



Diagnostic Efficacy of COVID-19 Rapid Antigen Detection Card in Diagnosis of SARS-CoV-2

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Abstract

Introduction The rapid surge of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) cases globally makes it essential for rapid diagnosis of coronavirus disease 2019 (COVID-19). Real-time reverse-transcription polymerase chain reaction (rtRT-PCR) remains as the gold standard to detect COVID-19 cases because of its greater sensitivity and specificity. However, because of its prolonged turnaround time and technical expertise, recommendations have been made to employ the use of rapid diagnostic test for rapid diagnosis and to curb the spread of the disease.

Methods This prospective study was performed in a tertiary COVID-19 care hospital located amidst the semi-urban settings. Both nasopharyngeal and throat swabs collected from the COVID 19 suspected study participants were subjected to both COVID 19 rtRT-PCR and rapid antigen testing.

Results Of the total 599 samples tested by rtRT-PCR, 310 (52%) were positive and 289 (48%) tested negative for SARS-CoV-2. Of the 599 samples tested by rapid antigen test (RAT), 230 (38%) were positive and 369 (62%) were negative. The overall sensitivity and specificity of our study kit was found to be 74.19 and 100%, respectively. The sensitivity of the RAT greatly overlaps with the viral load which is determined by the cycle threshold (CT) values of SARS-CoV-2, E gene, and RdRp gene.

Conclusion RAT yields rapid results within a short-turnaround time and found to be cost effective. Therefore, this test can be adopted in areas with rapid surge in SARS-CoV-2 cases which can help to rapidly identify the positive cases and to implement isolation and infection control measures.

Keywords

- ▶ novel corona virus
- ▶ SARS-CoV-2
- ▶ rapid diagnostic test
- ▶ real-time RT-PCR
- ▶ sensitivity
- ▶ specificity
- ▶ point of care test

Introduction

In December 2019, a new coronavirus disease emerged in Wuhan province in China which rapidly spread throughout the world. The disease caused by the virus has been termed as novel coronavirus disease 2019 (COVID-19), and the

causative virus has been named as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).¹

The number of COVID-19 patients has dramatically increased worldwide.² Globally, as on May 24, 2021, there have been 166,860,081 confirmed cases of COVID-19, including 3,459,996 deaths, reported to the World Health Organization

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(WHO). In India, 26,752,447 confirmed cases and 303,720 deaths had been reported by May 2021.³

The rapid surge of COVID-19 cases in the country makes it essential to rapidly identify the cases for isolation and adequate treatment which will in turn limit the spread of the disease. Rapid detection, effective isolation of symptomatic cases, and systematic tracing of close contacts are paramount to blunt the community spread of SARS-CoV-2 infection.⁴ Reverse-transcription polymerase chain reaction (RT-PCR) is considered as the “gold-standard” test to diagnose SARS-CoV-2 because of its better specificity and sensitivity.⁵ RT-PCR is considered to be the diagnostic reference standard for COVID-19.⁵ Disadvantages of RT-PCR include requirement for specialized instruments and technical expertise to conduct RT-PCR assays.⁴ The RT-PCR testing also requires a sophisticated laboratory with a biosafety level (BSL)-2/BSL3 setup and trained technicians to run the test and interpret results.⁶ The RT-PCR procedure has a minimum turnaround time of 8 to 10 hours from the collection of swabs to reporting of results which can further increase in resource-limited and high-burden settings. In semiurban and rural settings, molecular diagnostic laboratories are scanty and the reagents/viral transport medium (VTM) and resources are difficult to procure. Therefore, the need of the hour is to rapidly detect and isolate positive cases to contain the disease spread to quickly triage patients with severe acute respiratory illness (SARI) in emergency departments (EDs) and to ramp up testing facilities. The rapid surge in cases and increased sample load has resulted in a prolonged turnaround time and delay of the reports to more than 72 hours. This has led to the Indian Council of Medical Research (ICMR) recommendation to increase the use of rapid antigen detection tests for COVID-19 detection on May 5, 2021. Many diagnostic test kit manufacturers are in the process of developing or have already developed rapid diagnostic kits and devices to facilitate point-of-care testing.

