



SHORT COMMUNICATION

Evaluation of a rapid antigen detection test (Panbio™ COVID-19 Ag Rapid Test Device) as a point-of-care diagnostic tool for COVID-19 in a pediatric emergency department

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Abstract

We evaluated the Panbio™ COVID-19 Ag Rapid Test Device as a point-of-care diagnostic tool for COVID-19 in 357 patients at a pediatric emergency department. Thirty-four patients tested positive by reverse transcription polymerase chain reaction, of which 24 were positive by the antigen assay. The sensitivity and specificity of the assay were 70.5% and 100%, respectively.

KEYWORDS

clinical sensitivity, emergency department, field evaluation, pediatric patients, rapid antigen assay, SARS-CoV-2 RNA viral load

1 | INTRODUCTION

Molecular assays (i.e., reverse transcription polymerase chain reaction [RT-PCR]) are the gold standard for SARS-CoV-2 detection in clinical specimens.¹ Nevertheless, lateral flow immunochromatography-based rapid antigen detection tests (RAD) have emerged as a routine diagnostic tool of COVID-19 at the point-of-care (POC), as they are simple to perform, thus circumventing the need for special equipment and personnel qualification, and low cost.² Notable experience has been gathered as to the performance of SARS-CoV-2 RAD in adult patients presenting with clinically compatible COVID-19,³ in whom they have shown to display a variable sensitivity, ranging from 45% to 96%, largely depending on the range of SARS-CoV-2 load in the specimens tested, which ultimately relates to the timing of specimen collection since the onset of symptoms. There is sparse information on how RAD performs in children suspected of having COVID-19.^{4–6} Real-world evaluation studies are mandatory to gauge the utility of RAD assays in clinical practice. Here, we evaluated the Panbio™ COVID-19 Ag Rapid

Test Device, which targets SARS-CoV-2 nucleocapsid protein, as a POC diagnostic tool for COVID-19 in a pediatric emergency department.

2 | MATERIAL AND METHODS

2.1 | Patients

This prospective, single-center study enrolled 357 consecutive patients (aged 0–14 years) in the Emergency Department of Hospital Clínico Universitario of Valencia (HCUV) between November 2020 and February 2021, with clinical suspicion of COVID-19. Patients at ≤5 days since symptoms onset were recruited. Demographic and clinical variables were recorded. Number of days since symptom onset, hours of fever before sampling, and previous contact with COVID-19 cases were annotated. The study was approved by the HCUV INCLIVA Research Ethics Committee.

2.2 | SARS-COV-2 testing

Two nasopharyngeal (NP) swabs were obtained from each patient by trained personnel, and specimens were randomly used for performing either RAD or RT-PCR. RAD (Panbio™ COVID-19 Ag Rapid Test Device; Abbott Diagnostic GmbH) was carried out after specimen collection and interpreted by the pediatrician in charge. NP specimens for RT-PCR were placed in 3 ml of Universal Transport Medium (Becton Dickinson). RT-PCR was performed within 4 h of specimen collection at the Microbiology Service of the HCUV.⁴ The TaqPath COVID-19 Combo Kit (Thermo Fisher Scientific) was used following RNA extraction carried out using the Applied Biosystems™ Mag-MAX™ Viral/Pathogen II Nucleic Acid Isolation Kits coupled with Thermo Scientific™ KingFisher Flex automated instrument. The AMPLIRUN® TOTAL SARS-CoV-2 RNA Control (Vircell SA) was used as reference material for estimating SARS-CoV-2 RNA load (in copies/ml, taking RT-PCR CTs for N gene).

2.3 | PCR multiplex targeting respiratory viruses

As detailed below, a number of NP specimens were tested by the Luminex xTAG Respiratory Viral Panel FAST v2 assay (Luminex Co.) following the manufacturer's recommendations.

