

“Evaluation of a COVID-19 IgM and IgG Rapid Test and Assessment of Specific Antibody Response in COVID-19 patients, Tunisia 2020”

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Abstract

Background

COVID-19 pandemic is a massive global health emergency. Although RT-PCR is the gold standard for diagnosing suspected cases, there is a need of serological tests to investigate antibody responses. Many serologic immunoassays have been developed to detect antibodies to SARS-CoV2, including rapid tests. This study assessed the clinical performance of the SARS-CoV-2 antibody test (colloidal gold immunochromatography, LEPU TECHNOLOGY) and evaluated the kinetic antibody response in COVID-19 patients.

Methods:

Samples collected by finger stick; obtained from RT-PCR confirmed cases and samples of negative controls were tested with the IgM/IgG Detection Kit .

Results:

The kit shows a clinical sensitivity of 65.7 % [59.7%-71.3%] and a specificity of 96.3% [93.0%-98.3%]. The predictive positive value and negative predictive value were respectively 95.2% [91.0%-97.8%] and 71.4% [66.1%-76.2%]. The seroconversion of specific IgM and IgG antibodies were observed as early as the 2nd day after symptom onset.

Conclusions:

This test is quite useful for assessing previous virus exposure, although negative results may be unreliable during the first weeks after infection. Longitudinal studies on antibody responses during and post infection are needed.

Background

On 12th March 2020, WHO declared COVID-19 outbreak caused by SARS-Cov-2 as a pandemic [1, 2]. Accurate diagnosis of COVID-19 is critical, for early identification and isolation of SARS-CoV-2 infected people, including asymptomatic carriers, to limit virus spread and to ensure appropriate case management [3].

Viral nucleic acid (RNA) detection in respiratory samples with real-time RT-PCR is the current gold standard for the detection of SARS-CoV2 RNA during the acute stage of COVID-19 disease [4, 5]. RT-PCR has many limitations including the need for specialized equipment, certified laboratories (Biosafety level 2), skilled laboratory staff and PCR reagents [6]. During the pandemic, materials such as nasopharyngeal swabs and viral transport media required have been scarce [7]. Moreover quality or timing of swabs affects the sensitivity of RT-PCR and for recovered individuals, this technique does not provide information about prior exposure or immunity[8].

These limitations impede large scale testing, a necessity for rapidly controlling the ongoing COVID 19 pandemic [9–11]. Serology testing to provide evidence of recent infections and potential immunity may be a cost-efficient, simple and reliable alternative to overcome these challenges, in particular in medium and low income countries.

In February 2020, a WHO expert group identified research into rapid tests, including serologic testing, as one of eight key actions necessary to the control the COVID-19 pandemic[12]. These tests have to be sensitive to mild and asymptomatic infections to help early effective identification and isolation of cases in order to reduce transmission within high risk groups; consistent to reliably monitor disease progression and aid clinical decisions; and scalable to inform public health policies, such as safe individual release from quarantine and population lock-down exit strategies [13].A lot of rapid serological tests, that can be realized at the point -of -care (POCTs), with a large portion of them being Lateral Flow Immunoassays (LFIA) have been developed and made available rapidly under urgent demands. However, there is scarce information about their diagnostic performance and validation.

The present study assessed the performance characteristics of a commercially available LFIA, the COVID-19 IgG/IgM Rapid diagnostic test (RDT) (colloidal gold immunochromatography, LEPU TECHNOLOGY), and evaluated SARS-CoV-2–specific antibody response among confirmed cases.

Methods

1-Population and study period:

This study was conducted by the National Observatory of New and Emerging Diseases supported by WHO (EMRO), in the hot spot areas of SARS-CoV-2 (cumulative incidence $\geq 10 /100.000$ inhabitants) in the Great Tunis (North), Kebili (South) and Monastir (Center) on April-May 2020.

The study population included two groups:

Group 1: A sample of RT-PCR COVID-19 confirmed cases (active and convalescent cases) with a documented day of onset of symptoms.

The dynamics of antibodies according to the disease progress was analyzed. Disease course was calculated from the day of onset of symptoms to the day of the survey.

Group 2: A randomly selected serum samples collected during the 2014–2015 national survey on hepatitis prevalence in Tunisia, were used as reference group.

Capillary blood samples from all RT-PCR confirmed COVID-19 cases and all reference group sera were tested by the test kit.

