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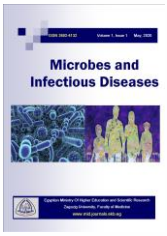

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Original article

Rapid antigen test in diagnosis of SARS-COV-2 in a specialized care facility Urology and Nephrology Center–Mansoura University- Egypt

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ABSTRACT

Background: Polymerase chain reaction (PCR) is the benchmark in diagnosing of corona virus disease. It takes at least 4 hours. Multiple studies reported that rapid antigen test could be used. Their role in diagnosing corona virus disease 2019 (COVID-19) is questionable. This study was conducted to assess the accuracy of rapid antigen test in Urology and Nephrology Center Mansoura University, Egypt. **Methods:** COVID-19 rapid ag test was evaluated in comparison to real time PCR as a gold standard in diagnosis of COVID-19 infection in employees and patients with respiratory symptoms in specialized care facility Urology and Nephrology Center of Mansoura University from March 2020 till August 2021. Complete blood picture and non-contrast computerized tomography (CT) was done. **Results:** Eight hundred and eighty-four (884) individuals (median age 36 years) were included in this study: 478 healthcare workers, 217 non-healthcare workers, and 189 patients. PCR was positive in 569 samples and negative in 315. Out of 315 negative PCR samples, 8 were positive by rapid antigen test with a specificity of 97.4%. **Conclusion:** Rapid antigen tests in comparison to PCR test have a good accuracy in diagnosis in of COVID-19 infection and can be used during pandemics in low-resource areas.

Introduction

In December 2019 in Wuhan, the first case of Corona virus disease 2019 (COVID-19) was diagnosed in China. Since that date, the virus had been found around the globe, to be mentioned as a global health emergency by the World Health Organization (WHO) in January 2020. Two months later, WHO considered we were in a pandemic [1]. No clinical features have been identified specific for this pandemic as it can mimic other viral respiratory infections [2]. However, some specific features would raise the clinical suspicion like dyspnea

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following days of illness, anosmia and myalgia [3]. This pandemic had a wide range of respiratory manifestations, starting from being asymptomatic to having severe pneumonia. The reported mortality in severe cases ranged from 1 to 14.4% [4].

The sensitivity of chest CT is more than conventional chest radiographs. CT findings include any of this finding ground- glass opacities, interlobar septal thickening, consolidation, pleural thickening and air bronchograms [5]. Although chest imaging (especially CT) is considered an important tool in the diagnosis of COVID-19 infection, the final and decisive diagnosis should depend on polymerase chain reaction (PCR) results [6].

It is absolutely necessary to accurately diagnose infections, whether they are current or historical. Molecular diagnostics can identify acute infections. Serologic testing are helpful for infections from the past. Although standard PCR takes a while, it is exceedingly sensitive and specific. There are other nucleic acid amplification techniques with faster turnaround times, but they are more expensive. The preferred laboratory inquiry to confirm the infection is a PCR test. But, even in the hands of a professional technician, it takes at least four hours to provide the outcome. Therefore more rapid tests with acceptable accuracy are needed [4].

Multiple recent studies have reported that lateral flow immunoassays, using monoclonal antibodies for COVID-19 that target the viral antigens, could be used as screening tests if they showed acceptable accuracy to PCR [7]. This kind of testing has a definite advantage over PCR in saving time as it can provide results in minutes. This can lead to a great relief in both workload and turn-around time [7].

Another test is antibody testing. The value of these tests is very low in the diagnosis of acute cases. IgM and IgG directed against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may appear as early as 3-6 days after the onset of symptoms. By three weeks, nearly all patients have seroconverted, and the antibodies persist for at least two months, with IgG showing greater persistence [8]. This study was conducted in Urology and Nephrology center NCCT in Mansoura University.

This study aimed to assess the accuracy of rapid antigen test in diagnosis of COVID 19.

Patients and Methods

Study population

This is a retrospective study including employees and patients in Urology and Nephrology center, Mansoura University who presented to COVID-19 surveillance clinic by respiratory symptoms together with asymptomatic contacts of confirmed COVID 19 positive cases.

From March 2020 till August 2021they underwent complete blood count (CBC), non-contrast computed tomography of chest (NCCT), rapid antigen testing for COVID 19 and Real-time polymerase chain reaction (PCR) to diagnose COVID 19 positive cases.

