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The VivaDiag COVID-19 IgM/IgG Rapid Test for the Screening and Early Diagnosis of COVID-19 in Patients with No Clinical Signs of the Disease

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Abstract

COVID-19 is a viral disease secondary to the infection by the SARS-CoV-2 virus that can lead to a severe respiratory distress. The diagnosis of COVID-19 represents a major challenge. Currently the nasopharyngeal or throat swabs for the detection of SARS-CoV-2 RNA by Polymerase Chain Reaction (PCR) is considered the only validated method for the confirmation of SARS-CoV-2 infection. However, this test has some limitations, and its use for the screening of a negative, asymptomatic population remains controversial. The serological essay is a possible alternative both for the diagnosis, when associated with clinical and epidemiological feature, and for the continuous screening of the population and of people with a high-risk profile. We observed in a primary care setting were rapid serological testing has been performed, a possible good correlation with the rapid test and the early detection of SARS-CoV-2 infection. We thus designed the clinical protocol [clinicaltrials.gov ID Number NCT04316728] presented in this paper to evaluate the clinical performance and the real effectiveness of the serological rapid test for the screening and monitoring of Covid-19 in a pool of negative asymptomatic high-risk population in a primary care setting.

Keywords: COVID-19; Rapid test; Serological assay; IgG antibodies; IgM antibodies; Primary care; screening

Introduction

COVID-19 is a viral disease secondary to SARS-CoV-2 infection that can lead to a severe respiratory distress [1]. The early diagnosis of COVID-19 represents a major challenge, especially in primary care settings, where patients generally ask for a medical consultation because of the onset of minor symptoms or for a routine check-up. Nasopharyngeal or throat swabs are the specimen commonly used for the detection of SARS-Cov-2 RNA by Polymerase Chain Reaction (PCR), although considering this testing techniques as the gold standard for the diagnosis of COVID-19 at the moment is highly controversial [2,3]. RT-PCR on Bronchoalveolar lavage fluid demonstrated the highest positive rates (93%) followed by sputum with 72% [4,5].

Although PCR has a high specificity and sensitivity, it has some limitations as the number of patients that can be tested at the same time and the time from the sampling to the response. Besides, the use of swabs in an emergency setting makes the health workers more susceptible to infection when this procedure is compared with other sampling techniques.

In addition, this is an operator-dependent procedure: if the sample is not properly collected it could result in a high number of false negative. This is the case of an emergency screening in case of a major outbreak, where a single operator can perform hundreds of swabs in a single shift [6,7].

For all of these reasons, the World Health Organization (WHO) encourages the development of new protocols to standardize diagnosis and therapy [8].

Recent literature [9,10] suggest that the development of a rapid testing for the current and future outbreaks is needed. The use of a more performant test in fact may reduce the time-lapse from clinical suspect of COVID-19 to diagnosis, and may increase the number of people that could be tested in a given timeframe.

This has two main relevant consequences:

A. Give a rapid diagnosis that could help medical doctors to take clinical decisions, to give a prognosis, and to take public health actions as containment and isolation of the case and of the contacts [11].

B. Give a more accurate pictures of the spreading of the disease, that can produce more accurate epidemiological data, triggering therefore tailored public health responses and measures [12,13].

C. Indicate a specific immune response for the RNA confirmed patient [14].

VivaDiag™ COVID-19 IgM/IgG Rapid Test is an *in vitro* diagnostic test for the qualitative determination of COVID-19's IgM and IgG antibodies. It can be used in primary care settings or in secondary and tertiary health facilities, can be serially used on patients and the number of patients that can be tested at the same time depend exclusively on organizational limitations (as the number of health workers performing the test, and physical restraints of the health facility that may reduce the number of people-waiting to be tested or already tested and waiting for the response-attending the department).

Following the observation on a pool of patients that for public health and clinical reason have been tested both with the Covid-19 serological essay and the RT-PCR, we designed a research protocol for the early diagnosis and screening of SARS-CoV-2 infection.

The aim of this study, thus, is to understand how effective is the VivaDiag™ test for the screening of patients during a COVID-19 outbreak, and how effective is the test in monitoring the clinical progression, the recovery and the relapse of the disease.

