Letter to the Editor

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Diagnostic performance of a SARS-CoV-2 IgG/IgM lateral flow immunochromatography assay in symptomatic patients presenting to the emergency department

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To the Editor,

The first cases of coronavirus disease 2019 (COVID-19), a new form of respiratory and systemic disorder caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were reported in December 2019. Since then, the spread of the virus has reached pandemic magnitude. Due to the high numbers of symptomatic patients presenting at the emergency departments (ED), hospitals are facing enormous challenges. Therefore, rapid diagnostic algorithms are urgently needed in order to accelerate patient flows to wards with isolation standards corresponding to their diagnoses. To date, the gold standard assay for the diagnosis of COVID-19 is the real-time reverse transcription polymerase chain reaction (RT-PCR) performed in swab samples from the upper or fluid samples from the lower respiratory tract. The detection of viral nucleic acid allows a highly specific diagnosis, however false-negative

results were described, especially in either very early or very late presentation [1, 2]. Additionally, RT-PCR is time-consuming, requiring high laboratory expertise and expensive instrumentation. In the last few weeks, in vitro diagnostic manufacturers all over the world have released many rapid assays based on lateral flow immunochromatography assay (LFIA). These tests allow the rapid and cost-effective detection of SARS-CoV-2-specific antibodies.

We evaluated the performance and usefulness of the Maccura LFIA (SARS-CoV-2 IgM/IgG, Maccura Biotechnology, Chengdu, China) to rapidly detect IgG and IgM immune response against recombinant spike and nucleocapsid proteins of the SARS-CoV-2 in symptomatic patients presenting to the ED of the Kantonsspital Aarau, Switzerland from March to April 2020. Patients' enrollment was based on clinical suspicion of acute airway infection. Molecular testing for SARS-CoV-2 by RT-PCR (Seegene Inc., Seoul, Republic of Korea) on nasopharyngeal swab samples (transportation medium ESwab, Copan Italia, Brescia, Italy) or nasopharyngeal fluid was done in parallel. Diagnosis of COVID-19 was based on clinical, microbiological and radiological criteria according to in-house, national and international recommendations and guidelines [3]. The study was approved by the local Ethics Committee.

A total of 215 samples from 139 ED patients (67 COVID-19 positive and 72 COVID-19 negative) and 100 SARS-CoV-2 seronegative samples collected between May and October 2018 (pre-COVID-19 outbreak control group) were included in the study. Demographics, clinical data and assay performance are summarized in Table 1. Sixty percent (40/67) of the COVID-19 patients had positive serology already at ED presentation, 38% (15/40) of them with isolated IgM, 63% (25/40) with IgM/IgG double positivity and none with isolated IgG. The seropositivity rate of patients presenting 1–6 or ≥ 7 days from symptom onset was 43% (9/21) and 67% (31/46), respectively. The positive predictive value (PPV) for the COVID-19 diagnosis of isolated IgM was 65%, whereas the simultaneous IgG and IgM detection showed a PPV of 100%. The negative predictive value (NPV) at presentation was 70%.

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Table 1: Summary data.

	#	%
Sex (n = 143)		
Male	84	59
Female	59	41
Age		
Median, years	69	
Min, years	22	
Max, years	95	
Final diagnosis (n = 143)		
COVID-19	67	47
Bacterial co-infection	2	3
Viral co-infection	0	0
Non-COVID-19	76	53
Bacterial infection	3	4
Viral infection	5	7
Infections without proven cause	19	25
Non-infectious	49	64
COVID-19-positive patients (n = 67)		
Days since symptoms onset at presentation		
<7 days onset	21	31
≥7 days onset	46	69
Seropositive at presentation (IgM and/or IgG)		
<7 days onset (n = 21)	9	43
≥7 days onset (n = 46)	31	67
PPV		81
Double positive IgM and IgG at presentation		
<7 days onset (n = 21)	5	24
≥7 days onset (n = 46)	19	41
PPV		100

Specificity measured in recent (72 symptomatic COVID-19-negative patients at presentation) and historical (100 pre-COVID-19 outbreak specimens) control groups was 88.2% (nine false positive out of 76) and 90% (10 false positive out of 100), respectively. Mainly weak isolated IgM reactions accounted for the majority of false-positive results. No viral or bacterial pathogen was identified in symptomatic patients showing false-positive results.

Seroconversion was observed at a median of 9.5 days (IQR, 6–12) from symptom onset in 19 of 27 hospitalized patients, who had been seronegative at presentation (seven patients between day 1 and 6 and 12 patients after 7 days). Our data confirm previous findings, reporting that both IgG and IgM antibodies rapidly increase and are detectable already 1 week after symptom onset [4–6]. Eight COVID-19 patients did not seroconvert during follow-up. These patients had in general a short median follow-up time due to early hospital discharge (2.4 days), high median age (87 years) or immunosuppression (2/8).

Figure 1 describes the cumulative IgG/IgM seropositive rate of all COVID-19 patients over time after symptom onset. The cumulative IgG/IgM positive rate was 50% at day 10–12, reaching nearly 90% after 18 days. These results are in concordance with other reports, demonstrating the presence of SARS-CoV-2-specific antibodies in almost all patients already on day 15 [7, 8].

To date none of the commercially available SARS-CoV-2 immunoassays has undergone extensive clinical validation. In a recent statement, the WHO encourages laboratories to perform assay validation in appropriate populations and settings, in particular regarding the

Figure 1: Cumulative IgG/IgM seropositive rate over time after symptom onset.

clinical utilization of rapid, easy-to-use devices [9]. The short turnaround time of serology based on LFIA (about 30 min) compared to that of RT-PCR (about 12 h) prompted us to investigate its usefulness to confirm clinical suspicion of COVID-19 infection in the ED. In our hands, the simultaneous detection of IgG and IgM was found in 36% of COVID-19 patients presenting at the ED and showed a PPV of 100%. These observations indicate that the use of a rapid serological assay complementary to RT-PCR can accelerate the management of a relevant part of the COVID-19 patients by confirming the diagnosis with the shortest possible turnaround time. However, considering the low PPV of isolated IgM and the expected seroconversion time, uniquely double positive (IgG and IgM) results should be integrated in the diagnostic work-up of patients presenting after more than 6 days of symptoms onset. Moreover, the clinical usefulness of the LFIA in the ED will decline with the increasing prevalence of IgG antibodies against SARS-CoV-2 in the population over time. In an uprising pandemic, the expected prevalence of IgG is very low (<5%), simplifying the interpretation of serological results in symptomatic patients.

Due to the low specificity observed in the two control groups, the detection of isolated IgM should not be used for COVID-19 diagnosis at presentation. In similar cases, we suggest to perform follow-up serology to detect IgG seroconversion.

In conclusion, our results show a satisfactory analytical performance of the Maccura SARS-CoV-2 IgG/IgM LFIA in clinical practice and suggest a potential utility of serology testing as a supplemental tool for the rapid diagnostic work-up in the ED.

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