Sample size estimation was determined considering a power of 0.90, a type I error of 0.05 and a SARS-CoV-2 prevalence of 1.3% [9]. Sensitivity values and specificity of 96.52 and 99.68 respectively were assumed as previously reported in clinical setting [10]. The estimated sample size for rejecting the null hypothesis of non-inferiority to PCR testing was 740 participants. Recruitment coincided with the first and only visit and all participants were randomly selected to this study.

Inclusion criteria: Employees (healthcare worker or non-healthcare worker) and patients presented with one or more of the respiratory symptoms of COVID as fever, cough, anosmia, chest pain and difficulty of breathing or diarrhea. Regardless of their age and gender

Healthcare workers are those in direct contact with hospital patients, such as doctors, nurses, nurse assistants, and lab workers. At the same time, non-healthcare workers work in our medical center but are not in direct contact with the hospital patients, such as the administration staff.

Exclusion criteria: Employees (healthcare worker or non-healthcare worker) and patients who were diagnosed previously with any respiratory diseases other than COVID 19.

Ethical approval

The study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of faculty of Medicine- Mansoura University (R.22.03.1662). Consent was taken from each participate in this study.

COVID-19 PCR:

- **Samples**

Nasopharyngeal and oropharyngeal swabs were taken from each patient for PCR and mixed in one

tube. Samples were collected using collection Dacron or polyester flocked swabs in viral transport medium. It was transported at temperature of 4°C and stored at - 4°C for ≤ 5 days or -70°C for longer periods**.**

- **RNA extraction**

RNA was extracted from clinical samples with QIAamp 96 Virus QIAcube HT Kit (Cat. No. / ID: 57731; Germany). The kit is intended for automated purification of viral RNA from human samples using QIAcube HT instrument.

First lysis of the samples in room temperature under denaturing conditions was done by proteinase K and Buffer ACL of extraction kit (QIAGEN, Germany) then Buffer ACB was added to provide the binding conditions for the co-purification of RNA. This lysate was transferred to a QIAamp 96 plate. During this stage absorption of nucleic acids were done on onto the silica membranes. Wash steps were done to remove any contaminants. At last elution in AVE buffer were done.

- **Detection of COVID-19 viral RNA**

The Genesig Real-Time PCR Coronavirus (COVID-19) (CE IVD) was used for qualitative detection of COVID-19 viral RNA collected from nasopharyngeal and oropharyngeal swabs by using DNA technology PCR. A mix of master mix and Coronavirus (COVID-19) primer/probe was prepared. Twelve (12) µl were added into the number of wells required for our testing into an appropriate 96 well plate, including positive and negative control. Eight (8) µl of the following (Sample, Positive control, and negative control) were added into the appropriate wells according to plate setup. The plate was sealed with an appropriate seal and placed in the device.

SARS-CoV-2 rapid antigen test

Nasopharyngeal sample was obtained by careful insertion of the swab through the nose until we met resistance at the level of the turbinate. First rotate soft and withdraw the swab.

Two validated rapid antigen tests were used; RAPIGEN BIOCREDIT COVID-19 Ag (Cat.No. G61RHA20) (Korea) during the period from March to December 2020 and SARS-CoV-2 SD BIOSENSOR STANDARD Q COVID-19 Ag (Cat. No.# 09COV130D) (SD biosensor standard Inc. Republic of Korea) from January 2021 till August 2021. Both rapid ag tests were used as recommended by the manufacturers, using only materials provided in the kit. Both assays were manually read.

Both tests are rapid chromatographic immunoassay for the qualitative detection of SARS-CoV-2 nucleocapsid antigen present in human nasal sample.

Test has two lines, C (Control line) and T (Test line) on nitrocellulose membrane. Both lines are not visible before putting any samples. During the test, SARS-CoV-2 antigen in the sample interacted with anti-SARS-CoV-2 antibody making antigen-antibody color particle complex. A colored band on the test line appears if SARS-CoV-2 antigens are present in the sample. If antigens are not found in the specimen, no band appears in the T line. A colored band in the C line (control line) will indicate that test is performed well **(Figure 1).**

Nasopharyngeal swab was put in the diluent and swirled many times (5~10 times) with pressing the swab against the side and bottom of the collection tube. The swab was squeezed and withdrawn. The tube was covered with its filter cap. The tube was inverted and squeezed to draw 3~4 drops into a sample well of the device. After a time of 5 to 8 minutes for RAPIGEN BIOCREDIT or about 15-30 minutes in standard Q COVID-19 ag test the result was taken.

