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LETTER TO THE EDITOR

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Performance of VivaDiag COVID-19 IgM/IgG Rapid Test is inadequate for diagnosis of COVID-19 in acute patients referring to emergency room department

To the Editor,

From late December 2019, coronavirus infectious disease (COVID-19) epidemics spread from Wuhan, China, to all over the world, including Italy.[1-3]

To date, real-time reverse transcription-polymerase chain reaction (RT-PCR) in respiratory samples is the current gold standard method for the diagnosis of COVID-19.[4,5] However, molecular testings are time consuming and require specialized operators, factors that limit their use in real life when the rapid diagnosis is required for fast intervention decisions. Recently, an easy to perform serological assay has been assessed[6] to differentiate COVID-19 positive patients from negative subjects.

We herein report results of a real-life study performed in an emergency room department of a tertiary hospital in Northern Italy to validate VivaDiag COVID-19 IgM/IgG Rapid Test lateral flow immunoassay (LFIA) for the rapid diagnosis of COVID-19.

Overall 110 subjects were tested for COVID-19-specific serological assay at Fondazione IRCCS Policlinico San Matteo. In detail, we enrolled 30 healthy volunteers with documented negative results for COVID-19 RT-PCR in respiratory samples (M 11/F 19; median age, 38.5; range, 25-69 years). Ten of them (33.3%) had been infected in the past with one of the common OC43, 229E, HKU1, and NL63 coronavirus. Thirty COVID-19-positive patients (25 M/5 F; median age, 73.5; range, 38-86 years) admitted to the Infectious Diseases Department or at the Intensive Care Unit were tested as positive controls. Finally, the performance of VivaDiag COVID-19 IgM/IgG Rapid Test LFIA was tested in 50 patients at their first access at emergency room department with fever and respiratory syndrome (34 M/16 F; median age, 61.50; range, 33-97 years) in comparison with results of nasal swab molecular screening.[5]

VivaDiag COVID-19 IgM/IgG from VivaChek was performed according to manufacturer's instruction by adding 10 μL of serum or whole blood sample into the sample port followed by adding 2 to 3 drops (70-100 μL) of dilution buffer.[6] After about 15 minutes, results were read.

Respiratory samples (FLOQSwabs; Copan Italia, Brescia, Italy) were collected from all the patients. Total nucleic acids (DNA/RNA) were extracted from 200 μL of UTM using the QIAsymphony instrument with QIAsymphony DSP Virus/Pathogen Midi Kit (complex 400 protocols) according to the manufacturer's instructions (QIAGEN; Qiagen, Hilden, Germany). Specific real-time RT-PCR targeting RNA-dependent RNA polymerase and E genes were used to detect the presence of SARS-CoV-2 according to the WHO guidelines[7] and Corman et al[5] protocols.

In the cohort of patients admitted to the emergency room department, data from serological tests were compared to molecular results to define specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) of the rapid serological test.

As expected, all 30 COVID-19 negative volunteers were negative for both immunoglobulin G (IgG) and immunoglobulin M (IgM) using the VivaDiag COVID-19 IgM/IgG Rapid Test. No cross-reactivity was detected in the 10 subjects with previous coronaviruses infection, supporting the high specificity of the VivaDiag COVID-19 IgM/IgG Rapid Test LFIA.

Serum samples were obtained at a median 7 days (interquartile range, 4-11) after the first COVID-19 positive result from 30 hospitalized patients. A total of 19 of 30 (63.3%) were positive for both IgM and IgG, 5 of 30 (16.7%) were negative for both IgG and IgM, 5 of 30 (16.7%) were weakly positive for both IgM and IgG, and only 1 of 30 (3.3%) was positive for IgM and negative for IgG. Thus, the sensitivity of the rapid assay was suboptimal (data not are shown). A possible explanation is the low antibody titers or a delayed humoral response.[6]

Focusing on acute patients enrolled from the emergency room department, 12 of 50 (24%) were negative for COVID-19 by real-time RT-PCR. Of these, 1 (8.3%) showed a positive results for the VivaDiag COVID-19 IgM/IgG Rapid Test, while the other 11 of 12 (91.7%) tested negative. On the other side, 38 patients were positive for COVID-19 by real-time RT-PCR. Of these, only 7 (18.4%) showed a positive or weak positive serology for IgM and/or IgG, while the other 31 of 38 (81.6%) tested negative for the rapid serology assay (Table 1). Thus, the sensitivity of the VivaDiag COVID-19 IgM/IgG Rapid Test was 18.4%, specificity was 91.7%, while NPV was 26.2%, and PPV was 87.5% in patients enrolled from emergency room department. In contrast with the high levels of sensitivity reported in the previous study,[6] VivaDiag COVID-19 IgM/IgG Rapid Test revealed a very poor