2.4 | Statistical analyses

Percentages, medians, SDs, and interquartile ranges (IQR) were used to describe population characteristics and for descriptive analyses. Agreement between RAD and RT-PCR tests was assessed using Cohen's κ statistics. Differences between medians were compared using the Mann-Whitney U test. The χ^2 test was used for frequency comparisons. A logistic regression model was built to assess the association between clinical variables and RDA positivity. To identify the optimal SARS-CoV-2 RNA load (C_T) predicting RAD positivity, receiver operating characteristic (ROC) curve analysis was performed. Two-sided $p < 0.05$ were considered statistically significant. Statistical analyses were performed using the Epidat® 4.2 program.

3 | RESULTS

3.1 | Patient population

During the study period, 3522 patients attended, of whom 357 had suspected COVID-19 and were tested for the presence of SARS-CoV-2 in NP specimens (Table 1). The most common manifestations in these latter patients were <24 h fever (75.0%), rhinorrhea, dry cough (44.8%), bronchospasms (21.9%), and diarrhea (17.9%). A total of 35 (9.8%) patients required hospital admission.

3.2 | Overall clinical performance of the RAD assay at the pediatric emergency department

Of the 357 patients, 34 (9.5%) tested positive by RT-PCR, 24 (6.7%) of whom also had positive results by RAD. There were no RAD+/RT-PCR- cases, while both tests returned negative results in 323 patients (90.4%). Thus, the level of agreement between the results provided by the two tests was good (κ index, 0.81; 95% confidence interval [CI], 0.70–0.92). Accordingly, the overall sensitivity of RAD was 70.6% (95% CI, 52.2–84.9), while its specificity was 100% (95% CI, 98.9–100). Adjusted to the median prevalence of positive cases within the study period in our Department of Health (15%), the overall negative and positive predictive values of the RAD assay were 95.0% (95% CI, 91.9–97.0) and 100%, respectively. In turn, the diagnostic accuracy was 95.6% (95% CI, 93.0–97.5). Seven out of the 10 specimens yielding discordant results (RT-PCR+/RAD-) were run in a multiplexed PCR assay targeting common respiratory viruses. Interestingly, two of the seven specimens tested positive for *Rhinovirus/Enterovirus*.

3.3 | SARS-COV-2 RNA load in specimens and clinical sensitivity of the RAD assay

Median SARS-CoV-2 RNA load was significantly higher ($p < .001$) in NP specimens returning positive results by both tests (median C_T , 17.4, equivalent to 8.3 \log_{10} copies/ml; IQR, C_T , 13.7–20.2 and 9.4–7.4 \log_{10} copies/ml) than in RT-PCR-positive, RAD-negative specimens (median C_T , 29.3, equivalent to 4.5 \log_{10} copies/ml; IQR, C_T 24.4–30.9 and 6.1–4.0 \log_{10} copies/ml). As shown in Table 2, the sensitivity of the RAD assay was inversely related to the RT-PCR C_T (directly related to the SARS-CoV-2 RNA load). ROC analyses identified a RT-PCR C_T value of 21.8 (7.0 \log_{10} copies/ml) as the best discriminator between RAD positive and negative specimens (sensitivity, 100%; specificity, 100%).

3.4 | Clinical characteristics of patients testing positive or negative by RT-PCR and RAD assays

Among patients suspected of having COVID-19, those testing RT-PCR positive were older, had close contact with a COVID-19 case, and were more likely to display diarrhea, nausea, asthenia, and headache, whereas rhinorrhea was present more frequently in RT-PCR-negative individuals (Table 1). Four out of the 10 patients testing RT-PCR+/RAD- required hospitalization. As shown in Table S1, the shorter time lag from symptoms onset and close contact with a COVID-19 case within the previous 2 weeks were more common in COVID-19 patients testing positive by RAD. The latter parameter was found to be an independent risk factor for RAD positivity (odds ratio, 34.5; 95% CI, 10.9–109.5).