Statistical analysis

Descriptive statistics data were used to describe demographic and clinical about the study population. Categorical data were presented in numbers and percentages. Rapid antigen test results were compared to those of PCR as the reference standard. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated. All analyses were carried out using SPSS, version 25.

Results

From March 2020 to August 2021, suspected cases of SARS-CoV-2 infection were tested using both rapid antigen and real-time PCR testing as shown in **table (1).**

According to real time PCR results (after one sample), 315 samples were negative and 569 were positive. Of 315 specimens tested SARS-CoV-2 PCR negative, eight samples had positive results in the SARS-CoV-2 rapid antigen test. Specificity was calculated to be 97.4 %. Of the 569 specimens tested, SARS-CoV-2 PCR positive 480 were positive by rapid antigen test. This translates into an overall sensitivity of 84.3%. **Table 2**

presents the sensitivity, specificity, Positive Predictive Value, Negative Predictive Value and Accuracy of the rapid antigen test in relation to the study populations' symptoms, using PCR test as a reference method.

Among 108 asymptomatic patients, real time PCR and COVID-19 Ag were positive in 64 and 52 respectively, while 44 and 56 were negative by PCR and rapid antigen. Seven hunderd and seventy six (776) patients were symptomatic and their symptoms included fever, cough, loss of smell and taste, fatigue, shortness of breath, muscle aches, sore throat, congestion, runny nose, nausea, vomiting and diarrhea.

All patients with at least one symptom were classified into the symptomatic group (776 patients). In relation to the symptoms the sensitivity and specificity of PCR test in the symptomatic group were 88.7% and 13.9% respectively with increased sensitivity up to 97.7% when both symptoms and rapid Ag test were added together while specificity was 13.7% with a positive predictive value of 67.1% and a negative predictive value of 76.8%.

Among PCR positive cases, 474 (83.3%) patients were evaluated radiologically by NCCT chest of whom 154 (32.4%) showed ground glass opacity, 66 patients (13.9%) showed consolidation, 13 patients (2.7%) showed combined ground glass and consolidation and 241 patients (50.8%) showed normal CT chest finding **(Table 3).**

In the current study, 711 CBC samples were taken. The hematological abnormalities in patients with positive findings were leucopenia and lymphopenia occurring in 13% and 22.3% respec tively.

The sensitivity of abnormal CBC findings (leucopenia and/or lymphopenia) was 76.7%, and when combined with positive results of rapid antigen assay, it increased to 88.5%.

Figure 1. Results of COVID 19 rapid ag test (RAPIGEN BIOCREDIT COVID-19 Ag).

Table 1. Characteristics of COVID-19 cases.

Patients with rapid antigen test and PCR swab test	884
Patients with positive PCR swab test	569 (64.4%)
Gender **Male** **Female**	 354 (40%) 530 (60%)
Age (median range)	36 (29 – 48)
Healthcare worker **Non-healthcare worker** **Patients**	478 (54.1%) 217 (24.5%) 189 (21.4%)
Clinical presentation	108 asymptomatic 776 symptomatic

Table 2. The sensitivity and specificity of the rapid antigen assay.

PCR assay	Rapid antigen assay							
	Positive	**Negative**	**Total**	**Sensitivity % (CI)**	**Specificity % (CI)**	**Positive Predictive Value % (CI)**	**Negative Predictive Value % (CI)**	**Accuracy % (CI)**
PCR positive	480	89	569	84.3% (81.1% to 87.2%)	97.4% (95.1% to 98.8%)	98.3% (96.7% to 99.1%)	77.5% (74% to 80.6%)	89% (86.% to 91%)
PCR negative	8	307	315					
Total	488	396	884					

CI = confidence interval

Table 3. Relation between CT Findings and CT Findings with rapid antigen test in relation to PCR results as reference test (Total= 708 patients).

