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Utility of serological VivaDiag IgM/IgG rapid test kits for COVID-19 screening, during disease progression and following recovery

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Abstract

Objectives: This study evaluated VivaDiag IgM/IgG Rapid Test (VDtest) for covid-19 screening, during disease progression and following recovery.

Methods: Prospectively, 969 patients RT-PCR positive for SARS-CoV-2 virus were compared to VDtest in 166 individuals upon airport arrival; 62 active inpatient COVID-19 cases ranging 2-23 days; 741 recovered COVID-19 patients from diagnosis date (median 24-days). **Findings:** Screening; VDtest assay sensitivity 7.6% (95% CI 2.8–15.8%), specificity 94.3% (95% CI 87.1–98.1%). Active disease patients, positive IgG rate 27.4% and IgM positivity 0 of 62 patients. Recovery phase **patients:** positive rates of IgM and IgG were 0.7% and 1.2%, respectively, within 14-days of diagnosis date, increasing to 25.9% and 43.4%, respectively 14-days after diagnosis. **Novelty:** VDtest kit showed poor sensitivity and identification of COVID-19 infection for screening, moreover, need for larger sample study to confirm our findings.

Keywords: COVID19; SARSCoV2; RTPCR; serological testing; rapid test

1 Introduction

In late December 2019, an acute febrile illness associated with respiratory distress emerged in Wuhan, China⁽¹⁾ due to a virus that showed 79.5% homology at the whole genome level to the SARS-CoV virus that caused an outbreak in 2002⁽¹⁾. Identification of the genetic sequence information has led to the development of diagnostic tests that are based on detection of the viral sequence by RT-PCR or next generation sequencing⁽¹⁾ detected from nasal and pharyngeal swabs, bronchoalveolar lavage and blood plasma⁽¹⁾.

RT-PCR is the gold standard test for the diagnosis of COVID-19, but usage of RT-PCR kits require expertise, expensive equipment and specialized laboratories⁽²⁾. Thus, these tests do not provide for rapid diagnosis and mass rapid screening in the setting of a public health emergency such as the COVID-19 pandemic⁽²⁾. Despite being the gold standard test, patients who displayed clinical and radiological manifestations of COVID-19 have tested negative for RT-PCR^(1,3). These limitations of the RT-PCR tests may also hinder the process of outbreak control.

All travelers arriving through Bahrain International Airport are tested by RT-PCR; those from high risk areas are quarantined until the result is available whilst those from low risk areas are asked to self-isolate and are contacted the following days.

It has been proven that early detection, diagnosis, and control of symptoms are useful in the clinical course of COVID-19⁽⁴⁾. Due to the limitations of RT-PCR screening noted above and the increasing severity and scope of the current COVID-19 pandemic, rapid serologic assays can serve as a convenient and timely method to complement RT-PCR tests⁽⁵⁾. According to data from the previous SARS-CoV-1 infection, a specific IgM antibody could be detected in the blood in 3 to 6 days from the date of infection and IgG antibodies could be detected 8 days after the onset of symptoms⁽²⁾. It may be therefore surmised that as SARS-CoV-2 antibody responses generated during the disease course would be similar to that of the coronaviruses responsible for the MERS and SARS outbreaks⁽²⁾. However, recent studies on COVID-19 have concluded that the majority of antibodies are seen after the second week of symptom onset^(6,7). Whilst serologic testing could facilitate epidemiologic monitoring and proper isolation of patients⁽¹⁾, these tests are yet to be validated for use in clinical settings. The COVID-19 incubation period is estimated at 6.4 days^(8,9) and it has been suggested that 30.8% of the population may be asymptomatic⁽¹⁰⁾.

Therefore, the aims of this study were to evaluate the VivaDiag IgM/IgG Rapid Test for covid-19 screening in individuals, during disease progression and following disease recovery.

2 Methods

This was a prospective comparative study. The blood samples from 969 patients who were tested positive with nasopharyngeal swab in RT-PCR were tested using the VivaDiag IgM/IgG Rapid tests (VivaChek Biotech (Hangzhou)) that uses finger prick blood samples in accord with the manufacturer's instructions, in 3 different clinical scenarios; disease screening, during active covid-19 symptomatic disease, and following disease recovery. The study was done within the Kingdom of Bahrain and ethical permission was granted by the National Research Committee of COVID19.

Prospective study in screening for COVID-19

Screening of 166 individuals was undertaken using the VivaDiag IgM/IgG rapid test at the same time as the nasopharyngeal swab PCR testing on arrival to the Kingdom of Bahrain international airport.

