Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Diagnostic accuracy and utility of SARS-CoV-2 antigen lateral flow assays in medical admissions with possible COVID-19

Sir,

The scale-up of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antigen lateral flow assays (LFAs) has caused much controversy, with concerns about lower sensitivity in asymptomatic individuals and when assays are performed by operators without healthcare training [1,2]. The proposed benefits of SARS-CoV-2 antigen LFAs are high specificity, fast turnaround times for results (<30 min) and ease of scalability [3]. These assays are of potential use for rapid identification of SARS-CoV-2 in patients who fit the case definition for coronavirus disease 2019 (COVID-19) and require hospital admission, as prompt isolation prevents nosocomial transmission. Isolation rooms are often limited and capacity is easily overwhelmed, necessitating the cohorting of patients with proven COVID-19. Even using rapid platforms, the turnaround times of SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) assays are often too slow to inform patient placement from emergency departments (EDs) [4]. SARS-CoV-2 LFAs could help to improve the flow of patients from the ED into 'COVID-19-positive' cohorts, and reduce pressure on limited hospital isolation rooms. However, few data exist on the diagnostic accuracy of SARS-CoV-2 LFAs in this setting.

Table I

Baseline characteristics and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) reverse transcription polymerase chain reaction (RT-PCR) results for patients testing positive and negative on Innova lateral flow assay (LFA)

Baseline characteristics	LFA negative	LFA positive	Total	*P*-value[a]
	N=464	*N*=264	*N*=728	
Age on arrival (years), median (IQR)	71 (53.5–83) (*N*=464)	65 (49.5–80) (*N*=264)	67.5 (52–82) (*N*=728)	0.038
Age >65 years, *N* (%, 95% CI)	260 (56.0%, 51.5–60.6)	125 (47.3%, 41.3–53.4)	385 (52.9%, 49.3–56.5)	0.024
Female sex, *N* (%)	211 (45.5%, 40.9–50.0)	116 (43.9%, 38.0–49.9)	327 (44.9%, 41.3–48.5)	0.69
Male sex, *N* (%)	253 (54.5%, 50.0–59.1)	148 (56.1%, 50.1–62.0)	401 (55.1%, 51.5–59.7)	
NEWS, median (IQR)	3 (1–6) (*N*=422)	5 (3–7) (*N*=230)	4 (2–6) (*N*=652)	<0.001
Pulse (beats/min), median (IQR)	94 (82–111) (*N*=426)	96 (84–108) (*N*=229)	95 (82–110) (*N*=655)	0.66
Systolic BP (mmHg), median (IQR)	136 (120–151) (*N*=421)	135.5 (122.5–149) (*N*=228)	136 (121–151) (*N*=649)	0.93
Diastolic BP (mmHg), median (IQR)	78 (68–88) (*N*=421)	80 (71–89) (*N*=228)	79 (70–88) (*N*=649)	0.10
Respiratory rate (breaths/min), median (IQR)	20 (18–27) (*N*=425)	24 (20–32) (*N*=228)	22 (18–28) (*N*=653)	<0.001
SpO_2 <94%, *N* (%, 95% CI)	55 (12.9%, 9.8–16.1)	68 (29.7%, 23.8–35.6)	123 (18.8%, 15.8–21.8)	<0.001
Required supplemental oxygen, *N* (%, 95% CI)	72 (16.9%, 13.3–20.4)	69 (29.9%, 24.0–35.8)	141 (21.4%, 18.3–24.6)	<0.001
Temperature >38°C, *N* (%, 95% CI)	67 (15.8%, 12.3–19.2)	96 (41.9%, 35.5–48.3)	163 (24.9%, 21.6–28.2)	<0.001

IQR, interquartile range; CI, confidence interval; BP, blood pressure; NEWS, National Early Warning Score; SpO_2, oxygen saturation.
For observations on arrival, 9.6–10.9% of data were missing. Pair-wise comparisons were performed using Chi-squared tests for proportions, *t*-tests for means and Wilcoxon rank sum tests for medians.

[a] *P*-values are shown for the comparison between LFA-positive and LFA-negative groups.

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Table II
Diagnostic performance of the Innova lateral flow assay (LFA) compared with a single severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal swab on admission

Diagnostic performance	LFA negative	LFA positive	Total	
	N=464	*N*=264	*N*=728	
SARS-CoV-2 RNA detectable on RT-PCR, *N* (%)	38	242	280	Sensitivity = 86.4% (95% CI 81.9—90.0)
SARS-CoV-2 RNA undetectable on RT-PCR, *N* (%)	426	22	448	Specificity = 95.1% (95% CI 92.6—96.7)
	NPV = 91.8% (95% CI 87.7—94.5)	PPV = 91.8% (95% CI 87.7—94.5)		

PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

As such, the diagnostic accuracy of the Innova SARS-CoV-2 Antigen Rapid Qualitative Test (Lotus Global Company, London, UK) was compared with SARS-CoV-2 RT-PCR from nasopharyngeal swabs (NPS) in adult admissions who met the COVID-19 case definition at a busy acute hospital in the UK [5]. The Innova LFA was performed in accordance with the manufacturer's instructions by appropriately trained healthcare assistants in the ED. A second NPS was sent for SARS-CoV-2 RT-PCR at the same time. Between 17th November 2020 and 31st December 2020, 728 patients presenting to the ED met the COVID-19 case definition and had valid Innova LFA and RT-PCR results. Baseline characteristics are shown in Table I. Just over half (55.1%) were male and the median age was 67.5 years. Two hundred and sixty-four patients tested positive on Innova LFA. Patients with positive LFA results were younger (median age 65 vs 71 years; $P=0.038$), more unwell (National Early Warning Score 5 vs 3; $P<0.001$) and more often febrile on arrival (temperature >38°C in 41.9% vs 15.8%; $P<0.001$) compared with patients with negative LFA results. Overall, admission SARS-CoV-2 RT-PCR was positive in 38.5% (280/728) of patients.

