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Title Page

Title: SARS-CoV-2 IgM and IgG rapid serologic test for the diagnosis of COVID-19 in the emergency department

Running title: SARS-CoV-2 IgM/IgG rapid test in the Emergency Department.

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Introduction

On December 31, 2019, the World Health Organization (WHO) China Country Office was informed of cases of pneumonia of unknown etiology detected in Wuhan City, Hubei Province of China. Subsequently, pathogenic gene sequencing confirmed that the infectious pathogen was a novel coronavirus, named SARS-CoV-2. It was the official beginning of an epidemic that has rapidly become worldwide. The continued spread of coronavirus disease 2019 (COVID-19) around the world led WHO to declare COVID-19 a pandemic on 11 March 2020(1).

Given the acute and rapid spread of COVID-19 around the world and the great number of hospital admissions, there is an urgent need for rapid tests for SARS-CoV-2 diagnostic confirmation. Actually, the molecular testing of upper or lower respiratory tract samples by reverse transcription polymerase chain reaction (RT-PCR) remains the gold-standard diagnostic test (2). However RT-PCR test suffers from several limitations (3): long turnaround times and up to 30% of false negatives, due to technical errors and time sampling (4,5).

In addition to molecular testing, there is a growing interest for serologic assays to detect antibodies against SARS-CoV-2 (6). High levels of IgM and IgG can be detected from the second week symptom onset, although IgM can be found positive from the fourth day and IgG after 8 days (3,6).

In the French emergency departments (ED) there is a rising number of suspected cases of COVID-19 from mid-march and a huge effort is made in order to isolate these suspected patients to avoid hospital SARS-CoV spread and transmission. However, it is difficult to differentiate only on clinical presentation, the COVID-19 cases from the non COVID-19 ones. The typical clinical picture with symptoms including fever, cough, dyspnea, myalgia, chest pain or fatigue (7) can be encountered with flu or another viral infection, as non-specific/unusual clinical presentations of COVID-19 are also reported. Molecular tests and classic serology immunoassays have a relatively long turnaround times, which are not suitable for EDs to take fast disposition decisions. The recent development of rapid antibody detection tests for Sars-CoV2 can be very useful in this context.

We therefore have evaluated a rapid antibody IgG/IgM based test for Sars-CoV2 (lateral flow immunoassay, LFI) in two EDs and compared it to the RT-PCR of a nasopharyngeal swab gold standard.

Methods

This is a prospective routine care study performed in the ED of two academic hospitals in Paris, France, in April 2020. Both hospitals were designated referent for COVID-19 in Paris area (Pitié-Salpêtrière and Bichat-Claude Bernard hospitals).

The patients admitted to the ED were included if 1) COVID-19 was suspected on presenting symptoms, with at least one of those: fever, cough, myalgia, dyspnea, chest pain, vomiting, diarrhea, headache, ageusia and anosmia; and 2) if a nasopharynx swab was prescribed for SARS-CoV-2 RT-PCR. Waived informed consent was obtained because of the routine care design.

The LFI used for evaluation was SGTi-flex COVID-19 IgM/IgG (Sugentech, republic of Korea) which is a nanoparticle-based immunochromatographic test kit for qualitative determination of COVID-19's IgM and IgG antibodies in human whole blood (finger prick or venous), serum or plasma. The results can be observed within 10 minutes after applying the sample and 3 drops of diluent. At the same time of first ED blood collection, a sample was also drawn in parallel for SARS-CoV-2 IgG detection with a chemiluminescent microparticle immunoassay (CMIA) in human serum (Abbott Architect).

RT-PCR assay on nasopharyngeal swab was taken as the reference standard for the diagnosis of COVID-19 (SARS-CoV-2 Cobas assay, Roche).