Test validation *versus* RT-PCR: observation and studio hypothesis

Following the recommendation to increment the number of tests for COVID-19 infection in the population, we propose the serological test on non-symptomatic patients attending a primary care facility for routine check-ups or follow-ups and on healthcare workers that worked in the outpatient clinic. Starting from the results of the tests and matching the results of the COVID-19 RT-PCR test in those patients that developed symptoms or that underwent to the molecular test because of epidemiological criteria and that have a serological test in the meanwhile, we observed a fair correspondence among the results coming from the different testing techniques that prompt our research hypothesis.

As shown in figure 1, the subjects that we observed in the outpatient clinics were 30 (56% males, 44% female; overall age 60,9+2,71 years; x ± SEM). All the subjects have a RT-PCR test (subjected to oropharyngeal swab) as carriers of symptoms for Covid19 (n=15) or as high-risk medical personnel (n=15).

RT-PCR was performed according with the methods suggested by WHO and with the indications of the Italian Health Authority. On the same day of PCR test, the rapid immunochromatographic test with VivaDiag™ was performed. In four patients the results of RT-PCR have not yet been provided due to the emergency and the difficulties in performing PCR tests by specialized laboratories. So, the calculations were made on the 26 available results.

The statistical analysis was performed using the McNemar exact test and then by calculating the Cohen's k, which explains the amount of concordance not determined by chance [Table 1].

Following our observation, we speculated that the use of the serological test in a primary care setting can be useful for the early diagnosis and for the screening of patients and healthcare workers with a possible SARS-CoV-2 infection. We therefore designed the following research protocol aimed to better evaluate the clinical performance of serological essay and the effectiveness of the serological rapid test for the detection and diagnosis of Covid-19 in a pool of negative asymptomatic high-risk population.

Materials and Methods

Patients attending routinely an outpatient department or a primary care clinic and the health workers working are tested for SASR-CoV-2 *via* VivaDiag™ COVID-19 IgM/IgG rapid test.

As per the full protocol published on and available from clinicaltrial.gov [15], we included in our study adult patients attending a medical clinic with a known diagnosis of at least two chronic conditions, and healthcare workers working in the same facility.

This study aims to evaluate the immune response of negative patients during a COVID-19 outbreak, the clinical performance of the test in early detecting the infection, and the reliability of the test in those patients who develop clinical signs of COVID-19 during the trial. Thus, patients attending the clinics are serially tested according to protocol and medical history is taken during every encounter to assess the absence of symptoms suggestive of SARS-CoV-2 infection, and the possible contact with other people with a diagnosis of COVID-19.

The exclusion criteria are: patients with chronic respiratory conditions, with known immunodepression, or under treatment with drugs that may reduce the immune response.

Patients with clinical signs of COVID-19 will be tested with COVID-19 PCR RT and with the VivaDiag™ COVID-19 IgM/IgG Rapid Test.

Patients with or without symptoms, with a positive rapid test will be tested with the COVID-19 RT-PCR to evaluate the correspondence of the two tests.

The VivaDiag™ COVID-19 IgM/IgG Rapid Test is positive when it meets the following conditions:

1. The anti-COVID-19 IgM antibody is detected;

2. The anti-COVID-19 IgG antibody is detected;

3. The IgG and IgM anti-COVID-19 antibodies are both detected.

We consider a result Negative if the anti-COVID-19 IgG and IgM antibodies are not detected, and we consider the test invalid if the quality control band C does not colour, regardless of whether the IgG and IgM bands are coloured or not.

Results

Expected outcomes

Primary outcomes: To better understand the clinical performance of the test, we will evaluate the number of patients with constant negative results that do not develop clinical signs of COVID-19 at the end of the trial (true negative), and the number of patients that during