Compared with SARS-CoV-2 RT-PCR as the reference standard, the Innova LFA had sensitivity of 86.4% [242/280, 95% confidence interval (CI) 81.9—90.0] and specificity of 95.1% (426/448, 95% CI 92.6—96.7) (Table II). Twenty-two of 448 (4.9%) patients with a negative SARS-CoV-2 RT-PCR on admission had a positive LFA result. Eight of these 22 patients reported a positive COVID-19 test result up to 14 days prior to admission, and five patients subsequently had a positive PCR result within 5 days of admission. Thirteen of 22 patients had chest radiograph features consistent with 'classic/probable COVID-19' as reported by a radiologist. Only five of 22 patients had no PCR or radiological evidence of COVID-19; one reported a confirmed household contact, and two left hospital with a diagnosis other than COVID-19. This suggests that the lower-than-expected specificity of Innova LFA is likely to be the result of an imperfect reference standard, and specificity would be higher if using a clinical and RT-PCR-based composite reference standard [6].

Thirty-eight patients had negative Innova LFA results but positive PCR results. Twenty of these patients had cycle threshold (Ct) values available, with a median Ct value of 29 [interquartile range (IQR) 27—35]. Innova LFA results were available 3.2 h (median) after arrival at the ED (IQR 2.0—4.3, *N*=681) compared with 13.8 h (IQR 9.9—18.2, *N*=679) for RT-PCR. Thirty-five (57.1%) patients had chest radiographs that were reported as typical for COVID-19. Of those with symptom duration recorded, 77.3% (17/22) were symptomatic for at least 7 days prior to attending the ED.

Accounting for the inadequacy of a single SARS-CoV-2 RT-PCR as a reference standard, the Innova SARS-CoV-2 Antigen Rapid Qualitative Test was found to have good specificity in patients with symptoms of COVID-19 presenting to hospital. Sensitivity in this setting was high (86.4%) compared with preclinical evaluation studies [1]. Furthermore, results were mainly available within a few hours of presentation, allowing transfer of patients to COVID-19 cohort areas and reducing demand for isolation rooms whilst awaiting PCR results. Placing patients in the 'right bed' first time is also likely to reduce delays in care and increase efficiency, and allows isolation rooms to be prioritized for individuals requiring admission with suspected COVID-19 but negative LFA results. Of the 38 patients with COVID-19 (based on SARS-CoV-2 RT-PCR) who

were 'missed' by the Innova LFA, median Ct values were reasonably high, and corresponded to viral loads associated with lower sensitivity in previous studies [1]. However, sensitivity of the Innova LFA appears to be lower than that for some other SARS-CoV-2 viral antigen LFAs [7]. Importantly, individuals requiring admission with suspected COVID-19 should not be moved out of isolation on the basis of a negative SARS-CoV-2 viral antigen LFA result.

In summary, the Innova LFA can be used with good diagnostic accuracy for rapid identification of patients with COVID-19 amongst hospital admissions meeting the COVID-19 case definition, and patients that can be allocated to COVID-19 cohort areas. Based on these data, this application of COVID-19 LFAs has been recommended by NHS England [8].

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References

[1] Public Health England and University of Oxford SARS-CoV-2 Test Development and Validation Cell. Preliminary report: Rapid evaluation of lateral flow viral antigen detection devices (LFDs) for mass community testing. Oxford: University of Oxford; 2020. Available at: https://www.ox.ac.uk/sites/files/oxford/media_wysiwyg/UK%20evaluation_PHE%20Porton%20Down%20%20University%20of%20Oxford_final.pdf [last accessed December 2020]

[2] Deeks JJ. Operation Moonshot proposals are scientifically unsound. BMJ 2020;370:m3699.

[3] World Health Organization. SARS-CoV-2 antigen-detecting rapid diagnostic tests: an implementation guide. Geneva: WHO; 2020. Available at: https://www.who.int/publications/i/item/9789240017740 [last accessed January 2021].

[4] Brendish NJ, Poole S, Naidu VV, Mansbridge CT, Norton NJ, Wheeler H, et al. Clinical impact of molecular point-of-care testing for suspected COVID-19 in hospital (COV-19POC): a prospective, interventional, non-randomised, controlled study. Lancet Respir Med 2020;8:1192—200.

[5] World Health Organization. WHO COVID-19 case definition. Geneva: WHO; 2020. Available at: https://apps.who.int/iris/handle/10665/333912 [last accessed January 2021].

[6] Woloshin S, Patel N, Kesselheim AS. False negative tests for SARS-CoV-2 infection — challenges and implications. N Engl J Med 2020;383:e38.

[7] Pilarowski G, Marquez C, Rubio L, Peng J, Martinez J, Black D, et al. Field performance and public health response using the BinaxNOW TM Rapid SARS-CoV-2 antigen detection assay during community-based testing. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa1890.

[8] NHS England. Novel coronavirus (COVID-19) standard operating procedure: lateral flow device testing for emergency department patient pathways. London: NHS England; 2020. Available at: https://www.england.nhs.uk/coronavirus/publication/standard-operating-procedure-lateral-flow-device-testing-for-emergency-department-patient-pathways/ [last accessed January 2021].

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