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Sensitivity and specificity of a rapid antigen assay for the detection of SARS-CoV-2 during the surge of B.1.1.529 variant

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ABSTRACT

Background: As COVID-19 spread across the globe, the new variants continued to emerge, leading to a rapid surge in the cases and thereby overwhelming the testing laboratories. As Rapid antigen test kits became available, they complimented the reverse transcription polymerase chain reaction (RT-PCR) based testing and thereby moderately disburdening the testing laboratories. However, to increase the testing capacities, the regulatory authorities approved these rapid kits with little scrutiny. Therefore, validation of rapid antigen testing kits becomes essential before they are used as viable alternatives to RT-PCR based testing. **Aims and Objectives:** The aim of this study was to compare the sensitivity and specificity of OSKIT SARS-CoV-2 corona antigen test (Oscar Medicare Pvt. Ltd., India) to that of COVID-19 ONE-STEP RT-PCR KIT (Meril Diagnostics Pvt. Ltd., India). **Materials and Methods:** In this prospective study, spanning the peak of third wave in India (Between December 1 and January 31, 2022), 242 specimens were collected and analyzed by comparing their results both by OSKIT SARS-CoV-2 Corona Antigen Test and COVID-19 ONE-STEP RT-PCR KIT. The various clinico-epidemiological attributes of the patients were taken into consideration and used to analyze the results. **Results:** Rapid antigen tests (RAT) was positive in 44 individuals, giving an overall sensitivity of 67.31%. Sensitivity increased when Ct value of below 30 was taken a positive or when only symptomatic individuals were taken for analysis. Sensitivity was highest in case the duration of symptoms was <5 days (92.86%). When comparing RAT results with Ct value of the screening gene (N gene), a higher proportion of positive cases was observed for lower Ct values. Further analysis revealed that majority of the RAT positive cases were from that subset of symptomatic patients who had a history of symptoms of <5 days. **Conclusion:** The COVID-19 rapid antigen test evaluated in this study was able to detect SARS-CoV-2 infection with high viral loads in both asymptomatic and symptomatic individuals. Thus, this test can serve as a rapid tool for reducing community spread of the virus. The study concludes that the duration since symptom onset greatly affects sensitivity of antigen testing.

Key words: Severe acute respiratory syndrome-coronavirus-2; OSKIT SARS-CoV-2 corona antigen test; Meril-COVID-19 one-step reverse transcription polymerase chain reaction KIT

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INTRODUCTION

As the COVID-19 pandemic spread across borders, it highlighted the need for rapid and reliable diagnostics to limit transmission of the disease, both within the community and across countries.[1] For prompt diagnosis, the World Health Organization advocated targeted testing in March 2020 to contain the spread of the SARS-CoV-2 virus.[2] Testing was projected as the backbone of the global pandemic response alongside isolation and contact tracing

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combined with social distancing to reduce the spread of the pandemic.[3]

During the initial days, the real-time reverse transcription polymerase chain reaction (RT-PCR) was widely used as the primary diagnostic modality as it had a high sensitivity and specificity, making it the gold standard for COVID-19 diagnosis.[4] This led to a substantial burden on diagnostic laboratories which were not equipped to handle such a huge number of samples, leading to large delays in analysis and reporting.[5] In addition, the cost, technical expertise needed, limited facilities having the infrastructure to perform the RT-PCR tests, and shortage of reagents and consumables led to an unfulfilled need for testing.[3]

What ensued was a surge in research and development of easier and less time-consuming tests. Rapid antigen tests (RAT) emerged as a promising tool to complement RT-PCR testing.[1] They were advertised as a point-of-care alternative to the highly technical and time-consuming RT-PCR testing.[3] RATs, based on the principle of lateral flow, were deployed extensively to provide immediate results and lessen the burden on diagnostic laboratories. Easy availability and a low cost, along with ease of use allowed minimally trained individuals to perform the test even outside of healthcare facilities.[6]

As the pandemic spread and a continuous barrage of fresh waves struck, driven by the emergence of new variants of the virus, a variety of RATs became available in the market. Proper validation of these kits became imperative before they could be advocated for use as a supportive diagnostic method.[1] Studies conducted across the world have concluded that the sensitivity of a single RAT may differ by up to 20% points between non-symptomatic and symptomatic individuals.[7]

Aims and objectives

This prospective study was carried out to compare the sensitivity and specificity of the OSKIT SARS-CoV-2 Corona Antigen Test (Oscar Medicare Pvt. Ltd., India) to that of COVID-19 ONE-STEP RT-PCR KIT (Meril Diagnostics Pvt. Ltd., India) using 242 respiratory specimens.

