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Original Article

Microbiology Section

From Bench to Bedside: A Retrospective Study on the Utility of Rapid Antigen Testing for Coronavirus Disease from Firozabad, Uttar Pradesh, India

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ABSTRACT

Introduction: Ever since the Coronavirus Disease-2019 (COVID-19) pandemic hit, there have been constant efforts to develop rapid, sensitive and specific diagnostic methods to detect the virus in order to curb the further spread of the disease. There is an array of tests available for the detection of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Time being a very crucial factor and Rapid Antigen Testing (RAT) is very helpful in detecting the virus.

Aim: To discuss the importance of rapid antigen testing among symptomatic and asymptomatic cases in different age groups and gender with association to infection.

Materials and Methods: This retrospective study was conducted in Department of Microbiology, Autonomous State Medical College and SNM Hospital, Firozabad, Uttar Pradesh, India, from April 2020 to August 2021. A total of 16,258 samples were collected from symptomatic patients having Influenza Like Illness (ILI), Severe Acute Respiratory Illness (SARI), those seeking hospitalisation, contacts (symptomatic and asymptomatic) and travellers were subjected to antigen detection by the Standard Q COVID-19 antigen kit following proper precautions. The cases were divided into Group A of patients who presented with symptoms ≤7 days, Group B of patients who presented with signs and symptoms >7 days and group C comprised of asymptomatic patients. The Chi-square test was done to test the statistical significance of association of symptomatic patients with outcome of the antigen test.

Results: Of the total 16,258 samples tested, the maximum number of positive cases were found in the age group 30-39 years followed by 20-29 years. The least number of positive cases were found in extreme age group, i.e., six cases in >90 years and no case was found in below 9 years. No significant impact was found on the positivity rates on the basis of gender. The percentage positivity as detected by rapid antigen was 2.1% and maximum patients were found in the group having symptoms ≤7 days ($p<0.05$).

Conclusion: Rapid Antigen Detection Test (RADT) for SARS-CoV-2 is a simple, portable, fast and easy to perform test. It could be easily used in rural areas as it does not require special laboratory setup. It could be used for mass testing and helped as a good epidemiological tool. However, few symptomatic cases which could not be detected by rapid testing had to be cross checked with Real Time-Reverse Transcriptase Polymerase Chain Reaction (RT-PCR). Thus, when used in conjunction with molecular methods, the sensitivity of the test increased.

Keywords: Epidemiological, Point of care, Rapid antigen detection test

INTRODUCTION

The hurricane of COVID-19 outbreak has affected the mankind in the past two years causing immense damage in all spheres of life. Ever since it started in March 2020, there have been constant efforts to devise a fast, sensitive and specific test for its detection which can also be used in rural and peripheral areas easily and reach out to the outreach. The timely detection of the virus is very important as the prompt isolation of the patients curtails the further dissemination of the virus. The high transmission rates and limited testing capacity has been a hindrance in managing the pandemic [1].

Besides, the conventional gold standard techniques are time taking and there is an increased risk of cross contamination, pipetting errors, etc. There has been a race to develop nucleic acid assays, hybridisation microarray assays and amplicon based metagenomics sequencing [2]. The need of the hour has been to develop rapid, inexpensive testing methods which can be deployed without using special equipments or infrastructure. The Lateral Flow Detection (LFD) tests have given promising results and are cost-effective [3]. The other rapid tests like the Quidel's Antigen test besides testing for the SARS-CoV-2 also checks for the Influenza virus antigens and got an Emergency Use Authorisation (EUA) from the Food and Drug Administration (FDA) [4]. The Nucleic Acid Amplification Test (NAAT) and RT-PCR assays available for COVID-19 detection are automated and molecular based methods but take more time in comparison to rapid testing. The rapid tests have also served as good diagnostic tools for surveillance [5]. Other studies from different parts of India have shown that RADT has proved to be a good epidemiological tool in detection of COVID-19 [6]. The Indian Council of Medical Research (ICMR) certified the studies on RADT which accounted for close to 50% testing of COVID-19 [7-9]. This is the first study from Northern India (Firozabad, Uttar Pradesh) which was conducted to discuss the utility of the rapid testing for COVID-19 in a tertiary care hospital in different age groups, gender and associating it with symptoms.