2- Covid-19 Igg/igm Rapid Diagnostic Test (rdt)

The SARS-CoV-2 antibody test (colloidal gold immunochromatography, LEPU TECHNOLOGY) is a LFIA qualitative IgG/IgM detection system. The test was performed according to the manufacturer's instructions. At room temperature, 20 µl of finger-prick blood carefully dropped and added to the specimen well on the individual test cassettes followed by 80 µl the supplied buffer (two to three drops). The result was read visually after 10 minutes (maximum 20 minutes) and based on the appearance of colored bands. The test allowed detection of a single antibody or combinations of both. A test was considered positive (control and test bands present), negative (control band only), or invalid (no band or absent control band) f. Weak signals for IgM and IgG, together or separate, were considered positive.

4-data Analysis:

Data from RDT's were compared to RT-PCR results (gold standard method), to define specificity (Sp), sensitivity (Se), positive predictive value (PPV), and negative predictive value (NPV) for total antibodies (Ab), IgM and IgG.

We calculated Se, Sp, PPV, NPV using True positive (TP), False positive (FP), True negative (TN), False negative (FN), and consistency rate. 95% Confidence interval (CI) was calculated using binomial distribution.

Se (%) = $100 * [TP / (TP + FN)]$; the proportion of patients with disease who test positive.

Sp (%) = $100 * [TN / (TN + FP)]$; the proportion of patients without disease who test negative.

PPV (%) = $100 * [TP / (TP + FP)]$; the proportion of patients with positive tests who have the disease.

NPV (%) = $100 * [TN / (TN + FN)]$; the proportion of patients with negative tests who do not have the disease.

FP (%) = $100 * [FP / (FP + TP + VN + FN)]$; the proportion of false positive.

FN (%) = $100 * [FN / (FN + TP + VN + FP)]$; the proportion of false negative.

Consistency rate = $100 * [(TP + TN) / (FN + TP + VN + FP)]$; the accuracy of the test.

Seropositive rate = $100 * [\text{Number of positive antibodies} / \text{total of confirmed cases}]$

Results

Overall, 512 subjects were tested with the COVID-19 IgG/IgM rapid diagnostic test. In detail, we enrolled 271 confirmed cases (171 active cases and 100 convalescents) and 241 healthy reference group.

1-serological Test Validation:

For patients included in group 2 (reference group), 232 showed negative results for serological tests, 5 specimens were positive for IgM and 6 positive for IgG. Thus test presented a specificity of 96.3% [93.0%-98.3%]. The overall sensitivity of the test was 65.7 % [59.7%-71.3%] compared to RT-PCR (Table 1).

The predictive positive value and negative predictive value were respectively 95.2% [91.0%-97.8%] and 71.4% [66.1%-76.2%] (Table 1). The proportion of false positive and false negative was respectively 1.8% [0.8%-3.3%] and 18.2% [14.9%-21.8%]. The consistency rate was 80.1% [76.3%-83.4%] (Table 1).

For IgM, Sensitivity and Specificity were respectively 36.5% [30.8%-42.6%] and 97.9% [95.2%-99.3%]. The predictive positive value and negative predictive value were respectively 95.2% [89.1%-98.4%] and 57.8% [52.9%-62.7%] (Table 1). The proportion of false positive and false negative were 1.0% [0.3%-2.3%] and 33.6% [29.5%-37.9%] respectively. The consistency rate was 65.4% [61.1%-69.6%] (Table 1).

For IgG, Sensitivity and Specificity were respectively 61.2% [55.2%-67.1%] and 97.5% [94.7%-99.1%]. The predictive positive value and negative predictive value were respectively 96.5% [92.6%-98.7%] and 69.1% [63.9%-73.4%]. The proportion of false positive and false negative was respectively 1.2% [0.4%-2.5%] and 20.5% [17.1%-24.3%]. The consistency rate was 78.3% [74.5%-81.8%] (Table 1).

Table 1
Comparison of RDTs performance using RT-PCR confirmed COVID-19 cases and reference group (N = 512)

	Gold Standard RT-PCR		Total
	Confirmed cases (n = 271)	Reference group (n = 241)	
IgM			
positive	99	5	104
negative	172	236	408
IgG			
positive	166	6	172
negative	105	235	340
RDT			
positive	178	9	187
negative	93	232	325

2–Kinetic of antibodies response in group 1 patients (PCR positive):

The median time at seroconversion was 33.5 days [26.75days – 41.0 days].