[Correction added after online publication on 29 April 2020: Conflict of Interest statement was added]

TABLE 1 Characteristics and VivaDiag COVID-19 IgM/IgG Rapid Test results of 50 consecutive patients referred to the emergency room department

Patient	Sex	Age	Result of COVID-19 real-time RT-PCR on NS	VivaDiag COVID-19 IgM/IgG Rapid Test	
				IgM	IgG
1	M	33	neg	–	–
2	M	51	pos	–	–
3	M	51	pos	–	–
4	M	38	pos	–	–
5	F	80	pos	–	–
6	F	64	neg	–	–
7	M	81	neg	–	–
8	M	76	pos	+/–	–
9	M	33	pos	–	–
10	M	37	neg	–	–
11	F	45	pos	–	–
12	M	53	pos	–	–
13	M	66	neg	–	–
14	M	78	pos	–	–
15	F	97	pos	–	–
16	M	38	pos	–	–
17	M	72	pos	–	–
18	M	56	pos	–	–
19	M	80	pos	–	+/–
20	M	72	pos	–	–
21	F	55	pos	–	–
22	M	82	pos	–	–
23	M	47	pos	+	+/–
24	F	63	pos	–	–
25	F	80	pos	+/–	–
26	M	59	pos	–	–
27	M	66	pos	–	–
28	M	39	pos	–	–
29	F	78	neg	–	–
30	M	71	neg	–	–
31	F	46	neg	–	–
32	F	51	pos	–	–
33	F	75	pos	–	–
34	F	82	pos	+	+/–
35	F	51	pos	+/–	+/–
36	M	84	pos	–	–
37	M	50	pos	–	–

(Continues)

TABLE 1 (Continued)

Patient	Sex	Age	Result of COVID-19 real-time RT-PCR on NS	VivaDiag COVID-19 IgM/IgG Rapid Test	
				IgM	IgG
38	M	50	pos	+	+/−
39	F	72	neg	−	−
40	M	54	neg	−	−
41	F	64	neg	+	−
42	M	64	pos	−	−
43	M	70	pos	−	−
44	M	56	pos	−	−
45	M	68	pos	−	−
46	F	36	pos	−	−
47	M	60	pos	−	−
48	M	66	pos	−	−
49	M	54	neg	−	−
50	M	56	pos	−	−

Abbreviations: −, negative result; +, positive result; +/−, weakly positive result; COVID-19, coronavirus infectious disease 2019; IgG, immunoglobulin G; IgM, immunoglobulin M; NS, nasopharyngeal swab; RT-PCR, reverse transcription-polymerase chain reaction.

sensitivity (less than 20%). Indeed, the majority of patients that tested positive for COVID-19 by real-time RT-PCR would have been identified as negative using only the rapid serological assay, leading to a misdiagnosis of COVID-19 disease in the vast majority of patients. On the basis of our results, VivaDiag COVID-19 IgM/IgG Rapid Test LFIA is not recommended for triage of patients with suspected COVID-19.

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CONFLICT OF INTERESTS

As widely documented to the Editor of the Journal of Medical Virology, I and my collaborators don't have any conflict of interest. On March 25, 2020, after submission of this manuscript, Foundation

IRCCS Policlinico San Matteo signed a research contract with DiaSorin on different projects: i) validation of a rapid assay for detection of SARS CoV2 RNA and ii) validation of an automated CLIA assay for detection of SARS CoV2 neutralizing antibodies. The authors don't have any economical or any other forms of conflict of interest.

AUTHOR CONTRIBUTIONS

IC, FN, FG, FS, MS, SP, RB, FM, FB, and the other members of the San Matteo Pavia COVID-19 Task Force listed reviewed and approved the manuscript. IC and FN discussed results, data analysis, and wrote the paper. FG, FS, and MS collected the samples. SP, RB, and FM discussed results. FB conceived the study.

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