TABLE 1 Demographic, clinical, and laboratory characteristics of patients with suspected COVID-19 included in the study

Parameter	All patients	SARS-CoV-2 RT-PCR positive patients	SARS-CoV-2 RT-PCR negative patients	p value
Total number	357	34	323	
Sex, male/female (%)	202/155 (56.5/43.4)	15/19 (44.1/55.8)	187/136 (57.8/42.1)	0.12
Age (years), Median (IQR)	2 (1–6)	4.5 (1–11)	2 (1–5)	0.03
Days after symptoms onset, median (IQR)	1 (1–3)	1 (1–2)	1 (1–3)	1.0
Reported contact with positive COVID-19 case within the last 14 days, No. (%)	46 (12.8)	21 (61.7)	25 (7.7)	<0.000-1
<i>Clinical features</i>				
Fever no. (%)	268 (75.1)	29 (85.3)	239 (73.9)	0.15
Hours of fever, median (IQR)	18 (0–24)	13 (2–48)	18 (0–24)	0.58
Dry cough no. (%)	160 (44.8)	12 (35.2)	148 (45.8)	0.24
Rhinorrhea no. (%)	171 (47.9)	8 (23.5)	163 (50.4)	0.002
Dyspnea no. (%)	76 (21.3)	4 (11.7)	72 (22.3)	0.15
Odynophagia no. (%)	31 (8.7)	3 (8.8)	28 (8.6)	0.97
Asthenia no. (%)	9 (2.5)	3 (8.8)	6 (1.8)	0.014
Myalgia no. (%)	2 (0.5)	0	2 (0.62)	-
Anosmia no. (%)	2 (0.5)	1 (2.9)	1 (0.3)	0.052
Ageusia no. (%)	5 (1.4)	1 (2.9)	4 (1.2)	0.42
Diarrhea no. (%)	61 (17.1)	11 (32.3)	50 (15.5)	0.013
Nausea no. (%)	21 (5.9)	5 (14.7)	16 (4.9)	0.022
Vomiting no. (%)	61 (17.1)	7 (20.6)	54 (16.7)	0.57
Chest pain no. (%)	5 (1.4)	0	5 (1.5)	-
Headache no. (%)	14 (3.9)	4 (11.7)	10 (3.1)	0.013
Rash no. (%)	7 (1.9)	1 (2.9)	6 (1.8)	0.66
Conjunctivitis no. (%)	4 (1.1)	1 (2.9)	3 (0.9)	0.28

Abbreviation: IQR, interquartile range.

TABLE 2 Sensitivity of the Panbio™ COVID-19 Ag Rapid Test Device as a point-of-care diagnostic tool for COVID-19 in a pediatric emergency department according to the RT-PCR cycle threshold (C_T)

C_T value/estimated SARS-CoV-2 load in \log_{10} copies/ml	Number of patients with the corresponding RT-PCR C_T threshold/estimated SARS-CoV-2 RNA load	Number of patients testing positive by rapid antigen assay	Sensitivity (%)
<15/9.0	7/34	7/7	100
<20/7.4	17/34	17/17	100
<25/5.9	25/34	24/25	96
<30/4.3	29/34	24/29	82.7
<35/2.7	34/34	24/34	70.6

Additionally, COVID-19 RAD-positive patients reported a shorter duration of fever. In addition, vomiting and dyspnea were reported less frequently among this subgroup.