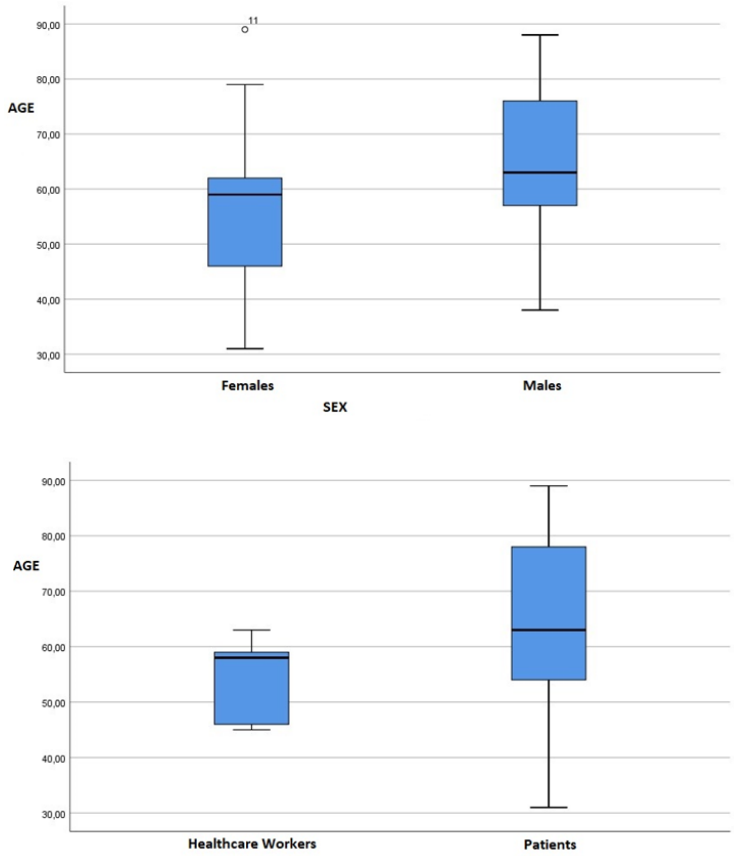

Figure 1: Demographic characteristics of the case series: left Age distribution by sex (males and female); right age distribution by groups (medical staff and patients).

Table 1: The exact McNemar test obtained by table gave p>0.9999, while the Cohen's k was equal to 1 (CI95% from 1.0 to 1.0), e.g., the concordance is not attributable at all to any random cause.

		VivaDiag		
		Negatives	**Positives**	**Total**
RT-PCR	Negatives	17	0	17
	Positives	0	9	9
	Total	17	9	26

the trial become positive to the rapid test early detecting COVID-19 before developing clinical symptoms of SARS-CoV-2 infection.

In those patients with an exposure to SARS-CoV-2 that develop symptoms, we aim to assess after how many days from the suspected time of contagion the test become positive. In addition, we will consider how many patients with no symptoms that become positive to the rapid test during the trial, are also positive to the PCR RT.

Secondary outcomes: The secondary goal of this study is to assess the accuracy and precision of VivaDiag™ rapid test when compared to the PCR RT in those patients that become positive to the rapid test.

Moreover, to better understand the exposure to the virus in a primary care setting, we will evaluate how many patients and how many healthcare workers become positive during the time of the trial.

Discussion

Although serological assay is frequently used for screening and diagnosis in patients with suspected viral infections, there are only few reports on SARS-CoV-2 in the scientific literature. VivaDiag™ COVID-19 IgM/IgG Rapid Test is an *in vitro* rapid diagnostic test for the qualitative determination of COVID-19's IgM and IgG antibodies. The study that we designed and whose protocol we are presenting, aims to assess the immune response to the clinical performance of the rapid test in early detecting the infection of SARS-CoV-2 in patients with no clinical signs of COVID-19 in a primary care setting.

The main input for this research derives from the observation of the results of the test that we have performed in a pool of patients routinely attending a primary care facility, when compared with the RT-PCR for SARS-CoV-2. This observation matches the emblematic study by Li Z, et al [16] about the role of specific monoclonal antibody IgM and IgG anti SARS-CoV-2. Li's study seems to confirm the validity of the test and the advantages compared to RT-PCR.

Similar results are reported by Liu L, et al. [17] in a study on 238 patients admitted to the hospital. In contrast, Cassaniti I, et al. reported a poor performance of the test, when the test was performed in emergency settings and in acute patients [18]. However, our study design is intended for the evaluation of the rapid serologic test in primary care settings and mainly for the screening of SARS-CoV-2 infection in high-risk asymptomatic patients.

According to the previous findings, we speculate that the serological test can be used for the early detection of positive patients before the onset of clinical symptoms. Moreover, the antibody tests can play an important role in addition to RT-PCR tests [14]. Because the test does not require special equipment and training, and can be performed with the use of basic personal protective equipment, it may be particularly useful in a primary care setting and for the rapid screening of a high number of patients and of healthcare workers, improving the response of the health systems to the current pandemics. Moreover, as long as a rapid test may be the only possible strategy for a population screening in poor-income areas and in developing countries, the results that will come from our study may become crucial to better design and implement future interventions in those areas.