MATERIALS AND METHODS

This retrospective study was conducted in Department of Microbiology, Autonomous State Medical College and SNM Hospital, Firozabad, Uttar Pradesh, India. A total of 16,258 samples were collected from April 2020 to August 2021 (thereafter the data was analysed from September 2021 to December 2021) from the Firozabad district and all the neighbouring areas.

Inclusion criteria: RAT was done on the samples taken from the patients who presented with ILI and SARI like symptoms as and

when they reported and also from patients seeking hospitalisation, from contacts (asymptomatic direct or high risk contacts) and travellers (domestic and International). The data of symptoms and clinical history/travel history was collected from hospital records or patient summary reports.

Exclusion criteria: The samples from places with low prevalence of infection (orange and green containment zones of neighbouring areas of Firozabad, UP for e.g., Etah, Kasganj, etc.,) [10] were excluded to avoid false positive results.

The details of age and gender were recorded along with signs and symptoms. The cases were divided into three groups viz., group A patients who presented with symptoms ≤7 days, group B patients who presented with signs and symptoms >7 days [11] and group C comprised of asymptomatic patients (who had been in direct contact with symptomatic patients and high risk contacts with co-morbid conditions like diabetes, heart ailments, etc., and people coming from red containment zone) and those who were seeking to travel within the country (domestic) or outside the country (International) when lockdown was suspended.

The Standard Q COVID-19 antigen kit manufactured by SD Biosensor was used, which comprises of a rapid immunochromatographic assay, for the qualitative detection of specific antigens to SARS-CoV-2. The sample was collected from the surface of the posterior nasopharynx of the patient with the help of a sterile swab by trained staff following proper precautions and processed as per the manufacturers' instructions without any delay. The swab was then inserted in the extraction buffer, stirred and removed following which the nozzle cap was pressed tightly on the tube. Three drops of the extracted specimen was put on the cassette well and the result was read within 15-30 minutes.

Principle

The test is based on immunochromatographic assay which comprises of a nitrocellulose membrane precoated with mouse monoclonal antichicken IgY antibody on the control line region and mouse monoclonal anti SARS-CoV-2 antibody (conjugated with colour particles used as antigen detectors) on the test line region. The sample containing SARS-CoV-2 antigen interacted with monoclonal anti SARS-CoV-2 antibody making an antigen-antibody colour particle complex which migrated via capillary action on the membrane until the test line where it was captured by the mouse monoclonal anti SARS-CoV-2 antibody. The intensity of the coloured line depend upon the amount of antigen present in the specimen. The control line always appeared which indicated that the test procedure was performed properly.

Interpretation of the result- The specimens which showed coloured line in both the test and control were considered positive, the ones which showed line only in the control and not in the test well were considered negative and those which showed coloured line in test well but not in the control were considered invalid and were repeated.

STATISTICAL ANALYSIS

All the variables have been presented in the form of frequencies and percentages and these percentages have been calculated from the total number of antigen tests done which were 16,258, besides being depicted in suitable diagrammatical representation for the bird-eye-view. Thereafter, the Chi-square test was done to test the statistical significance of association of symptomatic patients with outcome of the antigen test. All the analysis was performed using R software version 3.6.2 and MS Excel 2007. A p-value <0.05 was considered to be statistically significant.

RESULTS

A total of 16,258 samples were included and analysed. The maximum testing for the COVID-19 Rapid antigen was done in males of age group 20-29 years [Table/Fig-1]. The maximum occurrence of the infection was in the age group 30-39 years followed by 20-29 years and the least positivity was found in the higher age groups above 90 years followed by age group below 9 years. The people seeking to travel in the age group 30-39 years showed 23 (0.1%) positivity [Table/Fig-2]. The patients in different categories for Coronavirus antigen testing showed maximum positivity 102 (0.6%) in the group of contacts of positive cases [Table/Fig-3].

