in the diagnosis of COVID-19.

Methods

Compliance with Ethical Standards

This study was prospective, single-center crosssectional. It was approved by University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinical Research Ethics Committee (reference no.: 2022/370). This study was conducted in accordance with the Declaration of Helsinki. Participants were informed about the study, and written consent was obtained.

Participants and Samples

This study consists of 169 participants aged 18 years and older with a suspicion of COVID-19 who applied to the emergency service of University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital between November 28, 2022, and December 30, 2022. All participants' contact history, symptoms, number of days since the onset of symptoms, vaccination information, and demographic data were questioned. Two simultaneous nasopharyngeal swab samples were collected from the participants for Ag-RDT and real-time RT-PCR testing.

Rapid Antigen Test

The Panbio™ COVID-19 Ag-RDT (Abbott Rapid Diagnostics, Jena, Germany) was used for the qualitative detection of specific SARS-CoV-2 antigens [viral nucleocapsid

(N) protein] in nasopharyngeal samples. It contains a membrane strip pre-coated with immobilized anti-SARS-CoV-2 antibodies in the test line and a monoclonal antibody in the control line. This lateral flow test detects viral N antigens with color change as assessed by naked eye reading. The test is interpreted in 15 minutes in accordance with the manufacturer's recommendations, so that the test results of the patients are obtained in less than 30 minutes.

SARS-Cov-2 RNA Detection Using Real-Time RT-PCR

SARS-CoV-2 RNA was analyzed using a Bio-Speedy[®] SARS-CoV-2 double gene RT-PCR kit (Bioeksen, Istanbul, Turkey) on a CFX96 Touch System (Bio-Rad Laboratories, Inc., United States). The kit is a one-step reverse transcription and qualitative real-time RT-PCR test that provides qualitative detection of SARS-CoV-2 RNA in respiratory tract samples. The kit's limit of detection is 500 copies/mL for nasopharyngeal swab samples. It targets virus-specific open reading frame 1ab and N genes. Internal control (Human RNAseP mRNA) and negative and positive controls were used in each run. A cycle threshold (Ct) value of <36 was considered a positive result.

Statistical Analysis

Statistical analyses were performed using the SPSS Statistics v21 software (SPSS Inc., Chicago, USA). Visual (histograms) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk's test) methods were used to test the normality of the distributions of continuous variables. The Mann-Whitney U test was used to compare parametric variables between groups. The chi-square test was used for categorical comparisons of nominal values between groups. The diagnostic decision-making properties of PCR Ct values in predicting Ag-RDT results were analyzed using receiver operating characteristic (ROC) curve analysis. When a significant cut-off value was observed, the sensitivity, specificity, PPV, and NPV were calculated. A p-value of <0.05 was considered significant.

Results

In this study, the median age of the 169 participants was 35 [minimum: 18 - maximum: 84; interquartile range (IQR): 26-46], and 59.2% (n=100) were male. The RT-PCR results were positive in 90 (53.2%) of 169 patients. The Ag-RDT was able to detect 66 (73.3%) as positive, while it missed 24 (26.7%) (p<0.001). In all positive samples by the Ag-RDT, RT-PCR was positive (Table 1). The sensitivity, specificity, NPV, and PPV of Ag-RDT were 73.3%, 100%, 76.7%, and 100%, respectively, was used as the gold standard.

The median Ct value of the PCR-positive samples was 19 (IQR: 16-22). A significant difference was found between the Ct values of PCR +/ Ag-RDT + samples (median Ct: 18)

and PCR +/Ag-RDT - samples (median Ct: 24) (p<0.001). Ag-RDT results according to PCR Ct values are shown in Figure 1. The Ag-RDT was positive in 85% (51/60) of those with high viral load (Ct \leq 20) and 50% (15/30) of those with low viral load (Ct>20). The virus detection performance of Ag-RDT was significantly more successful in the Ct≤20 (p<0.001) (Table 1). The sensitivity and specificity values of the Aq-RDT were 71% and 65%, respectively, when the ROC analysis set the cut-off value of the PCR Ct at 19.9. The area under the ROC curve was 0.76 (95% confidence interval: 0.64-0.88) and was statistically significant (p<0.001).