Our protocol has some limitations. Because the main aim of the study is not to assess the specificity and sensitivity of the serological rapid test when compared to the RT-PCR, we can only rely on the results of previous publications to assess the correspondence among the two tests. This also means that the results that will come from our study may apply only to the VivaDiag™ rapid test; although we can speculate that the findings from our research will be similar when other serological rapid tests are used in the same settings. In addition, as the research will take place in a primary care department, we cannot follow-up patients admitted to the hospital secondary to Covid-19 diagnosis, and data missing from these same patients may affect the results of the future trial. Nevertheless, we believe that this study will provide valuable information enlightening an area where at the moment we are walking totally blindly.

Conclusion

In conclusion, considering the favorable result of the test of validation against RT-PCR-that come from the preliminary observations that triggered our study protocol, the exact concordance between the methods even excluding the concordance due to chance (Cohen's k=1; CI95%: from 1 to 1), and based on the considerations set out above, we believe it is urgent to better understand if the rapid test is actually effective and reliable, especially for the screening purpose that we have presented in our protocol. We reckon that the protocol we have designed can provide relevant information to establish the effectiveness of the rapid serological test in real clinical settings we therefore foster other studies based on our research protocol to better understand the clinical performance of the test. If the results are consistent with our preliminary observations, this or similar rapid tests may be broadly used for the clinical screening of Covid-19, both in the medical staff and in the general population, improving the prevention strategies and the response to the epidemic, and augmenting at the same time the chance of making an early diagnosis in patients with or without symptoms of COVID-19.

Conflict of Interest

The authors have no conflict of interest to report.

References

1. Wang C, Horby PW, Hayden FG, Gao GF (2020) A novel coronavirus outbreak of global health concern. Lancet 15: 470-473.
2. Lan L, Xu D, Ye G, Xia C, Wang S, et al. (2020) Positive RT-PCR Test Results in Patients Recovered From COVID-19. JAMA.
3. Zhang JC, Wang SB, Xue YD (2020) Fecal specimen diagnosis 2019 novel coronavirus-infected pneumonia. J Med Virol 92: 680-682.
4. Wang W, Xu Y, Gao R, Lu R, Han K, et al. (2020) Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA.
5. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, et al. (2020) Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 25: 1560-7917.
6. Winichakoon P, Chaiwarith R, Liwsrisakun C, Salee P, Goonna A, et al. (2020) Negative Nasopharyngeal and Oropharyngeal Swabs Do Not Rule Out COVID-19. J Clin Microbiol 23: e00297-e00320.
7. Yu F, Yan L, Wang N, Yang S, Wang L, et al. (2020) Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients. Clin Infect Dis pii: ciaa345.
8. World Health Organization (2020) Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases: Interim guidance.
9. Xiao SY, Wu Y, Liu H (2020) Evolving status of the 2019 novel coronavirus infection: Proposal of conventional serologic assays for disease diagnosis and infection monitoring. J Med Virol 92: 464-467.
10. Hick JL, Biddinger PD (2020) Novel Coronavirus and Old Lessons-Preparing the Health System for the Pandemic. N Engl J Med.
11. Wang Y, Wang Y, Chen Y, Qin Q (2020) Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol 92: 568-576.
12. Dong X, Cao YY, Lu XX, Zhang JJ, Du H, et al. (2020) Eleven faces of coronavirus disease 2019. Allergy.
13. Li Q, Guan X, Wu P, Wang X, Zhou L, et al. (2020) Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med 382: 1199-1207.
14. Zhao J, Yuan Q, Wang H, Liu W, Liao X, et al. (2020) Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis pii: ciaa344.
15. Gaddi AV, Capello FV (2020) Clinical Performance of the VivaDiag™ COVID-19 IgM/IgG Rapid Test in Early Detecting the Infection of COVID-19. ClinicalTrails.gov.
16. Li Z, Yi Y, Luo X, Xiong N, Liu Y, et al. (2020) Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol.
17. Liu L, Liu W, Wang S, Zheng S (2020) A preliminary study on serological assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 238 admitted hospital patients. medRxiv.
18. Cassaniti I, Novazzi F, Giardina F, Salinaro F, Sachs M, et al. (2020) Performance of VivaDiag COVID-19 IgM/IgG Rapid Test is inadequate for diagnosis of COVID-19 in acute patients referring to emergency room department. J Med Virol.