Age group (years)	Female n (%)	Male n (%)	Transgender n (%)	Grand total n (%)	p-value
0-9	88 (0.5)	121 (0.7)	0 (0)	209 (1.3)	Independence of antigen result and gender p-value=0.07
10-19	783 (4.8)	1196 (7.4)	0 (0)	1979 (12.2)	
20-29	3142 (19.3)	4030 (24.8)	1 (0)	7173 (44.1)	
30-39	1076 (6.6)	1986 (12.2)	0 (0)	3062 (18.8)	
40-49	525 (3.2)	1065 (6.6)	0 (0)	1590 (9.8)	
50-59	360 (2.2)	841 (5.2)	0 (0)	1201 (7.4)	Independence of antigen result and age-group p-value=0.02×10^{-14} (<0.05)
60-69	255 (1.6)	445 (2.7)	0 (0)	700 (4.3)	
70-79	90 (0.6)	175 (1.1)	0 (0)	265 (1.6)	
80-89	24 (0.1)	42 (0.3)	0 (0)	66 (0.4)	
90-99	4 (0)	8 (0)	1 (0)	13 (0.1)	
Grand total	6347 (39)	9909 (61)	2 (0)	16258 (100)	

[Table/Fig-1]: Age and gender wise testing for Coronavirus Rapid antigen.
p-value <0.05 considered significant

Age group (years)	Negative antigen			Positive antigen			Repeat sampling required			Grand total n (%)
	For travel purpose n (%)	Other than travel n (%)	Total n (%)	For travel purpose n (%)	Other than travel n (%)	Total n (%)	For travel purpose n (%)	Other than travel n (%)	Total n (%)	
0-9	21 (0.1)	183 (1.1)	204 (1.3)	0 (0)	5 (0)	5 (0)	0 (0)	0 (0)	0 (0)	209 (1.3)
10-19	128 (0.8)	1839 (11.3)	1967 (12.1)	2 (0)	10 (0.1)	12 (0.1)	0 (0)	0 (0)	0 (0)	1979 (12.2)
20-29	2067 (12.7)	5039 (31)	7106 (43.7)	19 (0.1)	45 (0.3)	64 (0.4)	1 (0)	2 (0)	3 (0)	7173 (44.1)
30-39	1008 (6.2)	1982 (12.2)	2990 (18.4)	23 (0.1)	47 (0.3)	70 (0.4)	0 (0)	2 (0)	2 (0)	3062 (18.8)
40-49	387 (2.4)	1149 (7.1)	1536 (9.4)	18 (0.1)	35 (0.2)	53 (0.3)	0 (0)	1 (0)	1 (0)	1590 (9.8)
50-59	168 (1)	985 (6.1)	1153 (7.1)	11 (0.1)	37 (0.2)	48 (0.3)	0 (0)	0 (0)	0 (0)	1201 (7.4)
60-69	59 (0.4)	592 (3.6)	651 (4)	8 (0)	41 (0.3)	49 (0.3)	0 (0)	0 (0)	0 (0)	700 (4.3)
70-79	26 (0.2)	222 (1.4)	248 (1.5)	3 (0)	14 (0.1)	17 (0.1)	0 (0)	0 (0)	0 (0)	265 (1.6)
80-89	4 (0)	52 (0.3)	56 (0.3)	2 (0)	8 (0)	10 (0.1)	0 (0)	0 (0)	0 (0)	66 (0.4)
90-99	0 (0)	12 (0.1)	12 (0.1)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	13 (0.1)
Grand total	3868 (23.8)	12055 (74.1)	15923 (97.9)	86 (0.5)	243 (1.5)	329 (2)	1 (0)	5 (0)	6 (0)	16258 (100)

[Table/Fig-2]: Percentage positivity of Coronavirus antigen in different age groups with travel details.