The seroconversion rate for Ab, IgM and IgG was 65.7% [59.7%-71.3%], 36.5% [30.8%- 42.6%] and 61.3% [55.2%-67.1%] respectively.

The seroconversion of specific IgM and IgG antibodies were observed as early as the 2nd day after symptom onset. Then, the positive rate peaked on week 7 (43–49 days) for both IgM and IgG (Fig. 1, Table 2). Moreover, the IgG immune response was comparatively to IgM immune response but more extensive.

Table 2
Serologic results in group 1 patients (RT-PCR confirmed cases) according to the time from the onset of symptoms (n = 271)

Weeks	Number of confirmed cases COVID-19	Number of IgM positive	Positive rate (%)	Number of IgG positive	Positive rate (%)	Number of IgM and or IgG positive	Positive rate (%)
Week 1	15	3	20.0	6	40.0	6	40.0
Week 2	15	1	6.7	3	20.0	3	20.0
Week 3	29	12	41.4	19	65.5	20	69.0
Week 4	44	12	27.3	23	52.3	24	54.4
Week 5	73	23	31.5	45	61.6	49	67.1
Week 6	55	27	49.1	40	72.7	42	76.4
Week 7	33	18	54.5	25	75.8	29	87.9
Week 8	7	3	42.9	5	71.4	5	71.4
Total	271	99	36.5	166	61.3	178	65.7

Discussion

This study reported clinical validation of a new commercially CE marking LFIA test intended for the qualitative detection of anti-SARS-CoV-2 IgM and IgG antibodies in clinical samples (Serum/ Plasma/whole blood) by comparison with RT-PCR considered as gold standard diagnostic test. We used capillary blood obtained from a finger stick sample. Based on our knowledge, this is the first nationwide and in EMRO region study that evaluated a commercial rapid SARS-CoV 2 antibody test.

Our study is based in the principles of quality assurance process. Performance of RDTs may be different than that reported by manufacturers. Prior to their deployment as standalone diagnostic tests ,performing clinical validation of the diagnostic performance of tests for COVID-19 by comparison with a reference standard is considered best practice according to the working document published by the European Commission on April 2020[14].

Confirmed cases results were compared to those of negative control samples archived before the emergence of SARSCoV-2. One of the challenges facing conducting evaluation of performance of antigen and antibody tests, is the current absence of control samples and reference materials [14].

Overall the kit reaches a sensitivity of 65.7 % [59.7%-71.3%] and a specificity of 96.3% [93.0%-98.3%]. The specificity of rapid antibody tests is critical, as a false-positive result could provide incorrect assurance that an individual is immune to SARS-CoV-2 when he is still at risk of contracting the infection [15]. A review of the characteristics of a selection of RDTs for COVID-19 antibodies showed that clinical sensitivity ranged from 85–100%, and clinical specificity ranged from 96–100%. Sensitivity and specificity evaluated here are quite in line with these findings. Data of this review are collected from manufacturer websites and technical documentation, and the reference test used for comparison of diagnostic performance was infrequently reported. Therefore; these findings should be interpreted carefully and require confirmation using larger more robust studies[16].

The PPV of this IgM/IgG rapid test kit was 95.2% [91.0%-97.8%]. Prevalence impacts PPV, thus, this result may be explained by the population study, belonging to the hot spot areas of SARS-CoV-2 in Tunisia. The NPV of this test kit was 71.4% [66.1%-76.2%]. Even though this value, negative IgM/IgG test results cannot eliminate SARS-COV 2 past infection, the levels of antibodies may be too low to be detected, and repeating testing is recommended [17].The proportion of false positive and false negative was respectively 1.8% [0.8%-3.3%] and 18.2% [14.9%-21.8%]. The consistency rate was 80.1% [76.3%-83.4%]. These indicators provide rapid and reliable information on the past exposure to SARS-COV-2 and are in favor of using RDT in settings where access to PCR is limited.

At the early stages of SARS–CoV-2 infection, IgM/IgG assays are likely to have false negative results and miss detection of cases due to low antibody concentrations; a detectable antibody response to SARS–CoV-2 infection can take more than 10 days after the onset of symptoms. [15]. A complementary testing by a molecular RT-PCR should be considered to rule out infection in individuals with negative results.

This study investigated also the IgM and IgG responses in COVID-19 confirmed cases according to symptoms onset. At this time, few studies have presented information about the immune response during the SARS-Co V2 infection. Compared with published ones, one of our strengths was that we recorded disease course for each patient.