Rapid antigen test (RAT) is found to have a high specificity, high positive predictive value (PPV), less sensitivity, less negative predictive value (NPV), and have the advantage of a turnaround time of 15 to 30 minutes for the results.^{4,7} Studies suggest that there is an increase in sensitivity of RAT corresponding to lower cycle threshold (CT) values in RT-PCR and vice versa.⁸ A team of scientists from the All India Institute of Medical Sciences (AIIMS) in November 2020 evaluated a rapid antigen immunochromatographic card.⁶

Several COVID-19 antigen (Ag) rapid tests have been approved by the Drugs Controller General of India (DCGI) and their performances are yet to be assessed by diagnostic laboratories. Our study aims to evaluate the performance of Athenese-Dx COVID-19 RAT results in comparison with the RT-PCR results of patients to evaluate the specificity, sensitivity, NPV, and PPV which can help in contributing the rapid diagnosis of the disease and taking measures to curb the spread of the disease.

Materials and Methods

This prospective study was performed at Chettinad Hospital and Research Institute, a tertiary COVID-19 care hospital

located in Chengalpattu District, amidst the semiurban settings on the outskirts of Chennai, Tamil Nadu. The Molecular Virology division of Microbiology laboratory at Chettinad Hospital is an ICMR permitted laboratory for COVID-19 testing. The study commenced after obtaining the Institutional Human Ethics Committee clearance.

Patient consent was obtained prior to sample collection. All patients who were suspected to have COVID-19 disease and who had been prescribed the RT-PCR test for COVID-19 were included in this study. Both nasal and throat swabs were collected from the study participants. For RT-PCR, the sample was collected using the Dacron swabs and transported in HiViral transport medium taking appropriate precautions to maintain the cold chain. The nasopharyngeal (NP) swab specimens for both RT-PCR and RAT were collected by inserting the sterile swab into the nostril until it reached the posterior nasopharynx. Then the swab was rotated a few times against the nasopharyngeal wall and removed carefully from nostril. Throat swabs were collected by inserting the swab into the posterior pharynx and the tonsillar areas and posterior oropharynx without any contact with the tongue, teeth, and gums. For RT-PCR analysis, the nasopharyngeal and throat swabs collected from the patients were placed into the Hi-viral transport medium and for RAT, the nasopharyngeal swabs were inserted into the extraction tube having COVID-19 Ag lysis buffer (~0.3 mL) and mixed well. Both HiViral transport medium and the extraction tube samples were transported to the laboratory for testing.

The patient samples were tested soon after collecting. If not tested immediately, swab specimens were stored in a clean and closed container at 2 to 8°C for up to 8 hours.

Rapid antigen detection procedure: Athenese-Dx COVID-19 RAT kit was used for rapid Ag detection. In brief, all the specimens and test components were brought to room temperature (15–30°C). This was followed by the specimen extraction procedure where 11 drops (~0.3 mL) of the sample extraction buffer were added to the extraction tube, or extraction buffer was filled up to the marked line on the extraction tube, and then kept upright. The swab was inserted into the extraction tube containing 0.3 mL of the extraction buffer and swirled at least five times. The swab was squeezed several times against the inside of the tube. Then the swab was removed and discarded. The extracted specimen in the tube was ready for testing. The test device was removed from the sealed pouch just prior to testing and placed on a clean, flat surface. The nozzle was inserted into the sample extraction tube containing extracted specimen. The tube was inverted and three drops (~80–90 µL) of the test sample were added into the sample well by gently squeezing the tube. The results were read at 15 minutes. Some instances, positive results could be visible in as soon as 3 minutes. All results were confirmed at the end of 15 minutes. The used devices were discarded as per the Biomedical Waste disposal guidelines.

The test was interpreted as follows: if only the C-line develops, the test indicates that no detectable SARS-CoV-2 virus is present in the specimen. The result is negative or nonreactive. If both C line and T line develop, the test

indicates presence of SARS-CoV-2 virus. The result is COVID-19 positive or reactive. If no C line develops, the assay is invalid regardless of color development on the T line.

Procedure for RT-PCR: as per ICMR guidelines, RNA extraction was automated and PCR performed using Rotor Gene Q (QIAGEN) RT-PCR for COVID-19 was performed using SD Biosensor Real Time PCR kit. Briefly, SD Biosensor RT-PCR detection kit detects two genes, *ORF1ab* (*RdRp*) and *E* genes, from oropharyngeal and nasopharyngeal samples. The kit is based on the TaqMan probe real-time fluorescent technology. FAM channel qualitatively detects *ORF1ab* (*RdRp* gene), JOE channel qualitatively detects *E* gene, and CY5 channel detects internal reference gene.