Age group (years)		0-9 n (%)	10-19 n (%)	20-29 n (%)	30-39 n (%)	40-49 n (%)	50-59 n (%)	60-69 n (%)	70-79 n (%)	80-89 n (%)	90-99 n (%)	Grand total n (%)
Negative antigen	SARI	5 (0)	28 (0.2)	92 (0.6)	56 (0.3)	49 (0.3)	23 (0.1)	18 (0.1)	12 (0.1)	7 (0)	1 (0)	291 (1.8)
	ILI	9 (0.1)	35 (0.2)	124 (0.8)	73 (0.4)	68 (0.4)	41 (0.3)	31 (0.2)	29 (0.2)	11 (0.1)	2 (0)	423 (2.6)
	Patients seeking hospitalisation	67 (0.4)	872 (5.4)	1821 (11.2)	941 (5.8)	465 (2.9)	409 (2.5)	222 (1.4)	79 (0.5)	16 (0.1)	4 (0)	4896 (30.1)
	Contacts of positive cases	102 (0.6)	904 (5.6)	3002 (18.5)	912 (5.6)	567 (3.5)	512 (3.1)	321 (2)	102 (0.6)	18 (0.1)	5 (0)	6445 (39.6)
	Total	183 (1.1)	1839 (11.3)	5039 (31)	1982 (12.2)	1149 (7.1)	985 (6.1)	592 (3.6)	222 (1.4)	52 (0.3)	12 (0.1)	12055 (74.1)
Positive antigen	SARI	0 (0)	1 (0)	6 (0)	4 (0)	3 (0)	2 (0)	3 (0)	1 (0)	0 (0)	0 (0)	20 (0.1)
	ILI	1 (0)	2 (0)	8 (0)	9 (0.1)	7 (0)	4 (0)	4 (0)	2 (0)	2 (0)	0 (0)	39 (0.2)
	Patients seeking hospitalisation	1 (0)	2 (0)	13 (0.1)	14 (0.1)	13 (0.1)	15 (0.1)	17 (0.1)	5 (0)	2 (0)	0 (0)	82 (0.5)
	Contacts of positive cases	3 (0)	5 (0)	18 (0.1)	20 (0.1)	12 (0.1)	16 (0.1)	17 (0.1)	6 (0)	4 (0)	1 (0)	102 (0.6)
	Total	5 (0)	10 (0.1)	45 (0.3)	47 (0.3)	35 (0.2)	37 (0.2)	41 (0.3)	14 (0.1)	8 (0)	1 (0)	243 (1.5)
Repeat sampling required	SARI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	ILI	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
	Patients seeking hospitalisation	0 (0)	0 (0)	1 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0)
	Contacts of positive cases	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
	Total	0 (0)	0 (0)	2 (0)	2 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (0)

[Table/Fig-3]: Percentage positivity of Coronavirus antigen in different patient categories.
ILI: Influenza like illness, SARI: Severe acute respiratory illness

The percentage positivity as detected by Rapid antigen was 2.1% out of a total number of 16,258 samples tested. There was no effect of positivity on the basis of gender (p>0.05) [Table/Fig-1]. There were six samples that gave invalid results and were repeated. Patients that presented with symptoms less than a week showed maximum 142 (0.9%) antigen positivity [Table/Fig-4].

Groups	Negative antigen n (%)	Positive antigen n (%)	Repeat sampling required n (%)	p-value
Group A (Symptomatic ≤7 days)	1783 (11.0)	142 (0.9)	1 (0.0)	<0.05
Group B (Symptomatic >7 days)	5128 (31.5)	126 (0.8)	2 (0.0)	
Group C Asymptomatic	9012 (55.4)	61 (0.4)	3 (0.0)	

[Table/Fig-4]: Percentage positivity of COVID-19 Rapid antigen in reference to duration of symptoms.
p-value <0.05 considered significant

DISCUSSION

COVID-19 pandemic has hit the population of all age groups irrespective of gender. In this study, a preponderance of the infection in the age groups of 30-39 years (p-value <0.05) followed by 20-29 years age was observed. This was due to more locomotion of these age groups owing to job and travel. Bello-Chavolla OY et al., in their study also had similar findings [11]. In their study Bello-Chavolla OY et al., found higher mortality (29.5%) and severity of infection in older Mexican adults due to COVID-19 infection [12]. In the present study, testing was done more in males compared to females, which could be attributed to more movement of males than females in search of livelihood especially from rural to urban areas. However, there was no significant impact on the positivity rates on the basis of gender (p>0.05). The SARS-CoV-2 binds to the host cells on the Angiotensin-Converting Enzyme 2 (ACE2) receptors on different human tissues [13-15]. In one of the pioneer studies done by Li MY et al., they did not find any significant difference in ACE2 expression levels in males and females or younger and older age groups indicating that the virus may infect the different genders and age groups equally [16].