Immune response to SARS-CoV-2 implies cell and antibody mediated immunity. Studies have reported that the IgM and IgG antibodies to SARS-CoV-2 are produced 6 to 15 days after infection. Post diseases onset, the median seroconversion time for Ab, IgM and IgG were day-11, day-12 and day-14 respectively

[18]. Other studies have reported detection of antibodies three days after the onset of symptoms using antibody assays. Such tests may not be reliable in the early phase of infection and should not be used for case detection in patients with clinically suspected COVID-19 according to WHO guidance[19]. Combined IgM and IgG tests are suitable for different stages of the COVID 19 infection. Studies had shown that the sensibility was higher in IgG-IgM combined antibody test than in individual IgG or IgM antibody test and so better test for screening COVID-19 cases [15]. Moreover, IgG/IgM test kit likely can remedy some false negatives inherent in respiratory swab samples and can be served as a complementary option to RT-PCR[17].

Compared to SARS-CoV infection, the seroconversion timing for SARS-CoV-2 antibodies is similar or slightly earlier [20, 21]. Similar to our findings; some studies have demonstrated that the positive rate and titer variance of IgG are higher than those of IgM in COVID-19 [22, 23]. A positive correlation between antibodies production and disease severity has been found. Moreover, antibody production may be delayed, weak or ineffective in the elderly and among immunocompromised [24]. Our study did not explore a potential link between case severity and antibody response. The study population was among non-hospitalized cases (non severe cases), and antibodies detection in mild cases may take longer time (four weeks or more) or even be impossible at least during the studies' time scale [25, 26].

Comparison to other coronaviruses to SARS-CoV-2 suggests a possibly contrasting pattern to MERS-CoV: while IgM antibodies appear at the same time in severe and non-severe cases, IgG appears sooner in severe cases. On the other hand, titers of neutralizing antibody were higher in severe cases [27].

There are still unknowns about COVID 19 immunity, such as the effectiveness and durability of the antibody response, and the probability of re-infection with the same or a different antigenic strain of the SARS-CoV-2 virus [28]. It's critical to investigate the dynamics of protective immunity by longitudinal serological studies to understand the course of the pandemic and the post-pandemic dynamics [26]. RT-PCR and serology testing should not be considered competing alternatives; both techniques are relevant at different time points during the clinical course of COVID-19. While Carrying out both RT-PCR and antibody tests is optimal for accurate diagnosis, antibody detection will be pertinent for the later stages of infection where the virus has been eliminated [16]. Besides the diagnostic value of antibody testing, it will identify individuals who developed immunity after infection that may protect against subsequent re-infection, as well as define and monitor the extent of virus spread and a population's herd immunity on a societal level [29]. Serology RDT results should always be considered in the context of clinical observations, molecular testing and epidemiological data in making a final diagnosis and case management and treatment decisions [28]. In case of use at POC, traceability of serology RDT results may be lacking and results may not be reported to the health authorities for seroprevalence studies [15]. At present, according to WHO, using these POC immunodiagnostic tests is limited outside of well-constructed seroprevalence studies,, until there is evidence supporting their use for specific indications [30].

Conclusions

Our study showed a satisfactory performance of a rapid test, that can meet the ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users) criteria suggested by the WHO, to select the most appropriate diagnostic test(s) among available testing alternatives in resource constrained settings[31]. This evaluation is limited by being compared only to PCR co confirmed cases, so it is necessary to compare this test to other serological tests such as ELISA.

Abbreviations

Ab : Antibodies
CI : Confidence interval
FN : False negative
FP : False positive
LFIA : Lateral Flow Immunoassays
NPV : Negative predictive value
POCT s : Point -of -care tests
PPV : Positive predictive value
RDT : Rapid diagnostic test
Se : sensitivity
Sp : Specificity
TN : True negative
TP : True positive

Declarations

Ethics approval and consent to participate:

Administrative permission was granted from National Authority For Protection of Personal Data. Participating in this survey was voluntary. All individuals accepted testing via written informed consent. No formal ethics approval was acquired because of the emergency of COVID-19's outbreak. All samples were analyzed anonymously and according to the Tunisian regulation law, which allows anonymized diagnostic patient samples and archived samples to be used for research purposes.

Consent for publication

All authors consent to the publication of the manuscript

Availability of data and materials

All data on which this study is based are available from the corresponding author on request

Competing interests

Authors declare no conflict of interest

Funding

Not applicable

Authors' contributions

MC and NBA conceived the study.