Results

A total of 599 samples were tested by both RT-PCR and RAT methods. Of the total 599 samples tested by RT-PCR, 310 (52%) were positive and 289 (48%) tested negative for SARS-CoV-2. Of the 599 samples tested by RAT, 230 (38%) were positive and 369 (62%) were negative (► **Table 1**).

Of the 310 RT-PCR-positive samples, 230 (74%) were RAT positive (true positives) and 80 (26%) were RAT negative (false negatives). Of the 289 RT-PCR negative samples, all were RAT negative. None of the samples which were negative by RT-PCR were positive by RAT (► **Table 2**).

Sensitivity of RAT was 74.19% and the specificity was 100%. PPV was 100% and the NPV was 78.3%.

Considering CT values for RT-PCR, 66 (21%) patient samples, out of the total 310 positives, had CT values of between 10 and 20 for both *E* and *RdRp* genes. Of the 66 samples, RAT was positive in 64 samples (97%) and negative in 2 (3%) samples. Also, 149 (48%) patient samples had CT values of greater than 20 and up to 30 for both *E* and *RdRp* genes. RAT was positive for 116 (78%) samples and negative for 33 (22%) samples. Further, 49 (16%) samples had CT values of greater than 30 for both *E* and *RdRp* genes. Of the 49 samples, RAT was positive for 14 (29%) samples and negative for 35 (71%) samples (► **Table 3**).

Of the 66 (21%) samples with CT values of over 10 and up to 20 for *E* gene, RAT was positive for 64 (97%) samples and only 2 (3%) samples were negative for RAT. Of the 95 (31%) samples with CT values of over 10 and up to 20 for *RdRp* gene, 91 (96%) samples were positive by RAT and only 4 (4%) samples were negative by RAT.

Table 1 Percentage of samples detected positive and negative by RT-PCR and RAT ($n = 599$)

Methodology	% of positivity	% of negativity
SARS-CoV2—rtRT-PCR	52	48
SARS-CoV2—RAT	38	62

Abbreviations: RAT, rapid antigen test; rtRT-PCR, real-time reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

Table 2 Overall sensitivity and specificity of the kit

	RT-PCR positive	RT-PCR negative	Total
RAT positive	230	0	230
RAT negative	80	289	369
Total	310	289	599

Abbreviations: RAT, rapid antigen test; RT-PCR, reverse-transcription polymerase chain reaction.

Considering the CT pattern for individual genes and RAT positivity, of the 178 (57%) samples tested positive, with an *E* gene, CT value of more than 20 up to 30, RAT was positive in 143 (80%) samples and negative in 35 (20%) samples. Moreover, 168 (54%) samples had CT of more than 20 up to 30 for *RdRp* gene and of the 168 samples, 125 (74%) samples were positive by RAT and 43 (26%) samples were negative by RAT.

Of 68 (22%) RT-PCR positive samples which had a CT of more than 30 for *E* gene, RAT was positive in 22 (32%) samples and negative in 45 (66%) samples. Also, 49 (16%) samples had a CT value of more than 30 for *RdRp* gene and out of which 14 (29%) samples were positive and 35 (71%) samples were negative by RAT (► **Table 4**).

When the CT values for both *E* and *RdRp* genes were greater than 10 and up to 20, the sensitivity and specificity of RAT were 97 and 100%, respectively. However, when the CT values for both *E* and *RdRp* genes were greater than 20 and up to 30, the sensitivity and specificity of RAT were 78 and 100%, respectively. When the CT values of both *E* and *RdRp* genes were greater than 30, the sensitivity and specificity of RAT were found to be only 28 and 100%, respectively.