MATERIALS AND METHODS

Study design

This study was performed in a tertiary care hospital in North India between December 1, 2021, and January 31, 2022, in the midst of the surge of the Omicron variant which was driving the third wave of COVID-19 in India. This study included 242 eligible subjects who reported to the collection center with either of the following criteria:

1. Symptoms suspicious for COVID-19 infection (fever, dyspnea, cough, sore throat, diarrhea, vomiting, asthenia, myalgias, conjunctivitis, and deficits in smell and taste)
2. Patients without COVID-19-like symptoms but with an increased temperature (>37.3°C)
3. One positive epidemiological criterion
    i. Provenance from areas with a high incidence of SARS-CoV-2 cases
    ii. International travellers (tourist or worker)
    iii. Reporting contacts with a person who tested positive for SARS-CoV-2
    iv. Pre-procedural testing and/or testing required for special purposes.

Two simultaneous nasopharyngeal swabs were collected from the subjects using standard procedures. As data were anonymized, the study was exempted from Institutional Review. Positive cases were defined using RT-PCR as the reference method. All procedures in this study were performed in accordance with the Declaration of Helsinki guidelines.

The first swab was analyzed using the Oscar COVID-19 Antigen Rapid Test Kit which has a turnaround time of 15 min. The second swab was mixed in 5 mL of viral transport media (VTM), comprising Hanks' balanced salt, 0.4% fetal bovine serum, and HEPES, as well as antifungal and antibiotic agents. Samples were transported at 2–8°C to the laboratory and processed within few hours. All samples were processed in biosafety level-2 facility with proper personal protective equipment.

SARS-CoV-2 rapid antigen test

The COVID-19 Antigen Rapid Test Kit is a membrane-based immunochromatographic assay. It detects the nucleocapsid protein of SARS-CoV-2 in nasopharyngeal samples. A healthcare professional first collected the nasopharyngeal swab sample. The assay was performed and interpreted by on-site technicians according to the manufacturer's instructions. The RAT test device had two precoated lines on the result window: test (T) and control (C) lines. The test (T) region was coated with mouse monoclonal anti-SARS-CoV-2 antibody against SARS-CoV-2 N antigen, and the control (C) region was coated with mouse monoclonal anti-chicken IgG antibody. For COVID-19 antigen testing positivity, two colored lines of test (T) and control (C) lines are presented.

SARS-CoV-2 real-time RT-PCR

Another nasopharyngeal swab specimen was collected from patients with suspected COVID-19 using specimen collection

swab kits in 5 mL VTM and processed further for RT-PCR analysis as described previously.[8] Briefly Ribonucleic acid (RNA) extraction and purification from the nasopharyngeal swabs was done using Genetix RNA extraction kit using manufacturer's instructions. The reverse transcription and amplification was carried out by usingCOVID-19 ONE-STEP RT-PCR KIT (Meril Diagnostics Pvt. Ltd., India) in Applied Biosystems 7500/7500 Fast Real-Time PCR Instrument System (ThermoFisher Scientific, USA). A combination of nucleoprotein (N gene) and open reading frame 1b (ORF-1b) genes of Sars-Cov-2 were targeted for the amplification.

Statistical analysis

Specificity and sensitivity with 95% confidence intervals of RAT were calculated using the RT-PCR results as a reference method. Analyses were performed using IBM SPSS v22. Anonymized data on the number of RAT and RT-PCR tests were used. We report the number of cases detected with each test and evaluate the sensitivity of RAT as compared with the gold-standard RT-PCR for this study. Data were analyzed across age, gender, pre-test duration of symptoms, and Ct-value in conjunction with the outcomes of the two tests.

