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High negative predictive value of RT-PCR in patients with high likelihood of SARS-CoV-2 infection

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SARS-CoV-2 epidemic mitigation efforts rely on effective tests that should have a high negative predictive value to accurately exclude SARS-CoV-2 infection when the test is negative. A systematic review, despite the large heterogeneity, showed the rate of false negative results of SARS-CoV-2 RT-PCR tests could range from 1.8% to 58% [1]. France faced a major SARS-CoV-2 epidemic in the spring of 2020, with 5.3% of the population estimated to have been infected by May 2020 [2], thus bringing the pre-test probability of SARS-CoV-2 RT-PCR tests to high levels during this period. We aimed to estimate the negative predictive value of SARS-CoV-2 RT-PCR in patients with a high pre-test probability of SARS-CoV-2 infection.

We conducted a serological study in patients managed in eight French hospitals and who tested negative for SARS-CoV-2 using an RT-PCR test on nasopharyngeal or throat swab, either for symptoms consistent with COVID-19 or following contact with a confirmed case of SARS-CoV-2 infection. Blood was sampled for serological testing at least two weeks after symptom onset, to allow time for a potential seroconversion to take place [3]. Participants were questioned about recent symptoms consistent with COVID-19. Anti-SARS-CoV-2 antibodies were tested using an S-Flow assay, a flow cytometry-based assay detecting anti-S IgG antibodies with specificity and sensitivity rates above 99% [4,5]. This study was registered with ClinicalTrials.gov (NCT04325646) and received ethical approval by the Ile-de-France III institutional review board. Informed consent was obtained from all participants.

From March 13, 2020 to May 14, 2020, a total of 116 patients were enrolled. Five did not meet eligibility criteria and five were lost to follow-up, leaving 106 participants (58 women, 48 men) with a median age of 35 years (interquartile range [IQR]: 28-48). All participants reported symptoms consistent with COVID-19 and 41 (38.7%) participants reported prior contact with a confirmed case of SARS-CoV-2 infection. Two participants (1.9%) had to be hospitalized. Median time from symptom onset to RT-PCR test was 3 days (IQR 2-6) and median time from RT-PCR test to blood sampling was 21 days (IQR 18-29).

Four participants (3.8%) tested positive for anti-SARS-CoV-2 antibodies, resulting in a negative predictive value of SARS-CoV-2 RT-PCR of 96.2% (95% confidence interval: 90.6%–99.0%). All four participants had been tested in the same participating center for symptoms compatible with COVID-19 (including one with anosmia and ageusia), two of whom also reported contact with a confirmed case of SARS-CoV-2 infection. None of them had to be hospitalized. In these four participants, time from symptom onset to RT-PCR test ranged from 2 to 11 days and blood sampling for serology was performed between 21 and 29 days after symptom onset and between 10 and 21 days after RT-PCR test.

In a population with high pre-test probability of SARS-CoV-2 infection, the negative predictive value of SARS-CoV-2 RT-PCR was high. The serology technique we used has a very high sensitivity, which makes it very unlikely that a seropositive participant went undetected [5]. Seropositive participants might have been infected between RT-PCR sampling and blood sampling. However, this is unlikely given the short time interval between RT-PCR and serology samplings. Furthermore, all seropositive participants had symptoms compatible with COVID-19 at the time of RT-PCR testing, including one with anosmia and ageusia, two symptoms that have a high positive predictive value for COVID-19 diagnosis [6,7]. A systematic review of false-negative results of SARS-CoV-2 RT-PCR showed that the probability of false-negative results decreases from the day of exposure to 3 days after symptom onset and then increases again over the following days [8]. Three of the four false-negative patients in this study were tested at least 5 days after symptom onset, which may help explain the false-negative results. As all seropositive participants underwent RT-PCR testing in a single center, we may raise the hypothesis of swab performance or defective RT-PCR kit issues. Other possible explanations for false-negative RT-PCR tests include the absence of detectable viral shedding throughout the disease or a swab for RT-PCR testing performed outside the time period of detectable viral shedding

(especially in the two participants in whom swabs were performed respectively 8 and 11 days after symptom onset) [9]. As many countries have implemented mitigation strategies, resulting in bringing incidence rates at lower levels than those observed during the study period, the current negative predictive value is probably even higher than estimated here.

Limitations of this study include the absence of repeated RT-PCR tests, which could have identified a transient detectable viral shedding period, and the lack of detailed information on the RT-PCR kits used in the various centers.

The negative predictive value of SARS-CoV-2 RT-PCR in patients with a high pre-test probability of having a SARS-CoV-2 infection was high. This finding supports strategies based on isolation of patients when COVID-19 is suspected and on lifting isolation if the RT-PCR test is negative.

Data availability

Data used to generate the research will be made available upon request as per the French data protection rules.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Informed consent and patient details

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article and that this report does not contain any personal information that could lead to their identification.

Disclosure of interest

The authors declare that they have no competing interest.

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