Considering the CT values of only *RdRp* gene and RAT, sensitivity and specificity are as follows: when the CT value of *RdRp* gene is greater than 10 up to 20, the sensitivity and

Table 3 Comparative analysis of RAT positivity with common CT value range for both *E* and *RdRp* genes

RAT positive/negative	Total samples with CT values of > 10 up to 20 for both <i>E</i> and <i>RdRp</i> genes	Total samples with CT values more than 20 up to 30 for <i>E</i> gene and > 10 up to 20 for <i>RdRp</i> gene	Total samples with CT values of > 20 up to 30 for <i>E</i> and <i>RdRp</i> gene	Total samples with CT values for more than 30 <i>E</i> gene and > 20 up to 30 <i>RdRp</i> gene	Total samples with CT values of > 30 for <i>E</i> and <i>RdRp</i> genes
Total RAT-positive samples	64	27	116	9	14
Total RAT-negative samples	2	8	33	2	35

Abbreviations: CT, cycle threshold; RAT, rapid antigen test.

Table 4 Comparative analysis of RAT positivity and CT value range for individual genes (*E* and *RdRp* genes)

CT value range for <i>E</i> and <i>RdRp</i> gene	Total RAT-positive samples	Total RAT-negative samples
Total samples with <i>E</i> gene > 10 up to 20	64	2
Total samples with <i>RdRp</i> gene > 10 up to 20	91	4
Total samples with <i>E</i> gene > 20 up to 30	143	35
Total samples with <i>RdRp</i> gene > 20 up to 30	125	43
Total samples with <i>E</i> gene > 30	22	45
Total samples with <i>RdRp</i> gene > 30	14	35

Abbreviations: CT, cycle threshold; RAT, rapid antigen test.

specificity were 96 and 100%; for CT values of *RdRp* gene is greater than 20 up to 30, the RAT sensitivity and specificity were 74 and 100%, respectively. However, when the CT values of *RdRp* gene is greater than 30, the RAT sensitivity and specificity were found to be only 29 and 100%, respectively.

SARS-CoV-2 symptom wise comparative analysis with RAT positivity and RT-PCR positivity were done in this study (► **Tables 5** and **6**).

The sensitivity and specificity of RAT among samples obtained from symptomatic individuals include 73.7 and 100%, respectively. The sensitivity and specificity of RAT among samples obtained from asymptomatic individuals include 79 and 100%, respectively.

Discussion

Molecular tests, like real-time RT-PCR, remain as the gold-standard laboratory diagnostic test and also remain as a widely used confirmatory test for SARS-CoV-2 infection. In order to limit the spread of infection caused by SARS-CoV-2 and proper management of the infected patients, rapid and cost-effective laboratory tests are needed. In this study, we evaluated the performance of Athenese Onsite COVID Antigen Rapid Test with the standard SARS-CoV-2 real-time RT-PCR assay that we routinely employ in our laboratory. The overall sensitivity and specificity of RAT was found to be 74.19 and 100%, respectively. Therefore, the true positives in our study were found to be 74% and the false negatives were 26% by RAT with RT-PCR as the reference standard. The false

Table 5 Total asymptomatic and symptomatic samples analyzed

Symptomatic/Asymptomatic	Total number of samples analyzed
Symptomatic patient samples	570
Asymptomatic patient samples	29

negatives obtained in our study by RAT could be due to improper sample collection, or low viral load can be some reasons for the false negativity of RAT.³ As per the study of Pérez-García et al,⁹ the sensitivity and specificity of Panbio and SD biosensor kits and as per our study, the sensitivity and specificity of Athenese Rapid Antigen detection card have been tabulated (► **Table 7**).

The CT value-dependent evaluation of RAT sensitivity was also done in our study. The sensitivity of RAT was found to be 97% when the CT values for *E* and *RdRp* genes were greater than 10 up to 20. But when the CT values for *E* and *RdRp* genes were greater than 20 up to 30 and greater than 30, the sensitivity of RAT showed significant decrease with 78 and 28%, respectively. A similar study was done by Pérez-García et al, showing that for Pan bio and SD RAT's, when the CT value was up to 20, the sensitivity exhibited by both the diagnostic kits was found to be 100%.⁹ However, when the CT values were between 20 to 25, the sensitivity of Pan bio and SD biosensor was found to be 93 and 95%, respectively. When the CT values were between 25 to 30, the sensitivity of Pan bio and SD was found to be 41 and 52%. When the CT values were more than or equal to 30, the sensitivity of the kits was found to be 5 and 17%, respectively.⁹

Therefore, this evaluation clearly highlights that the sensitivity of RAT is good when the CT values are greater than 10 up to 30 for both *E* and *RdRp* genes, and hence RAT can help to detect SARS-CoV-2 positivity within 15 to 20 minutes and further directs to isolate the positive patients to contain the spread of infection in very less time. RAT can also be used as a point-of-care diagnostic in rural areas where sophisticated SARS-CoV-2 instruments are not available. However, the

Table 7 Comparative analysis of sensitivity and specificity pattern of Athenese-Dx with other RAT's

	Pan Bio	SD biosensor	Athenese-Dx
% of specificity	100	97.3	100
% of sensitivity	60	66.5	74

Abbreviation: RAT, rapid antigen test.