HL, SD, NBA, MC carried out the analysis. HL and SD collected the data. AH and NBA checked and validated symptom onset data. HL drafted the first manuscript. AH, MS provided helpful information. NBA and MC provided guidance and carefully revised the manuscript. All authors discussed the results, critically read and revised the manuscript, and gave final approval for publication.

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Figures

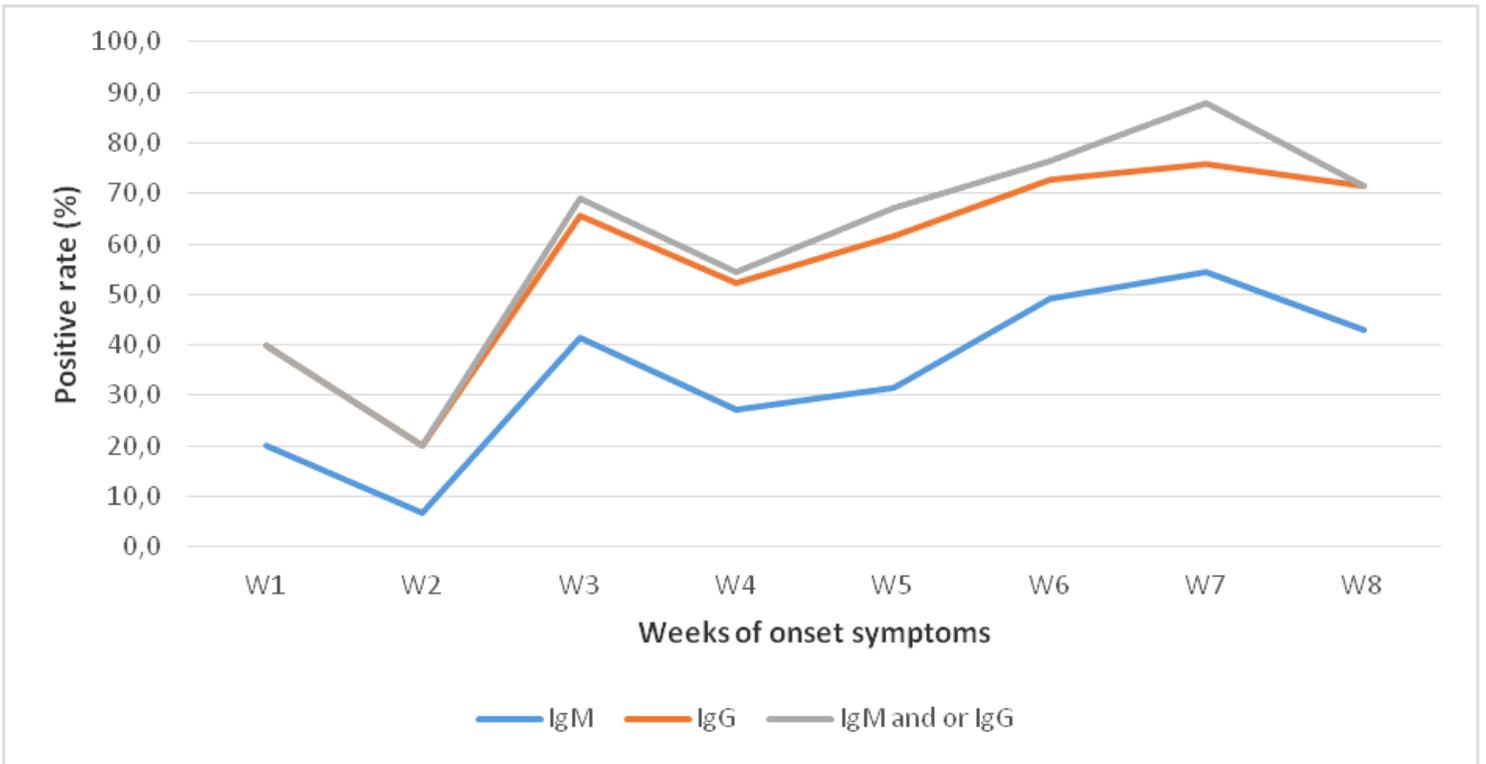


Figure 1

Weekly kinetic of specific antibodies anti Sars-Cov-2 among group 1 (RT-PCR confirmed cases) (n=271)