Cohort of active COVID-19 cases

62 active cases of COVID-19 who had been admitted to the isolation facilities after a positive PCR result from a nasopharyngeal sample were followed. Nasopharyngeal swab PCR and VivaDiag IgM/IgG rapid tests were performed every 48hrs for patients until PCR negative, then the tests were repeated at 24 hours until two consecutive PCR results were negative. Patients were discharged after two consecutive negative PCR tests.

Cohort of Recovered COVID-19 cases

741 recovered cases of COVID-19 were tested on day 7 and day 14 after discharge by both nasopharyngeal swab PCR and the VivaDiag IgM/IgG Rapid test Rapid test was then repeated again at day 28 after discharge.

2.1 Statistical analysis

Data analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA). All statistics used were descriptive. Continuous variables were expressed as medians, ranges and interquartile ranges (IQR). Categorical variables were expressed as percentages and counts.

3 Results

Cross sectional study in screening for COVID-19

47.5% (79/166) of arrivals from endemic countries tested positive for COVID19 by PCR of nasopharyngeal samples, of these, only 6 of 79 (7.6%) had a positive rapid test result. 52% of Arrivals tested negative for COVID19 by PCR, of those 5 (5.7%) had a positive IgM/IgG rapid test result. Thus, the sensitivity of the VivaDiag IgM/IgG rapid test to diagnose COVID19 was 7.6% (95% CI 2.8–15.8%), the specificity was 94.3% (95% CI 87.1–98.1%). The negative predictive value and positive predictive value were 52.9% (95% CI 50.9–54.9%), and 54.5% (95% CI 27.6–79.1%), respectively.

Cohort of active COVID-19 cases

In active COVID19 cases within an isolation facility in Bahrain, 62 tests were done on 62 patients. Samples were collected at different time intervals ranging from 2 to 23 days. The rate of positive IgG was 27.4% (17 of 62 patients). None of the patients tested positive for IgM. PCR was positive in 21% of the tests. The frequency of IgG results within PCR results is shown in Table 1.

Table 1. Cross sectional study in screening for COVID-19 by qPCR and rapid test (VivaDiag IgM/IgG rapid test)

Methods	Total samples	Positive, n (%)	Negative, n (%)
qPCR	166	79 (47.6)	87 (52.4)
Rapid test for positive qPCR samples	79	6 (7.6)	73 (92.4)
Rapid test for negative qPCR samples	87	5 (5.7)	82 (94.3)
Sensitivity	7.6% (95% CI 2.8–15.8%)		
Specificity	94.3% (95% CI 87.1–98.1%)		
Negative predictive value	52.9% (95% CI 50.9–54.9%)		
Positive predictive value	54.5% (95% CI 27.6–79.1%)		

Cohort of recovered COVID-19 cases

A group of 741 recovered COVID-19 patients (confirmed by two consecutive nasopharyngeal RT-PCR 24 hours apart) were followed up for a median of 24 days (IQR= 13) from the day of the first swab on the date of admission. The time period calculated from the date of admission to the date of rapid testing was divided into early (< 14 days) and late (>=14 days). The positive rates of IgM and IgG were low at the early time period, but increased in the late time period (Table 2). The positive rate of IgM increased from 0.7% in the early time period to 25.9% in the late time period. Similarly, the IgG positive rate went from 1.2% in the early stage to 43.4% in the late stage.

Table 2. Cohort of active COVID-19 cases by VivaDiag IgM/IgG rapid test

Methods	Sample number	Positive, n (%)	Negative, n (%)
qPCR	62	13 (21)	49 (79)
IgG	62	17 (27.4)	45 (2.6)
IgM	62	0 (0)	0 (0)

Table 3. Cohort of recovered COVID-19 cases by VivaDiag IgM/IgG rapid test

Methods	Sample number	<14 Days from discharge, n (%)	≥14 Days from discharge, n (%)
IgG positive	741	9 (1.2)	321 (43.4)
IgM positive	741	5 (0.7)	192 (25.9)