4 | DISCUSSION

Data on the performance of SARS-CoV-2 RAD assays at POC in children are scarce and divergent to some extent.⁴⁻⁶ Here, we conducted a prospective study enrolling 357 patients presenting with suspected COVID-19 within 5 days after the onset of symptoms at the Emergency Department to assess the clinical performance of the Panbio™ COVID-19 Ag Rapid Test Device at POC. The overall sensitivity of the Panbio RAD assay was 70.6%, which nevertheless was notably dependent upon the range of SARS-CoV-RNA loads in NP specimens, as it has been systematically reported for adults.³ In fact, the sensitivity of the RAD assay reached 100% when only specimens with high viral load, specifically those returning RT-PCR $C_T < 22$, were considered for the analyses. Two large studies assessing the clinical performance at POC of the Panbio assay and strictly focusing on pediatric patients of all ages have been recently published yielding rather dissimilar results in terms of sensitivity.^{5,6} In the study by Villaverde et al.⁵ the reported overall sensitivity of the Panbio assay was 45%, whereas in that of González-Donapetry et al.⁶ it was 77%, which approaches that found in the current study. Neither of the above studies provided the range of RT-PCR C_T or the estimated SARS-CoV-2 RNA loads in NP specimens. Interestingly, both studies differed in the timing of specimen collection since the onset of symptoms: ≤ 5 days in the former study and ≤ 3 days in the latter, which may explain the discrepancy, provided that SARS-CoV-2 RNA peak load is reached within 48 h after symptoms onset.⁷ In this context, the data presented herein, as well as data previously published from our group in a rather small group of children⁴ indicated that the likelihood of having a positive RAD assay was significantly higher when NP specimens were collected within that timeframe.

The sensitivity of the Panbio RAD assay reported here and in the above-mentioned studies in children^{5,6} with COVID-19 is notably lower than that reported for adults sampled within a comparable time window (>80% in most studies).⁴ Such difference is unlikely to be related to dissimilarities across age groups in terms of SARS-CoV-2 RNA peak load achieved early after COVID-19 presentation.⁷⁻⁹ In our view, three nonmutually exclusive explanations may account for that discrepancy: (i) dating of symptoms onset could be less accurate in children than in adults; (ii) a co- or superinfecting respiratory virus infection in a subject with evolved SARS-CoV-2 infection may be responsible of the clinical syndrome at admission. In this sense, *Rhinovirus/Enterovirus* RNA was detected in two out of seven children testing positive by RT-PCR, but negative by the RAD assay; (iii) SARS-CoV-2 RNA clearance in the upper respiratory tract may proceed at a faster rate in children when compared to adults.¹⁰

On the other hand, the Panbio RAD assay was found to display an exquisite specificity (100%) and notable prevalence-adjusted NPV and PPV, in line with previous reports.^{5,6}

As could be anticipated, patients referring a close contact with a COVID-19 case were more likely to test positive by both RT-PCR and the RAD assay. A novel finding of the current study was that among patients returning a positive RT-PCR result, no specific clinical signature was recognized in those eventually testing positive by the RAD assay. Nevertheless, the very limited number of events precludes drawing firm conclusions on this subject.

The main limitation of the current study is the rather small number of COVID-19 cases in the cohort. This precluded a meaningful analysis regarding the clinical performance of the RAD assay across different pediatric ages. Another limitation, shared by most studies, was that two different NP specimens, which may have differed in terms of quality (cellularity) were used for RT-PCR and RAD testing. The strength of the study is that it provides a realistic view of the performance of the assay carried out at POC.

In summary, although the Panbio RAD assay failed to meet one of the criteria (at least 80% sensitivity) recommended in WHO interim guidance for RAD diagnosis of SARS-CoV-2 infection,¹¹ its excellent performance at POC in identifying children exhibiting high SARS-CoV-2 RNA loads in the upper respiratory tract, which associate with virus culturability and hence contagiousness,^{4,12} early after the onset of symptoms, makes it, in our opinion, a valuable tool for the management of children with suspected COVID-19 attended to at the emergency department.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Medical care of patients, performance of the RAD assay and data analysis: Silvia Carbonell-Sahuquillo, María I. Lázaro-Carreño, Ana Barrés-Fernández, and José R. Bretón-Martínez. *RT-PCR methodology and validation of data:* Jorge Camacho, Eliseo Albert, and Ignacio Torres. *Conceptualization and supervision:* Cecilia Martínez-Costa and David Navarro. *Writing the original draft:* Silvia Carbonell-Sahuquillo, Cecilia Martínez-Costa, and David Navarro. All authors reviewed the original draft.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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