RESULTS

A total of 242 individuals were sampled during the study period. The mean age of the sampled population was 35.09 years (range 3–81 years). COVID-19 positivity was decided on the basis of a positive RT-PCR result, which came positive for 52 individuals. Of a total of 110 males, 19 were positive; while for the 132 females, 33 were positive (P>0.05). Amongst the 73 vaccinated individuals, 15 were positive; while of the 169 non-vaccinated, 37 were positive (P>0.05). Furthermore, for the 140 symptomatic individuals, 31 were positive, while among the 102 asymptomatic individuals, 21 were positive (P>0.05) (Table 1).

RAT was positive in 44 individuals, giving an overall sensitivity of 67.31%. Sensitivity increased when Ct value of below 30 was taken a positive or when only symptomatic individuals were taken for analysis. Sensitivity was highest in case the duration of symptoms was <5 days (92.86%) (Table 2).

Table 1: RT-PCR positivity according to demographic variables

Demographic details	RT-PCR positive	RT-PCR negative	Total	P-value
Female	33	99	132	χ^2=2.124; P=0.145; P>0.05
Male	19	91	110	
Total	52	190	242	
Vaccinated	15	58	73	χ^2=0.055; P=0.085; P>0.05
Not-vaccinated	37	132	169	
Total	52	190	242	
Symptomatic	31	109	140	χ^2=0.085; P=0.771; P>0.05
Asymptomatic	21	81	102	
Total	52	190	242	
Symptomatic<5 days	14	43	57	χ^2=0.418; P=0.811; P>0.05
Symptomatic more than 5	17	66	83	
Total	31	109	140	

RT-PCR: Reverse transcription polymerase chain reaction

Table 2: Performance of RAT with respect to RT-PCR according to different variables

RT-PCR Status	Total, n	Subtotal, n	RAT Positive, n	RAT Negative, n	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Accuracy, % (95% CI)
RT-PCR positive	242	52	35	17	67.31	95.26	89.26
RT-PCR negative		190	9	181	(52.89–79.67)	(91.2-97.81)	(84.66–92.86)
Total		242	44	198			
CT below 30					69.57	93.88	89.26
RT-PCR Positive	242	46	32	14	(54.25–82.26)	(89.55–96.80)	(84.66–92.86)
RT-PCR Negative		196	12	184			
Total		242	44	198			
Symptomatic					67.74	96.33	90.00
RT-PCR Positive	140	31	21	10	(48.63–83.32)	(90.87–98.99)	(83.79–94.60)
RT-PCR Negative		109	4	105			
Total		140	25	115			
Symptomatic, <5 days					92.86	90.70	91.23
RT-PCR Positive	57	14	13	1	(66.13–99.82)	(77.86–97.41)	(80.7–97.09)
RT-PCR Negative		43	4	39			
Total		57	17	40			

RT-PCR: Reverse transcription polymerase chain reaction, RAT: Rapid antigen test

The majority of the study population was of a younger age group (20–40 years) both amongst males and females (Figure 1) along with the symptomatic population, which also had a predilection for the younger subset (Figure 2) A higher proportion of younger people were vaccinated among the study population (Figure 3) and a higher percentage of positive cases also were from the younger subset (Figure 4). When comparing RAT results with Ct value of the screening gene (N gene), a higher proportion of positive cases was observed for lower Ct values (Figure 5). Further analysis revealed that majority of the RAT positive cases were from that subset of symptomatic patients who had a history of symptoms of <5 days (Figure 6).