Briefly, after ED admission and first medical contact, if a patient presented with consistent COVID-19 symptoms, a SARS-CoV-2 RT-PCR was prescribed. At Pitié-Salpêtrière hospital, the ED nurse, soon after obtaining the nasopharynx swab, tested the whole blood from finger prick on the LFI and collected a blood sample for SARS-CoV2 CMIA IgG test. After 10-15 minutes, the LFI result was read and noted in the medical chart and then sent together with the swab and the blood sample tube to the virology

laboratory to test for RT-PCR and CMIA IgG test. Then the LFI was read one more time by a virologist who was blinded to the result obtained in the ED. In case of disagreement between both readings, it was decided to take into account the LFI result from the ED in order to follow the real-life course of diagnosis in the ED. At Bichat-Claude Bernard hospital, LFI was not performed at ED but at by at the Virology Department on total blood samples collected on EDTA.

The SARS-CoV-2 RT-PCR results were available within five hours during the day, and the day after, if the swab was sent during the evening or night. The IgG CMIA tests were performed altogether by batch on frozen serum samples 1 week later.

Current clinical data collection was performed independently by two emergency physicians who had access to the entire medical chart of the patients. They extracted manually the information from the electronic medical chart into an Excel preformatted sheet. The patient was excluded if the result of either RT-PCR or LFI missed.

Statistical Analysis

The patients were divided in two groups according to the SARS-CoV-2 RT-PCR test results: positive or negative.

Characteristics of the patients are described in each group by percentage and effective for qualitative variable; or by median and interquartile range, for continuous variable.

Sensitivity, specificity, positive predictive value and negative predictive value were then calculated with 95% confidential interval according to Clopper-Pearson exact binomial method. Statistical analyses were performed using R studio version 3.6.1.

We then compared the agreement between LFI and RT-PCR and CMIA and related with symptom's onset and thoracic CT scan.

Results

Overall, during the 2-weeks period of the study, 164 subjects were tested for SARS-CoV-2 RT-PCR at both hospitals.

7 patients were excluded because of a missing test result (LFI or RT-PCR) (flow-chart), resulting in 157 analyzed patients.

There were only 5 discrepancies in LFI reading by ED nurse and the virologist in the laboratory: for 2 patients the first reading in the ED was positive for IgM, then it was read as negative in the laboratory; for 3 patients, the opposite happened.

The median age was 70 years and there were 53% of men (table 1).

The main described symptoms are also reported and included dyspnea (43%), cough (36%), fever (25%) and chest pain (25%). Almost three-quarter (73.3%) of patients had symptoms onset in the last 7 days. Chest CT-scan of 26 patients (16.6%) showed typical ground glass opacity, evocative of COVID-19, which was more frequently found in the positive-PCR group (11 patients – 69%).

There were 20 (13%) patients that were tested **positive for SARS-CoV-2 RT-PCR**, of which 15 (75%) were positive for the LFI (2 for IgM, 3 for IgG and 10 for IgM + IgG) and 5 (25%) tested negative (Table 2). From the 13 patients from which the LFI showed an IgG band, 12 had an IgG detected by CMIA (Table 3).

Three of the RT-PCR +/LFI- patients had their first symptoms in the 7 days and the 2 last (40%) before 14 days. Three of them had a chest-CT scan, of which 2 were compatible with COVID-19 (Supplemental Material 1).

Among the 137 patients **who were tested negative for RT-PCR**, there were 27 (20%) with a positive LFI, of whom 16 (59%) exhibited an IgM band, 4 (15%) an IgG band and 7 (26%) both bands. These results agreed with ELISA IgG detection which was positive for 10 patients (Table 3). Of these PCR-/LFI+

patients, 17 (63%) had their first symptoms in 7 days, 5 (18%) in the first 14 days and 5 (18%) after 14 days. Seventeen had a chest CT-scan, from which 4 (23%) were evocative of COVID-19.

Within the 42 positive LFI, 18 (42.8%) were positive for IgM with symptoms onset varying from 0 to 21 days (12 had first symptoms within the first 7 days, 2 between 7 and 14 days and 4 after 14 days); 7 (16.7%) were positive for IgG, all with symptom's onset within the first 7 days; and 17 (40.5%) were positive for both, with symptoms onset varying from 0 to 30 days (9 had first symptoms in 7 days and 4 between 7 and 14 days).