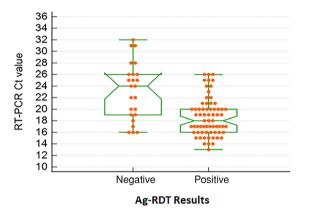


Figure 1. Comparison of SARS-CoV-2 antigen rapid diagnostic test (Ag-RDT) results with RT-PCR cycle threshold (Ct) values SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, RT-PCR: Reverse transcription-polymerase chain reaction

The samples were collected on the median day 3 of symptom onset. There was no significant difference in the RT-PCR and Ag-RDT test results for samples collected on days \leq 4 and >4 of symptom onset (Table 2). Of the patients. 50.3% had fever, 22.5% had loss of taste or smell, and 1.8% had pneumonia (Table 3). Seven participants with a history of exposure were asymptomatic, and four of them were both the RT-PCR and Aq-RDT positive.

Out of the 153 individuals who received an average of two doses of vaccination. 112 received the Biontech vaccine, and 84 (54.9%) of these cases showed RT-PCR positive results despite the vaccination. Comorbidities were present in 24 (14.2%) study participants. The symptoms, time since vaccination, and comorbidities of the participants are detailed in Table 3.

Discussion

Given the global consequences of the COVID-19 pandemic, rapid and reliable diagnosis is crucial in identifying potentially contagious individuals, ensuring correct clinical management of patients, and taking necessary measures (14,15). The present study compared the results of a diagnostic test based on the lateral flow principle, which rapidly detects the SARS-CoV-2 N protein, with the results of RT-PCR. The RT-PCR and Aq-RDT results of 169 samples were compared, and discordant results were obtained in 24 of 90 positive samples. The Aq-RDT missed all of the discordant results, which were false negatives (Ag-RDT-/RT-PCR+). According to the statistics performed

Table 1. Evaluation of the diagnostic performance of Panbio™ COVID-19 Ag-RDT							
	Tatal (m. 460)	Panbio™ COVID-19 Ag-RDT					
RT-PCR	Total (n=169)	Antigen negative (n=103)	Antigen positive (n=66)	p-value			
Negative	79	79	0				
Positive	90	24	66				
Ct, median (IQR)	90	24 (19-26)	18 (16-20)	<0.001*			
Ct ≤20	60	9	51	-0.001**			
Ct >20	30	15	15	<0.001**			
*Mann-Whitney U test, **Pe	earson chi-square test	÷		·			

COVID-19: Coronavirus disease-2019, Ag-RDT: Antigen rapid diagnostic test, RT-PCR: Reverse transcription-polymerase chain reaction, IQR: Interquartile range, Ct: Cycle threshold

Table 2. Comparison of R	ſ-PCR and Panbio™ COVIĽ	0-19 Ag-RDT results a	ccording to participants' symp	otom days
	Onset of sympto	ms the sample was col		
	≤4 days	>4 days	Total	p-values
PCR negative	64	6	70	0.00*
PCR positive	77 (90.6%)	8 (9.4%)	85 (100%)	0.86*
Antigen negative	83	9	92	o cot
Antigen positive	58 (92.1%)	5 (7.9%)	63 (100%)	0.69*
*Pearson chi-square test			· · ·	

COVID-19: Coronavirus disease-2019, Aq-RDT: Antigen rapid diagnostic test, RT-PCR: Reverse transcription-polymerase chain reaction

	Total (n=169)	RT-PCR			
		Negative	Positive	p-value	
URTI	144 (85.2%)	66 (39.1%)	78 (46.1%)	0.57*	
Symptoms	158 (93.5%)	72 (42.6%)	86 (50.9%)	0.25*	
Fever	85 (50.3%)	31 (18.3%)	54 (32%)	0.007*	
Loss of taste/smell	38 (22.5%)	15 (8.9%)	23 (13.6%)	0.31*	
Pneumonia	3 (1.8%)	1 (0.6%)	2 (1.2%)		
Vaccinated individuals	153 (90.5%)	69 (45.1%)	84 (54.9%)	0.18*	
Time since vaccination					
In 1-3 months	7 (4.1%)	3	4		
In 4-6 months	46 (27.2%)	25	21		
6 months ago	79 (46.7%)	35	44		
Unvaccinated	37	16	21		
Comorbidity	24 (14.2%)	8	16 (67%)		
CLD	1	1	0		
COPD	1	1	0		
Asthma	7	2	5		
Diabetes	11	3	8		
CKF	2	1	1		
Steroid use	2	0	2		
Immunosuppression	0	0	0		

*Pearson chi-square test

URTI: Upper respiratory tract infection, CLD: Chronic lung disease, COPD: Chronic obstructive pulmonary disease, CKF: Chronic kidney failure, RT-PCR: Reverse transcriptionpolymerase chain reaction

by accepting RT-PCR as the gold standard, the sensitivity of Ag-RDT was 73.3%, specificity 100%, NPV 76.7%, and PPV 100%. Studies conducted in various populations and countries during the pandemic period detected sensitivity performances of Ag-RDT ranging from 24% to 93% (16). In more than 10 clinical studies involving more than 6000 subjects evaluating the performance of Panbio[™] Ag-RDT, sensitivity and specificity ranges of 71.4-91.7% and 94.9-100%, respectively, were reported (17-19). Treggiari et al. (20) found the sensitivity, specificity, PPV, and NPV values of the Ag-RDT to be 66.82%, 99.89%, 97.87%, and 97.62%, respectively. In three different studies conducted in our country, the sensitivity and specificity rates were found to be 61.8% and 97.6%, 88.7 and 98.0, 70% and 100%, respectively (21-23). The sensitivity and specificity values determined in our study were consistent with those of previous studies.