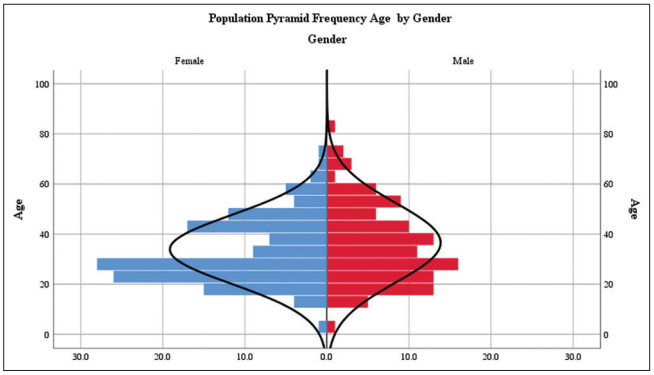

Figure 1: Gender distribution and age composition of the study population

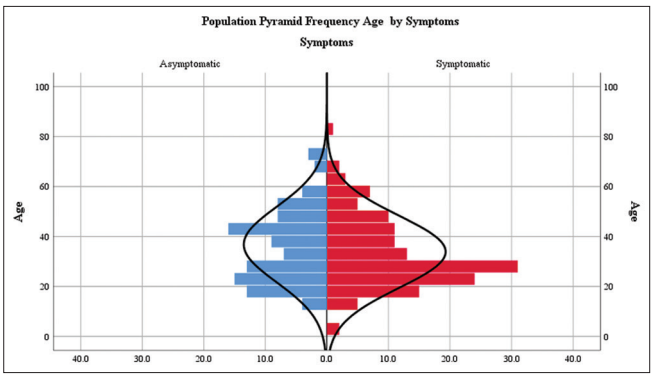

Figure 2: Age distribution of the study population according to the symptoms

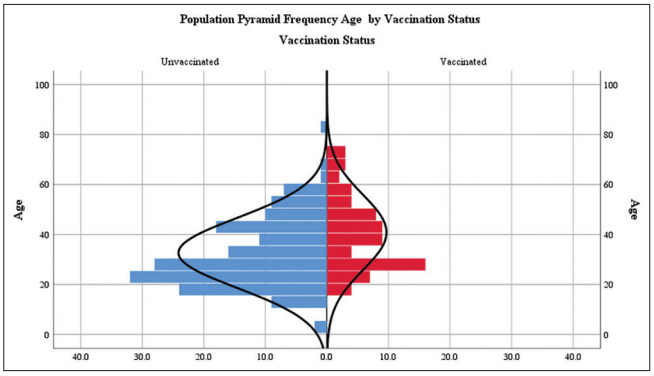

Figure 3: Vaccination status of the studied population

DISCUSSION

In this study, we assessed the performance of the Oscar Rapid antigen test, a recently commercialized RAT in India for the detection of SARS-CoV-2 as compared to RT-PCR in 242 parallel samples. The samples were collected from individuals who sought testing for COVID-19-related symptoms or following the protocols established by the regional health authorities.