Concordance between LFI and CMIA IgG calculated on 155 samples with conclusive results was 94.8%. Globally, in these 157 suspected COVID-19 cases attending the ED, LFI had (Table 2) a sensitivity of 75% [95% CI 69.5-80.5], specificity 80.3% [95% CI 75.2-85.4], positive predictive value 35.7% [95% CI 29.6-41.8] and negative predictive value 95.7% [95% CI 93.1-98.3], compared to RT-PCR as the gold standard.

Discussion

In this study we evaluated in the ED a nanoparticle-based immunochromatographic test kit for qualitative determination of COVID-19's IgM and IgG antibodies in human whole blood. With the SARS-CoV-2 spreading all over the world, there is a great number of patients admitted to the ED with symptoms that can be related to COVID-19. These patients must be isolated while waiting for RT-PCR test results. This can result in ED overcrowding as we usually need to wait for COVID-19 diagnosis confirmation to admit the patient into the general wards in order to avoid in-hospital contamination. Therefore, there is an unmet need to have rapid reliable confirmatory tests that could help the ED physicians in patient's triage.

The results of our study are in favor of the utilization of LFI IgM/IgG test for the detection of SARS-CoV-2 together with the RT-PCR at ED admission.

There was 21% of patients who had a negative RT-PCR but a positive LFI for either IgM, IgG or both. In those patients the rapid LFI has a really benefit. As RT-PCR has up to 30% false negatives results (4,6), the ED physician takes the risk to admit a patient currently infected with SARS-CoV-2 in a COVID-free area of the wards and so to spread the virus to the hospital staff and patients. If LFI is positive for IgM or IgG or both, the physician may anticipate the admission of the patient in a COVID-19 + area avoiding long waiting time and ED staff exposition and crowding.

Cassaniti et al. (8) compared a rapid IgM/IgG test with RT-PCR in the ED and reported that 8.3% exhibited a positive result for IgM/IgG LFI while RT-PCR was negative. Other studies found similar rates of 11% (9), which are slightly lower than our results but still suggesting an added value of LFI to identify some COVID-19 positive patients with negative RT-PCR.

We report that 6 (30%) of RT-PCR confirmed SARS-CoV-2 cases had both negative IgM and IgG on LFI. All of them were tested before 14 days and among these, 4 were tested before day 7 from the symptom's onset. As recent reports showed that the median time for IgM and IgG detection are 11 and 14 days from symptoms onset respectively (5,6,9), we interpret that these 6 false negative LFI were likely too early tests. Other explanations for the false-negative LFI may be due to a low antibody level below the detection limit of this LFI and to the immune response variability in individual antibodies production (3).

There are few peer-reviewed publications that have reported the accuracy of COVID-19 diagnostic results obtained by LFI with respect to RT-PCR tests (3,8–13). Sensibility and specificity varied from a study to another: Li et al found 88.66% and 90.63%, respectively while Shen et al. found 71.1% and 96.2% (3,10). In our study we report a sensitivity of 75% and specificity of 80%, slightly lower than what was described by previous studies and that's the reason why we recommend to use LFI together with RT-PCR in order to have the lowest false negative's number of patients.

Our study has some limits. Even though it is a bi-centric study, the recruitment started late after the epidemic peak of COVID-19 patients admitted in the ED in France, and there was only a few number of positive cases. Therefore, the sensibility and specificity of LFI might be different if we started our study earlier, at time of epidemic peak, when more SARS-CoV-2 cases were circulating. Moreover, the results reported here were produced with one commercialized LFI and might not reflect the performance of other LFIs available on the market.

Although LFIs cannot confirm the virus presence and replace RT-PCR, it provides important immunological evidence for physicians to complete the diagnosis along with other tests and to decide where to admit the patients. It has the advantage, in comparison with RT-PCR, of saving time without necessitating any extensive equipment; it is simple to use and requiring minimal training.

From our point of view, LFIs should be used in the ED as a complementary assay to the existing SARS-Cov-2 RT-PCR, to better and quicker diagnose COVID-19 patients.