4 Discussion

This study showed that a large proportion of individuals who were positive for COVID-19 by RT-PCR would be identified as negative based on the IgM/IgG rapid test alone and the test was not sensitive for screening or predictive of an acute infection from SARS-CoV-2. Our study revealed that the sensitivity of the IgM/IgG rapid test to detect infection with SARS-CoV-2 was 7.6% with a positive predictive value to be 54.5%, a negative predictive value was found to be 52.9%; therefore in this population only half of individuals who test negative on VivaDiag IgM/IgG rapid test are actually negative for COVID-19. These results are in accord with the poor performance of this test for the diagnosis of COVID-19 in acute patients reported in Italy⁽¹¹⁾. The high false negative rates that were observed are likely due to low antibody concentrations through insufficient time for individuals to mount an immune response, in accord with these individuals being screened upon arrival from a high risk country, suggesting a recent exposure. Studies have demonstrated that the sensitivity of Rapid IgM/IgG test kits increase with time from infection being poor at 0-7 days and performing best at 2 weeks^(2,12). Given that a large proportion of COVID-19 may be asymptomatic⁽¹⁰⁾ in patients who may have had the disease for 14 days such serological test may have had utility in screening, but this was not found to be the case.

In those patients tested during active infection with COVID-19 between 2 and 23 days from diagnosis our results showed lower rates of positive RT-PCR and higher rates of positive IgG within this group shown by 15 subjects who were IgG positive

whilst PCR negative, conversely only 2 who were IgG positive were also PCR positive. These findings are in accord with another study performed on hospitalized COVID-19 patients that reported IgG levels increased during the infection course as the RNA viral levels declined⁽¹³⁾. However, IgM results for active cases in our study were negative throughout that was not consistent with the pattern seen in SARS-Cov-1 or SARS-Cov-2^(2,6). We believe that this might be due to either an inadequate immune response by the host or a suboptimal test to detect those antibodies. Others have reported that IgM/IgG Rapid test kits showed a larger proportion of patients who were seropositive for IgG rather than IgM on day 0 and day 5 of admission⁽¹³⁾. It is not known if these findings are due to low sensitivity of the rapid test kits or due to an unknown antibody response to COVID-19. Antibody responses are determined by the interplay of many factors such as age, disease severity, nutritional and immunological status^(6,7,14). Current evidence suggests that the acute antibody response to COVID-19 infection is similar to the pattern of other viral infections^(2,6,12). Studies have described a seroconversion to total antibodies, IgM and IgG, on day 14 of illness with IgM appearing earlier in the infection^(6,7). Additionally, it is believed that combined IgM and IgG testing is a better indicative of the infection timeline and is associated with higher sensitivity^(6,7).

Our study reflected the results seen in other papers for recovering cohorts of COVID-19 where positive immunoglobulin rates increased with time and specifically after day 14^(2,6,12). Not the entire population achieved seroconversion to IgG despite a long follow up period of up to 60 days. However, it has been reported that the seroconversion rates for both IgM and IgG were 100% after about 1 month of illness⁽⁶⁾. The timing of seroconversion is important as it determines the ideal time for antibody testing⁽¹⁵⁾, and potentially guide the optimal time for peripheral blood B cells collection to develop therapeutic antibodies⁽¹⁵⁾. Few studies showed that COVID-19 IgM/IgG Rapid Test for the screening and early diagnosis of COVID-19 in patients with no clinical signs of the disease and screening health care workers to avoid the high risk^(16,17).

Limitations of the study include the relatively small number of patients in the prospective study on the diagnostic screening for SARS-CoV-2 virus, and in the active COVID-19 patients studied. In order to better evaluate the antibody response of patients, larger cohorts should be studied and compared at different stages of disease.

5 Conclusion

This study showed that VivaDiag Rapid test kit showed poor sensitivity for its use in screening, or being predictive of an acute infection in hospitalized patients. IgM and IgG detection rates in recovered cases after 14 days from diagnosis identified 25.9% and 43.4% of patients respectively that suggests that this serological test would not have utility in population screening. Large sample analysis is warranted to confirm our results to use VivaDiag rapid test kit to in COVID-19 detection.

Declarations

Ethics approval and consent to participate: The study was approved by the Bahrain Defense Force Hospital Ethics Committee.

Consent for publication: All authors gave their consent for publication.

Availability of data and materials: All the data for this study will be made available upon reasonable request to the corresponding author.

Funding: No funding was received to perform this study.

Conflict of interest: The authors have declared that no conflict of interest exists.

Author contributions

DA, AA and SA analyzed the data and wrote the manuscript. OY and SA contributed to study design, collected, analysed, and interpreted data and edited the manuscript. MA supervised data collection, data analysis and edited the manuscript. All authors reviewed and approved the final version of the manuscript. Manaf Alqahtani is the guarantor of this work.

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