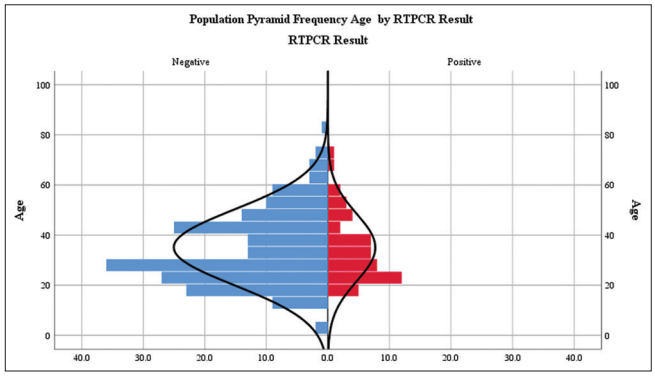

Figure 4: Age distribution of the study population as per COVID-19 positivity

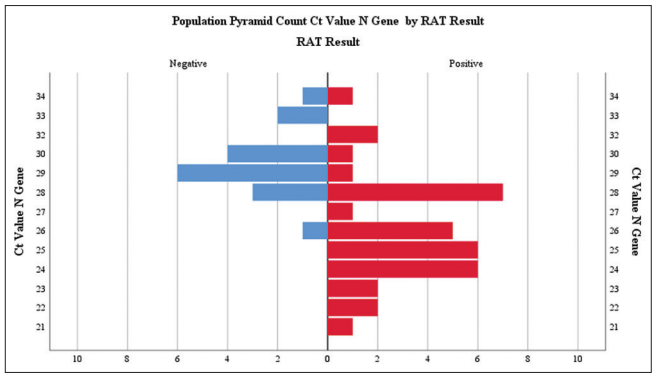

Figure 5: Ct value of screening gene as compared with RAT results

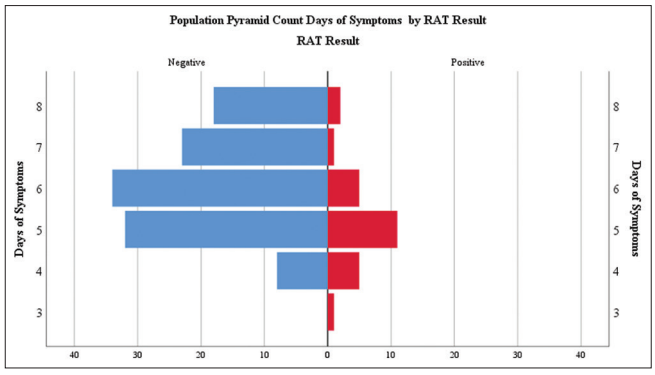

Figure 6: Rapid antigen test positivity as compared with days of symptom onset

Various RATs have been introduced since the onset of the pandemic and as such determining their diagnostic performance is of vital importance as this indicates their reliability and clinical utility.[9] To the best of our knowledge, this study deems the first one in the region that provides a detailed evaluation of the diagnostic performance of a commercialized RAT against the gold-standard RT-PCR. Although RAT and RT-PCR have a wide difference in terms of protocols, the core ideas, targets, and application,[10] both were widely used during the COVID-19 pandemic, and as such comparing their ability to identify true positives is a logical point of research**.** Furthermore, evaluation of RAT is essential as many virus variants can be circulating at diverse periods with varying dominance which can be different from the virus strain against which the antibodies coated in the RAT were raised.[11] Due to these scenarios, it is recommended to continuously evaluate and update the validity of RAT when applied in different communities and during different time intervals.

In the 242 cases, the overall sensitivity of the RAT was 67.31%. In comparison, the sensitivity was higher for the samples that were RTPCR positive with high viral loads (sensitivity 69.57% in samples with ct values <30) and also for people who presented with symptoms suggestive of COVID-19 (67.74%). Recent large prospective studies on various RATs have been conducted on a diverse range of participants and performed in settings with extremes of SARS-CoV-2 prevalence.[12-15] The variations in the results may be due to the differences in the study population, their clinical features, the sample type used for processing, RT-PCR protocol, and viral load in the samples. The overall sensitivity reported by the aforesaid studies varied from 60.5% to 90.5%. The studies consisting of symptomatic patients reported a higher sensitivity, while those where the study population comprised a large subset of the population reported lower sensitivities.[16]

Furthermore, the Ct values were higher in the PCR-positive samples from the asymptomatic population as compared to the symptomatic group (mean 28.1 vs. 27.41, respectively), implying that a lower viral load might be the reason for the lower sensitivity in that subset of patients. RAT, as has been previously stated, is based on the detection of antigens specifically the SARS-CoV-2 nucleocapsid (N) protein, while the gold standard for SARS-CoV-2 detection; RT-PCR, utilizes the principle of amplification of RNA to millions of copies.[17] Understandably, the sensitivity of RATs is lower. Despite this significant disadvantage, several authors have proposed that RATs could be used as a test of infectiousness rather than of the clinical disease,[18] and modeling studies performed have indicated that if done with intent, the sensitivity is less important than the test frequency and turn-around time.[17]

Studies have shown that viral loads of 1 million RNA copies per mL (or per swab) of a respiratory sample have been proposed as a practical cut-off for assessing the infectiousness of the patient.[18] It has been suggested that 1 million RNA copies/mL roughly corresponds to a Ct value of 30 in several RT-PCR-based studies.[18] In this study, samples with Ct values below 30, RAT's sensitivity was found to be 69.57%. As we did not proceed to isolate live viruses from the samples, infectiousness remained unknown. The presence of symptoms in such patients does not necessarily indicate their infectiousness as has been previously documented.[19] This is reassuring as RAT can safely identify the majority of infectious cases, which can prove valuable in resource-limited settings like ours. Nonetheless, in our study 14 among the potentially infectious individuals (ct values <30) were found to be negative by RAT, highlighting the fact that negative results should be interpreted cautiously. A false negative individual can act as a source of infection for the community. We suggest that in the case of symptomatic patients, those with a strong suspicion of infection may be tested repeatedly by RAT or parallel PCR testing may be done. In resource-limited settings, where there is a paucity of RT- PCR facilities, it seems logical that RAT results be interpreted with other laboratory and clinical findings to enhance the performance of RAT.