Conclusion

SARS-CoV-2 LFI IgM/IgG tests may be sensitive and specific enough to be used as a complementary assay to the existing RT-PCR in the ED. These tests are easy to implement and to use, providing a result in less than 15 minutes and could contribute and improve the ED triage. Furthermore, these tests can be helpful for the detection of SARS-CoV-2 infected patients with false negative RT-PCR test.

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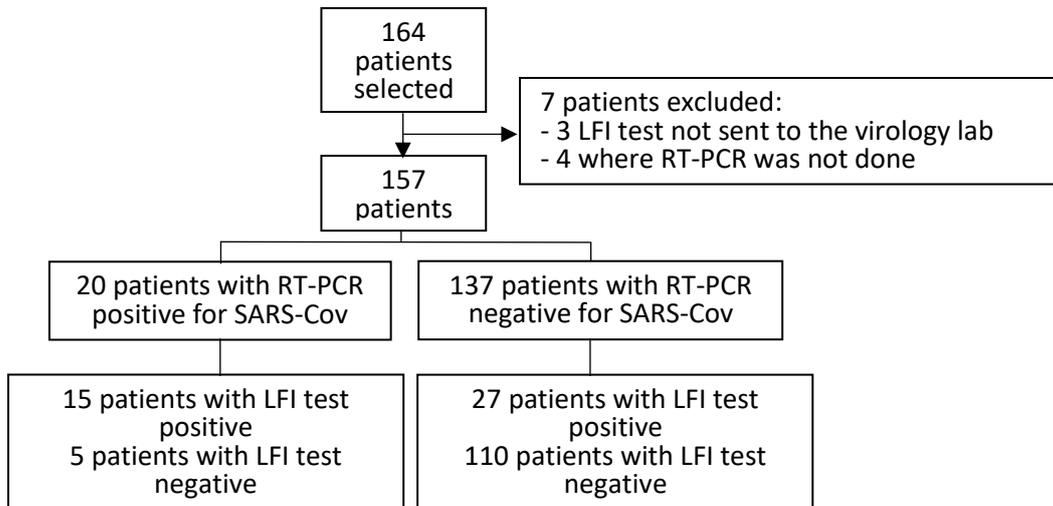


Figure 1. Flow-chart

Table 1: Emergency Department's patient's characteristics according to group (RT-PCR positive or negative)

Characteristics	Total (n= 157)	RT-PCR negative (n = 137)	RT-PCR positive (n= 20)
Sex			
Male	83 (52.9%)	74 (46%)	9 (45%)
Female	74 (47.1%)	63 (54%)	11 (55%)
Median	70	71	62.00
Age (years)	(54-80)	(54-81)	(52.5-75.8)
Symptoms onset			
0-7 days	115 (73.3%)	101 (73.7%)	14 (70%)
8-14 days	16 (10.2%)	12 (8.8%)	4 (20%)
15-21 days	14 (8.9%)	12 (8.8%)	2 (10%)
> 21 days	12 (7.6%)	12 (8.8%)	0 (0%)
Symptoms			
Fever	39 (24.8%)	32 (23.4%)	7 (35%)
Cough	57 (36.3%)	45 (32.8%)	12 (60%)
Myalgia	17 (10.8%)	12 (8.8%)	5 (25%)
Dyspnea	68 (43.3%)	57 (41.6%)	11 (55%)
Chest pain	39 (24.8%)	34 (24.8%)	5 (25%)
Diarrhea	22(14%)	20 (14.6%)	2 (10%)
Vomiting	25 (15.9%)	23 (16.8%)	2 (10%)
Ageusia	6 (3.8%)	5 (3.6%)	1 (5%)
Anosmia	5 (3.2%)	3 (2.2%)	2 (10%)
Asthenia	40 (25.5%)	36 (26.3%)	4 (20%)
Falling	11 (7%)	11 (8%)	0 (0%)
Headache	21 (13.4%)	16 (11.7%)	5 (25%)
Chest CT scan	106 (67,51%)	90 (65.7%)	16 (80%)
Chest CT scan	n = 106	n = 90	n = 16
evocative COVID-19	26 (24.5%)	15 (16.7%)	11 (68,8%)
Median Leucocytes (Giga/L)	8,33 (6.44-10.85)	8,33 (6.46-11.15)	8,46 (5.35-9.59)
Lymphocytes	1,31 (0.88-1.78)	1,27 (0,83-1,59)	1,79 (1.27-2.21)
Protein-C-reactive	16 (3-54)	16 (3-54)	27.5 (14-71.1)