		PCR						
CT Findings		**Negative**	**Positive**	**Sensitivity (CI)**	**Specificity (CI)**	**Positive Predictive Value % (CI)**	**Negative Predictive Value % (CI)**	**Accuracy (CI)**
	Negative	148	241	49.2% (44.5% to 53.7%)	63.2% (56.7% to 69.4%)	73% (69.1% to 76.6%)	38% (34.9% to 41.1%)	53.8% (50.1% to 57.5%)
	Positive	86	233					
CT& Rapid Ag testing	**Negative**	146	30	93.7% (50.1% to 57.5%)	62.4% (55.8% to 68.6%)	83.5% (81% to 85.6%)	83% (77.2% to 87.4%)	83.3% (80% to 86%)
	Positive	88	444					

Discussion

From March 2020 to August 2021, suspected cases of SARS-CoV-2 infection were tested using both rapid antigen and Real-time PCR testing. The aim of the study was to know the accuracy of rapid antigen test in diagnosis of COVID-19 cases.

Polymerase chain reaction had high sensitivity but it had false positive results and requires skilled professionals [11]. Rapid lateral flow tests exhibited definite merits, including low cost, simple maneuver in a short time which doesn`t need a special equipment or skills compared to molecular techniques [12]. However, using nasopharyngeal swabs is still an invasive procedure, annoying and aerosolizing. That`s why, the Centers for Disease Control and Prevention (CDC) permitted self-sampling via nasal swabs [13].

The rapid Ag test results had 84.3% sensitivity and 97.4% specificity. This result agrees with the results of **Berger and his colleagues** who reported a 87.6% (95%) sensitivity and 99.9% (95%) specificity and they highlighted the importance of Ag-RDTs as a valid diagnostic tool in symptomatic individuals, while its benefit in asymptomatic patients or those with minor symptoms should still be investigated [14]. Also our results came in hand with **Alemany et al.** [15] and **Fenollar et al.** [16] (evaluated performance of the Panbio COVID-19 ag rapid test device assay Abbott) who reported a sensitivity ranging from 73.3-91.7% and specificity of 94.9 to 100%.

Khairat et al. [17] evaluated the performance of two COVID-19 rapid antigen tests, which are BIOCREDIT COVID-19 Ag (RapiGEN Inc., Korea) and Standard Q COVID-19 Ag (SD Biosensor, Korea), in comparison with RT-PCR.

BIOCREDIT COVID-19 Ag and SD Biosensor RAD kits recorded total sensitivities of 52.5% and 68.7% and specificities of 46% and 96%, respectively. In high viral load samples, BIOCREDIT COVID-19 Ag and SD Biosensor RAD kits recorded higher sensitivities of 60% and 77%. In another study, 7471 participants were included in the analysis. Sensitivity across Ag-RDTs ranged from 70·4%-90·1%, specificity was above 97·2% [18].

Also, **Shidlovskaya et al.** [19] evaluated the sensitivity of the test used by our team (BIOCREDIT COVID-19 Ag) and other tests. Sensitivity was 78.6% (95% CI, from 49.2% to 95.3%) for SGTI-flex COVID-19 Ag and 100% (95% CI, from 76.8% to 100%) for Bio credit COVID-19 Ag. The specificity of rapid tests was significantly higher than that of RT-PCR and was 66.3% (95% CI, from 55.7% to 75.8%) and 67.4% (95% CI, from 56.8% to 76.8%) for SGTI-flex COVID-19 Ag and Bio credit COVID-19 Ag versus 30.4% (95% CI, from 21.3% to 40.9%) obtained for PCR.

In a study of **Ristić et al.** [20] 25 out of 120 samples who have been tested positive using STANDARD Q COVID-19 Ag Test were also tested positive using RT-qPCR. Overall, the STANDARD Q COVID-19 Ag Test showed sensitivity of 58.1% (95% CI 42.1–73.0) but it was higher in the early days of disease, when the highest viral loads were detected. During the first five days after the symptom onset, the sensitivity ranged from 66.7% to 100%.

Sang-Min et al. [21] evaluated the Standard Q COVID-19 Ag test for the diagnosis of (COVID-19) compared to RT-PCR test. The overall sensitivity and specificity for detecting SARS-CoV-2 for the Standard Q COVID-19 Ag test compared to RT-PCR were 17.5% (95% confidence interval [CI], 8.8–32.0%) and 100% (95% CI, 95.3–100.0%).

It was reported that the best sensitivity was found in COVID-19 symptomatic patients, early in the course of the disease between day 1 and 5 [14]. In high-viral load infections, the SD Biosensor, Inc. STANDARD Q COVID-19 Ag test give perfect sensitivity and good performance in the cohort overall was 76·6% (CI 62·8-86·4) with very good specificity (99·3%; CI 98·6-99·6) according to these results antigen tests can be used in pandemic in low resource areas [22].