In the present study, the percentage positivity was 2.1% out of a total of 16,258 samples. Other studies also showed positivity rates between 1-8% [1,17], whereas, some showed a slightly higher (more than 10%) prevalence of the infection [18,19]. The positivity 0.9% was found more in patients who presented with signs and symptoms for ≤7 days (p<0.05). Harmon A et al., also observed the maximum sensitivity of rapid tests done between days 0 to day 3 of the onset of symptoms in the patients [1]. The results of this study were in concordance with other studies in which maximum number of infected persons were detected with the help of rapid tests in the first week of symptom onset [11,20,21]. This was due to higher viral load and concentrations in the first week of infection [22]. Researchers have concluded that within the first week of symptoms onset the results of rapid tests were better than RT-PCR and correlated with the presence of SARS-CoV-2 virus which could be cultured [19]. The efficacy of the test reflects in it detecting 0.4% positive cases among asymptomatic individuals in this study. Previous data conclude that asymptomatic people account for approximately 40-45% of infection and pose a threat of spreading the virus over an extended period of even more than 14 days [23]. Others also showed that asymptomatic residents had the potential of spreading the SARS-CoV-2 infection thus, indicating additional prevention measures [24].

The performance of Standard Q COVID-19 Rapid test was evaluated by using it on Quantitative Reverse Transcription PCR (RT-qPCR) and viral culture positive samples and it could not only detect samples with high Ribonucleic Acid (RNA) loads reliably but the negative results corresponded to non cultivable samples in Vero E6 cells [17]. However, there have been studies that have questioned the sensitivity of the Lateral Flow antigen Testing (LFT) [25-27]. The testing of COVID-19 has largely depended on PCR which is a reliable and powerful testing method having the potential of detecting the virus even in very minute quantities. Since the viral RNA fragments can be found in the patients even after the clearing of the infectious virus, PCR can detect these not only in infected but also in individuals who have been recently infected [28]. It can also detect the viral RNA in asymptomatic individuals [29]. However, when mass spread of the SARS-CoV-2 needs to be curtailed then it is more important to have a test which would detect the presence of the virus in the patient on the present day rather than from an earlier infection [30]. This will be helpful in prompt isolation of the patients which is required to stop the further spread of the disease.

Bello-Chavolla OY et al., in their study also concluded that RAT could be used for a large scale testing of SARS-CoV-2 but keeping a check on the false negatives [11]. False negatives could be a result of testing patients too early after the infection [31]. This is of great epidemiological significance as an unknown person harbouring the virus may act as a vector thus spreading it to many people. The increase in false negatives can also be attributed to local outbreaks [32]. Kweon OJ et al., concluded that RAT should be done in conjunction with other molecular tests in order not to miss any positive cases [33]. ICMR in its advisory had also recommended the use of RADT in combination of RT-PCR test especially in cases of suspected individuals who gave a negative result in RADT [34]. Besides, the ICMR in its advisory stated to use RADT as the first test of choice [35]. The 0.1% people who were seeking to travel could be detected by the test, which was by and large the most beneficial outcome of the testing as they were immediately isolated which helped to curb the spread of infection not only locally but also across the boundaries. Besides, the detection of positive contacts of patients was a major help and the test helped in contact tracing also. The RAT has been an effective testing method for Coronavirus in low resource settings [36,37] and has been used as point of care test giving results in a short time period even in outside central laboratory testing facilities.

Limitation(s)

In some suspected cases with negative RADT, the test results had to be cross checked with RT-PCR. Getting a proper clinical history in some cases was difficult due to the fear and stigma of the disease among the patients, their attendants and also the healthcare professionals. The worst experience was to witness the elderly (who could not explain their condition properly) being abandoned by their own kin. This caused a hindrance in taking proper history in such cases.

CONCLUSION(S)

Thus, RADT for SARS-CoV-2 is a simple, fast, cheap, easy to perform point of care test which does not require special laboratory setups. Since it is not much expertise dependant, it can be used in rural areas and at home following proper precautions and disposal instructions. Being portable it enabled mass testing and helped as a good epidemiological tool. In the study RADT was found to be a sensitive test.

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