Table 2 : Comparison of SARS-CoV-2 RT-PCR and LFI's results and LFI's sensitivity, specificity, positive predictive value and negative predictive value

		RT-PCR		Rapid IgM/IgG	
		Positive	Negative	Sensitivity (95% CI)	75% (69.5-80.5)
Rapid IgM/IgG	Positive	15	27	Specificity (95% CI)	80.3% (75.2-85.4)
	Negative	5	110	Positive predictive value (95% CI)	35.7% (29.6-41.8)
Total		20	137	Negative predictive value (95% CI)	95.7% (93.1-98.3)

Table 3: Comparison of SARS-CoV-2 IgG detection by a chemiluminescent microparticle immunoassay (CMIA) with lateral flow immunoassay (LFI) and RT-PCR

	CMIA Positive (n=26)		CMIA Negative (n=129)		CMIA inconclusive (n=2)
	RT-PCR		RT-PCR		RT-PCR
	positive	negative	positive	negative	positive
LFI IgM + / IgG -	0	1	1	15	1
LFI IgM - IgG +	2	3	1	1	0
LFI IgM + IgG +	10	6	0	1	0
LFI Ig M - /IgG -	1	3	3	107	1

Supplemental Material 1 : ED Symptoms, Chest CT-scan result and Diagnosis of patients from with LFI and RT-PCR mismatch

RT-PCR	LFI	Symptom's onset	Symptoms	Chest CT evocative of COVID	ED Diagnosis
positive	Negative	2	Fever, myalgia, cough, vomiting, headaches	yes	Flu-like syndrome
	Negative	5	Myalgia	no	Low back pain
	Negative	10	Fever, cough, dyspnea, chest pain, diarrhea, headaches	not performed (NP)	Dyspnea
	Negative	8	Fever, cough, dyspnea, anosmia	yes	COVID
	Negative	6	Dyspnea, asthenia	NP	COVID
negative	IgM	1	Cough, dyspnea, chest pain, vomiting, diarrhea	yes	Pneumonia
	IgM + IgG	30	Fever, cough, dyspnea, vomiting	no	Asthenia
	IgM	15	Cough, dyspnea	no	Heart Failure
	IgM + IgG	6	fever	no	Pneumonia
	IgM	7	Cough, diarrhea	no	Asthenia
	IgM	9	Fever, chest pain, vomiting, diarrhea	NP	Chest pain
	IgM + IgG	0	Vomiting, falling	yes	Falling
	IgM	1	Dyspnea, Asthenia	NP	Respiratory Distress
	IgM + IgG	0	Dyspnea, chest pain	yes	Chest pain
	IgM	21	Vomiting	NP	Intestinal Occlusion
	IgG	3	chest pain, Vomiting	no	Chest pain
	IgM	3	Fever, asthenia	no	Epilepsy
	IgM	4	Cough, dyspnea	no	Asthma
	IgM + IgG	7	Dyspnea	no	COPD
	IgM	21	Chest pain	no	Acute coronary syndrome
	IgG	1	Fever, cough, dyspnea, headaches	NP	Asthenia
	IgM + IgG	7	Fever, diarrhea, headaches	NP	Flu-like syndrome
	IgM	0	Dyspnea	No	Heart Failure
	IgM + IgG	4	Fever, myalgia, cough, dyspnea	NP	Asthenia
	IgM	6	Falling	NP	Anemia
	IgM	14	Chest pain	NP	Vertigo
	IgM	1	Bleeding	NP	Hemorrhage
	IgG	7	Limb pain	NP	Limb ischemia
	IgM	0	Myalgia, cough, dyspnea, chest pain	no	Pneumonia
	IgM	2	Dyspnea	yes	COVID
IgM	3	Dyspnea, vomiting, asthenia	no	Asthenia	
IgG	2	Fever, dyspnea, asthenia	no	Pneumonia	