In March 2022, the U.S. Food and Drug Administration (FDA) [23] issued warning regarding the use of SD Biosensor Inc. STANDARD Q COVID-19 Ag Home Test. The FDA cited false positive and negative results. We tried to decrease the contamination and any factor that might change the result of the test and it done at the hospital not in the home. The negative predictive value of the test is 77.5 % (74% to 80.6%). The positive predictive value was 98.3 % (96.7% to 99.1%) in our series.

Although nucleic acid detection technologies provided an accurate method for SARS-COV-2 infection, a false negative result still can't be avoided and depending on chest CT scan may be helpful for diagnosis and evaluation of disease severity. However, some drawbacks of CT chest include excessive unnecessary performance of it and limitations in differentiating between types of viral pneumonias [24].

The most common finding in chest CT of patients infected with COVID-19 is ground-glass opacity with or without consolidation [25]. In our patients, ground glass opacities were seen in 27.1% of positive PCR cases while consolidation was noted only in 11.6% and mixed ground-glass with pneumonia were reported in 2.3% which comes in agreement with a systematic review including 2700 patients which reported ground-glass opacity in 83% of confirmed positive cases [5] and another study on 90 patients from China, that reported ground glass opacities in 65 (72%), and consolidation in 12 (13%) [26].

Although positive findings in chest CT may be diagnostic of COVID-19, normal chest CT can`t exclude the possibility of COVID-19 infection as in our study 241 infected persons who were diagnosed by COVID-19 PCR had a normal CT findings with a sensitivity of only 49.2% (table 6), that's why the American College of Radiology (ACR) don't recommend routine performance of chest CT for screening or diagnosis of COVID-19 but only doing it when it is expected to be helpful in management [27].

In this study, positive chest CT for COVID-19 had a sensitivity of 93.7% and a specificity of 62.4% using the PCR tests as a reference which comes in agreement with Ai T and his colleagues who reported a sensitivity of 97% [28]. The lower percentage of specificity may be due

to common radiological findings shared by other organisms causing chest infection.

While asymptomatic infections are contagious and their prevalence differs between studies, the respiratory manifestations of COVID-19 infection are not specific for the disease and cannot help in the differentiation of other causes of respiratory tract infections [29]. Although it was reported that smell or taste disorders may be more common with COVID-19 than with other viral respiratory infections, they are also nonspecific [30].**Cheng et al.** [31]found that both asymptomatic and symptomatic patients had a near equal viral load. Its prevalence varied significantly between studies [32-34]. In our study 108 patients were asymptomatic out of 884 patients (9.1%) which is similar to the results of an US study which presented a prevalence of asymptomatic infections ranging from 1% to 6.9% [35] while it reached up to 17.1% in the "Diamond Princess" cruise ship [36].

Frequency of leucopenia and lymphopenia were 13% and 22.3% respectively In contrary to our result, **Yuan et al.** [37] reported normal values for both white blood cell (WBC) count (4.5 to 11.0 × 109/L) and neutrophil percentage (40% to 60%). However, most critically ill patients had lymphopenia ($p < 0.01$) while in another study by **Anurag and his colleagues** [38], lymphopenia, high neutrophil-lymphocyte ratio (NLR) and neutrophil-monocyte ratio (NMR) were found in severe cases of COVID-19. Again **Goyal et al.** [39] reported lymphopenia in 90% of their patients while Illg Z and his colleagues [40], reported that the severity of COVID-19, specifically the requirement for intubation and mortality, correlates with the degree of lymphopenia and absolute lymphocytic count may act as a prognostic marker in COVID-19 patients, enabling doctors to pursue more aggressive treatment plans in patients at risk for developing severe disease.

This study has some limitations; Some data regarding CBC and radiological data of included subjects were missed as this study is retrospective one. Also, use of two different Ag detection assays without comparative analysis between them.

Conclusion

From this study we conclude that, the collective sensitivity of rapid antigen tests was 84.3%, specificity was 97.4% and overall accuracy was 89%. Rapid antigen tests can be used in diagnosis in COVID 19 together with symptoms, laboratory and radiological investigation and antigen tests can be used in pandemic in low resource areas.

Submission declaration

The manuscript has not been published elsewhere and has not been submitted simultaneously for publication elsewhere.

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