Table 6 Symptom wise comparative analysis of samples showing RT-PCR and RAT positivity

Symptomatic/asymptomatic	RT-PCR positive	RT-PCR negative	RAT positive	RAT negative
Total symptomatic patient samples	286 (50.2%)	284 (49.8%)	211 (37%)	359 (63%)
Total asymptomatic patient samples	24 (82.8%)	5 (17.3%)	19 (65.5%)	10 (34.5%)

Abbreviations: RAT, rapid antigen test; RT-PCR, reverse-transcription polymerase chain reaction.

sensitivity of RAT greatly decreases when the CT values are greater than 30 and RAT even fails to detect SARS-CoV-2 infection which leads to false negativity.^{10,11} Therefore, the viral load in the sample is an important factor determining the sensitivity of the test.

When the CT values of the SARS-CoV-2-specific target gene, *RdRp* was evaluated, the RAT sensitivity was 96% when the CT values for *RdRp* gene were greater than 10 up to 20 which was statistically significant. Also, when the *RdRp* gene CT values were greater than 20 up to 30, the RAT sensitivity was 74% which was found to be appreciable when compared with low sensitivity of RAT (29%) when CT values for *RdRp* gene were greater than 30. In our study, for few samples with CT values 28 and greater than 30, we observed faint bands while interpreting the test results by RAT. Therefore, further methodologies can be adopted to refine the sensitivity of the test kit.

The sensitivity and specificity of our RAT in detecting positivity in symptomatic individuals were found to be 73.7 and 100%, respectively. A similar study by Peña et al showed that SD biosensor RAT exhibited sensitivity and specificity of 69.8 and 100%, respectively.¹²

Strengths and Limitations

The main advantages of RAT include the following: it yields rapid results within a short turnaround time, cost-effective, and does not require sophisticated laboratory establishment and technical expertise. Therefore, this test can be adopted in areas with rapid surge in SARS-CoV-2 cases and help to identify the positive cases. Once detected by RAT, advisory can be given to the positive patients to get them admitted in COVID-19 care centers for further treatment protocols and to initiate infection control measures. This method of isolation protocols also helps to avoid further cross-transmission of SARS-CoV-2 infection to COVID-19-negative patients presenting with other respiratory illness in outpatient departments in hospital settings.

The limitation of RAT includes the following: SARS-CoV-2-negative results can only be confirmed by real-time RT-PCR. Also, it can present with higher degree of negativity when the samples are not collected properly and lower viral load with RT-PCR CT values of greater than 30. Therefore, RAT can work better only when the patients present clear symptoms with the viral load being high.

Conclusion

To conclude, Athenese-Dx COVID-19 Antigen Rapid Test kit gives an overall sensitivity and specificity of 74.19 and 100%. Minimum acceptance criteria of sensitivity and specificity of RAT kits should be more than/equal to 50 and more than/equal to 95%, respectively. Athenese-Dx COVID-19 Ag Rapid test met the ICMR acceptance criteria, and it could be a potential tool for point-of-care testing purpose. The sensitivity range of the kit greatly overlaps with the viral load which is reflected by the *E* and *RdRp* genes' CT values detected by SARS-CoV-2 RT-PCR. However, RAT can be potentially used as a point-of-care and screening tests,

especially in high-prevalence remote areas and hospital settings to contain the spread of infection and to establish infection prevention measures.

Ethical Approval

This study was approved by the Ethical Committee with proposal no.: 187/IHEC/November2020.

Authors' Contribution

P.S. and A.P.S.R. designed the study. A.P.S.R. and P.S. collected and analyzed the data. L.K., P.S., and A.P.S.R. participated in the manuscript revision. All authors approved the final draft of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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