Many studies have shown a clear relationship between the Ct value and the positivity rate of Ag-RDT (14,24-26). A study in China reported excellent performance of rapid tests in patients with higher viral loads, especially those with upper respiratory tract symptoms (16). In this study, Ag-RDT susceptibility was significantly higher in subjects with a high viral load (85%) than in those with a low viral load (50%). Eikelenboom-Boskamp et al. (27) conducted a study using the Panbio[™] Ag-RDT and found its sensitivity to be 81%. However, given the low contagiousness of patients with a Ct value >32, they found the test's sensitivity to be 92.7% when they used 32 as the cut-off Ct value instead of 40. Indeed, it may be more advantageous to detect Ag-RDT only in the acute phase of the disease, when the viral load is high, compared with highly sensitive PCR positivity (sometimes the positivity persists for a long time). Thus, unnecessary isolation of patients who are no longer contagious, that is, with a low viral load, can be avoided (24,28). Meanwhile, there are studies showing that the sensitivity of Ag-RDTs for asymptomatic patients is significantly lower than that for symptomatic patients (4). Ag-RDT may be a good option, especially for the early diagnosis of infectious symptomatic cases and the early taking of precautions, due to its fast and easy application in every laboratory and even at the point of care, and its advantages over PCR (29).

The prevalence of the disease affects the PPV of the tests. As prevalence increases, PPV also increases, but NPV decreases. The European Commission recommends the use of Ag-RDT in a publication on COVID-19 testing

procedures because the predictive rates of Ag-RDTs are high in populations with a high prevalence of SARS-CoV-2. However, the European Centre for Disease Prevention and Control suggests using RT-PCR or a different brand of Ag-RDT to confirm positive samples in settings where the prevalence is less than 10% (29).

The Centers for Disease Control and Prevention recommends that everyone over 6 months of age, especially the elderly and immunocompromised, who are at high risk of serious illness, receive an updated COVID-19 vaccine to protect against possible serious COVID-19 disease in the fall and winter months (30). There are randomized, placebocontrolled studies showing the high efficacy of COVID-19 vaccines. However, these data may vary depending on the characteristics of the population, vaccine, and viral strain (31). In a case-control study in Germany, the two-dose vaccine efficacy was 89% overall. It was 79% in patients with more than two comorbidities and 77% in adults aged 60-75 years. The third dose increased vaccine efficacy to over 93% in all patient subgroups (32). In this study, no correlation was found between PCR positivity and the time since vaccination (vaccinated in the last 3 months, 4-6 months, and in the last 6 months). Reasons for this may include the small number of participants vaccinated in the last 3 or 6 months, insufficient vaccine doses, or the vaccines not working.

Study Limitations

The study should be interpreted with some limitations. False-negative Ag-RDT tests could not be rerun from the same samples because there were not enough tests. As different variants dominate periodically for SARS-COV-2, this may affect the kit's performance, depending on the content of the kit. The strength of this study is that it shows that rapid diagnosis with Ag-RDT is critical, especially in cases with a high viral load (highly contagious).

Conclusion

The Panbio[™] Ag-RDT kit can be good option in the rapid identification of COVID-19 patients. However, it's important to acknowledge that this qualitative test cannot completely rule out the possibility of COVID-19 infection, particularly considering the potential for false negative results. Ag-RDTs can provide significant benefits in rapid diagnosis, using the right algorithms and confirmed by RT-PCR when necessary.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinical Research Ethics Committee (reference no.: 2022/370).

Informed Consent: Participants were informed about the study, and written consent was obtained.

Authorship Contributions

Surgical and Medical Practices: A.G., B.O., O.A.A., Concept: S.A., N.K., O.A.A., Design: S.A., N.K., O.A.A., Data Collection or Processing: S.A., A.G., B.O., Analysis or Interpretation: S.A., N.K., A.G., Literature Search: S.A., B.O., Writing: S.A., N.K.

Conflict of Interest: No conflicts of interest were declared by the authors.

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