Studies done around the world have depicted that SARS-CoV-2 viral load peaks in the 1st week after the onset of symptoms.[20] Thereafter, viral loads in the upper respiratory tract samples have been shown to drop significantly.[21] Our data reiterates this finding as for SARS-COV-2 infected patients presenting with a history of symptom onset of fewer than 5 days duration, the sensitivity of the RAT was about 92.86% as opposed to those presenting at a later stage. This is in line with other studies where the study group comprised a population reporting early during the onset of symptoms.[16]

In our study, the overall specificity of the RAT was very high (95.26%). This is consistent with the previous reports, wherein specificity numbers close to 100% were achieved.[15] This signifies that false positive rates for RAT are quite low; although in the low prevalence settings (<1%), the proportion of false positives rises.[22]

Lateral flow-based antigen detection tests have been used previously for various infectious diseases considering the ease of use and short turnaround time.[23] In the scenario of the current COVID-19 pandemic, RATs aid in the early assessment of infectiousness especially in densely populated areas and low-resource settings. As a rule, RAT is most effective when subjects have a history of symptoms suggestive of COVID-19 or have a history of contact with

a lab-confirmed case of COVID-19. The sensitivity further increases when testing is done within the first few days of the onset of symptoms. Worth mentioning is that many cases of COVID-19 can be asymptomatic, with a low viral load in the upper respiratory tract when compared with that of symptomatic cases.[24] Thus, RAT results need to be interpreted with caution, taking into consideration the clinical features of the individual to increase its sensitivity.

Limitations of the study

We have conducted this study for comparing the OSKIT with RT-PCR in a low to medium prevalence setting. A total of 77.8% of the samples were negative for SARS-CoV-2 in the subset of symptomatic patients. It is can be assumed that most of the SARS-CoV-2 negative samples of symptomatic patients contained other respiratory infection agents, which are common during the time of sample collection. Furthermore, lateral flow assays suffer from subjective interpretation, which may lead to difficulties in analysing weakly positive bands. Testing was made free of cost by the regional health agencies which led to liberal testing criteria. A direct consequence of this was a high percentage of negative results. One limitation of the study is therefore that the reasons for testing may have varied considerably amongst the study population. Poorly implemented indications for testing as well as a high proportion of asymptomatic individuals in the study population explain the lower sensitivity of the RAT in our study.

CONCLUSION

This study evaluated the performance of the OSKIT SARS-CoV-2 Corona Antigen Test in a community setting consisting of both symptomatic and asymptomatic subjects. The RAT was able to detect the SARS-CoV-2 B.1.1.529 variant during the third pandemic wave in India. This is, to the best of our knowledge, the largest prospective study comparing the performance of the OSKIT with RT-PCR. In summary, the COVID-19 rapid antigen test evaluated in this study was able to detect SARS-CoV-2 infection with high viral loads in both asymptomatic and symptomatic individuals. Thus, this test can serve as a rapid tool for reducing community spread of the virus. This study has implications that will help in tackling future waves of the pandemic. The study concludes that the duration since symptom onset greatly affects sensitivity of antigen testing. Although, this RAT has a lower sensitivity when compared to the well-established RT-PCR test, in some situations this might be outweighed by the advantages of identifying infectious individuals faster and thus allowing for rapid isolation and contact tracing.

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SAL- Performed the assays and critically revised the manuscript; **TA**- Performed the statistical analysis and wrote first draft of the manuscript; **AHA**- Acquired and interpreted the data; **UA**- Acquired the data and revised the manuscript; **KJ**- Acquired and analysed the data; **APK**- Acquired and analysed the data; **JA**- Conceptualized and designed the study.

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